

# GEORGIAN MEDICAL NEWS

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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии  
საქართველოს სამედიცინო სიახლენი

# GEORGIAN MEDICAL NEWS

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თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ  
ТБИЛИСИ - НЬЮ-ЙОРК

**GMN: Georgian Medical News** is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.



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SURGICAL METHODS OF TREATMENT OF END-STAGE HEART FAILURE

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In the developed countries, chronic heart failure (CHF) is one of the most common pathologies. Currently, there are more than 23 million people worldwide suffering from CHF, and this number is constantly growing [1,2]. At present, in the United States alone, 5,800,000 Americans suffer from heart failure, and by 2030 the figure could rise to 7,250,000. Annually, more than 600,000 new cases are reported in Europe. Worldwide, people with HF number 76,000,000, and one in five HF patients dies within 12 months after this diagnosis is made. The incidence rate shows that over the next 20 years, the number of patients with CHF will grow twice as much [3-6]. Standard drug therapy aimed at reducing the symptoms of CHF is able to ensure a sufficient quality of life for patients with minimal degrees of heart failure and remains ineffective at its end-stages. According to statistics from the American College of Cardiologists/American Heart Association (ACC/AHA), the five-year mortality of patients with FC IV after NYHA amounts up to 80% [7,8]. These data allow infer that the treatment of CHF and improving the quality of life of patients will not lose its relevance, on the contrary, they will continue growing rapidly [9-14]

Heart failure is a pathological process observed in a large number of patients, the pumping function of heart being unable to supply sufficient blood circulation to meet the needs of the body. Management of cardiac patients with chronic heart failure

has recently been expanded from medical treatment to the use of the supplementary blood circulation systems strategy [15-20].

Currently, heart transplant is the “gold standard” of the treatment of the end-stage CHF resistant to drug therapy [9]. However, the major factor limiting the number of operations performed under the situation of shortage of donor organs [15]. According to the International Society of Heart and Lung Transplantation [16], 5,200 HTs were registered worldwide in 2019, more than a half of which were made in the United States (Fig. 1).

Currently, the mechanical support of blood circulation before heart transplantation is used in every fourth recipient (Fig. 2).

Auxiliary circulatory systems are used for the following purposes:

- bridge-to-transplantation (BTT): enlisted on a waiting list are the patients with severe hemodynamic abnormalities that would not allow them to expect a transplant without mechanical circulation support;
- bridge to candidacy (BTC): patients with multiple organ failure or high pulmonary hypertension which does not allow them to be put on a waiting list;
- destination therapy (DT): patients with heart failure refractory to medical treatment, though have contraindications or restrictions for heart transplantation like age being over 65-70 years (50% of patients are disqualified from the waiting list due to age).

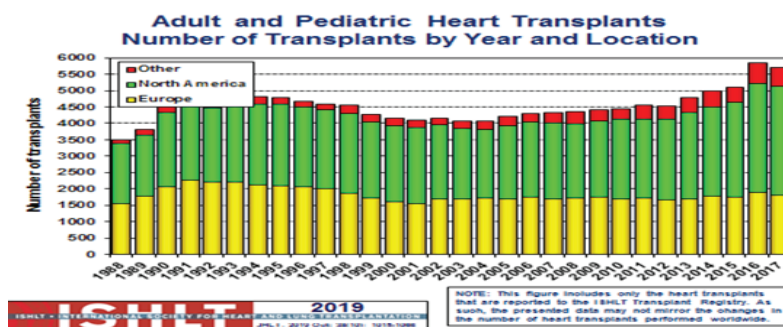


Fig. 1. Number of heart transplants by year according to the International Society of Heart and Lung Transplantation

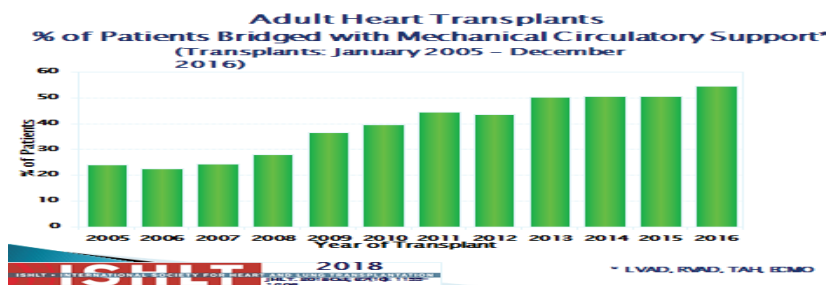


Fig. 2. According to the International Society of Heart and Lung Transplantation, 50% of patients are waiting for a HT being connected to a long-term MCS

- bridge to recovery (BTR): patients with potentially reversible cardiomyopathy though with severe hemodynamic disorders that will not allow them to survive without mechanical circulatory support;

- bridge to decision (BTD) which concept has been introduced since 2010: patients with heart and/or multiple organ failure, with severe hemodynamic disturbances, but the decision on the need for transplantation cannot be made now;

- bridge to bridge (BTB).

The aim of the study is to establish the effectiveness of mechanical support of blood circulation of patients with end-stage heart failure depending on the method of surgical correction.

**Material that methods.** The results of the study are based on the 73 patients' (median age 44 (16-69) years, men 68 patients, women 5 patients) survey and dynamic monitoring who were treated within 2008-2019 at the "Cardiology" Republican Research and Practical Centre, Minsk, Republic of Belarus and in the Cardiac Surgery Center on the basis of the State Executive Secretariat Clinical Hospital "Feofania", Kyiv, Ukraine. Patients were examined during the primary inspection, after 3 months and in 1 year.

After establishing compliance with the criteria of inclusion / expulsion depending on the presence of chronic heart failure with surgical treatment conducted, after receiving the data of instrumental and laboratory methods of the study the division of patients into groups was carried out:

Therefore, based on the criteria outlined in our study, all patients were divided into groups:

Group 1 - are patients who were administrated direct heart transplantation primary OHT (n=26); group 2 are patients who were administrated implantation of left ventricular bypass LVAD therapy, bridge to the OHT (Bridge-to-transplant therapy) (n=39); group 3 are patients who have been administrated the implantation of biventricular circulatory support BIVAD-therapy, bridge to the OHT (Bridge-to-transplant therapy) (n=8).

Groups of patients were compared based on age and social status. Verification of the diagnosis was performed as follows: CHF - taking into account the recommendations of ESH/ESC (2012, 2016).

The distribution of patients depending on the functional class of heart failure according to NYNA is presented on Fig. 3.

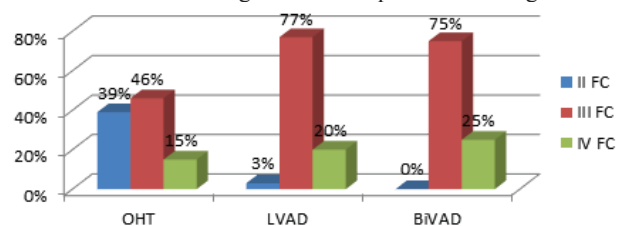


Fig. 3. Distribution of patients according to functional classes of heart failure according to NYNA

As for the functional class of heart failure according to NYNA among patients, the group of OHT II FC according to NYNA consisted of 39% of patients, III FC according to NYNA - 46% of patients, IV FC according to NYNA - 15% of patients.

As for the group of LVAD II FC according to NYNA consisted of 3 % of patients, III FC according to NYNA – 77 % of patients, IV FC according to NYNA – 20 % of patients. As for the group of BIVAD III FC according to NYNA - 75% of patients, IV FC according to NYNA - 25% of patients.

The distribution of patients depending on the inadequate blood flow is presented on Fig. 4.

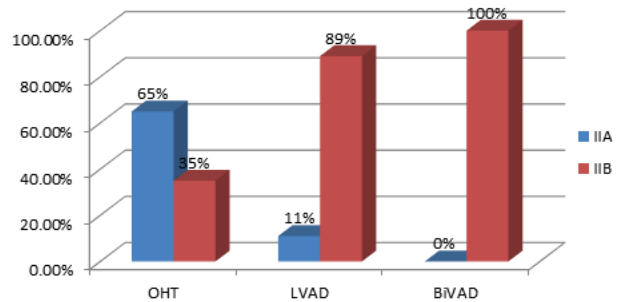


Fig. 4. Distribution of patients depending on the inadequate blood flow

Assessing the inadequate blood flow (IBF) among patients with CHF, in the group with OHT 65% of patients were characterized by the IBF IIA and 35% of patients were characterized by IBF IIB.

As for the group with LVAD, 11% of patients were characterized by IBF IIA, and 89% of patients – by IBF IIB.

As for the group with BiVAD, 100% of patients were characterized by IBF IIB.

Distribution of patients depending on the INTERMACS status are given on Fig. 5.

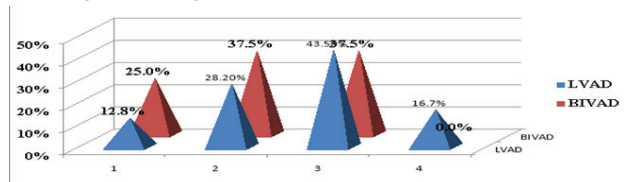


Fig. 5. Distribution of patients according to the INTERMACS status

The INTERMACS scale (Interdepartmental Register for Mechanical Assistance in Blood Support) helps to assign patients with advanced cardiac insufficiency (CI) to seven levels, according to the hemodynamic profile and the level of the target group organ's damage. This classification was defined within the context of a multicenter registry of ventricular assist devices to combine criteria for describing the clinical condition of patients with progressive CHF, optimizing perioperative risk forecasting, and refining instructions for each of the available alternative treatments.

**Results and discussion.** Currently, there are systems of mechanical auxiliary IR (bridge of choice or bridge to transplant) for ventricular discharge for the treatment of patients with severe heart failure, refractory to drug therapy, provided there are no contraindications to their implantation. The use of mechanical heart support systems results in reduced consumption and increased delivery of oxygen to the myocardium and other organs by improving coronary and systemic perfusion.

Therefore, based on the criteria outlined in our study, all patients were divided into groups:

Group 1 - are patients who were administrated direct heart transplantation primary OHT (n=26); group 2 are patients who were administrated implantation of left ventricular bypass LVAD therapy, bridge to the OHT (Bridge-to-transplant therapy) (n=39); group 3 are patients who have been administrated the implantation of biventricular circulatory support BIVAD-therapy, bridge to the OHT (Bridge-to-transplant therapy) (n=8).

Table 1 presents the results of structural and functional indicators of the left and right ventricles for groups 1-3 patients with

Table 1. The results of structural and functional indicators of the left and right ventricles for groups 1-3 Patients with CHF

Index	Mean observation			F-criterion	p-level	Van der Waerden criterion ( $\chi^2$ )	p-level
	Group 1 Patients with CHF on OHT (n=26)	Group 2 Patients with CHF on LVAD (n=39)	Group 3 Patients with CHF on BIVAD (n=8)				
RV EDV	94,5 [185;36]	103 [162;30]	161 [258;80]	17.2337	<.0001	27.5086	<.0001
RV ESV	61 [138;18]	67,5 [120;14]	125 [171;91]	15.0504	<.0001	23.6480	<.0001
LVEF (B-mode)	21 [41;10]	19,5 [40;12]	16,7 [24;10]	8.8203	0.0004	15.7125	0.0004
LV ESV (M-mode)	218 [309;102]	248 [410;130]	300 [410;219]	5.0684	0.0086	8.6819	0.0130
LV EDV (M-mode)	278 [414;147]	327 [630;174]	370 [472;304]	4.9031	0.0099	8.7838	0.0124
LV ESV (B-mode)	236 [367;93]	255 [443;100]	258 [410;19]	4.0150	0.0220	6.8787	0.0321
TAPSE	11,5 [19;7]	10,6 [17,8;6]	8,4 [11;6]	3.0021	0.0556	5.1455	0.0763

CHF, it should be noted: evaluating the structural and functional indicators of the right ventricle – the RV EDV, the average value is higher among group 3 patients with CHF on BiVAD161 [258; 80] than in group 2 patients with CHF on LVAD103 [162; 30], and in group 1 patients with CHF for direct OHT 94.5 [185; 36] while ( $p<0001$ ).

The increase in the volume of the RV EDV indicates dilatation of the right ventricle in case of the biventricular insufficiency.

The index of RV ESV the average value is higher in group 3 patients with CHF on BiVAD125 [171;91] than in group 1 patients with CHF for direct OHT 61 [138;18], and in group 2 patients with CHF on LVAD (n=39) 67.5 [120;14], while ( $p<0001$ ).

An increase in the RV ESV volume ncreas indicates the biventricular insufficiency.

This indicator of LV EF to (B-mode) - the average value is higher in group 1 patients with CHF for direct OHT 21 [41;10] than in group 2 patients with CHF on LVAD19.5 [40;12] and group 3 patients with CHF on BIVAD16.7 [24;10], while ( $p<0001$ ).

Decreased LV EF indicates the progression of left ventricular insufficiency. LV ESV (M-mode) - the average value is higher in group 3 patients with CHF fo BIVAD 300 [410; 219] than in group 2 patients with CHF on LVAD248 [410; 130], and in group 1 patients with CHF for direct OHT 218 [309; 102], while ( $p<0001$ ). An increase in LV ESV indicates the progression of left ventricular insufficiency. As for such an index as LV EDV (M-mode), the average value is higher in group 3 patients with CHF on BiVAD370 [472; 304] than in group 1 Patients with CHF for direct OHT 278 [414; 147] and in group 2 patients with CHF on LVAD327 [630; 174], while ( $p<0001$ ).

An increase in LV EDV indicates progression of left ventricular insufficiency. LV ESV (B-mode) - the average value is higher in group 3 patients with CHF on BiVAD258 [410; 194] than in group 2 patients with CHF on LVAD255 [443; 100], and in group 1 patients with CHF for direct OHT 236 [367; 93], while ( $p<0001$ ).

Thus, the following functional indexes of the left and right ventricles in the examined patients were established:

In group 1 of patients with CHF for direct OHT in this group, we observe a decrease in LV EF, which indicates the progression of left ventricular insufficiency.

In group 2 patients with CHF on LVAD- in this group we observe an increase in left ventricular volume.

In group 3 patients with CHF on BIVAD- in this group we observe an increase in LV ESV and an increase in LV EDV, which indicates the progression of left ventricular insufficiency.

An increase in the RV EDV volume, an increase in the RV ESV volume indicate the progression of biventricular insufficiency.

All potential heart transplant recipients should be probed in the right compartments of heart. Catheterization of the heart right departments and the study of central hemodynamics with determination of the rate of cardiac output (CB), cardiac index (CI), pressure in the heart cavities, pulmonary artery pressure (PAP), central venous pressure (CVP), pulmonary vascular resistance (PVS), transpulmonary pressure gradient (TPG), are presented in Table 2.

Let's analyze Table 2, based on the indexes of pulmonary artery tonometry: PVR-Wood index - the average value was higher in group 2 patients with CHF fo LVAD 5.5 [8,2; 2.4] and in group 3 patients with CHF on BIVAD5.4 [7; 2.7] than in group 1 patients with CHF for direct OHT 3.5 [5; 1.7], while ( $p<0001$ ). The high value of pulmonary vascular resistance, refractory to drug therapy, is a contraindication for direct heart transplantation. In case of such patients, mechanical circulatory support devices are used.

As for the PAP index, the average value is significantly higher in group 2 patients with CHF on LVAD 46.9 [85; 35] and in group 3 patients with CHF on BiVAD 44.5 [56; 29], than in 1 group of patients with CHF for direct OHT 37 [52; 19], while ( $p<0001$ ).

As for the TPG index, the mean value is higher in group 2 patients with CHF on LVAD15 [22; 10] than in group 1 patients with CHF for direct OHT 11.8 [19; 7] and in group 3 patients with CHF on BIVAD10.8 [15; 7], while ( $p<0001$ ).

Table 2. The results of direct tonometry of the pulmonary artery for patients with CHF in groups 1-3

Index	Mean observation			F-criterion	p-level	Van der Waerden criterion ( $\chi^2$ )	p-level
	Group 1 Patients with CHF on OHT (n=26)	Group 2 Patients with CHF on LVAD (n=39)	Group 3 Patients with CHF on BIVAD (n=8)				
Wood	3.5 [5; 1,7]	5,5 [8,2;2,4]	5.4 [7; 2,7]	36.7722	<.0001	40.8302	<.0001
PAP	37 [52;1 9]	46,9 [85; 35]	44,5 [56; 29]	17.6052	<.0001	27.7535	<.0001
TPG	11,8 [19; 7]	15 [22; 10]	10,8 [15; 7]	13.3210	<.0001	23.0940	<.0001

Table 3. The results of structural and functional parameters of the left and right ventricles for patients with CHI after a month after the direct OHT

Index	Mean observation	F-criterion	p-level	Van der Waerden criterion ( $\chi^2$ )	p-level
	Group 1 Patients with CHI after OHT (n=24)				
LV EF (B-mode)	67 [83;59]	8.8203	0.0004	15.7125	0.0004
LV ESV (M-mode)	33 [54;11]	5.0684	0.0086	8.6819	0.0130
LV EDV (M-режим)	96 [123;66]	4.9031	0.0099	8.7838	0.0124

The results of treatment of patients with CHI on direct OHT. As for this group of patients, 26 patients underwent direct heart transplantation. Out of them, 24 patients were treated with a positive result, which stands for 92%. 2 patients died, that is, 8%, 1 patient was diagnosed the case of acute cerebrovascular accident, intraoperative complication, accounting for 4%, the patient died 2 months after the intervention. 1 patient was diagnosed the case of iliac passion, which stands for 4%, the patient died 2.5 months after the intervention.

The results of structural and functional parameters of the left and right ventricles for patients with CHI after the direct OHT after 1 month presented in Table 3: the end-diastolic volume of the left ventricle 96 [123;66] milliliters, after the direct OHT the EDV size is within normal limits, while (p<0001).

The end-systolic volume of the left ventricle 33 [54; 11] milliliters, the ESV (M-mode) size is within normal limits, while (p<0001).

The left ventricular ejection fraction 67 [83;59]%, after the direct OHT, the left ventricular fraction ejection is within the age norm, with (p<0001).

One month later, 24 patients who underwent the direct OHT, were assessed for the heart failure's functional class according to the NYHA: I FC by NYHA for 38% of patients, and II FC by NYHA for 63% of patients.

Data on the severity of the patients' condition before and after surgical treatment according to the HF functional class according to the NYHA are presented in Fig. 6.

Fig. 6 presents the assessment of the HF functional class according to the NYHA before OHT - II FC according to NYHA - 39 % of patients, III FC according to NYHA - 46 % of patients, IV FC according to NYHA - 15 % of patients, after a month after OHT - I FC according to NYHA - 38% of patients, and II FC according to NYHA - 62% of patients.

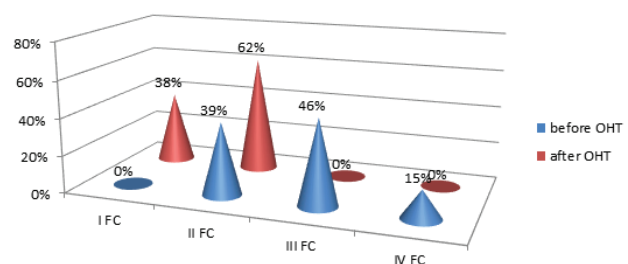


Fig. 6. Data on the severity of the patients' condition before and after surgical treatment according to the HF functional class

Data on the severity of the patients' condition before and after the surgical treatment of circulatory inefficiency (CI) are presented in Fig. 7.

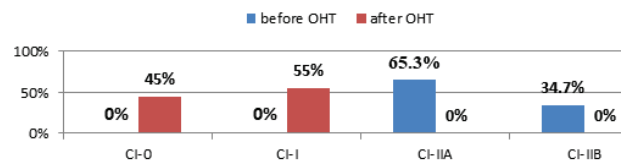


Fig. 7. Data on the severity of the patients' condition before and after the surgical treatment of CI

Fig. 7 shows the data on the severity of the patients' condition before and after surgery for circulatory inefficiency: CI IIA for 65.3% of patients, CI IIB for 34.7% of patients, after a month after OHT: CI o for 45% of patients, CI I for 55% of patients.

Table 4. The results of structural and functional parameters of the left and right ventricles for patients on mechanical support of circulation among group 2 patients with CHI on LVAD

Index	Mean observation:		F-criterion	p-level	Van der Waerden criterion ( $\chi^2$ )	p-level
	Group 2 Patients with CHI before LVAD (n =39)	Group 2 Patients with CHI on LVAD 3 months (n =39)				
RV EDV	103 [162;30]	76,7 [162;36]	17.2337	<.0001	27.5086	<.0001
RV ESV	67,5 [120;14]	46,6 [101;19]	15.0504	<.0001	23.6480	<.0001
LV EF (B-mode)	19,5 [40;12]	24,6 [47;12]	8.8203	0.0004	15.7125	0.0004
LV ESV (M-mode)	248 [410;130]	159,3 [385;35]	5.0684	0.0086	8.6819	0.0130
LV EDV (M-mode)	327 [630;174]	228,1 [496;80]	4.9031	0.0099	8.7838	0.0124
LV ESV (B-mode)	255 [443;100]	156 [240;38]	4.0150	0.0220	6.8787	0.0321
TAPSE	10,6 [17,8;6]	11,2 [16;6]	3.0021	0.0556	5.1455	0.0763

Thus, after the direct OHT performed, 92% of patients were treated with a positive result, 2 patients died, which stands for 8%. All parameters of structural and functional parameters of the heart after the orthotopic heart transplantation were within normal limits, an increase in maximum oxygen consumption by the myocardium by 58%, and an increase in exercise tolerance by 71% were noted. The HF functional class according to the NYHA after a month after OHT - I FC according to NYHA - 38% of patients, and II FC according to NYHA - 63% of patients. CI after a month after OHT: CI 0 for 45% of patients, CI I for 55% of patients.

*Results of the lvad therapy as a mechanical bridge to the OHT.* As for this group of patients, 39 patients underwent the left ventricular bypass LVAD therapy implantation as a bridge to the OHT. Out of them, 18 patients underwent secondary OHT, which stands for 46%. Patients continuing LVAD therapy - 18 patients, which stands for 46%. Patients who died on LVAD - 3 patients, this is 8%. The cause of death in 3 cases is purulent-septic lesions (100%).

The results of the left and right ventricle structural and functional parameters for patients on LVAD therapy are shown in Table 4: the end-diastolic volume of the right ventricle for group 2 patients with CHI on LVAD 76.7 [162; 36], a decrease in RV EDV by 25.5%, with (p<0001). The end-systolic volume of the right ventricle for group 2 patients with CHI on LVAD 46.6 [101; 19], a decrease in RV ESV by 31%, with (p<0001).

Left ventricular ejection fraction for group 2 patients with CHI on LVAD 24.6 [47; 12], an increase in LV EF by 21%, with (p<0001).

The end-systolic volume of the left ventricle (M-mode) for group 2 patients with CHI on LVAD 159.3 [385; 35], reduction of ESV (M-mode) by 36%, with (p<0001).

The end-diastolic volume of the left ventricle (M-mode) for group 2 patients with CHI on LVAD 228.1 [496; 80], reduction of LV EDV (M-mode) by 30%, with (p<0001).

The end-systolic volume of the left ventricle (B-mode) for group 2 patients with CHI on LVAD 156 [240; 38], reduction of LV ESV (B-mode) by 31%, with (p<0001).

TAPSE tricuspid systolic excursion for group 2 patients with CHI on LVAD 11.2 [16; 6], an increase in TAPSE by 5%, with (p<0001).

While studying the structural and functional parameters of the heart for group 2 patients with CHI on LVAD therapy, the decrease/increase of the following parameters is determined: RV EDV by 25.5%, RV ESV by 31%, an increase in LV EF by 21%, a decrease in LV EDV (M-mode) by 36%, decrease in LV EDV (M-mode) by 30%, decrease in LV ESV (B-mode) by 31%, increase in TAPSE by 5%.

The use of LVAD therapy has led to positive changes in the normalization of intracardiac hemodynamics. Hemodynamic unloading of the ventricle can completely change and in some cases normalize several aspects of the structure and function of the heart. In our study, we showed a decrease in the left ventricular cavity by 30%, as well as a decrease in the right ventricular cavity by 25.5%, an increase in the left ventricle ejection fraction by 21%.

The results of direct pulmonary artery tonometry indexes for group 2 patients with CHI on LVAD therapy for 3 months are presented in Table 5. According to the direct pulmonary artery tonometer after 3 months of LVAD-therapy the following was noted: Wood's ratio is 3.65 [6;1.7], a decrease in pulmonary vascular resistance according to Wood by 34%, with (p<0001).

Pulmonary artery pressure 35.6 [56;27], reduction of PAP by 24%, while (p<0001).

Transpulmonary gradient for group 2 patients with CHI on LVAD 11.9 [17;8], a decrease in TPG by 21%, with (p<0001).

Data on the severity of patients in group 2 patients with CHI

Table 5. The results of direct pulmonary artery tonometry for group 2 patients with CHI on LVAD on mechanical support of the blood circulation

Index	Mean observation:		F-criterion	p-level	Van der Waerden criterion ( $\chi^2$ )	p-level
	Group 1 Patients with CHF on OHT (n=26)	Group 2 Patients with CHF on LVAD (n=39)				
Wood	3.5 [5; 1,7]	5,5 [8,2;2,4]	36.7722	<.0001	40.8302	<.0001
PAP	37 [52;1 9]	46,9 [85; 35]	17.6052	<.0001	27.7535	<.0001
TPG	11,8 [19; 7]	15 [22; 10]	13.3210	<.0001	23.0940	<.0001

on LVAD: before LVAD therapy, on LVAD therapy and after OHT by a functional class of HI according to NYHA are presented in Fig. 8.

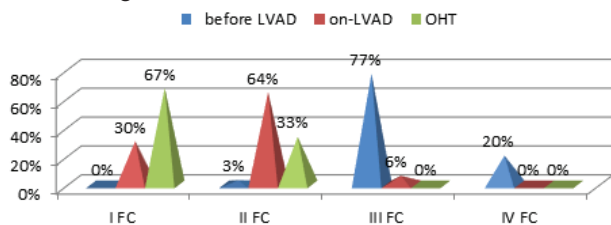


Fig. 8. Data on the severity of patients in group 2 patients with CHI on LVAD

Assessment of functional class of heart failure according to NYHA before LVAD-therapy - II FC according to NYHA - 2.5% of patients, III FC according to NYHA - 76.91% of patients, IV FC according to NYHA - 20.5% of patients, for LVAD therapy I FC according to NYHA - 30.5% of patients, II FC according to NYHA - 64% of patients, III FC according to NYHA - 5.5%, after OHT I FC according to NYHA - 67% of patients, II FC according to NYHA - 33% of patients (Fig. 8).

Data on the severity of patients before LVAD-therapy, LVAD-therapy, after OHT because of circulatory inefficiency are shown on Fig. 9.

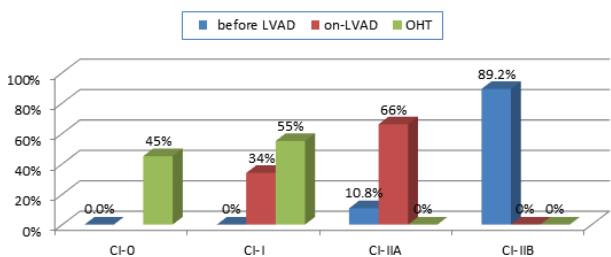


Fig. 9. Data on the severity of patients before LVAD-therapy, LVAD-therapy, after OHT because of circulatory inefficiency

Fig. 9 shows the assessment of the severity of patients before LVAD-therapy, LVAD-therapy, after OHT according to circulatory inefficiency: CI IIA - 10.8% of patients, CI II B - 89.2% of patients, LVAD-therapy CI I - 34% patients, CI IIA - 66% of patients, after OHT: CI 0 - 45% of patients, CI I - 55% of patients.

In the last decade, long-term left ventricular bypass (LVB) systems have been implanted, which have become the leading method of mechanical circulatory support (MCS) in patients with terminal congestive heart inefficiency (CHI), which allows

them to survive to bridge transplantation. According to the register of the International Society for Heart and Lung Transplantation (ISHLT) in 2018, more than 55% of THs were performed for recipients with pre-transplantation MCS by the method of implantable long-term LVB. Thus, out of the 39 patients who were on LVAD therapy as a bridge to the OHT, in 3 months there was a decrease in the left ventricular cavity by 30%, with (p<0001), a decrease in the pancreatic cavity by 25.5%, while (p<0001), increasing the fraction of LV emissions by 21%, while (p<0001). According to the direct tonometer of the pulmonary artery when using LVAD-therapy, we observe a decrease in pulmonary vascular resistance "Wood" by 34%, with (p<0001), a decrease in PAP by 24%, while (p<0001), a decrease in TPG on 21%, with (p<0001). The results of changes in functional parameters in patients on LVAD therapy after 3 months: an increase in maximum myocardial oxygen consumption by 6%, with (p<0001), as well as an increase in exercise tolerance by 15%. In this case (p<0001). Assessment of functional class of heart failure according to NYHA on LVAD therapy I FC according to NYHA - 30.5% of patients, II FC according to NYHA - 64% of patients, III FC according to NYHA - 5.5%. Estimation of the severity of the condition of patients on LVAD-therapy by circulatory insufficiency of CI I in 34% of patients, NCI IIA in 66% of patients. Patients were prepared for the second stage of surgical treatment of secondary heart transplantation. Of these, 18 patients underwent secondary OHT - 18 patients, which is 46%. Patients who continue LVAD therapy - 18 patients, which is 46%. Patients who died on LVAD - 3 patients, which is 8%. The cause of death in 3 cases of purulent-septic lesions 100%. Assessment of functional class of heart failure by NYHA after secondary OHT after 1 month I FC according to NYHA - 67% of patients, II FC according to NYHA - 33% of patients. Assessment of the severity of the patients' condition after secondary OHT after 1 month CI 0 - 45% of patients, CI I - 55% of patients.

*Results of BiVAD therapy as a mechanical bridge to the OHT.* As for this group of patients, 8 patients underwent implantation of biventricular bypass: BiVAD therapy as a bridge to the OHT. Out of these patients, secondary OHT was performed for 4 patients, which stands for 50%. Patients who died on BIVAD - 4 patients, which stands for 50%. The cause of death in 2 cases - purulent-septic lesions, which stands for 50%. Ascending cable infection. In addition, 2 more cases are multi-organ insufficiency, which stands for 50%.

The high value of the rate of pulmonary vascular resistance refractory to drug therapy is a contraindication for direct heart transplantation. Such patients use devices to mechanically support blood circulation.



Table 6. The results of structural and functional parameters of the left and right ventricles for group 3 patients with CHI on BiVAD

Index	Mean observation:		F-criterion	p-level	Van der Waerden criterion ( $\chi^2$ )	p-level
	Group 3 Patients with CHI before BIVAD (n=8)	Group 3 Patients with CHI on BIVAD (n=4) 3 months				
RV EDV	161 [258;80]	151,7 [220;110]	17.2337	<.0001	27.5086	<.0001
RV ESV	125 [171;91]	112,5 [144;80]	15.0504	<.0001	23.6480	<.0001
LVEF (B-mode)	16,7 [24;10]	24,8 [46;10]	8.8203	0.0004	15.7125	0.0004
LV ESV (M-mode)	300 [410;219]	191,1[279;51]	5.0684	0.0086	8.6819	0.0130
LV EDV (M-mode)	370 [472;304]	259,4 [367;102]	4.9031	0.0099	8.7838	0.0124
LV ESV (B-mode)	258 [410;194]	199,7 316;51]	4.0150	0.0220	6.8787	0.0321
TAPSE	8,4 [11;6]	10,7 [14;8]	3.0021	0.0556	5.1455	0.0763

Table 7. The results of direct tonometry of the pulmonary artery for group 3 patients with CHF on BIVAD on mechanical support of circulation

Index	Mean observation:		F-criterion	p-level	Van der Waerden criterion ( $\chi^2$ )	p-level
	Group 3 Patients with CHI before BIVAD (n=8)	Group 3 Patients with CHI on BIVAD (n=4)				
Wood	5.4 [7; 2,7]	4,2 [5;2,7]	36.7722	<.0001	40.8302	<.0001
PAP	44,5 [56; 29]	37,7 [56;27]	17.6052	<.0001	27.7535	<.0001
TPG	10,8 [15; 7]	9,3 [10;6]	13.3210	<.0001	23.0940	<.0001

Biventricular support is required for patients with high central venous pressure, increased pulmonary vascular resistance, or with malignant arrhythmia resistant to drug therapy.

The analysis of Echo-CG data presented in table 6 was performed to study the condition of patients on BiVAD therapy as a mechanical bridge to the OHT.

The results of structural and functional parameters of the left and right ventricles for group 3 patients with CHI on BiVAD therapy after 3 months are shown in table 6: the end-diastolic volume of the left ventricle 151.7 [220;110] milliliters, reduction of EDV by 6%, with (p<0001). The end-systolic volume of the left ventricle 112.5 [144; 80] milliliters, reducing ESV (M-mode) by 10%, while (p<0001). Left ventricular ejection fraction 24.8 [46; 10]%, increase in the left ventricular ejection fraction by 33%, while (p<0001), the end-systolic volume of the left ventricle (M-mode) 191.1 [279; 51], reduction of ESV (M-mode) by 36.3%, with (p<0001), the end-diastolic volume of the left ventricle (M-mode) 259.4 [367; 102], reduction of EDV (M-mode) by 30%, while (p<0001), the end-systolic volume of the left ventricle (B-mode) 199.7 [316; 51], reduction of ESV (B-mode) by 22.5%, while (p<0001) TAPSE tricuspid systolic excursion 10.7 [14; 8], increase in TAPSE by 21.4%, while (p<0001).

The study of structural and functional parameters of the heart revealed changes in group 3 patients on BiVAD, due to mechanical support of blood circulation: reduction of RV EDV of the pancreas by 6%, reduction of RV ESV of the pancreas by 10%, increase of LV EF by 33%, decrease of LV ESV (M-mode) by 36.3%, decrease in LV EDV (M-mode) by 30%, decrease in LV ESV (B-mode) by 22.5%, increase in TAPSE tricuspid systolic excursion by 21.4%.

As it has been indicated, one of the important results of long-term MCS is the creation of conditions for myocardial remodeling at the background of mechanical unloading of the heart. We have shown that patients receiving BiVAD therapy have shown effective myocardial unloading and decreased end-diastolic ventricular volume (LV).

The results of direct pulmonary artery tonometry for group 3 patients with CHI on BIVAD on mechanical support of blood circulation after 3 months are presented in table 7: Wood's ratio is 4.2 [5; 2.7], a decrease in pulmonary vascular resistance according to Wood by 22%, with (p<0001).

PAP average value 37.7 [56; 27], reduction of PAP by 15%, with (p<0001).

Transpulmonary TPG gradient 9.3 [10; 6], a decrease in TPG by 14%, with (p<0001).

Data on the severity of the condition of group 3 patients with CHI on BiVAD: before BiVAD-therapy, on BiVAD-therapy and after OHT according to the functional class of CI according to NYHA are presented in Fig. 10.

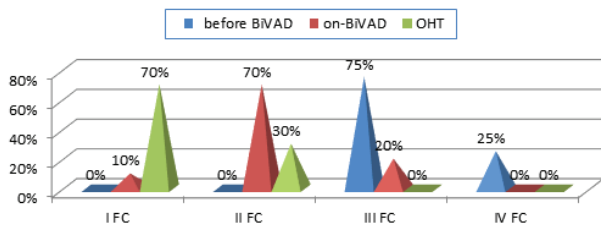


Fig. 10. Data on the severity of the condition of group 3 patients with CHI on BiVAD

Assessment of the functional class of heart failure according to NYHA before BiVAD therapy - III FC according to NYHA - 75% of patients, IV FC according to NYHA - 25% of patients, on BiVAD therapy I FC according to NYHA - 10% of patients, II FC according to NYHA - 70% of patients III FC according to NYHA - 30%, after OHT I FC according to NYHA - 70% of patients, II FC according to NYHA - 30% of patients (Fig. 10).

Data on the severity of the condition of patients before BiVAD-therapy, on BiVAD-therapy and after OHT according to circulatory failure, presented in Fig. 11.

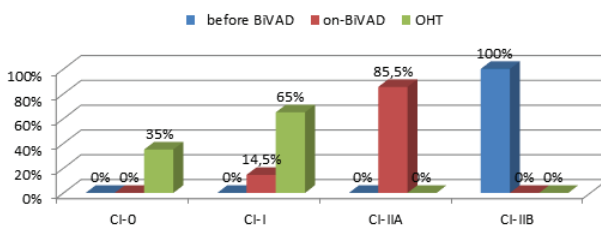


Fig. 11. Data on the severity of the condition of patients before BiVAD-therapy, on BiVAD-therapy and after OHT according to circulatory failure

Assessment of the severity of the patients' condition according to the circulatory failure before BiVAD - therapy: CI IIB in 100% of patients, on BiVAD - CI I in 14.5% of patients, CI IIA in 85.5% of patients, after OHT: CI 0 in 35% of patients, CI I in 65% of patients. Implantation of the BiVAD system for patients with severe dilatation and critical decrease in systolic function of both right and left compartments of the heart allows not only to survive to heart transplantation, but also to improve hemodynamic parameters, achieve regression of heart failure, restore functional disorders of organs and systems, and as a consequence, reduce the risk of complications after transplantation (Fig. 11).

Thus, out of the 8 patients who were on BiVAD therapy as a bridge to the OHT, after 3 months there was a decrease in the cavity of the RV EDV by 6%, with (p<0001), a decrease in RV ESV by 10%, while (p<0001), an increase in LV EF by 33%, with (p<0001), a decrease in LV ESV (M-mode) by 36.3%, with (p<0001), a decrease in LV EDV (M-mode) by 30%, with (p<0001), a decrease in LV ESV (B-mode) by 22.5%, with (p<0001), an increase in tricuspid systolic excursion "TAPSE" by 21.4%, with (p<0001). According to the direct tonometers of the pulmonary artery when using BiVAD-therapy: a reasonable solution of pulmonary vascular resistance of Wood by 22%, while (p<0001), the PAP decrease by 15%, while (p<0001), the

TPG decrease by 14%, while (p<0001), patients are prepared for the second stage of surgical treatment of secondary heart transplantation.

The results of the dynamics of changes in functional parameters in patients on BiVAD-therapy after 3 months: an increase in maximum myocardial oxygen consumption by 46%, as well as an increase in exercise tolerance by 5%. Assessment of functional class of heart failure according to NYHA before BiVAD-therapy - NYHA III FC according to NYHA - 75% of patients, IV FC according to NYHA - 25% of patients, on BiVAD therapy I FC according to NYHA - 10% of patients, II FC according to NYHA 70% of patients, III FC according to NYHA - 30%. Estimation of the severity of the condition of patients with circulatory insufficiency before BiVAD - therapy of CI IIB in 100% of patients, and on BiVAD - CI I in 14.5% of patients, CI IIA in 85.7% of patients. In the group of 3 patients with CHI on BiVAD therapy as a mechanical bridge to the UTS, patients who underwent secondary - OHT - 4 patients, which is 50%.

Patients who died on BiVAD - 4 patients, which is 50%. The cause of death in 2 cases - purulent-septic lesions, which is 50%. Ascending cable infection. And 2 more cases - multiorgan insufficiency that makes 50%. Assessment of functional class of heart failure according to NYHA before BiVAD-therapy - NYHA III FC according to NYHA - 75% of patients, IV FC according to NYHA - 25% of patients, on BiVAD therapy I FC according to NYHA - 10% of patients, II FC according to NYHA - 70% of patients, III FC according to NYHA - 30%, after OHT: I FC according to NYHA - 70% of patients, II FC according to NYHA - 30% of diseases. Estimation of the severity of the condition of patients with circulatory insufficiency before BiVAD - therapy of CI IIB in 100% of patients, and on BiVAD - CI I in 14.5% of patients, CI IIA in 85.7% of patients, after OHT CI 0 in 35% of patients, CI I in 65% of patients.

**Conclusions.** 1. Indications for direct heart transplantation are the following criteria: left ventricular ejection fraction (LVEF) is <20%, (p<0001); pulmonary artery occlusion pressure (PAWP) is from 25 mm Hg up to 35 mm Hg (p<0001); peak myocardial oxygen consumption is <14 ml/kg/min at the background of maximum drug therapy (p<0001); pulmonary vascular resistance (PVR) is <5 in Wood units (p<0001); transpulmonary gradient (TPG) is up to 15 mm Hg (p<0001).

2. Indications for LVAD-therapy are the following criteria: left ventricular ejection fraction (LVEF) is <20%, (p<0001); pulmonary artery occlusion pressure (PAWP) is >35 mm Hg (p<0001); pulmonary vascular resistance (PVR) is >5 in Wood units (p<0001); transpulmonary gradient (TPG) is >15 mm Hg (p<0001). The three-months connection of LVAD resulted in a decrease in the left ventricular atrium by 30% (p<0001); a decrease in the LV atrium is by 25.5%, (p<0001); an increase in the LV ejection fraction is by 21%, (p<0001). According to the direct tonometry of the pulmonary artery when using LVAD therapy, there was a decrease of the Wood index of pulmonary vascular resistance by 34%, (p<0001); a decrease in PAP was by 24%, (p<0001); a decrease in TPG was by 21%, (p<0001). The results for the changes in functional parameters in patients on LVAD therapy after 3 months are the next: the maximum oxygen consumption by the myocardium increased by 6% (p<0001) and exercise tolerance increased by 15% (p<0001).

3. Indications for BiVAD-therapy are the following criteria: biventricular insufficiency, (p<0001); pulmonary artery occlusion pressure (PAWP) is >35 mm Hg (p<0001); pulmonary vascular resistance (PVR) is >5 in Wood units (p<0001); transpulmonary gradient (TPG) is > 15 mm Hg (p<0001).

After three-months BiVAD connection there was a decrease in the atrium of the RV EDV by 6% ( $p<0001$ ), a decrease in RV ESV was by 10% ( $p<0001$ ), an increase in LVEF was by 33%, ( $p<0001$ ), a decrease in LV ESV (M-mode) was by 36.3%, ( $p<0001$ ), decrease in LV EDV (M-mode) was by 30%, ( $p<0001$ ), decrease in LV ESV (B-mode) was by 22.5%, ( $p<0001$ ), increase in tricuspid systolic excursion (TAPSE) was by 21.4%, ( $p<0001$ ). According to the direct tonometry of the pulmonary artery when using BiVAD-therapy the data were the following: reduction of the Wood index of pulmonary vascular resistance was by 22%, ( $p<0001$ ) in Wood units, reduction of DLA by 15%, ( $p<0001$ ), reduction of LNG by 14%, ( $p<0001$ ).

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## SUMMARY

### SURGICAL METHODS OF TREATMENT OF END-STAGE HEART FAILURE

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The aim of the study is to establish the effectiveness of mechanical support of blood circulation of patients with end-stage heart failure depending on the method of surgical correction.

The results of the study are based on the data of examination and dynamic observation of 73 patients (median age 44 (16–69) years, men 68 patients, women 5 patients) who were treated from 2008–2019 in the following medical institutions: Republican Scientific and Practical Center «Cardiology», Minsk, Republic of Belarus; in the Center of Cardiac Surgery on the Basis of KL «Feofania» DUS. Patients were examined during the initial examination, after 3 months and after a year.

The results of surgical treatment of patients with critical heart disease insufficiency: after direct UTS: 24 (92%) patients were treated with positive result, 2 (8%) patients died. There were 18 (46%) patients performed secondary UTS, patients who were on LVAD therapy. 18 (46%) patients who continue LVAD therapy. On LVAD-therapy 3 (8%) patients died. The cause of death is purulent-septic lesions. Which patients were on BiVAD - therapy: secondary UTS performed 4 patients (50%). 4 (50%) patients died on BIVAD therapy. The cause of death in 2 (50%) cases of purulent-septic lesions, and in 2 (50%) cases it is an organ field insufficiency. Analysis of the results of the differential approach to surgical treatment patients with heart failure III-IV FC according to NYHA: patients with critical heart failure in the presence of contraindications to direct transplantation heart rate, it is advisable to consider the use of long-term mechanical circulatory support based on LVAD therapy ( $p<0001$ ) and BiVAD - therapy ( $p<0001$ ) as a mechanical bridge to heart transplantation. Applied long-term mechanical support of blood circulation in patients with high indicators of pulmonary hypertension ( $p<0001$ ), allows to normalize the pressure in the pulmonary artery and consider performing a secondary heart transplant.

**Keywords:** chronic heart failure, LVAD-therapy, BiVAD - therapy, orthotopic heart transplantation.

## РЕЗЮМЕ

### ХИРУРГИЧЕСКИЕ МЕТОДЫ В ЛЕЧЕНИИ ТЕРМИНАЛЬНОЙ СТАДИИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

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Цель исследования - оценка эффективности механической поддержки кровообращения у пациентов с терминальной сердечной недостаточностью в зависимости от метода хирургической коррекции.

Результаты исследования основаны на данных обследования и динамического наблюдения за 73 пациентами (средний возраст 44 года), из них 68 мужчин, 5 женщин), которые лечились с 2008-2019 гг. в Республиканском научно-практическом центре «Кардиология», Минск и в Клинической больнице “Феофания” Государственного управления внутренними делами, Киев. Пациенты обследованы при первичном осмотре и спустя 3 месяца и 1 год.

Показаниями к хирургическому лечению пациентов с терминальной сердечной недостаточностью являются: фракция выброса левого желудочка (ФВ ЛЖ) <20%, (p<0001); давление легочной артерии (ДЛА) от 25 до 35 мм.рт.ст (p<0001); пиковое потребление кислорода миокардом <14 мл/кг/мин на фоне максимальной медикаментозной терапии (p<0001); легочно-сосудистое сопротивление (ЛСС) <5 единиц по Вуду (p<0001); транспульмональный градиент (ТПГ) до 15 мм.рт.ст. (P<0001). Показаниями к терапии LVAD являются: ФВ ЛЖ <20% (p<0001); ДЛА >35 ммрт.ст. (p<0001); ЛСС >5 единиц по Вуду (p<0001); ТПГ > 15 мм рт. Ст. (P<0001). На фоне терапии LVAD спустя 3 месяца произошло уменьшение полости левого желудочка на 30%, (p<0001), полости поджелудочной железы - на 25,5%, (p<0001), увеличение фракции ЛЖ - на 21% (p<0001). По данным прямой тонометрии легочной артерии с терапией LVAD отмечалось снижение ЛСС по Вуду на 34%, (p<0001), ДЛА - на 24%, (p<0001), ТПГ - на 21% (p<0001). Показаниями к применению BiVAD-терапии являются: бивентрикулярная недостаточность (p<0001); ДЛА >35 мм.рт.ст., (p<0001); ЛСС >5 единиц по Вуду (p<0001); ТПГ >15 мм рт. ст. (p<0001).

Анализ результатов дифференциального подхода к хирургическому лечению пациентов с сердечной недостаточностью III-IV ФК по NYHA выявил, что пациентам с критической сердечной недостаточностью при наличии противопоказаний к прямой трансплантации целесообразно рассматривать возможность применения длительного лечения, механической поддержки кровообращения на основе LVAD-терапии (p<0001) и BiVAD-терапии (p<0001) в качестве механического моста к трансплантации сердца. Применяется длительная механическая поддержка кровообращения у пациентов с высокими показа-

телями легочной гипертензии (p<0001), что позволяет в короткие сроки (недели) нормализовать давление в легочной артерии, обеспечивая возможность проведения вторичной трансплантации сердца.

## რეზიუმე

ქირურგიული მეთოდები გულის უკმარისობის ტერმინალური სტადიის მკურნალობაში

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კლინიკური საავადმყოფო “ფეოფანია”, კიევი, უკრაინა; რესპუბლიკური სამეცნიერო-პრაქტიკული ცენტრი “კარდიოლოგია” მინსკი, რესპუბლიკა ბელარუსი

კვლევის მიზანს წარმოადგენდა სისხლის მიმოქცევის მექანიკური მხარდაჭერის ეფექტურობის შეფასება პაციენტებში გულის ტერმინალური უკმარისობით ქირურგიული კორექციის მეთოდზე დამოკიდებულებით.

კვლევის შედეგები ეფუძნება 73 პაციენტის (საშუალო ასაკი - 44 წ., 68 - მამაკაცი, 5 - ქალი) გამოკვლევის და დინამიკური დაკვირვების შედეგებს, რომლებიც მკურნალობდნენ რესპუბლიკურ სამეცნიერო-პრაქტიკულ ცენტრში “კარდიოლოგია” (მინსკი) და კლინიკურ საავადმყოფოში “ფეოფანია” (კიევი). პაციენტები გამოკვლეულია პირველადი გასინჯვის ეტაპზე, 3 თვის და 1 წლის შემდეგ.

ჩვენებას ქირურგიული ჩარევისათვის პაციენტებში გულის ტერმინალური უკმარისობით წარმოადგენს: მარცხენა პარკუჭის განდევნის ფრაქცია - < 20% (p<0001), წნევა ფილტვის არტერიაში - 25-35 მმ ვწყ. სვ. (p<0001), მთკარდიუმის მიერ ჟანგბადის პიკური მოხმარება - < 14 მლ/კგ/წთ მაქსიმალური მედიკამენტოზური თერაპიის ფონზე (p<0001), ფილტვ-სისხლძარღვოვანი წინაღობა - < 5 ერთეულზე გულის მიხედვით (p<0001), ტრანსპულმონური გრადიენტი - 15 მმ ვწყ. სვ.-მდე (p<0001). ჩვენებას LVAD თერაპიისათვის წარმოადგენს: მარცხენა პარკუჭის განდევნის ფრაქცია - <20% (p<0001), წნევა ფილტვის არტერიაში - >35 მმ ვწყ. სვ. (p<0001), ფილტვ-სისხლძარღვოვანი წინაღობა - > 5 ერთეულზე გულის მიხედვით (p<0001), ტრანსპულმონური გრადიენტი - > 15 მმ ვწყ. სვ.-მდე (p<0001).

გულის უკმარისობის III-IV ფუნქციური კლასის (NYHA) მქონე პაციენტების ქირურგიული მკურნალობისადმი დიფერენციული მიდგომის შედეგების ანალიზით გამოვლინდა, რომ პაციენტებში გულის კრიტიკული უკმარისობით პირდაპირი ტრანსპლანტაციის უკუჩვენებების არსებობისას მიზანშეწონილია განხილულ იქნას ხანგრძლივი მკურნალობის გამოყენების შესაძლებლობა, სისხლის მიმოქცევის მექანიკური მხარდაჭერა LVAD-თერაპიის (p<0001) და BiVAD-თერაპიის (p<0001) საფუძველზე მექანიკური ხიდის სახით გულის ტრანსპლანტაციისაკენ. სისხლის მიმოქცევის ხანგრძლივი მექანიკური მხარდაჭერა გამოიყენება პაციენტებში ფილტვის ჰიპერტენზიის მაღალი მაჩვენებლებით (p<0001), რაც იძლევა ფილტვის არტერიაში წნევის მოკლე ვადაში (კვირის განმავლობაში) ნორმალისების საშუალებას და ამით უზრუნველყოფს გულის მეორადი ტრანსპლანტაციის განხორციელების შესაძლებლობას.

## ENHANCED RECOVERY AFTER SURGERY VS TRADITIONAL CARE IN ELECTIVE COLORECTAL SURGERY: A RETROSPECTIVE COHORT STUDY

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Colorectal surgeries were associated with an in-hospital stay days from 6 to 11 days and a complication rate of 15% to 20%. For decreasing these numbers Enhanced recovery after surgery (ERAS) protocols were created [1-3].

ERAS protocols are multimodal preoperative, intraoperative and postoperative care pathways designed to achieve early recovery after surgical procedures by maintaining preoperative organ function and reducing the profound stress response following surgery. The key elements of ERAS protocols include preoperative counselling, patient optimization prior to admission, minimal fasting, which includes carbohydrate drinks and clear liquids until two hours before anesthesia; goal directed fluid therapy, standardized multimodal analgesia with minimal use of opioids, and anesthetic regimens and early mobilization, increased patients' satisfaction, outcomes, reduced hospital stay and reduction in cost of care (Table 1).

Traditional preoperative care includes: prolonged fasting, mobility limitations, mechanical bowel preparation, routine use of drains, and slow return to eating normally postoperatively [4,5].

Implementing ERAS successfully depends on many different factors, beginning from patient and staff education, specially trained team including surgeons, anesthesiologists and nurses, till to interdisciplinary team relationships. Also, ERAS's challenge to traditional surgical doctrine has led to slow implementation. Every member of the team must overcome the resistance to change and embrace ERAS protocol. Resistance to change, however, is just one of the many barriers [6,7]. Because of these difficulties

these protocols are implemented in very few centers worldwide, but adoption of ERAS is increasing. After special trainings of this multidisciplinary team, we also started this somehow difficult implementation process, comparing data to the data collected retrospectively.

The purpose and the goal of this study was to observe and define if it really reduced hospital stay days and other complications rates in case of open colorectal surgery, compared to traditional care methods.

**Material and methods.** In October 2016 we started to implement ERAS protocol for elective colorectal open surgery in our clinic. Exclusion criteria were patients younger than 23 years and an ASA grade 4-5. Based on ERAS society criteria, this protocol was developed by both doctors and nurses of General surgery and Anesthesiology departments. Our ERAS protocol for elective open colorectal surgery included: antimicrobial prophylaxis, multimodal analgesia, postoperative nausea and vomiting (PONV) prophylaxis, early oral intake, less infusion volume, antithrombotic prophylaxis, early removal of drainages and urinary catheters, early mobilization, discharge criteria and follow-up plan. We also collected data from last 2 years elective colorectal surgery cases-120 patients in traditional care group, as a control group. We observed patients' preoperative, intraoperative surgical and anesthesia data, postoperative analgesia, all type of complications. The medical records of these patients, who underwent elective open colorectal surgeries according to traditional care principals were retrospectively reviewed. For

Table 1. A Sample Enhanced Recovery After Surgery (ERAS) Protocol [20]

Period	ERAS	Traditional Care
Pre-operative	<ul style="list-style-type: none"> <li>• Provide complete information about the protocol and take an informed consent</li> <li>• Advice given regarding exercise, smoking and alcohol cessation</li> <li>• Optimise any pre-existing co-morbidity</li> <li>• Minimal starvation (6 hrs for solids and 2 hrs for liquids)                             <ul style="list-style-type: none"> <li>• 100g oral carbohydrate drink</li> </ul> </li> <li>• Avoid mechanical bowel preparation</li> <li>• Pre-operative antibiotic</li> </ul>	<ul style="list-style-type: none"> <li>• Overnight starvation</li> <li>• No carbohydrate drinks</li> <li>• Mechanical bowel preparation</li> <li>• Parenteral hydration (to compensate for bowel preparation)</li> </ul>
Intra-operative	<ul style="list-style-type: none"> <li>• Epidural anesthesia (0.125% bupivacaine, continuous infusion) along with spinal or general anesthesia</li> <li>• Arterial/Central lines inserted only if unavoidable                             <ul style="list-style-type: none"> <li>• Goal directed fluid therapy</li> </ul> </li> <li>• Maintain optimal oxygenation                             <ul style="list-style-type: none"> <li>• Avoid hypothermia</li> </ul> </li> <li>• Minimal tissue handling</li> <li>• Elective use of nasogastric tubes, abdominal drains and urinary catheters</li> </ul>	<ul style="list-style-type: none"> <li>• Done under spinal or general anesthesia</li> <li>• Routine use of Nasogastric tubes, abdominal drain and urinary catheter</li> <li>• Liberal hydration</li> </ul>
Post-operative	<ul style="list-style-type: none"> <li>• Maintain supplemental oxygen</li> <li>• Strict post-operative nausea and vomiting prophylaxis                             <ul style="list-style-type: none"> <li>• Early enforced mobilization</li> <li>• Early enteral nutrition</li> </ul> </li> <li>• Removal of epidural catheter by day 2</li> <li>• Ensuring adequate analgesia after epidural catheter removal                             <ul style="list-style-type: none"> <li>• Early removal of all tubes, drains and catheters</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• No emphasis on PONV prophylaxis                             <ul style="list-style-type: none"> <li>• No enforced mobilization</li> </ul> </li> <li>• Removal of nasogastric tube and abdominal drain delayed till markers of bowel motility are observed</li> <li>• Oral or Enteral nutrition given once bowel motility is restored</li> </ul>

objective comparative Analysis, we studied prognostic criteria between the traditional care group and ERAS group, to be clear that age, sex, obesity, alcohol intake, smoking status, surgical duration, intraoperative blood loss, or other comorbidities. Our observation lasted till to October 2018. Eighty-seven adult patients from ERAS-group were electively operated on because of colorectal different pathologies. All relevant characteristics of all patients from each group, preoperative, intraoperative and postoperative data were collected, summarized and compared to each other.

The study was reviewed and approved by the institutional review board of Tbilisi State Medical University (Tbilisi, Georgia) and High Technology Medical Centre, University Clinic (Tbilisi, Georgia) ethics committee.

Descriptive statistics methods were used to characterize each variable. Comparison of continuous variables was performed by independent samples t-test or the Mann-Whitney U test according to the normality of the variables. Categorical variables were evaluated by two-tailed Chi-square test or Fisher's exact test where appropriate. The threshold for statistical significance was set to  $P < 0.05$ . Statistical tests were performed by IBM SPSS statistics package v23.0 (IBM Corporation, Armonk, New York).

**Results and discussion.** Eighty-seven patients (54 males, 33 females, age range 23-75), treated according to ERAS program, were matched with 120 (80 male, 30 female, age range 23-75) retrospective controls, who had traditional perioperative care.

The clinical characteristics of the ERAS and traditional care groups were not statistically different (Table 2).

For those moment, in our center colorectal surgery was often associated with long length of stay (8-10 days for open surgery), high rates of surgical site infection approaching 24.2% and according to these - high costs as well. During the hospital stay for elective colorectal surgery, the incidence of perioperative nausea and vomiting (PONV) was 44.2%. Because of high demand on opioids, respiratory complications also had high incidence 6.7%. Deep vein thrombosis also was reported in 3,3% of patients, associated with late activation. In the patients' group where no complications were presented, patients' hospital stay was still increasing because of prolonged postoperative ileus 16.7%.

The results of this study suggest that Enhanced Recovery after Surgery program is superior to conventional postoperative care for patients undergoing elective colonic or rectal resection surgery. Patients treated according to an ERAS program developed significantly less complications and had shorter hospital stay days.

In ERAS care group, where the data were collected prospectively, our study showed big reduction of hospital stay days and it was average 5 days. Since patients were operated by the same team of surgeons, selection bias seems to be small. Compared to traditional care group incidence of respiratory complications was 0 in ERAS care group, preoperative PONV was significantly reduced and it was 6.9%, postoperative ileus 5.7%, deep vein thrombosis 0, urinary retention 0, surgical site infection 3.4% (Table 3).

The key principals of ERAS care group in preoperative level was preventing long fasting time, recommending carbohydrate

Table 2. The clinical characteristics of the ERAS and traditional care groups

Characteristic	ERAS Group (n=87)	Control Group (n=120)	P Value
Average age	49	49	1.0
Gender:			
Male	54	80	0,13
Female	33	40	
ASA Score:			
ASA I	3	2	0,65
ASA II	82	115	0,75
ASA III	2	3	1.0
Comorbidity:			
Diabetes Mellitus	16	12	0,10
Cardiovascular disease	27	38	1.0
BMI (mean)	25,13+/- 3,34	24,55+/-3,29	0,24
Smoke	35	44	0,66
Alcohol	17	39	0,40
Average operation time, min	125±10	130±33	0,17
Mean intraoperative bleeding, ml	115±8	104±60	0,09

ASA-American Society of Anesthesiologists; BMI-Body mass index

Table 3. Traditional vs ERAS care complications

Event	Traditional care (n=120)	ERAS care (n=87)	P value
Respiratory complications	8(6.7%)	0%	0.02
PONV	53(44.2%)	6 (6,9%)	0,0001
Postoperative ileus	20(16.7%)	5 (5.7%)	0.02
Deep vein thrombosis	4(3.3%)	0	0.14
Urinary retention	3(2.5%)	0	0.27
30-day readmission	37(30.8%)	0	0.0001
Surgical site infection	29(24.2%)	3 (3,4%)	0.0001
Length of stay (days)	8±2 days	5±2 days	0.0001

rich drinks 200ml 3 hours earlier before surgery, avoiding routine bowel preparation. Intraoperative 2 main anesthetic factors were fluid management optimization through goal directed fluid therapy and second-opioids minimization through epidural catheters. Otherwise postoperative ileus could be prolonged. Avoidance of routine use of drainages, nasogastric tubes, urinary catheters and early activation.

About reduced fasting duration, according to protocols we allowed the patients to eat solid foods until 12 midnight and clear liquids until 3 hours before surgery. Patients were recommended to drink carbohydrates rich drinks 200-300ml before surgery.

Mechanical bowel preparation (MBP) has adverse physiologic effects attributed to dehydration, is distressing for the patient, and is associated with prolonged ileus after colonic surgery [8]. MBP is not recommended for patients having colorectal procedures including open or laparoscopic total or segmental colonic resections, Hartmann procedure, abdominoperineal resection (APR), total proctocolectomy (TPC), ileal pouch anal anastomosis (IPAA). The only exception is patients having anterior resection with an anastomosis at or below the sacral promontory [9]. Antibiotic prophylaxis for patients undergoing colorectal surgery is imperative to reduce the risk of surgical-site infections. For intravenous antibiotics, it is accepted that the best time for administration is 30–60 min before the incision is made [10]. Also different types of skin cleaning showed that the overall prevalence of surgical-site infection was 40 % lower in a concentration Chlorhexidine alcohol group than in a povidone-iodine group [11].

According to patient experiences, postoperative nausea and vomiting (PONV) is more stressful than pain. The risk factors for these symptoms include female gender, non-smokers, history of motion sickness, and postoperative use of opioids [6]. A multimodal approach to PONV prophylaxis should be considered in all patients with at least 2 or more risk factors undergoing major colorectal surgery. If PONV is present, treatment should be given using a multimodal approach. This combines non-pharmacological and pharmacological antiemetic techniques in addition to ERAS programmes [12,13]. Non-pharmacological techniques include the avoidance of emetogenic stimuli such as inhalation anaesthetics, and the increased use of Propofol for the induction and maintenance of anaesthesia [14]. Regional anaesthetic techniques such as epidurals and transversus abdominal plane (TAP) blocks, have been proven to reduce postoperative opiate use, which may in turn influence the prevalence of PONV. The use of non-steroidal anti-inflammatory drugs (NSAIDS) as an alternative to opiate analgesia is well established. From pharmacological agents Ondansetron 4 mg ± Dexamethasone 4mg [10].

Fluid management in ERAS should be viewed as a continuum through the preoperative, Intraoperative and postoperative phases. Maintenance infusion of 1.5 - 2 mL/kg/h of balanced crystalloid solution is sufficient to cover the needs derived from salt–water homeostasis during major abdominal surgery [15-17]. In high-risk patients and in patients undergoing major colorectal surgery associated with significant intravascular losses, the use of goal directed fluid therapy is recommended [18,19].

About surgical issues, of course minimally invasive surgical approach should be used whenever the expertise is available and appropriate. The routine use of intra-abdominal drains and nasogastric tubes for colorectal surgery should be avoided.

From postoperative interventions, early and progressive patient mobilization is associated with shorter length of stay. Intravenous fluids should be discontinued in the early postoperative

period after recovery room discharge. For ileus prevention patients should be offered a regular diet immediately after elective colorectal surgery. Chewing sugar-free gum for ≥10 minutes 3 to 4 times per day after colorectal surgery could be safe, results in small improvements in GI recovery, and may be associated with a reduction in the length of hospital stay. Urinary catheter should be removed within maximum 48 hours.

**Conclusion.** This study demonstrates that ERAS program as a whole is clearly beneficial and is not followed with any unexpected negative effects. Epidural analgesia and a restricted fluid administration are thought to be the main contributing factors to a desirable outcome.

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## SUMMARY

### ENHANCED RECOVERY AFTER SURGERY VS TRADITIONAL CARE IN ELECTIVE COLORECTAL SURGERY: A RETROSPECTIVE COHORT STUDY

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The objective and the goal of this study was to determine how ERAS guidelines affected on hospital stay days and other complications rates in case of elective colorectal surgery in our clinic, compared to traditional care methods.

First of all, all team members including surgeons, anesthetists, nurses were being trained in ERAS guidelines principals during two months and we started active implementation process after this. 87 patients, who were needed to be done colorectal surgery treatment, were actively treated according to ERAS guidelines and these patients were gathered in experimental group. At the same time, we started to collect data retrospectively from last 2 years elective colorectal surgery cases and sorted them according to preoperative, intraoperative surgical and anesthesia data, postoperative analgesia, all type of complications. 120 patients were placed in traditional care group (control group).

In traditional care group open colorectal surgery was associated with long length of stay 8-10 days. High rates of surgical site infection-24.2%, readmission rate during 30 days-30.8%, PONV-44.2%, respiratory complication-6.7%, deep vein thrombosis-3.3%, urinary retention-2.5%, prolonged postoperative ileus 16.7%.

We included 87 patients in ERAS care group during 2 years. In this group our study showed big reduction of hospital stay days and it was average 5 days. Compared to traditional care group incidence of respiratory complications was 0, postoperative PONV- 6.9%, postoperative ileus-5.7%, deep vein throm-

bosis-0, urinary retention-0, readmission rate-0, surgical site infection-3.4%.

**Keywords:** ERAS guidelines, colorectal surgery, length of hospital stay.

## РЕЗЮМЕ

### УСКОРЕННОЕ ВОССТАНОВЛЕНИЕ ПОСЛЕ ХИРУРГИЧЕСКОГО ВМЕШАТЕЛЬСТВА ПРОТИВ ТРАДИЦИОННОГО ЛЕЧЕНИЯ В КОЛОРЕКТАЛЬНОЙ ХИРУРГИИ: РЕТРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ КОГОРТНОЙ ГРУППЫ

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Целью исследования явилась оценка влияния руководящих принципов Enhanced Recovery After Surgery (ERAS), ускоренная реабилитация после операции) на количество послеоперационных дней в стационаре (срок госпитализации) при проведении колоректальных операций традиционным полостным методом.

Весь медперсонал, включая хирургов, анестезиологов и медсестер, в течение 2 месяцев проходили обучение (тренинги) по ознакомлению с принципами ERAS для их внедрения в повседневную практику. 87 пациентов, которые нуждались в колоректальном хирургическом лечении, полностью проведены согласно протоколам ERAS гайдлайнов. Эти пациенты составили экспериментальную группу.

Ретроспективно собраны материалы по плановым колоректальным операциям за последние 2 года и разделены с учетом предоперационных, интраоперационных, хирургических и анестезиологических данных, послеоперационной анальгезии и других осложнений. В группу традиционной терапии включены данные 120 пациентов (контрольная группа).

В группе традиционного лечения плановая колоректальная операция часто ассоциировалась с предусмотренным длительным сроком госпитализации в течение 8-10 дней. Выявлен высокий уровень инфекции, который составил 24.2%, повторная госпитализация в течении 30 дней - 30.8%, PONV - 44.2%, респираторные осложнения - 6.7%, тромбоз глубоких вен составил 3.3%, длительная послеоперационная кишечная непроходимость - 16.7%.

В течение двух лет в группу ERAS включены 87 пациентов. Проведенное исследование показало значительное сокращение времени пребывания этих больных в стационаре на 5 дней в сравнении с группой с традиционным ведением.

Общее число послеоперационных осложнений было достоверно ниже в группе с ускоренным восстановлением в сравнении с контрольной группой: послеоперационных PONV - 6.7%, длительная послеоперационная кишечная непроходимость - 5.7%, инфекция хирургического разреза составила 3.4%, респираторные осложнения, тромбоз глубоких вен, задержка мочеиспускания и повторная госпитализация в течение 30 дней не выявлены.



## რეზიუმე

დაჩქარებული გამოჯანმრთელება ქირურგიული ჩარევის შემდეგ ტრადიციული მკურნალობის წინააღმდეგ გეგმიურ კოლორექტულ ქირურგიაში: რესტროსპექტული კოჰორტული კვლევა

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; მაღალი სამედიცინო ტექნოლოგიების ცენტრი, საუნივერსიტეტო კლინიკა, საქართველო

კვლევის მიზანს წარმოადგენდა ERAS გაიდლაინების გავლენის განსაზღვრა კოლორექტული ქირურგიის დროს საწოდლეების რაოდენობასა და სხვა გართულებების რიცხვზე ტრადიციული მკურნალობის მეთოდებთან შედარებით.

ჩატარდა აღნიშნული გაიდლაინების აქტიური იმპლემენტაცია ყოველდღიურ პრაქტიკაში. 87 პაციენტი, რომლებსაც კოლორექტული ქირურგიული მკურნალობა ჩატარდა ERAS გაიდლაინების პრინციპების მიხედვით, გაერთიანდა საკვლევ ჯგუფში. ამავდროულად, რეტროსპექტულად შეგროვდა ბოლო 2

წლის მანძილზე ჩატარებული 120 პაციენტის გეგმიური კოლორექტული ქირურგიის შემთხვევების მასალები, დახარისხდა პრეოპერაციული, ინტრაოპერაციული ქირურგიული და ანესთეზიო-ლოგიური მონაცემების, პოსტოპერაციული ანალგეზიისა და ნებისმიერი სახის გართულებების გათვალისწინებით და გაერთიანდა ტრადიციული მკურნალობის ჯგუფში (საკონტროლო ჯგუფი).

ტრადიციული მკურნალობის ჯგუფში გეგმიური კოლორექტული ქირურგია ხშირად ასოცირდებოდა გახანგრძლივებულ საწოდლეებთან - 8-10 დღე, ასევე, დაფიქსირდა ინფექციების მაღალი რიცხვი - 24.2%, 30 დღის განმავლობაში რეჰოსპიტალიზაციების რიცხვმა შეადგინა 30.8%, PONV - 44.2%, რესპირატორული გართულებები - 6.7%, ღრმა ვენების თრომბოზი - 3.3%, გახანგრძლივებული პოსტოპერაციული ილეუსი - 16.7%.

ჩათარებულმა კვლევამ აჩვენა, რომ ERAS-ის ჯგუფში ტრადიციული მკურნალობის ჯგუფთან შედარებით საწოდლეების რიცხვი იყო შემცირებული, საშუალოდ, 5 დღემდე, პოსტოპერაციული PONV შეადგინა 6.9%, პოსტოპერაციული ილეუსი - 5.7%, ქირურგიული მიდამოს ჭრილობის ინფექცია - 3.4%, ღრმა ვენების თრომბოზი, შარდის შეკავება, 30 დღის განმავლობაში რეჰოსპიტალიზაციები და რესპირატორული გართულებები არ გამოვლინდა.

## NECROTIC FASCIITIS AS A COMPLICATION OF ACUTE DESTRUCTIVE APPENDICITIS

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Acute appendicitis is the second most frequent cause (after acute cholecystitis) of hospitalization in a surgical hospital for urgent indications of 10-30% and the first in the number of emergency operations performed is 60-80% [8]. The social significance of the problem of acute appendicitis is due to its high prevalence. Acute appendicitis is the cause of acute abdomen in 7-8% of cases worldwide [2,13]. The timely diagnosis of acute appendicitis is difficult due to the variability of the clinical picture and depends on the degree of inflammatory changes in the appendix wall, localization, age, reactivity, and the presence or absence of complications of concomitant diseases.

Necrotic fasciitis (NF) is an extremely rare fatal complication of acute appendicitis [7,12]. It is characterized by a rapidly fatal necrotic infection, which progresses rapidly in fascia and soft tissues and, with untimely medical care, leads to the development of septic shock and multiple organ failure. Early diagnosis of this fatal complication is critical to achieving optimal treatment outcomes.

Necrotic fasciitis, the most commonly used term to describe necrotic soft tissue infection (NSTIs), but it is only one of its manifestations. The term necrotic fasciitis was first coined by Wilson [24].

Necrotic fasciitis is a secondary complicated infection of the skin and soft tissues of 3rd-4th level according to the classification of surgical infections of the skin and soft tissues as per Russian national guidelines 2015 [15].

We present here a clinical case of necrotic fasciitis of the right lower limb, without damage to the anterior abdominal wall, secondary to the perforated process, as an extremely rare complication of appendicitis.

**Case report.** In January 2019 a 78-year-old patient with a 2-day history of general weakness, pain in the right lumbar region and in the right leg with impaired sensitivity was delivered to the admission department of the Clinical Hospital named after S.S. Yudina by the ambulance team.

Upon admission, the general condition of the patient was severe. Blood pressure 80/40mm Hg, pulse 95 beats per minute, respiratory rate 17 min, body temperature 36.9 ° C, lack of urine, 200 ml of urine was obtained during catheterization of the bladder. On physical examination: the tongue is dry, not taxed. The abdomen is symmetrical, moderately swollen, locally tense and painful in the right iliac region, where positive symptoms of peritoneal irritation are determined, the right leg is swollen, subcutaneous fatty tissue is infiltrated, and soreness along the large saphenous vein is noted. Subcutaneous emphysema in the lower abdomen and right lower limb was not determined. Laboratory data showed white blood cells  $9.6 \times 10^9/l$ , myelocytes 1%, metamyelocytes 2%, hemoglobin 12.1 g/dl, creatinine  $137 \mu\text{mol/l}$  (1.55 mg/dl), C reactive protein 388.2 mg/l, sodium 121.1 mmol/l, glucose 5.0 mmol/l (90.75 mg/dl).

Ultrasound of the abdominal cavity and pelvis revealed calculi in the gall bladder up to 5 mm without signs of acute inflammation, there was no free fluid in the abdominal cavity, an intestinal loop was expanded to 40 mm, pendulum-like peristalsis was determined in the right half of the abdominal cavity.

During computed tomography of the abdominal cavity with bolus contrast, the appendicular infiltrate was measured 25x31x35 mm, with the location of the appendix retrocecal up to 12 mm wide, with fuzzy contours. Infiltration of the right lumbar muscle with hypo-intensive areas and the right piriformis muscle was noted. Cholecystolithiasis. CT scan of the right lower limb was not performed.

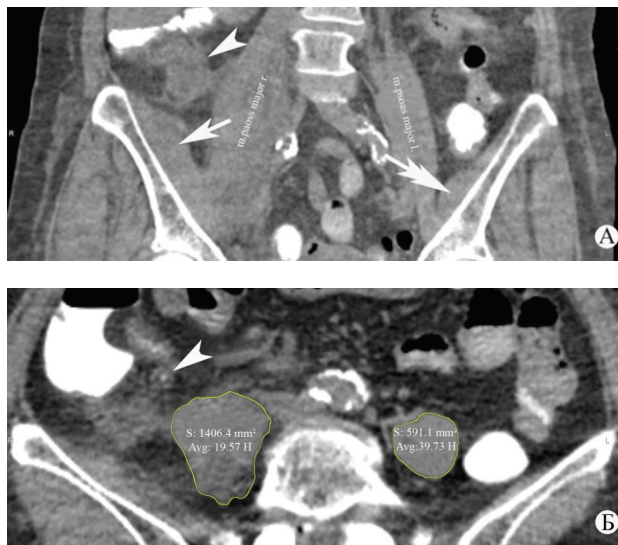


Fig. 1. CT scan of the abdomen and pelvis

The head of the white arrow indicates the area of fiber compaction around the appendix and is regarded as a periappendicular infiltrate. It is noteworthy that there is a close relationship between this appendicular infiltrate and the fascia of the right lumbar muscle, which is increased in volume compared to the contralateral one. The presence of the fluid component both in the subfascial space and between fibers of the abdomen of the muscle are noted (X-ray density of the right lumbar muscle is 19 units .N, left-39 units.N). (A). Also noteworthy is the increase in the volume of the right ileal muscle (white arrow) compared with the left ileal muscle (double-headed arrow).

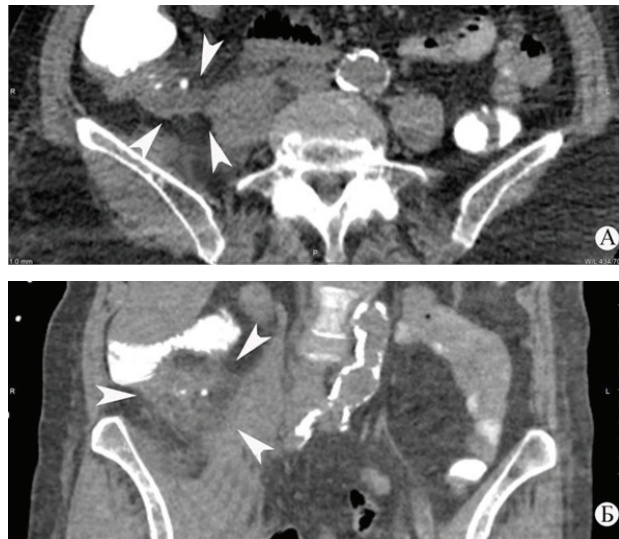


Fig. 2. CT scan of the abdomen and pelvis

The heads of the white arrows indicate the area of compaction and radial severity of the fiber located around the appendix and regarded as a periappendicular infiltrate (A).

It is noteworthy that there is a close relationship between this appendicular infiltrate and fascia of the lumbar muscle (coronary projection, B).

Numerous rounded inclusions (most likely appendicular stones) are visualized in the area of the appendix.

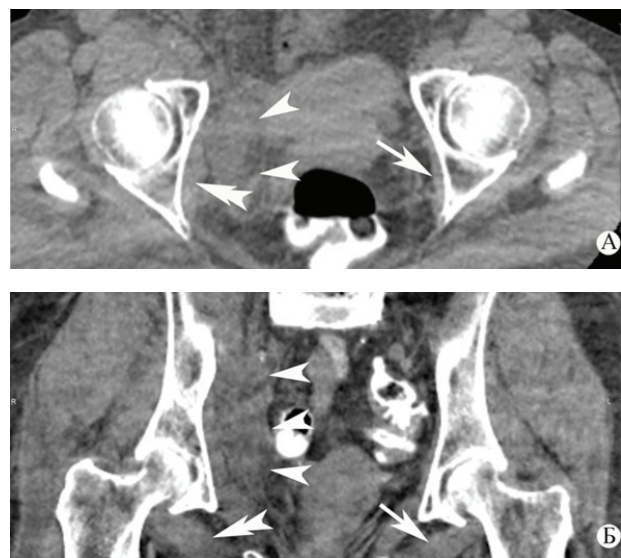


Fig. 3. CT scan of the abdomen and pelvis

On the axial section of the middle floor of the pelvis, the heads of the white arrows indicate the zone of the increased cellular tissue lateral space of the cavity of the pelvis, the head of the double arrow shows the increased abdominal volume of the internal obstructive muscle. The white arrow shows the intact abdomen of the internal obstructive muscle on the left (A)

On the coronary section of the central region of the small pelvis, the heads of the white arrows indicate edematous and densified fiber of the lateral space, with propagation through the obstruction hole into the femoral canal. The double head of the white arrow indicates the enlarged abdominal volume of the

external obturator muscle. The white arrow indicates the intact abdomen of the external obturator muscle on the left (B).

Ultrasound dopplerography of the veins of the lower extremities: ultrasound signs of thrombosis were not detected. Necrotic fasciitis has not been diagnosed.

The patient was urgently operated on laparoscopically for acute gangrenous appendicitis. Upon surgery during the audit in the right iliac region, a loose infiltrate (dome of the cecum and parietal peritoneum) with fibrin and scanty effusion was revealed. The appendix was located retrocecaly, the apex retroperitoneally. When the infiltrate was divided, an abscess opened and revealed gangrenous appendix with perforation. Appendectomy, debridement and drainage of the abdominal cavity were performed. Sowing taken.

Ten hours after the operation, a deterioration was noted: an increase in body temperature to 38.5° C, leukocytosis - 15.4x10<sup>9</sup>/L, a linear section of hyperemia appeared on the medial surface of the right thigh. In the popliteal fossa sections of linear necrosis were noted. In the region of the tibia on the medial surface, a large area of the skin turned bluish-purple without clear boundaries (Fig. 4,5).



Fig. 4.



Fig. 5.

Fig. 4, 5. Skin changes in the lower leg and popliteal fossa

The patient was diagnosed with necrotic fasciitis of the right lower limb and reoperated. An autopsy of phlegmon of the right thigh and lower leg was performed, revision of the retroperitoneal space on the right. During the operation, pronounced edema of the soft tissues and muscles was established, purulent, turbid discharge with gas bubbles located in the subcutaneous tissue and under the fascia. Fascias are dull gray, mucus, with patches

of necrosis on the fascia of the thigh, lower leg and popliteal region, on the calf muscle. Purulent streaks were revealed on the posterior thigh, between the calf and soleus muscles. In the proximal direction, access was made to the retroperitoneal space, purulent discharge was not revealed (Figure 7,8). Wounds sanitized with antiseptic solutions and drained. Crops taken. Microbiological examination of the material from the appendicular abscess, peritoneum, and muscles yielded: *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (necrotic fasciitis type I).

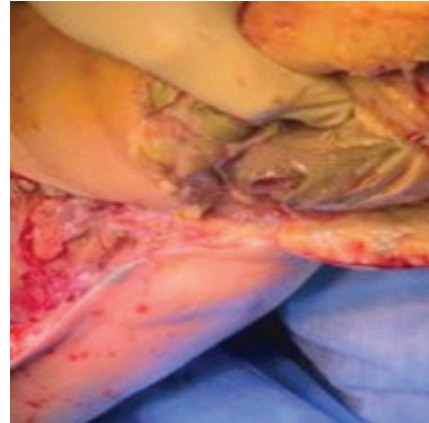


Fig. 7.

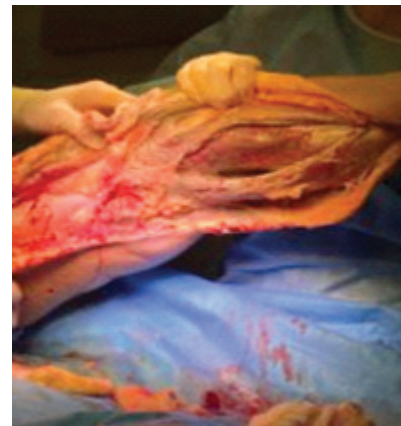


Fig. 8.

Fig. 7,8. Open phlegmon of the right thigh and lower leg

In the postoperative period, the patient was in the intensive care unit on mechanical ventilation with unstable hemodynamics, on inotropic support. On the 4th day from admission to the clinic, a lower tracheostomy was applied. Complex treatment was carried out, which included infusion therapy aimed at correcting water-electrolyte, acid-base, protein, carbohydrate balance. Antibacterial therapy with the following antibiotics: invaz, meronem, linezolid, metronidazole, fluconazole. Sanitation and surgical treatment of purulent foci were performed. During the control CT scan 4 days after the hospitalization in the hospital and 6 days from the onset of the disease, an undrained retroperitoneal abscess on the right was revealed. An autopsy and sanitation, drainage of the retroperitoneal space were performed. An abscess of 150 ml was revealed medially to the inside of the right lumbar muscle and caudally to the sacrum. But despite the treatment, the disease progressed, wet gangrene of the right lower limb developed. The patient underwent amputation at the level of the upper third of the right thigh.

Table 1. Elements of a Laboratory Risk Index for Necrotic Fasciitis (LRINEC)

Laboratory marker	Grade Evaluation
SRP (mg/dl)	<150 = 0 point > 150 = 4 point
WBC (mm <sup>3</sup> )	<15 = 0 points 15-25 = 1 point > 25 = 2 point
Hgb (g/dl)	> 13,5 = 0point 11,6-13,5 = 1point <11,5 = 2 point
Serum sodium	> 135 = 0point <135 = 2point
Serum creatinine	≤ 1.6 = 0point > 1.6 = 2 point
Serum glucose	<180 = 0point > 180 = 1 point

SRP - S-reactive protein

The course of the disease was complicated by sepsis, septic shock, bilateral pneumonia, multiple organ failure syndrome, cerebral edema. The patient died on the 8th day from the moment of hospitalization.

Necrotic fasciitis is one of the life-threatening manifestations of necrotic soft tissue infections (NSTIs) and is characterized primarily by damage of the fascia and subcutaneous fat. The mortality rate is high from 6 to 76% [10,14,19,25]. NF morbidity is low: 0.4 cases per 100,000 in the UK [4].

We did not find any data in the Russian literature on the incidence of NF. In the United States 1,000 cases of NSTIs are recorded per year; however, there is a tendency towards an increase in the incidence rate [12,11], and the objective reasons for this are unclear. It is possible that this is due to an increased understanding of the problem and a clearer registration of these cases, increased resistance to antimicrobials, bacterial virulence, and a rise in the number of patients with weakened immunity due to diabetes mellitus, treatment of malignant tumors, HIV.

Necrotic fasciitis as one of the manifestations of NSTIs is divided into 3 bacteriological types [20]. Type I - NF caused by polymicrobial infection with various types of gram-positive cocci, gram-negative rods and anaerobes, including clostridial. Type II - NF caused by  $\beta$ -hemolytic group A streptococci, either individually or in combination with staphylococcal species. Type III - NF caused by gram-negative marine organisms (*V. vulnificus*).

Necrotic fasciitis, which develops as a fatal complication of acute appendicitis, is extremely rare, we did not find a single article in Russian-language literature, and only 18 cases were recorded in English literature, with a mortality rate of 35% [3,5,6,9,16,18,23].

In an article by Taif and Alravi [16], only three cases of acute appendicitis complicated by NF were noted, with a predominant lesion of the right lower limb, which is probably due to the direct spread of the infection along the neurovascular bundles of the right thigh.

A high mortality rate is associated with the rapid progression of the disease with the development of septic shock and multiple organ failure. This is almost always associated with perforation of the retrocecal, retroperitoneally located process and with delayed diagnosis and surgical treatment.

The rarity of this formidable and fatal disease determines the difficulties of early diagnosis and timely treatment, since most

doctors can see one case of NSTIs throughout their medical career. Diagnosis is also complicated by the fact that a necrotizing infection of soft tissues spreads into the deep layers, and skin manifestations (erythema, edema, discoloration of the skin, bulla, subcutaneous emphysema) already indicate a progressive stage of the disease. And in the early stages, mild erythema on the skin can be mistaken for cellulite. The disproportion of skin manifestations with severe pain and signs of a systemic reaction to inflammation should alert the doctor regarding necrotic fasciitis.

To facilitate the diagnosis of necrotizing soft tissue infection (NSTIs), several assessment systems have been developed. Wall and colleagues [21,22] found that white blood cell count (WBC) <15,000 cells/mm<sup>3</sup> and serum sodium levels above 135 mmol/L had a negative predictive value of 99% and a sensitivity of 90% for detecting NSTIs. The most widely accepted indicator is the laboratory risk indicator of necrotic fasciitis (LRINEC), developed by Wong and colleagues [26] LRINEC is based on determining the level of C-reactive protein, the number of leukocytes, the level of hemoglobin, sodium, creatinine and glucose in the blood serum of patients (Table 1)

Points  $\geq 6$  were found to have 92% positive predictive value and 96% negative predictive value. Although this indicator is widely used, it has never been confirmed, and the authors themselves noted that many other conditions can cause similar laboratory disorders. In addition, its use is limited in the presence of competing inflammatory conditions.

An X-ray examination for the diagnosis of NF is ineffective, since the detection of subcutaneous emphysema is characteristic only for clostridial infection, and with other types of infection it is extremely rare, and then in the later stages of the disease.

Ultrasound gives good results for the detection of superficial abscesses; as for assess of the deeper layers there is a lack of sensitivity and specificity [20].

Computed tomography is the preferred diagnostic method, due to its higher sensitivity. However, CT scans are not specific. With CT, it is possible to determine the asymmetric thickening of the fascia to reveal subcutaneous accumulation of gas along the fascial planes, abscess. With CT treatment can be monitored.

Magnetic resonance imaging is also quite sensitive, but does not have specificity, since tissue enhancement during T2-weighted imaging is often observed after trauma and other non-infectious inflammatory processes [1].

The gold standard for the diagnosis of NF is an early operative (surgical) audit, subject to a high clinical suspicion of NF.

**Conclusions.** Due to the rarity of this potential fatal complication, knowledge of the clinical manifestations of NF is a key factor. The early clinical manifestations of NF may be insignificant, therefore, early recognition and clinical alertness, aggressive surgical treatment with antibacterial therapy with broad-spectrum antibiotics are the main factors necessary to reduce the level of complications and mortality.

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## SUMMARY

### NECROTIC FASCIITIS AS A COMPLICATION OF ACUTE DESTRUCTIVE APPENDICITIS

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The timely diagnosis of necrotic fasciitis (NF) – an extremely rare fatal complication of acute appendicitis is difficult due to the variability of the clinical picture and depends on the degree of inflammatory changes in the appendix wall, localization, age, reactivity, and the presence or absence of comorbidities. It is characterized by high mortality rate, associated with the rapid progression of the disease with the development of septic shock and multiple organ failure.

A clinical case of necrotic fasciitis of the right lower limb without damage of the anterior abdominal wall, secondary to the perforated process, as an extremely rare complication of appendicitis is presented. A 78-year-old patient was urgently operated on laparoscopically for acute gangrenous appendicitis. Necrotic fasciitis has not been diagnosed. Ten hours after the operation, the diagnosis of NF was established and the patient underwent

phlegmon autopsy of the right thigh and lower leg, revision of the retroperitoneal space on the right. Subsequently, sanitation and surgical treatment of purulent foci were performed. Despite the ongoing comprehensive treatment in the intensive care unit using broad-spectrum antibiotics the disease progressed, and wet gangrene of the right lower limb developed. The patient underwent amputation at the level of the upper third of the right thigh. The course of the disease was complicated by sepsis, septic shock, bilateral pneumonia, multiple organ failure syndrome, cerebral edema. The patient

died on the 8th day from the moment of hospitalization.

The rarity of this formidable and fatal disease determines the difficulties of early diagnosis and timely treatment, since most doctors can see one case of NSTIs throughout their medical career. Our case shows how important the early diagnosis of this fatal complication is, as it is crucial for achieving optimal treatment results.

**Keywords:** necrotic fasciitis, necrotic soft tissue infection, complications of appendicitis, retroperitoneal phlegmon, purulent surgery.

## РЕЗЮМЕ

### НЕКРОТИЧЕСКИЙ ФАСЦИИТ - ОСЛОЖНЕНИЕ ОСТРОГО ДЕСТРУКТИВНОГО АППЕНДИЦИТА (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Острый аппендицит – вторая по частоте (после острого холецистита) причина госпитализации в хирургический стационар по неотложным показаниям (10-30%) и первая – по количеству выполняемых экстренных операций – 60-80%. Социальная значимость проблемы острого аппендицита обусловлена его высокой распространенностью.

Некротический фасциит (НФ) является крайне редким фатальным осложнением острого аппендицита. Он характеризуется быстро прогрессирующей по фасции и мягким тканям потенциально смертельной некротической инфекцией, которая при несвоевременно оказанной медицинской помощи приводит к развитию септического шока и полиорганной недостаточности. НФ является одним из опасных для жизни проявлений некротической инфекции мягких тканей (НИМТ) и характеризуется поражением в первую очередь фасции и подкожной жировой клетчатки. Уровень смертности высокий – от 6 до 76%.

В статье представлен клинический случай НФ правой нижней конечности без поражения передней брюшной стенки, вторичного по отношению к перфорированному отростку, как

крайне редкое осложнение аппендицита. Пациентка, 78 лет, по поводу острого гангренозного аппендицита экстренно прооперирована лапароскопически. НФ не диагностирован. Спустя 10 часов после операции установлен диагноз НФ и пациентке выполнено вскрытие флегмоны правого бедра и голени, ревизия забрюшинного пространства справа. В дальнейшем выполнялась санация и хирургическая обработка гнойных очагов. Несмотря на проводимое комплексное лечение в отделении реанимации с использованием антибиотиков широкого спектра действия, заболевание прогрессировало, развилась влажная гангрена правой нижней конечности. Пациентке выполнена ампутация на уровне верхней трети правого бедра. Течение заболевания осложнилось сепсисом, септическим шоком, двусторонней пневмонией, синдромом полиорганной недостаточности, отеком головного мозга. Пациентка умерла на 8-е сутки от момента госпитализации.

Приведенный случай является подтверждением решающего значения ранней диагностики НФ для достижения оптимальных результатов лечения.

## რეზიუმე

ნეკროზული ფასციტი - მწვავე დესტრუქციული აპენდიციტის გართულება (კლინიკური შემთხვევა)

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მოსკოვის ი. სეჩენოვის სახ. პირველი სახელმწიფო სამედიცინო უნივერსიტეტი (სეჩენოვის უნივერსიტეტი);  
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პოსპიტალური ქირურგიის კათედრა, რუსეთის ფედერაცია

მწვავე აპენდიციტი გადაუდებელი ჩვენების გამო ქირურგიულ კლინიკაში პოსპიტალიზაციის ყველაზე ხშირ მიზეზს წარმოადგენს, მწვავე ქოლეცისტიტის შემდეგ (10-30%), ჩატარებული გადაუდებელი ოპერაციების რაოდენობის მიხედვით კი - ყველაზე ხშირს (60-80%). მწვავე აპენდიციტის პრობლემის სოციალური მნიშვნელობა მისი მაღალი გავრცელებითაა პირობადებული.

ნეკროზული ფასციტი მწვავე აპენდიციტის საკმაოდ იშვიათი ფატალური გართულებაა. იგი ხასიათდება პოტენციურად სასიკვდილო ნეკროზული ინფექციით, რომელიც სწრაფად ვითარდება ფასციებსა და რბილ ქსოვილებში, დროული სამედიცინო ჩარევის გარეშე იწვევს სეპტიურ შოკს და პოლიორგანულ უკმარისობას. ნეკროზული ფასციტი დანეკროზებული რბილი ქსოვილების ინფექციის სიცოცხლისათვის საშიში მანიფესტაციაა და ხასიათდება უპირველესად, ფასციებისა და კანქვეშა ცხიმოვანი ქსოვილის დაზიანებით; სიკვდილობის მაჩვენებელი მაღალია – 6 -76%.

სტატიაში წარმოდგენილია მარჯვენა ქვედა კიდურის ნეკროზული ფასციტის კლინიკური შემთხვევა მუცლის წინა კედლის დაზიანების გარეშე. ეს

სტატიაში წარმოდგენილია მარჯვენა ქვედა კიდურის ნეკროზული ფასციტის კლინიკური შემთხვევა მუცლის წინა კედლის დაზიანების გარეშე. ეს

აპენდიციტის მეტად იშვიათი გართულების მაგალითია. 78 წლის ქალს მწვავე განგრუნული აპენდიციტის გამო სასწრაფოდ გაუკეთდა ოპერაცია ლაპაროსკოპიულად. ნეკროზული ფასციიტი იმთავითვე დიაგნოსტირებული არ იყო. ნეკროზული ფასციიტი დიაგნოსტირდა ოპერაციიდან 10 საათის შემდეგ. პაციენტს ჩაუტარდა მარჯვენა ბარძაყის და ქვედა ფეხის ფლევმონის გაკვეთა, მარჯვენა რეტროპერიტონეული სივრცის რევიზია. შემდგომ ჩატარდა ჩირქოვანი კერების სანაცია და ქირურგიული მკურნალობა. მიუხედავად ინტენსიური თერაპიის განყოფილებაში ჩატარებული კომპლექსური მკურნალობისა ფართო სპექტრის ან-

ტიბიოტიკების გამოყენებით, დაავადება პროგრესირდა, განვითარდა მარჯვენა ქვედა კიდურის სველი განგრუნა. პაციენტს ჩაუტარდა ამპუტაცია მარჯვენა ბარძაყის ზედა მესამედის დონეზე. დაავადება გართულდა სეფსისით, სეპტიური შოკით, ორმხრივი პნევმონიით, პოლიორგანული უკმარისობით და ცერებრული შეშუპებით. პოსტიტალიზაციიდან მე-8 დღეს დადგა ლეტალური შედეგი.

აღწერილი კლინიკური შემთხვევა ადასტურებს მწვავე ფასციიტის ადრეული დიაგნოსტიკის მნიშვნელობას მკურნალობის ოპტიმალური შედეგების მისაღწევად.

## EVALUATION OF NOVEL PORCINE PERICARDIAL BIOMATERIAL FOR VENTRAL AND INGUINAL HERNIA REPAIR. THE RESULTS OF A NON-RANDOMIZED CLINICAL TRIAL

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More than 20 million hernias are estimated to be repaired every year around the world [1]. Per year, approximately 700,000 hernia repairs are carried out in the USA [2]. Currently, surgery possesses huge arsenal of various surgical methods of ventral and inguinal hernia repair. Recently, usage of meshes created from various synthetic and biological materials have become quite popular in the herniology.

There are many types of meshes and multiple methods of their placement during the hernia repair. Meshes vary by their origin (synthetic, biologic, composite), absorbability, pore size, weight (light- and heavyweight), elasticity and mesh durability [3-7].

The vast majority of synthetic meshes are made from polypropylene (PP), polytetrafluoroethylene (PTFE), prolene dacron, orlon, mylar. There are different situations in which a surgeon must make a decision about what type of a mesh to use. For example, in a case of infected ventral hernia, generally, absorbable synthetic meshes are used, however, since they are absorbed, recurrence rate is very high and additional surgical intervention is needed to achieve permanent repair [5,8]. PTFE and PP are the most common meshes used to repair large ventral hernias [9,10]. However, when the macroporous meshes are placed so that they come in contact with abdominal viscera, they are associated with the development of bowel adhesions, obstructions, and enterocutaneous fistulae. Polytetrafluoroethylene (PTFE) meshes can lead to the development of encapsulation, collection of periprosthetic fluid, and excessive growth of bacteria [11].

Despite the fact, that there are vast number of synthetic and composite meshes from which you could pick an individual treatment method, complications are still a major problem. As it is reported in the manuscript, ventral hernia repair with prosthetic mesh has recurrence rates up to 54% and is contraindicated in the setting of infection [12].

The complications include post-operative pain and movement restriction, recurrence, adhesions, calcification, mesh migration and seroma. Chronic post-operative pain develops often in patients who underwent either open or laparoscopic ventral hernia repair, regardless of fixation type. Studies claim, that 26 to 34%

of the patients reported chronic discomfort due to pain [13,14].

Recurrence of ventral hernia is still a major challenge in VH repair. Even though, the rate of recurrence has decreased from 50% to 10-23% after meshes were introduced, it still is quite frequent and traumatic experience for patients, since there is need for additional surgical interventions, which are performed in case of relapse of the disease [15-17]. Although, studies suggest, that VH recurrence can almost be eliminated by utilizing underlay technique, this method increases risk of adhesions, which are discussed below [17,18].

Adhesions are generally associated with intraperitoneal underlay technique, during which the mesh has direct contact with bowel. Increased risk of adhesions has been associated with macroporous structure of the mesh [19]. Incidence of unplanned surgical intervention done due to adhesions and enterocutaneous fistulas after ventral hernia is about 4% [20].

Calcification is a result of prolonged foreign body reaction, which may develop to certain meshes and, in the end, may result in generating chronic pain [21, 22].

Seroma are relatively minor complication of hernia and they typically develop with any type of a mesh. However, it is well known, that meshes with larger pores are less likely to lead to seroma. Overall incidence of seromas is 2% and they commonly resolve without any intervention after 6-8 weeks [23].

Migration is another severe complication, during which mesh may migrate into organs such as urinary bladder, sigmoid colon, hollow viscus, spleen, and it may cause respective discomfort, depending where mesh migrates into [24-27].

Also, in the cases when the wounds are heavily contaminated, prosthetic meshes are frequently considered to be contraindicated due to the high risk of infection. Additionally, prosthetic meshes are associated with the development of erosions adhesions, and chronic pain in the abdominal viscera. In the cases when the wounds are contaminated the mesh representing a biological tissue matrix (BTM) can be an alternative to synthetic mesh the use of which is related to the ability of the material to tolerate cutaneous exposure and withstand placement into a contaminated defect [28-35].

The aim of this study was to provide preliminary results of a non-randomized clinical trials evaluation of XI-S+® porcine pericardial biomaterial (Colorado Therapeutics LLC. USA) for ventral and inguinal hernia repair.

**Material and methods.** All patients signed written informed consent for the study, which was conducted according to the guidelines of the 1975 Declaration of Helsinki and approved by the Ethics Committee of the Tbilisi State Medical University, Tbilisi, Georgia.

Inclusion criteria were the following: M/F  $\geq$  21 years of age, negative for pregnancy, no known allergic reaction to porcine, IC signed, and candidates for open procedure. Exclusion criteria: lactating women, not available for follow-up, severe malnutrition, use of investigational agent, known malignancy, life expectancy  $\leq$  two years, clinical symptoms of infected hernia site, or evidence of contaminated or clean contaminated fields, ascites, preexisting liver disease, immune compromised subjects, morbid obese, BMI  $\geq$ 35, and diabetic subjects, insulin dependent.

**Operative procedure.** Ventral hernia repair in ten patients consisted of a midline laparotomy or through the old incision, which was removed. The fascial edges were trimmed to healthy tissue and the hernia sac excised. Hernia hilus was then closed by suturing the right and left side of the aponeurosis of external abdominal oblique muscle together. The sutures were done by 2-0 Prolene thread. Then, the onlay technique was performed with the XI-S+® mesh which was sutured by multiple simple interrupted sutures with 2-0 Prolene thread. One silicon surgical drain was placed above the mesh. The skin was sutured with 2-0 prolene thread.

Inguinal hernia repair in ten patients were done in the following fashion. After incising the skin, subcutaneous tissue, and external oblique aponeurosis, the hernial sac was identified, adhesions were removed and the sac excised according to standard Lichtenstein tension-free method. XI-S+® mesh (6 × 15 CM) was trimmed to fit individual patient inguinal canal floor. The mesh was then anchored to the conjoined tendon by simple interrupted sutures (Prolene 2-0). The skin was sutured with 2-0 prolene thread.

The mean hospital stay duration post-operatively was 2 days. The patients was followed up during the postoperative visits at the following time points: 1 week, 1 month, 3 months, 5 months, 12 months, 1 year, 2 years and 3 years. At each post-operative visit and at the initial preoperative evaluation and screening, to assess the quality of life changes related to the hernia and hernia repair procedure patients were given a copy of the Carolinas Comfort Scale (CCS). CCS itself allows us to evaluate quality of life in three areas: pain, sensation of mesh, movement limitations.

**Results and discussion.** The average age of the patients with ventral hernia was 54±1.4 years, and 30% of patients were female and 70% of patients were male. The average age of the patients with inguinal hernia was 62.5±9.4 years, and 10% of patients were female and 90% of patients were male. The average hospitalization length was 2 days. Table 1 and 2 lists patient demographics and operative details. All patients that were enrolled into the study had primary hernias. Results of Carolina Comfort Scale survey for all the patients are depicted in Table 3 and 4.

Table 1. Ventral hernia repair patient characteristics and operative details

Ventral Hernia					
Variable	Mean	SD	Median	Minimum	Maximum
Age (years)	53.3	12.7	5.8	24	70
BMI (kg/m <sup>2</sup> )	27.9	3.9	29.4	21.4	34.8
Fascial defect size (cm <sup>2</sup> )	30.7	13.8	30	12	60
Mesh size (cm <sup>2</sup> )	90	0	90	90	90
Incision length (cm)	14.2	4.8	12	10	20
Length of stay (days)	2.6	0.5	3	2	3
Operative time (min)	75.4	27.3	70	40	135

Table 2. Inguinal hernia repair patient characteristics and operative details

Inguinal Hernia					
Variable	Mean	SD	Median	Minimum	Maximum
Age (years)	53.6	9	61	49	77
BMI (kg/m <sup>2</sup> )	25.8	2.5	25.7	22.4	31.1
Fascial defect size (cm <sup>2</sup> )	34.2	24.4	20	12	80
Mesh size (cm <sup>2</sup> )	59.2	24.5	72	30	90
Incision length (cm)	5.9	0.9	6	5	8
Length of stay (days)	2.1	0.3	2	2	3
Operative time (min)	51	4.6	50	45	55



Table 3. Mean Carolinas Comfort Scale Scores with Change (Ventral Hernia)

	Baseline	1 Week	1 Month	3 Months	5 Months	1 Year	2 Years	3 Years
N	10	10	10	10	10	10	10	10
Pain	1.27	0.84	0.09	0.06	0	0	0	0
Sensation of mesh	N/A	0.25	0.29	0.01	0.01	0	0	0
Movement limitation	1.60	0.85	0.10	0.03	0.02	0	0	0

Table 4. Mean Carolinas Comfort Scale Scores with Change (Inguinal Hernia)

	Baseline	1 Week	1 Month	3 Months	5 Months	1 Year	2 Years	3 Years
N	10	10	10	10	10	10	10	10
Pain	1.2	1.6	0.2	0	0	0	0	0
Sensation of mesh	N/A	0	0	0	0	0	0	0
Movement limitation	1.3	1.5	0.4	0	0	0	0	0

The XI-S+® mesh was used for all surgeries. It provided secure and adequate overlap in the periphery of each fascial defect; minimal mesh overlap was defined as not less than 3 cm by the study criteria.

Biologic mesh materials derived from human and animal donor source are based on a matrix of proteins, including collagen, elastin, glycoproteins and growth factors. They represent so-called “third-generation” mesh which provides ingrowth of host cells and generates “tissue-mesh” composite for replace the tissue in the hernia defect [36, 37].

The literature widely highlights issues of related to the use of such biologic mesh like human acellular dermis [38-40], porcine-derived acellular dermal matrix [41-43], porcine small intestine submucosa [44-47], bovine pericardium [48-50].

The pivotal part of achieving permanent hernia repair is vascularization and remodelling, which, in contrast to synthetic materials, biologic materials can be subjected to [51].

Decellularized human dermal tissue was really popular and promising upon introduction, however, long-term follow-up studies showed very high rate of recurrent herniation, eventration and low long-term durability [52,53].

Porcine small intestinal submucosa tissue has widely been tested and studied and many authors suggest that it could cause tissue rejection [54]. While other studies claim, that severe tissue rejection decreased durability, it is frequently infected with B hemolytic Streptococcus [55, 56]. Authors also state, that it is durable, when it is not infected, however, it does not hold up well in contaminated areas [51,57].

Decellularized porcine dermal tissue was tested in animal and clinical trials, It has been proven that adhesions to intestinal segment is significantly lower than in synthetic materials, although, recurrences are at peak when it is bridged over hernia defect [51].

Studies claim, that decellularized bovine pericardium is a far superior biologic material, as it is as durable as synthetic material, has minimal adhesion rate, it is easy to suture and its structure remains consistent [58,59].

We have chosen XI-S+® for study because it is a novel mesh produced from porcine pericardial sac with a new method and similar to decellularized bovine pericardium shows tremendous promise since it has high durability, ability of remodeling and vascularization.

The clinical studies have shown that almost in all patients the post-operative pain was minimal and easily controlled by the use of single analgesics. In the immediate post-operative period

we had 5 complications; 3 ventral and 1 inguinal hernia repair patient had seroma. 2 inguinal hernia repair patient had hematoma and testicular swelling occurred in 1 patients. We have not observed abscess formation or acute infection related to the presence of XI-S+® mesh.

We suppose that hematoma must have been linked to surgical procedure. In case of seroma, we think that it must be linked to the fixation of mesh, during which a closed environment (sac) between the mesh and the host tissue has been created and inflammatory cells were trapped, which led to the formation of seroma. With short-term and long-term (more than three years) observation, there were no recurrences of hernia.

Carolinas comfort scale surveys were successfully completed by all patients on 1<sup>st</sup> week, 1<sup>st</sup>, 3<sup>rd</sup>, 5<sup>th</sup> and 12<sup>th</sup> months, and 2<sup>nd</sup> and 3<sup>rd</sup> years of follow-up visits. In all patients, both with ventral and inguinal hernias, the feeling of relief was evident starting from the 1<sup>st</sup> week after surgery. After 1 month from surgery, the level of discomfort in patients has been significantly decreased, and after 3 months, it has been practically non-existent. As for the sensation of the mesh, in some patients it has been present up until 1 month after the surgery, but it fully disappeared by the end of the 3<sup>rd</sup> month.

In our opinion, it is very interesting to analyze the level of discomfort in patients depending on their type of activeness. Various conclusions can be made from the results. For example, one week after surgery, pain syndrome has been increased only in the cases of ventral hernias when the patient was lying down and bending over, it stayed the same when the patient was sitting up, and the pain syndrome has been decreased in all other cases. After 1 week from surgery, the biggest discomfort has been caused while the patient was coughing or deep breathing in ventral cases, and for the inguinal cases – while the patient was sitting up. After 1 month from surgery, pain syndrome has been still present while the patient was sitting up, performing activities of daily living and coughing or deep breathing, and for the ventral cases - additionally when the patient was bending over or walking. It has to be underlined that all pain sensations have been gone after 3 months from surgery.

Studies have shown that the XI-S+® mesh possesses homogeneous (multidirectional) elasticity that causes minimal shrinkage after the implantation and its structure significantly increases hydrophilic features which provide a better adhesion and cell proliferation on its surface. Soft and elastic structure of XI-S+® mesh fully covers large surfaces in the cases of ventral post-

operative hernias, it ensures fast and quality formation of the “mesh-tissue” complex, which enables the creation of the thick layer of biological tissue on the basis of somewhat scaffold, which itself provides resilience of the anterior abdominal wall.

XI-S+® mesh possesses anti-adhesion features that prevent the formation of adhesions between the host tissue and the implanted mesh. Additionally, the mesh is extremely resistant to an infection that allows its use in patients with incarcerated hernias with infected wounds. XI-S+® mesh provides the favorable conditions for engraftment, early activity and rehabilitation of patient.

**Conclusion.** The clinical studies of the patients that underwent ventral and inguinal hernia repair using XI-S+® mesh have shown that the post-operative pain was minimal and easily controlled by the use of analgesics. As for the sensation of the mesh, in some patients it has been present up until 1 month from surgery, but it fully disappeared by the end of the 3rd month.

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## SUMMARY

### EVALUATION OF NOVEL PORCINE PERICARDIAL BIOMATERIAL FOR VENTRAL AND INGUINAL HERNIA REPAIR. THE RESULTS OF A NON-RANDOMIZED CLINICAL TRIAL

**Kakabadze Z., Janelidze M., Chakhunashvili D., Kandashvili T., Paresishvili T., Chakhunashvili D.G.**

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Using the mesh for hernia repair is the most common type of hernia surgery. There are many types of meshes made of various synthetic materials, but all of these meshes have their own respective disadvantages. The aim of this study was to provide preliminary results of a non-randomized clinical trial evaluation of novel porcine grafts XI-S+® (Colorado Therapeutics LLC, USA) for ventral and inguinal hernia repair.

All patients underwent a standardized surgical procedure. Onlay surgical repair technique has been performed in ten patients with ventral hernia and Lichtenstein tension-free method has been used for ten patients with inguinal hernia repair. The XI-S+® mesh fixation was performed with multiple simple interrupted sutures using prolene thread.

The average age of the patients with ventral hernia was 54±14 years, and 30% of patients were female and 70% of patients were male. The average age of the patients with inguinal hernia was 62.5±9.4 years, and 10% of patients were female and 90% of patients were male. The average hospitalization length was 2 days. During three years of observation, no recurrence of hernia

was observed in patients. The XI-S + ® mesh has anti-adhesive properties, is extremely resistant to infections, provides favorable conditions for engraftment, early activity and patient rehabilitation.

The clinical studies of the patients that underwent ventral and inguinal hernia repair using XI-S+® mesh have shown that the post-operative pain was minimal and easily controlled by the use of analgesics. As for the sensation of the mesh, in some patients it has been present up until 1 month from surgery, but it fully disappeared by the end of the 3rd month.

**Keywords:** ventral hernia repair; inguinal hernia repair; biological mesh.

## РЕЗЮМЕ

### ОЦЕНКА НОВОГО БИОМАТЕРИАЛА СВИНОГО ПЕРИКАРДА ДЛЯ ПЛАСТИКИ ВЕНТРАЛЬНОЙ И ПАХОВОЙ ГРЫЖ. РЕЗУЛЬТАТЫ НЕРАНДОМИЗИРОВАННОГО КЛИНИЧЕСКОГО ИССЛЕДОВАНИЯ

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В хирургии грыж часто используются сетчатые имплантаты, которые изготовлены из различных синтетических материалов. Однако, большинство из них вызывают различные послеоперационные осложнения.

Целью исследования явилось представить предварительные результаты нерандомизированного клинического исследования новых биологических имплантатов XI-S+® (Colorado Therapeutics LLC. США) для пластики вентральной и паховой грыж. Всем пациентам проведена стандартная хирургическая процедура. Техника хирургической пластики Onlay выполнена у десяти пациентов с вентральной грыжей, а метод без натяжения по Лихтенштейну использован у десяти пациентов с пластикой паховой грыжи. Фиксация имплантата выполнялась простыми узловыми швами с использованием проленовой нити.

Средний возраст пациентов с вентральной грыжей составил 54±14 лет, из них 30% пациентов составили женщины, 70% пациентов - мужчины. Средний возраст пациентов с паховой грыжей составил 62,5±9,4 года, из них 10% пациентов составляли женщины, а 90% пациентов - мужчины. Средняя продолжительность госпитализации составила 2 дня. Обследования по шкале комфорта Carolinas успешно завершены всеми пациентами спустя 1 неделю, 1, 3, 5, 12 месяцев, 2 и 3 года последующих посещений. Почти у всех пациентов, как с вентральными, так и с паховыми грыжами, чувство облегчения проявлялось уже спустя 1 неделю после операции. Спустя 1 месяц после операции уровень дискомфорта у пациентов значительно снизился, а спустя 3 месяца практически исчез. Сетка XI-S+® обладает антиадгезионными свойствами, чрезвычайно устойчива к инфекциям, обеспечивает благоприятные условия для приживления, ранней активности и реабилитации пациента. В течение трех лет наблюдения рецидивов грыжи у пациентов не наблюдалось.

Клинические исследования пациентов, перенесших пластику вентральной и паховой грыжи с использованием сетки XI-S + ®, показали, что послеоперационная боль была минимальной и легко контролировалась с помощью анальгетиков. Что касается ощущения сетки, то у некоторых пациентов она сохранялась до 1 месяца после операции, но полностью исчезла к концу 3 месяца.

## რეზიუმე

ლორის პერიკარდიუმისგან მიღებული ახალი ბიომასალის შეფასება ვენტრალური და საზარდულის თიაქრების დროს. არარანდომიზებული კლინიკური კვლევის შედეგები

ზ.კაკაბაძე, მ.ჯანელიძე, დ.ჩახუნაშვილი,  
თ.ყანდაშვილი, თ.ფარესიშვილი, დ.განაშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი,  
საქართველო

თიაქრების სამკურნალოდ ქირურგიული ბადეები საკმაოდ ხშირად გამოიყენება. არსებობს უამრავი სინთეტიკური ბადეების ნაირსახეობა, რომელთაც აქვთ სხვადასხვა გართულებები.

კვლევის მიზანს წარმოადგენდა ღორის პერიკარდიუმისგან მიღებული ახალი მასალის XI-S+® (Colorado Therapeutics LLC. USA) შეფასება ვენტრალური და საზარდულის თიაქრების დროს არარანდომიზებული კლინიკური კვლევის წინასწარი შედეგების სახით.

ათივე ვენტრალური თიაქრის მქონე პაციენტს ჩაუტარდა სტანდარტული ქირურგიული პროცედურა Onlay ტექნიკის გამოყენებით, ხოლო 10 პაციენტს საზარდულის თიაქრით ჩაუტარდა ოპერაცია Lichtenstein tension-free მეთოდის გამოყენებით. XI-S+® ბადე დაფიქსირდა რამოდენიმე პროლენის უწყვეტი ნაკერის საშუალებით.

ვენტრალური თიაქრების მქონე პაციენტების საშუალო ასაკი იყო 62.5±9.4 წ. ამ პაციენტების 10% იყო მდედრობითი და 90% მამრობითი სქესის. საზარდულის თიაქრის მქონე პაციენტების საშუალო ასაკი წარმოადგენდა 54±14 წელს. ამ პაციენტების 30% იყო მდედრობითი და 70% მამრობითი სქესის. პოსპიტალიზაციის საშუალო ხანგრძლივობა შეადგენდა 2 დღეს. 3 წლიანი დაკვირვების შედეგად არცერთ პაციენტში თიაქრის რეციდივი არ აღინიშნა. XI-S+® ბადეს გააჩნია ანტიადჰეზიური თვისებები, არის ინფექციებისადმი რეზისტენტული, ქმნის ხელსაყრელ პირობებს შეხორცებისათვის, ადრეული აქტივობის დაწყებისა და პაციენტის სრული რეაბილიტაციისთვის.

ვენტრალური და საზარდულის თიაქრებით პაციენტებში ჩატარებულ კლინიკურ კვლევაში, მკურნალობის მიზნით გამოყენებულმა XI-S+® ბადემ აჩვენა, რომ პოსტოპერაციული ტკივილი იყო მინიმალური და მარტივად ექვემდებარებოდა ანალგეტიკებს. ბადის მგრძობელობა ერთი თვის განმავლობაში შენარჩუნებული იყო რამოდენიმე პაციენტში, ხოლო მესამე თვის ბოლოს აღარ აღინიშნებოდა არცერთ პაციენტში.

## INTRAVASCULAR LIPOMA OF THE RIGHT BRACHIOCEPHALIC VEIN AND SUPERIOR VENA CAVA: A CASE REPORT AND LITERATURE REVIEW

Podobed A.

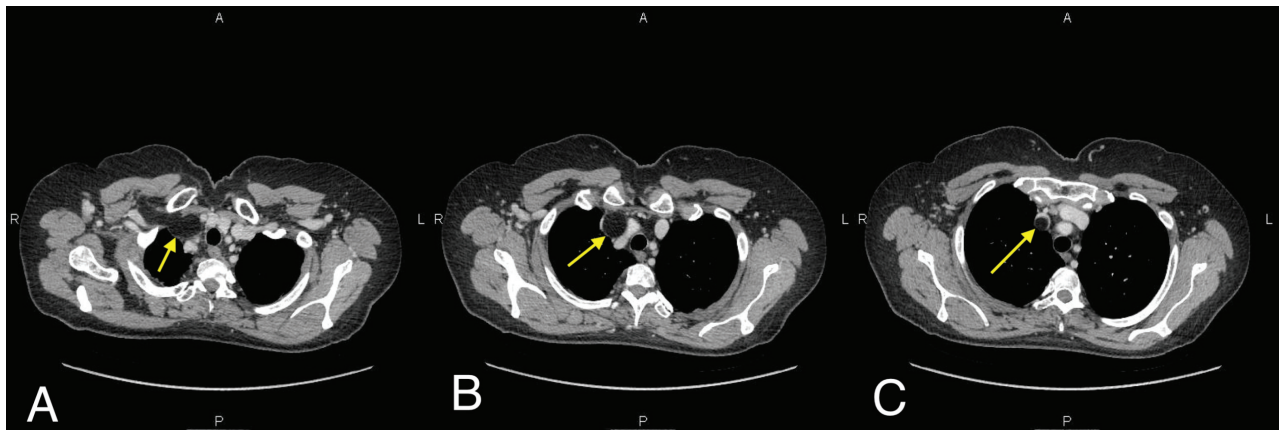
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Lipomas of the major central veins are very rare tumors that have mostly been described in the inferior vena cava. They may be identified in as many as 0.5% of all CT scans [1]. Intravenous lipoma of the vena cava superior is a rare tumor, which usually remains asymptomatic and is incidentally detected during routine computed tomography or magnetic resonance studies. Patients with symptomatic intravenous lipomas may present with indicative signs of vascular occlusion.

We present a case of intravascular lipoma of the superior vena cava in a 53-year-old woman with upper extremity swelling. Short literature review of the data from sixteen cases of lipoma within the superior vena cava and brachiocephalic or subclavian veins was done in order to compare the main features. This work was reported in line with the SCARE criteria [2].

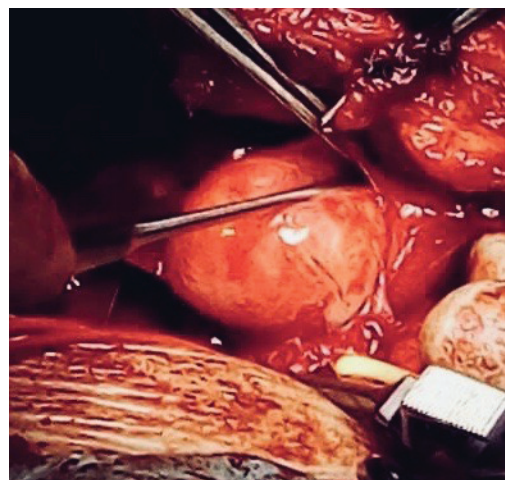
**Case of report.** We report a rare case of superior vena cava (SVC) lipoma in a 53-year-old woman with a history of trauma.

She complained of upper extremity swelling. On physical examination, there was distension of neck veins, facial plethora or upper extremity oedema. The history was explored for predisposition to SVC thrombosis. She denied recent central venous catheterisation or blood clots in her extremities. An ultrasonography showed a filling defect of intermediate echogenicity in right subclavian vein (RSV), right brachiocephalic vein (RBV) and the SVC. Anticoagulation therapy with rivaroxaban 15 mg orally twice a day was commenced. No significant change was noted on repeat scan at one month. The patient continued to have upper extremity oedema, which raised concern for possible intermittent transient obstruction of SVC by the mass. Computed tomography (CT) with intravenous contrast showed the mass, lying within the lumen of the SVC with fatty densitometric values. It extended up from the SVC to the subclavian vein for about 12 cm. The lumen was reduced to a tiny marginal slit (Fig. 1. A, B, C).



*Fig. 1. Preoperative intravenous contrast-enhanced thoracic computed tomographic scan showing the hypodense tumor (arrows) filling the lumen of the right subclavian (A) and brachiocephalic (B) veins and of the SVC (C)*

Given the location of the tumor a preoperative histologic sampling was deemed unfeasible. Because of the symptoms, she was taken into surgery. The surgical approach combined a partial median sternotomy with a right supraclavicular cervicotomy, allowing control of the SVC as well as the right subclavian, right internal jugular, and azygos veins. The superior vena cava was incised and opened. A lobulated fatty tumor was found to be occupying the lumen of the SVC; however, the tumor was free of adhesions to the SVC wall. The origin of the tumor was adherent to the wall of the junction between the right brachiocephalic vein and SVC. The mass was completely removed by pulling it out from the right subclavian vein and partial resection of the superior vena cava bifurcation (Fig. 2). The surgical defect was closed by using a bovine pericardial patch. Histopathological evaluation confirmed the diagnosis of lipoma. Her postoperative course was uneventful, and the patient was discharged home in stable condition a few days later. After 3 years of follow-up, the patient is doing well, without evidence of recurrence on CT scan.



*Fig. 2. Operative view showing the extraction of the tumor from the lumen of SVC*

Table. Case reports of SVC lipoma including this case

First author (year)	Sex/Age	Location	Clinical presentation	Diagnostic method	Surgery
Winchcombe (1994) [3]	F/42	RBV, SVC	Oedema of face and hand	CT venography	Yes
Thorogood (1996) [4]	M/73	RBV, SVC	Asymptomatic	CT, MRI	No
Trabut (1999) [5]	M/55	SVC	Asymptomatic	CT	Yes
Lomeo (2007) [6]	M/60	RSV, SVC	Asymptomatic	CT, Echocardiography	Yes
Moore (2008) [7]	M/58	RBV	Asymptomatic	CT	No
Ryu (2009) [8]	M/47	RSV, RIV	Asymptomatic	CT, MRI	No
Mordant (2010) [9]	F/55	SVC	Asymptomatic	CT, MRI	Yes
Bravi (2011) [10]	M/63	SVC	Asymptomatic	CT, MRI	Yes
Santos (2012) [11]	M/47	RSV, RBV	Asymptomatic	CT	No
Lococo (2013) [12]	M/61	RBV	Fever	CT	Yes
Tanyeli (2015) [13]	M/48	SVC	Oedema and numbness of hand	CT, MRI	Yes
Concetto (2015) [14]	M/58	SVC	Asymptomatic	CT, MRI	Yes
Wahab (2017) [15]	F/70	SVC	Headache and palpitation	MRI, Echocardiography	Yes
Iqbal (2017) [16]	M/51	RBV	Asymptomatic	CT, MRI	No
Vetthus (2017) [17]	F/60	RBV	Asymptomatic	CT	No
Beliaev (2019) [18]	F/49	SVC	Asymptomatic	CT	Yes
Podobed (2020)*	F/53	RBV, SVC	Oedema of face and hand	CT, Echocardiography	Yes

CT - computed tomography; MRI - magnetic resonance imaging; RBV - right brachiocephalic vein; RSV - right subclavian vein; SVC - superior vena cava; (\*) - The present case study

To our knowledge, there are only sixteen other cases of SVC lipoma reported in the literature (Table).

Intravascular lipomas may be asymptomatic. In most cases (70%), the lipoma is incidentally revealed by imaging. Four (23,5%) patients had venous obstructive symptoms, including upper limb swelling, headache, palpitation, oedema of face and numbness of hand [3,12,13,15]. The average age of patients with intravascular lipoma of the right brachiocephalic vein and superior vena cava was 55.9±8.3 years. The ratio of men to women is 2:1. The literature on pathology gives two hypotheses to explain this peculiar presentation: the tumor may arise from the vein wall or external to it (fatty perivascular tissue) [6,11]. In the first instance, the tumor grows into the vein wall protruding out-side and inside the lumen (but the media layer of veins is poorly developed with few fatty cells). The second hypothesis suggests that the tumor arises from perivascular tissue, infiltrates the vein wall and then protrudes into the lumen (unusual attitude fora benign tumor). Four (23,5%) patients have a history of chest trauma

The diagnosis of a benign intravascular lipoma is arrived at by CT scan and magnetic resonance imaging. Contrast-enhanced CT reveals a well-defined rounded mass of fat attenuation occluding the lumen of the SVC. Magnetic resonance imaging confirms the fatty nature of the mass and its intraluminal localization.

Usually surgical excision is indicated only when the tumor causes pain or compression of adjacent structures. Of the 16 cases previously described in the literature, 5 cases did not lead to surgical resection because the mass was not symptomatic. On the contrary, we believe that surgical resection is mandatory in both symptomatic and asymptomatic patients. First, it is impossible to make a firm distinction between a benign lipoma and a liposarcoma before surgical resection [19]. Second, the growth of the tumor may eventually induce obstruction of the SVC or enter the right atrium and subsequent excision will require car-

diopulmonary bypass [10,15,18]. The optimal approach is to remove the intravascular mass with excision of the vessel wall at the tumor attachment site and vascular reconstruction and urgent intraoperative histological examination. If it is not possible to perform frozen section, en bloc resection and vascular graft for venous reconstruction is more advisable.

**Conclusion.** Surgery for intravascular tumors must be safe and complete. Combined transsternal and supraclavicular approach allows to control all the major thoracic veins and avoids pulmonary embolism, minimizes bleeding, and allows en bloc resection of the tumor.

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## SUMMARY

### INTRAVASCULAR LIPOMA OF THE RIGHT BRACHIOCEPHALIC VEIN AND SUPERIOR VENA CAVA: A CASE REPORT AND LITERATURE REVIEW

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Lipomas of the major central veins are very rare tumors that have mostly been described in the inferior vena cava. They may

be identified in as many as 0.5% of all CT scans. Intravenous lipoma of the right brachiocephalic vein end vena cava superior is a rare tumor. There are only sixteen other case reported in medical literature. A rare case of superior vena cava (SVC) lipoma and literature review are presented.

A 53-year-old woman with oedema of face and hand and history of chest trauma underwent computed tomography of the chest. Unenhanced CT showed a hypodense elongated lesion with fat density within the SVC. Surgical resection of the lesion was performed and histopathological evaluation confirmed the diagnosis of SVC lipoma.

Intravascular lipomas may be asymptomatic, or they may induce venous obstructive symptoms, including upper limb swelling. Surgical removal of intravenous lipoma is recommended in both symptomatic and asymptomatic patients to rule out malignancy, to prevent obstruction of the SVC, penetration of the right atrium, and thromboembolic complications.

Surgery for intravascular tumors must be safe and complete. Combined partial transsternal and supraclavicular approach allows to control all the major thoracic veins and avoids pulmonary embolism, minimizes bleeding, and allows en bloc resection of the tumor.

**Keywords:** Computed tomography; Intravascular lipoma; Superior vena cava.

## РЕЗЮМЕ

### ВНУТРИСОСУДИСТАЯ ЛИПОМА ПРАВОЙ ПЛЕЧЕГОЛОВНОЙ И ВЕРХНЕЙ ПОЛОЙ ВЕНЫ: КЛИНИЧЕСКИЙ СЛУЧАЙ И ОБЗОР ЛИТЕРАТУРЫ

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Липомы магистральных вен - редкие опухоли, большинство из них встречаются в нижней полой вене, где выявляются как случайные находки при компьютерной томографии в 0,5% случаев. Внутрисосудистая липома плечевого и верхней полой вены крайне редкая опухоль. В медицинской литературе по сей день описано только шестнадцать случаев.

Автором приводится описание случая: женщина 53 года с травмой грудной клетки в анамнезе обратилась с жалобами на отечность лица и правой руки. При компьютерной томографии выявлена опухоль жировой плотности в просвете верхней полой вены. Выполнено хирургическое вмешательство с удалением опухоли. Гистологическое исследование удаленного новообразования подтвердило диагноз внутрисосудистой липомы.

Внутрисосудистые липомы могут протекать бессимптомно или вызывать симптомы венозной обструкции. Хирургическое лечение показано даже при отсутствии клинической картины с целью исключения злокачественной опухоли, профилактики тромбозомболических осложнений, обструкции верхней полой вены, распространения в правое предсердие.

Внутрисосудистая липома может быть безопасно удалена хирургическим методом. Частичная стернотомия в комбинации с надключичным доступом обеспечивает надежный контроль магистральных вен грудной клетки и позволяет избежать легочную эмболию, минимизировать интраоперационную кровопотерю и моноблочно удалить опухоль.

## რეზიუმე

მარჯვენა ბრაქიოცეფალური და ზედა ღრუ ვენის სისხლძარღვშიდა ლიპომა: კლინიკური შემთხვევა და ლიტერატურის მიმოხილვა

ა. პოდობედი

ნ. ალექსანდროვის სახ. ონკოლოგიისა და სამედიცინო რადიოლოგიის რესპუბლიკური სამეცნიერო-პრაქტიკული ცენტრი, მინსკი, რესპუბლიკა ბელორუსი

მაგისტრალური ვენების ლიპომები იშვიათი სიმსივნეებია, რომელთა უმრავლესობა აღწერილია ქვედა ღრუ ვენაში და 0.5%-ში აღმოჩენილია შემთხვევით კომპიუტერული ტომოგრაფიის დროს. ბრაქიოცეფალური და ზედა ღრუ ვენის სისხლძარღვშიდა ლიპომა განსაკუთრებით იშვიათი სიმსივნეა. სამედიცინო ლიტერატურაში დღემდე მხოლოდ 16 შემთხვევაა აღწერილი.

სტატიაში მოტანილია შემთხვევის აღწერა: 53 წლის ქალმა, ანამნეზში გულმკერდის ღრუს ტრავმით, კლინი-

კას მიმართა ჩივილებით სახის და მარჯვენა ხელის შეშუპებაზე. კომპიუტერული ტომოგრაფიით გამოვლინდა ცხიმოვანი სიმკვრივის სიმსივნე მარჯვენა ღრუ ვენის სანათურში. განხორციელდა ქირურგიული ჩარევა სიმსივნის ამოკვეთით. ამოკვეთილი ახალწარმონაქმნის ჰისტოლოგიური კვლევით დადასტურდა სისხლძარღვშიდა ლიპომის დიაგნოზი.

სისხლძარღვშიდა ლიპომა შეიძლება მიმდინარეობდეს უსიმპტომოდ, ან იწვევდეს ვენური ობსტრუქციის სიმპტომებს. ქირურგიული მკურნალობა, ავთვისებიანი სიმსივნის გამორიცხვის, თრომბოემბოლიური გართულებების, ზედა ღრუ ვენის ობსტრუქციის, მარჯვენა წინაგულზე გავრცელების გამორიცხვის მიზნით, ნაჩვენებია კლინიკური სურათის არარსებობის დროსაც კი.

სისხლძარღვშიდა ლიპომა შეიძლება უსაფრთხოდ იქნეს მოცილებული ქირურგიული მეთოდით. ნაწილობრივ სტერნოტომია ლავიწზედა მიდგომასთან კომბინაციით უზრუნველყოფს გულმკერდის ღრუს მაგისტრალური ვენების საიმედო კონტროლს და იძლევა ფილტვის ემბოლიის თავიდან აცილების, ოპერაციის შემდგომი სისხლის დანაკარგის მინიმუმების და სიმსივნის მონობლოკურად მოცილების შესაძლებლობას.

## ПОСЛЕОПЕРАЦИОННАЯ КОНТРОЛИРУЕМАЯ АНАЛГЕЗИЯ У БОЛЬНЫХ С ОНКОПАТОЛОГИЕЙ ГОЛОВЫ И ШЕИ

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Эффективность обезболивания в послеоперационном периоде по сей день является серьезной проблемой в хирургии. Послеоперационная боль не всегда поддается купированию, а иногда переходит в хроническую форму [5]. От выраженного болевого синдрома в послеоперационном периоде страдают от 40 до 75% пациентов, среди них до 50% жалуются на боль средней и высокой интенсивности [5,9].

На сегодня существует множество препаратов для обезболивания, однако адекватность послеоперационной аналгезии по субъективным оценкам пациентов не превышает 50% [5,7]. Поэтому, наиболее успешное послеоперационное обезболивание может быть достигнуто методами проводникового обезболивания, непосредственно вблизи операционной раны [8]. В основе данной идеи лежат патофизиологические механизмы острого болевого синдрома. Принято считать, что вокруг послеоперационной раны развивается зона гипералгезии, т.е. область повышенной болевой чувствительности. Выделяют два вида гипералгезии: первичную и вторичную. Первичная связана с повышенной чувствительностью ноцицепторов и развивается непосредственно в зоне повреждения, т.е. в области операционного поля. Немного позже формируется вторичная гипералгезия вне зоны повреждения. Она развивается при включении центральных механизмов сенситизации ноцицептивных нейронов, которые размещены в задних рогах спинного мозга. В следующие 12-18 часов после операции происхо-

дит «разширение» зоны болевой чувствительности вокруг операционной раны и, тем самым, развивается усиление интенсивности послеоперационных болевых ощущений, примерно, ко вторым суткам после операции [9]. Поэтому, попытки блокировать острую боль вблизи раны всегда присутствуют в разных областях хирургии.

В области головы и шеи известно несколько методов, однако они не получили широкого распространения ввиду сложности методик и неохотно воспринимаются врачами, использующими обезболивающие препараты.

Так, известный метод блокады нижнечелюстного нерва Г. Брауна (1905), где точка укола лежит под серединой скуловой дуги, игла продвигается в косом направлении к крыловидному отростку клиновидной кости. После чего отмечается глубина продвижения иглы, дальше выдвигается до подкожной клетчатки и возвращается под небольшим углом кзади и вводится на отмеченную глубину [12]. Недостатком является неточность места укола и сложность манипуляции, а также однократность введения анестетика.

Позже, Ж. Берше (1922) предложил блокировать двигательные ветви нижнечелюстного нерва при рефлекторной контрактуре жевательной мышцы со стороны вырезки нижней челюсти. В. М. Уваров (1929), применяя элементы обезболивания по Берше, сочетая ее с методикой Г. Брауна, предложил погружать иглу на глубину 4-4,5 см, что позволяло осуществление блокады нижнечелюстного нерва [1].



Известно, что методы обезболивания точки вкола по середине скуловой дуги (Г. Браун, 1909) и по середине трагоорбитальной линии (С.Н.Вайсблат, 1961) не являются точными [2] и не обеспечивают длительного послеоперационного обезбоживания.

Известен также способ М.Д. Дубова и В.А. Дунаевского [3], который предусматривает комбинированное проведение блокады нижнечелюстного нерва у овального отверстия основания черепа (подскуловой путь) и инфильтрационной анестезии в поднижнечелюстной области с подведением анестетика к заднему краю грудино-ключично-сосцевидной мышцы для выключения поверхностных ветвей шейного сплетения. Недостатком данной методики является, что блокировка анестетиком языкоглоточного нерва не производится и обезбоживание рассчитано только для проведения оперативного вмешательства, без учета послеоперационного периода.

Столяренко П.Ю. предложил метод длительной проводниковой блокады ветвей тройничного нерва подскуловым методом [13]. Метод используется для послеоперационного обезбоживания ветвей тройничного нерва и используется методика по Берше-Дубову, где за основу взята метрическая методика определения данной точки, не учитывающая индивидуальных анатомических особенностей пациентов. Недостатком также является то, что не производится блокировка анестетиком языкоглоточного нерва и анастомозов шейного нервного сплетения с ветвями лицевого и тройничного нервов для полного обезбоживания нижней трети лица.

Существует несколько способов обезбоживания – это предупредительная, сбалансированная аналгезия и контролируемая пациентом. Контролируемая пациентом аналгезия дает возможность больному получать обезбоживание по требованию. Соответственно можно определить дозы медикаментов в зависимости от реальной потребности пациента, руководясь субъективными восприятиями болевых ощущений [3].

Целью исследования явилось создание оптимального комплекса проводниковой послеоперационной обезбоживания с учетом патофизиологии острой боли и особенностей послеоперационных дефектов у пациентов с патологией челюстно-лицевой области.

**Материал и методы.** На базе отделения опухолей головы и шеи Подольского Регионального центра онкологии у 14 больных с диагнозом - рак боковой поверхности языка, корня языка, передней небной дужки, слизистой дна полости рта, альвеолярного отростка использована предложенная нами методика длительного проводниковой обезбоживания в послеоперационном периоде у 4 женщин и 10 мужчин. Средний возраст пациентов составил  $45,94 \pm 1,74$  года.

Разработанная нами методика длительного послеоперационного проводниковой обезбоживания включала в себя блокады: центральная анестезия п. mandibularis, ангилярный языкоглоточного нерва и шейного сплетения (пат. Украины № 143135).

В качестве контроля обезбоживания использовали визуально-аналоговую шкалу (ВАШ). ВАШ имеет 7 видов интенсивности боли и 10 баллов: 0 - нет боли; 1 - едва заметная боль; 2-3 - слабая; 4-5 - умеренная; 6-7 - сильная; 8-9 - очень сильная; 10 - невыносимая боль. Наблюдали за особенностями клиники затрудненного приема пищи и возможностями питания, что включало степень ксеростомии

(сухость полости рта), сложность глотка (баллы), объем глотка, консистенция еды и эмоции во время еды.

Определяли степень ксеростомии, в которой выделяют три степени: первая (легкая), при которой сохранена функция подчелюстной и околоушной слюнной железы, поэтому слюна поступает в нормальном количестве. При осмотре полости рта слюна слегка пенистая, а сама слизистая оболочка влажная. При второй (умеренной) степени слюнные железы работают частично, сухость в полости рта постоянная, речь затруднена. Прием сухой пищи становится невозможным, ее приходится все время запивать водой. Слизистая оболочка слабо увлажнена и имеет бледно-розовый цвет, что хорошо видно при осмотре. И третья степень (тяжелая), при которой пациенты ощущают сильную сухость в полости рта и днем, и ночью, присутствует боль во время разговора и приема пищи. Слизистая оболочка сухая и бледная, иногда с очагами поражения [11].

Сложность глотка оценивали по предложенной нами шкале в баллах, где 0 - свободное проглатывание, 1- проглатывание с усилием, 2 – проглатывание с поперхиванием, 3 – невозможность проглотить. Оценивали также возможность объема глотка от 5 мл до 15 мл и эмоции, которые возникали у пациента во время проглатывания (без напряжения, незначительное напряжение, сильное напряжение).

В динамике определяли консистенцию еды, которую пациент употреблял на протяжении лечения.

**Результаты и обсуждение.** Для блокады нижнечелюстного нерва нами модифицирована точка укола при центральной анестезии у овального отверстия. Во время наркоза под скуловой дугой в проекции *incisurae mandibulae* пальпируется задний край поверхностного слоя *m. masseter*, а дальше будто соскальзывая с него попадаем в ямку, дном которой является глубокий слой этой мышцы. При определении данного участка и легком нажатии на нее пальцем ощущается небольшое углубление, которое находится под скуловым отростком височной кости, т.е. «подвисочное». Точкой укола является наиболее глубокая часть (дно) в центре углубления (рис. 1).



Рис. 1. Определение углубления под скуловой дугой

Свободное прохождение иглы по указанным ориентирам, на наш взгляд, следует объяснить небольшой толщиной мышечно-сухожильного слоя в данной области, которая проецируется на нижнечелюстной вырезке. Вкол иглы производится перпендикулярно к поверхности кожи, а кончик иглы направлен непосредственно к овальному отверстию, не требующего дополнительных изменений направления иглы. На глубине 4,0-4,5 см устанавливаем катетер (рис. 2).



Рис. 2. Подскуловой путь введения катетера к овальной отверстию

Далее проводим обезболивание языкоглоточного нерва, где точка укола находится на расстоянии 2-2,5см книзу от угла нижней челюсти. Иглу продвигаем в направлении нижнелатерального угла глазницы и направляем под углом 45° к ветви нижней челюсти (рис. 3) продвигая к корню языка на глубину 4,0-4,5см, где устанавливаем катетер (рис. 4).

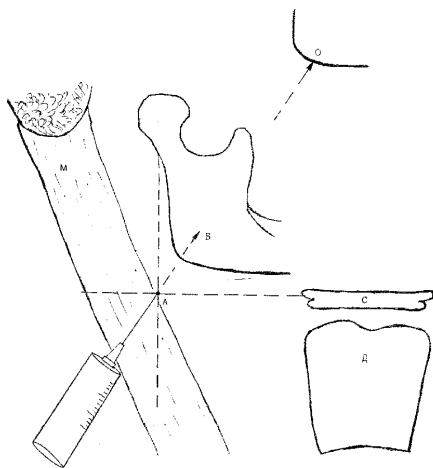


Рис.3. Точка укола и направление при ангулярной анестезии языкоглоточного нерва



Рис. 4. Ангулярный метод блокады языкоглоточного нерва

Учитывая данные литературы и клинический опыт, нами усовершенствован способ блокады поверхностного шейного сплетения. При этом следует иметь в виду, что n. transversus colli проходит под m. platysma, поэтому при выполнении инъекции необходимо в этом месте кожу и фасцию взять в складку. Точка вкола для блокады и катетризации шейного сплетения может быть определена двумя способами: первый ориентирован на пересечение наружной яремной вены с задним краем грудино-ключично-сосцевидной мышцы (рис. 5). Для визуализации наружной яремной вены необходимо задержать дыхание. При невыраженности наружной яремной вены необходимо определить точку вкола по месту пересечения линии проведенной от угла нижней челюсти до середины ключицы и задним краем грудино-ключично-сосцевидной мышцы, где и устанавливается катетер (рис. 6).



Рис. 5. Определение точки укола при блокаде поверхностного шейного сплетения. Кончик пальца указывает на место пересечения наружной яремной вены и заднего края грудино-ключично-сосцевидной мышцы



Рис. 6. Подведение катетера к поверхностному шейному сплетению

Во всех трех целевых пунктах устанавливали тонкий пластиковый катетер (G18, G20) через который вводили 1-2 мл анестетика. Использование методики длительного послеоперационного проводникового обезболивания у оперированных больных приводит к обезболиванию в среднем через 15-20 мин.

Адекватность обезболивания оценивали: в послеоперационном периоде до первого приема пищи (до первых признаков появления боли), после блокад, во время перевязки операционной раны и при приеме пищи по визуально-аналоговой шкале (ВАШ). Это измерение пациент проводил самостоятельно и под контролем врача.

До введения местного анестетика интенсивность боли составляла  $7,07 \pm 0,83$  баллов, после введения, спустя 20 минут –  $0,28 \pm 0,46$ . Признаки анальгезии сохранялись  $152,86 \pm 24,94$

мин, т.е. около 3 часов. В это время пациент производил прием пищи, параллельно, оценивалась сложность глотка до блокады и после нее -  $1,71 \pm 0,82$  баллов было до,  $0,28 \pm 0,46$  - после глотка. Объем глотка в динамике также увеличивался с 5 мл до 15-20 мл свободного прохождения. После анестезии у пациентов, которые отмечали сильное напряжение во время еды, эмоции менялись от легкого напряжения до полного отсутствия напряжения.

Проводили также комплекс проводникового послеоперационного обезбоживания перед перевязками в результате чего, во время манипуляций пациенты отмечали отсутствие боли (0 баллов по ВАШ).

Степень ксеростомии определяли во время госпитализации (до лечения) и спустя на первый, третий, пятый, седьмой и десятый дни после лечения. До лечения 6 пациентов составили группу со второй степенью ксеростомии, на первый и третий день после операции у пациентов отмечалась ксеростомия третьей степени, нормальная саливация была у одного пациента и то только в первые сутки. На пятые сутки после операции основную группу составили пациенты со второй степенью, а на седьмой день увеличилась группа с первой степенью ксеростомии. На десятый день отмечается положительная динамика – пациенты с третьей степенью ксеростомии не выявлены, со второй степенью – 3, с первой – 7, у четырех пациентов полностью отсутствуют признаки ксеростомии (рис. 7).

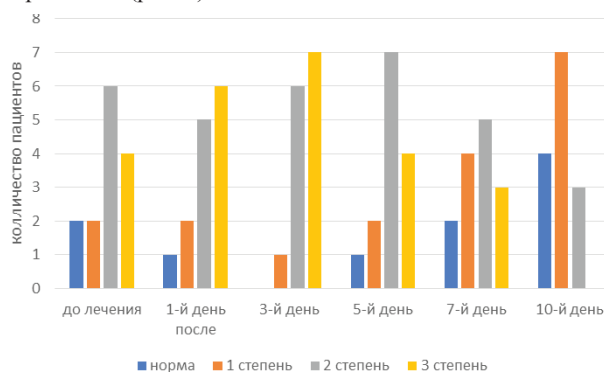


Рис. 7. Динамика выраженности ксеростомии у пациентов

Данная методика обезбоживания позволяет безболезненно и в полном объеме проводить перевязки и значительно улучшает возможность глотания, даже при наличии зонда. Положительно влияет на состояние увлажненности полости рта и общее состояние пациента, что весьма значимо для положительной реабилитации.

Эффект полного обезбоживания разработанной нами методики, прежде всего, связан с дополнительной блокадой языкоглоточного нерва и ветвей шейного сплетения. По всей вероятности, происходит обезбоживание анастомозов данных нервов с ветвями блуждающего и подъязычного. Таким образом, проводниковое обезбоживание способствует осуществлению блокады нервно-мышечных блоков сформированных из тканей I-II жаберных дуг, которые являются двумя первыми этапами формирования пищевого комка в полости рта и продвижения его в ротоглотку. Этот этап приема пищи у онкопациентов является наиболее сложным и болезненным. Разработанный нами метод эффективно решает эту проблему.

#### Выводы:

1. Разработанная система проводниковых блокад позволяет обезболить нейромышечный комплекс рта и ротоглотки,

тем самым блокировать зону первичной гипералгезии и предупредить развитие вторичной зоны.

2. Методика длительного послеоперационного проводникового обезбоживания значительно улучшает обезбоживание послеоперационных дефектов на протяжении  $152,86 \pm 24,94$  мин. и обеспечивает безболезненное глотание (0 баллов по ВАШ).

3. Применение данной методики послеоперационного обезбоживания позволило значительно снизить проявления ксеростомии на 7-й день, сократить заживление ран на 3-4 дня и ускорить восстановление общего состояния пациента.

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#### SUMMARY

#### POSTOPERATIVE CONTROLLED ANALGESIA IN PATIENTS WITH HEAD AND NECK CANCER

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Acute postoperative pain is still an urgent problem in surgery. Today there are many drugs for pain relief, but at the same time, the adequacy of postoperative analgesia for the subjective as-

assessments of patients does not exceed 50%. Therefore, taking into account the pathophysiology of acute pain syndrome, it is necessary to inject an anesthetic directly near the operating field, which can be achieved by long-term conduction anesthesia. So, in the area of the head and neck, there are several techniques (G. Brown, J. Bershet, V. M. Uvarov, J. S. Vaisblat, V. A. Dubov and V. D. Dunaevsky, P. Yu. Stolyarenko), but all of them have a metric definition of the point at the near and do not take into account the individual anatomical characteristics of patients, as well as anastomoses of the nerves.

Therefore, the goal of our work was to create an optimal complex of conductive postoperative pain relief taking into account the pathophysiology of acute pain and the characteristics of postoperative defects in patients with pathology of the maxillofacial region.

We have proposed a combination of three blockades: central anesthesia at the foramen ovale, angular glossopharyngeal nerve block and superficial cervical plexus block with prolonged catheterization. This technique of anesthesia allows you to carry out dressings painlessly and in full. It also significantly improves the ability to swallow, even with a probe. It has a positive effect on the state of moisture in the oral cavity.

**Keywords:** conduction postoperative anesthesia, pain, swallowing.

## РЕЗЮМЕ

### ПОСЛЕОПЕРАЦИОННАЯ КОНТРОЛИРУЕМАЯ АНАЛГЕЗИЯ У БОЛЬНЫХ С ОНКОПАТОЛОГИЕЙ ГОЛОВЫ И ШЕИ

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Острая послеоперационная боль по сей день является актуальной проблемой в хирургии. Существует множество препаратов для обезболивания, однако адекватность послеоперационной анальгезии по субъективным оценкам пациентов не превышает 50%. Учитывая патофизиологию острого болевого синдрома необходимо вводить анестетик непосредственно вблизи операционного поля, что достигается длительным проводниковым обезболиванием. Так, в области головы и шеи существует несколько методик обезбоживания (Г. Браун, Ж. Берше, В.М. Уваров, Й.С. Вайсблат, В.А. Дубов и В.Д. Дунаевский, П.Ю.Столяренко), все они имеют метрическое определение точки вкола и не учитывают индивидуальные анатомических особенностей пациентов и анастомозов нервов.

Исходя из вышеизложенного, целью исследования явилось создание оптимального комплекса проводникового послеоперационного обезбоживания с учетом патофизиологии острой боли и особенностей послеоперационных дефектов у пациентов с патологией челюстно-лицевой области.

Авторами предложена комбинация трех блокад: центральная анестезия у овального отверстия, ангулярная блокада языкоглоточного нерва и блокада поверхностно-го шейного сплетения с длительной катетеризацией.

Данная методика обезбоживания позволяет безболезненно и в полном объеме проводить перевязки, значительно улучшает возможность глотания даже при наличии зонда. Положительно влияет на состояние увлажненности полости рта.

## რეზიუმე

ოპერაციის შემდგომი კონტროლირებადი ანალგეზია თავისა და კისრის კიბოთი დაავადებულ პაციენტებში

ა.კუშტა, ს.შუვალოვი

ვინიცის ნ.პიროგოვის სახ. ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

მწვავე პოსტოპერაციული ტკივილი სადღეისოდ წარმოადგენს გადაუდებელ პრობლემას. ტკივილის შესამსუბუქებლად არსებობს მრავალი პრეპარატი, მიუხედავად ამისა, პოსტოპერაციული ანალგეზიის ადეკვატურობა პაციენტების სუბიექტური შეფასებით არ აღემატება 50%-ს.

მწვავე ტკივილის სინდრომის პათოფიზიოლოგიის გათვალისწინებით აუცილებელია საანესთეზიო ინექცია განხორციელდეს უშუალოდ ოპერაციულ ველთან, რის მიღწევაც შესაძლებელია ხანგრძლივი გამტარი ანესთეზიით. თავისა და კისრის მიდამოში არსებობს ანესთეზიის რამოდენიმე მეთოდიკა (გ. ბრაუნი, ჯ. ბერშეტი, ვ.უვაროვი, ვ.ვაისბლათი, ვ.დუბოვი და ვ.დუნაევსკი, პ.სტოლიარენკო), მათ ყველას გააჩნია ახლომდებარე წერტილის მეტრული განსაზღვრა და არ ითვალისწინებენ პაციენტების ინდივიდუალურ ანატომიურ მახასიათებლებს, ისევე როგორც ნერვების ანასტომოზებს.

კვლევის მიზანს წარმოადგენა გამტარ პოსტოპერაციული ანალგეზიის ოპტიმალური კომპლექსის შექმნა მწვავე ტკივილის პათოფიზიოლოგიისა და ოპერაციის შემდგომი დეფექტების მახასიათებლების გათვალისწინებით პაციენტებში ყბა-სახის რეგიონის პათოლოგიით.

ავტორების მიერ შემოთავაზებულია სამი ბლოკადის კომბინაცია: ცენტრალური ანესთეზია ოვალურ ხერხელთან, გლოსოფარინგეალური ნერვის ანგულარული ბლოკადა და ყელის ზედაპირული წნულის ბლოკადა ხანგრძლივი კათეტერიზაციით.

ანესთეზიის ზემოაღნიშნული მეთოდიკა საშუალებას იძლევა უმტკივნეულოდ ჩატარდეს შეხვევები, მნიშვნელოვნად აუმჯობესებს ყლაპვის უნარს, თუნდაც ზონდით და დადებითად მოქმედებს პირის ღრუს ტენიანობის მდგომარეობაზე.

## FEATURES OF ANTHROPOMETRIC PARAMETERS IN WOMEN OF DIFFERENT MORPHOTYPES WITH POLYCYSTIC OVARY SYNDROME

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Currently, reproductive life is associated with psycho-emotional and social conditions of women, which is reflected in the functional capacity of the female genitals and homeostasis in general and, thus, affects both the medical and social aspects of later life [1,2,3,6,7,10].

According to the literature, it is known that the harmonious development of the organism is influenced by its constitutional features, namely: anthropological parameters, physical development that contribute to human adaptation to changing living conditions in the environment. Given the constant change in the size of the human body and the possible impact of this factor on the function of internal organs, namely the reproductive sphere, requires the need for further study of this problem [5,8,9,12].

The pathogenesis of polycystic ovarian syndrome, as well as its clinical manifestations are being studied by many gynecological schools today. However, to some extent there is a problem in the correct diagnosis, because this pathology is associated with a problem not only in the proper functioning of the ovaries, but also the adrenal glands, hypothalamus and pituitary gland. Therefore, the possibility of not always adequate diagnosis of polycystic ovarian syndrome is associated with the fact that there is still no unanimity of scientists in determining the pathogenetic aspects of this problem [4,11].

Additional methods of examination, namely ultrasound, help in the diagnosis of polycystic ovarian syndrome. Quite often we observe another structure of the ovaries - multifollicular structure of the ovaries, which can be formally attributed to a variety of polycystic ovaries. However, these are different concepts, not the same in origin or in the impact on the health and reproductive function of women.

Therefore, it is very important today to correctly predict and create quality treatment schemes for this problem, which in the future will allow such patients to give birth to healthy offspring.

Thus, the aim of our study was to assess the body size of patients with polycystic ovary syndrome, to study their somatotypes and component composition of body weight.

**Material and methods.** 105 women aged 20 to 36 years of different morphotypes were selected for the study. These patients were interviewed according to a specially designed questionnaire and divided into groups: 50 women with multifol-

licular ovarian structure and 25 - women with polycystic ovary structure. The comparison group consisted of 30 women without disturbances of ovarian structure (healthy women).

In our work, we used a mathematical scheme of somatotyping according to Heath-Carter, which included the determination of ectomorphic, mesomorphic and endomorphic components of the somatotype.

J. Matiegka's formulas were used to determine the component composition of body weight.

The absolute amount of muscle tissue was determined according to the recommendations of the American Institute of Nutrition (ANI).

Variational-statistical processing of research results was performed using the program "Statistica 6.0" with the definition of the main variational indicators. The reliability of the results was determined using the Student's t test.

**Results and discussion.** When assessing the growth, weight, body surface area and Kettle II index in women of the study group, it was found that in patients with multifollicular (MFO) and polycystic ovarian structure (PCOS) the values of these indicators are significantly higher compared to those without polycystic ovarian structure ( $p < 0.05$ ), Table 1.

In patients with PCOS, it was found that body weight in this group was significantly higher than in the studied women with MFO ( $p < 0.001$ ). However, a significant difference in body weight in women with MFO and in healthy patients ( $p > 0.05$ ) was not detected (Table 1).

The body surface area of women with PCOS was significantly larger than in patients of the comparison group and the control group. It was also noted that patients with multifollicular structure of the ovaries had a significant increase in body area compared to healthy women ( $p < 0.05$ ), Table 1.

The mass growth rate was significantly higher in patients with polycystic ovarian structure compared to patients diagnosed with multifollicular ovarian structure, as well as patients in the control group ( $p < 0.001$ ), Table 1.

It was also noted that in patients with polycystic ovaries shoulder girth at rest and in a tense state was greater than in patients with multifollicular structure of the ovaries and, accordingly, the control group ( $p < 0.001$ ,  $p < 0.05$ ), Table 2.

Table 1. Indicators of length, weight, body surface area and Kettle II index in healthy women and women with MFO and PCOS ( $M \pm \sigma$ )

Indicator	Healthy women	MFO	PCOS	$P_{1-2}$	$P_{1-3}$	$P_{2-3}$
Weight (kg)	57,47±7,61	54,55±9,51	63,82±5,76	>0,05	<0,001	<0,001
Body length (sm)	165,2±5,6	162,1±7,2	161,6±8,2	<0,05	<0,05	>0,05
Body surface area (m <sup>2</sup> )	1,627±0,112	1,567±0,131	1,679±0,082	<0,05	<0,05	<0,01
Kettle II index	21,07±2,64	20,87±4,02	24,69±3,73	>0,05	<0,001	<0,00

notes: here and hereafter:  $p_{1-2}$  - the reliability of the differences between healthy and sick MFO women;

$p_{1-3}$  - the reliability of the differences between healthy and patients with PCOS women;

$p_{2-3}$  - the significance of differences between women with MFO and PCOS women.

MFO - women with multifollicular structure of the ovaries; PCOS - women with polycystic ovaries; H - healthy women

Table 2. Coverage of body size in healthy women and women with MFO and PCOS (M±σ)

Indicator	Healthy women	MFO	PCOS	P <sub>1-2</sub>	P <sub>1-3</sub>	P <sub>2-3</sub>
Shoulder in a tense state (sm)	26,13±2,87	24,08±1,62	25,05±1,45	<0,001	>0,05	<0,05
Shoulder at rest (sm)	27,48±2,82	23,09±1,69	24,07±1,32	<0,001	<0,001	<0,05
Forearms in the upper third (sm)	23,49±1,88	22,34±1,56	23,89±0,97	<0,001	>0,05	<0,001
Femur (sm)	53,02±4,37	47,79±3,70	49,57±5,88	<0,001	<0,01	<0,01
Shins in the upper third (sm)	34,76±2,68	31,97±1,94	33,23±2,00	<0,001	<0,01	<0,05
Chest at rest (sm)	85,31±6,06	85,16±6,74	89,77±3,22	>0,05	<0,001	<0,05

Table 3. Body diameters in healthy women and women with MFO and PCOS (M±σ)

Indicator	Healthy women	MFO	PCOS	P <sub>1-2</sub>	P <sub>1-3</sub>	P <sub>2-3</sub>
Transverse middle chest (sm)	25,04±1,64	23,46±1,98	24,39±1,90	<0,001	<0,05	>0,05
Transverse lower chest. (sm)	21,64±2,02	22,58±1,76	23,80±2,16	<0,01	<0,001	<0,05
Sagittal size of chest(sm)	17,31±1,61	19,69±1,61	21,17±2,12	<0,001	<0,001	<0,05

Table 4. The thickness of skin and fat folds in healthy women and women with MFO and PCOS (M±σ)

Indicator	Healthy women	MFO	PCOS	P <sub>1-2</sub>	P <sub>1-3</sub>	P <sub>2-3</sub>
On the back of the shoulder (mm)	7,468±3,012	5,018±0,918	5,568±0,785	<0,001	<0,01	<0,05
On the front surface of the shoulder (mm)	5,418±2,160	3,965±0,793	4,605±0,802	<0,001	>0,05	<0,05
On the forearm (mm)	3,654±1,850	3,192±0,634	3,800±0,652	>0,05	>0,05	<0,05
Under the shoulder blade (mm)	12,01±3,97	7,402±1,517	8,827±1,468	<0,001	<0,001	<0,001
On the chest (mm)	4,557±1,322	4,498±1,282	5,786±1,429	>0,05	<0,01	<0,001
On the abdomen (mm)	13,63±5,59	9,690±2,631	11,23±1,54	<0,001	≥0,05	<0,01
On the side (mm)	11,85±4,91	9,857±2,872	12,45±1,95	<0,05	>0,05	<0,001
On the femur (mm)	14,43±4,40	12,80±2,05	13,50±1,47	<0,05	>0,05	>0,05
On the shin (mm)	10,48±3,03	10,08±1,55	11,36±1,47	>0,05	>0,05	<0,01

It was also noted that the circumference of the anterior surface of the forearm was significantly reduced in patients with MFO compared with women with polycystic ovarian structure and the control group (p<0.001), Table 2.

The hip circumference in patients with polycystic ovaries significantly increased, which differs significantly from the hip girth in the group with multifollicular structure of the ovaries and the control group (p<0.001, p<0.01), Table 2.

Measuring the shin circumference in the upper third, we found that this value varies in all groups of subjects, and is the lowest in the group with multifollicular structure of the ovaries (p<0.001, p<0.05), Table 2.

Chest girth was statistically increased in women with polycystic ovarian structure compared with data from the group of healthy patients (p<0.001). And in patients with multifollicular ovarian structure, the assessment of the above indicator was statistically lower in contrast to patients with polycystic ovary structure (p<0.05), Table 2.

Regarding the examination of chest measurements, no significant changes in diameter, mid-sternum size, lower sternum size, transverse and sagittal measurements were found in patients of the studied groups. However, it was found that in the control group all the above indicators were significantly higher in contrast to patients with polycystic and multifollicular ovarian structure (p<0.001 and p<0.05, respectively), Table 3.

Patients in the study groups were also assessed for the thickness of skin and fat folds.

It was noted that in patients with polycystic ovary structure

the thickness of the fat fold on the posterior surface of the shoulder varied more than in women with multifollicular ovarian structure and patients of the control group (p<0.05), Table 4.

When measuring the thickness of the fat fold on the anterior surface of the shoulder, it was noted that there is a significant difference with women from the control group (p<0.001), and with patients with polycystosis (p<0.05), Table 4.

It was also noted that the thickness of the fat fold on the forearm in patients with multifollicular structure of the ovaries is significantly statistically lower than in the group of patients with polycystic ovaries (p<0.05), Table 4.

The thickness of the fat fold under the shoulder blade in all groups varies significantly (p<0.001) and is lowest in women with MFO. The same can be noted about the thickness of the fat fold on the leg (Table 4).

It was also found that the thickness of the fat fold on the breast in patients with polycystic ovarian structure is statistically significantly greater than in patients of the control group and patients with multifollicular ovarian structure (p<0.001, p<0.01), respectively (Table 4).

Regarding the thickness of the fat fold on the side, it was noted that in the group of patients with multifollicular ovarian structure it is the lowest in contrast to the group of patients with polycystic ovarian structure and the control group (p<0.001, p<0.05), Table 4.

The size of the shoulder was also assessed in all groups of patients. It was found that the width of the shoulder in patients with multifollicular structure of the ovaries is the lowest in the study group of patients with polycystic ovaries (p<0.01), Table 5.

Table 5. Indicators of the width of the distal pineal gland in healthy women and women with MFO and PCOS (M±σ)

Indicator	Healthy women	MFO	PCOS	P <sub>1-2</sub>	P <sub>1-3</sub>	P <sub>2-3</sub>
Shoulder (sm)	5,951±0,362	6,137±0,357	6,400±0,279	<0,01	<0,001	<0,01
Forearm (sm)	4,930±0,288	5,316±0,462	5,655±0,365	<0,001	<0,001	<0,01
Femur (sm)	8,132±0,537	7,861±0,614	8,105±0,487	<0,05	>0,05	=0,0571
Shins (sm)	6,481±0,465	6,563±0,412	6,777±0,366	>0,05	<0,01	<0,05

Table 6. Indicators of somatotype and component composition of body weight in healthy women and women with MFO and PCOS (M±σ)

Indicator	Healthy women	MFO	PCOS	P <sub>1-2</sub>	P <sub>1-3</sub>	P <sub>2-3</sub>
Endomorphic (points)	3,151±1,112	2,155±0,562	2,708±0,379	<0,001	<0,05	<0,001
Mesomorphic (points)	3,617±1,313	2,896±1,346	3,752±1,662	<0,01	>0,05	<0,05
Ectomorphic (points)	2,893±1,287	3,039±2,124	1,513±1,611	>0,05	<0,001	<0,01
Mateiko's muscle mass (kg)	27,28±4,09	22,42±3,06	23,91±2,23	<0,001	<0,001	<0,05
Bone mass according to Mateiko (kg)	10,20±3,33	8,150±1,034	8,811±0,668	<0,001	<0,05	<0,01
Fat mass according to Mateiko (kg)	8,171±1,139	7,594±1,746	9,142±1,202	<0,05	<0,001	<0,001
Muscle mass according to ANI (kg)	25,59±5,27	20,01±2,95	21,49±2,29	<0,001	<0,001	<0,05

Analyzing the measurement data of the width of the distal epiphysis of the forearm, we found that all patients in the three groups had a significant statistical difference (p<0.001), Table 5.

Regarding the measurement of the width of the distal epiphysis of the tibia in patients with polycystic ovarian structure, this figure is significantly higher than in patients with multifollicular ovarian structure, as well as the control group (p<0,01), Table 5.

Therefore, with the help of all measured body parameters, the somatotype and component composition of body weight of each patient of all study groups were calculated.

We found that patients with polycystic ovarian structure were dominated by the endomorphic Heath-Carter component in contrast to women with multifollicular ovarian structure (p<0.001), Table 6.

As for the ectomorphic component, it prevailed in patients with multifollicular structure of the ovaries in contrast to women with polycystic ovaries (p<0,01), Table 6.

Mateiko's muscle mass was statistically higher in women of the control group in contrast to the groups of women with multifollicular and polycystic ovary structure (p<0.001), Table 6.

We found that Mateiko's bone mass was lowest in patients with multifollicular ovarian structure compared with patients with polycystic ovarian structure (p<0.01), but Mateiko's fat mass was higher in patients with polycystic ovary syndrome (p<0.001), Table 6.

**Conclusions and perspectives of further developments.** Therefore, we proved that in patients with polycystic ovary structure, a mesomorphic component (54,0%; p<0.05), endomesomorphic component (9,1%; p<0.05) and indeterminate components were isolated and predominant (4,5%, p<0.05), and in patients with multifollicular structure of the ovaries is dominated by ectomorphic component (36,7%; p<0.05), ectomesomorphic component (8,2%; p<0.05).

It has been shown that the measurement of constitutional body parameters in women with anovulatory menstrual disorders is important and significant and this allowed to build discriminant models to determine the multifollicular and polycystic ovary structure.

Based on the results of research and constructed discriminant models, a computer program for predicting the multifollicular and polycystic ovarian structure was developed, which will further allow to develop optimal schemes for the correction of these conditions.

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## SUMMARY

### FEATURES OF ANTHROPOMETRIC PARAMETERS IN WOMEN OF DIFFERENT MORPHOTYPES WITH POLYCYSTIC OVARY SYNDROME

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The aim - to assess the body size of patients with polycystic ovary syndrome to study their somatotypes and component composition of body weight.

To solve the goals and objectives, were prospectively examined 105 women aged 20 to 36 years of different morphotypes. These patients were interviewed according to a specially designed questionnaire and divided into groups: 50 women with multifollicular ovarian structure and 25 - women with polycystic ovary structure. The comparison group consisted of 30 women without disturbances of ovarian structure (healthy women).

The body surface area of women with PCOS was significantly larger than in patients of the comparison group and the control group. It was also noted that patients with multifollicular structure of the ovaries had a significant increase in body area from healthy women ( $p < 0,05$ ).

The mass-growth rate was significantly higher in patients with polycystic ovary structure compared to patients diagnosed with multifollicular ovarian structure and patients in the control group ( $p < 0.001$ ).

It was also noted that in patients with polycystic ovary shoulder girth at rest and in a tense state was greater than in patients with multifollicular structure of the ovaries and, accordingly, the control group ( $p < 0,001$ ,  $p < 0,05$ ).

Regarding the examination of chest measurements, no significant changes in diameter, mid-sternum size, lower sternum size, transverse and sagittal measurements were found in patients of the studied groups. However, it was found that in the control group all the above indicators were significantly higher in contrast to patients with polycystic and multifollicular ovarian structure ( $p < 0.001$  and  $p < 0.05$ , respectively). Mateiko's muscle mass was statistically higher in women of the control group in contrast to the groups of women with multifollicular and polycystic ovary structure ( $p < 0.001$ ).

We found that Mateiko's bone mass was lowest in patients with multifollicular ovarian structure compared with patients with polycystic ovary structure ( $p < 0.01$ ), while Mateiko's fat mass was higher in patients with polycystic ovary disease ( $p < 0.001$ ).

Therefore, we proved that in patients with polycystic ovary structure isolated and predominant mesomorphic component (54.0%;  $p < 0.05$ ), endomesomorphic (9.1%;  $p < 0.05$ ) and indeterminate components 4.5%,  $p < 0.05$ ), and in patients with multifollicular structure of the ovaries is dominated by ectomorphic component (36.7%;  $p < 0.05$ ), ectomesomorphic component (8.2%;  $p < 0.05$ ).

**Keywords:** morphotype, polycystic ovarian structure, multifollicular ovarian structure, anthropometric measurements.

## РЕЗЮМЕ

### ОСОБЕННОСТИ АНТРОПОМЕТРИЧЕСКИХ ПАРАМЕТРОВ У ЖЕНЩИН РАЗНЫХ МОРФОТИПОВ С СИНДРОМОМ ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ

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Известно, что на гармоничное развитие организма влияют его конституциональные особенности, в частности антропологические параметры, физическое развитие, способствующие адаптации к изменяющимся условиям жизни в окружающей среде. Постоянное изменение размеров тела и возможное влияние этого фактора на функцию внутренних органов, а именно репродуктивной сферы, ставит перед необходимостью дальнейшего изучения данной проблемы.

Обследовано 105 женщин в возрасте от 20 до 36 лет разных морфотипов. Пациенты опрошены по специально разработанной анкете и разделены на группы: 50 женщин с мультифолликулярной структурой яичников, 25 - женщины с поликистозной структурой яичников. Группу сравнения составили 30 женщин без нарушения структуры яичников (здоровые женщины).

В исследовании использована математическая схема соматотипирования по Хит-Картеру, которая включала определение эктоморфного, мезоморфного и эндоморфного компонентов соматотипа. Для определения компонентного состава массы тела использовались формулы Матейко. Аб-

солютную массу мышечной ткани определяли согласно рекомендациям Американского института питания.

Площадь поверхности тела женщин с синдромом поликистозных яичников была значительно больше, чем у пациенток группы сравнения и контрольной группы. Отмечено, что у пациенток с мультифолликулярной структурой яичников наблюдалось достоверное увеличение площади тела в сравнении со здоровыми женщинами ( $p < 0,05$ ).

Скорость роста массы тела была значительно выше у пациенток с поликистозным строением яичников в сравнении с пациентками с диагнозом мультифолликулярная структура яичников и женщинами контрольной группы ( $p < 0,001$ ).

Выявлено, что у пациенток с поликистозом яичников хват плеча в покое и в напряженном состоянии был больше, чем у пациенток с мультифолликулярной структурой яичников и, соответственно, контрольной группы ( $p < 0,001$ ,  $p < 0,05$ ).

Что касается исследования размеров грудной клетки, то у пациентов исследуемых групп существенных изменений диаметра, среднего размера грудины, размера нижней ее ча-



сти, поперечных и сагиттальных размеров не обнаружено. Однако в контрольной группе все вышеперечисленные показатели достоверно были выше в отличие от пациенток с поликистозным и мультифолликулярным строением яичников ( $p < 0,001$  и  $p < 0,05$ , соответственно). Мышечная масса по Матейко была статистически выше у женщин контрольной группы в сравнении с группами женщин с мультифолликулярным и поликистозным строением яичников ( $p < 0,001$ ).

Обнаружено, что костная масса по Матейко самой низкой была у пациентов с мультифолликулярной структурой яичников в сравнении с пациентами с поликистозной структурой яичников ( $p < 0,01$ ), в то время как жировая масса по Матейко была выше у пациентов с поликистозом яичников ( $p < 0,001$ ).

Таким образом, доказано, что у пациенток с поликистозным строением яичников отмечались изолированный и преобладающий мезоморфный компоненты (54,0%;  $p < 0,05$ ), эндомезоморфный (9,1%;  $p < 0,05$ ) и неопределенный компоненты (4,5%,  $p < 0,05$ ), а у пациенток с мультифолликулярной структурой яичников преобладает эктоморфный (36,7%;  $p < 0,05$ ) и эктомезоморфный (8,2%;  $p < 0,05$ ) компоненты.

## რეზიუმე

საკვერცხეების პოლიკისტოზის სინდრომით სხვადასხვა მორფოტიპის ქალების ანთროპომეტრიული პარამეტრების თავისებურებები

ე.მალინინა, გ.ჩაიკა, ო.ტარანი

ვინიცას ნ.პიროგოვის სახ. ეროვნული სამედიცინო უნივერსიტეტი, მეანობისა და გინეკოლოგიის №1 კათედრა, უკრაინა

ცნობილია, რომ ორგანიზმის ჰარმონიულ განვითარებაზე მოქმედებს მისი კონსტიტუციური თავისებურებანი, კერძოდ, ანთროპოლოგიური პარამეტრები, ფიზიკური განვითარება, რაც ხელს უწყობს ადაპტაციას გარემოს ცვლადი პირობების მიმართ. სხეულის ზომების მუდმივი ცვლა და ამ ფაქტორის შესაძლო მოქმედება შინაგან ორგანოებზე, სახელდობრ რეპროდუქციულ სფეროზე, განსაზღვრავს ამ პრობლემის შემდგომი კვლევის აუცილებლობას.

გამოკვლეულია 20-36 წლის ასაკის სხვადასხვა მორფოტიპის 105 ქალი. პაციენტების გამოკითხვა ჩატარდა სპეციალურად შემუშავებული კითხვარით და ისინი დაიყო ჯგუფებად: 50 ქალი – საკვერცხეების მულტიფოლიკულური სტრუქტურით, 25 ქალი – საკვერცხეების პოლიკისტოზური სტრუქტურით; საკონტროლო ჯგუფი შეადგინა 30 ქალმა საკვერცხეების სტრუქტურის დარღვევის გარეშე (ჯანმრთელი ქალები).

კვლევაში გამოყენებულია სომატოტიპირების მათემატიკური სქემა ჰიტ-კარტერის მიხედვით, რო-

მელიც მოიცავს სომატოტიპის ექტომორფული, მეზომორფული და ენდომორფული კომპონენტების განსაზღვრას. სხეულის მასის კომპონენტური შემადგენლობის განსაზღვრისათვის გამოყენებულია მატეიკოს ფორმულა. კუნთოვანი ქსოვილის აბსოლუტური რაოდენობა განისაზღვრა ამერიკის კვების ინსტიტუტის რეკომენდაციების შესაბამისად.

სხეულის ზედაპირის ფართობი ქალებში პოლიკისტოზური საკვერცხეების სინდრომით იყო ბევრად მეტი, ვიდრე შედარების და საკონტროლო ჯგუფის პაციენტებში. აღნიშნულია, ასევე, რომ პაციენტებში საკვერცხეების მულტიფოლიკულური სტრუქტურით სხეულის ზედაპირის ფართობი სარწმუნოდ მეტია, ვიდრე ჯანმრთელ ქალებში ( $p < 0,05$ ).

სხეულის მასის ზრდის სიჩქარე მნიშვნელოვნად მეტი იყო პაციენტებში საკვერცხეების პოლიკისტოზური შენებით, ვიდრე პაციენტებში საკვერცხეების მულტიფოლიკულური სტრუქტურით და საკონტროლო ჯგუფის ქალებში ( $p < 0,001$ ).

დადგენილია, რომ პაციენტებში საკვერცხეების პოლიკისტოზით მხრის გარშემოწერილობა მოსვენების დროს და დაძაბვის პირობებში იყო მეტი, ვიდრე პაციენტებში საკვერცხეების მულტიფოლიკულური სტრუქტურით და, შესაბამისად, საკონტროლო ჯგუფში ( $p < 0,001$ ,  $p < 0,05$ ).

გულმკერდის გარშემოწერილობის პარამეტრების მხრივ (დიამეტრი, მკერდის ძვლის საშუალო ზომა, მკერდის ძვლის ქვედა ნაწილის ზომა, განივი და საგიტალური ზომები) პაციენტთა გამოკვლეულ ჯგუფებს შორის არსებითი განსხვავება დადგენილი არ არის. თუმცა, საკონტროლო ჯგუფში ყველა ზემოაღნიშნული მაჩვენებელი სარწმუნოდ მეტი იყო, ვიდრე პაციენტებში საკვერცხეების პოლიკისტოზური და მულტიფოლიკულური შენებით ( $p < 0,001$  და  $p < 0,05$ , შესაბამისად). კუნთოვანი მასა მატეიკოს მიხედვით სტატისტიკურად მეტი იყო საკონტროლო ჯგუფის ქალებში, საკვერცხეების პოლიკისტოზური და მულტიფოლიკულური შენების მქონე ქალების ჯგუფებთან შედარებით ( $p < 0,001$ ).

გამოვლინდა, რომ ძვლოვანი მასა მატეიკოს მიხედვით ყველაზე მცირე იყო პაციენტებში საკვერცხეების მულტიფოლიკულური სტრუქტურით, საკვერცხეების პოლიკისტოზური შენების მქონე ქალების ჯგუფებთან შედარებით ( $p < 0,01$ ), ამასთან, ცხიმოვანი მასა მატეიკოს მიხედვით მეტი იყო საკვერცხეების პოლიკისტოზური შენების მქონე პაციენტებთან შედარებით ( $p < 0,01$ ).

ამრიგად, დადგენილია, რომ პაციენტებში საკვერცხეების პოლიკისტოზური შენებით აღინიშნება იზოლირებული და უპირატესად მეზომორფული კომპონენტები (54,0%;  $p < 0,05$ ), ენდომეზომორფული (9,1%;  $p < 0,05$ ) და დაუდგენელი კომპონენტები 4,5%,  $p < 0,05$ ), ხოლო პაციენტებში საკვერცხეების მულტიფოლიკულური შენებით სჭარბობს ექტომორფული (36,7%;  $p < 0,05$ ) და ექტომეზომორფული (8,2%;  $p < 0,05$ ) კომპონენტები.

## COMPREHENSIVE BACTERIOLOGICAL STUDY OF THE VAGINAL DISCHARGE DURING BACTERIAL VAGINOSIS

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Despite some progress in the diagnosis and treatment of infectious and inflammatory diseases of the female genitalia system, the prevalence of these diseases is growing steadily and is, according to various authors, from 30% of inpatients to 60-65% of outpatients [4, 6]. Along with sexually transmitted infections, such as syphilis, gonorrhea, trichomoniasis, chlamydia, inguinal lymphogranuloma, herpes and papillomavirus infection, etc., opportunistic pathogens (OP) and microbiota are becoming increasingly clinically important. Optional - and obligate-anaerobic OP, which make up the resident microflora of the urogenital tract, under the conditions of realization of certain exo - and endogenous factors can lead to purulent-inflammatory process of the genitals [2, 10]. The etiological structure of pathogens of infectious processes in the last decade has changed significantly, which is due to the constant evolution of bacteria and involvement of OP in pathological processes [4].

Therefore, the aim of the study was a comprehensive determination of a wide range of OP on the background of normal flora in the vaginal discharge of women of different ages without signs of infectious-inflammatory process but in the presence of nonspecific bacterial vaginosis.

**Material and methods.** The study was conducted in 298 women aged from 16 to 64 years old. The first group included 53 clinically healthy patients aged from 18 to 52 years old. The laboratory criterion for inclusion in this group was the value of the index of opportunistic pathogenic microflora (IOPM) less than -3 conventional units (c.u.). The second and the third groups also included women aged from 16 to 64 years old with an infectious-inflammatory process in the vagina of varying severity. The criterion for differentiating them by groups was IOPM, which amounted to in the second group from -3 to -1 c.u., and in the third group it was more than -1 c.u. The material for the study was removed by scraping the posterior wall of the vagina with an urogenital probe in a test tube type "Eppendorf". The studies of the biocenosis of the vagina were performed by polymerase chain reaction (PCR) using a set of reagents "Femoflor" (LLC "NVF-DNA Technology") [1]. Nucleic acids were isolated using a set of reagents "Sample-HS"; amplification was performed using DT-Lite (LLC "NVF-DNA Technology"). With the help of special software, the amount (in genome equivalents such as GE/sample) of total bacterial mass (TBM), lactobacilli and each group of OP was calculated. Statistical data processing was performed by methods of variation and correlation analysis using the application package STATISTICA v.10 (StatSoft, Inc.).

**Results and discussion.** Qualitative and quantitative composition of the studied microflora in the selected groups is presented in Table 1.

The assessment was performed taking into account the following criteria [6, 9] - with a relative content of lactobacilli more than 90%, and opportunistic aerobes and anaerobes less than 10% of TBM and quantitative content of *Candida spp.*, *Mycoplasma hominis* and *genitalium*, *Ureaplasma urealyticum* and *parvum* less than  $10^4$  GE/sample - were considered as normocenosis [3,7]. In the case of a combination of lactobacilli (more than 90%) and fungi or mycoplasmas (more than  $10^4$  GE/

sample), the vaginal microflora was regarded as a relative normocenosis. The imbalance of the biocenosis of the I degree was confirmed when the share of lactobacilli decreased from 90% to 20% against the background of increasing the content of aerobes (aerobic imbalance) or anaerobes (anaerobic imbalance), and for the II degree it was below 20% [1,3,5].

Analysis of the obtained data allowed to assess the state of the biocenosis of the vagina in the 1st group as a normocenosis. TBM in these patients ranged from 7.0 to 8.0 lg GE/sample (median 7.7). The content of lactobacilli ranged from 96.3% to 100.0%, the median was 98.7%. The frequency of distribution of facultative anaerobic microorganisms was 0.115 c.u. Out of these, enterobacteria were the most common (98.1%), staphylococci and streptococci were 32.1% and 30.2%, respectively. However, in quantitative terms, their content did not exceed  $10^{4.7}$  (median for enterobacteria was  $10^{4.0}$ ; for staphylococci and streptococci median was 0). Out of the obligate anaerobic microorganisms, the more common were *Mobiluncus spp.* + *Corynebacterium spp.* (81.1%) and *Eubacterium spp.* (69.8%). Quantitatively, their content did not reach  $10^4$  (median for *Mobiluncus spp.* + *Corynebacterium spp.* was  $10^{2.2}$ ; median for *Eubacterium spp.* was  $10^{2.3}$ ). The number of *Gardnerella vaginalis* + *Prevotella bivia* + *Porphyromonas* was up to  $10^{3.9}$  (median was 0). Other representatives of OP were found less often. Microorganisms of the genera *Sneathia spp.* + *Leptotrichia spp.* + *Fusobacterium spp.* in patients of the 1st group were not detected. The maximum content of *Ureaplasma urealyticum* + *parvum* was  $10^{4.6}$ ; median was 0, while *Mycoplasma hominis* + *genitalium* in patients of the 1st group were absent. Yeast-like fungi were found in relatively small numbers (up to  $10^{4.4}$ , median was 3.2), although it should be noted that in 75% of women of the 1st group their quantity exceeded  $10^3$ .

The obtained results do not coincide with the data of other authors [1, 3], namely under the conditions of the normocenosis of the vagina there was revealed a higher content of *Mobiluncus spp.* + *Corynebacterium spp.* (81.1%) and *Eubacterium spp.* (69.8%) in comparison with the data [3], which were 30-38%. In addition, in our studies, the absolute number of OP did not exceed  $10^{4.5}$ , while the findings of other studies stated that there was possible the increase of OP content in the normocenosis up to  $10^5$  and above [1, 3]. After conducting a correlation analysis of the content of microorganisms, we, in contrast to other results [1, 3], found positive relationships between TBM and the content of lactobacilli (+0.98;  $p < 0.05$ ) and enterobacteria (+0.51;  $p < 0.05$ ). Accordingly, the indicators of lacto- and enterobacteria content had a positive correlation (+0.47;  $p < 0.05$ ). This, in our opinion, indicated the presence of factors of mutually beneficial coexistence of lacto - and enterobacteria, which provided indicators of bacterial contamination of the vaginal contents.

It is clear from the plethora of combinations and permutations of possible pathogens analyzed that no one organism or cluster of organisms can identify all cases of vaginosis, although many different molecular methods have been used in attempts to provide more definitive diagnostic information about vaginosis [8]. A careful analysis of the organisms identified by molecular

Table 1. Quantitative composition of the biocenosis of vaginal secretions depending on the value of IOPM, lg GE/sample (M±m)

Microorganisms	Clinical diagnosis according to the content of IOPM		
	Normocenosis, n=53, (1 group)	Imbalance of I level, n=128 (2 group)	Imbalance of II level, n=117 (3 group)
	IOPM ≤ -3 (lg GE/sample)	IOPM > -3; ≤ -1 lg GE/sample)	IOPM > -1 lg GE/sample)
Total bacterial mass	7,740±0,037	7,600±0,039 *	6,774±0,076 * #
Normobiota			
<i>Lactobacillus spp.</i>	7,622±0,039	7,009±0,044 *	4,945±0,173 * #
Faculty anaerobic (aerobic) microorganisms			
<i>Enterobacteriaceae spp.</i>	3,777±0,109	5,169±0,068 *	5,179±0,072 *
<i>Streptococcus spp.</i>	0,964±0,205	1,020±0,149	1,753±0,212 * #
<i>Staphylococcus spp.</i>	1,045±0,205	1,316±0,166	1,309±0,169
Obligate anaerobic microorganisms			
<i>Gardnerella vaginalis, Prevotella bivia, Porphyromonas spp.</i>	0,923±0,178	2,190±0,193 *	3,950±0,267 * #
<i>Eubacterium spp.</i>	1,840 ±0,174	3,276±0,165 *	4,150±0,202 * #
<i>Sneathia spp., Leptotrichia spp., Fusobacterium spp.</i>	0,000±0,000	0,465±0,112 *	1,301±0,231 * #
<i>Megasphaera spp., Veilonella spp., Dialister spp.</i>	0,357±0,121	1,038±0,159 *	2,704±0,264 * #
<i>Lachnobacterium spp., Clostridium spp.</i>	0,413±0,138	1,172±0,168 *	1,590±0,201 *
<i>Mobiluncus spp., Corynebacterium spp.</i>	1,951±0,143	3,010±0,106 *	3,085±0,134 *
<i>Peptostreptococcus spp.</i>	0,504±0,130	1,184±0,157 *	1,830±0,223 * #
<i>Atopobium vaginae</i>	0,489±0,123	0,699±0,119	2,356±0,267 * #
Mycoplasmas			
<i>Mycoplasma hominis+genitalium</i>	0,000±0,000	0,023±0,023 *	0,467±0,173 * #
<i>Ureaplasma urealyticum+parvum</i>	1,104±0,228	1,622±0,023 *	2,062±0,223 * #
Yeast-like fungi			
<i>Candida spp.</i>	2,864±0,177	3,197±0,092	2,832±0,137 #

note: \* –  $p < 0.05$  when comparing the indicators of the 1st group with the 2nd and the 3rd groups;  
# –  $p < 0.05$  when comparing the indicators of the 2nd and the 3rd groups (by t-test)

methods as part of vaginosis may be a self-fulfilling prophesy, because the scoring system was developed to specifically identify women with low numbers of lactobacilli and high numbers of small Gram-variable and anaerobic Gram-negative rods. Therefore, the clinical symptoms associated with vaginosis may occur in the absence of the changes identified by PCR, such as aerobic vaginitis. Subsequently in this scenario, the numbers of lactobacilli are also decreased but are replaced by aerobic organisms such enterobacteria and staphylococci [8, 9].

In patients of the 2nd group IUPM was from 3 to -1 lg GE/sample, which allowed determining of their imbalance of I degree. TBM ranged from 6.0 to 8.0 lg GE/sample (median 7.7). The proportion of lactobacilli ranged from 73.1% to 99.4%, the median was 95.0%. When comparing the mean values, it was found that the value of TBM in the 2nd group was lower than in the 1st by 1.8% ( $p < 0.05$ ). There was shown a decrease in the content of *Lactobacillus spp.* (by 8.0%;  $p < 0.05$ ) with an increase in almost all OP. Accordingly, the rate of normobiota (RNB), which is calculated as the difference between TBM and the number of lactobacilli, was higher in group 2 than in group 1 (0.1 and 0.6 lg GE/sample, respectively).

In group 2 as well as in group 1, enterobacteria (98.4%), staphylococci, and streptococci were most common in 34.4%

and 28.1% of cases, respectively. The number of enterobacteria was significantly higher (36.9%;  $p < 0.05$ ) than in group 1. At the same time, in all patients their absolute number was more than 104 (median for enterobacteria 5.2 lg GE/sample). In the 2nd group, as well as in the 1st, the more commonly met microorganisms were *Mobiluncus spp.* + *Corynebacterium spp.* (87.5%) and *Eubacterium spp.* (79.7%); in quantitative terms, their content was higher than in the 1st group (respectively, 54.3% and 78.0%;  $p < 0.05$  in both cases). The median for *Mobiluncus spp.* + *Corynebacterium spp.* amounted to  $10^{3.3}$ ; for *Eubacterium spp.* it was  $10^{3.5}$ . Contents of *Gardnerella vaginalis* + *Prevotella bivia* + *Porphyromonas spp.* exceeded  $10^4$  in 22.7% of women. The number of *Atopobium vaginalis* and *Peptostreptococcus spp.* increased, especially the latter (by 134.9%;  $p < 0.05$ ). Also, there was found more often the combination of *Megasphaera spp.* + *Veilonella spp.* + *Dialister spp.* and *Lachnobacterium spp.* + *Clostridium spp.* respectively, up to 26.6% and 29.7% of cases, which was statistically significant comparing to the 1st group (76.1% and 96.7%, respectively;  $p < 0.05$  for both cases). In contrast to the 1st group, in the 2nd there were microorganisms of *Sneathia spp.* + *Leptotrichia spp.* + *Fusobacterium spp.* The indicators of mycoplasmas and yeast-like fungi did not differ significantly from the 1st group, which however does not coincide with the literature [1,3,4,6].

Thus, such features as a decrease in TBM, the number of lactobacilli and the appearance of representatives of *Sneathia spp.* + *Leptotrichia spp.* + *Fusobacterium spp.* and *Mycoplasma hominis* + *genitalium* appeared to be characteristic for the 2nd group of patients. Our analysis showed a weakening of the positive correlation between SBM and lactobacilli content (+0.62;  $p < 0.05$ ) and the disappearance of the relationship between SBM and enterobacterial content. At the same time, there were revealed numerous positive connections of medium strength between indicators of facultative and obligate anaerobes. This, in turn, indicates the appearance in the 2nd group of factors that contribute to the growth of these microorganisms. No correlations between mycoplasmas and fungi, as in the first group of patients, were found.

The changes that were characteristic for the 2nd group were much more pronounced in the 3rd group. IOPM was more, namely 1 lg GE/sample, which allowed diagnosing of imbalance of II degree. There was a significant decrease in TBM, which was less than in the 1st group by 12.5% and less than in the 2nd by 10.9% ( $p < 0.05$  in both cases). The content of lactobacilli was sharply reduced, the share of which ranged from 0 to 98.6%. The value of TBM ranged from 4.5 to 8.0 lg GE/sample (median 7.5). PNB was 1.8 lg GE/sample (exceeded the same value in the 1st group by 15.5 times and in the 2nd group by 3.1 times;  $p < 0.05$  in both cases). The absolute number of enterobacteria compared to group 2 did not change. It was noted that in most patients (95.7%) their content exceeded  $10^4$  (median for enterobacteria 5.1 lg GE/sample). In the 3rd group, a significant number of streptococci was diagnosed, it appeared to be in 81.8% and 71.8% ( $p < 0.05$  in both cases) more than in the 1st and 2nd groups, respectively.

It should be noted that the amount of *Eubacterium spp.* exceeded not only in the 1st group, but also in the 2nd (by 26.7%;  $p < 0.05$ ), and the median for *Mobiluncus spp.* + *Corynebacterium spp.* amounted to  $10^{3.2}$ ; for *Eubacterium spp.* it was  $10^{3.5}$ . The less frequency was indicated for *Gardnerella vaginalis* + *Prevotella bivia* + *Porphyromonas spp.*, it appeared to be 69.2%. The content of *Atopobium vaginalis* and *Peptostreptococcus spp.* exceeded the indicators of the 1st group by 4.8 times and 3.6 times, respectively ( $p < 0.05$ ). *Megasphaera spp.* + *Veilonella spp.* + *Dialister spp.* and *Lachnobacterium spp.* + *Clostridium spp.* were diagnosed in 51.3% and 37.6% of patients, which exceeded the content of this microflora not only in the 1st but also in the 2nd group (2.6 times;  $p < 0.05$ ). In 39.3% of women, their absolute content was greater than  $10^4$ . *Ureaplasma urealyticum* + *parvum* were detected in 45.3% of cases. The appearance of *Mycoplasma hominis* + *genitalium* in the 3rd group was noted in 11.1% of cases, and their content above  $10^4$  was recorded in 6.8% of women. Yeast-like fungi occurred with the same frequency as in other groups (80.3% of cases).

In earlier works by using culture methods, *M. hominis* was detected in 24 to 75% of vaginosis cases and in 13 to 22% of women without vaginosis. Finding of *M. hominis* using PCR yielded similar results. There was reported a 53% carriage rate of *M. hominis* in women with vaginosis and zero detection in health women. In the same manner, it was reported that *M. hominis* was present in low numbers in the healthy vagina but that the concentration of *M. hominis* was increased by a factor of 10,000 in women with vaginosis. Moreover, studies using quantitative PCR have shown that women with vaginosis have larger quantities of *M. hominis* and that these levels correlate with Gram stain criteria for vaginosis [8].

Thus, for the 3rd group it was characteristic even more decrease in TBP, the number of lactobacilli with an increase in staphylococci and streptococci, and obligate anaerobes than in other groups of women. It should be noted that there appeared a positive correlation between TBM and the content of lactobacilli (+0.67;  $p < 0.05$ ) and between the content of facultative and obligate anaerobes, which indicated the inhibition of the growth effect on the biocenosis of the vagina. This fact, in turn, was confirmed by the numerous positive links of mycoplasmas with anaerobes. Correlation analysis data showed that with the deepening of the degree of dysbiosis there had increased the number and strength of positive links of OP. It was possible to assume that at a bacterial vaginosis the studied microflora acquired properties of self-support and progressive self-stimulation. The *Candida* family did not form correlations in all three studied groups of women.

**Conclusions.** Under the condition of normocenosis, enterobacteria predominated among the facultative-anaerobic flora of the vagina, and among the obligate-anaerobic flora of the vagina there predominated *Mobiluncus spp.* + *Corynebacterium spp.* and *Eubacterium spp.* Representatives of the species *Sneathia spp.* + *Leptotrichia spp.* + *Fusobacterium spp.* and *Mycoplasma hominis* + *genitalium* were absent in the normocenosis.

The dysbiosis of the I degree was characterized by a decrease in TBM and the number of lactobacilli on the background of increasing of the content of anaerobes, including *Sneathia spp.* + *Leptotrichia spp.* + *Fusobacterium spp.* and *Mycoplasma hominis* + *genitalium*.

In the conditions of the dysbiosis of II degree there were observed the lowest indicators of TBM and lactobacilli with a significant increase of the absolute number of streptococci and obligate anaerobes. According to the correlation analysis, it was found that with the deepening of the degree of the dysbiosis the direct dependence of TBM and the number of lactobacilli decreased with increasing of the number and strength of positive links of OP (but not yeast-like fungi), which indicated self-support and self-stimulation in bacterial vaginosis.

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## SUMMARY

### COMPREHENSIVE BACTERIOLOGICAL STUDY OF THE VAGINAL DISCHARGE DURING BACTERIAL VAGINOSIS

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Along with sexually transmitted infections opportunistic pathogens and normal microbiota are becoming increasingly clinically important. Opportunistic pathogens can lead to purulent-inflammatory process of the genitals. The aim of the current work was to detect qualitative and quantitative composition of vagina contents in non-specific bacterial vaginosis.

Vaginal microbiota of 298 women aged from 16 to 64 years old was analyzed. Examination was provided by polymerase chain reaction.

In normocenosis with domination of enterobacteria the prevalence index of conditionally-pathogenic microflora wasn't more than 3 lg GE/sample. With absence of mycoplasmas the quantity of conditionally-pathogenic microorganisms

wasn't more than 104,5. At same time in patients with dysbiosis of I and II levels index of conditionally-pathogenic microflora was from 3 to 1 and less than 1 lg GE/sample accordingly; there was diagnosed a significant decrease of the total bacterial mass. Simultaneously, decreasing of *Lactobacillus* quantity (more expressed in dysbiosis-II) meanwhile appearance of mycoplasmas and utmost constant quantity of *Candida* was revealed.

A comprehensive determination of a wide range of opportunistic pathogens on the background of normal flora in the vaginal discharge of women of different ages had been studied.

**Keywords:** bacterial vaginosis, polymerase chain reaction, dysbiosis, normocenosis.

## РЕЗЮМЕ

### РЕЗУЛЬТАТЫ КОМПЛЕКСНОГО БАКТЕРИОЛОГИЧЕСКОГО ИССЛЕДОВАНИЯ СОДЕРЖИМОГО ВЛАГАЛИЩА ПРИ БАКТЕРИАЛЬНОМ ВАГИНОЗЕ

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При инфекциях, передаваемых половым путем, все большее клиническое значение приобретают условно-патогенные микроорганизмы и нормальная микробиота.

Целью исследования явилось определение качественного и количественного состава содержимого влагалища при неспецифическом бактериальном вагинозе у женщин разных возрастных групп.

Проанализирована микробиота влагалища у 298 женщин в возрасте от 16 до 64 лет. Исследование проводилось методом полимеразной цепной реакции. При нормоценозе с преобладанием энтеробактерий, показатель

распространенности условно-патогенной микрофлоры не превышал 3 lg GE/образец. При отсутствии микоплазм количество условно-патогенных микроорганизмов было не более 104,5. У пациентов с дисбактериозом I и II степени индекс условно-патогенной микрофлоры составил от 3 до 1 и менее 1 lg GE/образец, соответственно. Установлено значительное уменьшение общей бактериальной массы. Выявлено уменьшение количества *Lactobacillus spp.* (более выраженное при дисбактериозе-II), появление микоплазм, и максимально постоянного количества *Candida spp.*

## რეზიუმე

საშოს შიგთავსის კომპლექსური ბაქტერიოლოგიური გამოკვლევის შედეგები ბაქტერიული ვაგინოზის დროს

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სქესობრივი გზით გადამცემი ინფექციების დროს სულ უფრო დიდ კლინიკურ მნიშვნელობას იძენს პირობით-პათოგენური მიკროორგანიზმები და ნორმული მიკრობიოტა.

კვლევის მიზანს წარმოადგენდა სხვადასხვა ასაკობრივი ჯგუფის ქალებში ბაქტერიული ვაგინოზის დროს საშოს შიგთავსის სახეობრივი და რაოდენობრივი შემადგენლობის შესწავლა.

ნორმოცენოზის პირობებში ენტერობაქტერიების დომინირებით პირობით-პათოგენური მიკროფლორის გავრცელების მანველებელი არ აღემატებოდა 3 ლგ GE/ნიმუშში. მიკოპლაზმების არ არსებობის დროს პირობით-პათოგენური მიკროორგანიზმების რაოდენობა იყო არაუმეტეს 10<sup>4,5</sup>-სა. I და II ხარისხის დისბაქტერიოზით პაციენტებში პირობით-პათოგენური მიკროფლორის ინდექსი შეადგენდა, შესაბამისად, 3-დან 1-მდე და უფრო ნაკლებს 1 ლგ GE/ნიმუშში. გამოვლენილია ბაქტერიული მასის მნიშვნელოვანი შემცირება, *Lactobacillus* spp. რაოდენობის შემცირება (უპირატესად II ხარისხის დისბაქტერიოზის დროს), ამავდროულად გამოვლინდა მიკოპლაზმები და სოკო კანდიდას მაქსიმალურად მუდმივი რაოდენობა.

ნური მიკროფლორის ინდექსი შეადგენდა, შესაბამისად, 3-დან 1-მდე და უფრო ნაკლებს 1 ლგ GE/ნიმუშში. გამოვლენილია ბაქტერიული მასის მნიშვნელოვანი შემცირება, *Lactobacillus* spp. რაოდენობის შემცირება (უპირატესად II ხარისხის დისბაქტერიოზის დროს), ამავდროულად გამოვლინდა მიკოპლაზმები და სოკო კანდიდას მაქსიმალურად მუდმივი რაოდენობა.

## MORPHOLOGICAL CHANGES IN PERIODONTAL TISSUE DURING PERIODONTITIS

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Periodontitis is a dental polymicrobial, chronic inflammatory condition, which begins with a simple inflammation of the gums and characterized by the loss of alveolar bone, supporting structures of teeth and periodontal complex, forming abnormal periodontal pockets and finally by loss of teeth [5,7,15,16,23,28].

An important factor in the development and progression of periodontitis is the symbiotic-antagonistic relationship between oral bacteria and the host [11,28].

The oral bacteria have the ability to retain plaque and create biofilms on the cervical surfaces of the teeth. The colonization and continued presence of bacteria in the subgingival area leads to the progression of the gingivitis, formation of the pocket and bone loss [19,26].

According to electron microscopic studies, the presence of fusiform, coccobacilli as well as spirochetes was demonstrated in the gingival oral epithelium, adjacent connective tissue and capillaries. The above-mentioned periodontopathic bacteria have the ability to colonize between gingival and subgingival tissue and damage the gingival epithelial and blood-dendritic cells [4,19,23].

As a result of the influence of the microorganisms on the periodontal attachment, the progression of the disease divides into the following steps: 1) colonization near the gum line, - 2) integration and survival in the biofilm milieu, - 3) migration below the gum and, - 4) suppression of the host mucosal defense [10].

There are up to 700 species of microorganisms in the oral cavity, including periodontopathogens [8,13,28], which cause the development of periodontitis [28]. According to certain authors, there are bacteria of red complexion that are most associated with the development of severe periodontitis, namely: *Porphyromonas gingivalis*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans* and *Treponema denticola* [3,11,15,28].

Women and men have an equal periodontal pathogen colonization. However, the women have a higher risk of periodontitis onsets and the most prevalent causative agent is *P. Gingivalis*, whilst the most prevalent causative agents of the periodontitis in men are *P. Gingivalis*, *P. Intermedia*, *T. Forsythensis* and *T. Denticola*. However, most frequently *T. Forsythensis* is observed [28].

Aggressive periodontitis usually affects people under the age of 30 and is characterized by the rapid development of destructive changes. The family cases are rare. Morphologically it is characterized by the plasmacytic inflammatory infiltration, the domination of neutrophils in the connective tissue and the presence of the fibrin-coated plaque [28].

There are many etiological factors causing periodontal disease, one of which is poor oral hygiene. Poor oral hygiene increases chances of the development of periodontal disease by two to five times [17].

According to epidemiological studies periodontitis is highly prevalent globally [25]. The data of studies held at Harvard School of Dental Medicine show that overall periodontitis prevalence is 55.5% ( $\pm 1.4\%$ ), from which 20.7% ( $\pm 1.2\%$ ) is moderate and, 2.8% ( $\pm 0.5\%$ ) is severe [5,14]. Approximately half of the adult USA population has periodontitis [16].

According to the analysis of the studies conducted by sex, age and countries from 1990 to 2017, 796 million people had severe periodontitis on a global scale [12].

Studies show that the prevalence of severe periodontitis varies throughout the world. The highest prevalence rates were reported in Africa (4.2%, 95% CI 2.0-7.1) and South America (4.0%, 95% CI 0.9-9.1) compared to Europe (0.1%, 95% CI 0.1-0.2). However, the lowest prevalence was found in Asia (1.2%, 95% CI 0.5-2.2) and North America (0.8%, 95% CI 0.4-1.4) [5]. In Georgia unhealthy periodontal tissues were found in 66.9% of men and 57.5% of women [2].

Periodontal pathogens are harmful not only to the oral cavity but also affect the development of the fetus and our body as a whole. There is also a link between periodontitis and general somatic diseases (Kvaratskhelia et al., 2020). Laboratory studies have established the presence of periodontopathogens in saliva, subgingival plaque and placenta [27].

Based on one of the systematic reviews, there is a connection between periodontitis and cancer [9]. In particular, patients diagnosed with periodontitis have a higher risk of developing mouth cancer, also lungs, and pancreatic cancer [22]. Women with periodontitis are two to three times more likely to develop breast cancer [24].

Due to above mentioned, histomorphological examination in patients with periodontitis is becoming more important, that is not well introduced in dental practice. The results of such studies may play an additional role in detecting the precancerous lesions oral cavity cancer and planning preventive measures for oral cancers [19].

The aim of our study was a morphological study of periodontal tissues in patients with severe generalized periodontitis in Georgia in order to detect signs of the possible precancerous lesions.

**Material and methods.** 59 patients with the severe periodontitis were studied. The patients were selected for the 3069 per-

sons examined in the dental clinic in town Senaki during the prophylactic oral examination in period of February 6 - December 12, 2020.

After having obtained a written consent, patients periodontal status was assessed by oral examination of a clinical trial method based on the WHO recommendation.

Periodontal status was assessed by the following indicators: 1) Plaque index - the presence of visible plaque on any surface of the tooth, 2) stone index, 3) the depth of periodontal pockets, 4) tooth mobility.

The presence of plaque and stones on the teeth was assessed by dental mirror examination; the depth of the periodontal pockets was measured by means of a periodontal probe in the areas of 16, 21, 24, 36, 41, 44 teeth.

The 59 patients selected for the study had severe generalized periodontitis, poor oral hygiene, grade III-IV teeth shaking, and abnormal pockets of 5 mm in depth and above.

After signing the informed concern form all patients underwent tooth extraction. The procedure was carried out by different means (Chef, Yang, Parchment, etc.). The extracted teeth along with the surrounding granulation tissue and the inner substance taken from the tooth cavity as a result of the curettage process

were placed in 10% formalin For 24 h and decalcified in 10% nitric acid solution for 24-48 days. The obtained species – were embedded in paraffin. 4-5  $\mu$ m thick slices stained with hematoxylin and eosin \_were studied microscopically (microscope Leica DM-1000 LED with digital camera Leica MC 170 HD).

**Results and discussion.** In all cases, the well-defined leukocyte-lymphohistiocytic infiltration and both intra (Fig. 1a) and subepithelial (Fig. 1b) edema were revealed. In particular, cell enlargement, filling of the cytoplasm with clear fluid, and nuclei movement toward the periphery were observed. In some cases, the above-mentioned changes were accompanied by the formation of micro-abscesses. Hyperplasia of the multilayered squamous epithelium with an increase in the number and the size of cells was observed in the majority of cases (Fig. 1c). In some of these cases, the foci of necrosis with the complete disintegration of cell components, disruption of the cytoplasmic membranes, cariolysis and eosinophilia, have been revealed (Fig. 1d).

Fibroblast and connective tissue proliferation was detected in predominantly young patients (Fig. 1e). Vascular sclerosis with endothelial cell proliferation has also been reported (Fig. 1f). It should also be emphasized that mild (Fig. 1j) and moderate (Fig. 1h) dysplasia of the epithelium occurred in 30% of cases.

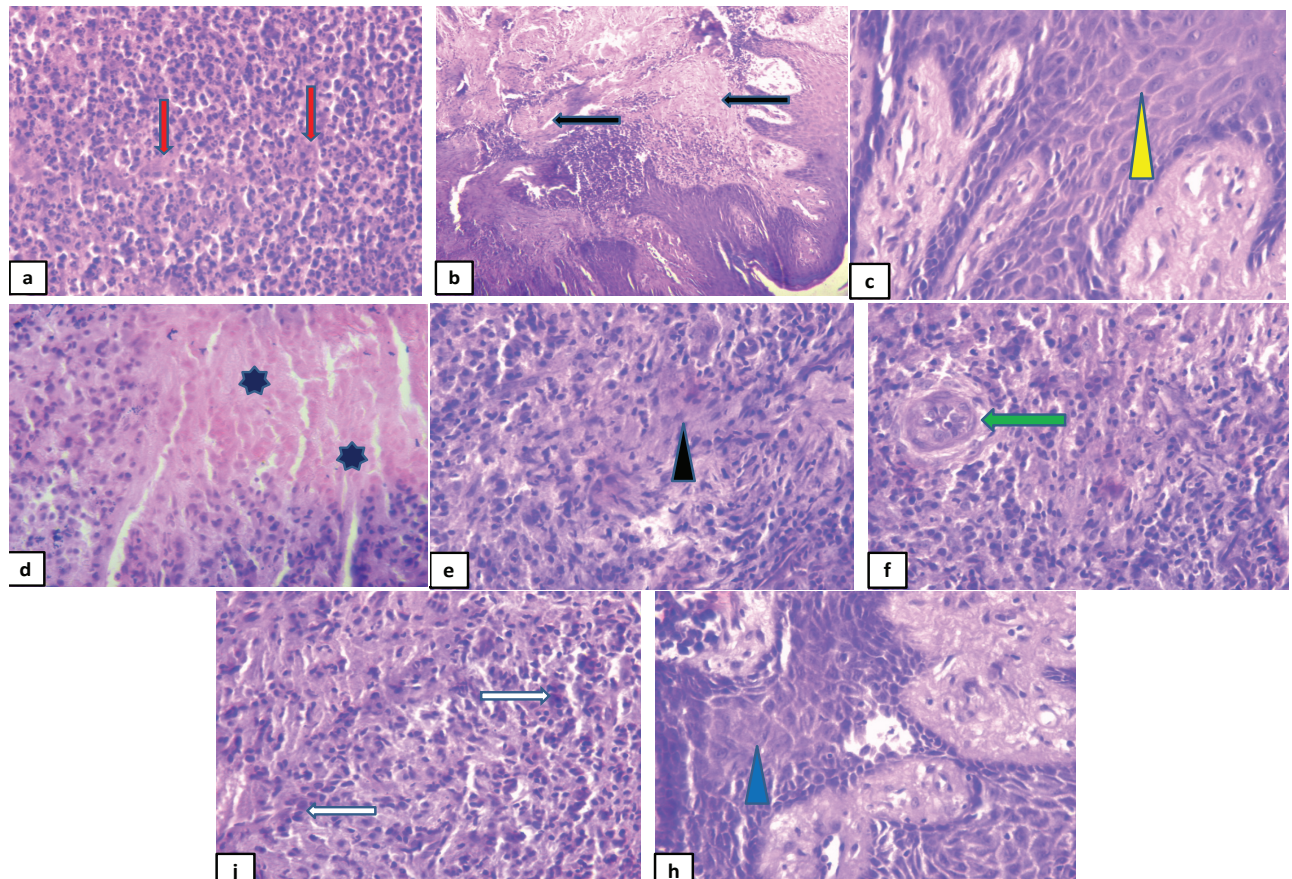


Fig. 1a - 2 teeth with an adjacent granulation tissue. 47 years-old woman; oedema; red arrows - the centre of leukocyte-histiocytic infiltration; b - 13 teeth with and adjacent granulation tissue. 49 year-old man; oedema; black arrows - the centre of leukocyte-lymphohistiocytic infiltration; c - 14 teeth with an adjacent granulation tissue. 50 years-old man; yellow arrowhead - area of multi-layered flat epithelium hyperplasia; d - 13 teeth with an adjacent granulation tissue. 66 years -old man; stars - foci of necrosis; e - 35 teeth with an adjacent granulation tissue. 26 years-old woman; black arrowhead - the centre of reproduction of a connective tissue; f - 21 teeth with surrounding granulation tissue. 48 years-old man; green arrow - the foci of vascular sclerosis with proliferation of endothelial cells; j - 11 teeth with surrounding granulation tissue. 57 years-old man; white arrows – an area of light dysplasia of the epithelium; h - 22 teeth with adjacent granulation tissue. 35 years-old man; blue arrowhead - the epithelium of moderate epithelial dysplasia

**Conclusion.** This study shows that severe generalized periodontitis is characterized by various morphological changes. Purulent-destructive inflammation should be considered as a morphological manifestation of aggressive periodontitis. In severe cases, foci of necrosis may also develop. Mild to moderate epithelial dysplasia, found in one third of all cases, may be considered an optional precancerous condition and should be considered when choosing a treatment.

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## SUMMARY

### MORPHOLOGICAL CHANGES IN PERIODONTAL TISSUE DURING PERIODONTITIS

Kvaratskhelia S., Nemsadze T., Puturidze S., Gogiberidze M., Jorbenadze T.

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Periodontitis is the most common oral disease worldwide and is the leading cause of tooth loss. It is considered to be a major burden in terms of costs of treatment and preventive measures.

According to the systematic reviews, there is a link between periodontitis and cancer. In particular, patients diagnosed with periodontitis have a higher risk of developing oral cancer. In this regard, the histomorphological examination of patients with periodontitis, which has not yet been sufficiently introduced in dental practice, is acquiring more and more importance.

The aim of the work is a morphological study of periodontal

tissues in patients with severe generalized periodontitis in Georgia - to identify signs of possible precancerous lesions.

The data obtained show that the morphological characteristic of severe periodontitis is purulent destructive inflammation. In addition, a third of severe periodontitis is accompanied by mild to moderate epithelial dysplasia, which should be taken into account when choosing a treatment method in terms of oncological alertness.

**Keywords:** Periodontitis, causative bacteria of periodontitis, periodontopathic bacteria, micromorphology.

## РЕЗЮМЕ

### МОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В ТКАНИ ПАРОДОНТА ПРИ ПАРОДОНТИТЕ

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Пародонтит - наиболее распространенное заболевание полости рта во всем мире, является основной причиной потери зубов. Он считается большим бременем с точки зрения затрат на лечение и профилактические меры.

Согласно результатам одного из систематических обзоров, существует связь между пародонтитом и развитием рака, в частности пациенты с диагнозом пародонтита имеют более высокий риск развития рака ротовой полости. В связи с этим, все большее значение приобретает гистоморфологическое обследование больных пародонтитом, которое по сей день не внедрено в стоматологическую практику.

Целью исследования является морфологическое исследование тканей пародонта у пациентов с тяжелым генерализованным пародонтитом - для выявления признаков возможных предраковых поражений.

Полученные данные показывают, что морфологической характеристикой пародонтита тяжелой степени является гнойное деструктивное воспаление. Кроме того, треть тяжелых пародонтитов сопровождаются дисплазией эпителия легкой и средней степени тяжести, что следует учитывать при выборе метода лечения с точки зрения онкологической настороженности.

## რეზიუმე

მორფოლოგიური ცვლილებები პაროდონტის ქსოვილში პაროდონტიტის დროს

ს. კვარაცხელია, თ. ნემსაძე, ს. ფუთურიძე, მ. გოგიბერიძე, თ. ჯორბენაძე

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პაროდონტიტი პირის დრუს საკმაოდ გავრცელებული დაავადებაა, როგორც მსოფლიოს მასშტაბით, ასევე საქართველოშიც და წარმოადგენს კბილების დაკარგვის ერთ-ერთ ძირითად მიზეზს და მნიშვნელოვან ტვირთს მკურნალობის და პროფილაქტიკის ხარჯების თვალსაზრისით.

სისტემური მიმოხილვის თანახმად, არსებობს კავ-

შირი პაროდონტიტსა და კბილის განვითარებას შორის. კერძოდ, პაროდონტიტით დაავადებულ პაციენტებს აქვთ პირის დრუს კბილის განვითარების მეტი რისკი. ამ მხრივ, სულ უფრო მეტ მნიშვნელობას იძენს პაროდონტის ქსოვილთა ჰისტომორფოლოგიური გამოკვლევა, რაც ჯერ კიდევ საკმარისად არ არის დანერგილი სტომატოლოგიურ პრაქტიკაში.

კვლევის მიზანს წარმოადგენს პაროდონტის ქსოვილების მორფოლოგიური გამოკვლევა საქართველოში მცხოვრებ პაციენტებში (n=59) მწვავე გენერალიზებული პაროდონტიტით შესაძლო კბოსწინარე დაზიანების ნიშნების გამოვლენისათვის.

მოპოვებული მონაცემების თანახმად, მძიმე პაროდონტიტის ძირითადი მორფოლოგიური მახასიათებელია ჩირქოვანი დესტრუქციული ანთება. ამასთანავე, შემთხვევათა ერთ მესამედში აღინიშნება მსუბუქი და საშუალო სიმძიმის ეპითელური დისპლაზია, რაც გასათვალისწინებელია მკურნალობის მეთოდის არჩევისას ონკოლოგიური სიფხიზლის თვალსაზრისით.

დონტიტის ძირითადი მორფოლოგიური მახასიათებელია ჩირქოვანი დესტრუქციული ანთება. ამასთანავე, შემთხვევათა ერთ მესამედში აღინიშნება მსუბუქი და საშუალო სიმძიმის ეპითელური დისპლაზია, რაც გასათვალისწინებელია მკურნალობის მეთოდის არჩევისას ონკოლოგიური სიფხიზლის თვალსაზრისით.

## ASSESSMENT OF LASER AND ANTIOXIDANT THERAPY EFFICACY IN TREATMENT OF CHRONIC GENERALIZED PERIODONTITIS

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An apparent tendency in continuous and steady rise in the incidence of pathological changes in periodontal tissue has been noted in the past few decades, reaching the prevalence of up to 95-100% among the population of Russian Federation [4,7,9]. This trend of growing prevalence of chronic generalized parodontitis as the most severe disorder among diseases of oral cavity and the complexity of its treatment present pressing challenges for all involved professionals [1,2,5,10,11].

Many different treatment modalities and practical recommendations have been developed to help the patients and to reduce the incidence [3,6,8,10], nevertheless this problem still remains not unresolved.

The purpose of this study was to assess the outcomes of conventional treatment and secondary prevention of chronic generalized parodontitis when combined with laser therapy and antioxidative treatment.

**Material and methods.** The prospective cohort study included 98 patients aged 30-50 years (31 male, 67 female) with history of 3 to 10 years duration of moderate chronic generalized parodontitis disease. All patients were divided into approximately equal three groups in accordance to the age, stage of disease and gender. The data collection has been performed at the time of admission, on the 6<sup>th</sup> day after the start of treatment, and on the 12<sup>th</sup> day and 6 months after completion of the course of treatment.

There has been no other disorder treated or a medication administered for treatment of any other disorder during the observation period. Conventional dental and oral cavity hygiene practices were observed.

The 1<sup>st</sup> Group (Control Group) consisting of 33 patients received the standard anti-inflammatory course of treatment: professional hygiene procedures with subsequent administration of Chlorhexidine and Metrogyl into gingival sulcus, irrigation with Dioxidine or Dimexidum, ointment dressing with Lingezine, Metrogyl Denta, Butadionum, Cholosal; Antimicrobial agents Flagyl, Kliostom, Metrogyl were combined with anti-allergic drugs (Diazolin) and vitamins (A,C,P). Non-steroidal anti-inflammatory drugs (NSAID) also were routinely used, and Indomethacin was a drug of choice in majority of cases.

The 2<sup>nd</sup> Group consisted of 32 individuals who underwent laser treatment using device "Matrix" with wave length 635 nm and energy level 10 mW. The irradiation of alveolar process started with 2 minutes duration for the first treatment session with daily increments of 30 seconds until reached the maximum duration of exposure up to 5 min. The full treatment course duration was 12 days.

Treatment in the 3<sup>rd</sup> Group (33 patients) was similar to that of the 2<sup>nd</sup> Group with addition of antioxidant drug Mexicor during the same course of 12 days conventional therapy and laser application.

Several clinical indices were utilized for assessment of periodontal tissue: PMA (Papillary Marginal Attachment), SBI (Sulcus Bleeding Index), API (Approximal Plaque Index). The resistance of gingival capillaries was measured by scaled vacuum application (V. Kulazhenko). The degree of osteal resorption was determined by assessment of intra alveolar septae of maxillary bones on X-ray.

The lipid peroxide oxidation was determined by levels of secondary products (malonic dialdehyde Fe<sup>2+</sup>+MDA) in patients' blood serum. Phospholipase A2 catalytic activity was determined based on the amount of free fatty acids by potential measurement in the following solution: 10 mmol tris-HCl-buffer (ph 8,0), 150 mmol Triton X-100, 10 mmol CaCl<sub>2</sub> and substratum (1,2 mmol phosphatidylcholine of egg yolk). Spectrophotometry was implemented to determine catalase activity.

The collected data were analyzed by use of basic scientific statistics and Student's t-test.

**Results and discussion.** In accordance with the API index the hygienic condition of oral cavity in patients with chronic generalized parodontitis has been found as non-satisfactory. The dynamics of PMA index have shown inflammatory changes in oral mucosa.

After completion of the course of treatment the values of PMA were reduced by 22,7-45,0% (p<0,05). The hygiene index (API) by the completion of therapy was reduced by 33,7% (p<0,05). The traditional treatment was also effective in decreasing gingival bleeding, according to the SBI index of 57,1% (p<0,05). The improvement functional condition of periodontal vessels was reflected by an increase in time for development of gingival haematoma by 55,8-107,7% (p<0,05).

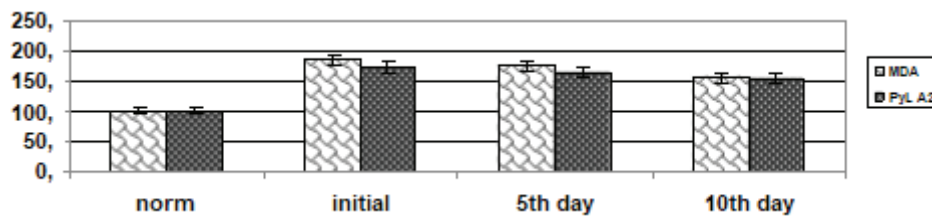


Fig. 1. Trend in MDA dynamics and phospholipase A2 activity during course of traditional treatment

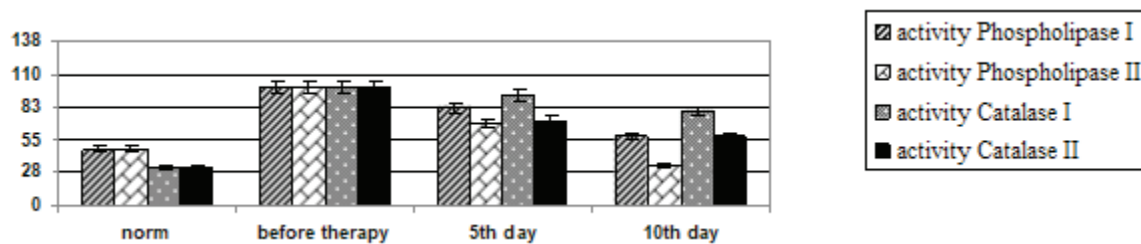


Fig. 2. Trends of phospholipase A2 and catalase activity in the 3<sup>rd</sup> Group of patients

The data collected during this investigation from patients with chronic generalized parodontitis have pointed to intensive development of free radical processes and high activity of red blood cells phosphatase A2 among 75% of subjects, which is an evidence of important role of peroxide actions in the pathogenesis. A considerable growth of Malonic dialdehyde (MDA) and a triggered MDA were observed in 86,0% and 27,2% ( $p < 0,05$ ), respectively. An activity catalase before treatment was elevated by 14,3% ( $p < 0,05$ ) and similar tendency had erythrocytic phospholipase A2 with values ranging 55,6 - 74,7% ( $p < 0,05$ ). The intensity of lipoperoxidation and enzymatic activity in red blood cells with use of conventional therapy were decreased but did not reach the range within the baseline values (Fig. 1).

A process of membrane destabilization has been found in 71,7% patients with chronic parodontitis. Meanwhile the amount of all phospholipids was reduced by 9,2% ( $p < 0,05$ ) before the start of treatment and among them was noted a remarkable rise of fractions of lysoforms and phosphatidylserine which were higher than normal range by up to 74,4% and 32,4% ( $p < 0,05$ ), respectively. The values of cholesterol and free fatty acids also were elevated. The positive dynamics of all parameters has been noted toward the end of the conventional treatment, however, not reaching the normal ranges until the 10<sup>th</sup> day of the treatment regimen.

The study results showed certain limitations of conventional therapy and necessity in enhancement by medications with capacities to influence the above mentioned pathological deviations of homeostasis.

The efficacy of laser therapy in the treatment of chronic moderate parodontitis and prevention of relapses has been investigated in the 2<sup>nd</sup> Group.

The performance of quantum therapy as a solitary treatment regimen of chronic moderate parodontitis has shown an improvement of oxidative stress indices. A decline of free radical reactions intensity and recovery of reserves enzyme antioxidants were also observed. Anti-inflammatory efficacy of laser therapy could be connected by antibacterial effect, inhibition of prostaglandin E2,  $\Phi$ HO-a. There was a direct influence on a group of interleukins (IL-1 $\beta$ , IL 6, IL-10 and thermal shock proteins that was in result similar to the action of systemic glucocorticoids (Lima a. et al., 2014). No evident membrane stabilising effects were seen after an application of laser therapy to a conventional treatment regime.

The supplementation of laser irradiation with anti oxidative drug Meksicor to a conventional therapy produced the better results among third group of patients with chronic moderate parodontitis. After completion of the treatment there were no gingival bleeding, pain, itching, hypersensitivity necks of teeth and burning as well as malodour from oral cavity. According to visual inspection of oral cavity the local signs of inflammation were less prominent or absent (swelling of mucosa, hyperaemia, bleeding from gingival margins, depth of gingival pockets and discharge).

An improvement in general condition, appetite and sleep were also noted with diminishing levels of distress, weakness, and irritability. Index of inflammation PMA was reduced by 43,9 - 70,1% ( $p < 0,05$ ) and in comparison with Control Group - by 24,0 - 40,9% ( $p < 0,05$ ). The implemented regimen of treatment by laser and Mexicor was connected with reduction of hygiene index API by 30,1 - 79,9% ( $p < 0,05$ ) and was lower compared to the Control Group by 16,5 - 33,1% ( $p < 0,05$ ). Similar results were seen in terms of gingival bleeding and SBI was decreased from the onset of treatment by 33,9 - 78,8% ( $p < 0,05$ ); conventional management results showed lesser figures: 24,9 - 51,4% ( $p < 0,05$ ). Therapy with Mexicor contributed to the rise in indicator of functional condition of periodontal vessels by 24,9 - 51,4% ( $p < 0,05$ ) and in comparison with the Control Group this rise comprised of 19,1 - 36,0% ( $p < 0,05$ ).

The level of Malondialdehyde was reduced by 25,5 - 47,4 % ( $p < 0,05$ ) and by the end of the treatment was less than in the Control Group by 4,9 - 29,7% ( $p < 0,05$ ).

The reaction of lipid peroxidation in patients with chronic generalized parodontitis was accompanied with an increased activity of phospholipase A2 and catalase. Combining conventional therapy with laser and Mexicor resulted reduction of the levels of phospholipase by 40,9 - 53,6% ( $p < 0,05$ ) and catalase activity - by 32,3 - 52,9% ( $p < 0,05$ ) (Fig. 2).

The results of this investigation have revealed high efficacy of conventional treatment of chronic generalized parodontitis especially when combined with laser irradiation and Mexicor regimen.

The longterm results of treatment of the patients with chronic moderate generalized parodontitis achieved in this study are significant for the dental and medical practices. The addition of laser therapy and antioxidant Mexicor to conventional treatment

regimen showed unequivocal improvement in long-term results in terms of local changes and general condition in 92,0% of cases ( $p<0,05$ ), while solely a conventional therapy was effective only in 25% cases.

Combining the conventional treatment regimen with laser irradiation and antioxidant Mexicor facilitated the moderation of oxidative processes on local and general body levels. This conclusion is supported by the evidence of decrease in lipoperoxidation products and recovery of antioxidative ferments in saliva and blood serum. The level of malonic dialdehyde in the blood plasma on the 12<sup>th</sup> day of treatment was reduced by 15,8% ( $p<0,05$ ) compared to the Control Group. Activity of superoxide dismutase was within normal range and elevated by 22,5% ( $p<0,05$ ) from the initial values. Phospholipase A2 activity by the completion of treatment was lower than Control Group values by 13,4 % ( $p<0,05$ ) and approaching the normal ranges.

The positive changes were registered for oxidative processes in saliva and by the completion of treatment TBARS-reactive substances were reduced by 28,6% ( $p<0,05$ ). Activity of superoxide dismutase at the second stage of investigation was lower than Control Group values by 17,0% ( $p<0,05$ ).

The results of this study revealed the efficacy of the laser and metabolic therapies not only for a treatment but also as preventive measure for relapses of chronic parodontitis. There is strong correlation between indices of morphofunctional condition of periodontal tissue and microcirculation, hemostatic system, oxidative processes and phospholipase activity.

**Conclusions.** 1. The efficacy of conventional anti-inflammatory therapy of chronic generalized parodontitis is often insufficient and is associated with relapses.

2. Combining conventional treatment of chronic parodontitis with laser therapy helped improving indices of oxidative stress and did not have significant influence on correction of homeostatic deviations.

3. Additional implementation of laser and metabolic therapies sufficiently increased efficacy of conventional therapy and improved secondary prevention of chronic parodontitis. There is a marked decrease in structural-functional deviations and apparent recovery of microcirculatory vascular bed of periodontal tissue noted.

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## SUMMARY

### ASSESSMENT OF LASER AND ANTIOXIDANT THERAPY EFFICACY IN TREATMENT OF CHRONIC GENERALIZED PERIODONTITIS

<sup>1</sup>Akimov V.V., <sup>1</sup>Kuzmina D., <sup>2</sup>Fedoskina A., <sup>2</sup>Vlasova T., <sup>3</sup>Dvaladze L., <sup>4</sup>Ryzhkov V., <sup>4</sup>Akimov V.P.

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Chronic generalized parodontitis is one of the most prevalent disorders among diseases of oral cavity, making the search for optimal treatment modalities of this disorder one of the most pressing matters to this day.

The purpose of this study was to assess outcomes of conventional therapy and secondary prevention of chronic generalized parodontitis with in combination with use of laser therapy and antioxidant drug treatment.

The study is presented as a joint multi-site investigation conducted by the group of authors from St. Petersburg and Saransk medical teaching and clinical institutions. The aim of the study was to improve the treatment and secondary prevention of chronic generalized parodontitis based on a pathogenetically substantiated scheme of laser and antioxidant therapy.

The total of 98 patients (31 male and 67 female) aged 30–50 years) with the 3 to 10 year history of moderate chronic generalized parodontitis were selected for the prospective study. All patients were approximately equally divided into three groups according to the received treatment regimens: conventional treatment, laser therapy, and laser therapy with antioxidant medication. Several clinical indices were utilized for parodontal tissue assessment (PMA, SBI, AP), resistance of gingival capillary bed, osteal resorption. The lipid peroxide oxidation was determined by MDA, Fe<sup>2+</sup> MDA<sup>-</sup> and phospholipase A2.

Additional implementation of laser and metabolic therapies sufficiently increases efficacy of conventional therapy and improves secondary prevention of chronic parodontitis. A marked decrease in structural-functional deviations and apparent recovery of microcirculatory vascular bed of parodontal tissue has been achieved.

**Keywords:** chronic generalized parodontitis, laser therapy, antioxidant therapy.

## РЕЗЮМЕ

### ОЦЕНКА ЭФФЕКТИВНОСТИ ЛАЗЕРНОЙ И АНТИ-ОКСИДАНТНОЙ ТЕРАПИИ ПРИ ХРОНИЧЕСКОМ ГЕНЕРАЛИЗОВАННОМ ПАРОДОНТИТЕ

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Хронический генерализованный пародонтит является одним из самых распространенных заболеваний среди других заболеваний полости рта, поэтому поиск оптимальных методов лечения весьма актуален.

Целью исследования явилось улучшение методов лечения и вторичной профилактики хронического генерализованного пародонтита на основе патогенетически обоснованной схемы лазерной и антиоксидантной терапии.

В когортное проспективное исследование включено 98 больных (31 мужчина и 67 женщин) хроническим генерализованным пародонтитом в возрасте от 30 до 50 лет, с давностью заболевания от 3 до 10 лет. Больные были разделены на три группы: стандартная противовоспалительная терапия, лазеротерапия, антиоксидантная терапия. Эффективность лечения пародонтита в группах оценивали по клинико-лабораторным данным, стоматологическим индексам (PMA, SBI, - API) стойкости капилляров десны; степени резорбции костной ткани. О состоянии перекисного окисления липидов (ПОЛ) судили по уровню малонового диальдегида (МДА, Fe<sup>2+</sup>-МДА) и фосфолипазы A<sub>2</sub>. Установлено, что применение лазерной и метаболической терапии существенно повышает эффективность стандартной схемы лечения и вторичной профилактики хронического пародонтита, что проявляется в значительном уменьшении структурно-функциональных изменений и восстановлении микроциркуляции тканей пародонта.

## რეზიუმე

ლაზერული და ანტიოქსიდანტური თერაპიის ეფექტურობის შეფასება ქრონიკული გენერალიზებული პაროდონტიტის დროს

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<sup>3</sup>ლ.ვლასოვა, <sup>4</sup>ვ.რიჟკოვი, <sup>4</sup>ვაკიმოვი

<sup>1</sup>სანქტ-პეტერბურგის სახელმწიფო უნივერსიტეტი, სტომატოლოგიისა და სამედიცინო ტექნოლოგიების ფაკულტეტი, სტომატოლოგიის დეპარტამენტი; <sup>2</sup>სსდ უპგ «ნ.პ.ოგარევის სახ. მორდოვიის უნივერსიტეტი, ფაკულტეტური ქირურგიის დეპარტამენტი, სარანსკი; <sup>3</sup>ფსბდ «ლ.გ. სოკოლოვის სახ. ჩრდილო-დასავლეთ რაიონული სამეცნიერო და კლინიკური ცენტრი» რუსეთის ფედერალური სამედიცინო-ბიოლოგიური სააკადემია, სანქტ-პეტერბურგი; <sup>4</sup>ჩრდილო-დასავლეთის იმპერიის სახ. სახელმწიფო სამედიცინო უნივერსიტეტი, რუსეთის ფედერაციის საზოგადოებრივი ჯანდაცვის სამინისტრო, სანქტ-პეტერბურგი, რუსეთი

ქრონიკული გენერალიზებული პაროდონტიტი პირის ღრუს სხვა დაავადებების შორის ერთ-ერთი ყველაზე გავრცელებული დაავადებაა, აქედან გამომდინარე, ოპტიმალური მკურნალობის მეთოდების ძიება მეტად აქტუალურია.

კვლევის მიზანი იყო ქრონიკული გენერალიზებული პაროდონტიტის მკურნალობისა და მეორადი პრევენციის მეთოდების გაუმჯობესება ლაზერული და ანტიოქსიდანტური თერაპიის პათოგენეტიკურად დაფუძნებული სქემის საფუძველზე. პერსპექტიული კოპორტის კვლევა მოიცავდა 98 პაციენტს (31 მამაკაცი და 67 ქალი) ქრონიკული გენერალიზებული პაროდონტიტით 30-დან 50 წლამდე, დაავადების ხანგრძლივობით 3-დან 10 წლამდე. პაციენტები მკურნალობის მეთოდის გათვალისწინებით დაყოფილი იყო სამ ჯგუფად (სტანდარტული ანთების საწინააღმდეგო თერაპია, ლაზერული თერაპია და ანტიოქსიდანტური თერაპია). ჯგუფებში პაროდონტიტის მკურნალობის ეფექტურობა შეფასდა კლინიკური და ლაბორატორიული მონაცემებით, კაპილარული წინააღმდეგობის სტომატოლოგიური ინდექსების (PMA, SBI, AP) და ძვლის რეორგანიზაციის ხარისხის გათვალისწინებით. ლიპიდური პეროქსიდირების მდგომარეობა (LPO) შეფასდა (MDA, Fe<sup>2+</sup>-MDA) და ფოსფოლიპაზის 2 დონეზე. აღმოჩნდა, რომ ლაზერული და მეტაბოლური თერაპიის გამოყენება მნიშვნელოვნად ზრდის სტანდარტული მკურნალობის რეჟიმის ეფექტურობას და ქრონიკული პაროდონტიტის მეორად პრევენციას, რაც გამოიხატება სტრუქტურული და ფუნქციური ცვლილებების მნიშვნელოვან შემცირებაში და პაროდონტიტის ქსოვილების მიკროცირკულაციის აღდგენაში.

## SURGICALLY ASSISTED RAPID MAXILLARY EXPANSION: RETROSPECTIVE ANALYSIS OF COMPLICATIONS 2012-2017

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Transverse maxillary deficiency (TMD) is one of the most common types of skeletal dysplasia in clinical practice [23]. TMD can be treated surgically or orthodontically, depending on the patient's age and clinical parameters [3]. Surgically assisted rapid maxillary expansion (SARME) has become the most common therapy in treating patients with TMD when orthodontic expansion is not sufficient due to the severity of TMD or not acceptable due to patient's skeletal maturity [1,18]. According to Mommaerts it is recommended to perform SARPE

if patient's age is >14 years, so SARME is used in patients with completely or almost finished craniofacial growth and mid-palatal suture ossification [14].

Some authors [2,5,23] describe surgically assisted rapid maxillary expansion as a relatively safe procedure, especially comparing to orthognathic surgery, though all of them mention the fact that SARME is not completely free of complications. With a constantly growing number of patients seeking orthognathic help, it is important to evaluate common complications of SARME in order to provide patients precise information about risks associated with surgery and to minimize possible risk factors as well. The aim of this study was to reveal the most typical postoperative SARME complications in a group of patients treated at a single clinical center.

Surgically assisted rapid maxillary expansion is a part of a complex treatment of patients with transverse maxillary deficiency more than 4 mm [1,6,9]. SARME minimizes the risks associated with orthodontic correction of severe TMD, such as root resorption, periodontal disease, lateral tooth extrusion and relapse [1,19]. Nevertheless, SARME itself is associated with several complications to be considered.

According to recent articles the most common SARME complications are neurosensory deficits, postoperative pain, asymmetric and/or inadequate expansion, epistaxis, dental complications [3,18,23,24]. Also there are complications associated with different SARME techniques: 1) performing or not performing pterygomaxillary osteotomy; 2) using bone-borne [14] or tooth-borne or combined (mini-implant- and tooth-borne) [25] distraction device.

Currently there is no consensus on either to perform pterygomaxillary disjunction (PMD) during SARME or not [8]. Not performing PMD is stated by some authors as a reason of an insufficient widening of the maxilla in the molars region (V-shaped widening) [2,10]. On the contrary Han et al. and Kilic et al. reported greater posterior maxilla widening in the group of patients who underwent SARME without PMD comparing to PMD SARME group [7,8]. Laudemann at al., recommend to perform PMD in patients older than 20 years and not to perform it in patients < 20 years in order to avoid the decline in transverse maxillary widening from anterior to posterior and lateral pterygoid bending [13]. Some authors consider performing pterygomaxillary osteotomy as a part of SARME risky due to the possibility of such complications as maxillary artery branches injury and the plates fracture [16,19,20]. So Zandi et al., due to the favorable outcomes of both techniques recommend to perform SARME without PMD so to decrease the risk of complications [27].

The choice of the distraction device is another factor to be considered while analyzing SARME complications. Currently there are two commonly used distraction device types: the transpalatal distractor (TPD) (bone-borne) and tooth-borne appliances such as Hyrax and Hass [14,18]. After TPD was introduced by Mommaerts in 1999 it was supposed it would help to avoid complications associated with tooth-borne distraction device such as buccal tipping of the teeth, root resorption and periodontal problems [12]. Nevertheless, in the systematic review by Verstraaten et al. only weak evidence was found that there is less buccal tipping of the teeth in bone-borne expansion [22]. According to Koudstaal et al. no differences in stability, tipping and relapse was found between SARME with bone-borne and tooth-borne distraction device [12]. Currently there is no strong evidence regarding which SARME technique is associated with less complications thus and so the choice should be made according to patient's individual requirements in each clinical case [26].

**Materials and methods.** Clinical cases of the patients who underwent SARME in period between 2012 and 2017 at the Clinical Center of Maxillofacial, Plastic Surgery and Dentistry, Moscow were evaluated during the study. All the patients had maxillary deficiency more than 4 mm and completed mid-palatal suture ossification. 679 clinical cases were originally selected for the study. 14 cases were excluded because patients had cleft in anamnesis or were treated using tooth-borne distraction device instead of the bone-borne. 665 patients remained in the study (247 males and 418 females, mean age 25,3 years).

### *Operation technique.*

All the operations were performed by five surgeons of the Clinical Center of Maxillofacial, Plastic Surgery and Dentistry, Moscow, using bone-borne distraction device (either monolithic or sectional construction). No pterygomaxillary suture separation was made.

To perform the operation general anesthesia with nasotracheal intubation was combined with local anesthesia (Naropine 0,75% - 20ml with vasoconstrictor).

Two cruciform incisions were made on the right and the left parts of the palatine mucosa between the second premolar and the first molar to position distractor properly (in case sectional construction was presented, at first, distractor modules were put subperiosteally and then distraction device was placed into modules). After that the device was activated.

One incision (horizontal or vertical) was made in the frenulum area between two central incisors. In period between 2012 and 2015 years V-shaped incision between upper canines was performed.

Mucoperiosteum was separated tunnelly from the piriform aperture towards the maxillary tuber both at the right and the left sides symmetrically. Nasal mucosa was separated from the nasal cavity bottom. The Le Fort I osteotomy was performed from the piriform aperture towards the maxillary tubers bilaterally using reciprocating saw. Mid-palatal suture osteotomy was performed by the reciprocating saw as well. Chisels were used for Le Fort I and nasal septum osteotomies. The distraction device was activated so that the gap between central incisors would reach at least 2 mm.

*Hemostasis during the operation. Sutures.* Distraction device activation starts on postoperative day 7 and reaches from 0.3 to 1 mm daily. 3 weeks after activation is finished patient should visit orthodontist for the further treatment. It is recommended not to remove the device for 4 months since operation. 3 weeks after activation is finished and before the distraction device is re-moved patient should visit surgeon every 2 weeks for a check-up.

*Radiological evaluations.*

CBCT scans were made for each patient 3 times: before the surgery (within 2 months) -T1, after the surgery before the activation started - T2 and a year after SARME - T3, using the "I-CAT" device (USA).

The following measurements were made to evaluate the amount of distraction and possible complications such as relapse, insufficient or asymmetric expansion: U6-U6 – maxillary denture width is measured as the distance between the most convex parts of the buccal surfaces of two upper first molars.

P1-P1 – palatal vault width between the upper canines.

P2-P2 – palatal vault width between the second upper premolars.

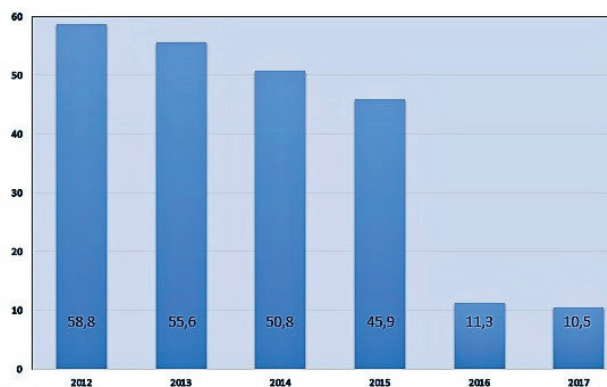
P3-P3 – palatal vault width between the first upper molars.

**Results and discussion.** All the operations were performed according to the described technique. After activation was complete the expansion between 1.1 and 2.1 achieved from 4 to 15 mm.

As the result of retrospective analysis 450 cases of SARME postoperative complications were identified in 665 patients between 2012 and 2017. One patient could have 1 or more complications.

The following postoperative complications were revealed: 1) Paresthesia of the infraorbital nerve branches and nasopalatine nerve was observed in 198 cases out of 665. Patients reported unilateral and bilateral paresthesia of the front teeth. All the cases resolved completely during 6 months postoperative.

It is needed to be mentioned that the lowest percent of paresthesia was noted in 2016 year (11,3% - 20/177) and 2017 (10,5% - 18/173) (Diagram 1).



*Diagram 1. The frequency of occurrence of the paresthesia of the infraorbital nerve branches and nasopalatine nerve in the Clinical Center of Maxillofacial, Plastic Surgery and Dentistry, Moscow 2012-2017 (%)*

2) Distraction device displacement. 61 patients presented with this complication. All of them had devices with sectional construction. In most cases there were no screw fixation of the device's modules so as to not perforate palatine roots of the teeth (Photo 1).



*Photo 1. Distraction device displacement*

3) Inflammation in distractor modules area was presented in a total of 57 cases: in patients whose level of oral hygiene was insufficient (Patient Hygiene Performance >1,7), and also in patients who had distraction device mobility (Photo 2).



*Photo 2. Inflammation in distractor modules area*

4) Asymmetric expansion was observed in 27 patients. In 24 cases the complication was compensated by the following orthodontic treatment and in 3 cases additional surgery was required.

5) Relapse frequency of occurrence – 18/665. This complication was taken into account in case of the relapse more than 2 mm in interdental width between right and left first upper molar.

6) Distractor's loss was presented in 20 cases. 1 distraction device was swallowed by the patient. The complication was observed in patients with sectional construction of the device and was associated with the loosening of the device and mechanic pressure during eating.

7) Insufficient expansion of the maxilla 10 patients didn't come for the activation of the distractor that's why it wasn't done completely.

32 out of 665 had an inadequate expansion in molars zone. That can be explained by the features of the operation technique (no pterygomaxillary osteotomy). To correct an inadequate expansion of the maxilla orthognathic surgery with segmental osteotomy was performed as a second step of surgical treatment.

8) Postoperative bleeding was observed in 7 patients. In 6 cases epistaxis took place (4 happened on the same day operation was performed, 1 - on the third day and 1 - on the 7<sup>th</sup> day).

In 1 case the bleeding was palatine (on the 5<sup>th</sup> day). In 4 cases of nasal bleeding anterior nasal pack was required and in 2 cases - posterior.

9) Soft tissue complications 5 patients had medial recession in the central incisors area and 1 had necrosis of the palatine mucosa caused by trauma during distraction device positioning (Photo 3).



Photo 3. After the removal of the distraction device. Medial recession of 1.1 is presented

10) Maxillary sinus perforation by the distractor's module was observed in 6 patients in postoperative period during the activation.

11) Dental complications in 3 cases there was a 1.1 tooth discoloration. Electro-odonto-diagnosis of this teeth was  $>200$  mkA.

12) Formation of defective bone regenerate was observed in 2 patients. After activation period was complete there was a defective bone regenerate presented by fibrous tissue in the anterior part of mid-palatal suture (Table 1).

Of the 665 patients presented in this article, 52,93% (352/665) had one or more postoperative complication. This corresponds with the results presented by Smeets et al., - 52.25% (58/111) [18] and is significantly higher than Carvalho et al. presented in the recent systematic review - 21.97% [4].

2016 and 2017 years had the lowest level of complications, that can be associated with using minimally invasive access. In 2016-2017 we performed a linear horizontal or vertical incision in frenulum zone instead of V-shaped one from tooth 1.3 to 2.3, that we used to do between 2012 and 2015. The amount of such complications as paresthesia of the infraorbital nerve branches and nasopalatine nerve, postoperative bleeding and dental complications were decreased noticeably possibly due to minimally invasive technique.

Paresthesia of the infraorbital nerve branches and nasopalatine nerve is the most frequent complication in this study (198/665). Patients experienced postoperative numbness of the teeth 1.5-2.5. One week after the operation EOD of this teeth resulted significantly higher numbers comparing to the normal marks before the operation. Paresthesia resolved during first 6 month after the operation. A number of authors in their studies noted not only numbness of the teeth but of the upper lip as well: Dergin [5] (11/60 cases of paresthesia, 4 of which included the numbness of the upper lip), Verquin [23] (16/55, 3 - paresthesia of the upper lip). In our study there was no lip paresthesia. We associate it with minimally invasive technique.

A number of complications presented in the study is associated with distraction device dislocation. Displacement 9,2% (61/665) and loss 3% (20/665) of the device was observed in following cases:

a) when there was no screw fixation of the distractor modules in order to avoid tooth roots perforation.

b) when patients missed activation procedures/checkups, that led to weakening of the device and its further loss/displacement.

The distractor's loss rate reported by Verlinden et. al. (4 cases out of 73 - 5,5%) [21], Ramieri et.al. (5/29 - 17,2%) [17] and Neyt et.al. (14/57 - 24,6%) [15] is higher than in this study (3%). Displacement of the distractor was observed by Koudstaal et.al. (1/10 - 10%) [11], Neyt et. al. (6/57 - 10,5%) [15], whose results are similar to the ones presented in this article. This group of complications was successfully corrected by the device change or repositioning. 35 patients out of 665 needed segmental osteotomy of the maxilla to be done during the following surgical treatment. The indications for segmental osteotomy were the following: 1) 3/35 patients had asymmetric expansion of the maxilla that couldn't be corrected by orthodontic treatment.

2) In 32/35 cases the expansion in the molars zone was inadequate while in incisors area the necessary level of distraction was achieved. In all the cases asymmetric/inadequate expansion was successfully corrected after segmental osteotomy of the maxilla was performed.

During the activation process 6 cases of palatine perforation were registered with the device modules dislocated in the maxilla sinus. In all 6 cases the protocol of activation wasn't followed properly. This complication was corrected by performing sinusotomy and module's removal out of sinus. 7 patients suffered postoperative bleeding. This complication was mentioned by Dergin [5] -12/60 nasal bleeding, 9 of which occurred at the following day after the operation. In the group of 120 patients Williams [24] observed 4 epistaxis within 7 days after SARME was performed. In our study 6 out of 7 bleeding were nasal, 4/7 happened on the first postoperative day, 1 - on the 3rd day, 1 - in the 7th. All 6 cases were stopped by nasal packing (4 by the-anterior and 2 by the posterior). 1/7 bleeding was palatine and it occurred on the postoperative day 5 in the zone of the left distractors module as the result of devices weakened pressure on the palate. The complication was resolved by soft tissue stitching.

As far as the operation technique doesn't include pterygomaxillary suture separation, the risk of bleeding because of pterygoid venous plexus trauma is minimized. Thus the main reasons of bleeding performing this technique are trauma of nasal mucosa while performing mid-palatal suture osteotomy or lateral nasal wall osteotomy and trauma of greater palatine artery [5].

Inflammation in distractor modules area was observed in 57 patients whose level of oral hygiene was insufficient (PHP $>1.7$ ), and also in patients whose distraction device wasn't stable. This complication can be prevented by the correction of patients' oral hygiene level and by the control of the devices fixation (check-ups every 2 weeks).

In 18 cases the relapse was observed in interdental width between first right and left molar, despite distraction device activation has been made with hypercorrection (2 mm).

In 5 cases patients had dental recession occurred due to trauma while performing midpalatal osteotomy and due to forced activation  $>1$  mm a day). All 5 recessions were on the medial surfaces of the teeth (in 4 cases tooth 1.1 had recession and in 1 case - 2.1).

All the recessions were self-corrected during the orthodontic treatment. In 1 case necrosis of the palatine mucosa was presented. It was caused by trauma during distraction device positioning. Dental complications were observed in 3 patients and were characterized by 1.1 teeth vitality loss ( $>200$  mkA) and discoloration. In all the cases the teeth were depulped and internal tooth bleaching was made. The complication was caused by



trauma during the osteotomy. In 2 cases formation of the defective bone regenerate in the anterior part of mid-palatal suture was noted. That could be caused by the forced activation of the distraction device.

**Conclusion.** SARME is an operation associated with the risks of postoperative complications. Treatment planning, following the operation protocol and using the minimally invasive access help to avoid the majority of complications.

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## SUMMARY

### SURGICALLY ASSISTED RAPID MAXILLARY EXPANSION: RETROSPECTIVE ANALYSIS OF COMPLICATIONS 2012-2017

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Surgically assisted rapid maxillary expansion (SARME) is a common technique developed to treat skeletally mature patients with transverse maxillary deficiency. Although SARME is supposed to be a relatively safe procedure, it is not completely free of complications. The purpose of this study was to reveal the most typical postoperative SARME complications.

Retrospective evaluation of the clinical cases of 665 patients (247 males and 418 females, mean age 25,3 years) with the diagnosis of maxillary transverse deficiency, who underwent SARME in period between 2012 and 2017 at the Clinical Center of Maxillofacial, Plastic Surgery and Dentistry, Moscow.

According to the results of the research, the most typical complications of SARME are paresthesia of the infraorbital nerve branches and nasopalatine nerve (198/665), distraction device dislocation (61/665), inflammation in the distraction device area (57/665), insufficient expansion of the maxilla (42/665), asymmetric expansion (27/665).

The number of complications revealed indicates that SARME is an operation associated with the risks of postoperative complications. Careful treatment planning, following the operation protocol and performing the minimally invasive access can help to avoid the majority of complications.

**Keywords:** maxillary transverse deficiency, surgically assisted rapid maxillary expansion, SARME, SARPE, RME, TMD, complications.

## РЕЗЮМЕ

### ХИРУРГИЧЕСКОЕ РАСШИРЕНИЕ ВЕРХНЕЙ ЧЕЛЮСТИ: РЕТРОСПЕКТИВНЫЙ АНАЛИЗ ОСЛОЖНЕНИЙ ЗА 2012-2017 ГГ.

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Хирургическое расширение верхней челюсти является общепринятым методом лечения пациентов с завершенным кранио-фасциальным ростом при недоразвитии верхней челюсти по трансверсальной плоскости. Несмотря на то, что хирургическое расширение верхней челюсти является относительно безопасной манипуляцией и сопряжено с риском возникновения осложнений.

Целью исследования явился анализ наиболее встречаемых послеоперационных осложнений хирургического расширения верхней челюсти.

Проведен ретроспективный анализ 665 клинических случаев пациентов (247 мужчин, 418 женщин, средний возраст 25.3 лет) с недоразвитой верхней челюстью по трансверсальной плоскости, которым проведено хирургическое расширение верхней челюсти с 2012 по 2017 гг. в Клиническом центре челюстно-лицевой, пластической хирургии и стоматологии, (Москва).

Согласно результатам анализа, наиболее частыми послеоперационными осложнениями хирургического расширения верхней челюсти являются парестезия ветвей подглазничного и носо-небного нерва (198/665), смещение дистракционного аппарата (61/665), воспаление слизистой в области дистракционного аппарата (57/665), недостаточное расширение верхней челюсти (42/665), асимметричное расширение верхней челюсти (27/665).

Выявленное число осложнений указывает, что хирургическое расширение верхней челюсти является вмешательством, сопряженным с риском возникновения послеоперационных осложнений. Тщательное планирование лечения, следование операционному протоколу и проведение операции через наименее инвазивный доступ позволяют избежать осложнения.

## რეზიუმე

ზედა ყბის ქირურგიული გაფართოება: გართულებების რეტროსპექტიული ანალიზი, 2012-2017 წწ.

ა.დრობიშვილი, ი.კლიპა, ნ.დრობიშვილი, ნ.ილინა, ი.ჟმირკო

მოსკოვის აკედოკიმოვის სახ. სახელმწიფო სამედიცინო-სტომატოლოგიური უნივერსიტეტი, რუსეთის ფედერაცია

კვლევის მიზანს წარმოადგენდა ზედა ყბის ქირურგიული გაფართოების ოპერაციის შემდგომი ყველაზე ხშირი გართულებების ანალიზი.

ჩატარებულია 665 კლინიკური შემთხვევის (247 - მამაკაცი, 418 - ქალი, საშუალო ასაკი - 25,3 წელი) რეტროსპექტიული ანალიზი პაციენტების განუვითარებელი ზედა ყბით ტრანსვერსულ სობრტყეში, რომელთაც მოსკოვის ყბა-სახის, პლასტიკური ქირურგიისა და სტომატოლოგიის კლინიკურ ცენტრში 2012-2017 წწ. ჩატარდა ზედა ყბის ქირურგიული გაფართოების ოპერაცია.

ჩატარებული ანალიზის შედეგების მიხედვით, ზედა ყბის ქირურგიული გაფართოების ოპერაციის შემდგომ ყველაზე ხშირ გართულებას წარმოადგენს თვალის და ცხვირ-სახის ნერვების ტოტების პარესთეზია (198/665), დისტრაქციული აპარატის ცდომა (61/665), ლორწოვანის ანთება დისტრაქციული აპარატის მიდამოში (57/665), ზედა ყბის არასაკმარისი გაფართოება (42/665), ზედა ყბის ასიმეტრიული გაფართოება (27/665).

გართულებების გამოვლენილი რაოდენობა მიუთითებს, რომ ზედა ყბის ქირურგიული გაფართოება წარმოადგენს ოპერაციის შემდგომ გართულებათა განვითარების რისკთან შეუდგებულ ოპერაციას. მკურნალობის გულდასმით დაგეგმვა, ოპერაციის პროტოკოლის დაცვა და ოპერაციის ჩატარება მინიმალურად ინვაზიური მიდგომით ხელს უწყობს გართულებათა მაღალი სიხშირის თავიდან აცილებას.

## WAYS TO IMPROVE THE EFFICACY OF ORTHOPEDIC TREATMENT OF PATIENTS WITH SEVERE EXCESSIVE TOOTH WEAR

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Excessive tooth wear is currently one of the main problems of oral health [1,2]. This pathology is one of the most difficult for teaching in medical universities [3]. Excessive tooth wear affects both function and aesthetics. Teeth with excessive tooth wear cannot be effectively used for biting and chewing food [4]. The clinical picture of increased tooth wear is extremely diverse and depends on the degree of damage, topography, prevalence and duration of the process, its etiology, the presence of concomitant general pathology and lesions of the dento-facial system.

The pathological process can affect the teeth of one or both jaws, on one or both sides. In practice, there are cases of varying degrees of damage to the teeth of one or both jaws. The nature and plane of the lesion can be identical, but it can also differ. All this determines the diversity of the clinical picture of pathological tooth wear, which is significantly complicated with partial adentia of one or both jaws.

Patient complaints can be different and depend on the degree of the increased abrasion of teeth, topography and extent of the lesion, the duration of the disease, concomitant pathology. With absence of concomitant lesions of the maxillofacial region, patients with pathological abrasion of teeth usually complain about cosmetic defect due to progressive loss of hard tissues of teeth, sometimes hyperesthesia of enamel and dentin, with acid necrosis - on tooth sensitivity and enamel roughness.

Excessive tooth wear includes mechanical attrition, abrasion, erosion. Mechanical attrition is the loss of occlusal surfaces of a tooth due to excessive pressure from the antagonist tooth. Abrasion is a lesion of tooth tissues on the buccal surfaces associated with forces caused by improper brushing of the teeth. Erosion is the loss of hard tissues of teeth from combined chemical-mechanical causes, mainly associated with acids from the diet.

There are several factors associated with various types of tooth wear [5-9]. As a rule, external factors of tooth erosion associated with food and diet [5]. Acid in the diet is the main cause of erosion. Food acids associated with acid erosion are found in citrus fruits or fruit juices, carbonated drinks, wine and vinegar. Important factors associated with teeth extraction are bruxism, chewing type, etc. [8]. Abrasion is usually associated with the influence of abrasive particles in toothpastes [9]. Excessive tooth wear treatment is complex and time consuming process [3].

In the absence of treatment, tissue wear progresses rapidly and the crowns of the teeth become significantly shorter.

The lower third of the face decreases, which is manifested by the formation of folds at the corners of the mouth. In persons with a significant decrease in bite, changes in the temporomandibular joint may occur and, as a consequence, there may be burning or pain in the mucous membrane, hearing loss and other symptoms common to low bite syndrome. With further progression of the process, the abrasion of the incisors reaches the necks.

The cavity of the tooth is visible through the dentin, but it is not opened due to the deposition of replacement dentin. In deep occlusion, the labial surface of the lower incisors contact the palatal surface of the maxillary incisors and these surfaces are significantly eroded. The most pronounced tissue wear is observed in the case of the absence of a part of the teeth. [7].

For example, in the absence of molars, on which the ratio of the dentition normally depends, the incisors and canines are intensively eroded, since they are overloaded. In addition, tooth displacement, bone resorption at the apex of the roots and interdental septa may occur due to overload. Quite often, tooth wear occurs due to improper design of removable and fixed dentures [8].

On numerous occasions, increased tooth wear occurs in a number of endocrine disorders - dysfunction of the thyroid, parathyroid glands, pituitary gland, etc. In this case, the mechanism of erosion is determined by a decrease in the structural resistance of tissues. In particular, increased tooth wear is found in cases of fluorosis, marble disease, Capdepon-Stainton syndrome, primary enamel and dentin underdevelopment [9].

In the case of pathological wear of the teeth, dysfunction of the masticatory muscles and the temporomandibular joint, due to a decrease in the interalveolar distance and a shortening of the lower third of the face is often observed. It is necessary to determine pain points by palpation, soreness or crunching in the temporomandibular joints, as well as the peculiarities of the movement of the articular heads of the lower jaw when opening and closing the mouth in patients suffering from muscle and facial pain. It is necessary to study radiographs, diagnostic models of the jaws to establish the correct diagnosis and an adequate plan of orthopedic treatment [1].

The first condition that should be resolved during treatment is the definition of etiological factors and their elimination [10, 11].

The second condition - is the restoration or compensation of the lost hard tissues of teeth. This can be done using different methods and technologies, depends on the experience of the dentist and the wishes of the patient. In many cases, all-ceramic crowns can be used as a treatment option, as well as metal-ceramic crowns, with the same success rate, if occlusal and other factors are considered and understood [12]. Restoration of the anatomical shape of worn teeth depends on the degree, type and form of the lesion.

The dentist should help the patient maintain the occlusal ratio obtained as a result of the treatment as long as possible. In this case, an individually designed prevention program helps, including professional hygiene, during which the condition of periodontal tissues and restoration structures are monitored. Frequently, the occlusal splint helps to preserve the restorations, minimizing the increased load during the night or day.

Treatment of increased tooth wear, complicated by a decrease in occlusal height, is carried out in several stages: 1) restoration of the occlusal height with temporary medical and diagnostic devices; 2) adaptation period; 3) permanent prosthetics.

At the first stage, the restoration of the occlusal height is carried out with the help of plastic dental and gingival aligners, removable plate or clasp prostheses with overlapping of the chewing surface of worn teeth. Such restoration can be instantaneous in the case of a decrease in the occlusal height to 10 mm from the height of physiological rest and stepwise - 5 mm every 1-2 months with a decrease of the occlusal height by more than

10 mm from the height of physiological rest. To establish the height of the future prosthesis, wax or plastic bases with bite rollers are made, the required «new» position of the lower jaw is determined and fixed in a conventional way in the clinic, X-ray control is mandatory. On radiographs of the temporomandibular joints with closed dentition in a position fixed with wax rollers, there should be a «correct» position of the articular head (on the slope of the articular tubercle), which is even on both sides. Only after that, this position is fixed with temporary prosthetic devices. [13]. The second stage is the adaptation period - required for the patient to completely get used to the «new» occlusal height, which occurs due to the restructuring of the myotatic reflex in the masticatory muscles and the temporomandibular joint. During this period, the patient should be under the supervision of the attending physician orthopedic dentist (at least 1 time per week, and in case of subjective discomfort, pain, discomfort, inconvenience when using medical diagnostic devices - more often). In the case of using fixed medical and diagnostic devices, the adaptation process proceeds faster compared to the restoration of the occlusal height with removable structures, especially plate structures. This is explained not only by the design features of the prostheses, but also by the fact that fixed aligners are secured with cement and patients use them constantly.

Third stage of treatment - permanent prosthetics - does not fundamentally differ in the type of denture designs used in the treatment of pathological tooth wear. It is important to note the need to use construction materials which guarantee the stability of the established occlusal height. The use of plastic on the chewing surface of bridges is inadmissible. It is preferable to use porcelain teeth, cast occlusal onlays for removable dentures. Counter inlays and crowns are used to stabilize the occlusal height. An important condition for achieving good results in permanent prosthetics is the manufacture of prostheses under the control of temporary medical and diagnostic aligners, as well as the phased production of permanent prostheses [14]. First, prostheses are made for one half of the upper and lower jaws in the area of the chewing teeth, while temporary aligners remain fixed in the frontal area and on the opposite half of both jaws. When fitting permanent prostheses, temporary aligners allow you to accurately set the occlusal height and optimal occlusal contacts in various phases of all types of occlusion to which the patient is adapted. After fixation of permanent dentures on one half of the jaws, temporary aligners are removed and the manufacture of permanent dentures for the rest of the dentition is started. Medical and diagnostic mouth guards are temporarily fixed for the period of manufacturing prostheses [15]. It should be noted the possibility of relapses in patients with pathological tooth wear on the background of bruxism and parafunction, which confirms the idea that only orthopedic interventions are insufficient without appropriate neuropsychiatric corrections [16].

Thus, well-known scientific works were carried out in the direction of studying the etiopathogenesis of excessive tooth wear associated with functional insufficiency and morphological inferiority of hard tissues of teeth, hereditary and congenital, endogenous character (disorders of the endocrine system and metabolism, impaired mineralization of hard tissues of teeth, chemical damage (acid necrosis, industrial hazards, abrasive dust, radiation necrosis of teeth), which in some cases allowed the authors to develop preventive measures. A number of studies are devoted to the third group of etiological factors, such as functional overload of teeth, which causes increased wear of teeth left after partial loss of teeth and overload of their parodontium. Medical errors in the design of prostheses and restora-

tion technologies for restoration of the crown part of the teeth can lead to functional overload, which leads to the occurrence of super contacts, leading to functional overload. However, there is no clear answer to questions about the features of the clinic, diagnosis and complex treatment of excessive tooth wear, combined with dentoalveolar anomalies, decreased occlusion, bruxism, parafunctions of the masticatory muscles, which can become etiological factors of excessive tooth wear and its complications. This is very important for the development of preventive and therapeutic measures that allow to suspend further teeth wear, contributing to a longer service of restorative structures used with excessive tooth wear of decompensated form.

To study the effectiveness of the action of transcutaneous electrical nerve stimulation (TENS) in the normalization of the masticatory muscles in the treatment of patients with severe excessive tooth wear.

**Material and methods.** We conducted a comparative study of 60 people with pronounced excessive tooth wear by measuring the electromyographic (EMG) activity of mm.masseter and temporalis during tooth compression (“Reporter” electromyograph, Biomedica, Italy) (Figs. 1, 2). The researchers were divided into two groups - in the first (30 people) preparation of the maxillofacial system for further prosthetics was carried out by wearing removable teeth guards, in the second group (30 people), TENS method was used together with mouth guards to rebuild the tone of the masticatory muscles. In both groups, an electromyographic research of mm.masseter and temporalis was performed after 1 week, 1 and 2 months of treatment. TENS of the temporal and masticatory muscles was performed in the amount of 8 sessions for 2 weeks.



Fig. 1. Pronounced excessive tooth wear of the teeth with a decrease in the height of the bite

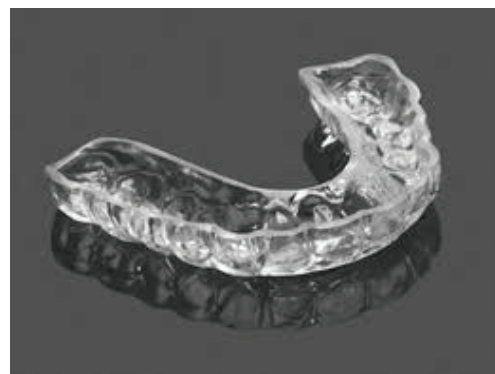


Fig. 2. Removable teeth guard for gradual formalization of the height of the bite and function of the masticatory muscles

Table 1. Functional characteristics of the left and right temporal muscles in patients of the first group (n=30)

Parameter	Group 1		
	7 days	1 month	2 months
Ta (s)	0,46±0,03	0,36±0,02	0,31±0,02
Trp (s)	0,41±0,02	0,33±0,02	0,30±0,03
A (µV)	114,2±0,3	130,0±0,3	144,2±0,4
K	1,12±0,03	1,09±0,03	1,03±0,02

Table 2. Functional characteristics of the right and left temporal muscles in patients of the second group (n=30)

Parameter	Group 2		
	7 days	1 month	2 months
Ta (s)	0,50±0,03	0,39±0,04	0,38±0,03
Trp (s)	0,29±0,04	0,35±0,03	0,37±0,05
A (µV)	133,6±0,7	160,0±0,7	161,3±0,6
K	1,70±0,03	1,07±0,03	1,08±0,04

Table 3. Functional characteristics of the right and left masticatory muscles in the 1st group of patients (n=30)

Parameter	Group 1		
	7 days	1 month	2 months
Ta (s)	0,40±0,05	0,39±0,03	0,38±0,04
Trp (s)	0,28±0,03	0,36±0,02	0,35±0,03
A (µV)	134,0±0,5	150,3±0,6	167,1±0,5
K	1,50±0,04	1,08±0,03	1,06±0,03

**Results and discussion.** The characteristics of the bioelectric activity of the right and left temporal muscles in patients of the first group are presented in table 1.

The average amplitude of the biopotentials of m.temporalis in the phase of bioelectric activity after 1 week of treatment in patients of the first group was 114,2±0,3 µV and significantly increased two months after the establishment of the teeth guard – 144,2±0,4 µV (p<0,05).

The time period of activity (Ta) on the electromyogram of the temporal muscles 1 week after the start of treatment was 0,46±0,03 s. From 1 month of the study, this indicator of EMG began to go down (0,36±0,03 s). The shortest time of the period of activity in an EMG research of the temporal muscles of patients of the 1st group was recorded for two months of using the teeth guard, where it was 0,31±0,02 s (p<0,05). In the future, the value of this indicator did not significantly change until the end of the study. The rest period (Trp) a week after the start of treatment was 0,41±0,02 s, but also stabilized after 2 months, when it was already 0,30±0,03 s (p<0,05).

The K coefficient (the ratio of the period of activity to the period of rest of the muscle) 1 week after the start of treatment in patients of the first group was 1,12±0,03 s. After 2 months, having obtained a value of 1,03±0,02, the K coefficient remained stable at this level until the end of the examination period.

Thus, the results of EMG of the temporal muscles in patients of the first group show that high values of the average amplitude of the bioelectric activity of these muscles are achieved two months after the use of teeth guards. The K coefficient also approached one two months after the application of the teeth splint, which indicated the normalization of the contractile function of mm.temporalis.

The research data of the right and left temporal muscles in patients of the second group are shown in Table 2.

The average amplitude of m.temporalis biopotentials in the phase of bioelectric activity of the temporal muscles after 1 week of treatment was 133,2±0,034 µV. After 1 month - 160,0±0,7 µV (p<0,05). After 2 months, the value of the studied parameter did not significantly change.

The phase activity time (Ta) on the electromyogram 1 week after the start of treatment was 0,50±0,03 s. The shortest time of activity was recorded after a month - it amounted to 0,35±0,03 s (p<0,05). In the future, the value of this indicator does not significantly decrease by the end of the research. The time of rest period (Trp) a week after the start of treatment was 0,29±0,04 s, after 1 month, it was already equal to 0,35±0,03 s (p<0,05).

The K coefficient 1 week after the start of treatment was 1,70±0,03 s. After 1 month, its value became 1,07±0,03.

Thus, the results of EMG mm.temporalis, high in amplitude, were observed in group 2 one month after the use of teeth guards and the use of TENS. The coefficient K also approached one, after one month of the installation of the teeth guards and the use of TENS, which indicated the normalization of the contractile function of mm.temporalis.

The research data of the right and left masticatory muscles in patients of the first group are shown in Table 3.

The average amplitude of the biopotentials in the phase of bioelectric activity of the masticatory muscles proper in the 1st group of patients reached their maximum value 2 months after the placement of the teeth guards and amounted to 167,1±0,5 µV (p<0,05).

The K coefficient of masticatory muscles 1 week after application of the teeth guards was 1,50±0,04. He began to approach one 2 months after the installation of the teeth guards and amounted to 1,06±0,03.

In patients of the second group (Table. 4), the data of the study of electrographic indicators of masticatory muscles are presented in Table 4.

Table 4. Functional characteristics of the right and left masticatory muscles in patients of the second group (n=30)

Parameter	Group 2		
	7 days	1 month	2 months
Ta (s)	0,42±0,05	0,37±0,04	0,40±0,05
Trp (s)	0,29±0,04	0,33±0,03	0,35±0,04
A (µV)	159,0±0,5	182,4±0,6	181,0±0,5
K	1,50±0,03	1,02±0,03	1,07±0,05

The average amplitude of the biopotentials in the phase of bioelectric activity of the masticatory muscles proper reached the optimal value 1 month after the installation of the teeth guards and application of TENS and amounted to 182,4±0,6 µV (p<0,05).

The K coefficient of masticatory muscles 1 week after application of the teeth guards and application of TENS was 1,50±0,03. He began to approach one after 1 month of the installation of the teeth guards and TENS and amounted to 1,02±0,03.

**Findings.** In patients with excessive tooth wear of the teeth and a significant decrease in the height of the bite, our preparation for prosthetics contributes to a more rapid increase in the average amplitude of biopotentials in the phase of muscle bioelectric activity and m.masseter, m.temporalis, a noticeable decrease in the duration of periods of activity and rest of the mm. masseter and mm.temporalis in the 2nd group of patients compared with the first group in each study period, which indicates a pronounced positive effect of using TENS together with the removable teeth guard to normalize the bioelectric activity of the masticatory muscles.

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#### SUMMARY

#### WAYS TO IMPROVE THE EFFICACY OF ORTHOPEDIC TREATMENT OF PATIENTS WITH SEVERE EXCESSIVE TOOTH WEAR

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Excessive tooth wear is currently one of the main problems of oral health. Excessive tooth wear affects both function and aesthetics. Teeth with excessive tooth wear cannot be effectively used for biting and chewing food. Treating excessive tooth wear is complex and time consuming. Studies on increasing the effectiveness of treatment of such patients are relevant.

The study involved 60 people with a significant degree of excessive tooth wear and a decrease in the height of the bite. We examined patients using measurements of the electromyographic (EMG) activity of mm.masseter and temporalis. The subjects were divided into two groups - in the first group (30 people), the maxillofacial system was prepared for further prosthetics by wearing a removable dental splint-teethguard, in the second group (30 people) we used both removable splint-teethguards and transcutaneous electrical nerve stimulation (TENS). In both groups, an electromyographic study of mm.masseter and temporalis was performed after 1 week, 1 and 2 months of treatment.

In patients with excessive tooth wear and a significant decrease in bite height, our method of preparation for orthopedic treatment contributed to a more rapid normalization of mm.masseter and temporalis functions.

The results indicate a pronounced positive effect of the use of removable teeth guard and TENS on the normalization of the bioelectric activity of the masticatory muscles in the preparation of patients for orthopedic treatment of excessive tooth wear.

**Keywords:** pathological tooth wear, masticatory muscle activity, removable splint, transcutaneous electrical nerve stimulation.

## РЕЗЮМЕ

### ПУТИ ПОВЫШЕНИЯ ЭФФЕКТИВНОСТИ ОРТОПЕДИЧЕСКОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С ВЫРАЖЕННЫМ ЧРЕЗМЕРНЫМ СТИРАНИЕМ ЗУБОВ

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Чрезмерное стирание зубов по сей день является одной из основных проблем здоровья полости рта. Чрезмерный износ зубов влияет как на функцию, так и на эстетику. Зубы с чрезмерным износом не могут эффективно использоваться для кусания и пережевывания пищи. Лечение чрезмерного износа зубов является сложным и трудоемким процессом. Исследования по повышению эффективности лечения таких больных по сей день весьма актуальны.

В исследовании приняли участие 60 лиц со значительной степенью чрезмерного износа зубов и с уменьшением высоты прикуса. Пациентов обследовали, используя измерения электромиографической (ЭМГ) активности mm.masseter и temporalis. Больные разделены на две группы: в I группе (n=30) челюстно-лицевую систему готовили к дальнейшему протезированию путем ношения съемной зубной шины-зубочелюстного протеза, во II группе (n=30) использовали как съемные шины-зубочелюстные протезы, так и чрескожную электростимуляцию нервов (TENS). В обеих группах электромиографическое исследование mm.masseter и temporalis выполнено спустя 1 неделю, 1 и 2 месяца после лечения.

У пациентов с чрезмерным износом зубов и значительным уменьшением высоты прикуса предложенный авторами метод подготовки к ортопедическому лечению способствовал более быстрой нормализации функции mm.masseter и temporalis.

Полученные результаты свидетельствуют о выраженном положительном влиянии применения съемных зубных кап и TENS на нормализацию биоэлектрической активности жевательных мышц при подготовке пациентов к ортопедическому лечению чрезмерного износа зубов.

## რეზიუმე

კბილების მომატებული ცვეთის მქონე პაციენტების ორთოპედიული მკურნალობის ეფექტურობის ამაღლების გზები

ო.სავჩუკი, ვ.კრასნოვი

პერსონალის მართვის რეგიონთაშორისი აკადემია, კიევი, უკრაინა

კბილების მომატებული ცვეთა წარმოადგენს პირის ღრუს ჯანმრთელობის ერთ-ერთ ძირითად პრობლემას, ვინაიდან მოქმედებს, როგორც მათ ფუნქციაზე, ასევე, ესთეტიკაზე. ასეთი კბილები ვერ იქნება ეფექტურად გამოყენებული საკვების მოკბენისა და დაღვწვისათვის. კბილების მომატებული ცვეთის მკურნალობა რთული და შრომატევადი პროცესია. ამ ტიპის პათოლოგიის მქონე პაციენტების მკურნალობის ეფექტურობის ამაღლება მეტად აქტუალურია.

კვლევაში ჩართული იყო 60 პირი კბილების მომატებული ცვეთის მნიშვნელოვანი ხარისხით და თანაკბილის სიმაღლის შემცირებით. პაციენტებში ელექტრომიოგრაფიულად შესწავლილია mm.masseter-ის და temporalis-ის აქტივობა. პაციენტები დაიყო ორ ჯგუფად: I ჯგუფში (n=30) ყბა-სახის სისტემა შემდგომი პროთეზირებისათვის მზადდებოდა მოსახსნელი პროთეზის (კაპის) ტარების გზით, II ჯგუფში (n=30) კი გამოყენებული იყო როგორც მოსახსნელი პროთეზები, ასევე, ნერვების კანგამტარი ელექტროსტიმულაცია (TENS). ორივე ჯგუფში mm.masseter-ის და temporalis-ის ელექტრომიოგრაფიული კვლევა ჩატარდა მკურნალობიდან 1 კვირის, 1 და 2 თვის შემდეგ.

ავტორების მიერ შემოთავაზებული ორთოპედიული მკურნალობისათვის მომზადების მეთოდი პაციენტებში კბილების მომატებული ცვეთით და თანაკბილის სიმაღლის მნიშვნელოვანი შემცირებით ხელს უწყობს mm.masseter-ის და temporalis-ის ფუნქციის უფრო სწრაფ ნორმალიზებას.

მიღებული შედეგები მიუთითებს კბილების მოსახსნელი კაპების და TENS-ის დადებითი გავლენის შესახებ სადეჭი კუნთების ბიოელექტრული აქტივობის ნორმალიზებაზე პაციენტების ორთოპედიული მკურნალობისათვის მომზადების პროცესში კბილების მომატებული ცვეთის დროს.

## PECULIARITIES OF EVALUATION OF THE ORAL FLUID ANTIOXIDANT ACTIVITY IN PATIENTS WITH LOCAL OR SYSTEMIC DISEASES

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Assessment of the state of oxidative homeostasis is one of the most prospective areas of laboratory diagnostics. Despite the low specificity of this marker, changes in its value serve as an important symptom that characterizes patients with a wide range of diseases, allows us to judge the severity of the pathological process, make prognosis and adjust therapy if necessary [4]. To assess the state of balance of the prooxidant - antioxidant system, a large number of markers of oxidative stress and the functional state of the antioxidant defense system are to be determined [7,14]. The intensity of free radical processes is judged by determination in the biofluids and tissues of the content of oxidative damage products of lipids (malondialdehyde, diene and triene conjugates, etc.) [20], proteins (bityrosine, carbonyl products, etc.) [1], nucleic acids (8-hydroxy-2-deoxyguanosine) [12], as well as the production of reactive oxygen species or the other radicals generated. On the other hand, oxidative stress develops not only as a result of the free radical reactions intensification but also of a decrease in the antioxidant system potential, so it is justified to assess its components' activity. For this reason, the concentration of low-molecular antioxidants, thiol groups of proteins, the activity of anti-radical protection enzymes, etc. are to be determined. One should consider the multicomponent antioxidant system functioning on stages of prevention of free radical processes initiation, the neutralization of radicals and reactive molecules such as hydrogen peroxide, and regeneration of own components, in particular of glutathione for its multiple reuses.

Besides, antioxidants that protect the hydrophilic and lipophilic phases can be conditionally clustered. Thus, assessing the real state of oxidative homeostasis becomes a rather difficult task, which consists of determining the number of parameters that can change in different directions. The way out of this situation can be an assessment of integral indicators determined by the state of several parameters and comprehensively characterize the state of a particular link in the body's nonspecific defense system [6,13]. One of these indicators is the total antioxidant activity, which is determined by various methods, such as amperometric one, which consists of analyzing the total content of substances that can be oxidized on the surface of the working electrode. Among the chemical methods for testing antioxidant capacity, methods based on the assessment of reducing capacity, in particular, the reduction of Fe<sup>3+</sup> or Cu<sup>2+</sup> with subsequent identification of the reduced form, as well as methods for the radical sorption assessment based on the registration of the neutralization rate of relatively stable radicals are common [2,3,11].

Each method has its advantages and disadvantages, but the most widely used are iron - or copper-reducing techniques, which are based on a few commercial kits designed for clinical laboratory diagnostics and adapted for use on automatic biochemical analyzers (Total antioxidant status assay kit, Randox Laboratories, United Kingdom) or microplate readers (Total Antioxidant Capacity Assay Kit, Abcam; OxiSelect™ Total Antioxidant Capacity (TAC) assay kit). Recently, the direction of development of non-invasive technologies has been actively developing in laboratory diagnostics, as a result, the significance of analysis of the mixed saliva or oral fluid composition is increasing [15].

In this direction, we can distinguish 2 main applications: the investigation of oral fluid's biochemical parameters to assess systemic pathology (substitution of blood by saliva) and the study of the perspectives for analyzing changes in the composition of bio-liquid on the background of the dental disease. On the one hand, it is widely known that many indicators of blood plasma and oral fluid are well correlated with each other; on the other hand, it is obvious that in presence of a pathological process affecting the oral cavity tissues, local inflammation will have a leading influence on the composition of saliva. The latter limits the use of salivadiagnostics in medical practice, but opens up perspectives in dentistry. The antioxidant system of saliva does not have any fundamental organizational differences from that of blood, and mainly differs in the content of individual components, which include enzymes (peroxidase, catalase, superoxide dismutase, glutathione peroxidase) and low-molecular antioxidants (uric acid, tocopherol, ascorbic acid) [8].

There is a thiol link represented by glutathione, enzymes of its metabolism and SH-groups of proteins [9]. Changes in the total antioxidant activity of oral fluid described by different authors differ dramatically. In a number of situations, the authors describe a decrease in the antioxidant potential of saliva in case of somatic and dental diseases and interpret them as a result of oxidative stress [16,19,22], other authors point out that the development of diseases of various profiles is accompanied by a statistically significant increase in the analyzed parameter, which is also associated with intensification of oxidative processes with the enhanced compensatory activity of the antioxidant defense system of saliva [18,21]. Some authors point to the possibility of the influence of orthopedic structures in the oral cavity on the level of total antioxidant activity [17].

Thus, the interpretation of the study results of oxidative homeostasis of oral fluid causes some difficulties, for the solution of which a parallel assessment of the dynamics of changes in the total antioxidant activity of blood plasma and oral fluid is studied in different categories of patients.

**Material and methods.** The study of changes of antioxidant activity in the presence of a disease, directly affecting tissues of the maxillofacial region were carried out at the Department of Maxillofacial Surgery of SBME "Krasnodar CBSE" "MOH KK with the participation of 42 patients with odontogenic phlegmons (group 2), localized in the pterygoid-maxillary, submandibular or peripharyngeal spaces. These patients were divided into 2 subgroups depending on the therapy. Patients of 2A subgroup (n=19) received traditional treatment, including surgical intervention to open and sanitize the purulent focus, antibiotic treatment and symptomatic therapy. Patients of 2B subgroup (n=23), in addition to the traditional treatment regimen received a solution of cytoflavin (NTTP Polisan, Russia) (a preparation of succinic acid and energy exchange cofactors), which has antioxidant and antihypoxant properties. The blood and oral fluid are taken from the patients of were collected before the start of treatment, on the 1st, 3rd, and 5th days after surgery.



The testing subjects with diseases of the oral cavity were represented by the patients with partial absence of 3-4 teeth (group 3, n=18), whose treatment was carried out based on the dental polyclinic of the Federal State Budgetary Educational Institution of KubSMU of the Ministry of Health of Russian Federation and included restoration of the integrity of the dentition using the method of dental implantation. In the group 4 patients, oral fluid was collected at different stages of treatment: before the installation of dental implants, after the removal of sutures, before the installation of the gum shaper, before the installation of orthopedic structures, and a year after the start of treatment (or 6 months after the installation of orthopedic systems).

To assess changes in antioxidant activity in presence of somatic diseases, the study included patients with the chronic inflammatory uterine disease with the combined course of salpingophoritis (group 4, n=30) and 20 patients with type 2 diabetes mellitus (group 5). From the group 5 patients the blood and oral fluid were taken once, and from group 4 patients - before and after 14 days of treatment. Herein, depending on the therapy, patients of the 4th group were divided into 2 subgroups of 15 testing subjects. Patients in subgroup 4A received standard treatment, including antibiotic therapy, non-steroidal anti-inflammatory drugs, and vaginal sanitation. Patients of the 4B subgroup additionally received antioxidant agents - retinol, tocopherol, and sodium thiosulfate. Patients of these groups were observed based on the clinic of the KubSMU. An essential criterion for selecting patients in the groups 4 and 5 was a sanitized oral cavity to exclude the influence of local pathological processes. In addition, the material was collected from practically healthy donors who were observed in the same clinic as part of the medical examination of the adult population. The testing subjects of the last category made up the control group (group 1).

The blood was collected from the ulnar vein in a volume of 4-5 ml in test tubes with sodium heparin. The oral fluid was collected by spitting into clean, dry test tubes made of polymer material without salivation stimulation.

The iron-reducing method's total antioxidant activity of the blood plasma and oral fluid was determined (FRAP-Ferric Reducing/Antioxidant Power). The blood plasma was obtained in a standard way; after centrifugation of heparinized blood, preparation of oral fluid also included centrifugation (2600g for 10 minutes), selection of the supernatant fluid and further laboratory operation with it. Biochemical studies were performed immediately after delivering fresh material from the clinic without pre-freezing and long-term storage [10]. The determination was performed under the conditions of incubation of the blood plasma or saliva with Fe<sup>3+</sup> ions (in the composition of iron chloride) and 2,2'-dipyridyl, which turns to a colored compound with Fe<sup>2+</sup> ions formed during the reduction of the tested bio-liquid by antioxidants. The color intensity evaluated photometrically at 520 nm is directly proportional to the total antioxidant activity. The obtained data were expressed in mM of ascorbic acid, accepted as a standard and tested under the similar conditions for the calibration graph construction [5]. The study was based on the principles set out in the WMA Helsinki Declaration (Fortaleza, 2013). All subjects provided voluntary informed consent before being included in the study. The independent ethics committee approved the study of the Federal State Budgetary Educational Institution of the Ministry of Health of the Russian Federation (Protocol No. 57 of 29.11.2017).

Statistical data analysis was performed using the Stat Plus program for Windows. The obtained data were compared using the nonparametric criteria of Mann-Whitney for independent

groups and of Wilcoxon for dependent groups (indices obtained at different stages of the study in patients of the same group). The article's data are presented in the form of median and quartiles (25th and 75th percentiles). The differences between the indices were considered statistically significant at the level of  $p < 0.05$ .

**Results and discussion.** Determination of the total antioxidant activity in the oral fluid of patients with dental profile showed a tendency to increase this index. In patients with phlegmon of the maxillofacial region, the level of the analyzed marker initially did not differ from the control value of the indices (Fig. 1). Still, after the surgical resolution of the purulent-necrotic process, the level of the antioxidant potential increased by 48% related to its initial value. On the 3rd day of treatment, a slight decrease in the considered index was registered, followed by a further increase in it. On the 5th day of treatment, the total antioxidant activity of the mixed saliva of group 2A patients receiving a course of traditional therapy exceeded the control parameter level by 95%. On the background of traditional therapy supplemented with cytoflavin, a lower level of iron-restoring ability of oral fluid was maintained. At any stage of treatment, the value of this parameter did not exceed the control values. Interpretation of these results is quite difficult; it is unclear how lower values of the integral index of the functional state of the antioxidant defense system can obviously indicate higher efficiency of energotropic correction. Only at the last stage of observation were different values of the index determined in patients of 2A and 2B subgroups. Patients receiving traditional treatment were characterized by the preservation of initially reduced values of total antioxidant activity. In contrast, in the blood plasma of patients receiving additional cytoflavin, the analyzed index level increased statistically significantly, reaching the level of control values of the same parameter.

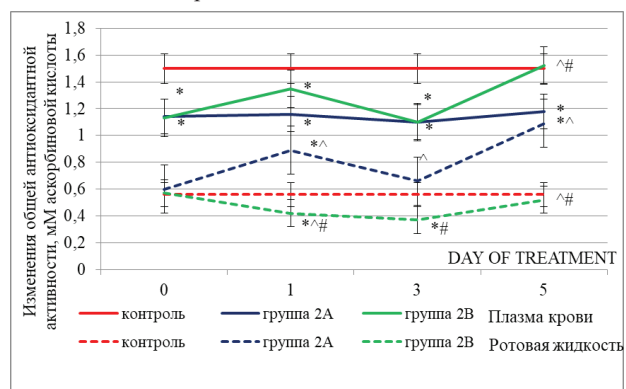


Fig. 1. Total antioxidant activity of blood and oral fluid in patients with phlegmon of the maxillofacial region during treatment (Me (p0.25-p0.75)) Note: \* - statistically significant differences from the indicator of the control group ( $p < 0.05$ ), ^ - statistically significant differences from the indicator obtained at the previous stage of treatment ( $p < 0.05$ ), # - statistically significant differences between the indicators of subgroups 2A and 2B at the corresponding periods of treatment ( $p < 0.05$ ). The control group's indicator was determined once but extended on the graph through all treatment periods for clarity of changes

The results of the study of the total antioxidant activity of the oral fluid of patients with partial absence of 3 and 4 teeth were somewhat similar to the data of the 2nd group. Initially, the level of the index under consideration was increased by 50% (Fig. 2), which was explained by the long-term existence of the patho-

logical process. The absence of teeth is not a harmless condition that has an exclusively aesthetic effect. On the background of even a few teeth absence, there is a significant redistribution of the load on the remaining elements of the dentoalveolar system and surrounding soft tissues, which is accompanied by metabolic changes and is reflected in the chemical composition of mixed saliva.

At the 2nd stage of the study, which took place 2 weeks after the installation of dental implants, the total antioxidant activity decreased to the level of control values, which we associated with the implementation of professional hygiene procedures at the initial examination stage and a high degree of adherence of patients to the recommendations of specialists in maintaining oral health at this stage. However, in the future, when determining the level of the antioxidant potential of mixed saliva after 3 months at the stage of the gum shaper installing, an increased value of 2.2 times still was recorded. At the last stages of the study, which was performed after the orthopedic structure's installation and the dentition integrity restoration, the oral fluid iron-restoring ability values were determined, which did not differ from the level of control.

The evaluation of antioxidant activity at local and systemic levels in the patients with somatic diseases in sanitized oral cavity conditions showed a different nature of changes. Thus, in the patients with inflammatory diseases of the pelvic organs, a reduced value of the analyzed blood plasma index in the acute

phase was recorded by 24% relatively to the level of the corresponding index of the control group; herein the oral fluid index corresponded to the value in the practically healthy volunteers' group (Fig. 3).

Therapy course according to the standard scheme did not contribute to statistically significant changes of total antioxidant activity of blood plasma, which remained below the control levels, and therapy, supplemented through an antioxidant orientation, there was a noticeable increase of the parameter by 52% relative to the initial value or to the level of the targets. In the oral fluid at any stage in any of the subgroups of group 4, there were no statistically significant differences between the value of the index and the similar parameter of group 1.

These changes can be interpreted as violations of oxidative homeostasis with a decrease in the protective potential of the antioxidant system of the blood. At the same time, due to the limited inflammatory process of the organs of women's reproductive tract, it was not possible to register these violations in the oral fluid.

As the 4th clinical example, patients with type 2 diabetes mellitus were selected, which were characterized by metabolic disorders affecting almost all organs and tissues of the human body. These should be associated with changes in biochemical parameters both at the systemic and local levels. Indeed, the total antioxidant activity analysis showed reduced values in both studied bio-liquids – the blood plasma and the oral fluid. In the blood

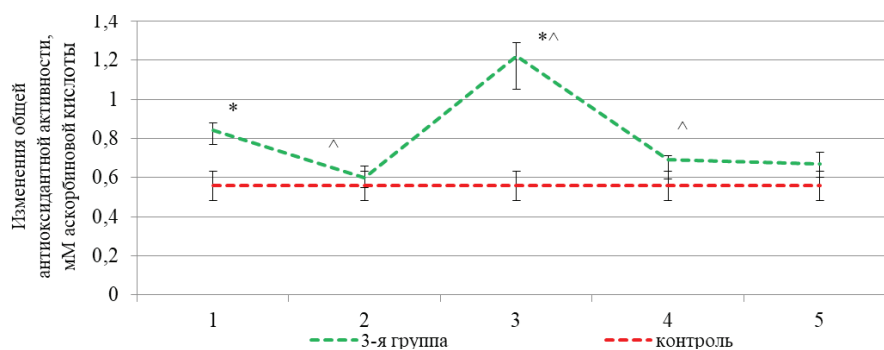


Fig 2. The total antioxidant activity of the oral fluid in patients with the absence of 3-4 teeth in the process of restoring the integrity of the dentition using dental implantation (Me (p0.25-p0.75))

Note: \* - statistically significant differences from the indicator of the control group ( $p < 0.05$ ), ^ - statistically significant differences from the indicator obtained at the previous stage of treatment ( $p < 0.05$ )

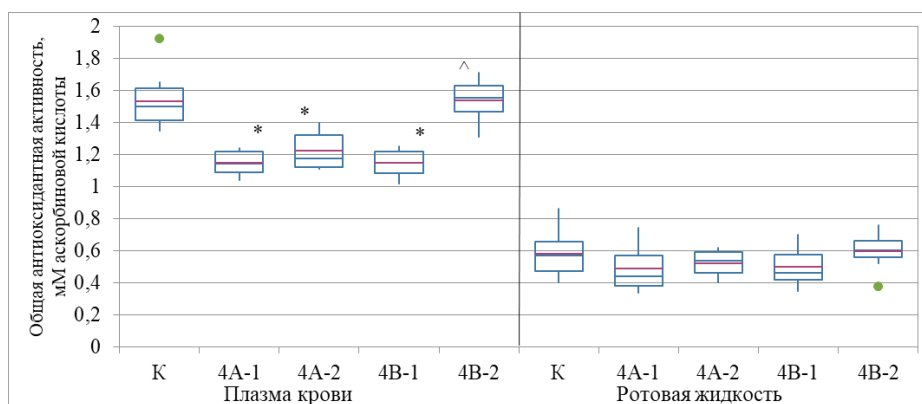


Fig. 3. Total antioxidant activity of blood plasma and oral fluid in patients with inflammatory diseases of the pelvic organs before and after treatment (Me (p0.25-p0.75))

Note: \* - statistically significant differences from the indicator of the control group ( $p < 0.05$ ), ^ - statistically significant differences from the indicator between the indicators before (subgroup 1) and after (subgroup 2) treatment ( $p < 0.05$ )

plasma, the level of iron-reducing ability was attenuated to 0.95 (0.89/1.05) mM of ascorbic acid, which was 37% lower than the control value. In the oral fluid, the decrease in the analyzed parameter reached 48% relative to the control (0.29 (0.25/0.36) mM of ascorbic acid).

Thus, in the course of investigations, multidirectional results of the blood plasma's and oral fluid's total antioxidant activity testing were obtained, even though in groups of patients with different nosological forms. To increase the information content of this index assessment, we propose a parallel assessment in both bio-liquids with the following interpretation of the results:

1. If both the studied indices at the local and systemic levels are determined within the typical values, we can indicate the absence of changes in oxidative metabolism and the normal functioning of the antioxidant defense system.

2. If the total antioxidant activity of blood plasma and oral fluid is simultaneously reduced, as in the example of patients with type 2 diabetes mellitus, we may indicate significant impairments of oxidative homeostasis of a systemic nature. This situation is typical for chronic long-term pathological processes, accompanied by an impairment of all metabolism types and a pronounced inflammatory reaction.

3. The Increase in the total antioxidant activity of both studied biological fluids most likely refers to reactive changes of an adaptive or compensatory character. However, we were not able to show such an example in our study. We assume that this situation may be characteristic to compensatory phases of systemic diseases. Still, it should be relatively short-term, since the connection of the prooxidant-antioxidant blood and saliva system provides some delay in the indices changes at the local level, relatively to the organism level. Thus, the presence of a hemato-salivary barrier and the peculiarities of biochemical processes in the oral cavity somewhat separate this location, which ensures the body's nonspecific resistance. Simultaneously, a simultaneous increase in both bio-liquids' studied parameters can be characteristic of an increase in the antioxidant system's protective potential. It is advisable to look for such a problem in athletes or persons undergoing treatment at a health resort.

4. A decrease in the total antioxidant activity of blood plasma on the background of an unchanged oral fluid index may be characteristic of the pathological processes localized outside the maxillofacial region and not having a noticeable prevalence at the systemic level. As an example of this situation, patients with inflammatory diseases of the pelvic organs can serve. The pronounced inflammatory component in this situation provides an intensification of free radical processes and the development of oxidative stress, which is characterized by a decrease in the iron-reducing ability of blood plasma, but not to affect the state of biochemical parameters of mixed saliva.

5. The latter situation occurs when determining an increased value of the oral fluid index on the background of a normal or even slightly reduced level of the antioxidant potential of blood plasma. This situation is most likely for the dental profile diseases, damage to the oral tissues in which it can provoke the leaching of cellular contents, including endogenous antioxidants or other components that have regenerative activity in the oral fluid. At the same time, changes in the antioxidant activity of blood plasma may reflect the prevalence of the pathological process at the systemic level or its limitation only in tissues and elements of the dentoalveolar system. As an example of such a situation, patients with phlegmon of the maxillofacial region or patients with partial absence of teeth can be cited. The last example in our case was incomplete since we have not determined

the iron-reducing ability of blood plasma. Still, in real dental practice, the blood sampling is often difficult to provide due to the absence of such a need in the attending physician.

**Conclusion.** Changes in the total antioxidant activity of blood and saliva can be multidirectional, i.e., an increase or decrease in the index of oral fluid and a decrease in blood plasma parameter can be recorded. Less common is an increase in the antioxidant potential of blood plasma. The depletion of endogenous antioxidants can explain the decrease in total antioxidant activity during the development of oxidative stress, which is especially characteristic of systemic or long-term and sluggish pathological processes. An increase of the analyzed index is explained either by an adaptive growth of the antioxidant defense system's protective potential or by the leaching of cellular antioxidants into the bio-liquid. The latter is the most likely cause of an increase in the iron-restoring ability of oral fluid in the case of damage to the oral cavity tissues and the dentoalveolar system.

To increase the objectivity of the interpretation of the results obtained, it is advisable to simultaneously assess both blood plasma and oral fluid's total antioxidant activity. At the same time, the following variants of detected disorders are possible: a simultaneous decrease in the indicators of both studied biological fluids, peculiar for somatic diseases of a systemic character with a pronounced metabolic disorder; a reduction in the total antioxidant activity of blood plasma on the background of an unchanged oral fluid index, characteristic to somatic diseases that have a limited prevalence and do not affect the tissues of the maxillofacial region; an increase in the total antioxidant activity of the oral fluid on the background of an average or even slightly reduced level of the antioxidant potential of blood plasma, which is typical for diseases of the dental profile. It is less common to find a simultaneous increase in the analyzed index at the local and systemic levels, which may be characteristic of adaptive changes in the antioxidant defense system or the whole system of nonspecific resistance of the human body. Suggestions for interpreting the data presented in the study aim to select the optimal marker in a given situation for monitoring the course of the disease, but not for assessing the prevalence or limitation of the pathological process.

Comparison of changes in the total antioxidant activity of blood plasma and oral fluid on the background of a traditional treatment regimen or the therapy supplemented with antioxidant agents showed the feasibility of correcting the imbalance of oxidative homeostasis and monitoring the effectiveness of such treatment by evaluating the iron-reducing capability of both biological fluids.

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## SUMMARY

### PECULIARITIES OF EVALUATION OF THE ORAL FLUID ANTIOXIDANT ACTIVITY IN PATIENTS WITH LOCAL OR SYSTEMIC DISEASES

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The aim - in the given research, the difficulties in interpreting the study results of oxidative homeostasis of oral fluid are analyzed. Changes in the total antioxidant activity of blood and saliva can be multidirectional – an increase or decrease in the oral fluid indicator and a reduction in the parameter of blood plasma can be recorded.

To resolve the emerging difficulties, there was proposed a parallel assessment of the dynamics of changes in the total antioxidant activity of blood plasma and oral fluid in the patients of 4 groups with nosological forms of fundamentally different in the distribution and localization of the pathological process, which include: phlegmons of the maxillofacial region, partial absence of teeth, type 2 diabetes mellitus and the pelvic inflammatory diseases.

As a result of the conducted studies, it was shown that a simultaneous decrease in the total antioxidant activity of blood plasma and oral fluid was attributable to the chronic long-term somatic diseases of a systemic character with a significant metabolic disorder, such as type 2 diabetes mellitus. A decrease in the total antioxidant activity of blood plasma and the unchanged oral fluid index was characteristic of somatic diseases of limited prevalence without affection of the maxillofacial region's tissues. In our case, such an example was a chronic inflammatory disease of the uterus with a combined course of bilateral salpingoophoritis. An increase in the oral fluid's total antioxidant activity on the background of a normal or even slightly reduced level of the antioxidant potential of blood plasma was characteristic of dental diseases.

The latter situation was most likely for the dental profile diseases, in which damage to the oral tissues can provoke the leaching of cellular contents, including endogenous antioxidants or other components of regenerative activity in the oral fluid. Herein, changes in the antioxidant activity of blood plasma may reflect the prevalence of a pathological process at the systemic level or its limitation only to the dentoalveolar system's tissues and elements. As an example of such a situation, the patients with phlegmon of the maxillofacial region or patients with partial absence of teeth can be cited.

**Keywords:** antioxidant activity, LPO, antioxidants.

## РЕЗЮМЕ

### АНТИОКСИДАНТНАЯ АКТИВНОСТЬ ОРАЛЬНОЙ ЖИДКОСТИ У БОЛЬНЫХ МЕСТНЫМИ И СИСТЕМНЫМИ ЗАБОЛЕВАНИЯМИ

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Цель исследования - анализ параметров оксидативного гомеостаза ротовой жидкости больных местными и системными заболеваниями.

Проведена параллельная оценка динамики изменений общей антиоксидантной активности плазмы крови и ротовой жидкости у 110 пациентов, которые с учетом нозологических форм, принципиально различных по распространению и локализации патологического процесса, разделены на 4 группы: флегмоны челюстно-лицевой области, частичное отсутствие зубов, сахарный диабет 2 типа и воспалительные заболевания тазовой области.

В результате проведенных исследований (анализ крови и ротовой жидкости) выявлено, что одновременное снижение общей антиоксидантной активности плазмы крови и ротовой жидкости связано с хроническими длительными соматическими заболеваниями системного характера и с нарушением обмена веществ (сахарный диабет 2 типа). Снижение общей антиоксидантной активности плазмы крови на фоне неизменного индекса ротовой жидкости характерно для соматических заболеваний ограниченной распространенности без поражения тканей челюстно-лицевой области, в частности хроническое воспалительное заболевание матки с сочетанным течением двустороннего сальпингоофорита. Повышение общей антиоксидантной активности ротовой жидкости на фоне нормального или даже несколько сниженного уровня антиоксидантного потенциала плазмы крови характерно для стоматологических заболеваний.

При заболеваниях стоматологического профиля, повреждение тканей ротовой полости может спровоцировать вымывание клеточного содержимого, в том числе эндогенных антиоксидантов или других компонентов регенеративного потенциала ротовой жидкости. Изменения антиоксидантной активности плазмы крови могут отражать преобладание патологического процесса на системном уровне или его ограничение тканями и элементами зубочелюстной систе-

мы, что характерно для пациентов с флегмоной челюстно-лицевой области или частичным отсутствием зубов.

## რეზიუმე

პირის ღრუს სითხის ანტიოქსიდაციური აქტივობა პაციენტებში ადგილობრივი და სისტემური დაავადებებით

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კვლევის მიზანს წარმოადგენდა პირის ღრუს სითხის ოქსიდაციური პოტენციალის პარამეტრების ანალიზი პაციენტებში ადგილობრივი და სისტემური დაავადებებით.

ჩატარებულია სისხლის პლაზმის და პირის ღრუს სითხის ზოგადი ანტიოქსიდაციური აქტივობის ცვლილებების დინამიკის შეფასება 110 პაციენტში, რომლებიც პათოლოგიური პროცესის გავრცელებისა და ლოკალიზაციის გათვალისწინებით გაყოფილი იყო 4 ნოზოლოგიურ ჯგუფად: ყბა-სახის მიდამოს ფლეგმონები, კბილების ნაწილობრივი არარსებობა, შაქრიანი დიაბეტი ტიპი 2 და მენჯის მიდამოს ანთებითი დაავადებები.

ჩატარებული კვლევის შედეგად დადგინდა, რომ სისხლის პლაზმის და პირის ღრუს სითხის ზოგადი ანტიოქსიდაციური აქტივობის ერთდროული შემცირება დაკავშირებულია სისტემური ხასიათის ხანგრძლივ ქრონიკულ სომატურ დაავადებებთან, ასევე, ნივთიერებათა ცვლის დარღვევასთან, მაგალითად, შაქრიანი დიაბეტი ტიპი 2-თან. სისხლის პლაზმის ზოგადი ანტიოქსიდაციური აქტივობის შემცირება პირის ღრუს სითხის ინდექსის უცვლელობის ფონზე დამახასიათებელია სომატური დაავადებებისათვის შეზღუდული გავრცელებით ყბა-სახის მიდამოს ქსოვილების დაზიანების გარეშე, სახელდობრ, საშვილოსნოს ქრონიკული ანთებითი დაავადება, შერწყმული ორმხრივ საღპინგოოფორიტთან. პირის ღრუს სითხის ანტიოქსიდაციური აქტივობის მატება სისხლის პლაზმის ნორმალური, ან მცირე შემცირებული ანტიოქსიდაციური პოტენციალის ფონზე დამახასიათებელია სტომატოლოგიური დაავადებებისათვის. აღნიშნული შესაძლოა განვითარდეს სტომატოლოგიური პროფილის დაავადებების დროს, როდესაც პირის ღრუს ქსოვილების დაზიანებამ შეიძლება დააპროვოციროს ენდოგენური ანტიოქსიდანტებისა და პირის ღრუს რეგენერაციული პოტენციალის სხვა კომპონენტების გამორეცხვა უჯრედებიდან. ამასთან, სისხლის პლაზმის ანტიოქსიდაციური აქტივობის ცვლილებები შეიძლება ასახავდეს პათოლოგიური პროცესის დომინირებას სისტემურ დონეზე, ან მის შემოფარგვლას მხოლოდ ყბა-კბილთა სისტემის ქსოვილებით და ელემენტებით. ამის მაგალითს წარმოადგენს პაციენტები ყბა-სახის მიდამოს ფლეგმონით და პაციენტები კბილების ნაწილობრივი არარსებობით.

## SONOGRAPHY OF THE FACE AND NECK REGION SOFT TISSUES IN ASSESSMENT OF THE COMPLICATIONS CAUSES AFTER FACIAL CONTOURING

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The annual growing number of injection procedures in aesthetic medicine inevitably leads to increasing of the complications, occurring after injections. According to the data of American Society of Aesthetic Plastic Surgery (ASAPS), there were more than 2,344,000 non-surgical procedures in 2018, 795 of which were accounted for fillers [1]. The echo signs of cosmetic agents were described in experimental studies, in order to assess the correlation of the obtained data with the chemical composition of the material [2-4]. To establish the chemical composition according to ultrasonography (US) and the injection of hyaluronidase agents, in the reviews, devoted to the diagnosis and treatment of complications after facial contouring, the emphasis is also on the analysis of the characteristics of the introduced material [5-8]. The studies devoted to comparing the results of US with the tomographic radiology methods diagnostics were published [9,10]. The analysis of the causes and structure of complications, location, the depth and the area of the pathological process in patients with complications after facial contouring, the relationship of clinical appearance with the presence of the filler, which is important for the correct diagnosis and determination of the patient treatment tactics, is the interest.

The aim of the study was to assess the capabilities of high-resolution US in the diagnosis of complications after facial contouring.

**Material and methods.** The US examination of 132 women after facial contouring at different stages of treatment was performed. The patients age ranged from 22 to 65 years. In this group, patients had been injected at various terms. The injections had taken place from 2 weeks to 15 years before the US examination.

The US cases presented in this article were performed with the «MyLab Twice» machine (Esaote, Italy) using linear probes that range between 15 to 18 MHz and 10 to 22 MHz, in B-mode (gray-scale) and color or power Doppler mode. No special preparation for the examination of the skin and face and neck soft tissues was required. US was performed while a patient was lying on his back.

At the first stage, the searching of subcutaneous fragments of the gel, the clear determination of their location relative to the anatomical structures of the facial skeleton and the depth from the epidermal layer of the skin of the face and neck were performed during US examination. Then, longitudinal and transverse sizes of filler bolus and its volume were measured, the relationship between the anatomical structures (vessels, facial muscles, septa) and filler deposits were assessed.

The structure of the studied object (hyperechoic, hypoechoic or anechoic formation; homogeneous or heterogeneous; the shape and the clarity of the contours, the presence or absence of a capsule or perifocal edema) was depicted in the description. Also the deviations of normal surrounding tissues were described: increased pastiness (dermis, hypodermis, the presence or absence of the vascularization, excessive fibrosis and other features).

Obtained by the history taking and US examination quantitative and qualitative data were exported to Excel tables and processed by Statistica 10 and MS Office Excel 2010 programs. The normal distribution test (Shapiro-Wilk test) was carried out for

quantitative parameters. The statistical significance of the differences between the compared parameters was determined by Student t-test number in the case of normal distribution. The parameters were presented as the median (Me) and 25%- and 75%-percentiles in the case of the absence of normal distribution. The medians comparison was performed with Mann Whitney U-test. The ratio of patients with the different qualitative indications was compared by the analysis of fourfold contingency tables on the basis of chi-squared test, Yates corrected chi-square test, Fisher's exact test. If the probability of error was less than 0.05 (<0.05) the differences between the compared pairs were considered as statistical significant.

The chemical characteristics of fillers and the terms of the treatment of patients after injection procedures were presented in Figs 1 and 2.

The chemical characteristic of injected materials according to anamnesis data (n=132)

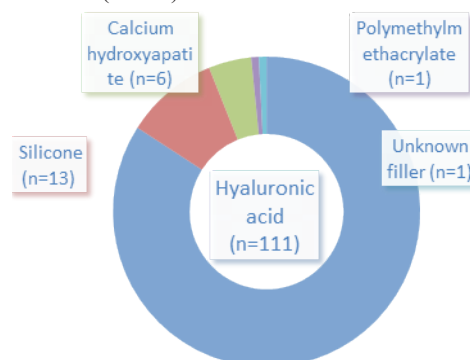


Fig. 1. HA fillers were injected in 111 cases (84,1%), in 13 cases (9,8%) – silicone, in 6 cases (4,5%) – calcium hydroxyapatite (CaHA), polymethylmethacrylate (PMMA) – in 1 (0,8%). There was 1 patient with non-hyaluronic filler with unknown genesis (0,8%)

The terms of treatment after the filler injection (n=132)

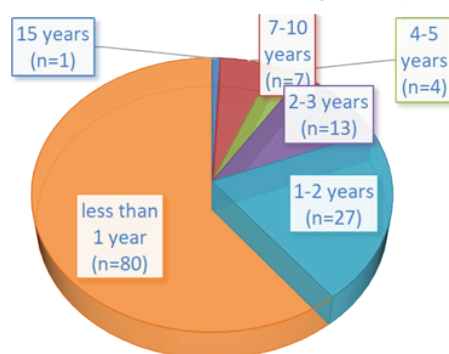


Fig. 2. The terms of treatment after the filler injection in 7 cases (5,3%) were from 7 to 10 years, in 4 cases (3,0%) - 4-5 years, in 13 cases (9,8%) – 2-3 years, in 27 (20,5%) – from 1 to 2 years, in 80 (60,6%) – from 2 weeks to 1 year. In 1 case (0,8%) the patient turns 15 years after the injection of non-hyaluronic filler

**Results and discussion.** The distribution of patients' complaints was as follows: dissatisfaction with the aesthetic result in 122 (92.4%) cases, patients expressed concern about the excess of the declared time spent into the tissues of the injected drugs in 10 (7.6%) cases. The characteristic structure of complaints of patients dissatisfied with the aesthetic result was presented in Fig. 3.

The structure of the complaints of patients, who were dissatisfied with the aesthetic result (n=122)

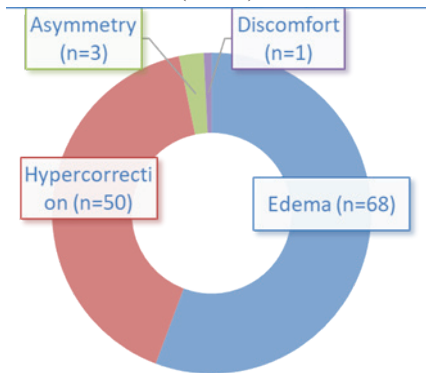


Fig. 3. Edema - 68 cases (55,7%), hypercorrection – 50 cases (41%), asymmetry - 3 cases (2,5%), discomfort - 1 case (0,8%)

According to the US examination data, the most common location area of fillers or echo signs of fibrotic changes in the projection of previously introduced agent were nasolacrimal and palpebromal grooves – 54 cases (40.9%), and the area of lips and nasolabial folds – in 52 (39.4%) cases (Tab. 1). The echo signs of fibrotic changes into the head and neck soft tissues were revealed in 66 patients (50.0%), which corresponded to the location of complaints of edema and hypercorrection in 22 (16.7%) cases. The fibrosis changes were identified at the site of filler injection in 5 patients (3.8%), who were interested in the excess period of the agent, in other 39 cases (29.5%) it was an accidental finding into adjacent anatomical areas that weren't clinically apparent and didn't disturb the patient. The filler has adjoined to the vessels in 36 cases (27.3%), requiring surgical treatment granulomas has formed in 2 cases (1.5%).

The dilated vessels with the fragments of fillers in the form of small boluses were visualized at the site of its injection in 3 cases (2.3%). The swelling of hypodermis and dermis without any fillers or echo signs of fibrosis was identified in 4 cases (3.0%). 1 patient didn't have any changes into the soft tissues (0.8%). The agent was located into the infraorbital region in 51 patient (38.6%), which didn't correspond to the site of the injection and the complaints. The US structure of the manifestations of edema and hypercorrection in patients with corresponding complaints was shown in Figs 4, 5.

Table 1. Location of the cosmetic fillers and echo signs of fibrosis into the soft tissues of head and neck according to the US data

Region	%	Number of patients (n=132)
Nasolacrimal and palpebromolar fissure	40,9	54
Lips and nasolabial folds	39,4	52
Zygomatic bone	9,8	13
Lack of filler and ultrasound signs of fibrosis	3,8	5
Frontal	1,5	2
Temporal	1,5	2
Neck	1,5	2
Mental	0,8	1
In the salivary gland	0,8	1

#### US structure of edema

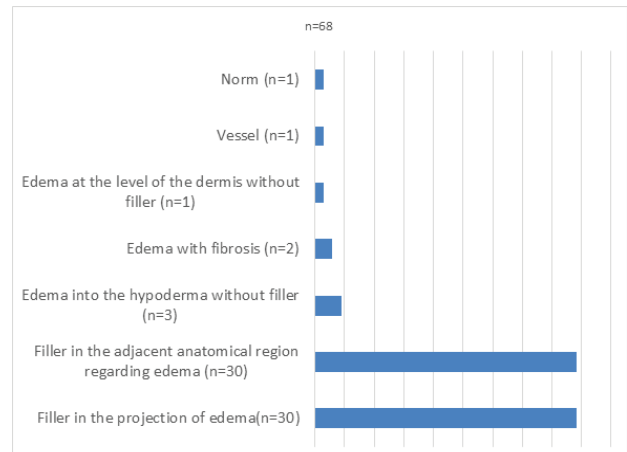


Fig. 4. Hypodermis with the filler into it was revealed in 30 patients. The same pathology without filler in the projection of it was diagnosed in 30 cases, and the agent was visualized in adjacent anatomical regions. Hypodermis edema in 3 cases and dermis edema in 1 case didn't have the filler into them. Hypodermis and dermis edema was combined with fibrosis in 2 cases. The enlarged vessel with an agent microbole, which the patient perceived as edema, was detected in one study. One patient showed no signs of tissue changes and the presence of a filler

#### US structure of the hypercorrection

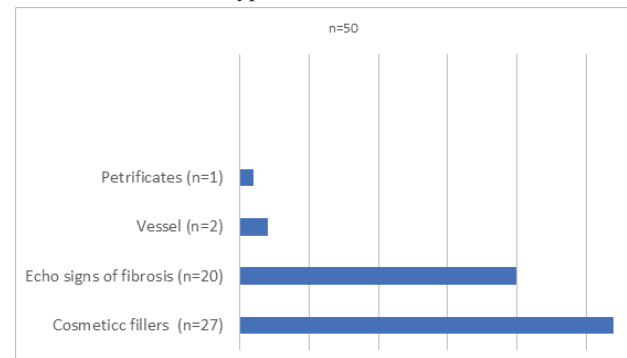


Fig. 5. The hypercorrection corresponded to the echo signs of the fibrotic changes in the form of hyperechoic formations with clear, uneven contours in 20 cases and in the form of the petrificates - in 1 case. The hypercorrection was visualized as the hypoechoic and anechoic formations with clear even contours, which was typical for echo signs of the fillers in 27

cases. The vessels with the agent microbubbles were revealed into palpebromolar grooves in 2 patients. They didn't seem to differ from the manifestations of hypercorrection but according to the spectrum of blood flow they were veins

The examples of different patients with the same complaints about the edema were presented in the Figures 6 and 7. There, the case when into same anatomical zone, with the same complaints and similar clinical appearance, the ultrasound picture is different, was clearly presented.

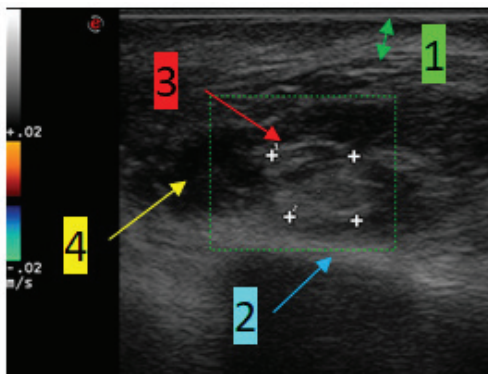


Fig. 6. Sonogram of the periorbital region in Color Doppler mode in the projection of the nasolacrimal groove, sagittal plane at the level of the bone edge of the orbit (arrow 1 – dermis, arrow 2 – bone). Hyperechoic, avascular rounded formation with clear even contours was visualized supraperiostally (arrow 3 – hyperechoic formation), with the signs of severe perifocal edema in the form of a zone of reduced echogenicity (arrow 4 - edema). Echo signs of fibrosis in the projection of the nasolacrimal groove and of the periorbital region soft tissues edema

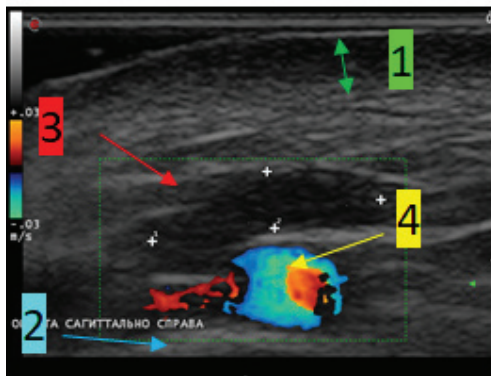


Fig. 7. Sonogram of the periorbital region in Color Doppler mode in the projection of the nasolacrimal groove, sagittal plane at the level of the bone edge of the orbit (arrow 1 – dermis, arrow 2 – bone). Hypoechoic avascular formation of an oblong shape with clear and even contours is visualized into the soft tissues of the examined area (arrow 3 – hypoechoic formation). It was adjacent to the vessel (arrow 4 - vein), the blood flow spectrum showed that it was vein, with no signs of tissue edema. Echo signs of adjacent to the vein cosmetic filler in the projection of the nasolacrimal groove

HA fillers in the patients who turned with complains during up to a year after the injection were visualized as round or oval shaped hypoechoic boluses with clear, fairly even

contours in 65 cases, with the fibrous capsule – in 5 cases (Fig. 8). The areas of increased echogenicity soft tissues into the places of HA injection were revealed in 13 patients, who turned at the same time (Fig. 9). HA agents with a presence into the tissues for more than a year were visualized as hypoechoic formations without perifocal edema in 26 cases during US, the fibrous capsule was visualized among them in 6 cases (Fig. 10). The hyperechoic avascular formation was identified at the site on the hyaluronic filler injection in 2 cases, which corresponded to the echo signs of fibrosis. Polymethylmethacrylate was visualized during US as a heterogeneous formation due to the alternation of the areas of reduced and increased echogenicity, with a predominance of the hyperechoic structures, with an acoustic shadow in the patient to whom this agent was injected (Fig. 11). Silicone fillers were visualized as hyperechoic formations in 16 cases, as hypoechoic structures with hyperechoic capsule without any signs of the perifocal edema – in 5 cases (Fig. 12,13).

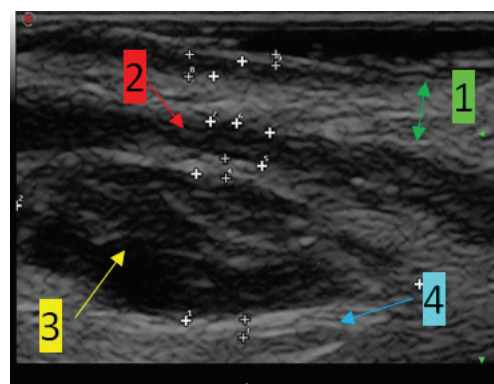


Fig. 8. Sonogram, B-mode, periorbital region in the projection of palpebromolar sulcus, horizontal plane at the level of the bone edge of the orbit along the mid-pupil line (arrow 1 – dermis, arrow 2 – m. orbicularis oculi). Hypoechoic, heterogeneous due to hyperechoic thickenings, filler bolus was visualized (arrow 3 - filler). It had clear even contours, was oval shaped, with fibrous capsule (arrow 4 – fibrous capsule) and located under the orbicularis oculi muscle, without signs of perifocal edema. Echo signs of incapsulated filler into periorbital region

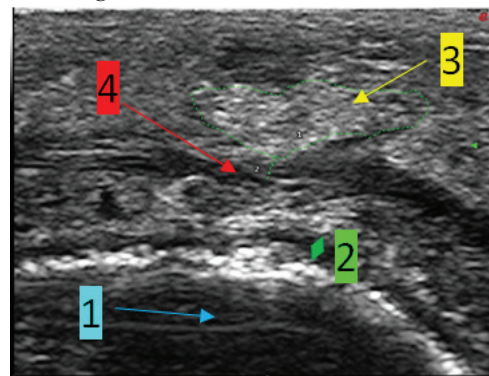


Fig. 9. Sonogram, B-mode, the lateral part of the upper lip, horizontal plane (arrow 1 – oral cavity, arrow 2 – submucosa). The hyperechoic formation (arrow 3 – hyperechoic formation) with clear uneven contours is visualized above the orbicularis oris muscle (arrow 4 – m. orbicularis oris). It was located at the site of HA filler injection. Echo signs of fibrotic changes into the soft tissues of the upper lip



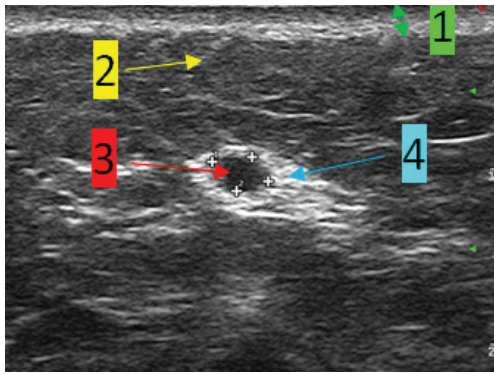


Fig. 10 Sonogram of the soft tissues in the projection of the left nasolabial fold (arrow 1 – dermis, arrow 2 – hypodermis). A hypoechoic HA filler bolus (arrow 3 - hypoechoic filler bolus) with a formed strongly marked hyperechoic capsule (arrow 4 – hyperechoic capsule) is visualized into hypodermis. The visualization of the underlying structures was not hindered. Echo signs of fibrotic changes into the nasolabial fold soft tissues

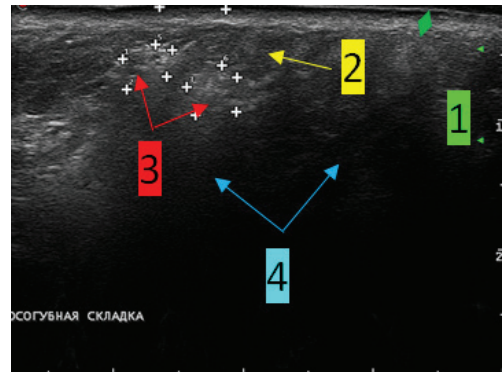


Fig. 11. Sonogram of the soft tissues in the projection of the left nasolabial fold (arrow 1 – dermis, arrow 2 – hypodermis). Hyper-echoic structures (arrow 3 – hyperechoic structures) with an acoustic shadow (arrow 4 – acoustic shadow) was visualized into the nasolabial fold soft tissues at the site of the injection of the PMMA filler. Visualization of the underlying structures was not hindered. Echo signs of fibrotic changes into the nasolabial fold soft tissues

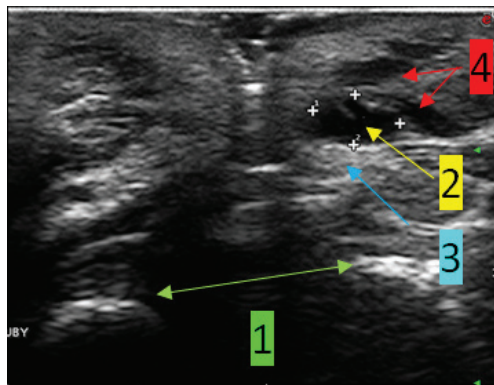


Fig. 12 Sonogram of the lips, sagittal plane (arrow 1 – teeth). An anechoic HA filler bolus (arrow 2 - the anechoic filler bolus), oval shaped, with clear and even contours, with dorsal echo enhancement (arrow 2 – dorsal filler enhancement) without a fibrous capsule or perifocal edema of the lower lip soft tissues was visualized. The lip soft tissues have had a typical structure, the visualization of the orbicularis oris muscle wasn't hindered (arrow 4 – m. orbicularis oris). Echo signs of iatrogenic inclusions of HA origin into the lower lip soft tissues

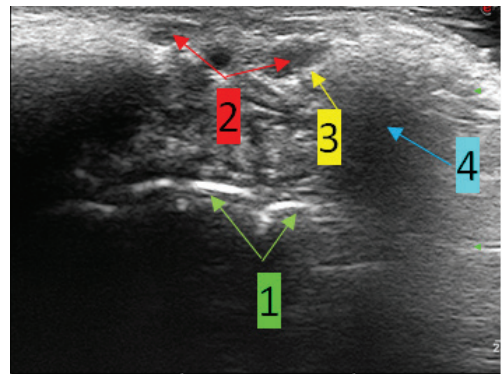


Fig. 13. Sonogram of the lips, sagittal plane (arrow 1 – teeth). The hypoechoic silicone filler boluses (arrow 2 – hypoechoic boluses), which was injected 8 years ago, oval shaped, with clear and even contours, with the fibrous capsule (arrow 3 – fibrous capsule) without a perifocal edema of the upper and lower lip soft tissues was visualized. The visualization of the upper and lower lip tissues had an atypical structure, visualization of the orbicularis oris muscle was hindered. There was also a posterior acoustic shadowing artifact caused by the superficial hyperechoic structures (arrow 4 – posterior acoustic shadowing artifact). Echo signs of fibrotic changes of the lips with encapsulated silicone filler fragments

Echo signs of fibrosis were revealed in 66 cases by the US examination, of which 27 cases were corresponded to the site of the filler injection. During the examination there were 39 cases of the random findings, which were not clinically apparent and didn't disturbed. The filler was located in the projection of the infraorbital foramen in 51 patients, but it wasn't corresponded to the site of the injection and the complaints. The analysis of the relationship between the sign of "filler dislocation" and its injection above or below the SMAS shows the strong correlation between the filler dislocation and it's injection below the SMAS ( $p < 0,05$ ). The agent dislocation was possible between the fascial spaces due to the facial muscles activity, which were the anatomical borders of the fascial spaces together with the ligamentous apparatus [11,12]. The filler was located in the projection of the edema and into the adjacent anatomical region in the patients with

complaints of edema. Analysis data shown that there was no correlation between the presence of edema and the presence of the filler in its area ( $p > 0,05$ ).

According to the data analysis, materials of different nature at different duration of stay into the soft tissues may be sonographically similar. For example, silicone and HA visualized as anechoic boluses, both with the presence of hyperechoic rim and without it. The fibrous changes were revealed at the site of the injection of all materials, as well as the absence of signs of biodegradation at different stages after the injection. Medical history, the terms of stay of the material in the tissues, clinical appearance had the great importance and should be compared with the US characteristics of the material. Conservative treatment is recommended in the case of the presence of HA fillers, and if there are echo signs of fibrosis of non-HA agents, the issue about surgical treatment should be brought up.

The obtained data indicate the need for a preliminary examination of the face and neck soft tissues to determine the level of edema, the presence of the filler into the soft tissues, differential diagnosis of the complications' causes, and at the planning stage of cosmetic procedures.

**Conclusions.** The characteristic echo signs of HA agents include hypoechoic structure, even and clear contours, the absence of an acoustic shadow.

The characteristic echo signs of non-HA fillers include hyper-echoic structure, uneven and unclear contours, with the presence of an acoustic shadow.

The US of the skin and the soft tissues of the face and neck region prescribed to the patients with complaints after facial contouring in order to carry out the differential diagnosis of their causes and to determine the treatment tactics.

The most frequent complaints that patients come with were edema and hypercorrection into the periorbital region for up a year after the HA filler injection.

There was the high probability of an agent dislocation if it is introduced below the SMAS level.

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## SUMMARY

### SONOGRAPHY OF THE FACE AND NECK REGION SOFT TISSUES IN ASSESSMENT OF THE COMPLICATIONS CAUSES AFTER FACIAL CONTOURING

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132 women after facial contouring on terms from 2 weeks to 15 years after filler injection were examined by sonography (US). They had complaints of the edema, hypercorrection, asymmetry, discomfort and anxiety about the excess of the terms that filler had spent into the soft tissues.

HA fillers were injected in 111 cases (84.1%), silicon agents – in 13 cases (9.8%), CaHA – in 6 (4.5%), PMMA – on 1 (0.8%) and one patient have had non-hyalouronic filler with unknown origin (0.8%). According to the US data, nasolacrimal and palpebromar

fissures were the most common location of fillers or the echo signs of fibrotic changes in the projection of their injection – 54 patients, just like the lips region and nasolabial folds – 52 cases.

The US of the skin and the soft tissues of the face and neck region prescribed to the patients in order to carry out the differential diagnosis of complaints' causes, to determine the treatment tactics and for planning cosmetic procedures.

**Keywords:** sonography, complications of facial contouring, fillers, filler injections.

## РЕЗЮМЕ

### СОНОГРАФИЯ МЯГКИХ ТКАНЕЙ ЛИЦА И ШЕИ, ОЦЕНКА ПРИЧИН ОСЛОЖНЕНИЙ ПОСЛЕ КОНТУРИРОВАНИЯ ЛИЦА

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С помощью ультразвукового исследования (УЗИ) обследовано 132 женщины после контурной пластики лица на сроках от двух недель до 15 лет после введения филлеров с жалобами на отек, гиперкоррекцию, асимметрию, дискомфорт и беспокойство по поводу превышения сроков нахождения препаратов в мягких тканях.

В 111 (84,1%) случаях вводили филлеры на основе гиалуроновой кислоты, в 13 (9,8%) – силикон, в 6 (4,5%) – гидро-

ксиапатит кальция, в одном (0,8%) – полиметилметакрилат, у одного (0,8%) пациента - филлер негиалуроновой природы неизвестного происхождения. По данным УЗИ наиболее частой областью локализации филлеров или ультразвуковых признаков фиброзных изменений в проекции их введения была область носослезной и пальпебромалярной борозд – 54 пациента, а также область губ и носогубных складок – 52 случая.

Пациентам с жалобами после контурной пластики лица показано ультразвуковое исследование кожи и мягких тканей для дифференциальной диагностики причин жалоб, определения тактики лечения и планирования косметологических процедур.

რეზიუმე

სახის და კისრის რბილი ქსოვილების სონოგრაფია, სახის კონტურების შემდგომი გართულებების მიზეზების შეფასება

ი.ბონდარენკო, ე.პრივალოვა, ი.შუშინა

სხივური დიაგნოსტიკის ცენტრალური სამეცნიერო-კვლევითი ინსტიტუტი, მოსკოვი, რუსეთის ფედერაცია

ულტრაბგერითი კვლევით შესწავლილია 132 ქალი სახის კონტურული პლასტიკის შემდეგ, ფილერების შეყვანიდან ორი კვირიდან 15 წლის ვადაში, ჩივილებით შეშუპებაზე, ჰიპერკორექციაზე, ასიმეტრიაზე და დისკომფორტზე, ასევე, წუხილის გამო რბილ ქსოვილებში

პრეპარატის არსებობის ვადების გახანგრძლივებასთან დაკავშირებით.

111 (84,1%) შემთხვევაში შეყვანილი იყო ფილერები ჰიალურონის მუცის საფუძველზე, 13 (9,8%) შემთხვევაში – სილიკონი, 6 (4,5%) შემთხვევაში – კალციუმის ჰიდროქსიპაპატიტი, 1 (0,8%) შემთხვევაში – პოლიმეთილმეტაკრილატი, 1 (0,8%) პაციენტს – უცნობი წარმოშობის არაჰიალურონული ბუნების ფილერი. ულტრაბგერითი კვლევის შედეგების მიხედვით, ფილერების ან ფიბროზული ცვლილებების ულტრაბგერითი ნიშნების ლოკალიზების ყველაზე ხშირ მიდამოს მათი შეყვანის პროექციაზე წარმოადგენდა ცხვირ-საცრემლე არხის მიდამო და წარბთშორისი ნაჭდევი – 54 პაციენტი, ასევე, ტუჩების და ცხვირტუჩის ნაოჭის არე – 52 შემთხვევა.

კონტურული პლასტიკის შემდეგ ჩივილების მიზეზების დიფერენციული დიაგნოსტიკისათვის, მკურნალობის ტაქტიკის განსაზღვრისა და კოსმეტოლოგიური პროცედურების დაგეგმვისათვის ნაჩვენებია კანის და რბილი ქსოვილების ულტრაბგერითი კვლევა.

## ASSESSMENT OF EFFECTS OF NON-FUNCTIONAL OVERREACHING AND OVERTRAINING ON RESPONSES OF SKELETAL MUSCLE AND CARDIAC BIOMARKERS FOR MONITORING OF OVERTRAINING SYNDROME IN ATHLETES

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In professional sports, the focus on success in training and competition creates a driving force for a higher level of fitness, which requires greater workload from athletes, longer sports season and greater frequency of competitions. Sports training program commonly comprises a component of repetitive overloading to initiate structural and functional changes in an attempt to achieve favorable adaptation to the workouts and enhance athlete's sports performance, but with an inadequate recovery time or an abrupt increase in training load, overloading may produce undesired effects. If overreaching is extreme and combined with an additional stressor, non-functional overreaching (NFO), and then overtraining syndrome (OTS) may result [12,13]. Because of imbalance between training and recovery, athletes are at risk of becoming overtrained, subsequently increasing the possibility of cardiac damage [9,16]. Early detection of NFO is very important in terms of prevention of overtraining, as well as for interruption of NFO/OTS progression.

Physiological, biochemical, immunological, psychological and performance markers of OTS are intensively investigated. During the last years, growing interest is set on biomarkers aiming at evaluating health-related aspects which can be modulated by regular physical activity and sport. The use of specific biochemical markers for the diagnosis of OTS are still in discussion. However, serum creatine phosphokinase (CK) has for years been measured and evaluated in exercise science as an essential parameter for the determination of muscular stress. Elevated baseline values of CK may indicate trauma or over-

training, also, its concentration can be used to monitor activity of athletes with a muscle injury [15].

Numerous studies have suggested that prolonged exercise may induce a transient appearance of cardiac-specific troponins (such as cTnI or cTnT), normally indicative of myocyte necrosis [14,17-20]. The troponin level post-exercise corresponds to release from the cytosolic compartment of cardiomyocytes. There are many causes of increased membrane permeability of cardiomyocytes and, among them, production of reactive oxygen species and imbalance between oxidative and antioxidant status is of growing interest. Other causes of permeability growth might be alterations in calcium, pH, glucose/fat metabolism or in communication between integrins, as well as various mechanisms can be suggested, among them increased cardiovascular stress, inflammation, vasculitis, dehydration, or expression of cardiac troponin in skeletal muscle [3,21]. However, "the presence of measurable troponin amounts in the blood should not be interpreted as cardiac damage in the absence of clinical symptoms or instrumental findings of myocardial disease" [1], such as alterations of echocardiographic parameters of systolic, diastolic or right-sided heart dysfunction. Results of previous studies about continuous ultraendurance activities were inconclusive in terms of appearance of cardiac-specific troponins in the blood. On the other hand, some studies on exercises like marathon and triathlon showed no increase in these markers [10]. Recent studies showed that cardiac troponin I and T were strongly correlated following exercise [7,8]. Therefore, with respect to abovementioned

tioned uncertainty regarding increase of the troponins after high and ultra endurance activities, it is critical to investigate changes in the biomarkers in high intensity and strengths oriented (sprinting, jumping, weight lifting, training with resistance, etc.) as well as in team sports (basketball, football, water-polo, etc.) owing that little detailed information is available on the level and pre-season/in-season dynamics of these biomarkers. On the other hand, it is very important to study chronic effects of exercises via responses of biomarkers for understanding of muscle fatigue and cardiac damage to identify athletes who are at risk of poor adaptation to training and development of OTS.

The aim was to study the effects of non-functional overreaching and overtraining on responses of biomarkers of the skeletal muscle cell (CK-NAC) and cardiomyocyte injury (cTnI and CK-MB) and their use in monitoring OTS.

**Material and methods.** Initial stages of the study were conducted in the Clinical Center of Sports Medicine and Rehabilitation of Tbilisi State Medical University during 2015-2018. Physical condition and health status of 348 high level male athletes (aged 22±4,7 y.o.) were examined and among them 43 subjects with NFO/OTS were revealed. Diagnosis of OTS was based on the checklist provided by the consensus statement of the European College of Sports Science (ECSS) and the American College of Sports Medicine (ACSM) [12], and other clinical conditions were ruled out as explanation for decreased performance. Out of 43 subjects with NFO/OTS, 37(10,6%) athletes met criteria for non-functional overreaching and 6 (1,7%) athletes fell under criteria of OTS of different severity and duration [4,5].

On the initial stage of this study, in abovementioned 348 elite male athletes a pre-season measurement of the serum creatine kinase (CK-NAC and CK-MB) took place. Therefore, in the following, prospective in-season evaluation of the dynamic of CK (CK-NAC and CK-MB) changes, along with in-season/peak-season measurement and interpretation of cardiac troponin with sensitive cTnI were performed. For this reason, along with 43 athletes with NFO/OTS, 40 age matched athletes of the same sporting disciplines but without NFO/OTS – control athletes (CA) were involved. Data were collected over a two-year period because of the rare nature of overtraining syndrome. Assessment of biomarkers in the blood serum were performed with analytical microprocessor-controlled photometer systems HUMALYZER 2000 for CK-NAC and CK-MB, and HUMAREADER Single Plus for cTnI Elisa test based on the principle a solid enzym linked immunosorbent assay (HUMAN, Gesellschaft für Biochemica und Diagnostica mbH, Germany). Normal range for CK-NAC levels is considered 24-190 U/I in men and 24-170 U/I in women, and for CK-MB levels <25U/I. Reference range for cardiac troponin I levels is considered <0,1 ng/ml. According to the most current approach [15], CK levels in the blood serum respond to the exercise duration and intensity, and there is smaller rise of CK concentration in athletes than in sedentary, showing adaptation due to training. Nevertheless, in athletes, interpretation of the baseline CK level in the blood serum has to be following: 200 U/I –training adaptation, 200-250U/I – elevated training levels, >300U/I – possible overtraining and muscle damage [15].

Experimental procedures included measurement of the CK and cTnI levels 24 hours before the strenuous exercise appropri-

ate to the sport-specific peak-season intensity, immediately after completion of the work-load, after 6 hours, 48 hours, and again after 72 hours post-exercise.

Baseline (24 hours before exercise) and post-exercise clinical assessment and echocardiography was performed within 6 hours, and then 48 hours after the strenuous session to evaluate cardiac symptoms and measure ventricular function, volumes, and wall motion. Echocardiography (M-mode, 2D, Doppler, Tissue Doppler Imaging-TDI) was performed in accordance with recommendations from the American Society of Echocardiography (2015) [11]. The presence of significant valvular disease or intracardiac shunts was excluded by means of color Doppler. Left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), as well as biplane LV ejection fraction (EF), were calculated from four-chamber and two chamber images, by modified Simpson rule. Mitral inflow measurements were obtained from the four-chamber view, and early filling LV velocity (E) and atrial filling velocity (A) waves, E/A ratio as well as E wave deceleration time (DT) were measured. TDI measurements were assessed in the apical four-chamber, and diastolic myocardial velocities - peak early myocardial tissue velocity (E'), peak late (or atrial) myocardial tissue velocity (A'), and E'/A' ration were recorded, as well as and E/E' ratio was calculated. Right ventricular (RV) measurements and tricuspid annular plane systolic excursion (TAPSE) performed.

Above mentioned specific time point was chosen based on the assumption, that 6 hours would allow sufficient time to develop and detect inflammation, corresponding to the time when cTnI is typically detectable in ischemic models [1]. On the other hand, 48 hours is sufficient recovery time due to high-level athletes' physiological adaptation to intensive physical training, among them in terms of stabilization and recovery of CK concentrations in blood serum.

SPSS 26 software was used for statistical analysis. Obtained data were processed according Student's t-criterion, and data are presented as mean ± SD. The level of statistical significance was set as p value <0,05.

**Results and discussion.** Retrospective analyzes of baseline data obtained during off-season, after at least 1 week resting period, showed no significant difference of CK levels between athletes with NFO/OTS and control group, and the values didn't exceed reference range, p>0.05 (Table 1).

Pre-exercise clinical assessment of study groups did not reveal subjective or objective cardiac symptoms, whereas in total 5 athletes mentioned mild injury of lower extremities during training and small pain associated to those injuries.

During the season pre-exercise measurements of CK in all athletes – athletes with NFO, athletes with OTS and control athletes exceeded off-season values, but were less than 300U/I, and fell within the “elevated training level” range (Table 2). Similar rising trend of CK-NAC and CK-MB values was observed immediately after exercise, reaching peak values after 6 hours in all athletes - with NFO/OTS and control group, however, the peak values in NFO athletes and OTS athletes were significantly greater than in controls. The CK-NAC and CK-MB values after 48 hours of recovery were significantly higher than entry values in athletes with NFO and athletes with OTS, but in controls it remained elevated solely for CK-MB parameter. As for inter-group comparison, in re-

Table 1. Off-season measurement of the serum creatine kinase (CK) in studied groups

	CK-NAC, U/I	CK-MB, U/I
Athletes with NFO/OTS	171±25.6	3.87±0.61
Control athletes	164±31.4	3.29±0.45

covery phase, after 48 hours, CK-NAC and CK-MB values were significantly higher in athletes with NFO and OTS athletes than in controls, showing greater retention of biomarkers in blood serum and slower/prolonged recovery, and CK-NAC levels falling within the “possible overtraining and muscle damage” levels in OTS athletes, even after 72 hours of recovery (Table 2). Concentrations of cTnI increased markedly from baseline, reaching peak values after

6 hours in all athletes - with NFO/OTS and control group, however, the peak values in athletes with NFO and athletes with OTS were significantly greater than in controls, and at the same time, slightly exceeded reference range. Cardiac TnI levels were declining after 48 hours, but remaining significantly higher than entry values in athletes with NFO and athletes with OTS. In these athletes pre-exercise levels of cTnI values were reached after 72 hours of recovery (Table 3).

Table 2. Levels of CK-NAC (U/l) and CK-MB (U/l) in studied groups pre- and post-exercise (Mean±SD)

	Pre-exercise		Immediately after exercise		After 6 hours		After 48 hours		After 72 hours	
	CK-NAC	CK-MB	CK-NAC	CK-MB	CK-NAC	CK-MB	CK-NAC	CK-MB	CK-NAC	CK-MB
Athletes with NFO	269±34,6	5.2±0.59	485±56,2	9.8±0.61	937±62,6*	18.2±4.3*	547±74,6 <sup>^</sup>	13.4±3.6 <sup>^</sup>	286±31,4	6.2±0.24
Athletes with OTS	276±24,7	5.4±0.36	493±45,6	10±0.42	955±81,3*	19.1±5.4*	601±56,2 <sup>^</sup>	15.2±3.9 <sup>^</sup>	325±42.6 <sup>^^</sup>	11.6±3.1 <sup>^^</sup>
Control athletes	257±56,8	4.7±0.81	461±74,4	9,3±0.45	807±54,1	15.6±2.7	324.7±57.3	9.3±2.5 <sup>^</sup>	243±27,4	4.2±3.7

\*p<0,05 - CK-NAC and CK-MB data after 6 hours, compared between NFO/OTS athletes and CA;

▪ p<0,05 - CK-NAC and CK-MB data after 48 hours, compared between NFO/OTS athletes and CA;

<sup>^</sup> p<0,05 - CK-NAC and CK-MB data pre-exercise and after 48 hours;

<sup>^^</sup> p<0,05 - CK-NAC and CK-MB data pre-exercise and after 72 hours

Table 3. Level of cTnI (ng/ml) in studied groups (Mean±SD)

	Pre-exercise	Post-exercise			
		Immediately after exercise	After 6 hours	After 48 hours	After 72 hours
Athletes with NFO	0.021±0.026	0.052±0.078	0.128±0.092*	0.041±0.046 <sup>^</sup>	0.024±0.035
Athletes with OTS	0.031±0.017	0.070±0.043	0.137±0.061*	0.053±0.075 <sup>^</sup>	0.035±0.012
Control athletes	0.023±0.034	0.061±0.012	0.081±0.046	0.028±0.008	0.019±0.017

\*p<0,05 - cTnI data after 6 hours, compared between NFO/OTS athletes and CA;

▪ p<0,05 - cTnI data after 48 hours, compared between NFO/OTS athletes and CA;

<sup>^</sup> p<0,05 - cTnI data pre-exercise and after 48 hours

Table 4. Echocardiographic variables of NFO/OTS athletes baseline (pre-exercise) and after strenuous exercise: within 6 hours and after 48 hours, (Mean±SD)

Variable	Pre-exercise	Post-exercise	
		Within 6 hours	After 48 hours
LV EDV, ml	116±22	103±25*	115±24
LV EDS, ml	41±17	38±21	40±26
LV EF, %	61±4	62±6	61±7
LA indexed volume, mL/m <sup>2</sup>	26±2	26±3	27±3
RV fractional area change, %	48±4	45±5	47±5
TAPSE, mm	22±2	24±3	23±2
E, m/s	0.78±0.11	0.69±0.17*	0.75±0.12
A, m/s	0.53±0.12	0.65±0.16*	0.59±0.11
E/A ratio	1.47±0.25	1.06±0.14*	1.40±0.09
DT, ms	209.14±29.78	214.35±24.01	210.23±30.15
E', cm/s	13.56±1.1	11.23±1.8*	13.15±2.6
A', cm/s	9.25±1.5	9.96±1.3*	9.46±1.7
E'/A'	1.45±0.8	1.13±1,5*	1.38±1.6
E/E' ratio	5.67±1.1	6.15±1.7	5.70±1.5

\*p<0.05 post- versus pre-exercise

When compared to pre-exercise echocardiography data, we detected small, but significant decrease ( $p < 0.05$ ) of post-exercise left ventricular end-diastolic volume, E/A ratio (due to a decrease of the E wave and an increase of the A wave), and E'/A' ratio (due to a decrease of the E' wave and an increase of the A' wave), but all still within the conventional reference ranges [11]. However, after 48 hours of recovery all mentioned changes were normalized. Other measurements post-exercise were not different from values observed pre-exercise. Thus, our study demonstrated that after strenuous workload LV systolic function as well as RV systolic parameters are preserved and there are only small decrease of LV diastolic volumes and minor signs of diastolic impairment detectable, even though transient, due to slight modifications of the LV filling patterns, but without additional signs of diastolic dysfunction (Table 4).

A, mitral A wave filling velocity; A', peak late (or atrial) myocardial tissue velocity; DT, mitral deceleration time; E, mitral E wave filling velocity; E', peak early myocardial tissue velocity; LVEDV, left ventricular end-diastolic volume; EF, ejection fraction; LVESV, left ventricular end-systolic volume; HR, heart rate; LA, left atrium; LV, left ventricular; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion

Post-exercise clinical assessment of the studied athletes didn't reveal any significant cardiac symptoms, whereas most of the athletes noted continuous trauma during game/combat contact events (football, basketball, rugby, boxing) and associated muscular pain of various severity, though, quite rapid recovery in vast majority of cases. Herewith, 2-year follow-up and retrospective analyze demonstrate that most of the OTS athletes showed no signs of full recovery. Three athletes (football player and two wrestlers) struggled from muscular pain, mostly lower limbs, and cramps in lower limbs. After 6 month of follow up, these athletes were not able to train regularly because of slow recovery from training and the presence of muscle pain and general fatigue, contributing to a detraining. Other OTS athletes were able to train regularly with some cautious planning, but their training volume had not returned to normal and they required more time for recovery from a training session than usual.

In our study prevalence of NFO and OTS was seen in team sports (football, water-polo, rugby, basketball) and in sporting disciplines with mixed high and high-to-moderate intensity workload (boxing, wrestling), among them 27(62,8%) NFO and 4 (9,3%) OTS cases, particularly, majority of NFO/OTS were revealed in wrestling: NFO- 19(44,2%) and OTS- 4(9,3%) [4]. Most of these sports can be considered as "tackle plays" (football, rugby) or "combats" (boxing, wrestling) causing muscular injury. Muscle damage and disruption of skeletal muscle membrane may cause plasma CK leakage. Higher pre-exercise values of CK compared to off-season, can be associated with various severity (mostly mild) of muscular trauma which may occur during training or competition, though, their persistence can be a signal of overtraining. However, in athletes, persistently elevated CK levels, and at the same time, reduced exercise tolerance can be suggestive of OTS. With regards of markers of myocardial injury, increased CK-MB levels post-exercise, though, never exceeding upper cut-off value, and cTnI slightly exceeding conventional reference range after 6 hours of strenuous exercise, may represent reversible involvement of cardiomyocyte membrane, benign by nature, caused by excessive cardiac workload. These changes were not associated with any sustained alterations of echo-parameters of LV and RV systolic and diastolic functions, and do not reflect clinically threatening myocardial damage. Minor diastolic changes

can be attributed to the isolated modification of the trans-mitral inflow pattern due to adaptation to the post-exercise haemodynamic changes rather than intrinsic alterations in LV relaxation or compliance properties [2].

Detection of elevated values of cardiac markers after strenuous exercise can be linked to increased cellular permeability and cardiac troponin leakage. On the other hand, oxidative stress existent in OTS athletes [6] may significantly contribute to increase of cardiomyocyte membrane permeability, owing higher values of cTnI in this group compared to controls and athletes with NFO. The release of troponins from the cardiomyocytes was transient and recovered quite rapidly, without irreversible pathophysiological and clinical consequences. Bearing in mind that after 48 hours of recovery in athletes with NFO and athletes with OTS the CK levels were still high, the training regimen comprised of proper set of intensive-to-less intensive exercise sessions and corresponding duration of recovery phases should be suggested. Such strategy could prevent overtraining, as well as could interrupt NFO to OTS progression.

**Conclusions.** In our study sport-specific intensive exercise could cause mild injury to skeletal muscle and transient increase of the CK-MB and cardiac TnI, without irreversible pathophysiological and clinical consequences, and any sustained alterations of echocardiographic parameters of systolic and diastolic functions, suggesting mostly benign cardiac involvement, though amplified by existent oxidative stress in athletes with OTS. Monitoring responses via alterations of biochemical parameters can be helpful to guide athletic training, reveal incomplete recovery and suggest trauma or overtraining, and prevent OTS or interrupt NFO to OTS progression.

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## SUMMARY

### ASSESSMENT OF EFFECTS OF NON-FUNCTIONAL OVERREACHING AND OVERTRAINING ON RESPONSES OF SKELETAL MUSCLE AND CARDIAC BIOMARKERS FOR MONITORING OF OVERTRAINING SYNDROME IN ATHLETES

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The aim was to study the effects of non-functional overreaching and overtraining on responses of biomarkers of the skeletal muscle cell (CK-NAC) and cardiomyocyte injury (cTnI and

CK-MB) and their use in monitoring OTS. In 43 athletes with non-functional overreaching (NFO)/overtraining syndrome (OTS) and 40 athletes without NFO/OTS –control athletes (CA) off-season measurements of creatine kinase (CK-NAC and CK-MB) were performed, followed by peak-season evaluation of the dynamic of CK-NAC, CK-MB and cardiac troponin I (cTnI) changes. CK and cTnI levels were obtained 24 hrs before the strenuous exercise appropriate to the sport-specific peak-season intensity, immediately after completion of the work-load, after 6, 48, and 72hrs. Baseline and post-exercise clinical assessment and echocardiography were performed in 6 and 48 hrs after strenuous session.

Similar rising trend of CK-NAC, CK-MB, and cTnI levels was observed immediately after exercise, reaching peak values after 6 hours in all athletes, though, significantly greater in NFO/OTS athletes than in controls. After 48 hours of recovery in athletes with NFO/OTS CK-NAC, CK-MB, and cTnI values were significantly higher than on entry, showing slower recovery. CK-NAC fell within the “possible overtraining and muscle damage” levels in OTS athletes, even after 72 hours of recovery. Most of the athletes noted continuous trauma during game/combat contact events, though, mostly recovered after 48 or 72 hours. Two year follow-up showed no signs of full recovery in the OTS athletes. Echocardiography didn’t reveal any sustained alterations of systolic and diastolic functions, or clinically threatening myocardial damage, only minor diastolic changes due to adaptation to the post-exercise haemodynamic. Elevated values of cardiac markers after strenuous exercise can be linked to increased cellular permeability and cardiac troponin leakage, amplified by oxidative stress existent in OTS athletes.

In our study sport-specific intensive exercise caused mild injury to skeletal muscle and transient increase of the CK-MB and cTnI, without irreversible pathophysiological and clinical consequences, suggesting mostly benign cardiac involvement, though amplified by existent oxidative stress in athletes with OTS. Monitoring responses via alterations of biochemical parameters can be helpful to guide athletic training, and prevent OTS or interrupt NFO to OTS progression.

**Keywords:** Non-functional overreaching, overtraining syndrome, biomarker, skeletal muscle damage, cardiomyocyte damage.

## РЕЗЮМЕ

### ОЦЕНКА ЭФФЕКТОВ НЕФУНКЦИОНАЛЬНОГО ПЕРЕНАПРЯЖЕНИЯ И ПЕРЕТРЕНИРОВКИ НА РЕАКЦИЮ СКЕЛЕТНЫХ МЫШЦ И СЕРДЕЧНЫХ БИОМАРКЕРОВ, С ЦЕЛЮ МОНИТОРИНГА СИНДРОМА ПЕРЕТРЕНИРОВКИ СПОРТСМЕНОВ

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Целью исследования явилось определение ответной реакции биомаркеров повреждения скелетных мышц (СК-НАС) и миокардиоцитов (сТнI и СК-МВ), вызванной нефункциональным перенапряжением и перетренировкой, для мониторинга синдрома перетренировки спортсменов.

У 43 спортсменов с нефункциональным перенапряжением (НФП)/синдромом перетренировки (СП) и спор-

тсменов без НФП/СП (контрольная группа - КГ) перед началом спортивного сезона оценивался уровень креатинкиназы - СК (СК-НАС и СК-МВ), затем, на пике сезона, исследовалась динамика изменений в уровнях СК-НАС, СК-МВ и кардиального тропонина I (сTnI). Измерения концентраций СК и сTnI проведены за 24 часа перед интенсивной, спорт-специфической, соответствующей пику сезона нагрузкой, затем сразу по окончании, спустя 6, 48, и 72 часа после нагрузки. Проведены начальная и после-нагрузочная (спустя 6 и 48 часов) клиническая оценка и эхокардиография.

Одинаковая тенденция роста уровней СК-НАС, СК-МВ и сTnI отмечена у всех спортсменов сразу по окончании нагрузки, которая достигала пиковых значений спустя 6 часов и была достоверно выше у НФП/СП, чем у спортсменов КГ. Спустя 48 часов восстановления у спортсменов с НФП/СП уровни СК-НАС, СК-МВ и сTnI были достоверно выше, чем перед нагрузкой, что свидетельствует о медленном восстановлении. У спортсменов с СП концентрация СК-НАС соответствовала уровню “возможная перетренировка и повреждение мышц” даже после 72 часов восстановления.

Большинство спортсменов отмечали частую травму во время игровых/боевых контактных событий, однако, в ос-

новном, спустя 48 или 72 часа восстановились. Два года наблюдения не выявили признаков полного восстановления у спортсменов с СП. Эхокардиография каких-либо устойчивых изменений систолической и диастолической функций сердца или клинически угрожающего повреждения миокарда не выявила, отмечались только незначительные диастолические изменения ввиду адаптации к гемодинамическим изменениям после нагрузки. Обнаружение повышенных значений сердечных маркеров после интенсивных нагрузок, по всей вероятности, связано с повышенной клеточной проницаемостью и утечкой сTnI, усиленной оксидационным стрессом, существующим у спортсменов с СП.

Спорт-специфические интенсивные нагрузки могут вызвать легкое повреждение скелетных мышц и временное увеличение СК-МВ и сердечного TnI, без необратимых патофизиологических и клинических последствий, что предполагает в основном доброкачественные изменения, усиливающиеся существующим оксидационным стрессом у спортсменов с СП. Использование изменений биохимических параметров с целью мониторинга обеспечит возможность управления спортивными тренировками, предотвращения СП или прерывания прогрессирования НФП в СП.

## რეზიუმე

ჩონჩხის კუნთების და კარდიული ბიომარკერების პასუხზე არაფუნქციური გადაძაბვის და გადაწვრთნის ეფექტის შეფასება, სპორტსმენთა გადაწვრთნის სინდრომის მონიტორინგის მიზნით

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კვლევის მიზანს წარმოადგენდა არაფუნქციური გადაძაბვით და გადაწვრთნით გამოწვეული ჩონჩხის კუნთებისა (CK-NAC) და კარდიომიოციტების დაზიანების (сTnI and CK-MB) ბიომარკერების პასუხის შესწავლა და შედეგების გამოყენება სპორტსმენებში გადაწვრთნის სინდრომის მონიტორინგისთვის. სპორტული სეზონის დაწყების წინ შეფასდა კრეატინინაზას (CK-NAC და CK-MB) დონე არაფუნქციური გადაძაბვით (ავგ/გადაწვრთნის სინდრომით (გწს) სპორტსმენებში (n=43) და საკონტროლო ჯგუფის (სჯ) სპორტსმენებში (n=40) ავგ/გწს-ს გარეშე. შემდეგ სეზონის პიკზე გამოკვლეულ იქნა CK-NAC, CK-MB და კარდიული ტროპონინ I (сTnI)-ს ცვლილებების დინამიკა. CK და сTnI მონაცემები მიღებულია ინტენსიური სპორტ-სპეციფიკური დატვირთვამდე 24 საათით ადრე, დატვირთვის დამთავრებისთანავე და დატვირთვის დასრულებიდან 6, 48 და 72 საათის შემდეგ. საწყისი და დატვირთვის შემდომი კლინიკური და ექოკარდიოგრაფიული შეფასება განხორციელდა 6 და 48 საათის შემდეგ.

მსგავსი ზრდის ტენდენციით ხასიათდებოდა CK-NAC, CK-MB და сTnI-ს დონე დატვირთვის დამთავრებისას და პიკს აღწევდა 6 საათის შემდეგ ყველა სპორტსმენში, თუმცა ავგ და გწს სპორტსმენებში პიკური მონაცემები სარწმუნოდ აღემატებოდა საკონტროლო ჯგუფისას. აღდგენის პერიოდში, 48 საათის შემდეგ ავგ და გწს სპორტსმენებში CK-NAC, CK-MB და сTnI-ს დონე სარწმუნოდ აღემატებოდა საწყის მნიშვნელობებს, რაც მეტყველებს შენელებულ აღდ-

გენაზე. აღდგენიდან 72 საათის შემდეგ გწს სპორტსმენებში CK-NAC -ის დონე “შესაძლო გადაწვრთნას და კუნთის დაზიანებას” შეესაბამებოდა.

სპორტსმენთა უმეტესობა აღნიშნავდა მუდმივ დაზიანებებს თამაშის/ორთაბრძოლის დროს, თუმცა, უმეტეს შემთხვევაში აღდგენა ხდებოდა 48 ან 72 საათში. ორწლიანი დაკვირვებით, გწს სპორტსმენებში სრული აღდგენის ნიშნები არ შეიმჩნეოდა. ექოკარდიოგრაფიით არ გამოვლინდა გულის სისტოლური და დიასტოლური ფუნქციის რაიმე მდგრადი ცვლილებები ან კლინიკურად სახიფათო დაზიანება. შესაძლოა, მცირე დიასტოლური ცვლილებები გამოწვეული იყოს ვარჯიშის შემდგომი ჰემოდინამიკური ადაპტაციით. სავარაუდოა, რომ კარდიული მარკერების გაზრდილი მნიშვნელობები კაშირშია უჯრულის შეღწევადობის ზრდასა და კარდიული ტროპონინების გადინებასთან, რომელიც გაძლიერებულია გწს-ს მქონე სპორტსმენებში არსებული ოქსიდაციური სტრესის გამო.

ამგვარად, სპორტ-სპეციფიკურმა ინტენსიურმა დატვირთვებმა შესაძლოა გამოიწვიოს ჩონჩხის კუნთების ზომიერი დაზიანება და CK-MB და сTnI-ს დონის გარდამავალი ზრდა, შეუქცევადი პათოფიზიოლოგიური და კლინიკური შედეგების გარეშე, თუმცა, გწს სპორტსმენებში გასათვალისწინებელია ოქსიდაციური სტრესის არსებობით განპირობებული გავლენა. მონიტორინგის მიზნით ბიოქიმიური პარამეტრების ცვლილებების გამოყენება უზრუნველყოფს სპორტული დატვირთვის მართვის, გწს-ს დროული დიაგნოსტიკის და ავგ/გწს-ს პროგრესირების პრევენციის შესაძლებლობას.



## PREVALENCE OF HYPERURICEMIA IN PATIENTS WITH CHRONIC HEART FAILURE

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Hyperuricemia (HU) is a common metabolic disorder, which approximately affects 5% of the general population. Its prevalence among hospitalized exceeds 25% [12]. Asymptomatic hyperuricemia is defined as elevated serum urate levels in the absence of signs and symptoms of monosodium urate crystal deposition disease. Asymptomatic hyperuricemia is frequently associated with hypertension, chronic kidney disease and cardiovascular diseases [1]. Currently, hyperuricemia is considered as a poor prognostic factor and a potential determinant of heart failure (HF) development.

The association between elevated uric acid (UA) levels and HF has been known for almost 50 years. Many studies have revealed a connection between increased UA levels and the New York Heart Association (NYHA) functional class; namely, increased HF symptoms, reduced exercise tolerance, systemic congestion and decreased cardiac function [2-4].

HU is correlated with a higher risk of development of HF. Studies showed that it has an unfavorable effect on the outcome of patients diagnosed with HF. A recent meta-analysis showed that, for every 1 mg/dl increase in serum UA, the odds of developing HF increase by 19% and the risk of all-cause mortality by 4% [5-7].

Although the positive relationship between increased UA levels and existence and severity of chronic HF, the clinical and prognostic role of increased levels of UA in acute settings remains controversial and still needs further evaluation.

**Material and methods.** 126 patients with HF who have been admitted to the hospital since September 2019 were included in the study. 75 patients with HF diagnosis and hyperuricemia were included in the main group. 51 HF patients without increased UA level consisted a control group. Inclusion criteria were as follows: patients age 18 years and more, left ventricular ejection fraction 45% or less documented by echocardiography and signs and symptoms of chronic HF. Written informed consent was obtained from all the study participants. Patients with acute infection, autoimmune disorders, severe renal disease (an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m<sup>2</sup>), liver failure and suspected malignancy were excluded from the study. All patients underwent a standardized clinical evaluation, including physical examination, determination of NYHA class and body mass index, full blood count and clinical chemistry, including creatinine for kidney functional assessment and serum ferritin for evaluation the level of iron metabolism.

Renal dysfunction was diagnosed if the eGFR was below 60 ml/min/1.73 m<sup>2</sup>, diabetes mellitus, if patients reported a history of diabetes or were on anti-diabetic drugs, and chronic obstructive pulmonary disease (COPD), if patients were on pharmacotherapy or had been previously diagnosed with COPD. Hyperuricemia was defined according to the World Health Organization criteria as uric acid level >5.7 mg/dl in women and >7 mg/dl in men. Echocardiographic assessment included interventricular septum thickness (IVS), posterior wall thickness (PW), left ventricular end diastolic diameter (LVEDd), left ventricular diastolic function (LVDF), left ventricular mass index (LVMI) and left ventricular ejection

fraction (LVEF). The LVEF was calculated using Simpson's method. Assessment of exercise capacity was performed by a 6-min walk test. Exercise capacity was categorized as reduced, if patients could not perform the median walking distance during the 6-min walk test.

Continuous variables are given as means with standard deviations. Non-normally distributed variables (serum uric acid, serum creatinine, serum C-reactive protein) were long-transformed to achieve normal distribution before analysis. Student's *t* test was used to test for between-group differences. *P* values of <0.05 were considered as statistically significant.

**Results and discussion.** Baseline characteristics are given in Table 1.

According to the data given in a Table 1, HU was present in 75 (59.5%) patients. Most patients in both groups were men. Mean age of patients with HU was higher in comparison with the mean age of control group patients (73.2±9.1 vs 65.2±8.1; *P*<0.05). Body weight was not different between the groups. Majority of patients were hypertensive in both groups (61 (81.3%) and 39 (76.4%); respectively). More patients with HU had Patients with diabetes mellitus were more in a main group (28(37.3%) vs 15 (29.4%); respectively. *P*<0.05). HF etiology was predominantly ischemic in both groups: 51 (68.0%) and 30 (58.8%), respectively. The NYHA distribution was 8% and 19.6% for NYHA class II, 78.66% and 58.8% for class III, and 21.3 and 35.2% for class IV. Patients with HU had significantly low LVEF (38.2±7.0 vs 44.5±5.1; respectively. *P*<0.05).

Main group patients had higher levels of serum C-reactive protein, lower levels of hemoglobin and estimated GFR. In contrast, chronic obstructive pulmonary disease and total cholesterol did not differ between the two groups (*p*=*NS*). No differences were recorded for body weight, diastolic blood pressure or serum creatinine.

The echocardiographic parameters of HF patients with and without HU are summarized in Table 2. Patients with HU had significantly thicker IVS, than those without HU (10.49±2.9 vs 10.93±1.64mm, respectively. *P*<0.006). LV mass index was larger in patients with HU (*P*<0.001); There were no significant differences in LV end-systolic (LVESd) and end-diastolic (LVEDd) dimensions; Additionally, there were no differences in LV diastolic functional parameters, the E, A, and E/A ratio were not significantly different between patients with and without HU.

Totally 75 patients, 50 from main group and 25 from the control group, underwent to the 6-min walk test; The results are presented in a Table 3.

In both groups was decreased average distance walked and percentage of expected distance for healthy persons. Study results point out that female gender, higher NYHA class, low level of LVEF, the presence of hyperuricemia, lower than normal eGFR predict lower exercise capacity.

There was seen negative correlation between serum uric acid levels and left ventricular ejection fraction; therefore, higher NYHA classes were related with the higher levels of uric acid.

Table 1. Baseline characteristics of HF patients with HU versus without HU

Characteristics	Patients with HU, n=75	Patients without HU, n=51	p
Age (years)	73.2±9.1	65.2±8.1	<0.05
Male gender (%)	60	50	
Body weight (kg)	80.2±8.2	79.1±7.0	0.16
Heart rate (min)	75.5±7.2	73.7±7.3	<0.05
Systolic BP (mmHg)	135±15.5	130±17.2	<0.05
Diastolic BP (mmHg)	70.0±8.2	71.5±8.1	0.16
Hypertension (%)	61 (81.3%)	39 (76.4%)	0.16
Renal dysfunction (%)	33 (44%)	10 (19.6%)	<0.05
COPD (%)	10 (14.3%)	9 (17.6%)	0.16
Diabetes mellitus (%)	28 (37.3%)	15 (29.4%)	<0.05
Ischemic etiology (%)	51 (68 %)	30 (58.8%)	0.26
NYHA class II	6 (8%)	10 (19.6%)	<0.05
NYHA class III	59 (78.66%)	30 (58.8%)	<0.05
NYHA class IV	16 (21.3%)	18 (35.2%)	0.16
LVEF (%)	38.2±7.0	44.5±5.1	<0.05
Anemia (%)	45 (60.0%)	20 (39.2%)	<0.05
Hemoglobin (g/l)	110.8±6.1	133±4.1	<0.05
Total cholesterol, mg/dl	175.4±42.4	179.0±41.4	0.13
HDL cholesterol, mg/dl	48.4±14.6	50.7±19.4	<0.05
LDL cholesterol, mg/dl	99.0±33.9	101.7±34.4	<0.05
Serum creatinine (μmol/L)	106.4±25.5	102.7±16.7	0.1
eGFR (ml/min 1.73m <sup>2</sup> )	53.2±23.2	69.7±26.3	0.1
CRP (mg/dl)	4.5±1.1	4.2±0.9	<0.05

Table 2. Echocardiographic parameters in HF patients with and without HU

	Patients with HU, n=70	Patients without HU, n= 56	P
Interventricular septum thickness, mm	10.49±2.9	10.93±1.64	P<0.006
LV end-diastolic dimension, mm	47.7±9.4	45.7±8.7	P<0.026
LV end-systolic dimension, mm	30.6±8.6	29.4±7.4	P<0.149
Posterior wall thickness, mm	11.3±2.2	11.3±3.7	P>0.927
Diastolic function	4.1±1.3	4.08±1.1	P<0.05
LV mass index, g/m <sup>2</sup>	120.8±21.5	105.0±18.4	P<0.001

Table 3. 6-min walk test results in a different study population

Characteristics	Distance - m	% of expected distance for healthy persons
Hyperuricemia	207.4±6.2	42.4±3.4
No hyperuricemia	225.8±6.7	55.1±2.1
NYHA II	224.6±5.8	52.5±4.8
NYHA III	184.2±6.1	40.3±1.5
Men	232.2±1.0	43.5±3.5
Women	192.6±3.1	39.1±2.0
eGFR<60 ml/min	217.5±7.0	49.2±0.0
eGFR>60 ml/min	186.7±3.7	41.5±3.0
LVEF <40	190.6±5.6	40.3±3.5
LVEF >40	181.3±5.8	37.7±2.5

Possible consequences of HU complicating HF have more recently been attracting increasing attention. Palazzouli et al. studied more than 300 patients with a diagnosis of congestive heart failure and revealed a high serum uric acid rate in 59% of patients with CHF [1]. Studies demonstrated that the serum UA level is associated with the incident HF. Krishnan et al. showed that subjects whose serum UA was more than 6.3 mg/dl had a 2.1 – fold higher risk of incident HF compared with those whose serum UA level was less than 3.4 mg/dl in 4912 individuals from the Framingham off-spring cohort [9]. Holmes et al. demonstrated that serum UA was an independent predictor of HF development in 417 734 Swedish individuals who underwent health check-ups in out-patient clinics [8]. Results of present study are in an agreement with these clinical studies. Our findings regarding HU prevalence and its role in HF development and severity are in an accordance with published data from several clinical cohorts.

**Conclusion.** This study demonstrated high prevalence of HU in patients with chronic heart failure. Despite high prevalence of HU in patients with HF, its meaning historically was underestimated in regards of prognosis. Given the clinical relevance, treatability, and independent association with reduced exercise capacity, existence of HU should be defined in all the patients with chronic heart failure to avoid future complications.

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## SUMMARY

### PREVALENCE OF HYPERURICEMIA IN PATIENTS WITH CHRONIC HEART FAILURE

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The aim of our study was to study prevalence and clinical importance of Hyperuricemia (HU) in patients with heart failure (HF).

126 patients with HF were involved in a study. Main group included 75 patients with HF and HU. 51 patients with HF without HU were included in the control group. All patients underwent to a standardized clinical evaluation, including physical examination, determination of NYHA class and laboratory studies; namely, full blood count, serum uric acid, creatinine and ferritin. Assessment of exercise capacity was performed using a 6-min walk test. Echocardiographic assessment included interventricular septum thickness, left ventricular systolic and diastolic dimensions, left ventricular diastolic function, posterior wall thickness, left ventricular mass index and LVEF.

Patients with HU had higher prevalence of diabetes mellitus than patients without HU. Patients with HU had significantly lower LVEF (38.2±7.0 and 44.5±5.1; respectively. P<0.05). No differences were recorded for body weight, diastolic blood pressure, platelets, serum creatinine, or presence of chronic obstructive pulmonary disease. Patients

with HU had significantly thicker IVS, than those without it (10.49±2.9 vs 10.93 ±1.64mm; respectively. P<0.006). LV mass index was larger in patients with HU (P<0.001); There were no significant differences in LV end-systolic (LVESd) and end-diastolic (LVEDd) dimensions. Additionally, there were no differences in LV diastolic functional parameters.

In both groups was decreased average distance walked and percentage of expected distance for healthy persons. Study results point out that female gender, higher NYHA class, low level of LVEF, the presence of hyperuricemia, lower than normal eGFR predict lower exercise capacity.

Presented study demonstrates high prevalence of HU in patients with chronic heart failure. Despite high prevalence, historically the meaning of HU was underestimated in patients with HF. Taken into account the clinical relevance, treatability, and independent association with reduced exercise capacity, it is highly recommended to define HU level in all the patients with chronic heart failure to avoid future complications.

**Keywords:** serum uric acid, hyperuricemia, exercise capacity, heart failure.

РЕЗЮМЕ

РАСПРОСТРАНЕННОСТЬ ГИПЕРУРИКЕМИИ У ПАЦИЕНТОВ  
С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Целью исследования явилось изучение распространенности и клинического течения гиперурикемии у пациентов с сердечной недостаточностью.

Наблюдались 126 пациентов с сердечной недостаточностью (СН). Основная группа состояла из 75 (59,5%) пациентов с гиперурикемией (ГУ) и контрольная группа – 51 (40,4%) пациент с СН без ГУ. Все пациенты прошли стандартизированную клиническую оценку, включая физическое обследование, определение хронической СН по функциональной классификации NYHA и лабораторные исследования. Оценка толерантности к физической нагрузке проведена тестом 6-минутной ходьбы. Выполнено эхокардиографическое исследование. У 61 (81,3%) пациента основной группы и 39 (76,4%) пациентов контрольной группы выявлена артериальная гипертензия; у 28 (37,3%) пациентов с ГУ выявлен сахарный диабет; в обеих группах СН была преимущественно ишемической; 59 (78,66%) па-

циентов с ГУ и 30 (58,8%) без ГУ принадлежали к III классу NYHA, пациенты основной группы имели значительно низкую фракцию выброса левого желудочка (LVEF). Различий по массе тела, диастолическому давлению крови, тромбоцитам или креатинину сыворотки не выявлено. Гиперурикемия связана со значительно более высоким классом NYHA. Выявлено, что пол, класс NYHA, LVEF, скорость клубочковой фильтрации коррелируют с более низкой толерантностью к физической нагрузке. Проведенное исследование демонстрирует высокую распространенность ГУ у пациентов с хронической сердечной недостаточностью. Несмотря на высокую распространенность, значение гиперурикемии по сей день недооценено у пациентов с СН. Принимая во внимание клиническую значимость, излечимость и толерантностью с низкой физической нагрузкой, авторы рекомендуют определять уровень ГУ у всех пациентов с хронической сердечной недостаточностью.

რეზიუმე

ჰიპერურიკემიის სიხელო პაციენტებში გულის ქრონიკული უკმარისობით

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ჰიპერურიკემია მნიშვნელოვან თანხსელებ პათოლოგიას წარმოადგენს გულის უკმარისობის მქონე პაციენტებში, ასოცირდება კლინიკური მდგომარეობის გაუარესებასთან და დაავადების გართულებასთან.

კვლევის მიზანს წარმოადგენდა ჰიპერურიკემიის გავრცელების შესწავლა გულის ქრონიკული უკმარისობით პაციენტებში.

გამოკვლეულია 126 პაციენტი (110 მამაკაცი, 16 ქალი) გულის უკმარისობით: 75 (59,5%) ჰიპერურიკემიით, საშუალო ასაკი 73,2±9,1 წ. (ძირითადი ჯგუფი) და 51 (40,4%) - ჰიპერურიკემიის გარაშე (საკონტროლო ჯგუფი). პაციენტებს ჩაუტარდათ კლინიკურ-ლაბორა-

ტორიული კვლევები, დატვირთვის მიმართ ტოლერანტობა განისაზღვრა 6-წუთიანი სიარულის ტესტით. ჰიპერურიკემიით პაციენტებში სიხელო იყო შაქრიანი დიაბეტის გავრცელება, არტერიული ჰიპერტენზია, ძირითადათ მიეკუთვნებოდნენ გულის უკმარისობის III ფკ და უფრო დაბალი ჰქონდათ მარცხენა პარკუჭის განდენის ფრაქცია. ჰიპერურიკემია სარწმუნოდ ასოცირდებოდა გულის უკმარისობის მაღალ ფუნქციურ კლასთან. კვლევამ გამოავლინა პაციენტთა სქესის, გულის უკმარისობის ფუნქციური კლასის, eGFR კავშირი ფიზიკური დატვირთვის მიმართ დაბალ ტოლერანტობასთან.

## FACTORS ASSOCIATED WITH DECLINE OF FEV1 IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Chronic obstructive pulmonary disease (COPD) is a major cause of illness and death worldwide [19]. As a chronic disease COPD is prone to progress for years and mortality rate is associated with both disease severity and its complications. Since 2016 COPD has been considered as the third-leading cause of death worldwide [3,8] and consequently the great problem in healthcare system in the terms of disease prevention and management [2]. According to the WHO COPD is reported as a global challenge for the modern health care system. Mortality rate due to the disease accounts for 2.75 million cases annually and it is predicted to increase disease morbidity and mortality due to environmental pollution as well as prolongation of lifetime of population in the future.

Chronic obstructive pulmonary disease is a heterogeneous, chronic inflammatory process of the airways often involving destruction of adjacent alveoli and vasculature. Symptoms range from chronic productive cough to debilitating dyspnea. Disease trajectory can vary from years of stability to devastating acute exacerbations and respiratory failure [9]. Exacerbations or episodes of acute worsening of the respirator symptoms are general characteristic of COPD. Exacerbations itself accelerate the decline in lung function resulting in reduction of physical activity, quality of life, and increased risk of death. The main characteristic of the lung function is forced expiratory volume in one second (FEV<sub>1</sub>), the maximum amount of air that the subject can forcibly expel during the first-second following maximal inhalation [11]. FEV<sub>1</sub> can be used to assess lung function capacity and categorize the severity of COPD.

Decline of FEV<sub>1</sub> as a direct indicator for the lung function capacity is one of the most unfavorable prognostic sign of COPD, associated with deterioration of lung function, frequency of disease exacerbations and increased risk of mortality [5,24,25]. Despite the importance of the issue factors that are associated with progressive decline of FEV<sub>1</sub> in COPD, is still area of challenge in medicine. Active smoking and frequency of exacerbations reliably correlate with the dynamics of FEV<sub>1</sub> decline [13]. Smokers are at greater risk of premature mortality than nonsmokers in COPD [15]. The other factor that may be related to disease progression and poor outcome is possibly the obesity. Although there is no evidence regarding the impact of body mass index (BMI) on severity and prognosis of COPD [4,21,20,23]. So, assessment of those relations are both useful and important [10]. At the same time, there is heterogeneous information regarding the influence of such factors as age, comorbidity and duration of COPD on disease progression and severity, mMRC (Modified Medical Research Council Questionnaire) gradation, Functional Questionnaire score, COPD duration, which are in correlation with FEV<sub>1</sub> progressive deterioration during COPD [21,16] The quite ambiguous data raises questions and needs for more profound and thorough investigations regarding the risk factors and predictors that contribute to more severe forms of the disease, frequency of exacerbations and poor outcome [1,6,17,18]. Identification of risk factors and reduction their exposure are important steps in prevention, management and prognosis of COPD.

According to the above mentioned the purpose of the study is to trace and reveal the correlation between the deterioration of FEV<sub>1</sub> and those risk factors that may be associated with the worsening of lung function in order to develop disease management strategy to prevent progression and improve the outcome of the disease.

Purpose of the study was to investigate the correlation between the pulmonary functional indexes, including FEV<sub>1</sub> and various risk factors that deteriorate lung functional capacity and cause poor outcome of COPD. Study results will promote better understanding of COPD's risk stratification which will improve disease management and outcome by prevention of modifying risk factors. The clinical evaluation of the patients with COPD included: gender, age, BMI, tobacco consumption (active or ex-smoker), history, presence of comorbidities; The severity of COPD was assessed by MMRC, CAT questionnaires, GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria, frequency of the disease exacerbations (determined as deterioration of COPD symptoms, that requires treatment with antibiotics or/and with glucocorticoids, or hospitalization).

**Material and methods.** The study was conducted at the L.T.D. "N. Kipshidze Central University Clinic". Pulmonary functional status was assessed by spirometry. To identify the severity of the disease we used criteria provided by GOLD [8].

The study included 78 patients. Demographic and clinical characteristics of the patients are given : Gender- Male -50 (64,10%), Female- 28 (35,90%), Age 61,56±10,72, Age of starting COPD complaints-54,92±10,52, Duration of COPD-6,64±4,05, Former Smoker-50,00 (64,10%), Smoker-28,00 (35,90%), P/Y-35,21±25,72, Duration of smoking-28,45±10,77, BMI-28,45±10,77, Normal Body Mass-20(25,64%), Excessive weight-18(23,08%), Obesity-40(51,28%), Treatment in History- Was not treated-26 (33,33%), Salbutamol-28(35,90%), Combined therapy-24 (30,77%), Exacerbation in history- No - 62 (79,49%), Yes - 16(20,51%), mMRC-gradation- Grade2-42(53,85%), Grade3- 36(46,15%), Questionnaire on Lung function-12,36±2,78, Arterial Hypertension-70(89,74%), CAD. angina of effort -26 (33,33%), Heart failure-10(12,82%), Atrial fibrillation-2 (2,56%), Type 2 diabetes -16(20,51%), Dyslipidemia -38(48,72%), Chronic kidney disease -2 (2,56%).

Identify the risk-factors that influence on severity, prognosis and outcome of COPD multiple regression analysis (Pearson coefficient R<sup>2</sup>, reliability considered as the value p<0.05) was performed including such factors as: age, BMI (kg/m<sup>2</sup>), smoking (age/pack), comorbidity, duration of COPD, frequency of hospitalization due to exacerbation. We also used mMRC (Modified Medical Research Council Questionnaire) gradation, Functional Questionnaire score.

**Results and discussion.** Statistically reliable correlation was not revealed between COPD severity and such factors as presence of comorbidity and Functional Questionnaire score. As to tobacco consumption, there was not revealed statistically reliable correlation, although smoking is among reliably proved risk-factors that provoking progression of the disease. Relationship of disease severity with other risk-factors and their statisti-

Table 1. Correlation Coefficients and Reliability values determined by Multiple linear regression pattern

#	Risk-factor	Coefficient	Coeff	SE	t-stat	p-value
		b	-5.3668	2.2012	-2.4381	0.0159
F1	Age	$\beta_1$	-0.2841	0.1051	-2.7042	0.0076
F2	BMI	$\beta_2$	-1.9836	0.0875	22.6767	< 0.0001
F5	mMRC	$\beta_5$	-7.4719	2.6276	2.8436	0.0051
F7	COPD Duration	$\beta_7$	-1.0925	0.2838	3.8497	0.0003
F8	Hospitalization Frequent Cases in Anamnesis	$\beta_8$	- 0.1895	0.3221	-0.2808	0.0056

cal reliability is provided in Table 1.

Study results demonstrated that COPD severity (based on FEV1 value) is statistically reliably related to frequent hospitalization due to disease exacerbation. Therefore, prevention of exacerbations is one of the main goals in managing COPD. Statistically reliable relationships were revealed between the severity of COPD and such factors as age, BMI, mMRC gradation, disease duration.

**Conclusion.** Take into account the study results we can conclude the following:

1. Early identification of COPD as well as early beginning of adequate treatment are essential in slow down the progression of the disease and consequently results in the development of less severe forms and more benign outcome of the disease.
2. Overweight and obesity are the risk-factors that should be considered as predictors of more severe forms of COPD.
3. Self-Assessment Questionnaire (mMRC gradation - Modified Medical Research Council Questionnaire) is important screening test to predict more severe course of the diseases.
4. Adequate management and prevention of hospitalization due to exacerbations in COPD are essential to maintain functional status of the lungs and provide more benign outcome of the disease.

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## SUMMARY

### FACTORS ASSOCIATED WITH DECLINE OF FEV1 IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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The purpose of the study was to search for a correlation between FEV1 and the possible predictors that determine disease progression and lung function deterioration in COPD patients.

The research was conducted at N. Kipshidze Central University Clinic. 78 COPD patients participated in it. Spirometry was used to diagnose the participants and GOLD guidelines for COPD were applied to estimate stages of disease severity.

Multiple regression analysis were conducted in order to estimate severity of COPD and its risk factors. The research revealed statistically significant correlation between lung function deterioration and the factors such as age, BMI, duration of COPD, hospitalization frequency due to COPD exacerbation based on the patient's anamnesis and self-assessment questionnaire for dyspnea. It can be considered statistically significant that early diagnosing of COPD and therefore timely and adequate treatment, prevention of disease exacerbation and adherence to a healthy lifestyle notably determines severity of the disease and its prognosis.

Statistically significant correlation that was revealed between FEV1 and dyspnea self-assessment questionnaire increases the clinical value of this questionnaire in estimating COPD severity.

**Keywords:** lung function deterioration, forced expiratory volume in one second (FEV<sub>1</sub>), chronic obstructive pulmonary disease (COPD), pulmonary functional status, spirometry.

## РЕЗЮМЕ

### ФАКТОРЫ, АССОЦИИРОВАННЫЕ С УХУДШЕНИЕМ FEV1 ПРИ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ

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Целью исследования явилось определение возможных предикторов, ассоциированных с прогрессированием болезни и ухудшением функционального состояния легких у больных хронической обструктивной болезнью легких. Исследование проведено на базе Центральной университетской клиники им. Н. Кипшидзе. В исследовании участвова-

ли 78 больных хронической обструктивной болезнью легких (ХОБЛ). Функциональное состояние легких оценивалось посредством спирометрии. При определении степени тяжести болезни учитывались критерии, представленные Глобальной инициативой по ХОБЛ (Global Initiative for Chronic Obstructive Lung Disease).

Множественный регрессионный анализ использован для определения степени тяжести и прогностических факторов риска ХОБЛ. Статистически значимая корреляция выявлена между нарушением легочной функции и такими факторами, как возраст, индекс массы тела, продолжительность ХОБЛ, частота госпитализаций ввиду обострений ХОБЛ и показатели Шкалы субъективной оценки одышки (ШСОО). Своевременное выявление и, соответственно, адекватное лечение ХОБЛ, а также профилактика обострения заболевания и ведение здорового образа жизни в значительной степени определяют тяжесть заболевания и его прогноз. Выявленная статистически значимая корреляция между FEV-1 и ШСОО повышает клиническую ценность Шкалы субъективной оценки одышки при определении степени тяжести ХОБЛ.

## რეზიუმე

ფილტვების ქრონიკული ობსტრუქციული დაავადების დროს FEV 1-ის გაუარესებასთან ასოცირებული ფაქტორები

ქ. ლობჯანიძე, მ. სულაქველიძე, რ. თაბუკაშვილი

აკად. ნ. ყიფშიძის სახ. ცენტრალური საუნივერსიტეტო კლინიკა, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა პაციენტებში ფილტვების ქრონიკული ობსტრუქციული დაავადებით FEV1-ის კორელაციის ძიება იმ შესაძლო პრედიქტორებთან, რომლებიც დაავადების პროგრესირებას და ფილტვის ფუნქციური მდგომარეობის გაუარესებას განაპირობებენ.

გამოკვლეულია 78 პაციენტი აკად ნ. ყიფშიძის სახ. ცენტრალური საუნივერსიტეტო კლინიკის ბაზაზე. დიაგნოზი დადგენილი იყო სპირომეტრიული კვლევით, ხოლო დაავადების სიმძიმის სტადიის დადგენა განხორციელდა GOLD-ის მიერ მოწოდებული კრიტერიუმებით.

ფილტვების ქრონიკული ობსტრუქციული დაავადების (ფქოდ) სიმძიმის და პროგნოზის რისკ-ფაქტორების გამოსავლენად ჩატარდა მრავლობითი რეგრესიული ანალიზი. სტატისტიკურად სარწმუნო კავშირი გამოვლინდა ფილტვის ფუნქციური მდგომარეობის გაუარესებასა და ისეთ ფაქტორებს შორის, როგორცაა ასაკი, სხეულის მასის ინდექსი, ფქოდ-ის ხანგრძლივობა, ანამნეზში ფქოდ-ის გამწვავების გამო ჰოსპიტალიზაციის სიხშირე და დისპნოეს თვითშეფასების სკალის მაჩვენებლები. სარწმუნოდ შეიძლება მივიჩნიოთ, რომ ფქოდ-ის დროული გამოვლენა და, შესაბამისად, დროული და ადეკვატური მკურნალობა, დაავადების გამწვავების პრევენცია და ცხოვრების ჯანსაღი წესის დამკვიდრება მნიშვნელოვნად განსაზღვრავს დაავადების სიმძიმეს და მის პროგნოზს. სტატისტიკურად სარწმუნო კავშირი გამოვლენილია FEV-1-სა და დისპნოეს თვითშეფასების სკალის მაჩვენებლების შორის ზრდის კოეფიციენტის კლინიკურ ღირებულებას ფქოდ-ის სიმძიმის შეფასებისას.

## ЭОЗИНОФИЛЬНЫЙ КАТИОННЫЙ ПРОТЕИН КАК ЧУВСТВИТЕЛЬНЫЙ БИОМАРКЕР ЭОЗИНОФИЛЬНОГО ВОСПАЛЕНИЯ И ПРЕДИКТОР ТЯЖЕЛОГО ТЕЧЕНИЯ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЁГКИХ

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Как известно, хроническая обструктивная болезнь лёгких (ХОБЛ) является одной из ведущих причин летальности, нетрудоспособности и значительных экономических затрат. В результате регулярного воздействия токсических частиц и газов развивается хроническое воспаление, усиливающееся при обострении. Многие клетки и медиаторы принимают участие в развитии воспалительного процесса, у некоторых пациентов может наблюдаться увеличение количества эозинофилов [9].

В последние годы предложены различные варианты выделения фенотипов ХОБЛ. Исходя из различий по характеру воспаления в бронхолегочной системе и преобладанию соответствующих клеточных элементов выделены нейтрофильный и эозинофильный типы воспалительной реакции и соответствующие им клинические фенотипы. Накопленные данные позволяют судить о том, что ХОБЛ с эозинофильным типом воспаления является отдельным фенотипом заболевания с характерными клиническими особенностями [25].

Данные об участии эозинофилов в воспалительном процессе при ХОБЛ появились еще в 1990-х годах. В 1994 г. M. Saetta с соавт. [23] показали, что пациенты с хроническим бронхитом в стадии обострения имели большее количество эозинофилов в мокроте и биоптатах бронхов, чем пациенты, обследованные при стабильном течении болезни. Доказательства участия эозинофилов в воспалении дыхательных путей при стабильной ХОБЛ представлены G. Balzano с соавт. [2], которые сравнили клеточный состав мокроты у клинически стабильных пациентов с ХОБЛ, здоровых курильщиков, пациентов с лёгкой бронхиальной астмой и у здоровых. Авторы показали, что процент эозинофилов в мокроте повышен у пациентов с ХОБЛ в сравнении со здоровыми в контрольной группе.

Эозинофилы являются многофункциональными клетками, которые участвуют в инициации и распространении воспалительных реакций, модуляции врожденного и адаптивного иммунитета [13]. По сей день нет однозначного ответа на вопрос о причинах и механизмах повышения уровня эозинофилов у пациентов с ХОБЛ [3]. Эозинофилы содержат гранулы, состоящие из основного (щёлочного) протеина, катионного белка эозинофилов (ЕСР), эозинофильной пероксидазы и эозинофильного нейротоксина [5]. Считается, что уровень ЕСР отражает состояние активации эозинофилов [4]. Продемонстрирована высокая чувствительность и специфичность ЕСР крови в качестве биомаркера обострения ХОБЛ [3,28]. В работе M. Miller с соавт. [19] показана связь уровня ЕСР с выраженностью эмфиземы. В работах других авторов показана обратная корреляция между

уровнем ЕСР и ОФВ1 [2,16]. На сегодняшний день имеется относительно небольшое количество данных о связи между уровнем ЕСР и особенностями течения ХОБЛ.

Цель исследования - определить взаимосвязь между уровнем катионного белка эозинофилов плазмы крови, как биомаркера активности эозинофильного воспаления, и частотой развития среднетяжелых и тяжелых обострений, пневмоний и характером изменений вентиляционной функции легких у пациентов с хронической обструктивной болезнью лёгких.

**Материал и методы.** Для определения вклада эозинофильного воспаления в клинико-функциональные особенности течения ХОБЛ в основную группу исследования включен 161 пациент, средний возраст составил 63 [55;70] г, индекс курения 40 [25;60] пачка/лет. Критериями включения в исследование являлись возраст пациента от 40 до 70 лет, подтвержденный диагноз ХОБЛ, поставленный не менее чем за 12 месяцев до момента включения в исследование, индекс курения более 10 пачка/лет, отсутствие атопии в анамнезе и уровень общего IgE <100 МЕ/мл. Пациенты должны были иметь постбронходилатационное значение ОФВ1/ФЖЕЛ <70%, отрицательный тест с бронхолитиком в период ремиссии заболевания.

Всем пациентам выполнялось физикальное обследование, спирометрия с проведением пробы на обратимость бронхообструкции (в соответствии с требованиями ATS/ERS) [17,20], 6-минутный шаговый тест. Оценка кашля проводилась при помощи шкалы тяжести кашля [1], степени гнойности мокроты - по шкале Murray sputum colour chart [21]. Выраженность одышки оценивалась в баллах по шкале mMRC [27]. С целью проведения комплексной оценки тяжести ХОБЛ рассчитывался индекс BODE [7]. В качестве критерия эозинофильного воспаления использовался уровень эозинофилов периферической крови вне обострения заболевания  $\geq 300$  клеток/мкл [9]. В качестве критерия эозинофильного воспаления использовался уровень эозинофилии  $\geq 100$  клеток/мкл в сочетании с 2 обострениями средней степени тяжести или госпитализацией пациента в течение года. Степень тяжести обострений ХОБЛ определялась согласно рекомендациям GOLD [9]. Всем пациентам проводилось определение уровня ЕСР периферической крови. В качестве критерия повышения ЕСР вне обострения заболевания использовался уровень ЕСР  $>24$  нг/мл [6,8].

Пациенты стратифицированы по уровню эозинофилов крови ( $\geq 300$  клеток/мкл,  $<300$  клеток/мкл), уровню ЕСР ( $\geq 24$  нг/мл,  $<24$  нг/мл), а также в зависимости от уровня эозинофилов крови  $\geq 100$  клеток/мкл в сочетании с  $\geq 2$  обо-



стрениями средней или тяжелой степени тяжести в течение года. С целью более детального изучения нарушений вентилиционной функции легких методом случайной выборки из основной группы отобрана группа из 64 пациентов, которым проведено дополнительное обследование. Средний возраст пациентов в этой группе составил 59 [52;65] лет, индекс курения 72 [44; 87] пачка/лет. Каждому пациенту в группе дополнительного обследования проведена общая бодиплетизмография с целью оценки остаточного объема лёгких, исследование диффузионной способности легких по монооксиду углерода (DL CO) [11,12,19], мультиспиральная компьютерная томография (МСКТ) грудной клетки на вдохе и выдохе с целью выявления «воздушных ловушек».

Всем пациентам проведён сравнительный анализ клинико-функциональных параметров, проводились корреляционный и дискриминационный анализы.

Статистическая обработка результатов исследования выполнялась при помощи пакета программ «Statistica for Windows 10.0». Качественные признаки представлены в виде относительных (%) частот, количественные данные – в виде Mediana [Q25; Q75]. Определение характера распределения проводилось при помощи W-теста Шапиро-Уилка. Тестирование данных выявило их несоответствие нормальному распределению, поэтому использовались непараметрические методы. Для оценки различий средних двух независимых групп использовался U-критерий Манна-Уитни. Для сравнения частот качественных признаков использовалось значение хи-квадрат ( $\chi^2$ ). Пороговый уровень статистической значимости принимался при значении критерия  $p < 0,05$ . При проведении корреляционного анализа использовали коэффициент Спирмена. Сила корреляционной связи оценивалась следующим образом: сильная - от  $\pm 0,7$  до  $\pm 1$ ; средняя - от  $\pm 0,3$  до  $\pm 0,699$ ; слабая - от 0 до  $\pm 0,299$ . Для количественного определения степени влияния исследуемых факторов на частоту обострений и развития пневмоний рассчитано отношение шансов с использованием функции odds ratio пакета fmsb языка программирования R.

**Результаты и обсуждение.** При сравнении клинико-функциональных показателей у пациентов с ХОБЛ с уровнем эозинофилов крови  $\geq 300$  клеток/мкл и  $< 300$  клеток/мкл кро-

ви статистически значимых различий не выявлено ( $p > 0,05$ ). При проведении сравнительного анализа клинико-функциональных показателей пациентов с разным уровнем ЕСР крови установлено, что пациенты с уровнем ЕСР  $\geq 24$  нг/мл имели большее количество баллов по шкале одышки mMRC и был более высокий индекс BODE, чаще происходили обострения ( $p < 0,05$ ). У 50% пациентов с ХОБЛ с ЕСР  $\geq 24$  нг/мл в течение года диагностировалась пневмония, что чаще, чем у пациентов с ЕСР  $< 24$  нг/мл. В то же время курсы антибактериальной терапии (АБТ) чаще назначались в группе пациентов с ЕСР  $< 24$  нг/мл. У пациентов с низкими значениями ЕСР чаще была продукция гнойной мокроты, чем в группе пациентов с уровнем ЕСР  $\geq 24$  нг/мл. Результаты сравнительного анализа клинико-функциональных показателей у пациентов с разным уровнем ЕСР представлены в таблице 1.

Сходные данные получены при проведении сравнительного анализа у пациентов, стратифицированных по уровню эозинофилов крови  $> 100$  клеток/мкл и количеству обострений/госпитализаций в течение года. Продemonстрировано, что в группе с уровнем эозинофилов  $\geq 100$  клеток/мкл в сочетании с  $\geq 2$  обострениями средней степени тяжести или госпитализацией в течение года, отмечалось более тяжелое течение ХОБЛ – большая выраженность одышки по шкале mMRC, более высокий индекс BODE, большая частота курсов АБТ ( $p < 0,05$ ), чаще диагностировалась пневмония в течение года. Данные представлены в таблице 2.

Пациенты, которым проведено дополнительное функциональное и лучевое обследование стратифицированы в зависимости от уровня ЕСР крови, а также в зависимости от уровня эозинофилов крови и количеству обострений/госпитализаций в течение года. Характеристика дополнительных клинико-функциональных параметров пациентов группы дополнительного обследования представлена в таблице 3.

Проведённый сравнительный анализ данных клинико-функционального обследования пациентов этой группы, стратифицированных в зависимости от уровня ЕСР крови, выявил ряд статистически значимых различий, которые представлены в таблице 4.

Таблица 1. Сравнительный анализ клинико-функциональных параметров пациентов с ХОБЛ с различным уровнем ЕСР периферической крови (основная группа)

Параметры	Пациенты с ХОБЛ, основная группа (n=161)		p ***
	ЕСР <24 нг/мл (n=123)	ЕСР $\geq 24$ нг/мл (n=38)	
Кашель, баллы*	1,9 [0,8; 2,5]	1,6 [0,5; 2,5]	>0,05
Продукция мокроты, баллы *	2 [1,5; 2,4]	1,7 [0,8; 2,1]	<0,05
MRC, баллы*	1 [0,5; 2]	3 [2; 4]	<0,05
ОФВ1, % от должного (после пробы с бронхолитиком)*	69 [53,75; 75]	67 [57; 76,5]	>0,05
ФЖЕЛ, % от должного (после пробы с бронхолитиком) *	78 [55,9; 81]	76 [53,5; 78,5]	>0,05
6-минутный шаговый тест, метры*	540 [372; 670]	450 [302,5; 637,5]	>0,05
Индекс BODE, баллы*	1 [1; 2]	3 [2; 4]	<0,05
Обострения за 12 мес., n*	1 [1; 2]	3[2; 3,75]	<0,05
Пневмонии за 12 мес., %**	22	50	–
Курсы АБТ за 12 мес., n*	1,5 [1; 3]	1 [0; 1]	<0,05

примечание: \* - данные представлены в виде «Mediana [Q25; Q75]»;

\*\* - данные представлены в виде % пациентов;

\*\*\* - сравнение показателей в группах ЕСР <24 нг/мл и ЕСР  $\geq 24$  нг/мл

Таблица 2. Сравнительный анализ клинико-функциональных параметров пациентов с ХОБЛ, стратифицированных по повышению уровня эозинофилов крови ( $\geq 100$  клеток/мкл) и количеству обострений/госпитализаций в течение года ( $\geq 2$  обострений/год)

Параметры	Пациенты с ХОБЛ, основная группа (n=161)		p
	эозинофилы крови <100клеток/мл и <2 обострений / год (n=112)	эозинофилы крови $\geq 100$ клеток/мл и $\geq 2$ обострений / год (n=49)	
MRC, баллы*	1 [0,5; 2]	3 [2; 4]	<0,05
ОФВ1, % от должного (после пробы с бронхолитиком)*	71 [56; 83]	64 [53; 76]	>0,05
6-минутный шаговый тест, метры*	620 [492; 738]	404 [278; 534]	>0,05
Индекс BODE, баллы*	1 [1; 2]	3,5 [2; 4]	<0,05
Пневмонии за 12 мес., %**	38	54	–
Курсы АБТ за 12 мес., n*	0,8 [0,5; 1,2]	2,3 [1,4; 3,3]	<0,05

примечание: \* - данные представлены в виде «Mediana [Q25; Q75]»;

\*\* - данные представлены в виде % пациентов;

\*\*\* - сравнение показателей в группах

Таблица 3. Характеристика клинико-функциональных параметров пациентов с ХОБЛ в группе дополнительного обследования

Параметры	Пациенты с ХОБЛ, стратифицированные по уровню ЕСР с дополнительным обследованием (n=64)
«Воздушные ловушки», n (% пациентов) *	41 (64,1)
КТ-признаки эмфиземы легких, n (% пациентов) **	10 [15; 63]
Денситометрический индекс эмфиземы, % **	2 [0,9; 3,5]
Остаточный объём лёгких, % от должного **	134 [112; 191]
Диффузионная способность легких по монооксиду углерода, % от должного **	83 [67; 96]

примечание: \* - данные представлены в виде n - абс. количество пациентов и процент;

\*\* - данные представлены в виде «Mediana [Q25; Q75]»

Таблица 4. Сравнительный анализ клинико-функциональных параметров пациентов, стратифицированных по уровню ЕСР крови в группе дополнительного обследования

Параметры	Пациенты с ХОБЛ, группа с проведением дополнительного обследования (n=64)		p
	ЕСР <24нг/мл (n=34)	ЕСР $\geq 24$ нг/мл (n=30)	
MRC, баллы*	2 [1; 2]	3 [2; 4]	<0,05
ОФВ1, % от должного (после пробы с бронхолитиком) *	65 [50; 85]	67 [50; 84]	>0,05
Индекс BODE, баллы *	2 [1; 3]	4 [3; 5]	<0,05
Остаточный объём лёгких, % от должного *	129 [109; 145]	175 [123; 223]	<0,05
Диффузионная способность легких по монооксиду углерода, % от должного *	79 [71; 87]	74,2 [68; 80]	>0,05
«Воздушные ловушки», % **	32,4	83,3	–
Денситометрический индекс эмфиземы, %*	1,8 [0,7; 2,9]	3,0 [2,3; 3,7]	<0,05
Обострения за 12 мес., n *	2 [1; 3]	4 [3; 5]	<0,05
Постоянный приём ИГКС, % **	19,5	52,6	–
Курсы АБТ за 12 мес., n *	1,5 [1; 3]	1 [0; 1]	<0,05

примечание: \* - данные представлены в виде «Mediana [Q25; Q75]»;

\*\* - данные представлены в виде % - процент пациентов;

\*\*\* - сравнение показателей в группах ЕСР <24нг/мл и ЕСР  $\geq 24$ нг/мл

Из таблицы 4 следует, что у пациентов с повышенным уровнем ЕСР продемонстрированы более выраженные признаки статической гиперинфляции – «воздушные ловушки», выявленные при проведении МСКТ и бодиплетизмографии. Достоверных различий по уровню DL CO не выявлено. Уста-

новлена положительная корреляционная связь между уровнем ЕСР и наличием статической гиперинфляции ( $r=+0,711$ ;  $p<0,05$ ). Сходные данные при сравнительном анализе групп пациентов, стратифицированных в зависимости от уровня эозинофилов в периферической крови и количества обострений/

госпитализаций в течение года. У пациентов с уровнем эозинофилов крови  $\geq 100$  клеток/мкл в сочетании с 2 обострениями средней степени тяжести или госпитализацией в течение года также выявлены статистически достоверно более выраженные признаки статической гиперинфляции ( $p < 0,05$ ).

Ингаляционные глюкокортикостероиды (ИГКС) получали чаще пациенты с уровнем ECP  $\geq 24$  нг/мл (53%), чем пациенты с ECP  $< 24$  нг/мл (20%). Пациенты с уровнем эозинофилов крови  $\geq 100$  клеток/мкл в сочетании с  $\geq 2$  обострениями средней степени тяжести или госпитализацией в течение года получали ИГКС чаще (55%), чем пациенты с уровнем эозинофилов крови  $< 100$  клеток/мкл и  $< 2$  обострений средней степени тяжести или госпитализацией в течение года (16%). Курсы АБТ чаще получали пациенты с уровнем эозинофилов крови  $< 100$  клеток/мкл и  $< 2$  обострений средней степени тяжести или госпитализацией в течение года (1,5 [1;3]), чем пациенты с уровнем эозинофилов крови  $\geq 100$  клеток/мкл в сочетании с  $\geq 2$  обострениями средней степени тяжести или госпитализацией в течение года (1 [0;1]).

С целью определения вклада каждого из клинико-функциональных параметров, а также уровня эозинофилов и ECP в стратификацию ХОБЛ по степени тяжести выполнен линейный дискриминантный анализ. Для таких показателей, как частота обострений/госпитализаций в течение года, уровень эозинофилов периферической крови, уровень ECP и их комбинаций рассчитаны отношения шансов их влияния на тяжесть течения ХОБЛ. При введении в качестве дискриминирующего фактора уровня ECP пациенты с ХОБЛ классифицированы на две группы. Однако, только после включения параметра «обострение» в качестве дискриминирующего фактора, 85,8% исходных сгруппированных по степени тяжести заболевания наблюдений классифицировано статистически правильно. Первая группа включала страту пациентов с ХОБЛ с ОФВ1  $\geq 50\%$  от должного, вторая – страту пациентов с ХОБЛ с ОФВ1  $< 50\%$  от должного (спирометрическая классификация GOLD) [9].

В проведенном исследовании подтверждено наличие клинико-функциональных особенностей у пациентов с фенотипом ХОБЛ с признаками эозинофильного характера воспаления, выбрав критерий, позволяющий исключить из исследования пациентов с различными аллергическими проявлениями и бронхиальной астмой.

Проведенный сравнительный анализ клинико-функциональных данных пациентов в группах с уровнем эозинофилов крови  $\geq 300$  клеток/мкл и  $< 300$  клеток/мкл не выявил статистически значимых различий между группами. Полученные данные свидетельствуют о том, что хотя топрогностические критерии течения ХОБЛ, основанные на повышении эозинофилов более 300 клеток/мкл в периферической крови, рекомендованные в GOLD, безусловно, определяют подходы к терапии [9], они не всегда отражают клинико-функциональные особенности пациентов с эозинофильным фенотипом. Например, такие показатели тяжести течения заболевания, как выраженность одышки, индекс BODE в группах с  $\geq 300$  клеток/мкл и  $< 300$  клеток/мкл крови в период ремиссии заболевания у обследованной группы пациентов статистически значимых различий не имели ( $p > 0,05$ ).

В ходе проведенного исследования продемонстрировано, что повышение ECP у пациентов с ХОБЛ с эозинофильным характером воспаления достоверно связано с более выраженными обструктивными нарушениями вентиляционной способности легких, наличием «воздушных ловушек» и признаками гиперинфляции. Корреляция между уровнем

ECP и наличием «воздушных ловушек» позволяет предположить, что активированные эозинофилы участвуют в патогенезе этого фенотипа ХОБЛ, что согласуется с данными других опубликованных исследований [2,12]. Включение механизма эозинофильного воспаления способствует развитию более выраженной статической гиперинфляции – одного из маркеров тяжести ХОБЛ [9].

Полученные данные демонстрируют, что пациенты с ХОБЛ с повышенным уровнем ECP крови получали ИГКС чаще, чем пациенты без повышения ECP (таблица 4). Это можно объяснить тем, что пациенты с ECP  $\geq 24$  нг/мл имели более тяжелое течение заболевания, с частыми обострениями, что приводит к более частому назначению ИГКС, в соответствии с рекомендациями GOLD [9]. Обращает на себя внимание, что в группе пациентов с уровнем ECP  $\geq 24$  нг/мл отмечалось не только более частое назначение ИГКС, но и более частое развитие пневмоний (таблица 1), что согласуется с данными других опубликованных исследований [14,15].

Выявленная связь между повышением уровня ECP и частотой развития обострений, пневмоний, приёмом ИГКС может быть объяснена биологическими свойствами ECP – антибактериальной, цитотоксической и противовирусной активностью, а также способностью ECP вызывать подавление пролиферации Т-клеток и синтез иммуноглобулинов В-клетками, стимулировать дегрануляцию тучных клеток, выработку слизи эпителием бронхов, продукцию гликозаминогликанов фибробластами [5,26]. Нарушение вентиляции, связанное с эозинофилией и более частые обострения становятся причиной бактериальной контаминации и, следовательно, фактором риска инфекционных обострений, чем и объясняется более тяжелое течение ХОБЛ у пациентов с эозинофильным фенотипом.

У пациентов, включенных в данное исследование, с низкими значениями ECP чаще назначались курсы АБТ, это можно объяснить тем, что при обострениях ХОБЛ у пациентов без активации эозинофилов основным этиологическим фактором является инфекционный фактор, тогда как у пациентов с активацией эозинофилов само эозинофильное воспаление становится предиктором последующих обострений, не требующих назначения АБТ. Данное предположение подтверждается более частой продукцией гнойной мокроты в группе пациентов с низкими значениями ECP в сравнении с пациентами с повышенным уровнем ECP (таблица 1).

В исследовании М. Miller с соавт. [19] показано, что более низкие значения ОФВ1 имеют связь с более высокой концентрацией ECP в мокроте, а у пациентов с ХОБЛ и эмфиземой значительно более высокие уровни ECP мокроты в сравнении с курильщиками без эмфиземы, что частично согласуется с полученными данными в нашем исследовании (таблица 4). Необходимо отметить, что и в других исследованиях предпринимались попытки найти связь между повышением количества эозинофилов крови и мокроты и развитием эмфиземы. Однозначного ответа на вопрос о наличии такой связи пока не получено, поскольку имеются противоречивые данные [13,23,26].

Полученные в ходе проведенного исследования данные свидетельствуют о том, что более достоверными маркерами участия эозинофилов в воспалительном процессе у пациентов с отдельным фенотипом ХОБЛ является не только повышение уровня эозинофилов  $\geq 300$  клеток/мкл, но и повышение ECP в сочетании с частотой среднетяжелых и тяжелых обострений ХОБЛ.

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## SUMMARY

### EOSINOPHILIC CATION PROTEIN AS A SENSITIVE BIOMARKER OF EOSINOPHILIC INFLAMMATION AND A PREDICTOR OF SEVERE COPD

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It has been established that the eosinophilic phenotype of COPD is separate phenotype of the disease. The results of some studies demonstrate the possibility that may presence a phenotype with an increased level of eosinophil activity. To study the relationship between the blood ECP level and the characteristics of the course of COPD, we examined 161 patients with COPD aged from 40 to 70 years old, smoking index > 10 pack-years, no history of atopy, total blood Ig E < 100 IU / ml. The following assessments was made: the severity of dyspnea on the mMRC scale, assessment of the degree of purulent sputum, the level of blood eosinophils, the level of ECP of the blood, whole-body plethysmograph, chest CT. Patients were stratified by the level of blood eosinophils ( $\geq 300$  cells/ $\mu$ l, < 300 cells/ $\mu$ l), by the level

of ECP ( $\geq 24$  ng/ml,  $< 24$  ng/ml), and by the level of blood eosinophils  $\geq 100$  cells/ $\mu$ L in combination with  $\geq 2$  moderate exacerbations or hospitalization per year. Comparative analysis showed that patients with ECP  $\geq 24$  ng/ml had a higher mMRC score and a higher BODE index, they developed exacerbations and pneumonia more often, ICS was prescribed more often, and signs of static hyperinflation were more pronounced. In patients with ECP  $< 24$  ng/ml, purulent sputum separation was more often detected, and antibiotics were prescribed more often. Similar data were obtained with stratification by the level of eosinophils in the blood  $> 100$  cells/ $\mu$ L in combination with  $\geq 2$  exacerbations of moderate or severe severity during the year, but not with stratification by the level of blood eosinophils ( $\geq 300$  cells/ $\mu$ L,  $< 300$  cells/ $\mu$ L). It has been shown that an increase in ECP in accordance with moderate and severe exacerbations is a more reliable markers of the development of the eosinophilic phenotype in patients with COPD.

**Keywords:** chronic obstructive pulmonary disease, COPD, blood eosinophils, eosinophilic phenotype, eosinophil cationic protein, blood ECP.

## РЕЗЮМЕ

### ЭОЗИНОФИЛЬНЫЙ КАТИОННЫЙ ПРОТЕИН КАК ЧУВСТВИТЕЛЬНЫЙ БИОМАРКЕР ЭОЗИНОФИЛЬНОГО ВОСПАЛЕНИЯ И ПРЕДИКТОР ТЯЖЕЛОГО ТЕЧЕНИЯ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЁГКИХ

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На сегодняшний день установлено, что эозинофильный фенотип хронической обструктивной болезни лёгких (ХОБЛ) является отдельным фенотипом заболевания. Результаты некоторых исследований свидетельствуют о возможности существования фенотипа с повышенным уровнем активности эозинофилов. Для изучения связи между уровнем катионного белка эозинофилов (ЕСР) крови и особенностями течения ХОБЛ обследован 161 пациент с ХОБЛ в возрасте от 40 до 70 лет, с индексом курения  $> 10$  пачка-лет, отсутствием атопии в анамнезе, уровнем общего IgE  $< 100$  МЕ/мл. Проведена оценка выраженности одышки по шкале mMRC, степени гнойности мокроты, уровня эозинофилов крови и ЕСР крови, выполнены общая сплюгмография, КТ грудной клетки. С целью проведения комплексной оценки тяжести ХОБЛ рассчитывался индекс BODE. Пациенты стратифици-

рованы по уровню эозинофилов в крови ( $\geq 300$  клеток/мкл,  $< 300$  клеток/мкл) и ЕСР ( $\geq 24$  нг/мл,  $< 24$  нг/мл), а также по уровню эозинофилов в крови  $\geq 100$  клеток/мкл в сочетании с  $\geq 2$  обострениями средней степени тяжести или госпитализацией в течение года. Сравнительный анализ показал, что пациенты с ЕСР  $\geq 24$  нг/мл имели более высокий балл по шкале mMRC и более высокий индекс BODE, у них чаще развивались обострения и пневмонии, чаще назначались ингаляционные глюкокортикостероиды, были более выражены признаки статической гиперинфляции. У пациентов с ЕСР  $< 24$  нг/мл чаще выявлялось отделение гнойной мокроты и назначались антибиотики. Аналогичные данные получены при стратификации по уровню эозинофилов в крови  $> 100$  клеток/мкл в сочетании с  $\geq 2$  обострениями средней или тяжёлой степени тяжести в течение года, однако не при стратификации только по уровню эозинофилов крови ( $\geq 300$  клеток/мкл,  $< 300$  клеток/мкл). Таким образом, показано, что более достоверными маркерами развития эозинофильного фенотипа у пациентов с ХОБЛ является повышение ЕСР в сочетании с частотой среднетяжелых и тяжелых обострений.

## რეზიუმე

ეოზინოფილური კათიონური პროტეინი, როგორც ეოზინოფილური ანთების მგრძობიარე მარკერი და ფილტვების ქრონიკული ობსტრუქციული დაავადების მძიმე მიმდინარეობის პრედიქტორი

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<sup>1</sup>მოსკოვის ი.სეჩენოვის სახ. პირველი სახელმწიფო სამედიცინო უნივერსიტეტი (სეჩენოვის უნივერსიტეტი); <sup>2</sup>რუსეთის ხალხთა მეგობრობის უნივერსიტეტი; <sup>3</sup>მოსკოვის ა.ეგლოკიმოვის სახ. სახელმწიფო სამედიცინო-სტომატოლოგიური უნივერსიტეტი; <sup>4</sup>რუსეთის ფედერაციის ეკონომიკური განვითარების სამინისტროს სამკურნალო-სარეაბილიტაციო ცენტრი, მოსკოვი, რუსეთის ფედერაცია

სადღეისოდ დადგენილია, რომ ფილტვების ქრონიკული ობსტრუქციული დაავადების (ფქოდ) ეოზინოფილური ფენოტიპი წარმოადგენს დაავადების ცალკე ფენოტიპს. ზოგიერთი კვლევის შედეგი მიუთითებს ფენოტიპის არსებობის შესაძლებლობის შესახებ ეოზინოფილების აქტივობის მომატებული დონით. სისხლის ეოზინოფილების კათიონური ცილის (ЕСР) დონესა და ფქოდ-ის მიმდინარეობის თავისებურებებს შორის კორელაციის დადგენისათვის გამოკვლეულია 40-70 წლის ასაკის 161 პაციენტი ფქოდ-ით, თამბაქოს მოწვევის ინდექსით  $> 10$  კოლოფი-წელი, ატოპიის არარსებობით ანამნეზში, საერთო IgE  $< 100$  МЕ/მლ. შეფასებულია ქოშინის გამოხატულება mMRC-ით, სველი გამონაყოფის ჩირქოვანობის ხარისხი, ეოზინოფილების რაოდენობა სისხლში და სისხლის ЕСР, ჩატარებულია საერთო პლეტისმოგრაფია, გულმკერდის ღრუს კომპიუტერული ტომოგრაფია. ფქოდ-ის სიმძიმის კომპლექსური შეფასებისათვის გამოთვლილია ინდექსი BODE. პაციენტები სტრატეფიცირებულია ეოზინოფილების დონის მიხედვით სისხლში ( $\geq 300$  უჯრედ/მკლ,  $< 300$  უჯრედ/მკლ), ЕСР-ის დონის მიხედვით ( $\geq 24$  ნგ/მლ,  $< 24$  ნგ/მლ), ასევე, ეოზინოფილების დონის ( $\geq 100$  უჯრედ/მკლ) კომბინაციით საშაულო სიმძიმის

≥2 გართულებასთან, ან პოსპიტალიზაციასთან ერთი წლის განმავლობაში.

შედარებით ანალიზით გამოვლინდა, რომ პაციენტებს ECP-ით ≥24 ნგ/მლ აქვთ უფრო მაღალი ქულა mMRC-ით და BODE-ს უფრო მაღალი ინდექსი, მათ უფრო ხშირად უვითარდებოდა გამწვავება და პნევმონია, ხშირად ენიშნებოდა ინჰალაციური გლუკოკორტიკოსტეროიდები, მეტად იყო გამოხატული სტატიკური პიპერიფლაციის ნიშნები. პაციენტებს ECP <24ნგ/მლ უფრო ხშირად უვლინდებოდა სველი ჩირქოვანი გამონაყოფი და ენიშნებოდა ანტიბიოტიკები. ანალოგი-

ური შედეგებია მიღებული სტრატეგიკაციისას ეოზინოფილების დონის (≥100 უჯრედი/მკლ) მიხედვით კომბინაციით საშუალო სიმძიმის ≥2 გართულებასთან, ან პოსპიტალიზაციასთან ერთი წლის განმავლობაში, მაგრამ არა სტრატეგიკაციისას ეოზინოფილების დონის მიხედვით სისხლში (≥300 უჯრედი/მკლ, <300 უჯრედი/მკლ). ამრიგად, ნახვენებია, რომ ფქოდ-ით პაციენტებში ეოზინოფილური ფენოტიპის განვითარების უფრო სარწმუნო მარკერს წარმოადგენს ECP-ის მატება, კომბინაციით საშუალო სიმძიმის გართულებებთან და მძიმე გამწვავებებთან.

## ПОДОСТРЫЙ ТИРЕОИДИТ И COVID-19 (ОБЗОР)

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Одной из наиболее сложных проблем сегодняшних реалий является пандемия коронавирусной болезни 2019 года (COVID-19), вызванная коронавирусом (SARS-CoV-2). Появившаяся в декабре 2019 года в Китае, COVID-19 постепенно распространилась на весь мир, и 11 марта 2020 г. ВОЗ объявил ее пандемией [55]. По состоянию на 7.02.2021 г. в мире зарегистрированы 105 764 730 случаев заболевания и 2 309 346 смертельных исходов. Основным клиническим проявлением COVID-19 является тяжелый острый респираторный синдром [56]. Классическими проявлениями инфекции COVID-19 считаются лихорадка, миалгия, кашель, усталость и желудочно-кишечные симптомы, такие как тошнота, рвота, диарея и боль в животе. Однако в научной литературе появляется все большее число публикаций о серьезных внелегочных проявлениях COVID-19, а именно отклонениях в деятельности органов желудочно-кишечного тракта, печени, почек, поджелудочной железы [40], сердца и сосудов, неврологических нарушениях [10], как на начальном этапе COVID-19, так и в отдаленные сроки. Помимо указанных нарушений в научной литературе стали появляться работы, посвященные менее известным клиническим проявлениям COVID-19. В связи с этим мы решили провести системный анализ литературы касательно связи SARS-CoV-2 и патологии щитовидной железы (ЩЖ), в частности подострого тиреоидита (ПТ).

Анализ литературы относительно связи новой коронавирусной инфекции SARS-CoV-2 и ПТ преимущественно за 2020-2021 гг. проведен по базам данных Web of Science, Scopus, PubMed, Google Scholar и SpringerLink. При анализе применены методы деконструкции, апперципирования, диахронический, голографический.

В 2020 году опубликованы несколько статей, посвященных эндокринным нарушениям при COVID-19 [24]. Интерес к данным изменениям связан с тем, что в отношении их по сей день нет полной ясности, и ведутся дебаты о том,

может ли SARS-CoV-2 напрямую атаковать эндокринные железы [3]. Представляет интерес также изучение течения COVID-19 у лиц с эндокринными нарушениями [37]. За время существования пандемии накопились данные, свидетельствующие о том, что лица с нарушениями эндокринной системы имеют более высокий риск тяжелого течения COVID-19 [31]. Однако в отношении пациентов с гипотиреозом, которые находились на заместительной терапии L-тироксинам увеличение риска госпитализации в связи с тяжелым течением COVID-19 не установлено [51].

Многочисленные публикации обсуждают, что COVID-19 может поражать практически все органы, однако данных о влиянии SARS-CoV-2 на щитовидную железу очень мало [41]. За 2020 г. в литературе появилось несколько работ, посвященных изменениям в щитовидной железе [14,22,45], вызываемых SARS-CoV-2. В частности, высказано мнение о том, что в ряде случаев вирус SARS-COV-2 может быть триггером (основным провоцирующим фактором) болезни Грейвса [19,29]. Chen M. с соавт. [6] установили, что у 56% пациентов с COVID-19 отмечается достоверное снижение уровней тиреотропного гормона (ТТГ) и сывороточного общего трийодтиронина (Т3). Снижение уровней ТТГ и Т3 имело положительную корреляцию и статистическую значимость с тяжестью течения заболевания (p<0,001).

Одним из возможных вариантов манифестации COVID-19 является подострый тиреоидит (ПТ) [4,34,20]. Подострый тиреоидит (синонимы подострый гранулематозный, подострый гигантоклеточный и тиреоидит де Кервена, De Quervain thyroiditis) встречается чаще у женщин [26]. Заболеваемость ПТ составляет 4,9 случая на 100000 населения в год [13]. Клиническая картина ПТ складывается из местных проявлений (интенсивная односторонняя или двусторонняя боль по передней поверхности шеи, иррадиирующая в челюсть или ухо, усиливающаяся при глотании и поворотах головы, интенсивная болезненность при пальпации щито-

видной железы [16], а также общих проявлений воспаления (лихорадка, недомогание и анорексия) и гипертиреоза [46]. Заболевание имеет признаки, характерные для вирусных инфекций, в частности предшествующая инфекция верхних дыхательных путей и продромальный период с миалгиями, недомоганием и утомляемостью [35]. Для подтверждения диагноза используют лабораторные исследования (повышенная скорость оседания эритроцитов, высокий уровень С-реактивного белка; низкий уровень ТТГ; повышенные уровни тиреоидных гормонов (Т4 и Т3) и тиреоглобулина; низкий титр циркулирующих антител к тиреопероксидазе и тиреоглобулину [42]) и лучевые методы диагностики [21]. Для заболевания характерна смена гормонального статуса, на начальном этапе регистрируются клинические и лабораторные признаки гипертиреоза, который сменяется гипотиреозом, а через несколько недель или месяцев в большинстве случаев наступает эутиреоз [46].

По данным патоморфологического исследования при ПТ в щитовидной железе определяется неравномерное распределение долек (неказеозных гранулем), состоящих из коллоида, малых лимфоцитов, нейтрофилов, макрофагов, плазматических моноцитов и многоядерных гигантских клеток инородных тел. В результате цитолитического распознавания Т-клетками вирусных и клеточных антигенов, присутствующих в тиреоцитах, происходит инфильтрация фолликулов, а в последующем разрыв базальной мембраны и разрыв фолликулов [23].

Считается, что причиной возникновения ПТ являются вирусные инфекции - непосредственно повреждение ткани щитовидной железы вирусами или поствирусная воспалительная реакция у генетически предрасположенных лиц [8]. Установлено, что гаплотипы человеческого лейкоцитарного антигена (HLA) HLA-Bw35, HLA-B67, HLA-B15/62 и HLA-Drw8 предрасполагают к развитию ПТ [12,36]. На сегодняшний день вирусные инфекции считаются основным этиологическим фактором не только при подостром тиреоидите, но и аутоиммунных поражениях щитовидной железы [11,42]. Достоверно установлено, что вирусы кори, эпидемического паротита, краснухи, коксаки, аденовирус, ортомиксовирус, ветряной оспы, цитомегаловирус, вирус Эпштейна-Барра, ВИЧ, гепатита E [28] и лихорадки денге [2] вызывают тиреоидит [8] через прямое воздействие на клетки или косвенно через его циркулирующий вирусный геном или вирусспецифические антитела [42,48]. В литературе имеются данные о развитии подострого тиреоидита, связанного с вирусом гриппа H1N1 [9,30], а также в результате сезонной вакцинации против гриппа [1,39]. Имеются убедительные данные, что при ПТ в ткани щитовидной железы могут присутствовать ретровирусы (HFV) или их компоненты. При тиреоидите Хашимото в ткани выявляются вирусы HTLV-1, энтеровирус, краснуха, вирус паротита, ВПГ, ВЭБ и парвовирус. В 2002 году при вспышке SARS-CoV при вскрытии погибших установлено повреждение щитовидной железы наряду с повреждением других органов [31,50].

Характер поражения ткани щитовидной железы вирусом SARS-CoV-2 до конца не изучен. Не исключено, что существует единый механизм поражения для всех вирусов. Также не до конца понятно, почему дисфункция щитовидной железы в ряде случаев является обратимой, а в других приводит к гипотиреозу. Корреляции между показателями уровня ТТГ на начальном этапе ПТ и спустя 1 год не существует. Отсутствуют данные о корреляции распространения поражения щитовидной железы на пике заболевания с

гормональным статусом в отдаленные сроки. Однако имеются данные о поражении щитовидной железы вирусом атипичной пневмонии (SARS-CoV) в 2002-2003 гг., летальность при которой составила 10% [48]. Среди тех, кто умер от атипичной пневмонии, в щитовидной железе выявлено разрушение фолликулярного эпителия с обширным отслоением апоптотических клеток в просвет фолликула. Повреждение фолликулов щитовидной железы иногда было очень серьезным, связанным с полной потерей парафолликулярных С-клеток, о чем свидетельствует полное отсутствие иммуноокрашивания кальцитонином. В качестве возможных механизмов повреждения ткани щитовидной железы при SARS-CoV рассматривают воспалительную реакцию и апоптоз [25]. Считается, что SARS-CoV вызывает тяжелую воспалительную реакцию [49] и запуск механизма апоптоза через экспрессию нескольких вирусных белков [58]. По данным аутопсии 5 пациентов с SARS-CoV Wei L с соавт. [54] выявили повреждение фолликулярного эпителия и клеточный апоптоз при отсутствии нейтрофильной или лимфоидной инфильтрации. Это позволило сделать авторам вывод, что наиболее значимыми патогенетическими факторами являются чрезмерная иммунная реакция пациента, возникающий иммунодефицит с разрушением лимфоцитов и прямое разрушение клеток. Установлено также, что апоптоз, доминирующий в патогенезе SARS, запускается экспрессией ряда неструктурных белков [25,58] в клетках различного типа, в том числе и щитовидной железы. Клетки с явлениями апоптоза обнаружены в щитовидных железах пациентов с атипичной пневмонией [7]. У пациентов с SARS-CoV-2 признаки воспалительной инфильтрации отмечены во многих тканях, в том числе и в щитовидной железе [57].

Одним из вариантов развития ПТ при COVID-19 предположительно является прямая вирусная репликация. При ПТ, возникшем после вирусных инфекций (грипп, паротит), в дегенерированном фолликулярном эпителии щитовидной железы выявляются вирусоподобные частицы [44]. В 2003 г. вирус SARS-CoV был выделен во многих органах, однако не в щитовидной железе. SARS-CoV-2 также по сей день не выделен в щитовидной железе, однако не исключена возможность прямого вирусного поражения.

Одной из гипотез, объясняющих развитие ПТ при SARS-CoV-2, является взаимодействие с рецепторами ангиотензин-превращающего фермента 2 (ACE2). Считается, что ACE2 играет решающую роль в патогенезе поражения легких коронавирусами [17]. Рецепторы ACE2 в щитовидной железе могут служить входными воротами для вируса и важным механизмом повреждения. SARS-CoV и SARS-CoV-2 используют рецепторы ACE2 на мембранах клеток щитовидной железы, чтобы проникнуть внутрь них. В отличие от MERS-CoV, который для внедрения задействует дипептидилпептидазы (DPP4) и сиалозидные рецепторы прикрепления [38], SARS-CoV и SARS-CoV-2 для инвазии в клетки хозяина используют рецепторы ACE2 [53], которые широко экспрессируются в легких, почках, надпочечниках, жировой ткани, щитовидной железе, эндотелии, поджелудочной железе, яичках, яичниках и гипофизе человека [17,50].

В 2003 году установлено, что SARS-CoV нарушает функцию щитовидной железы не только за счет ее разрушения, но и через центральные механизмы. Считается, что низкий уровень ТТГ может быть вторичным по отношению к гипоталамус-гипофизарной дисфункции, в подтверждение приводятся данные о развитии вторичного гипотиреоза и центрального гипокортицизма у больных ОРВИ [27].

В настоящее время описано более 20 случаев ПТ, ассоциируемого с COVID-19 [47]. У большей части пациентов ПТ возник в период реабилитации COVID-19 спустя 2-6 недель после выздоровления [22], хотя описаны 2 случая параллельных диагнозов COVID-19 и ПТ. Клиническая картина в большинстве наблюдений ПТ соответствовала «классическому» варианту. Помимо клинических данных у всех больных было лабораторное подтверждение гипертиреоза и ультразвуковой паттерн, соответствующий ПТ. Все пациенты положительно реагировали на противовоспалительную и кортикостероидную терапию. Однако имеются и нетипичные варианты течения ПТ [18]. В одном случае преобладала симптоматика гипертиреоза: сердцебиение, бессонница и возбуждение, отсутствовали лихорадка и местные симптомы (боли, отечность, реакция лимфоузлов). Врачи из университета Insubria-Ospedale Di Circolo Di Varese (Италия) обосновали свой диагноз данными ультразвукового исследования, недостаточным поглощением Тс 99-м щитовидной железы при скintiграфии, высоким содержанием тиреоглобулина в сыворотке крови и отсутствием аутоантител к щитовидной железе. Инструментальные и лабораторные показатели свидетельствовали о деструктивном процессе в щитовидной железе. Специалисты посчитали, что имеет место подострый тиреоидит, возможно, вызванный вирусом SARS-CoV-2. Отсутствие местных симптомов объясняется приемом пациентом больших доз обезболивающих препаратов по поводу коморбидной патологии. Точность диагноза подтвердила успешная терапия стероидами (начально - 40 мг метилпреднизолона внутривенно в течение 3 дней, затем преднизолон перорально с 25 мг с постепенным снижением дозы), несмотря на то, что контрольный мазок из носоглотки на SARS-CoV-2 после нормализации состояния дал положительный результат. Авторы сделали предположение, что потенциальная локализация SARS-CoV-2 в ткани щитовидной железы явилась причиной стойкой вирусной позитивности после исчезновения респираторных проявлений, однако эта гипотеза не имеет убедительных доказательств. Авторы считают также, что применение дексаметазона, широко используемого как препарат первой линии терапии при лечении COVID-19 [52], может снижать повреждения щитовидной железы за счет подавления гипертрофического ответа, вызванного цитокинами, и делать клиническую картину менее яркой.

В связи с этим сделаны выводы, что истинная частота поражения щитовидной железы SARS-CoV-2 значительно больше и нивелируется, в первую очередь, приоритетами диагностики легочных поражений.

San Juan MDJ с соавт. [43] считают, что ПТ может быть не следствием, а симптомом или вариантом течения COVID-19. В подтверждение этого они приводят наблюдение, когда у пациентки, проходившей лечение по поводу ПТ, по данным ПЦР диагностики на SARS-CoV-2 (мазки из носоглотки и ротоглотки) получен положительный результат. Campos-Barrera E. с соавт. [5] предполагают, что ПТ можно считать осложнением COVID-19 в связи с особенностями вирусного заболевания. T. Grassi с коллегами [15] предположили, что оценка COVID-19, как эндокринного заболевания поможет ученым понять неспецифический ответ иммунной системы на SARS-CoV-2, что приведет к лучшему пониманию природы и проявления COVID-19.

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## SUMMARY

### SUBACUTE THYROIDITIS AND COVID-19 (REVIEW)

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The COVID-19 pandemic has shown that there is not enough knowledge today to fully control it. Along with se-

vere respiratory syndrome, attention has recently been paid to extrapulmonary lesions, including endocrinopathies. The aim of the study was to summarize the current literature data about the effects of the SARS-CoV-2 coronavirus on the thyroid gland. One of the most striking manifestations of viral aggression is de Quervain's subacute thyroiditis. The analysis of works from the most authoritative international abstract bibliographic databases was carried out using methods of analysis and processing of scientific resources. Based on the analysis, it was concluded that subacute thyroiditis can be both a clinical manifestation and a complication of COVID-19. The SARS-CoV-2 coronavirus can also trigger other thyroid diseases. The causes of subacute thyroiditis are considered to be the direct effect of the SARS-CoV-2 coronavirus on thyroid cells due to the use of ACE2 receptors, the subsequent inflammatory reaction and apoptosis, as well as central hypothalamus-pituitary mechanisms. The clinical variants of subacute thyroiditis in COVID-19 are diverse and have not been fully evaluated. In this regard, it can be concluded that the true incidence of subacute thyroiditis in COVID-19 is much greater, since it is masked by severe lesions of other organs.

**Keywords:** subacute thyroiditis, COVID-19, thyroid gland.

## РЕЗЮМЕ

### ПОДОСТРЫЙ ТИРЕОИДИТ И COVID-19 (ОБЗОР)

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Целью исследования явилось обобщение современных литературных данных, посвященных воздействию коронавируса SARS-CoV-2 на щитовидную железу.

Одной из наиболее ярких манифестаций вирусной агрессии является подострый тиреоидит де Кервена. Проведен анализ работ из наиболее авторитетных международных реферативных библиографических баз с использованием методов анализа и обработки научных ресурсов. На основании анализа делается заключение, что подострый тиреоидит может быть как клиническим проявлением, так и осложнением COVID-19. Коронавирус SARS-CoV-2, по всей вероятности, является триггером и других заболеваний щитовидной железы. Причинами подострого тиреоидита являются прямое воздействие коронавируса SARS-CoV-2 на клетки щитовидной железы посредством рецепторов ACE2, в результате чего возникает воспалительная реакция и апоптоз клеток щитовидной железы; не исключен также центральный гипоталамус-гипофизарный механизм повреждения вирусом щитовидной железы. Клинические варианты подострого тиреоидита при COVID-19 многообразны и не изучены. В связи с этим авторами делается вывод, что показатели заболеваемости подострым тиреоидитом при COVID-19 значительно выше, поскольку маскируются тяжелыми поражениями других органов.

რეზიუმე

ქვემწვავე თირეოიდიტი და COVID-19 (მიმოხილვა)

იუ.ალექსანდროვი, ზ.სემიკოვი, ზ.შულუტკო,  
ზ.გოგოხია, ზ.აგორბაჩევა, ზ.მანსუროვა

რფ ჯანდაცვის სამინისტროს უმაღლესი განათლების ფედერალური სახელმწიფო საბიუჯეტო საგანმანათლებლო დაწესებულება იაროსლავის სახელმწიფო სამედიცინო უნივერსიტეტი, ქირურგიული დაავადებების კათედრა; რფ ჯანდაცვის სამინისტროს უმაღლესი განათლების ფედერალური სახელმწიფო ავტონომიური საგანმანათლებლო დაწესებულება ი. სენენოვის სახ. მოსკოვის პირველი სახელმწიფო სამედიცინო უნივერსიტეტი (სენენოვის უნივერსიტეტი), საფაკულტეტო ქირურგიის კათედრა №2, რუსეთი

კვლევის მიზანს წარმოადგენს SARS-CoV-2 კორონავირუსის ფარისებრ ჯირკვალზე ზეგავლენის საკითხზე სამეცნიერო ლიტერატურის ანალიზი. ვირუსული აგრესიის ერთ-ერთი ყველაზე ნათელი მანიფესტაცია არის დე კერვენის ქვემწვავე თირეოიდიტი.

განხილულია აღნიშნული საკითხის ირგვლივ სამედიცინო ლიტერატურა ავტორიტეტული საერთაშორისო რეფერატული ბიბლიოგრაფიული მონაცემთა ბაზებიდან სამეცნიერო რესურსების ანალიზისა და დამუშავების მეთოდების გამოყენებით. ანალიზის შედეგად გამოტანილია დასკვნა, რომ ქვემწვავე თირეოიდიტი შეიძლება იყოს COVID-19-ის როგორც კლინიკური გამოვლინება, ასევე მისი გართულება და ფარისებრი ჯირკვლის სხვა დაავადებების ტრიგერიც. ქვემწვავე თირეოიდიტის მიზეზს წარმოადგენს SARS-CoV-2 კორონავირუსის პირდაპირი ზემოქმედება ფარისებრი ჯირკვლის უჯრედებზე ACE2 რეცეპტორთან ურთიერთქმედებით, რის შედეგადაც წარმოიქმნება ანთებითი რეაქცია და ფარისებრი ჯირკვლის უჯრედების აპოპტოზი; თუმცა ასევე არ გამოირიცხება ვისრუსის მიერ ფარისებრი ჯირკვლის დაზიანების ცენტრალური მექანიზმიც. COVID-19-ის დროს ქვემწვავე თირეოიდიტის კლინიკური სურათი მრავალფეროვანია და ბოლომდე არ არის შეფასებული. ავტორებს გამოტანილი აქვთ დასკვნა, რომ ქვემწვავე თირეოიდიტის მანევრებლები COVID-19-ის დროს გაცილებით მზადალია, თუმცა ინიღბება სხვა ორგანოების მძიმე დაზიანებით.

## BONE MINERAL DENSITY AND THE PREVALENCE OF ITS DISORDERS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND SYNTROPIC COMORBID LESIONS

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The systemic lupus erythematosus (SLE) is a systemic autoimmune disease caused by various endogenous and exogenous factors with the inherent involvement in the pathological process of most organs and systems that are directly related to the local and systemic regulation of bone metabolism [3,4,7], adversely affecting bone mineral density [5,6,8]. The state of bone mineral density has not been properly examined yet in patients with SLE and the pathogenetically associated syntropic comorbid lesions of organs and systems, namely, hemorrhagic vasculitis, capillaritis, Raynaud syndrome, atherosclerosis, livedo reticularis, venous thrombosis, myocarditis, secondary hypertension, stable angina, pneumonitis, pneumosclerosis, autoimmune hepatitis, steatohepatitis, chronic pancreatitis, aseptic bone necrosis, arthralgia, myalgia, autoimmune thyroiditis, obesity, and alopecia [1,2,9,10].

Objective - to assess the state of bone mineral density and to determine the prevalence of its disorders in patients with SLE and syntropic comorbid lesions of organs and systems.

**Material and methods.** In a randomized manner, after stratification by the presence of SLE (according to the 2019 ACR criteria), we enrolled 123 patients (premenopausal women aged 21 to 51 years, average age 41.13±12.04) into the study. The written consents to participate in comprehensive examinations in accordance with the principles of the Helsinki Human Rights Declaration, Council of Europe Convention on Human Rights

and Biomedicine, as well as the relevant laws of Ukraine, were duly obtained. All patients were examined and received treatment at the Rheumatology Department of the Lviv Regional Clinical Hospital. The average duration of the disease was 10.08±0.72 years. All (100.00%) patients received glucocorticoids in terms of prednisolone from 5.0 to 30.0 mg/day (average dose 10.89±0.84 mg/day, the average dose of 31.50±2.07 g) and calcium (daily dose of 1000.0 mg) in combination with vitamin D (daily dose of 400.0 IU).

All patients underwent comprehensive clinical, laboratory, and instrumental examination of all organs and systems in accordance with the Order of the Ministry of Health of Ukraine № 676 of October 12, 2006 "On the Approval of Protocols for the Provision of Medical Care in the Rheumatology Specialty", the recommendations of the European League against Rheumatism (2010), the American College of Rheumatology (2019).

Patients with SLE, depending on the diagnosed pathogenetically associated syntropic comorbid lesions of organs and systems, were stratified into twenty groups (with hemorrhagic vasculitis, capillaritis, Raynaud syndrome, atherosclerosis, livedo reticularis, venous thrombosis, myocarditis, secondary hypertension, ischemic heart disease (including stable angina), pneumonitis, pneumosclerosis, autoimmune hepatitis, steatohepatitis, chronic pancreatitis, aseptic bone necrosis, arthralgia, myalgia, autoimmune thyroiditis, obesity, and alopecia). The

bone mineral density (BMD) was determined for patients in each group through dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine and proximal femur, taking into account the worst T-score result. As a result of DXA scans, all patients were divided into five groups: 27 patients with normal BMD (T-score  $\geq$  -1.0 standard deviation (SD), 25 patients with the first degree osteopenia (T-score  $<$ -1.0 SD, but  $>$ -1.5 SD), 25 patients with the second degree osteopenia (T-score  $<$ -1.5 SD, but  $>$ -2.0 SD), 23 patients with the third degree osteopenia (T-score  $<$ -2.0 SD, but  $>$ -2.5 SD), and 23 patients with osteoporosis (OP) (T-score  $\leq$  -2.5 SD).

Statistical analysis of the research results was carried out by using the Microsoft Excel application, differences were considered to be statistically significant when  $p < 0.05$ .

**Results and discussion.** Hemorrhagic vasculitis was detected in 6 (33.33%) patients, the 2 of them had also the first degree osteopenia and the 2 patients had OP. The second degree osteopenia was detected in 1 (16.6%) patient with hemorrhagic vasculitis. 1 (16.6%) of the patients with hemorrhagic vasculitis was also diagnosed with the third degree osteopenia. There were no statistically significant differences between the prevalences of the first, second, third degree osteopenia and osteoporosis.

4 (25.0%) patients with capillaritis were diagnosed with the first degree osteopenia, second degree osteopenia (25.00%), third degree osteopenia (25.00%), and OP (25.00%). There were no statistically significant differences between the prevalences of normal BMD and reduced BMD disorders ( $p > 0.05$ ).

Raynaud syndrome was detected in 49 patients. 8 (16.33%) of them had normal BMD, 7 (14.29%) patients had the first degree osteopenia, 13 (26.53%) patients had the second degree osteopenia, another 13 (26.53%) patients had the third degree osteopenia, and 8 (16.33%) patients had OP. The largest percentage of patients with Raynaud syndrome had second and third degree osteopenia, but there were no statistically significant differences between the prevalences of normal BMD, the first degree osteopenia, and OP.

Atherosclerosis was detected in 36 patients: 4 (11.11%) of them had normal BMD, another 4 (11.11%) patients had the first degree osteopenia, 6 (16.67%) patients had the second degree osteopenia, 10 (27.78%) patients had the third degree osteopenia, and 12 (33.33%) patients had OP. The prevalence of OP was the highest and the number of OP cases was statistically significantly different from the number of cases of normal BMD ( $p < 0.05$ ) and the cases of the first degree osteopenia ( $p < 0.05$ ). The number of the third degree osteopenia cases was also statistically significantly different from the number of cases of normal

BMD ( $p < 0.05$ ) and the first degree osteopenia ( $p < 0.05$ ).

Livedo reticularis was detected in 28 patients: 4 (14.29%) of them had normal BMD, 3 (10.71%) patients had the first degree osteopenia, 5 (17.86%) patients had the second degree osteopenia, 8 (28.57%) patients had the third degree osteopenia, and another 8 (28.57%) patients had OP. The prevalence of the third degree osteopenia ( $p < 0.05$ ) and OP ( $p < 0.05$ ) was statistically significantly higher than the prevalence of the first degree osteopenia. There were no statistically significant differences between the number of cases of the third degree osteopenia, OP, normal BMD ( $p > 0.05$ ), and second degree osteopenia ( $p > 0.05$ ), as well as between the number of the second degree osteopenia cases and the cases of normal BMD ( $p > 0.05$ ) and the first degree osteopenia ( $p > 0.05$ ) (Table 1).

Venous thrombosis was detected in ten patients: 4 (40.0%) of them had normal BMD, another 4 (40.0%) patients had the first degree osteopenia, 2 (20.0%) patients had the third degree osteopenia. There were no patients with the second degree osteopenia and OP. The prevalence of normal BMD and first degree osteopenia was statistically significantly higher than the prevalence of second degree osteopenia ( $p < 0.05$ ) and OP ( $p < 0.05$ ), but there were no statistically significant differences in the case of third degree osteopenia ( $p > 0.05$ ).

Myocarditis was detected in 12 patients: 2 (16.67%) of them had normal BMD, another 2 (16.67%) patients had the first degree osteopenia, 1 (8.33%) patient had the second degree osteopenia, 3 (25.0%) patients had the third degree osteopenia, and 4 (33.33%) patients had OP. The pairwise comparison between these groups did not reveal statistically significant differences between them ( $p > 0.05$ ).

Secondary hypertension was detected in 63 patients with SLE. According to the results of the densitometric examination, 10 (15.87%) patients had normal BMD, 9 (14.29%) patients had the first degree osteopenia, 13 (20.63%) patients had the second degree osteopenia, 16 (25.40%) patients had the third degree osteopenia and 15 (24.30%) patients had OP. The third degree osteopenia was the most prevalent BMD disorder in this group. However, there were no statistically significant differences between its prevalence and the prevalence of normal BMD, the first degree osteopenia, second degree osteopenia, and OP.

Ischemic heart disease (stable angina) was detected in six patients: 2 (33.33%) of them had the second degree osteopenia and 4 (66.67%) patients had the third degree osteopenia. The prevalence of third degree osteopenia was statistically significantly higher than the prevalence of normal BMD ( $p < 0.01$ ), first degree osteopenia ( $p < 0.01$ ), and OP ( $p < 0.01$ ).

Table 1. The prevalence of normal BMD and various reduced BMD disorders in patients with SLE depending on the pathogenetically associated syntropic comorbid lesions of organs and systems

BMD assessment	Hemorrhagic vasculitis		Capillaritis		Raynaud syndrome		Atherosclerosis		Livedo reticularis	
	N	%	N	%	N	%	N	%	N	%
Normal BMD	0	0.00	0	0.00	8	16.33	4	11.11	4	14.29
First degree osteopenia	2	33.33	1	25.00	7	14.29	4	11.11	3	10.71
Second degree osteopenia	1	16.67	1	25.00	13	26.53	6	16.67	5	17.86
Third degree osteopenia	1	16.66	1	25.00	13	26.53	10*	27.78	8	28.57
OP	2	33.33	1	25.00	8	16.33	12*	33.33	8	28.57
Total	6	100.00	4	100.00	49	100.00	36	100.00	28	100.00

notes: \* - statistically significant difference when compared with the prevalence of normal BMD cases,  $p < 0.05$ ;

□ - statistically significant difference when compared with the prevalence of the first degree osteopenia

Table 2. The prevalence of normal BMD and various reduced BMD disorders in patients with SLE depending on the pathogenetically associated syntropic comorbid lesions of organs and systems

BMD assessment	Venous thrombosis		Myocarditis		Secondary hypertension		IHD (stable angina)		Pneumonitis	
	N	%	N	%	N	%	N	%	N	%
Normal BMD	4	40.00	2	16.67	10	15.87	0	0.00	6	28.57
First degree osteopenia	4	40.00	2	16.67	9	14.29	0	0.00	3	14.29
Second degree osteopenia	0 * □	0.00	1	8.33	13	20.63	2	33.33	6	28.57
Third degree osteopenia	2	20.00	3	25.00	16	25.40	4 * □	66.67	2	9.52
OP	0 * □	0.00	4	33.33	15	28.30	0 □	0.00	4	19.05
Total	10	100.00	12	100.00	63	100.00	6	100.00	21	100.00

notes: \* - statistically significant difference when compared with the prevalence of normal BMD cases,  $p < 0,05$ ;

□ - statistically significant difference when compared with the prevalence of the first degree osteopenia,  $p < 0,05$

Pneumonitis was detected in 21 patients with SLE: 6 (28.57%) of them had normal BMD, 3 (14.29%) patients had the first degree osteopenia, 6 (28.57%) patients had the second degree osteopenia, 2 (9.52%) patients had third degree osteopenia, and 4 (19.05%) patients had OP. There were no statistically significant differences between the prevalence of normal BMD and various degrees of osteopenia (Table 2).

Pneumosclerosis was detected in 58 patients with SLE. According to the results of the densitometric examination, 8 (13.79%) patients had normal BMD, 13 (22.41%) patients had the first degree osteopenia, 11 (18.97%) patients had the second degree osteopenia, 14 (24.14%) patients had the third degree osteopenia, and 12 (20.69%) patients had OP. There were no statistically significant differences in prevalences of normal BMD and various reduced BMD disorders ( $p > 0.05$ ).

Autoimmune hepatitis was detected in 11 patients. 1 (9.09%) of them had first degree osteopenia, another one had second degree osteopenia. 2 (18.18%) patients had the third degree osteopenia, and 7 (63.64%) patients had OP. The prevalence of OP was significantly higher than the prevalence of normal BMD ( $p < 0.001$ ), the first degree osteopenia ( $p < 0.01$ ), the second degree osteopenia ( $p < 0.01$ ), and the third degree osteopenia ( $p < 0.05$ ).

Steatohepatitis was detected in 37 patients with SLE, all of them had reduced BMD disorders. 8 (21.62%) patients had the first degree osteopenia, 10 (27.03%) patients had the second degree osteopenia, 11 (29.73%) patients had the third degree osteopenia, and 8 (21.62%) patients had OP. There were no statistically significant differences in prevalences of all osteopenias and OP.

Chronic pancreatitis was detected in 40 patients with SLE. 4 (10.00%) patients had normal BMD. The rest had various reduced BMD disorders: 5 (12.50%) patients had the first degree osteopenia, 8 (20.00%) patients had the second degree osteopenia, 10 (25.00%) patients had third degree osteopenia and 13 (32.50%) patients had OP. The prevalence of the third degree osteopenia was statistically significantly higher than the prevalence of normal BMD ( $p < 0.05$ ). The number of cases of OP was statistically significantly higher than the number of normal BMD cases ( $p < 0.01$ ) and the cases of the first degree osteopenia ( $p < 0.05$ ).

Aseptic bone necrosis was detected in 3 patients: 1 (33.33%) of them had the first degree osteopenia, 1 (33.33%) patient had the third degree osteopenia and 1 (33.33%) patient had OP. There were no statistically significant differences between the prevalences of normal BMD and reduced BMD disorders (Table 3).

Table 3. The prevalence of normal BMD and various reduced BMD disorders in patients with SLE depending on the pathogenetically associated syntropic comorbid lesions of organs and systems

BMD assessment	Pneumosclerosis		Autoimmune hepatitis		Steatohepatitis		Chronic pancreatitis		Aseptic bone necrosis	
	N	%	N	%	N	%	N	%	N	%
Normal BMD	8	13.79	0	0.00	0	0.00	4	10.00	0	0.00
First degree osteopenia	13	22.41	1	9.09	8 *	21.62	5	12.50	1	33.33
Second degree osteopenia	11	18.97	1	9.09	10 *	27.03	8	20.00	0	0.00
Third degree osteopenia	14	24.14	2	18.18	11 *	29.73	10 *	25.00	1	33.33
OP	12	20.69	7 * □ #	63.64	8 *	21.62	13 * □	32.50	1	33.33
Total	58	100.00	11	100.00	37	100.00	40	100.00	3	100.00

notes: \* - statistically significant difference when compared with the prevalence of normal BMD cases,  $p < 0,05$ ;

□ - statistically significant difference when compared with the prevalence of the first degree osteopenia,  $p < 0,05$ ;

# - statistically significant difference when compared with the second degree osteopenia,  $p < 0,05$

Table 4. The prevalence of normal BMD and various reduced BMD disorders in patients with SLE depending on the pathogenetically associated syntropic comorbid lesions of organs and systems

BMD assessment	Arthralgia		Myalgia		Autoimmune thyroiditis		Obesity		Alopecia	
	N	%	N	%	N	%	N	%	N	%
Normal BMD	17	16.04	3	7.32	0	0.00	5	14.29	5	12.20
First degree osteopenia	22	20.75	8	19.51 *	2	8.33	9	25.71	8	19.51
Second degree osteopenia	25	22.58	9	21.95 *	5	20.83	9	25.71	7	17.07
Third degree osteopenia	21	19.81	11	26.83 *	7 * □	29.17	8	22.86	10	24.39
OP	21	19.81	10	24.39 *	10 * □	41.67	4	11.43	11 *	26.83
Total	106	100.00	41	100.00	24	100.00	35	100.00	41	100.00

notes: \* - statistically significant difference when compared with the prevalence of normal BMD cases,  $p < 0,05$ ;

□ - statistically significant difference when compared with the prevalence of the first degree osteopenia,  $p < 0,05$

Arthralgia was observed in 106 patients with SLE. 17 (16.04%) of them had normal BMD, 22 (20.75%) patients had the first degree osteopenia, 25 (23.58%) patients had the second degree osteopenia, 21 (19.81%) patients had the third degree osteopenia, and another 21 (19.81%) patients had OP. The prevalence of normal BMD did not differ statistically significantly from the prevalences of the first degree osteopenia ( $p < 0.05$ ), the second degree osteopenia ( $p < 0.001$ ), the third degree osteopenia ( $p < 0.001$ ), and OP ( $p < 0.001$ ). There were no statistically significant differences between the prevalences of first degree osteopenia, the second degree osteopenia ( $p > 0.05$ ), the third degree osteopenia ( $p > 0.05$ ), and OP ( $p > 0.05$ ). There were also no statistically significant differences between the prevalences of the second degree osteopenia, third degree osteopenia, and OP ( $p > 0.05$ ).

Myalgia was observed in 41 patients with SLE. 3 (7.32%) of them had normal BMD. 8 (19.51%) patients had the first degree osteopenia, 9 (21.95%) patients had the second degree osteopenia, 11 (26.83%) patients had the third degree osteopenia, and (24.39%) patients had OP. The prevalence of normal BMD was significantly lower than the prevalences of second degree osteopenia ( $p < 0.001$ ), third degree osteopenia ( $p < 0.001$ ), and OP ( $p < 0.01$ ). However, there were no statistically significant differences between the prevalences of various reduced BMD disorders ( $p > 0.05$ ).

Autoimmune thyroiditis was detected in 24 patients. According to the results of the densitometric examination, 2 (8.33%) patients had the first degree osteopenia, 5 (20.83%) patients had the second degree osteopenia, 7 (29.17%) patients had the third degree osteopenia, and 10 (41.67%) patients had OP. The prevalence of normal BMD was statistically significantly lower than the prevalences of second degree osteopenia ( $p < 0.01$ ), third degree osteopenia ( $p < 0.01$ ), and OP ( $p < 0.01$ ). The prevalences of the third degree osteopenia and OP were significantly higher than the prevalence of the first degree osteopenia ( $p < 0.05$ ).

35 patients were diagnosed with obesity – with a body mass index over 30 kg/m<sup>2</sup>. Five of them had normal BMD (14.29%), nine patients had the first degree osteopenia (25.71%), another nine patients had the second degree osteopenia (25.71%), eight patients had the third degree osteopenia (22.86%), and four patients had OP (11.43%). There were no statistically significant differences in the prevalences of normal BMD and various reduced BMD disorders ( $p > 0.05$ ).

Alopecia was observed in 41 patients. 5 (12.20%) of them had normal BMD, 8 (19.51%) patients had the first degree osteopenia, 7 (17.07%) patients had the second degree osteopenia, 10 (24.39%) patients had the third degree osteopenia and 11

(29.83%) patients had OP. The prevalence of OP was significantly higher than the prevalence of normal BMD. There were no statistically significant differences in prevalences between OP and first degree osteopenia, second degree osteopenia, and the third degree osteopenia (Table 4).

**Conclusions.** The prevalence of osteoporosis in SLE patients with atherosclerosis and chronic hepatitis was significantly higher than the prevalences of normal BMD cases and the first degree osteopenia; the prevalence of osteoporosis in SLE patients with autoimmune hepatitis was significantly higher than the prevalence of normal BMD cases and osteopenia. Pathogenetically associated syntropic comorbid lesions of organs and systems (atherosclerosis, autoimmune hepatitis, chronic pancreatitis) allow us to predict the reduction of BMD in patients with SLE.

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## SUMMARY

### BONE MINERAL DENSITY AND THE PREVALENCE OF ITS DISORDERS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND SYNTROPIC COMORBID LESIONS

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The state of bone mineral density has not been properly examined yet in patients with systemic lupus erythematosus (SLE) and the pathogenetically associated syntropic comorbid lesions of organs and systems. In a randomized manner, after stratification by the presence of SLE, we enrolled 123 premenopausal women aged 21 to 51 years into the study. Patients with SLE, depending on the diagnosed pathogenetically associated syntropic comorbid lesions of organs and systems, were stratified into twenty groups (with hemorrhagic vasculitis, capillaritis, Raynaud syndrome, atherosclerosis, livedo reticularis, venous thrombosis, myocarditis, secondary hypertension, stable angina, pneumonitis, pneumosclerosis, autoimmune hepatitis, steatohepatitis, chronic pancreatitis, aseptic bone necrosis, arthralgia, myalgia, autoimmune thyroiditis, obesity, and alopecia). The bone mineral density (BMD) was determined for patients in each group through dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine and proximal femur, taking into account the worst T-score result. Having analyzed the data from densitometric examinations of 20 patient groups, we arrived at the following conclusions: a) all patients from seven groups (with hemorrhagic vasculitis, capillaritis, stable angina, autoimmune hepatitis, steatohepatitis, aseptic bone necrosis, autoimmune thyroiditis) had reduced BMD disorders, and the largest proportion of patients with normal BMD were from the group with syntropic venous thrombosis; b) there was only one group of patients (with stable angina) without the cases of the first degree osteopenia, and the largest proportion of such patients was in the group with syntropic venous thrombosis; c) there was only one group of patients (with aseptic bone necrosis) without the cases of the second degree osteopenia, and the largest proportion of such patients was in the group with stable angina; d) there were patients with the third degree osteopenia in all groups, and the largest proportion of the third degree osteopenia cases was in the group with stable angina; e) there were no cases of osteoporosis in groups with syntropic venous thrombosis and stable angina, and the largest proportion of osteoporosis cases was in the groups with syntropic autoimmune hepatitis; the prevalence of osteoporosis is significantly higher than the prevalence of normal BMD and the first degree osteopenia in patients with atherosclerosis and chronic pancreatitis; the prevalence of osteoporosis is also significantly higher than the prevalence of normal BMD and all degrees of osteopenia in patients with autoimmune hepatitis.

**Keywords:** systemic lupus erythematosus, dual-energy X-ray absorptiometry, osteoporosis, bone mineral density.

## РЕЗЮМЕ

### СОСТОЯНИЕ МИНЕРАЛЬНОЙ ПЛОТНОСТИ КОСТНОЙ ТКАНИ И ЧАСТОТА ЕЕ НАРУШЕНИЙ У БОЛЬНЫХ СИСТЕМОЙ КРАСНОЙ ВОЛЧАНКОЙ С СИНТРОПИЧЕСКИМИ КОМОРБИДНЫМИ ПОРАЖЕНИЯМИ ОРГАНОВ И СИСТЕМ

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Системная красная волчанка (СКВ) – системное аутоиммунное заболевание, вызываемое различными эндогенными и экзогенными факторами, с вовлечением в патологический процесс большинства органов и систем, которые напрямую связаны с местной и системной регуляцией костного метаболизма. Состояние минеральной плотности костной ткани у пациентов с СКВ и патогенетически ассоциированными синтропическими коморбидными поражениями органов и систем должным образом не изучено. Рандомизированным образом после стратификации по наличию СКВ в исследовании включены 123 женщины с менопаузой в возрасте от 21 до 51 года. Пациенты с СКВ в зависимости от диагностированных патогенетически ассоциированных синтропических коморбидных поражений органов и систем разделены на двадцать групп (геморрагический васкулит, капиллярит, синдром Рейно, атеросклероз, ретикулярное ливедо, венозный тромбоз, миокардит, вторичная гипертензия, стабильная ангина, пневмонит, пневмосклероз, аутоиммунный гепатит, стеатогепатит, хронический панкреатит, асептический некроз костей, артралгия, миалгия, аутоиммунный тиреоидит, ожирение и алопеция). Минеральная плотность костной ткани (МПКТ) определялась для пациентов в каждой группе с помощью двухэнергетической рентгеновской абсорбциометрии поясничного отдела позвоночника и проксимального отдела бедренной кости с учетом наихудшего результата. Проанализировав данные денситометрического обследования 20 групп пациентов, авторы пришли к следующим выводам: а) у всех пациентов из семи групп - с геморрагическим васкулитом, капилляритом, стабильной стенокардией, аутоиммунным гепатитом, стеатогепатитом, асептическим некрозом костей, аутоиммунным тиреоидитом, наблюдалось снижение МПКТ; наибольшая доля пациентов с нормальной МПКТ выявлена в группе с синтропическим венозным тромбозом; б) одна группа пациентов со стабильной стенокардией не имела случаев остеопении I степени, и наибольшая доля таких пациентов приходилась на группу с синтропическим венозным тромбозом; в) одна группа пациентов с асептическим некрозом костей не имела случаев остеопении второй степени; наибольшая доля таких пациентов приходилась на группу со стабильной стенокардией; г) во всех группах были пациенты с остеопенией III степени, причем наибольшая доля случаев остеопении III степени приходилась на группу со стабильной стенокардией; д) в группах с синтропическим венозным тромбозом и стабильной стенокардией случаев остеопе-

роза не выявлено; наибольшая доля случаев остеопороза приходилась на группу с синтропным аутоиммунным гепатитом; у пациентов с атеросклерозом и хроническим панкреатитом показатели остеопороза были значительно выше, чем распространенность нормальной МПКТ и остеопении первой степени. Распространенность остеопороза была также значительно выше, чем распространенность нормальной МПКТ и всех степеней остеопении у пациентов с аутоиммунным гепатитом.

### რეზიუმე

ძვლის ქსოვილის მინერალური სიმკვრივის მდგომარეობა და მისი დარღვევის სისწორე წითელი მგლურით დაავადებულ პაციენტებში ორგანოების და სისტემების სინტროპული კომორბიდული დაზიანებით

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ღვოვის დანილო გალიცკის სახ. ნაციონალური სამედიცინო უნივერსიტეტი, უკრაინა

სისტემური წითელი მგლურა წარმოადგენს სისტემურ აუტოიმუნურ დაავადებას, რომელიც გამოწვეულია სხვადასხვა ენდოგენური და ეგზოგენური ფაქტორებით, პათოლოგიურ პროცესში უმეტეს იმ ორგანოთა და სისტემების გარდაუვალი ჩართულობით, რომლებიც პირდაპირ კავშირშია ძვლის მეტაბოლიზმის ადგილობრივ და სისტემურ რეგულაციასთან. ძვლის მინერალური სიმკვრივის მდგომარეობა პაციენტებში სისტემური წითელი მგლურით, რომლებსაც აღენიშნებოდა ორგანოების და სისტემების ასოცირებული სინტროპული თანმხლები დაზიანება, სადღეისოდ შესწავლილი არ არის.

სისტემური წითელი მგლურის დადასტურების შემდეგ კვლევაში მონაწილეობისთვის რანდომიზებულად შერჩეული იყო 123 ქალი პრემენოპაუზით 21-51 წ. ასაკში. სისტემური წითელი მგლურით პაციენტები ორგანოების და სისტემების თანმხლები სინტროპული დაზიანების გათვალისწინებით დაყოფილი იყო 20 ჯგუფად (ჰემორაგიული ვასკულიტი, კაპილარიტი, რეინოსინდრომი, ათეროსკლეროზი, რეტროკულური ლივედო,

ვენური თრომბოზი, მიოკარდიტი, მეორადი ჰიპერტენზია, სტაბილური ანგინა, პნევმონიტი, პნევმოცისტოზი, აუტოიმუნური ჰეპატიტი, სტეატოჰეპატიტი, ქრონიკული პანკრეატიტი, ასეპტიკური ძვლის ნეკროზი, ართრაღია, მიაღვია, აუტოიმუნური თირეოიდიტი, სიმსუქნე და ალოპეცია). ძვლის მინერალური სიმკვრივე (ძმს) განისაზღვრა პაციენტების თითოეულ ჯგუფში სერუმის ლუმბალური ნაწილის და ბარძაყის პროქსიმული ნაწილის ორმაგი ენერგეტიკული რენტგენის აბსორბციომეტრიის მეშვეობით ყველაზე უარესი შედეგის გათვალისწინებით. პაციენტების 20 ჯგუფის დენსიტომეტრიული გამოკვლევის მონაცემების ანალიზის შედეგად გამოტანილია შემდეგი დასკვნები: ა) 7 ჯგუფიდან ყველა პაციენტში (ჰემორაგიული ვასკულიტი, კაპილარიტი, სტაბილური სტენოკარდია, აუტოიმუნური ჰეპატიტი, სტეატოჰეპატიტი, ასეპტიკური ძვლის ნეკროზი, აუტოიმუნური თირეოიდიტი) ძმს-ს მანველებული იყო შემცირებული; ნორმალური ძმს-ს მანველებლით პაციენტების უდიდესი ნაწილი აღმოჩნდა სინტროპული ვენური თრომბოზის ჯგუფში; ბ) პაციენტების მხოლოდ ერთ ჯგუფს სტაბილური სტენოკარდიით არ ჰქონდა პირველი ხარისხის ოსტეოპენია და ასეთი პაციენტების უდიდეს ნაწილს აღმოჩნდა სინტროპული ვენური თრომბოზი; გ) პაციენტების ერთ ჯგუფს ასეპტიკური ძვლის ნეკროზით მეორე ხარისხის ოსტეოპენია არ აღენიშნებოდა და ასეთი პაციენტების უდიდეს ნაწილს ჰქონდა სტაბილური სტენოკარდია; დ) ყველა ჯგუფში იყო III ხარისხის ოსტეოპენიის მქონე პაციენტები და III ხარისხის ოსტეოპენიის შემთხვევების ყველაზე დიდი წილი გამოვლინდა სტაბილური სტენოკარდიის ჯგუფში; ე) ოსტეოპოროზის შემთხვევები სინტროპული ვენური თრომბოზისა და სტაბილური სტენოკარდიის ჯგუფებში არ აღინიშნა, ხოლო ოსტეოპოროზის შემთხვევების უდიდესი წილი გამოვლინდა სინტროპულ აუტოიმუნურ ჰეპატიტის ჯგუფში; პაციენტებში ათეროსკლეროზით და ქრონიკული პანკრეატიტით ოსტეოპოროზის გავრცელება მნიშვნელოვნად უფრო ხშირია ვიდრე ნორმალური ძმს და პირველი ხარისხის ოსტეოპენიის გავრცელება; ოსტეოპოროზის გავრცელება ასევე მნიშვნელოვნად აღემატება ნორმალური ძმს-ის და ოსტეოპენიის ყველა ხარისხის გავრცელებას აუტოიმუნური ჰეპატიტით პაციენტებში.



## ADVENTUROUSNESS OF PERSONALITY: CONSTRUCT AND DIAGNOSTICS

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Contemporary social world is characterized by rapid changes, active transformation processes that, in conditions of uncertainty, require from the individual a bold, sometimes instantaneous decision and choice. In such conditions, there is a threat of the emergence of risk, unforeseen consequences regarding the adoption of rapid, not always thoughtful actions, the efficiency of life and professional activity is distorted, the results of interaction with other people change, etc. That is why it is important to study those personality traits that are manifested in similar, changing conditions and which can facilitate (or slow down) a timely making of the right decision in order to obtain the desired result with less time and effort. One can consider adventurousness (a propensity to adventurous behavior) as such a personality trait, which can manifest itself in situations of uncertainty not only as a negative phenomenon, but also as a resource for creative decision-making.

*Theoretical background of studying adventurousness.* The notion of "adventurous personality", "adventurousness" in different historical times was considered from different standpoints depending on the general views on the problem of adventurousness. An important role was played by the idea of people about the norms of behavior of an individual as a member of a certain society. This concept was used mainly to refer to behavior as immoral, asocial, deviant and so on. Fraud, intrigue, trickery were ascribed to such a person [14].

And today it is believed that adventurousness as a personality trait hinders human activity. So, according to V.L. Bozadzhiev, the business characteristic of a psychologist provides for the obligatory consideration of qualities that are unacceptable or hindering successful professional activity. Among a rather large number of negative traits, such as irresponsibility, frivolity, lust for power, unsystematicity, arrogance, laziness, negligence, naivety, bashfulness, self-confidence, envy, formalism etc., the author also distinguishes adventurousness [3].

A.A. Aldasheva and N.G. Melnikova, when studying the value and semantic attitude of a person to activity in a situation of competitive selection of candidates, pointed out that "persons predisposed to risk can be provoked to participate in risky actions or adventures" [1]. It is this kind of adventurous behavior in regulated professions that the authors also define as professionally undesirable.

I.V. Antonenko studied the orientation of entrepreneur's personality and their psychological characteristics. The author showed that the dominance of a certain orientation forms such personality types as adventurous, conservative and constructive. The most successful entrepreneurs are characterized by a combination where the leading orientation is constructive, combined with a relatively small part of the adventurous and conservative orientation. At the same time, the advantage of a conservative and adventurous orientation leads to unsuccessful activity [2].

However, in the literature, the concept of "adventurousness" is not limited to the framework of antibehavior; its positive aspects are also considered. Thus, E. P. Ilyin describes the adventurer as a passionate seeker of the unknown, which leads to gaining benefits. A lot of geographical discoveries, according to the author, were made by people for whom adventurousness was a lifestyle. Such adventurers are not judged, but considered

brave victors. For a true adventurer, as E. P. Ilyin writes, belief in oneself is inseparable from the belief in the benevolence of fortune, and the feeling of one's originality from the feeling of one's chosenness [4].

Recently, the characteristics of adventurousness have been considered through the prism of positive psychology. Thus, Houge Mackenzie, S. & Brymer E. (2018), studying extreme, risky sports, showed that adventure sports are chosen by individuals with hedonistic tendencies, motivated exclusively by risk taking, which is mainly characteristic of representatives of the adventurous personality type [13].

Some studies recommend and use the so-called adventure therapy based on the outdoor activities and risk education. Adventure therapy is used for prevention, early intervention and treatment of people, especially young people, with behavioral, psychological and psychosocial problems [12].

It is known that in adventure therapy with the help of a reasonable use of risk (and this is the main characteristic of an adventurous personality), fears, anxiety and personal limitations are overcome, trust in other people is formed, self-esteem and confidence in decision-making increase, etc.

Herewith, in the mass consciousness we are faced with the existence of an erroneous thought that does not separate the concepts of adventurousness and *affaire*. However, these concepts should not be considered identical as they have different semantic meanings. According to E. P. Ilyin, *an affaire* (trickery) (from the French *affaire* – business) is deception, fraud, and *an adventure* is a hope for good luck, which is not supported by a thorough analysis of the situation [4].

In this work, adventurousness (disposition, propensity for adventurous behavior) is considered as a stable property, characterized by internal, mental activity (emotional experiences, thoughts, thought-forms, attitudes, expectations, etc.), which induces a person to a certain physical, external activity. This external activity is manifested in the corresponding actions, behavior, deeds that represent the social position of the adventurous personality. In general, the behavior of such a person is characterized by risky, often unprincipled actions, without taking into account real resources, reserves, abilities, opportunities, chances, forces and conditions, in order to achieve an accidental, expected result, easy success, quick benefit.

In other words, adventurousness is a selective orientation of a personality, sometimes to bold, but also to dubious behavior that meets adventurous experiences, thoughts, adventurous plans, intentions, which is manifested in incongruence, riskiness, courage, negligence, frivolity, etc. The main criterion for the presence of adventurousness is the discrepancy (incongruence) of the subjective vision of the situation, which exists in the imagination of the personality, of objective reality [15].

As far as adventurousness as a stable propensity for adventurous actions is concerned, it is characterized by: *adventurous intentionality* (focus on achieving easy and quick success, positive attitude and focus on luck); *appropriate emotional mood* (joyful expectation of quick and easy success); *a certain way of thinking* (frivolity, superficial logic, poor consideration of ongoing changes, lack of analysis of a specific situation, circumstances); *certain actions, behavior* (free from any restrictions,

requirements, conventions), etc. [10]. It is these characteristics that are manifested in the main components of the structure of adventurousness.

At the same time, although individual characteristics of adventurousness are analyzed in the literature, we did not find information on the structure of this personality trait and its features, by which one can study the “anatomy” of adventurousness as an integral personality trait.

In addition, acquaintance with psychodiagnostic tools showed that adventurousness as a multicomponent personality trait has not been specially studied, but its individual characteristics are diagnosed by “side” techniques that are intended for completely different diagnostic purposes. In connection with the above-said, it became necessary to develop a theoretical construct and psychodiagnostic tools aimed at empirical research of adventurousness and its components.

Thus, the aim of the article is to present the latest modified version of the author’s psychodiagnostic technique “Test-questionnaire of propensity to adventurousness (AVANT-7)”.

Objectives: 1. To consider the structure of adventurousness as the basis for the theoretical construct of the method. 2. To provide a description of the features (components) and give examples of indicators that are aimed at their study. 3. To provide the results of approbation (validity, reliability) of the latest version of the author’s psychodiagnostic method.

*The structure of adventurousness.* As a theoretical and methodological basis for the search for the adventurousness *macro-structure* (traits, dispositions), we have chosen a multilevel, continual and hierarchical approach to the study of the personality structure of O. P. Sannikova [8]. In the context of this approach, adventurousness is considered as a macrosystem, which consists of multilevel subsystems with specific characteristics. The following are distinguished as levels: 1) formal and dynamic – contains signs that reflect the peculiarities of the emergence and course of adventurous manifestations and the form of their implementation in risky situations; 2) content and personal – characterized by the orientation of the personality towards adventurous actions; need and motivational sphere, values that support or neutralize the manifestations of adventurousness; 3) social and imperative (normative) – a system of knowledge about the requirements of a given culture, religion, profession, social environment regarding possible images of adventurous actions, deeds; personal “norms” of adventurous behavior. The components of different levels of adventurousness complement each other, interact with each other and form a holistic integral property, which is not reduced to the sum of its components.

At this stage of the research, we mainly consider the micro-system of adventurousness, which covers its qualitative characteristics (an intermediate zone between the formal and dynamic, content and personal levels). The choice for regarding these characteristics, firstly, is explained by the fact that it is their basis where the content characteristics of adventurousness are formed; secondly, the qualitative characteristics include the psychological essence of another phenomenon, including adventurousness. We should note that the list of components is open. We have selected only those components that reflect the traits of adventurousness to the greatest extent.

*Methodological foundations (origins) of the development of psychodiagnostic technique.* Analysis of the literature makes it possible to study some of the individual characteristics and manifestations of adventurousness, which are indirectly diagnosed by multidirectional methods. As for the direct assessment of the manifestations of adventurousness, the method that was first

presented by John Oldham and Louis Morris as “Self-portrait of a Personality” are interesting for us. This method is intended not only to determine “personality types”, but also to study their “probabilistic disorders”. The theoretical platform for this questionnaire is the American Psychiatric Association’s (DSM-IV) robust classification of personality disorders. In addition, in the United States they also use the test “Examination of personality disorders”, which allows to identify all the transitions from the norm to mental pathology, to “accentuation” of personality types [11].

Today the technique is known as the “Oldham-Morris Personality Type Technique”. The questionnaire makes it possible to identify 14 personality types, while an individual psychological portrait consists of a combination of these types. Among the types, the technique also reveals the adventurous type (D-Type) [7]. In the interpretation, the adventurous type is described by eight features (as in the interpretation of other types), which may indicate the presence of features of the adventurous type in the character of the personality. Information is also provided on possible antisocial disorders, such as: lack of responsibility, fraud, aggressiveness, riskiness, absolute denial of the rules and norms of society, actions of a criminal nature, etc. [5]. At the same time, the authors rightly note that only a qualified professional, psychiatrist or other specialist in the relevant field is able to diagnose antisocial disorders.

In addition, there are methods by which certain personality traits, which may indicate the possibility of adventurous manifestations, are diagnosed. For example: “Test-questionnaire of the qualitative components of the risk-taking propensity” by O. P. Sannikova and S. V. Bykova [9]; “Methods of risk-taking propensity diagnostics” by A. G. Shmelev. Methods for diagnosing the need to seek sensations by M. Zuckerman (a high level of need for sensations can provoke an uncontrolled need for new impressions, for adventurous actions) and actions that “tickle the nerves” of the respondent [4]; “Personal change readiness survey (PCRS), developed by Canadian scientists Rodnik, Heather, Gold and Hal (translation and adaptation by N. A. Bazhanova and G. L. Bardier). The questionnaire diagnoses 7 scales, some of them show signs of an adventurous personality (passion, ingenuity, courage, enterprise, adaptability, confidence, tolerance for ambiguity) [6].

A wider range of techniques in the context of adventurousness was more thoroughly presented and described earlier [15].

So, the lack of techniques aimed specifically at adventurousness that diagnose its main features and peculiarities, contributed to the development of special psychodiagnostic tools that study adventurousness as a complex systemic property of a personality and the main components of its qualitative structure.

*Description of the original technique “Test-questionnaire of propensity to adventurousness (AVANT-7)”.* We developed this test-questionnaire according to all the rules of psychometrics [16].

Preliminarily, the technique was developed in Russian, which was caused by the specificity of the Odesa region and a specific sample of respondents. The first Russian-language version of the technique for studying the indicators (components) of adventurousness was elaborated and tested by the authors of the article in 2015. By that time, the sample was made up of students of the South Ukrainian National Pedagogical University named after K.D. Ushynsky and Odesa National University named after I.I. Mechnikov (n=359). This version of the technique showed a high degree of reliability and validity. The same year, the Ukrainian-language version of the technique was adapted and tested. Translation of the technique into Ukrainian required a separate

study, its cultural, linguistic adaptation with further full testing of this version of the methods. Standardization was carried out on a sample of Drohobych Ivan Franko State Pedagogical University. Approbation of the technique was conducted with the invitation of 245 respondents. It should be noted that the retest reliability of this version of the technique is quite high, as well as the reliability of its internal consistency, its construct validity [10].

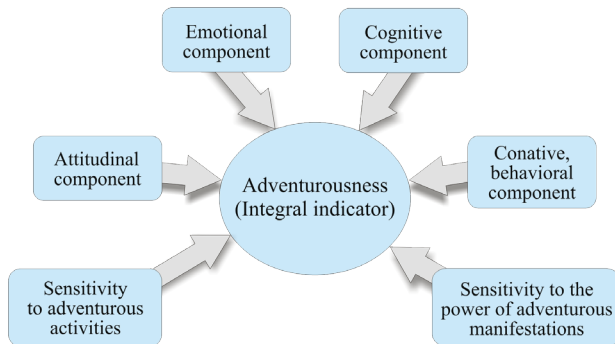


Fig. Qualitative Components of Propensity to Adventurousness

Thus, according to the theoretical construct, the technique (AVANT-7) diagnoses the following *bipolar* components of adventurousness (Fig.).

*The attitudinal component (AdAt)* belongs to the highest levels of adventurousness. It is based on the ideas and beliefs of a person, which present a picture of the world of a particular person, a very stable system of their views. This system is based on their life experience, knowledge, desires and ideas, on an individual system of relations to the world around them, to themselves and, in general, to anything. Thus, the attitudinal component reflects the position of the individual, which he/she adheres to and accepts.

With regard to adventurousness, the set component as a position is manifested in a certain attitude towards *adventure* as a phenomenon, towards *adventurous behavior* and its manifestations, towards *adventurers* as individuals of a special kind. We studied the attitude to the phenomenon of “adventurism, adventurous behavior, adventurousness” with the help of verbal reports [11]. And, of course, against the background of the general neutral attitude of the survey participants, we identified two positions: acceptance and extreme rejection of adventurous traits, manifestations and actions of the individual. This group of persons assessed the actions of people predisposed to adventure as ignoble, unworthy, while endowing adventurous individuals with such negative traits as a tendency to deception, bragging, irresponsibility, impulsiveness, etc.

It is interesting to note that during the subsequent study of the adventurousness propensity of the same respondents using the test-questionnaire discussed above, people with *high values* of the integral component of adventurousness positively accepted the idea of adventure, in contrast to another group of people who demonstrated *low values* of most adventurousness indicators. In principle, it was to be expected; consciously or unconsciously, the rejection of adventurousness could lead to the denial of its manifestations in oneself. This assumption, of course, requires further verification. At the same time, it gives us confidence in the need to include this component in the structure of adventurousness and in the theoretical construct of the technique in order to study the extent to which a person supports or does not support manifestations of adventurousness.

Here are some statements that carry a high load on the attitudinal parameter of adventurousness: “Success in life depends more on a case than on calculation”; “It’s pretty silly to take failure seriously”; “Most people like to overcome difficulties”; “The effort put into making the plans isn’t worth it”; “To have fun, break the rules and prohibitions”; “The expression “Get into a fight and then sort it out” is absolutely correct”; “Most people don’t think about what is bad for them and what is good”; “Successful individuals, as a rule, have the most unexpected vices,” etc. This block of questions is aimed at assessing the positive attitude towards manifestations of adventurousness. The rejection of adventurous manifestations, their condemnation is revealed by those respondents who choose, for example, the following statements: “The best job is the one which provides the reliable and determined future”; “In a well-established business, you need to be careful with new ideas”; “Adventurous actions and deeds are unworthy of a good person”; “You should not neglect the accepted rules for your own benefit”, etc. In terms of their content, people’s actions are assessed as noble or unworthy, positive or negative. After completing a certain action, a person sums up the results, evaluates what has been achieved, if the goal was not realized, reveals the reasons for the failure.

*The emotional component (AdEm)* reflects the presence (or absence) of emotional experiences associated with adventure. The propensity to adventurousness is accompanied by a bright, rich palette of positive emotional experiences associated with adventurous situations. Here are a few statements that have a high load on this indicator: “I am happy to indulge in new ideas, even if I am in trouble”; “I am attracted and worried by dangerous things”; “I am often drawn to new impressions”, “I am irritated by long, painstaking work”, “I am irritated by caution and prudence in people”, etc. Emotional rejection of adventurous manifestations is revealed with the help of such statements: “I like to work and study according to the arranged plan”, “I am more attracted by the business, the success of which I am confident about”, “I don’t like gambling”, “I am afraid of the affair whose result I doubt about”, “I do not enjoy the feeling of risk”; “Caution and prudence in people annoys me,” and so on.

The next component – *The cognitive component (AdKg)* – characterizes the presence of thoughts, considerations, judgments, fantasies about adventurous actions, or their complete absence or very insignificant manifestation. We formulate statements that give information about the high level of this component as follows: “I usually make a decision, especially without thinking”; “It so happens that, absorbed in thoughts of success, I forget about the precautions”; “They say that I often risk recklessly”; “It happens that I decisively immerse myself in a new business, without thinking over its outcome,” etc. Low values of this component indicate a reluctance to adventurous thoughts and are reflected, for example, in such indicators: “Abstract ideas are not for me”; “I think new ideas need to be tested before they are put into practice”; “I cannot be called a frivolous person”; “In my business I am always prudent and I consider all possible options”; “I always clearly understand what I want to help with in my life and what I want to achieve”, etc.

*Conative component (AdKo)* is the presence (absence) of external actions, manifestations of adventurousness that are observed by other people. They come to light in a bright external expression of adventurous aspirations, in expressive movements, in facial expressions, voice, postures, in general in specific adventurous actions, in behavior, actions. High scores for this component are diagnosed with statements such as: “You can say that I am prone to reckless actions”; “I always achieve my

Table. The values of the correlation coefficients, which were obtained when checking the reliability and validity of the modified version of the original technique (AVANT-7)

Test scales	Ways of searching information about reliability and validity of the latest version of the test-questionnaire				
	Reliability of test parts (n=570)	Test-retest Reliability (xi – xii) (n=320)	Reliability of parallel forms (N=550)		
			“Adventurous type” J. Oldham, L. Morris	“Location on the adventurousness scales”	Method (AVANT-1)
AdAt	652**	475**	455**	545**	701**
AdEm	598**	485**	502**	521**	679**
AdKg	695**	434**	435**	499**	715**
AdKo	554**	598**	522**	605**	698**
AdON	563**	399**	454**	571**	659**
AdOP	657**	457**	500**	489**	595**
AdTot	470**	590**	494**	532**	669**

note: 1) Marking *xI - xII* indicates the value of correlations between the results of the first and repeated testing;

2) zeros and commas are omitted; 3) marking \*\* –  $p < 0,01$ ; 4) abbreviation: AdAt – attitudinal component; AdEm – emotional; AdKg – cognitive; AdKo – conative (behavioral) component; AdON – sensitivity to one’s own adventurous manifestations (reflexive sensitivity); AdOP – sensitivity to the adventurous manifestations of others;

AdTot is a general component of adventurousness (AdAt + AdEm + AdKg + AdKo + AdON + AdOP):6

goal, even if I have to overcome a lot of obstacles on the way to it”; “I can do a dangerous thing for fun”; “I would play roulette if I had such an opportunity”; “I often get down to business without having any idea about it”; “I can choose a dubious path to achieve an important goal”; “It is always difficult for me to give up my intentions, even if serious obstacles arise,” etc. Low scores are revealed by the statements: “Usually I do not give up on my plans”; “During planned travels and trips, I do not like to deviate from the planned routes”; “I avoid adventurous affairs, even if they promise benefits”, “I prefer dreaming about my plans rather than implementing them in real life”; etc.

*Sensitivity to manifestations of one’s own adventurousness (AdON - reflexive sensitivity)* is sensitivity to situations and their acceptance (or avoidance), in which their own adventurous behavior can manifest; the tendency to constantly “engage” in risky, uncertain, adventurous situations (subject oneself to various adventures), etc. Let us consider an example of some indicators that reveal propensity, sensitivity to one’s own adventurous actions: “I always control my actions in a strange situation and do not risk in vain”; “Usually I feel my luck in some business”, “I always see my benefit and go ahead to achieve it”; “I always believe in myself and achieve my goal despite obstacles”, “With my sixth sense, I guess easy success without much analysis of a specific situation”; “Usually I feel joy in anticipation of quick and easy success” etc. Individuals who do not have the traits of adventurousness and do not see them in themselves, most often choose the following statements: “Success is the result of a lucky chance and there is no point in analyzing and weighing your chances”; “I don’t strive for quick success and I don’t see when a chance can give it to me”; “I often get into trouble; “It happens that I grab onto some business and only eventually realize that it is not mine”; etc.

*Sensitivity to the adventurous manifestations of other person (AdOP).* This indicator testifies to the insight of the person regarding the adventurous actions of other person. It characterizes the respondent’s ability to recognize the adventurous intentions, suggestions, actions of other person in relation to himself, and to others, and to the world in general. Among the statements that have a high load on this indicator, we chose the following: “I see

how often people take risks in life, even when they themselves do not know about it”; “I feel adventurers “at a distance”, “I usually see when people show adventurous intentions, mislead others”, “I am surprised at people who, for the sake of easy success, put themselves in danger”; “As a rule, I feel when they want to deceive me, “deceive others”, etc.

An example of statements that have a low load on this indicator: “I cannot always recognize and warn other people in advance if they commit an ill-considered action”; “I am often told that I do not recognize and do not beware of people with dubious proposals and behavior”, “I do not trust people, who, without realizing it themselves, “grab onto” things to which they have no propensity at all”, etc.

*The overall (total) component of adventurousness is calculated by the formula: AdTot = (AdAt + AdEm + AdKg + AdKo + AdON + AdOP) : 6.*

It is important to note that the distribution of statements by indicators is confirmed and refined by the results of factor analysis.

So, the latest version of the “Test-questionnaire of the propensity to adventurousness (AVANT-7)”, the presentation of which this article is devoted to, is aimed at studying the described above components of adventurousness. It is a modified and supplemented psychodiagnostic technique which diagnoses the characteristics and forms of behavior corresponding to these or those personal and social orientations that are embodied in the concept of “adventurous personality”.

Mathematical and statistical data processing was carried out using the SPSS 13.0 software for Windows. Correlation analysis was conducted to find the relationships between the indicators of the methods, which are compared with each other. The goal of the *factor analysis* was to find fundamental factors that would explain most of the dispersion in the group of evaluations for different questions (statements) used in our study (72 in total). Also, with the help of this procedure, we tested our hypothesis regarding the structure of the propensity to adventurousness and in accordance with the theoretical construct of the method presented above. The results of the factor analysis confirm the presence of six factors that correspond to the components (indicators) of adventurousness (Fig.).

In order to check the final version of the methods for reliability and validity, we used the traditional in psychodiagnostics split-half method (dividing the test in half), repeated and parallel tests [16].

As parallel, the following tests were used: the method of determining the type of personality and probabilistic disorders of each type by J. Oldham, L. Morris, in particular, the “adventurous type” indicator [5], specially developed by us procedure “Self-assessment of the components of adventurousness” and the first version of the author’s technique “Test-questionnaire of propensity to adventurousness (AVANT-1)” [10].

Thus, we checked: a) the reliability of parts of the test (checking the measure of the internal consistency of the test content); b) test-retest reliability (checking the stability of test results over time); c) the reliability of parallel forms (checking the consistency of the respondents’ answers to different tasks).

Thus, the analysis of Table allows us to make a general conclusion that most of the indicators are linked at a high level, which proves the validity and sufficient reliability level of the latest version of the author’s psychodiagnostic technique (AVANT-7).

We hope that the final version of the test-questionnaire presented in this article may be of interest to foreign language readers for the purpose of using it both for scientific and practical purposes. Let us just recall that in this case that it is also necessary to adapt this test to the population that will be chosen by the reader for its subsequent full testing. Such work in labor costs corresponds to the efforts for the development of new psychodiagnostic methods.

#### Conclusions.

1. On the basis of the theoretical and methodological analysis of psychological sources, the essence of the phenomenon of “propensity to adventurous actions” (propensity to adventurousness) and its structure are clarified, the component composition of indicators of adventurousness as a multilevel personality trait is explicated and described.

2. Adventurousness is considered as a stable personality trait, the psychological essence of which is the hope for good luck in the presence of an attractive final goal. Adventurousness is characterized by a certain internal, mental activity (emotional experiences, thoughts, thought-forms, attitudes, expectations, etc.), which induce a person to external, physical activity, manifested in the social position of an adventurous person, in appropriate actions and behavior.

3. The behavior of a person predisposed to adventurousness is characterized by risky, often unprincipled actions, without a thorough analysis of real external circumstances and conditions, without taking into account their own capabilities (resources, abilities, forces, chances, etc.) and ways of solving the problem in order to achieve the random expected result, quick benefit, easy and quick success.

4. Psychodiagnostic technique “Test-questionnaire of propensity to adventurousness (AVANT-7)” is aimed at identifying and quantifying specific components of adventurousness, such as: attitudinal, emotional, cognitive, conative (behavioral) component, sensitivity to one’s own adventurous manifestations (reflexive sensitivity), sensitivity to the adventurous manifestations of others, a general indicator of adventurousness. This modified and supplemented psychodiagnostic methods diagnose the characteristics and forms of behavior that correspond to the personal and social orientation that are embodied in the concept of “adventurous personality”.

5. Approbation of the original psychodiagnostic tool presented in this article was carried out according to all the require-

ments of psychometrics. The reliability and validity of the “Test-Questionnaire of Propensity to Adventurousness (AVANT-7)” has been proved.

6. The practical area of application of the methods is individual and group psychological, psychotherapeutic and psychocorrectional work. The technique allows to measure and describe individual’s propensity to adventurousness, and this *propensity is personal*, which is not studied by any other psychodiagnostic methods.

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## SUMMARY

### ADVENTUROUSNESS OF PERSONALITY: CONSTRUCT AND DIAGNOSTICS

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The article presents the results of the development and testing of the latest, supplemented and modified version of the author's psychodiagnostic technique "Test-questionnaire of propensity adventurousness (AVANT-1)". Adventurousness is viewed as a personality trait, as a stable propensity to adventurous behavior, which is characterized by the internal, mental activity of a person (attitudes, expectations, emotional experiences, thoughts, thought-forms, etc.). This mental activity (energy) induces the person to the corresponding external, physical activity, which manifests itself in adventurous actions, behavior, deeds.

The theoretical construct of the latest version of the technique (AVANT-7) is given and described; it diagnoses 7 components of adventurousness, reflecting, mainly, the qualitative level of its continuum and hierarchical structure: attitudinal, emotional, cognitive, conative (behavioral) components of adventurousness; sensitivity to one's own and other's adventurous intentions, actions, behavior; integral (general) indicator of adventurousness. The results of approbation of this psychodiagnostic tool, which was carried out according to all the requirements of psychometrics, are analyzed. The theoretical construct of the method was empirically verified, its reliability and validity were proved.

The practical area of the technique application is individual and group psychological, psychotherapeutic and psychocorrectional work. The technique allows to measure and describe an individual's propensity to adventurousness, moreover, a personal propensity, which has not been studied by other psychodiagnostic methods, but which manifests itself both in persons with a mental norm and in persons with behavioral, psychological and psychosocial problems up to the transition to character accentuations, to psychopathies and psychopathology.

**Keywords:** adventurousness, disposition, propensity to adventurous behavior, structure of adventurousness, qualitative components, test-questionnaire, approbation, reliability, validity.

## РЕЗЮМЕ

### АВАНТЮРНОСТЬ ЛИЧНОСТИ: КОНСТРУКТ И ДИАГНОСТИКА

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В статье представлены результаты разработки и апробации дополненной и модифицированной версии авторской

психодиагностической методики «Тест-опросник склонности к авантюренности (АВАНТ-1)». Авантюренность рассматривается как свойство личности, устойчивая склонность к авантюренному поведению, которая характеризуется внутренней, психической активностью человека - установками, ожиданиями, эмоциональными переживаниями, мыслями, мыслеформами. Эта психическая активность (энергия) побуждает личность к соответствующей внешней, физической активности, что проявляется в авантюрных действиях, поведении, поступках.

Приводится и описывается теоретический конструкт последней версии методики (АВАНТ-7), которая диагностирует 7 компонентов авантюренности, отражающих, преимущественно, качественный уровень ее континуально-иерархической структуры: установочный, эмоциональный, когнитивный, конативный (поведенческий) компоненты авантюренности; чувствительность к своим и чужим авантюрным намерениям, действиям, поведению; интегральный (общий) показатель авантюренности. Анализируются результаты апробации этого психодиагностического инструмента, которая проводилась по всем требованиям психометрики. Эмпирически верифицирован теоретический конструкт методики, доказана ее надежность и валидность.

Практическая область применения методики – индивидуальная и групповая психологическая, психотерапевтическая и психокоррекционная работа. Методика позволяет измерить и описать склонность индивида к авантюренности, причем склонность личностную, которая не изучается другими психодиагностическими методиками, однако проявляется как у лиц с психической нормой, так и у лиц с поведенческими, психологическими и психосоциальными проблемами вплоть до перехода к акцентуациям характера, психопатиям и психопатологии.

## რეზიუმე

პიროვნების ავანტიურულობა: კონსტრუქტი და დიაგნოსტიკა

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სამხრეთ უკრაინის კ.უშინსკის სახ. ეროვნული პედაგოგიური უნივერსიტეტი, ოდესა, უკრაინა

სტატიაში წარმოდგენილია ფსიქოდიავანოსტიკის საავანტიურული მეთოდის "ავანტიურულობისკენ მიდრეკილების ტესტ-კითხვარი" შევსებული და მოდიფიცირებული ვერსიის შემუშავებისა და აპრობაციის შედეგები. ავანტიურულობა განიხილება, როგორც პიროვნების ავანტიურული ქცევისკენ მიდრეკილების თვისება, რაც ხასიათდება ადამიანის შინაგანი, ფსიქიკური აქტივობით – განწყობებით, მოლოდინებით, ემოციური განცდებით, აზრებით, აზრთა ფორმებით. ეს ფსიქიკური აქტივობა (ენერჯია) პიროვნებას აღუძრავს შესაბამის გარეგან, ფიზიკურ აქტივობას, რაც ვლინდება ავანტიურულ მოქმედებებში, ქცევაში, საქციელში.

სტატიაში აღწერილია ამ მეთოდის ბოლო ვერსიის თეორიული კონსტრუქტი, რომლითაც დიაგნოსტიკა ავანტიურულობის, უპირატესად, კონტინუურ-იერარქიული სტრუქტურის თვისობრივი დონის ამსახველი 7 კომპონენტი: ავანტიურულობის განწყობითი, ემოციური, კოგნიტური, ქცევითი კომპონენტები, მგრძობელობა საკუთარი და სხვისი ავანტიურული

ზრახვების, ქმედებების და ქცევის მიმართ, ავანტიურულობის ინტეგრალური მანკენებელი. ამ ფსიქოდიანოსტიკური ინსტრუმენტის აპრობაციის შედეგების ფსიქომეტრიის მოთხოვნების შესაბამისად ჩატარებული ანალიზის საფუძველზე ემპირიულად ვერიფიცირებულია მეთოდის თეორიული კონსტრუქტი, დამტკიცებულია მისი საიმედოობა და ვალიდობა.

მეთოდის გამოყენების პრაქტიკული სფეროა ინდივიდური და ჯგუფური ფსიქოლოგიური, ფსიქოთე-

რაპიული და ფსიქოკორექციული მუშაობა. მეთოდის იდეალური საშუალებას გაიზომოს და აღიწეროს ინდივიდის მიდრეკილება ავანტიურულობისაკენ, ამასთან – პიროვნული მიდრეკილება, რაც ფსიქოდიანოსტიკის სხვა მეთოდებით არ შეისწავლება, თუმცა, ვლინდება ადამიანებში, როგორც ფსიქიკური ნორმით, ასევე, პირებში სხვადასხვა ტიპის და ხარისხის ქცევითი, ფსიქოლოგიური და ფსიქოსოციალური პრობლემებით.

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## RECONSTRUCTIVE FUNCTIONAL RESERVOIRS IN TREATMENT OF CHILDREN WITH AGANGLIONOSIS AFTER TOTAL COLECTOMY

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Operations on aganglionosis in children, who need complete colectomy, have their own peculiarities. In order to reconstruct the consequences of colectomy in children, complex reconstructive plastic operations have to be performed while restoring integrity of the digestive tract [9,14]. In these cases, the optimal intervention is formation of functionally advantageous reservoir that would be able to provide to some extent all the functions of the distal bowel, namely, the rectum. There is a wide range of views referring to the effectiveness of such reconstructive operation after total colectomy [4,17].

After removal of the large intestine and demucosation of the rectum, the reconstructive plastic surgery is performed at the expense of the small intestine. In this case, the well-known J-shaped reservoir, S-shaped reservoir, primary ileo-rectal anastomosis and others [7,13,16] are the most likely to be used to restore the integrity of the intestinal tract in children. However, some techniques do not provide full elimination of all adverse results of colon removal, while others are imperfect and technically difficult to perform in children [5,11,18].

Successful implementation of such complicated interventions as reconstructive plastic operations with total colectomy requires stabilization of general state of patients, normalization of indicators of protein metabolism, of water-electrolyte and acid-base balance and of markers of immune status. If those indicators are neglected, performing of mentioned difficult surgical interventions can lead to severe course of the early postoperative period, problematic healing of anastomoses, development of suppurative-inflammatory complications, combination of several severe complications, which would possibly lead to lethal exit [1,12,15,19].

Surgical treatment of aganglionosis in children with total colectomy is the most difficult operation even for surgeons with considerable experience. Taking into account the problems of pre-operative care, the operation itself, the management of

the postoperative period, we notice and analyze many tactical and technical features, without which it is difficult to achieve reliable postoperative stabilization and social adaptation of the child in the future [2,6,8,10].

The object of the study is to develop optimal reconstructive functional reservoirs for the treatment of children with aganglionosis after total colectomy.

**Material and methods.** The doctors of Children's Surgery Clinic of O.O. Bogomolets National Medical University, which bases on the National Children's Specialized Hospital "Ohmatdit", have been treating surgically 1184 children (from birth to 18 years) with various forms of bowel aganglionosis during the period from 1980 to the beginning of 2020 (Table 1). All patients were operated on with help of both classical and minimally invasive eradication methods.

We identified a special group with common characteristic among these patients; 53 children needed total colectomy. These were 12 children with subtotal and 41 patients with total aganglionosis, both ranging from birth to 3 years. We performed a complete removal of the colon in patients with total aganglionosis and subtotal aganglionosis (in case, there was significant damage to upper parts of colon).

Various variants of optimal reconstructive surgery were performed and ended up with the formation of a functionally beneficial intestinal reservoir in 53 children with aganglionosis after total colectomy.

In order to reach correct diagnosis and to evaluate the rate of treatment during the postoperative monitoring, we used the results of general clinical diagnostic methods (thorough history taking, examination, blood and urine tests, ECG, ultrasound of the internal organs) and specific diagnostic methods (irrigography, irrigoscopy; passage of contrast, rectoromanoscopy, colonoscopy, morphological methods, anorectal manometry, absorbance-based AChE activity).

Table 1. Patients' distribution depending on age and form of aganglionosis

Form of aganglionosis	Patients' age					Total amount:	
	0-6 months	6-12 months	1-3 years	3-7 years	>7 years		
Rectal	39	61	74	95	117	386	32,60%
Rectosigmoid	98	94	187	143	76	598	50,50%
Subtotal	102	48	7	2	3	162	13,68%
Total	38	-	-	-	-	38	3,22%
Total amount:	277 23,40%	203 17,14%	268 22,63%	240 20,27%	196 16,56%	1184	100%

Table 2. Periods between the imposition of protective intestinal stoma and radical surgery

Type of pathology	Interoperation period			Total
	4-8 moths	8-12 moths	12-14 moths	
Subtotal aganglionosis	-	3	9	12 (22,64%)
Total aganglionosis	3	11	27	41 (77,36%)
Total:	3 (5,66%)	14 (26,42%)	36 (67,92%)	53 (100%)

**Results and discussion.** The surgeons intensively discuss the advantages and disadvantages of a particular procedure of reconstructive plastic surgery after total colectomy, so we managed to find some compromises in differentiated approach to choosing the best way to correct this condition.

The main technical elements of operations on the restoration of integrity of the intestinal tract after total colectomy in our children are various options for the formation of ileo-rectal anastomosis with a functionally beneficial reservoir ("neorectum"). Renovation of the technical elements was carried out to facilitate the actual surgical intervention and to make such operations less traumatic. In addition, the postoperative period was handled more easily, the rehabilitation period was accelerated and the quality of life of the patients improved after the modernization of surgical correction of the effects of the absence of the colon.

While solving the problems with reconstructive plastic surgery in children with aganglionosis we used a three-step approach: imposing a protective small intestinal stoma (stage 1); radical surgery was presented by colectomy with reconstructive plastic formation of functionally advantageous reservoir, namely "neorectum" (stage 2); and closure of ileostomy after adaptation of formed small intestinal reservoir was performed (stage 3).

The inter-stage period ranged from 4 to 14 months. It depended on the origin of the pathology, the presence of accompanying anomalies of development and severe complications. This period allowed to eliminate changes in the intestine and stabilize the general state of patients (Table 2).

The formation of a protective intestinal stoma was performed in all patients after medial access, which allowed to perform detailed revision of the intestine and abdominal organs in order to identify concomitant developmental abnormalities. This rule was followed both in elective and urgent cases.

Intestinal stoma was closed in 3-4 months after radical surgery, depending on general state of patients and the presence of common cold.

Reconstructive plastic operations after total colectomy in children have some common technical issues, but they deserve detailed consideration. They require a detailed individual approach, as each case is unique in technical performance and the result.

The patients, who underwent research, were divided into groups according to a type of particular functionally advantageous reservoir.

The choice of the option of restoration of integrity of the intestinal tract after total colectomy in children was made accordingly to process of searching, improving, development and implementation of the best ways of forming a functionally beneficial reservoir ("neorectum") from the small intestine (Table 3).

Thus, various options of surgical restoration of the functionally advantageous reservoir ("neorectum") after total colectomy were performed in our patients:

- intrarectal bringing together of the ileum with primary ileo-rectal anastomosis (n=1);
- formation of entero-enteroanastomosis "end-to-side" with invagination valve (n=8);
- formation of "end-to-side" entero-enteroanastomosis by implantation of an ileocecal valve toward the ileum (n=1);
- formation of reservoir from a double ileotransplant in the form of a J- reservoir (n=2);
- formation of reservoir from double "side-to-side" ileo-ileo-transplant (n=34);
- formation of reservoir from double "side-to-side" ileo-colo-transplant (n=7).

At the beginning of the study, 1 patient with total aganglionosis after colectomy underwent operation on bringing together of the ileum with anastomosis according to Duhamel. In the postoperative period the frequency of stool of this child was 15 or more times a day, and also the stenosis of ileo-rectal anastomosis was noted. This complication was corrected by Soave-Boley operation with resection of the stenotic area and the formation of primary ileo-rectal anastomosis manually after 12 months. The rate of defecation decreased only to 10 times or less after second surgery. Taking this course of the postoperative period into account, we subsequently refused to perform this operation.

Therefore, in order to prevent frequent defecation of the liquid stool after total colectomy in the future and to save normal functioning of the sphincter complex of the rectum, we have developed a technique for replacing the colon and rectum with ileotransplant with its intrarectal bringing together and restora-



Table 3. The type of operations in 53 patients with a total colectomy

Operation	Form of aganglionosis		Total
	Subtotal aganglionosis	Total aganglionosis	
Colectomy + intrarectal bringing together of the ileum	-	1	1 (1,89%)
Colectomy + entero-enteroanastomosis with invagination valve	4	4	8 (15,09%)
Colectomy + entero-enteroanastomosis with implantation of an ileocecal valve	1	-	1 (1,89%)
Colectomy + double ileotransplant in the form of a J- anastomosis	1	1	2 (3,78%)
Colectomy + double ileo-ileotransplant with "side-to-side" anastomosis	6	28	34 (64,15%)
Colectomy + double ileo-colotransplant with "side-to-side" anastomosis	-	7	7 (13,20%)
Total	12 (22,64%)	41 (77,36%)	53 100%

tion of integrity of the intestine by an invagination anastomosis "end-to-side". This operation was performed on 8 children: in case of subtotal aganglionosis (with significant decompensation of function of the colon) (n=4) and total aganglionosis (n=4). The formation of the anastomosis was based on the technique of transverse end-lateral ("end-to-side") invagination anastomosis according to Vitebsky YaD (1973) [3].

Almost normal process of bowel movements started to develop in children after performing these operations. Unfortunately, there were frequent urges for defecation in the first months after surgery (up to 10-16 times a day), and up to a year after surgery, the frequency of bowel movements decreased to 5-8 times a day.

The irrigograms showed a dynamic of colonization of the ileotransplant during the growth of the baby; no specific pathological organic changes at the site of the anastomoses and in the ileotransplant were noted.

A patient with subtotal agangliosis underwent restoration of functionally beneficial reservoir («neorectum») after total colectomy according to the developed method, which consists of bringing together of a segment of the ileum with restoration of the integrity of the intestine, implantation of Baugine damper towards transplant and the closure of ileostomy after 3-4 months. This technique was able to prevent frequent stool defecation after total resection of the colon to some extent. The rate of bowel movements during first months after this operation was up to 10 times a day, then it gradually decreased to 5-6 times a day. The control irrigograms showed correctly formed rectum and the colonization of the ileotransplant.

However, this technique has its technical specialties, which may not always be used in infants and young children. Implantation of Baugine damper towards the ileotransplant, even under the cover of an ileostomy, does not always guarantee reliable healing of this type of anastomosis. Such anastomosis can become stenosed after a long time due to scar changes along the line of fixation of this valve to the lateral wall of the ileotransplant. In case of total agangliosis, the area of the ileocecal valve may also be affected by aganglionosis, which may subsequently cause recurrence of obstruction.

In order to increase the size of the ileotransplant and to improve its cumulative function after colectomy, it is necessary to form a functionally advantageous small intestine reservoir with a valve.

In our clinic, we did not do an S-shaped reservoir after total colectomy, as we believe that there is a risk of impaired circulation in the distal part of the ileum due to the flexing of the mesentery of this segment of the bowel, especially if it is thick, which often happens in case of total agangliosis. As a result, there is a delay of defecation because of feces storing in the pocket of the formed reservoir. This complication is typical and it causes the reservoir to be emptied using an intrarectal catheter.

We performed colectomy with double ileotransplant and J-anastomosis in 1 child with total and 1 patient with subtotal agangliosis. The function of the intestine in operated patients has become satisfactory with age. The irrigogram showed formed rectum of sufficient reservoir sizes with significant colonization of the reservoir and the upper parts of the colon.

An important disadvantage of the J-shaped reservoir is that its lower edge is located close to the anus. This leads to difficulty in bringing together the reservoir towards the anus without tension. In addition, the imposition of "ileum-to-anus" side of anastomosis is technically more complicated than the "end-to-end" anastomosis.

The next time we were guided by the principle that it is necessary to find a technically simpler functionally advantageous variant of reservoir for reconstructive plastic operations, which would be able to provide valve mechanism and forming of more complete reservoir in the parts of distal bowel.

A functionally beneficial reservoir in the distal colon was formed from double side-to-side ileo-colotransplant in 7 patients with total agangliosis. This way of forming a "neorectum" laid in sewing up the lateral wall of small intestine stump with a patch of large intestine. The stump of the ascending colon was used for this purpose in 3 cases, and the stump of the sigmoid colon was used in 4.

Due to the necessity of the formation of a technically simpler functionally advantageous reservoir for reconstructive plastic operation, which includes providing a valve mechanism and formation of a more complete reservoir in the distal bowel. For the first time in the world, we developed and introduced a method of forming a "neorectum" in the distal part of the small intestine in patient with total colectomy. We performed such operations on 6 patients with subtotal and on 28 patients with total agangliosis.

In general, there were no complications in the postoperative period. All the children survived. After the formation of a func-

tionally advantageous reservoir in a short time was needed to stabilize water-electrolyte balance, improve normobiosis, which prevents the development of other metabolic disorders. Intestinal function is satisfactory in all patients after a long term, especially in those who have a functionally advantageous reservoir in the distal colon formed by a double ileo-colotransplant and "side-to-side" ileo-ileotransplant.

The presence of the formed functionally advantageous reservoir provides a significant dynamic slowdown of the passage of the chyme along the digestive tract. That is why the conditions for the formation and accumulation of feces in these patients were improved. During first 3 months the frequency of the defecation was 10-15 times a day, and after 1 year it ranged between 2-4 times a day. The irrigograms showed formed rectum of sufficient sizes with sufficient colonization in the reservoir and the in upper parts of colon.

#### Conclusions.

1. Restoration of the integrity of the intestinal tract with the formation of a functionally advantageous reservoir in the form of a double ileo-colotransplant and "side-to-side" ileotransplant is the best option for reconstructive operation after total colectomy in children with aganglionosis.

2. Formation of a functionally beneficial reservoir in children prevents deviation of the water-electrolyte balance, improves normobiosis, improves the formation and accumulation of feces, slows down the passage through the digestive tract and prevents the development of other metabolic disorders.

3. Modernized renovated surgical approach with the creation of various options for formation of functionally beneficial reservoir for eliminating the effects of colon absence in children contributes to facilitating the postoperative period, accelerating rehabilitation, improving social adaptation and quality of life of patients.

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#### SUMMARY

#### RECONSTRUCTIVE FUNCTIONAL RESERVOIRS IN TREATMENT OF CHILDREN WITH AGANGLIONOSIS AFTER TOTAL COLECTOMY

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The object of the study is to develop optimal reconstructive functional reservoirs for the treatment of children with aganglionosis after total colectomy.

Since 1980 till 2020 we have been treating 53 children up to 3 years with aganglionosis after total colectomy using optimal reconstructive surgery technique lying in the formation of a functional intestinal reservoir.

Colostomy was performed as the first stage of surgical treatment of all children. Effective ways of restoring the integrity of the intestinal tract after a total colostomy with creating of functionally advantageous circumstances for reservoirs formation were presented as “J” - reservoirs (n=2); ileotransplant with lateral ileo-ileoanastomosis (n=34); ileotransplant with lateral ileo-colonoanastomosis (n=7); ileorectal primary anastomosis (n=1) or entero-enteroanastomosis with an invagination valve (n=8) or implantation of an ileocecal valve (n=1). The colostomy was closed after 3-4 months.

There were no results in the postoperative period. After 3 months the frequency of defecation often is 10-15 times a day, and after 1 year it changes to 2-4 times a day. All the children survived. The results of functional tests are good. Bowl function is tolerable. The radiographs show a formed rectum with a sufficient reservoir and normal colonization.

Restoration of integrity of the intestinal tract with the formation of functionally advantageous reservoir in the form of double ileo-colotransplant and ileo-ileotransplant “side-to-side” is the best option for reconstructive surgery performing in children with aganglionosis after total colectomy. Formation of functionally advantageous reservoir prevents impaired water-electrolyte balance, improves normobiosis, improves formation and accumulation of feces, slows down passage through the digestive tract and prevents the development of other metabolic disorders. A modernized surgical approach, which lies in creation of various options for functionally advantageous reservoir in order to eliminate effects of colon absence in children, contributes to facilitating the postoperative period, accelerating rehabilitation, improving social adaptation and patients quality of life.

**Keywords:** total aganglionosis, treatment, colectomy, results, children.

## РЕЗЮМЕ

### РЕКОНСТРУКТИВНЫЕ ФУНКЦИОНАЛЬНЫЕ РЕЗЕРВУАРЫ В ЛЕЧЕНИИ ДЕТЕЙ С АГАНГЛИОЗОМ ПОСЛЕ ТОТАЛЬНОЙ КОЛЭКТОМИИ

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Лечение аганглиоза у детей, которым требуется полная колэктомия с оптимальным реконструктивным функциональным резервуаром, является наиболее сложным. Существует широкий спектр мнений, связанных с выбором метода реконструктивной хирургии после выполнения тотальной колэктомии. После тотальной колэктомии наблюдается нарушение водно-электролитного баланса, ухудшение нормобиоза, снижение вероятности образования и накопления кала, ускоренное прохождение пищи через пищеварительный тракт и развитие других метаболических нарушений у детей.

Целью исследования является разработка оптимальных реконструктивных функциональных резервуаров для лечения детей с аганглиозом после тотальной колэктомии.

С 1980 по 2020 гг. на базе Национальной детской спе-

циализированной больницы «Охматдет» пролечены дети (n=53) в возрасте до 3 лет с аганглиозом после тотальной колэктомии с использованием оптимальной техники реконструктивной хирургии, заключающейся в формировании функционального кишечного резервуара.

Колостомия выполнена как первый этап хирургического лечения всех детей. Эффективные способы восстановления целостности кишечного тракта после тотальной колостомии с созданием функционально выгодных условий для формирования резервуаров представлены как «J» - резервуары - 2 случая; илеотрансплантат с латеральным илео-илеоанастомозом – 34 случая, илеотрансплантат с латеральным илеоколоноанастомозом – 7, первичный илеоректальный анастомоз - 1 или энтеро-энтероанастомоз с инвагинационным клапаном - 8 или имплантация илеоцекального клапана – 1 случай. Колостома закрыта спустя 3-4 месяца.

Явных изменений в послеоперационном периоде не отмечалось. Спустя 3 месяца частота дефекации составила 10-15 раз в день, а спустя 1 год уменьшилась до 2-4 раз в день. Все дети выжили. Результаты функциональных тестов хорошие. Функция кишечника удовлетворительная. Рентгенограммы показали сформированную прямую кишку с достаточным объемом резервуара и нормальной колонизацией.

Восстановление целостности кишечного тракта с образованием функционально выгодного резервуара в виде двойного анастомоза «бок в бок», созданного из илео-колотрансплантата и илео-илеотрансплантата, является наилучшим вариантом реконструктивной хирургии, выполняемой у детей с аганглиозом после тотальной колэктомии. Формирование функционально выгодного резервуара предотвращает нарушение водно-электролитного баланса, улучшает нормобиоз, образование и накопление кала, замедляет прохождение пищи через пищеварительный тракт и предотвращает развитие других нарушений обмена веществ. Модернизированный хирургический подход, заключающийся в создании различных вариантов функционально выгодного резервуара для устранения последствий отсутствия толстой кишки у детей, способствует облегчению послеоперационного периода, ускорению реабилитации, улучшению социальной адаптации и качества жизни пациентов.

## რეზიუმე

რეკონსტრუქციული ფუნქციური რეზერვები აგანგლიოზის მქონე ბავშვების მკურნალობაში ტოტალური კოლექტომიის შემდეგ

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კვლევის მიზანს წარმოადგენდა ოპტიმალური რეკონსტრუქციული ფუნქციური რეზერვუარების შემუშავება აგანგლიოზის მქონე ბავშვების მკურნალობისათვის ტოტალური კოლექტომიის შემდეგ.

1980-2020 წწ. ბავშვთა სპეციალიზებული ეროვნული საავადმყოფოს “ოხმატდეთი” ბაზაზე ნამკურნალებია 3 წლამდე ასაკის 53 ბავშვი აგანგლიოზით ტოტალური კოლექტომიის შემდეგ რეკონსტრუქციული ქირურგიის ოპტიმალური ტექნიკის გამოყენებით - ფუნქციური ნაწლავური რეზერვუარის შექმნით.

კოლოსტომია ჩატარებულია, როგორც ყველა ბავშვის ქირურგიული მკურნალობის პირველი ეტაპი. ტოტალური კოლექტომიის შემდეგ კუჭ-ნაწლავის ტრაქტის მთლიანობის აღდგენის ეფექტურ საშუალებებად რეზერვუარების ფორმირების ფუნქციურად მომგებიანი პირობების შექმნით წარმოდგენილია: "J" -რეზერვუარები – 2 შემთხვევა, ილეოტრანსპლანტანტი ლატერალური ილეო-ილეოანასტომოზით – 34, ილეოტრანსპლანტანტი ლატერალური ილეოკოლონოანასტომოზით – 7, პირველადი ილეორექტული ანასტომოზი - 1, ენტეროანასტომოზი ინვაგინაციური სარქველით – 8, ილეოცეკალური სარქველის იმპლანტაცია – 1 შემთხვევა. კოლოსტომა დაიხურა 3-4 თვის შემდეგ.

პოსტოპერაციულ პერიოდში მკაფიო ცვლილებები არ აღინიშნა. 3 თვის შემდეგ დეფეკაციის სიხშირემ შეადგინა 10-15 დღეში, 1 წლის შემდეგ შემცირდა 2-4-მდე დღეში. ყველა ბავშვი გადარჩა. ფუნქციური ტესტების შედეგები კარგია; ნაწლავების ფუნქცია დამაკმაყოფილებელია; რენტგენოგრაფიულად სახეზეა ფორმირებული სწორი ნაწლავი საკმარისი მოცულობის რეზერვუარით და ნორმალური კოლონიზებით.

ნაწლავური ტრაქტის მთლიანობის აღდგენა ფუნქციურად ვარგისი რეზერვუარის შექმნით ორმაგი ანასტომოზის სახით "გვერდი გვერდში", შექმნილი ილეოკოლოტრანსპლანტაციისა და ილეო-ილეოტრანსპლანტაციისაგან წარმოადგენს რეკონსტრუქციული ქირურგიის საუკეთესო ვარიანტს აგანგლიოზის მქონე ბავშვებისათვის ტოტალური კოლექტომიის შემდეგ. ფუნქციურად ვარგისი რეზერვუარის შექმნა შესაძლებლობას იძლევა თავიდან იქნეს აცილებული წყალ-ელექტროლიტური დისბალანსი, გაუმჯობესდეს ნორმობიოზი, განავლის წარმოქმნა და დაგროვება, შენედეტს საკვების გადაადგილება საჭმლის მომნელებელ ტრაქტში და თავიდან იქნას აცილებული ნივთიერებათა ცვლის სხვა დარღვევები. ბავშვებში მსხვილი ნაწლავის არარსებობის შედეგების ლიკვიდაციის მიზნით, მოდერნიზებული ქირურგიული მიდგომა, რომელიც მდგომარეობს ფუნქციურად ვარგისი/ მომგებიანი რეზერვუარის სხვადასხვა ვარიანტის შექმნაში, ხელს უწყობს ოპერაციის შემდგომი პერიოდის გაადვილებას, რეაბილიტაციის დაჩქარებას, სოციალური ადაპტაციის და პაციენტების ცხოვრების ხარისხის გაუმჯობესებას.

## INFLUENCE OF CARBOHYDRATE MALABSORPTION SYNDROME ON THE CLINICAL COURSE OF ROTAVIRUS INFECTION IN CHILDREN AT AN EARLY AGE

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Worldwide, diarrhoeal diseases are reported as the leading cause of mortality among children aged five years and below, accounting for approximately 8 percent of all deaths among them [12,16]. Viral diarrhea occupies a leading place in the structure of acute intestinal infections in children [4]. Most common and severe among them is rotavirus infection (RVI) that causes about 450,000 deaths per year in children under 5 years of age and hospitalizes millions more [7,8].

Rotavirus primarily infects enterocytes and induces diarrhoea through the destruction of absorptive enterocytes (leading to malabsorption), intestinal secretion stimulated by rotavirus NSP 4 protein and activation of the enteric nervous system [10].

The carbohydrate malabsorption syndrome occurs due to the defeat of the highly degraded enterocytes of the small intestine microvilli (which are responsible for the production of disaccharidases and intestinal absorption function) by the rotavirus. From 1st to 7th days of infection, their apoptosis and proliferation of immature epithelial cells are observed, that leads to atrophy of the villi. Besides, Boshuizen J. A., Reimerink J. H. et al showed that rotavirus causes a decrease in the expression of enterocyte-specific genes (lactase, SGLT1 and L-FABP) in infected cells at the mRNA and protein levels, starting as early as 6 hours after infection [9]. Induced by NSP4 - rotavirus enterotoxin decreasing in SGLT1 activity on the membranes of villous enterocytes leads to disruption

of the Na + -D-glucose symport, which ensures the reabsorption of large volumes of water under physiological conditions [10,11]. The shutoff of enterocyte-specific gene expression, together with the loss of mature enterocytes through apoptosis and the replacement of these cells by less differentiated dividing cells, leads to a defective absorptive function of the intestinal epithelium and disaccharidase (mainly lactase) deficiency [3,9]. Unsplit carbohydrates, that have high osmotic activity, accumulate in the lumen of the small intestine and contribute to the subsequent extravasation of tissue fluid into the intestinal cavity [3].

Carbohydrate malabsorption syndrome is one of the main pathological components of RVI, which occupies a special place in young children, because milk and dairy products form the basis of their diet, and lactose is 80-85% of milk carbohydrates [14]. In scientific sources on the study of sugar malabsorption and lactase deficiency in children with rotavirus gastroenteritis [2,3,4,15], we did not find data on the influence of its laboratory parameters (total carbohydrates, lactose, glucose in feces) on the severity of clinical manifestations of RVI in dynamics of the diseases, as well as criteria for the severity of the main symptoms depending on the laboratory manifestations of the carbohydrate malabsorption syndrome.

The aim of the work - to determine the pathogenetic role of carbohydrate malabsorption syndrome in severity and duration of rotavirus infection symptoms in early aged children.

Table 1. Characteristics of the main symptoms of RVI in children of the study group (n=60), Me [Q25; Q75]

Symptom	n (%)	Characteristics		Duration, days
		The maximum value, times a day	Day of maximum manifestation	
Diarrhea	59 (98%)	7,00 [5,00; 10,00]	3,00 [2,00; 5,00]	8,50 [6,50;10,00]
Vomiting	37 (62%)	3,00 [2,00; 4,00]	2,00 [1,00; 3,00]	1,00 [1,00; 2,00]
Fever, ° C	51 (85%)	38,80 [38,15; 39,20]	2,00 [1,00; 2,00]	2,00 [2,00; 3,00]

**Material and methods.** The study included 60 breastfed children aged 1-24 months with RVI, who were treated at the Department №4 of the municipal institution “Regional Infectious Clinical Disease Hospital” of the Zaporizhzhia Regional Council. There were criteria for inclusion in the study: hospitalization no later than the 3rd day of illness, detection of rotavirus antigen in feces (immunochromatographic method using CITO TEST ROTA test systems), absence of pathogenic intestinal flora in feces, absence of congenital and chronic gastrointestinal pathology, congenital or acquired immunodeficiency. All patients were included into the study by informed parental consent. Among the hospitalized children there were 38 (63,3%) boys and 22 (36,7%) girls. The patients were divided into 3 groups depending on the age: children under 6 months - 14 (23.3%), 6-12 months - 18 (30%), 12-24 months - 28 (46.7%).

One of the main clinical manifestations of RVI was diarrhea, that appeared during the first two days of the disease in 98% of children and lasted 8,50 [6,50; 10,00] days (Table 1). In most cases (37/61,7%) diarrheal syndrome was accompanied by flatulence and intestinal colic [1]. Clinical signs of carbohydrate malabsorption syndrome were registered 1,6 times more often in children under 6 months (in 84,6%), compared with children older than 1 year (in 51,8%) ( $p < 0,05$ ).

The severity of RVI was determined by the Vesikari scale and expressed in points (1 to 20). According to the Vesikari scale the severe course of the disease had 70% of children in the study group, the moderate course – 23,3% and the mild course – 6,7% of patients.

In order to study the rates of carbohydrate malabsorption total amount of carbohydrates, levels of lactose and glucose in coprofiltrates were semi-quantitative determined in all children in the dynamics of the disease (on II-III, V, VII and X days). The total level of carbohydrates in the feces was determined by the Benedict’s method, which reflects the general ability to split and absorb oligosaccharides in the intestine and is based on the detection of sugars capable of reducing copper from  $Cu^{2+}$  to  $Cu^+$  (glucose, galactose, lactose, fructose, maltose) [13]. Children were divided into three groups, depending on the level of carbohydrates in the feces:  $\leq 0,5\%$ , 0,6-1,0% and  $\geq 1\%$ .

The severity of lactase deficiency was assessed by determining the level of an excreted lactose in the stool by Malfatti’s reaction, based on the ability of lactose with ammonia in an alkaline environment when heated to form colored substances. The result was evaluated on a color scale: no color change “0” - no lactose, light yellow “+” – 0,2% - 0,4% lactose, maple syrup color “++” – 0,5% - 1,0% lactose; color of red amber “+++” - 1,1%-1,5%; ruby color “++++” - 2% and above lactose [5]. The severity of impaired absorption of monosaccharides in the intestine was judged by the level of glucose in the stool, that was determined using test systems “Glucophane” (Erba Lachema, Czech Republic) [2].

Statistical processing of the obtained results was performed

using software packages “STATISTICA for Windows 13” (Stat-SoftInc., №JPZ804I382130ARCN10-J). The normality of the distribution was determined using the W-test Shapiro-Wilk. Due to deviations from the normal distribution law, nonparametric methods were used. Quantitative values were presented as median (Me) and interquartile range (IQR: Q25-Q75). The Mann-Whitney U test was used to compare the two independent groups. When comparing more than two groups, the Kruskal-Wallis test was used. Comparison of frequencies of nominal features was determined using the method  $\chi^2$ . The null hypothesis was rejected at a level of statistical significance ( $p < 0,05$ ). The direction, strength and reliability of correlations (R) were determined by Spearman’s correlation analysis. Regression analysis was used to assess the relationship between indicators. To determine the effect of total level of excreted carbohydrates in the feces on the duration of diarrhea and the severity of diarrhea in the dynamics of the disease used simple linear regression. Analysis of the frequency of residual effects in children at the time of discharge from the hospital depending on the total number of carbohydrates in the feces on the 10th day of RVI was performed using logistic regression.

**Results and discussion.** A comparative analysis of the daily frequency of bowel movements in children with different levels of reducing sugars in the feces was performed in the dynamics of the disease to confirm the influence of carbohydrate malabsorption on the severity of rotavirus diarrhea. It showed no relationship between these indicators in the first days of RVI (Fig. 1). From the fifth day of illness, there was an increase in the severity of diarrhea with an increase in Benedict’s test scores (however, without a significant difference in data). A statistically significant difference in the frequency of bowel movements between children with minimum ( $\leq 0,5\%$ ), medium (0,6-1,0%) and maximum ( $\geq 1\%$ ) levels of reducing sugars in the stool was observed on the seventh day of illness. In children with their level  $\leq 0,5\%$ , the daily frequency of diarrhea was 2,00 [1,00; 3,00] times and was 2 and 2,25 times lower than in children with a level of fecal carbohydrates 0,6-1,0% and  $\geq 1\%$ , respectively ( $p < 0,01$ ). Moreover, starting from the seventh day of RVI, a statistically significant strong direct correlation was found between the daily frequency of diarrhea and the total amount of carbohydrates in the feces ( $r=0,76$ ;  $p < 0,05$ ) (Fig. 2). This dependence is described by the following linear simple regression equation:

$$y=1,45+1,97x$$

where  $y$  is the frequency of defecation (times per day),  $x$  is the level of carbohydrates in the feces on the 7th day of RVI (%).

Thus, it was found that carbohydrate malabsorption affects severity of diarrhea on the seventh day of the disease: an increase in carbohydrate levels by 0,5% leads to an increase in the frequency of diarrhea once a day. The total level of reducing sugars in the stool determines 51% of the variance of liquid stools frequency in this period of the disease.

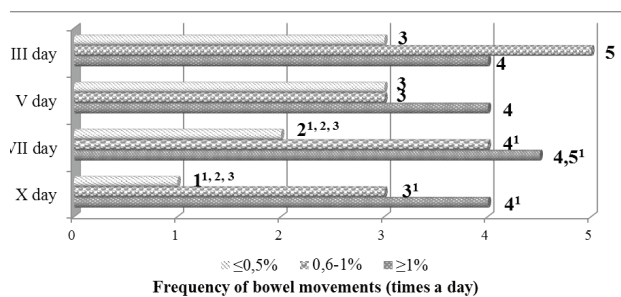


Fig. 1. Characteristics of the daily frequency of bowel movements in children in the dynamics of RVI depending on the total amount of carbohydrates in the feces (n=60)

Note: <sup>1</sup> -  $p < 0,01$  - the difference is significant according to the Kruskal-Wallis criterion; <sup>2</sup> -  $p < 0,01$  - the difference is significant compared with children with a carbohydrate level in the feces 0,6-1%; <sup>3</sup> -  $p < 0,01$  - compared with children with carbohydrate levels in feces  $\ge 1\%$

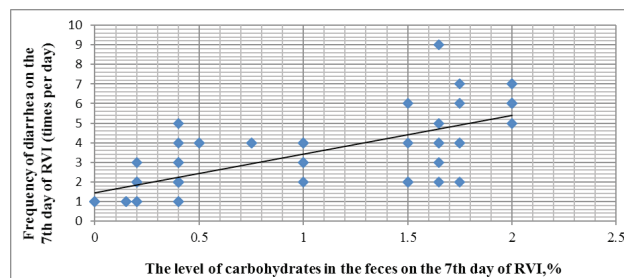


Fig. 2. Dependence of the severity of diarrheal syndrome on the carbohydrate level in the feces on the 7th day of RVI ( $R=0,76$ ,  $p < 0,05$ ,  $n=58$ )

During the convalescence period of RVI, there were also statistically significant differences in the daily frequency of bowel movements in children depending on the level of malabsorbed carbohydrates in the feces. On the tenth day of the disease the frequency of bowel movements was normalized and was 1,00 [1,00; 2,00] times a day in patients with minimal Benedict's test scores ( $\le 0.5\%$ ), against 3,00 [3,00; 4,00] times at the level of fecal sugars of 0,6-1% ( $p < 0,01$ ). The highest frequency of diarrhea at this time was observed in patients with the most pronounced malabsorption of carbohydrates ( $\ge 1\%$ ) ( $p < 0,01$ , relative to the first group). At this stage of RVI a statistically significant strong correlation between the frequency of defecation and the total amount of carbohydrates in the feces maintained ( $r=0,80$ ;  $p < 0,05$ ), that can be described by the following linear simple regression equation:

$$y=1,05+1,83x$$

where  $y$  is the frequency of defecation (times per day),  $x$  is the level of carbohydrates in the feces on the 10th day of RVI (%).

Table 2. Comparison of the frequency of liquid stools per day in children in the dynamics of RVI depending on the level of lactose in the feces (n=60), Me [Q25; Q75]

Day of RVI	The level of lactose in the feces			p
	0-1 «+»	2 «+»	3-4 «+»	
III	3,00 [2,00; 6,50]	3,50 [2,00; 6,00]	4,00 [3,00; 5,00]	0,57
V	3,00 [2,00; 5,00]	4,00 [3,00; 7,00]	4,00 [3,00; 4,00]	0,39
VII	2,00 [1,00; 3,00] <sup>1,2,3</sup>	4,00 [2,00; 6,00] <sup>1</sup>	4,00 [3,00; 4,50] <sup>1</sup>	<b>0,01</b>
X	1,00 [1,00; 2,00] <sup>1</sup>	2,50 [2,00; 3,00] <sup>1</sup>	4,00 [3,00; 5,00] <sup>1</sup>	<b>0,0001</b>

note: <sup>1</sup> -  $p < 0,01$  - the difference is significant according to the Kruskal-Wallis criterion; <sup>2</sup> -  $p < 0,01$  - the difference is significant compared with children with a lactose level in the feces 2 «+»; <sup>3</sup> -  $p < 0,01$  - compared with children with lactose level in feces 3-4 «+»

This dependence is presented as a linear function in Fig. 3, which shows that increasing the level of carbohydrates in the feces by 0,5% leads to an increase in the frequency of defecation once a day. The total level of reducing sugars in the stool determines 55% of the variance of diarrhea frequency values on the 10th day of RVI.

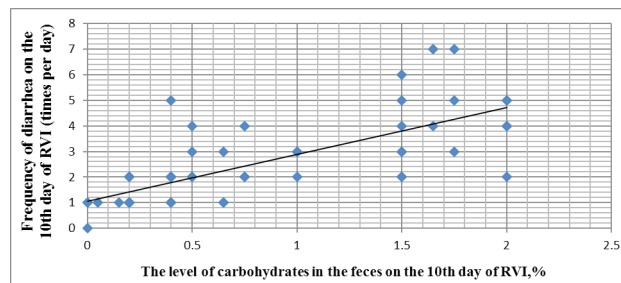


Fig. 3. Dependence of the severity of diarrheal syndrome on the carbohydrate level in the feces on the 10th day of RVI ( $R=0,80$ ,  $p < 0,05$ ,  $n=60$ )

Further analysis showed a similar dependence between the severity of rotavirus diarrhea and the level of excreted lactose in the feces at all stages of the disease (Table 2). A statistically significant difference in the daily frequency of liquid stools between children with levels of the fecal lactose 0-1 «+», 2 «+» and 3-4 «+» appeared after the fifth day of illness ( $p < 0,05$  and  $p < 0,01$  on the seventh and tenth day, respectively). In addition, strong direct correlations were observed between the total level of carbohydrates and lactose in the feces ( $r=0,91$ ;  $r=0,86$ ;  $r=0,91$ ;  $r=0,89$ ;  $p < 0,05$ , on the second, third, fifth, seventh and tenth days of the disease, respectively), which indicates the leading role of lactase deficiency among other mechanisms of oligosaccharide malabsorption in the maintenance of rotavirus diarrhea.

The obtained data indicate that in the early stages of RVI other pathogenetic mechanisms, namely the secretory component, come to the fore in causing diarrheal syndrome. According to the literature, as early as 7-12 hours after infection with rotavirus, its NSP4 protein, by binding to the receptor of the epithelial cell membranes of villi, crypts and enteroendocrine cells, stimulates intracellular molecular pathways, causing the development of secretory diarrhea. After activation of phospholipase C by NSP4-enterotoxin, the intracellular concentration of  $Ca^{2+}$  increases, that induces the secretion of  $Cl^-$  ions. The NSP4 fragment (114-13) causes increased secretion and slows down the reabsorption of  $Na^+$  ions [10,17]. All these pathogenetic processes are likely to cause and maintain diarrhea to a greater extent in the first days of RVI. After the fifth day of the disease and in its later stages, the leading role in the maintenance of diarrhea is played by the syndrome of oligosaccharide malabsorption, which is based on lactase deficiency and impaired absorption of monosaccharides by enterocytes.

According to our data, in the first five days of RVI, the pathogenetic mechanisms of carbohydrate malabsorption syndrome did not affect the severity of diarrhea syndrome. It should also be noted that the level of excreted sugars  $> 0,5\%$  was found to be clinically significant only after the fifth day of illness.

The study found statistically significant differences between the duration of rotavirus diarrhea and the total amount of malabsorbed oligosaccharides in the feces, starting from the fifth day of RVI. In patients with a Benedict's test score  $\leq 0,5\%$ , diarrhea was the least prolonged – 7,00 [6,00; 9,00] days; at the level of carbohydrates 0,6-1% it lasted 7,50 [6,00; 9,00] days; children with  $\geq 1\%$  of excreted carbohydrates had the longest diarrheal syndrome – 9,00 [8,00; 11,00] days ( $p < 0,01$ ). It should be noted that a significant difference was observed between the children of the first and second groups, who had a carbohydrate level of  $\leq 1\%$  and the third group of children with their highest ( $\geq 1\%$ ) values ( $p < 0,01$ ;  $p < 0,05$ , respectively). On the seventh and tenth days of the disease, a similar pattern was observed in the differences in the duration of diarrhea between groups of children with different levels of excreted carbohydrates in the feces ( $p < 0,01$ , according to the Kruskal-Wallis test).

Direct correlations of medium strength were found between the duration of diarrhea in children of the study group and the level of excreted carbohydrates and lactose, starting from the fifth day of RVI ( $r = 0,58$  and  $r = 0,33$ ;  $p < 0,05$ , respectively), which increased in the dynamics of the disease, gaining maximum values on the tenth day ( $r = 0,59$  and  $r = 0,51$ ;  $p < 0,05$ , respectively). A similar pattern was observed for the correlation between the level of excreted glucose in the stool and the duration of diarrhea ( $r = 0,29$ ,  $r = 0,31$ ;  $p < 0,05$ , on the fifth and tenth days, respectively).

To analyze the prognostic effect of carbohydrate malabsorption in the acute period of RVI on the duration of diarrhea, a model of linear simple regression was constructed, where  $y$  is the duration of diarrhea (days),  $x$  is the level of carbohydrates in the feces on the 5th day of RVI (%).

After estimating the parameters of this model by the method of least squares, the following equation of linear pair wise regression is obtained (Fig. 4):

$$y = 5,37 + 2,69x$$

If the total level of carbohydrates in the feces increases by 0,4% on the fifth day of RVI, the duration of diarrhea should be increased by 1 day.

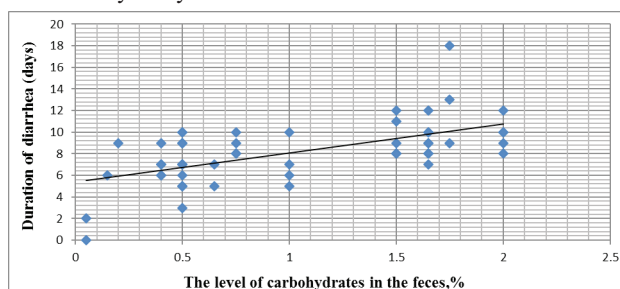


Fig. 4. Dependence of the duration of diarrheal syndrome on the carbohydrate level in the feces on the 5th day of RVI ( $R = 0,58$ ,  $p < 0,05$ ,  $n = 55$ )

Thus, the severity of laboratory manifestations of carbohydrate malabsorption affects both the severity of diarrheal syndrome after the 5th day of RVI and its duration. The obtained data indicate the pathogenetic role of oligosaccharide malabsorption, namely lactase deficiency and impaired absorption of

monosaccharides in the small intestine, in causing and maintaining diarrhea in RVI, starting from the height of the disease and especially at the end of the first and beginning of the second week of gastroenteritis. Furthermore, the significant severity of carbohydrate malabsorption ( $\geq 1\%$  according to the Benedict's test) on the fifth day of RVI may be a prognostic sign of prolonged ( $\geq 9$  days) diarrheal syndrome in children aged 1-24 months.

It was found that 45% of children at the time of discharge from the hospital had residual symptoms of the disease, such as unstable stools 2-3 times a day and flatulence. During the period of convalescence of RVI they showed significantly higher levels of carbohydrates and lactose in the feces, compared with children without residual symptoms: 1,57 [0,75; 1,70]% and 2,5 [2,00; 4,00] +, against 0,40 (0,20; 1,25)% and 1,00 [1,00; 2,00] +, respectively, on the seventh day ( $p < 0,05$ ;  $p < 0,01$ ). On the tenth day of RVI, in addition to three times higher levels of excreted carbohydrates and lactose, a significantly higher level of glucose in the feces was found in them: 2,00 [1,00; 4,00] +, against 1,00 [0,00; 1,00] + ( $p < 0,01$ ). This indicates, firstly, that carbohydrate malabsorption syndrome is the main reason for the development of these residual effects of RVI, and secondly, emphasizes the importance of both components of this syndrome: lactase deficiency and malabsorption monosaccharides in the small intestine.

To accurately assess the impact of carbohydrate malabsorption on the likelihood of residual manifestations of the disease, a model logistic regression was built. It describes the dependence of residual effects on the total level of carbohydrates in the feces on the tenth day of illness:

$$y = 1 / (1 + e^{2,56 - 2,88x})$$

where  $y$  is the probability,  $x$  is the carbohydrate level in the feces on the 10th day of RVI (%).

The sensitivity of this model is 77,8%, specificity – 90,9%. Thus, with the total level of fecal carbohydrates on the tenth day of RVI above 0,75% the probability of unstable bowel movements and flatulence on discharge from the hospital increases.

It should be noted that these residual symptoms were mainly in younger children: they were observed in 64,3% of children in the first 6 months, against 28,6% of patients older than 1 year ( $\chi^2 = 4,94$ ,  $p < 0,05$ ).

According to the results of the research the severity of rotavirus gastroenteritis, which was determined by the Vesikari scale, did not depend on the severity of carbohydrate malabsorption in children of the study group. In our opinion, this is due to determining the severity of the disease by the sum of scores obtained by assessing seven indicators (maximum number of bowel movements and episodes of vomiting per day, duration of diarrhea and vomiting, fever, dehydration and the need for inpatient treatment) [6], on which, with the exception of diarrhea, carbohydrate malabsorption syndrome has no pathogenetic effects.

#### Conclusion.

1. Significant effect of oligosaccharide malabsorption (mainly due to lactase deficiency) on the severity of rotavirus diarrhea is observed after the fifth day of the disease, as evidenced by twice the frequency of bowel movements in children with a level of reducing sugars in the stool  $\geq 1\%$ , compared with patients with  $\leq 0,5\%$  on the seventh day of the disease ( $p < 0,01$ ) with the preservation of this dependence at the beginning of the second week of RVI ( $p < 0,01$  on the tenth day). Starting from the seventh day of RVI, with an increase in the level of fecal carbohydrates by 0,5%, the daily frequency of diarrhea increases by 1 time per day.

2. The total level of carbohydrates in the feces  $\geq 1\%$  on the fifth day of RVI is a prognostic sign of long-term ( $\geq 9$  days) diarrhea in children aged 1-24 months. An increase in the level of fecal oligosaccharides by 0,4% in this term will increase the duration of diarrhea by 1 day.

3. The cause of residual effects of RVI such as sparse stools 2-3 times a day and flatulence on discharge from the hospital, which are observed in almost half (45%) of patients, mostly in the first 6 months of life, is carbohydrate malabsorption syndrome, namely lactase deficiency and impaired absorption of monosaccharides in the small intestine. The probability of residual manifestations increases with the level of carbohydrates in the feces above 0,75 on the tenth day of the disease.

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## SUMMARY

### INFLUENCE OF CARBOHYDRATE MALABSORPTION SYNDROME ON THE CLINICAL COURSE OF ROTAVIRUS INFECTION IN CHILDREN AT AN EARLY AGE

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The aim of the work - to determine the pathogenetic role of carbohydrate malabsorption syndrome in severity and duration of rotavirus infection symptoms in early aged children.

The study included 60 breastfed children aged 1-24 months with rotavirus infection. The severity and duration of the main symptoms of rotavirus gastroenteritis were analyzed depending on the dynamic changes in laboratory parameters of carbohydrate malabsorption syndrome: the total amount of reducing carbohydrates in feces, lactose and glucose in feces, which were determined on II-III, V, VII and X days of the disease. To determine the total amount of reducing sugars in the coprofiltrates, the Benedict's test was used, the lactose in the feces was determined using the Malfatti's test, and the glucose was determined by the Glucophane test systems (Erba Lachema).

It was found that the syndrome of carbohydrate malabsorption had the maximum pathogenetic effect on the severity of rotavirus diarrhea after the fifth day of the disease mainly due to lactase deficiency. Starting from the seventh day of rotavirus infection, with an increase in the level of carbohydrates in the feces by 0,5%, the frequency of liquid stools increases by 1 time per day. The prognostic sign of long-term diarrheal syndrome ( $\geq 9$  days) is the total level of reducing sugars in the feces  $\geq 1\%$  on the fifth day of illness. If the result of the Benedict's test increases by 0,4% in this term, the duration of diarrhea increases by 1 day. When the level of carbohydrates in the stool  $\geq 0,75\%$  on the tenth day of the disease the risk of residual effects on discharge from the hospital (such as unstable stools 2-3 times a day, meteorism and flatulence) increases.

**Keywords:** rotavirus infection, carbohydrate malabsorption syndrome, lactase deficiency, early age children, Benedict's test.

## РЕЗЮМЕ

### ВЛИЯНИЕ СИНДРОМА МАЛЬАБСОРБЦИИ УГЛЕВОДОВ НА КЛИНИЧЕСКОЕ ТЕЧЕНИЕ РОТАВИРУСНОЙ ИНФЕКЦИИ У ДЕТЕЙ РАННЕГО ВОЗРАСТА

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Обследовано 60 детей в возрасте 1-24 месяцев, на грудном вскармливании с ротавирусной инфекцией. Проведен анализ тяжести и длительности основных симптомов болезни в зависимости от динамических изменений лабора-



торных показателей синдрома мальабсорбции углеводов: общего количества восстанавливающих сахаров, лактозы и глюкозы в кале, которые определяли на II, III, V, VII и X дни болезни. Для определения общего количества углеводов в копрофильтрагах использовали пробу Бенедикта, лактозы – пробу Мальфатти, глюкозы – тест-системы «Глюкофан» производства Erba Lachema (Чехия).

Установлено, что синдром мальабсорбции углеводов оказывает максимальное патогенетическое влияние на тяжесть ротавирусной диареи после пятых суток болезни и реализуется в большей мере за счет лактазной недостаточности.

Начиная с седьмого дня при увеличении уровня углеводов в кале на 0,5%, частота жидких испражнений возрастает на 1 раз в сутки. Прогностическим признаком длительного диарейного синдрома ( $\geq 9$  дней) при ротавирусной инфекции является общий уровень олигосахаридов в кале  $\geq 1\%$  на пятый день болезни. При увеличении показателя пробы Бенедикта на 0,4% длительность диареи увеличивается на 1 день. При уровне углеводов в кале  $>0,75\%$  на десятые сутки болезни увеличивается риск возникновения остаточных явлений при выписке из стационара, таких как неустойчивый стул 2-3 раза в сутки, метеоризм и флатуленция.

### რეზიუმე

ნახშირწყლების მალაბსორბციის სინდრომის გავლენა როტავირუსული ინფექციის კლინიკურ მიმდინარეობაზე ადრეული ასაკის ბავშვებში

ნ.ვორობიოვა, ე.უსანოვა

ზაპოროჟიეს სახელმწიფო სამედიცინო უნივერსიტეტი, უკრაინა

გამოკვლეულია ძუძუთი კვებაზე მყოფი 1-24 თვის ასაკის 60 ბავშვი როტავირუსული ინფექციით. ჩატარებულია დაავადების ძირითადი სიმპტომების სიმძიმისა და ხანგრძლივობის ანალიზი ნახშირწყლების მალაბსორბციის სინდრომის ლაბორატორიული მანკვებლების დინამიკურ ცვლილებებზე დამოკიდებულებით: ადღგენილი შაქრების, ლაქტოზას და გლუკოზას რაოდენობა განავალში, რაც განისაზღვრებოდა დაავადების II, III, V, VII და X დღეს. ნახშირწყლების საერთო რაოდენობის განსაზღვრისათვის კოპროფილტრებში გამოყენებულია ბენედიქტის სინჯი, ლაქტოზისათვის – მალფატის სინჯი, გლუკოზისთვის – ტესტ-სისტემა “გლუკოფანი” (Erba Lachema, ჩეხეთი).

დადგენილია, რომ ნახშირწყლების მალაბსორბციის სინდრომი მინიმალურ პათოგენეზურ გავლენას ახდენს როტავირუსული დიარეის სიმძიმეზე დაავადების

მეხუთე დღიდან და მეტწილად რეალიზდება ლაქტოზური უკმარისობის ხარჯზე. მეშვიდე დღიდან განავალში ნახშირწყლების დონის 0,5%-ით მატებისას თხევადი გამონაყოფის გამოდგენის სინჯი დღეში ერთით მატულობს. ხანგრძლივი დიარეის სინდრომის ( $\geq 9$  დღე) პროგნოზულ ნიშანს როტავირუსული ინფექციის დროს წარმოადგენს დაავადების მეხუთე დღეს ოლიგოსაქარიდების საერთო რაოდენობა განავალში -  $\geq 1\%$ . ბენედიქტის სინჯის მანკვებლების ზრდისას 0,4%-ით დიარეის ხანგრძლივობა მატულობს 1 დღით. დაავადების მეათე დღეს განავალში ნახშირწყლების დონის  $>0,75\%$  შემთხვევაში სტაციონარიდან გაწერის შემდეგ მატულობს ნარჩენი მოვლენების განვითარების რისკი - არამდგრადი დეფეკაცია 2-3-ჯერ დღეში, მეტეორიზმი და ფლატულენცია.

## PSYCHO-EMOTIONAL CHARACTERISTICS OF CYBER-ADDICTION IN YOUNGSTER ADOLESCENTS

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The issue of such non-chemical addictions as cyber-addiction has been actively studied by teachers, philosophers, sociologists, psychologists, psychiatrists and other scientists in various fields, which emphasizes its multidisciplinary. Cyber-addictions as a phenomenon of addictive behavior were studied by Cole M., Voiskunsky A.E., Arestova O.N., Khudyakov A.B., Kiselyova M.S. and others. It should be noted that this type of addiction is considered not only in the psychological field, but also becomes an object of medicine, the symptoms are studied and there is an active search for treatment and rehabilitation programs.

Research aimed at substantiating the features of individual psychological and clinical manifestations of cyber-addictions in

adolescents is becoming important. Needs to expand the understanding of nosology and stages of formation of cyber-addictions and their destructive influence on the personality in adolescence.

The current list of behavioral addictions, according to some authors, has more than a thousand different addictive «agents» that lead to the formation of non-pharmacological addiction. The most famous and widespread among them are: cyber-addictions, gambling, shopping, gadget addiction, zipping, collecting, promiscuity, bulimia, anorexia, selfie, gambling, computer addiction, Internet surfing, fabing, workaholism, overwork and other repetitive information-behavioral acts that coincide with hedonistic motives or improve well-being [4-7]. Most studies

of the phenomenon of cyber-addiction, Internet addiction and computer addiction are conducted from the standpoint of medicine as a type of non-chemical addiction, in psychology and age psychology from the standpoint of research of these types of addiction as a tendency to deviant behavior in a crisis period. this issue from the standpoint of psychological, pedagogical and medical and psychological aspects is clearly insufficient.

**The purpose of the analysis** of empirically obtained data on the detection of psycho-emotional states of adolescents who have manifestations of cyber-addictions.

**Materials and methods of research.** Bibliographic and historical (analysis, systematization, theoretical data and literature sources), psychodiagnostic - test method «Toronto Alexithymia Scale» (TAS) and mathematical and statistical (mathematical and statistical data processing made using the program «Microsoft Excel, XP», and statistical analysis package SPSS 26.0 for Windows XP, «Statistic for Windows XP» [8].

The study has been conducted since 2016 to date. A total of 663 people took part in the study, to date, 104 people have already refused to participate in the study. This study included 559 people, 408 of whom had certain types of cyber-addictions, and 151 people who agreed to join the control group (relatively healthy).

**Adherence to ethical aspects.** The research is conducted in compliance with the principles of bioethics and deontology on the basis of Odessa National Medical University; «Youth-friendly clinic» at Non-commercial enterprise «City Student Polyclinic» of Odessa City Council. All respondents were announced the topic and purpose of the research, and during the conversation it was repeatedly emphasized that participation in this study is completely voluntary and confidential. Respondents were given the right not to answer any questions and were given the opportunity to interrupt the survey or participate in the survey without explaining anything. Among the total number of respondents, 559 adolescents were selected to participate in further work. Of these, 269 youngsters (48.12% of the sample) aged 14-21 years, 290 girls (51.88% of the sample) aged 14-21 years. Three blocks of respondents depending on age were separated, which had an internal division into the main and control groups in age categories: from 14 to 15 years, it is OGY1 - 59 youngsters with signs of dependence; CGY1 - 21 conditionally healthy youngsters; MGG1 - 65 girls with signs of addiction;

CGG1 - 25 conditionally healthy girls; from 16 to 18 years, it is MGY2 - 72 youngsters with signs of dependence; CGY2 - 26 relatively healthy youngster; MGG2 - 76 girls with signs of addiction; CGG2 - 28 relatively healthy girls; from 19 to 21 years, it is MGY3 - 67 youngsters with signs of dependence; CGY3 - 24 conditionally healthy youngsters; MGG3 - 69 girls with signs of addiction; CGG3 - 27 relatively healthy girls.

**Inclusion and exclusion criteria.** The study involved only those participants who met all of the following inclusion criteria, namely:

- were able to read and understand the data provided in the informed consent to participate in the study, as well as understand the instructions given in psychological test methods;

- personally signed an informed consent to participate in the study, psychodiagnostic survey and counseling and therapeutic assistance;

- adolescents whose parents gave informed consent for their children's participation in the study;

- were in the age group of 14-21 years.

The exclusion criteria were the following:

- age under 14 years or over 21 years;

- Lack of information consent to participate in the study signed personally for persons aged 18 to 21 years;

- Lack of information consent provided by parents or persons who are responsible for the child in accordance with the legislation of Ukraine (parents, guardians, foster parents) for adolescents from 14 years to 18 years;

- adolescents who have had psychotic disorders or severe manifestations of personality disorders (including schizophrenic conditions or severe depressive disorders);

- severe forms of somatic or neurological pathology.

**Data reliability and statistical analysis.** Mathematical and statistical methods. All data obtained as a result of the study were entered into a specially designed map of each respondent for further processing using modern statistical methods using programs «Microsoft Excel, XP», and statistical analysis package SPSS 26.0 for Windows XP [8]. For statistical data processing we used the procedures of primary and secondary (correlation and variation) statistics. In the process of statistical processing, the relative values (p), arithmetic mean (m) were calculated with the determination of the error of the mean (t), the standard deviation (δ). Assessment of the probability of the results of the

Table 1. Features of psycho-emotional properties of respondents

Age	Groups of respondents	Non-alexithymic	Risk group	Alexithymic
14 to 15 years.	MGY1 (n-59)	18,64	35,59	45,76
	CGY1 (n-21)	47,62	33,33	19,05
	MGG1 (n-65)	21,54	52,31	26,15
	CGG1 (n-25)	64,00	24,00	12,00
16 to 18 years	MGY2 (n-72)	16,67	33,33	50,00
	CGY2 (n-26)	50,00	30,77	19,23
	MGG2 (n-76)	19,74	50,00	30,26
	CGG2 (n-28)	60,71	25,00	14,29
19 to 21 years	MGY3 (n-67)	16,42	37,31	46,27
	CGY3 (n-24)	58,33	29,17	12,50
	MGG3 (n-69)	17,39	49,28	33,33
	CGG3 (n-27)	62,96	25,93	11,11

note: the results of the study are given as a percentage, the difference between the groups is significant,  $p \leq 0.05$

study involved determining the errors of representativeness, confidence limits of averages and relative values, the probability of their differences by Student's test (for parametric), Fisher's test (to check the equality of variances of the two samples). All data obtained are reliable ( $p \leq 0.05$ ). Based on comparative statistical analysis, we made the main conclusions of the study.

**Results and discussion.** For psychodiagnostics, we chose the Toronto Alexithymia Scale (TAS) test method, which allows us to better understand our condition, as well as the strength and depth of our feelings and their causes. The results are given in Table 1.

Because alexithymia is a reduced ability or difficulty in verbalizing emotional states and feelings. Its consequences can be excessive pragmatism, lack of creative attitude to life, ease of short-term emotional outbursts, the causes of which are poorly understood. It is difficult for such people to look at themselves from the side, to understand the meaning of their own life and activities, to see them in a temporary relationship, to make a meaningful connection between the present and the past and future, which allows a person to create and maintain inner harmony and not be completely in control of the situation. In the presence of alexithymia, not only the emotional sphere can be disturbed, but also the personal sphere and the sphere of thinking. In the personal sphere, it manifests itself as an inability to reflect, which, in turn, leads to a simplification of life orientation, impoverishment of relationships with the outside world, that is, the psycho-social sphere is destroyed.

Detecting the manifestations or absence of alexithymia will allow us to better understand the causes of aggression, anxiety, depression, conflict and disruption in interpersonal communication between cyber addicts.

According to the results of the obtained data, it is possible to note that young people of the main groups are more prone to manifestations of alexithymia (MGY1 - 45.76% of respondents, MGY2 - 50.00% of respondents, MGY3 - 46.27% of respondents). Among girls of the main groups, 20% - 35% of respondents with alexithymia were identified (MGG1 - 26.15% of respondents, MGG2 - 30.26% of respondents, MGG3 - 33.33% of respondents).

More respondents from the main groups were found in the risk group than among the control groups, and the number of girls was much higher than that of boys. Thus, in the risk group with MGY1 - 35.59% of respondents, and in MGG1 - 52.31% of respondents; in MGY2 - 33.33% of respondents, and in MGG2 - 50.00% of respondents; in MGY3 - 37.31% of respondents, and in MGG3 - 49.28% of respondents.

Absence of alexithymia is typical for respondents of control groups (CGY1 - 47.62% of respondents, CGG1 - 64.00% of respondents; CGY2 - 50.00% of respondents, CGG2 - 60.71% of respondents; CGY3 - 58.33% of respondents, CGG3 - 62.96% of respondents), they are characterized by the absence of problems with the definition and verbal description of their own experiences and feelings; they can easily distinguish between feelings and bodily sensations; have a developed imagination, propensity for creativity and reflection, vividly experience emotions and can demonstrate them outwardly.

Respondents of the main groups who have manifestations of alexithymia can be described as incapable of reflection. As well as people prone to the manifestation of short-term sharply expressed in the behavior of emotional outbursts, the causes of which are poorly understood, as well as have manifestations of depression and anxiety.

Modern clinical scientists distinguish between mental and physical symptoms of addiction. Mental include: euphoria and

well-being, inability to stop and increase the amount of time spent on the computer, gadget or the Internet, neglect of family and friends, problems with work or study, lies, feelings of emptiness, depression and irritation outside cyberspace. Physical symptoms include headaches and back pain, dry eyes, carpal tunnel syndrome (carpal tunnel syndrome or carpal tunnel syndrome), sleep disorders, irregular eating and neglect of personal hygiene [9,10].

Traditionally, the factors that determine addictive behavior are divided into biological, social and psychological. Biological factors include: the degree of initial tolerance, organic brain damage, burden of heredity, chronic diseases and the nature of substance use [11,12]. The group of social factors influencing the formation of dependence includes the processes taking place in society, accessibility, degree of danger, responsibility, fashion, group influence, social disorientation in microsocial conditions [13,14]. The group of psychological factors includes personal characteristics, type of accentuation, attractiveness of emerging sensations, development of hedonic attitudes, the desire for self-affirmation, curiosity, the presence of psychological trauma in different periods of life. Children's injuries play a leading role in the formation of dependence [15,16].

It should be noted that in the WHO classification of gambling addiction is assigned the code 6C51, and it falls into the category of mental, behavioral disorders and disorders of the nervous system. The ICD-11, which will include 55,000 diseases and significantly expand the classification of health hazards, will enter into force on 1 January 2022 in 194 WHO member countries. It (ICD-11) identifies gambling addiction, which is considered a disorder that has «serious behavioral disorders that adversely affect personal, family, community, educational, professional or other important aspects of life» [3]. However, in our opinion, and in the opinion of some modern scientists (M. Cole, A.E. Voiskunsky, O.N. Arestova, A.B. Khudyakov, M.S. Kiselyov, etc.), we should already talk about cyber-addiction, which is a much broader concept that includes: gaming, the Internet, computer and cybercommunication addictions, and selfie.

To date, scientists have identified some characteristic features of cyber addicts. Violations in the emotional, volitional, communicative and motivational spheres are taken into account. There are a number of studies on the separation of preconditions, stages of development, symptoms, proposed diagnostic criteria for cyber-addictions, the possibility of its formation on the basis of other forms of addictive behavior, and others. Currently, the diagnosis of cyber addiction and the identification of risk groups and markers for the formation of psycho-correctional programs play an important role in the prevention of this type of addiction, and research on this issue is almost non-existent.

**Conclusions.** On the basis of the analyzed theoretical and empirical material and the conducted experimental research on the peculiarities of psycho-emotional states of persons prone to cyber-addiction, the following conclusions were formed.

1. Cyber-addiction is a multidisciplinary problem. Refers to one of the types of non-chemical dependencies. It is a mental disorder caused by an obsessive desire to be constantly in virtual reality, to live and be realized in cyberspace through the use of gadgets or electronic devices, despite the destruction of material and social reality, negative consequences for health and life in general.

2. According to the results of the study, it was found that the majority of respondents in the control groups are non-alexithymic (over 80%), and respondents in the main groups 30% - 50% have manifestations of alexithymia. 30% of respondents in the control groups are at risk.

3. Respondents with manifestations of cyber-addictions can be described as persons who have manifestations of alexithymia and are unable to reflect. They are prone to short-term emotional outbursts, which are poorly understood and depressed and anxious.

**Prospects for further research.** The study provides us with the opportunity to include alexithymic manifestations in markers for the development of psycho-correctional programs for adolescents who are prone to cyber-addictions. However, for a detailed analysis of the nosology and verification of signs of cyber-addiction, additional research should also be conducted to establish individual psychological characteristics and styles of family upbringing and to perform a correlation analysis of the data to develop an adequate psychocorrection program.

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## SUMMARY

### PSYCHO-EMOTIONAL CHARACTERISTICS OF CYBER-ADDICTION IN YOUNGSTER ADOLESCENTS

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The aim of the study is to analyze empirically obtained data to identify psychoemotional states of adolescents with manifestations of cyber addiction.

The study, conducted from 2016 to the present, involved 559 respondents, 408 of whom with certain types of cyber addictions made up the main group and 151 were relatively healthy, who were included in the control group. All respondents were diagnosed using a psychodiagnostic technique - Toronto Alexithymia Scale (TAS).

According to the results of the study, it was found that the majority (more than 80%) of respondents in the age group from 14 to 21 years old, who made up the control group, did not show signs of alexithymia (passive aggression, difficulty in choosing words when describing their own feelings and interpersonal contacts, depression and anxiety they were not typical), and respondents with cyber-addiction demonstrate manifestations of alexithymia in 30-50% of cases. The highest indicators of alexithymia manifestation were found among the respondents of the main group of males aged 16 to 18 years - 50.00% of the respondents, as well as high indicators of manifestation of alexithymia were revealed among young men of the main group aged 14 to 15 years - 45.76% and at the age from 19 to 21 years old - 46.27% of respondents. Among girls of the main group, manifestations of alexithymia were revealed in more than 25% of the respondents (MGG1 - 26.15%, MGG2 - 30.26%, MGG3 - 33.33% of the respondents).

This made it possible for us to characterize cyber addicts as persons, mainly with manifestations of alexithymia, capable of reflection, prone to the manifestation of short-term, sharply expressed in the behavior of emotional outbursts, the causes of which are poorly understood, and also have manifestations of depression and anxiety. The study made it possible to include alexithymic manifestations in research markers for the further development of psychocorrectional programs for adolescents suffering from various types of cyber addictions.

**Keywords:** non-chemical addictions, alexithymia, cyber-addictions, game addiction, Internet addictions, adolescence.

РЕЗЮМЕ

**ПСИХОЭМОЦИОНАЛЬНАЯ ХАРАКТЕРИСТИКА КИБЕР-АДИКТИВ ПОДРОСТКОВО-ЮНОШЕСКОГО ВОЗРАСТА**

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Цель исследования – анализ эмпирически полученных данных для выявления психоэмоциональных состояний подростков, имеющих проявления кибер-аддикций.

В исследовании, проводимом с 2016 года по настоящее время, приняли участие 559 респондентов, из них 408 с определенными типами кибер-аддикций составили основную группу и 151 – относительно здоровые, которые вошли в контрольную группу. Все респонденты продиагностированы с помощью психодиагностической методики Toronto Alexithymia Scale.

По результатам проведенного исследования установлено, что большинство (более 80%) респондентов в возрастной категории от 14 до 21 года, которые составили контрольную группу, не проявляли признаков алекситимии (пассивная агрессия, трудности в подборе слов при описании собственных ощущений и межличностных контактах, депрессия и тревога); респонденты с кибер-аддикцией демонстрируют проявления алекситимии в 30-50% случаев. Наивысшие показатели проявления алекситимии выявлены среди респондентов основной группы мужского пола в возрасте от 16 до 18 лет – 50% респондентов, также высокие показатели проявления алекситимии выявлены среди юношей основной группы в возрасте от 14 до 15 лет – 45,76% и в возрасте от 19 до 21 года – 46,27% респондентов. Среди девочек основной группы проявления алекситимии выявлены у 25,00% респондентов.

Вышеизложенное позволяет охарактеризовать кибер-аддиктов как имеющих проявления алекситимии, способных к рефлексии, проявлению депрессии и тревоги, кратковременных, резко выраженных в поведении эмоциональных взрывов, причины которых плохо осознаются. Результаты проведенного исследования диктуют необходимость включения алекситимических проявлений в маркеры исследований для дальнейшей разработки психокоррекционных программ для лиц подростково-юношеского возраста, страдающих от различных видов кибер-аддикций.

რეზიუმე

მოზარდი ასაკის კიბერ-ადიქტივის ფსიქოემოციური მახასიათებლები

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კვლევის მიზანს წარმოადგენდა ემპირიულად მიღებული მონაცემების ანალიზი კიბერ-ადიქტივის მქონე მოზარდების ფსიქოემოციური მდგომარეობის გამოვლენის მიზნით.

2016 წლიდან დღემდე ჩატარებულ კვლევაში მონაწილეობა მიიღო 559 რესპოდენტმა, მათგან 408 - კიბერ-ადიქტივის სხვადასხვა ტიპით (ძირითადი ჯგუფი), 151 – შედარებით ჯანმრთელი (საკონტროლო ჯგუფი). ყველა რესპოდენტი დიაგნოსტირებული იყო ფსიქო-დიაგნოსტიკური მეთოდის Toronto Alexithymia Scale გამოყენებით.

ჩატარებული კვლევის შედეგების მიხედვით დადგინდა, რომ 14-21 წლის ასაკის რესპოდენტების უმეტესობა (80%) საკონტროლო ჯგუფიდან არ ავლენს ალექსითიმის ნიშნებს (პასიური აგრესია, სიტყვების შერჩევის გაძნელება საკუთარი შეგრძნებების აღწერისას და პიროვნებათშორისი კონტაქტების დროს, დებრესია და შფოთვის), ხოლო რესპოდენტები კიბერ-ადიქტივით შემთხვევათა 30-50%-ში ავლენენ ალექსითიმიას.

ალექსითიმის გამოვლინების მაქსიმალური მაჩვენებლები აღინიშნა ძირითადი ჯგუფის მამრობითი სქესის 16-18 წლის ასაკის რესპოდენტებში – 50%, ასევე, ალექსითიმის მაღალი მაჩვენებლები გამოვლინდა ძირითადი ჯგუფის 14-15 წლის ჭაბუკებში – 45,76% და 19-21 წლის ასაკის რესპოდენტებში – 46,27%. ძირითადი ჯგუფის გოგონებში ალექსითიმია გამოვლინდა რესპოდენტების 25,00%-ში.

ყოველივე ზემოაღნიშნული იძლევა საფუძველს, რომ კიბერ-ადიქტივი დახასიათდეს, როგორც ალექსითიმის გამოვლინების მქონე, რომელთაც აქვთ რეფლექსიის, დებრესიის და შფოთვის, ხანმოკლე, მკვეთრად გამოხატული ემოციური ქცევითი გამოვლინებების უნარი, რომელთა მიზეზები რთულად ცნობიერდება. ჩატარებული კვლევის შედეგები მიანიშნებს ალექსითიმური გამოვლინებების ჩართვის აუცილებლობაზე კვლევის მარკეტა შორის ფსიქოკორექციული პროგრამების შემდგომი შემუშავებისათვის კიბერ-ადიქტივის სხვადასხვა სახის მქონე მოზარდი ასაკის პირებში.

## REACTIVE ARTHRITIS IN CHILDREN (REVIEW)

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Reactive arthritis (ReA) is an inflammatory arthritis related to the subset of seronegative spondyloarthropathies which manifests 1 to 4 weeks after an intestinal, urogenital, or nasopharyngeal infections. The absence of pathogenic microorganisms in the joint fluid or in the synovial membrane distinguishes it from infectious arthritis, also called septic arthritis. ReA is the most common among rheumatic diseases in children and adolescents and represents a systemic clinical manifestation of the above mentioned infections [18].

Additionally, ReA is included into the subset of juvenile spondyloarthropathies (JSpA) that refers to a group of related rheumatic diseases characterized by involvement of peripheral large joints, axial joints, and enthesitis that begin in the early years of life (before reaching the age of 16). The nomenclature and concept of spondyloarthropathies has changed over the past few decades. Though there is no any specific classification of juvenile spondyloarthropathies, diseases related to the nomenclature of spondyloarthropathies in young patients involve: the seronegative enthesitis and arthropathy, juvenile ankylosing spondylitis, reactive arthritis and inflammatory bowel disease-associated arthritis [47].

Depending on the entrance gate, ReA infections are classified into the following three groups: 1) postenterocolitic (enterogenic/intestinal); 2) urogenital (urogenic); 3) arthritis with nasopharyngeal infection that is preceded by the acute infections of the upper respiratory tract such as an acute respiratory disease, angina, pharyngitis, or bronchitis. Some authors refer to the latter as “post-respiratory ReA (priReA)” [2-4,18].

Furthermore, it should be noted that joint disorders are less common among children compared to adults. But, the course of the disease is different and more complicated in children. Recently, there is an increase in the number of preschool children suffering from reactive arthritis [12].

Joint lesions with clinically similar manifestations in certain cases can be the sign of other more serious, often systemic rheumatic diseases [15]. The appropriate treatment does not necessarily bring about a cure of the arthritis. On many occasions it can progress to a chronic condition, thereby increasing the likelihood of juvenile idiopathic arthritis, osteoarthritis, and other severe immunoaggressive diseases [12,48,60]. According to some authors, chronic and recurring arthritis or spondylitis occurs in almost 15-30% of patients [42].

Despite the fact that the interest towards ReA has been lost over the past 10 years, this disease still remains a serious issue in rheumatology and requires an early and individual treatment [24].

In this regard, patients who are diagnosed with reactive arthritis should continue to be monitored regularly by a rheumatologist to maintain control and prevent long-term complications.

**Epidemiology.** The epidemiological data for ReA varies across the world. The factors behind this diversity involve different approaches to performing the diagnostic process and a variety of clinical presentations, the lack of specific laboratory biomarkers, different geographical locations that predispose to multiple pathogens, different genetic backgrounds, different grades of infection, and recently identified changes in the intestinal microbiome [31,34,46].

The scarcity of epidemiological data and prevalence studies is due to the heterogeneity of the disease manifestations and lack of definitive diagnostic criteria, respectively [59]. In Scandinavia, where most studies were conducted, the incidence is around 0.6 to 27 per 100,000 inhabitants [36].

ReA typically affects young adults of working age. Though children also suffer from ReA, its prevalence among children is lower [38,49,63]. The incidence of ReA varies considerably in Europe. It ranges from 0.9 to 9.3 per 100,000 inhabitants depending on the study [36,37,58]. The recent study shows an increase in annual incidence of ReA following intestinal infection [63]; however, the incidence rates range from 1% to 15% across studies due to different research designs [51]. Since intestinal infections are common in developing countries, the incidence of ReA in such countries is higher in comparison to developed countries [35].

In a research conducted by Brinster et al., the clinical presentation and microbiological context of ReA in Canada appears without considerable difference over the period of 30 years [24]. According to the systematic review by Horton et al. in which authors analyze the ReA following intestinal infections, arthritis is recorded in 9 cases out of 1000 for *Campylobacter* and 12 out of 1000 for *Salmonella* and *Shigella* [39]. The incidence of reactive arthritis after *Clostridia* infection among children constitutes 1.4%, while its incidence following *Chlamydia* infection varies from 4% to 8%. The relative risk of ReA in women is 1.5 times higher than in men. Besides, the frequency of ReA in adults is 2.5 times higher compared to children [19]. According to certain data, the frequency of ReA with urogenital etiology constitutes 2: 1 in favour of males, with nasopharyngeal etiology is 3:1 in favour of males, whereas in arthritis with enteral etiology it is the same among both sexes [45]. A recent systematic review by Ajene et al. demonstrates that the incidence of *Campylobacter*-associated arthritis ranges from 8% to 16% with a median of 8% among adults compared to 0% to 6% with a median of 3% among children. *Salmonella*-associated arthritis ranges from 1% to 24% with a median of 11% among adults compared to 0% to 12% with a median of 5% among children. *Shigella*-associated ReA ranges from 7% to 12% among adults and from 0% to 7% with a median of 3.5% among children [19].

If we observe the season of onset for causative bacterial agents, we notice that: reactive arthritis caused by bacteria from urinary tract is present throughout the year. Reactive arthritis caused by bacterial agents from enteral tract is more frequent during the summer season, whereas reactive arthritis caused by nasopharyngeal agents is more present during the winter season [45].

The results of a bicentre retrospective analysis of features and outcomes of ReA show that the incidence of ReA in two cohorts of patients diagnosed between 1986 and 1996 as well as between 2002 and 2012 was similar. But, currently ReA more frequently leads to spondyloarthritis [29]. Other authors came to the similar conclusion that ReA tends to progress into the chronic disorders and definitely requires closer attention [24].

**Pathophysiology.** ReA is a very complex pathological process that reflects the dynamic interface between the triggers of the disease and genetic predisposition. In fact, the development of ReA depends on four main factors – the etiological agents that

caused it, cytokines, the participation of a genetic factor (HLA-B27) and the gut microbiota [63].

**Etiological factor.** Some bacteria are known to trigger the reactive arthritis. They can enter the joints through the intestine or by urogenital route [31,55]. Moreover, it has been proven that the synovial fluid may contain bacterial antigens, and the persistence of these elements can cause the progress of acute ReA to chronic arthritis [63]. Recent studies show that the synovial fluid of patients with ReA contains immunogenic products such as bacterial DNA, antigenic proteins, lipopolymers, and saccharides [46].

In case of ReA being transmitted by urogenital route, *Chlamydia trachomatis* is the most common cause, followed by *Ureaplasma urealyticum* and other less common microbes [31]. The constant persistence of bacterial components of *Chlamydia trachomatis* induces a chronic inflammatory state [33]. This fact also explains the ability of *Chlamydia* to inhibit the formation of phagosomes and lysosomes which allows *Chlamydia* to persist in cells [26,63].

The bacterial antigens are transferred from the primary centre to the synovial membrane, which causes the activation of T-lymphocytes and, as a result, leads to the rapid release of inflammatory cytokines, resulting in synovial inflammation [46,63].

**Factor of cytokines.** Previous studies have demonstrated that levels of inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ) and interferon gamma (IFN- $\gamma$ ) were reduced in acute ReA [22,62]. In contrast, the level of TNF- $\alpha$  increases in chronic ReA which allows assuming that this cytokine plays a dual role at various stages of the pathogenesis of this disease [64]. Researchers have found that the imbalance of cytokines and their concentrations depends on the duration of ReA [10].

The comparison of cytokine level in coprofiltrates and serum showed that the acute ReA is associated with a high level of TNF- $\alpha$  in coprofiltrates, and the chronic ReA is correlated with increasing values of interleukin-6 (IL-6) and interleukin-10 (IL-10) [17]. Probably, the determination of serum interleukin-10 (IL-10) concentration is useful for assessing and monitoring the activity of the inflammatory process in ReA [13]. Katsikas et al. provide data on the pathogenetic role of pro-inflammatory cytokines, especially TNF- $\alpha$ , in the pathogenesis of juvenile spondyloarthropathies. Besides, authors suggest that interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-17 (IL-17) also play a significant pathogenetic role in these diseases [47].

A few studies aimed at determining the connections between the cytokine gene polymorphisms and the development of ReA (as the one conducted in Mexico to analyze the links with TNF- $\alpha$  polymorphisms) showed that TNF- $\alpha$  polymorphism (-308) is associated with a predisposition to undifferentiated spondyloarthritis, but at the same time, the association of ReA with TNF- $\alpha$  gene polymorphisms was not found since the sample size did not allow to assess the association [61].

One of the first studies revealed that the IL-10 gene promoter is associated with the development of ReA, i.e. high IL-10 production in the joints of patients may be genetically determined. This hypothesis requires further verification [41]. The results of studies among siblings and twins point out that the proportion of susceptibility to spondyloarthritis (SpA) is not determined by HLA genes, but rather by the level of secretion of TNF- $\alpha$  and IL-10 cytokines which affect their production and the course of SpA. The balance is regulated at the genetic level and depends on genetic polymorphisms of interleukin genes [54]. There are studies in which IL-17 levels were elevated in synovial fluid in patients with *Chlamydia*-induced ReA [64].

Several research focused on the study of patients with ReA following typhoid fever have shown that *Salmonella adientitia* proteins can stimulate the synovial immune cells to produce IL-17 or IL-23 [27]. Various cytokine genes polymorphisms have been described including polymorphisms in monocytes, TNF- $\alpha$  (-238), and TNFR polymorphisms. The exact pathogenesis of the Th1/Th2 imbalance has not been clarified. However, it is likely that genetic factors are involved [58].

Cytokine imbalance in ReA has been the subject of numerous scientific studies for many years; however, the results are quite contradictory. Therefore, the analysis of the correlation between the cytokine gene polymorphisms and their level of production in patients with ReA can be recommended for further molecular genetic studies which are one of the priority areas in rheumatology currently.

**Genetic factor.** The association of HLA-B27 with ReA is well known, but its involvement in the pathogenesis is still not fully investigated. The studies have shown that HLA-B27 is present in 50-80% of patients with ReA and 90% of patients with ankylosing spondylitis (AS) [21,46,49,52,63]. For example, it is assumed that HLA-B\*2703 increases the risk of a typical clinical triad of ReA [30]. Besides, it is known that the persistence of pathogens in organism, especially *Chlamydia* and *Salmonella*, can be caused by HLA-B27 [32,43]. HLA-B27 expression enhances bacterial replication and thereby reduces the threshold of endoplasmic reticulum (ER) induction, so that *Salmonella* can induce an unfolded protein response. According to numerous studies, HLA-B27 is laid down more slowly than other types of HLA when ER is assembled, which leads to the accumulation of a homologous HLA-B27 dimer and b2-microglobulin in the synovial membrane, finally resulting in the activation of the inflammatory process [20,28].

Current research suggests a number of theories, including the theory of molecular mimicry between a gene and a pathogen. It has been proven that there is a similarity between the amino acid sequences in HLA-B27 and *Yersinia* or *Shigella* proteins, which leads to cross-reactivity, tolerance, and hence triggers an immuno-inflammatory response [28,57,64].

**Gut microbiota.** The intestinal microbiome and its role in the pathogenesis of arthritis has been gaining attention in recent years [64]. In fact, new research is focused on identifying the associations between the microbiome and spondyloarthritis, as well as other inflammatory arthritis [31].

The important information obtained claims that changes in microbiota can lead to aberrant immune responses of the intestinal flora, intestinal dysbiosis, inflammation, and, therefore, to spondyloarthritis [55]. Inflammatory bowel disease, psoriasis, and SpA are all characterized by intestinal dysbiosis. Though all diseases display a decrease in bacterial diversity in intestinal microbiota, this does not happen in ReA [46,64].

A similar conclusion has been drawn by researchers who compared two groups - patients with ReA and patients after an intestinal infection which did not develop into arthritis; that is, significant differences in the diversity of intestinal microbiota were not found [46]. It is stated that the prevalence of enteropathogens is high in patients with ReA and post-infectious peripheral spondyloarthritis. In addition, those patients have a reduced concentration of gut commensals [31,46]. Severe violations of intestinal microbiocenosis are observed in patients with acute and recurrent course, while the degree of dysbiosis is mainly moderate in patients with a prolonged course [12].

It is important to note that all children (100%) with acute ReA have violations of the intestinal microbiocenosis, though there

are considerable differences among children. 62.5% had II degree, and 37.5% had I degree of dysbiosis [16]. Clinical and microbiological studies in children with reactive and infectious arthritis have shown that dysbiotic disorders of the intestinal microbiota along with previously known factors are an important risk factor for the development of arthritis. Connective tissue dysplasia can serve as a factor for the development of reactive arthritis [8].

Thus, further in-depth study of pathogenetic factors, such as the level of certain cytokines and genetic polymorphisms in ReA, and the role of dysplasia in the development of ReA is very promising.

**Clinical manifestations of ReA.** It is well known that ReA and SpA belong to the same group of spondyloarthropathies [64]. In fact, Kaarela et al. showed that chronic ReA and AS have common clinical manifestations, such as sacroiliitis, peripheral arthritis and iritis [40,52].

The most common clinical presentation of ReA is its acute form. In some patients the disease resolves spontaneously within the first six months, while in others (10 to 30%) it tends to progress into the chronic ReA [25].

Oligoarthritis is the most frequent manifestation of ReA. Oligoarticular type is the most common in 70% of women and 73% of men. Monoarticular is characteristic to 13% of female patients and 14% of male patients, and polyarticular type is detected in 14% females and 10% males among adults [44].

The presence of asymmetric mono or oligoarthritis of the lower extremities is a typical manifestation of joint syndrome in children. In certain cases, the disease can also manifest as an arthritis in small joints [3,12,36]. Approximately 4% of children have polyarticular joint syndrome which is accompanied by limited functioning of joints and impaired self-care due to severe pain syndrome [7]. The analysis of the number of affected joints depending on the age group illustrates the predominance of monoarticular type of joint damage in preschool children, while oligoarthritis is more common in the middle and older age groups. Regardless of age and gender, the joints of the lower extremities are more often affected [6,11]. The joint syndrome is characterized by arthralgias without obvious inflammatory changes in the joint area and impaired functioning as well as by morning stiffness of short duration in majority of children [5,7]. It is also characterized by an asymmetric lesion of the interphalangeal and metatarsophalangeal joints and periarticular tissues of the hands and feet with expressed swelling of the fingers, soreness, hyperemia of the skin and the formation of the so-called "sausage-shaped deformity" which is observed in 5-10% of children [7,11]. Enthesitis is an inflammation of the entheses. It represents the site of attachment of a tendon, ligament, fascia or capsule to the bone. The lesion seen in the lower extremities such as Achilles tendinitis or plantar fasciitis is a common condition in enthesitis [55]. Frequent heel pain, stiffness, reduced mobility in the cervical and lumbar spine, as well as in the ileo-sacral joints are noted in boys over the age of 6 who are carriers of HLA-B27 [1]. Such patients are at risk of developing juvenile spondyloarthritis [9].

Typically, skin lesions occur in a prolonged course. These symptoms include skin lesions in the form of keratoderma of the palms and soles, plaque psoriasis of the skin on face, torso and limbs. Onychodystrophy (nail dyschromia, brittleness, roughness, tuberosity) develops as a result of prolonged arthritis, which is often interpreted as a mycotic lesion [58].

Along with the joint syndrome, the symptoms of the gastrointestinal tract, urinary tract and visual organs disorders in the

form of dyspepsia, bowel problems, dysuric phenomena and conjunctivitis are described in children with ReA [12]. The manifestations of the gastrointestinal infection caused by *Salmonella enteritidis* or *Salmonella typhimurium* are diarrhea and fever. The symptoms may be relatively mild. *Salmonella* can affect bones and joints, so it is important to exclude septic arthritis or osteomyelitis caused by these microorganisms. Leukopenia may be present in the early period of infection. In case of reactive arthritis, the joint syndrome develops at 1-3 weeks after an acute intestinal infection [55]. Intestinal infection caused by *Campylobacter jejuni* is accompanied by febrile body temperature, abdominal pain, vomiting, and moderate diarrhea. Clinical manifestations of the intestinal infection caused by *Yersinia enterocolitica* vary depending on the age of the child. Diarrhea often prevails in children under the age of 5. Tension and pain in the lower right quadrant of the abdomen are dominant in children aged 5 to 14 [53]. Acute gastroenteritis is followed by arthritis within 1 to 2 weeks. In children at an older age, the clinical presentation may resemble the manifestations of terminal ileitis or mesenteric lymphadenitis which are similar to the signs of appendicitis [50,53]. Intestinal infections caused by *Shigella* usually occur in a more acute form characterised by the presence of blood in the stool and high fever [55].

Thus, regardless of the etiological agent, the clinical presentation of arthritis proceeds in the same way. For instance, lesions of the joints of the lower extremities prevail in all age groups among adult patients [44].

Burdened premorbid background were the majority of children with ReA: 85% had frequent respiratory diseases, 64% had chronic focus of infection (adenoids, tonsillar hyperplasia, chronic tonsillitis, dental caries), 20% had exudative diathesis in a medical history, 25% had residual rickets features, and 6% of patients had a trauma preceding ReA [5,14].

**Diagnostic criteria.** There is no consensus on the validated diagnostic criteria for ReA to date. Mainly, it is a clinical diagnosis based on a thorough analysis of a medical history, physical examination, and a combination of microbiological criteria [29,55]. The microbiological profile of potential triggers depends on the detection method. Direct evidence of infection is hard to obtain, since the microorganism is not present in the focus of infection when arthritis occurs. As for indirect assessments, mainly serological tests, they have limitations [24].

Currently, the diagnostic criteria combining the recommendations of the American College of Rheumatology (ACR) and the Berlin Criteria (1999) which were adopted during the fourth international seminar on ReA are used.

The criteria are divided into main and additional ones. The main criteria include: 1. the presence of arthritis, asymmetric, mono or oligoarthritis, lesion of the joints of the lower extremities; 2. preceding infection accompanied by enteritis (manifested with diarrhea lasting at least 1 day which occurs within 3 days to 6 weeks after getting arthritis) or by urethritis (manifested with dysuria or urethral or vaginal discharge lasting at least 1 day which occurs within 3 days to 6 weeks before getting arthritis). Additional criteria include at least one of the following signs: 1. the presence of an initiating infection which is indicated by a positive urine culture, a smear from the cervix/urethra, a positive bacteriological stool examination for arthritic intestinal infections; 2. the presence of persistent synovial infection confirmed using immunohistology or PCR for *Chlamydia*. A reliable diagnosis of ReA is made if the patient meets both main criteria and one additional. A probable diagnosis of ReA



is made if the patient satisfies both main criteria or if s/he fulfils one main and one or more additional criteria [23,56].

**Conclusion.** Despite the progress being achieved towards understanding ReA, there are still many controversial issues in pediatrics in various directions. A comprehensive analysis of the literature from the past ten years have shown that insufficient attention was paid to this topic in pediatrics. To date, the studies of ReA among children in foreign sources are significantly less compared to the number of similar studies among adults.

Unfortunately, the available research on prognostic factors as well as analysis of the disease outcomes was focused only on adults, though everything that happens in adults is often laid down in childhood. Therefore, it is crucial to prevent the development of serious rheumatic diseases in childhood, especially in the presence of certain genetic predispositions and risk factors.

The study of ReA in children with a detailed analysis of clinical manifestations and constitutional symptoms can help not only in the diagnosis of a specific case, but also in the justification of complex adequate treatment of such patients, thereby reducing the frequency of adverse outcomes.

It is also important to develop an algorithm of subsequent personalized pediatric observation of children who suffered from ReA because the progress of ReA to chronic disease or other forms of spondyloarthritis requires rheumatological treatment, and in some cases can lead to disability in working age.

This information requires further fundamental research and verification of assumptions.

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## SUMMARY

### REACTIVE ARTHRITIS IN CHILDREN (REVIEW)

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Reactive arthritis is an aseptic inflammatory arthritis that is associated with intestinal, urogenital, and nasopharyngeal infections, and represents a systemic clinical presentation of these infections. Reactive arthritis among children still remains an issue in pediatric rheumatology. The variety of the clinical manifestations makes it difficult to diagnose and detect reactive

arthritis. Moreover, there is a risk that reactive arthritis without a proper treatment can lead to chronic destructive joint diseases. As the articles' analysis has shown, this topic in pediatrics has been neglected over the past 10 years. Thus, the paper presents data on the epidemiology, pathophysiology, clinical presentation and diagnosis of this disease, as well as recommendations for further studies.

**Keywords:** reactive arthritis, children, epidemiology, pathophysiology, clinical presentation.

## РЕЗЮМЕ

### РЕАКТИВНЫЕ АРТРИТЫ У ДЕТЕЙ (ОБЗОР)

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Реактивный артрит – асептическое воспалительное заболевание суставов, ассоциируется с кишечной, урогенной, носоглоточной инфекцией и является ее системным клиническим проявлением. Реактивный артрит у детей по сей день является актуальной проблемой детской ревматологии, так как из-за разнообразия клинических проявлений установить диагноз весьма сложно. На основании анализа ретроспективной и текущей научной литературы по указанному вопросу за последние 10 лет представлены сведения об эпидемиологии, патофизиологии, клинической картине и диагностике заболевания и возможные перспективы в лечении данной патологии у детей. Авторы статьи рекомендуют разработать алгоритм последующего персонализированного педиатрического наблюдения за детьми, страдающими реактивным артритом.

## რეზიუმე

### რეაქტიული ართრიტები ბავშვებში (მიმოხილვა)

**ა.ტუგელბაევა, რ.ივანოვა, მ.გორემიკინა, თ.რიმბაევა, ბ.ტოკტაბევა**

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რეაქტიული ართრიტი წარმოადგენს სახსრების ასეპტიკურ ანთებით დაავადებას, რომელიც ასოცირდება ნაწლავურ, უროგენულ, ნაზოფარინგეალურ ინფექციასთან და წარმოადგენს ამ ინფექციის სისტემურ კლინიკურ გამოვლინებას. რეაქტიული ართრიტი ბავშვებში სადღეისოდაც წარმოადგენს პედიატრული რემატოლოგიის აქტუალურ პრობლემას მისი კლინიკური გამოვლინებების მრავალფეროვნების და დიაგნოზის დასმის სიძნელის გამო. საკითხის ირგვლივ გაანალიზებულია რეტროსპექტიული და თანამედროვე სამეცნიერო ლიტერატურა ბოლო 10 წლის მანძილზე, რის შედეგადაც მიმოხილვაში მოცემულია ინფორმაცია ბავშვებში ამ პათოლოგიის ეპიდემიოლოგიის, პათოფიზიოლოგიის, კლინიკური დიაგნოზის და მკურნალობის შესაძლო პერსპექტივების შესახებ. ავტორების მიერ რეკომენდებულია რეაქტიული ართრიტით დაავადებული ბავშვების შემდგომი პერსონალიზებული პედიატრიული მეთვალყურეობის ალგორითმის შემუშავება.

## RECONSTRUCTION OF THE ABDOMINAL WALL DEFECTS USING GELATIN-COATED DECELLULARIZED AND LYOPHILIZED HUMAN AMNIOTIC MEMBRANE

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Ventral hernias, with 50% reoccurrence rate, still remain to be a real problem for many surgeons around the world. European Hernia Society (EHS) classifies ventral hernias as primary and incisional [1]. Primary ventral hernias include epigastric, umbilical, lumbar and spigelian regions. Incisional hernias, which include suprabubic, iliac, suprapubic sites on the abdominal wall, may be caused by obstetrical surgical procedures, trauma, surgical interventions and operations for other indications. If left untreated, incisional hernias may cause the reduction in the strength and integrity of the anterior abdominal wall, as well as the incarceration of the intestines [2]. It is reported that the use of mesh in the repair of abdominal wall defects reduces the incidence of reherniation; however, the dispute between surgeons still exist about the ventral hernia defect reconstruction approach and the selection of the most suitable mesh type in different circumstances [3-8]. The development of meshes has evolved and advanced through the years. Meshes can be made from either synthetic or biologic materials [9,10]. Despite the popularity of non-absorbable mesh (For example Teflon, Dacron, Polypropylene, Marlex), its application may lead to certain complications like - adhesions, seroma formation, infection, chronic inflammation, fibrosis, voiding difficulty, pain [11-13]. The usage of absorbable mesh (polyglactin, polyglycolic acid) may have several drawbacks like - lack of mesh strength, high recurrence rates [14,15]. Postoperative complications following abdominal wall hernia repair with prosthetic mesh may include abscess, hematoma, bowel obstruction, mesh retraction, granuloma formation and erosion into adjacent structures including the intestine, enterocutaneous fistula and recurrent hernia. However, these complications are quite rare and depend both on the material of which the mesh is constructed and on the location of the prosthetic mesh, which can be located in the extrafascial, subfascial, or intraperitoneal position. Biological materials, compared to synthetic ones provide better neovascularization, fibroblast proliferation, is less prone to formation of fistula and adhesion formation [10,14,16]. Despite the favorable outcomes of the biologic materials, after the application of biological prostheses several complications like infection, seroma formation, and evisceration, low mechanical strength of the mesh can also be reported [9,17,18].

The hypothesis for this study was that gelatin-coated decellularized and lyophilized human amniotic membrane grafts (GCDLHAM) may contribute to the effective reconstruction of the abdominal wall defects, prevent complications, as well as adhesions of organs and tissues in the abdominal cavity. The aim of the study was to develop a method for producing GCDLHAM graft and to determine its effectiveness in the reconstruction of the anterior abdominal wall defects in rats.

**Material and methods.** This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of the Institutional Animal Care Committee. The protocol #358 was approved by the Committee on the Ethics of the Tbilisi State Medical University in Tbilisi, Georgia.

Experiments were conducted on 40 Lewis white laboratory rats aged 8–10 weeks, weighing 200–250g, which were obtained from the breeding facility of the Tbilisi State Medical Univer-

sity (Georgia). The animals were housed in standard laboratory conditions under 12-hour day-night cycles with provision of pelleted rodent diet and water ad libitum.

All surgical procedures were conducted under anesthesia with 0.1 ml / 100g of ketamine (Ketalar®) and 0.05 ml / 100g of xylazine (Xilazin®), intraperitoneally.

*Preparation of decellularized and lyophilized human amniotic membrane.* Before the fabrication procedure of biological membrane from human chorion amnion, five placentas were obtained from patients who delivered newborn babies ranging from 38 to 42 weeks of gestation. These donors signed a form of informed consent in advance before giving birth. All patients have undergone adequate pregnancy period and the newborns were delivered healthy with normal weights varying from 2700 to 3700 grams.

The process of decellularization was conducted according to the reports mentioned by Z. Kakabadze et al [19-22]. Upon delivering the placenta to the laboratory, the catheterization of placental umbilical vein and artery was performed via polyethylene catheters which were attached to the vessels with the help of sutures. After insertion and fixation of catheters 0,9% saline solution and heparin were used to irrigate placenta under physiological pressure at 37°C in order to avoid clotting of blood during drainage. After irrigation, placentas were placed in the refrigerator at -80°C for 24 hours and then thawed at room temperature. Then, the placenta was being flushed overnight with Phosphate Buffered Saline (PBS, Sigma) solution via the catheter in the umbilical artery. Afterwards, the process of 72 hours decellularization was performed. In the first 24 hours, placentas were flushed with the mixture of Sodium Dodecyl Sulfate (SDS, Sigma) and distilled water with the SDS concentration of 0,01%. For the following 24 hours the perfusion was performed with the SDS concentration of 0,1% and ultimately, with 1% SDS for the last 24 hours. Finally, in order to free the placenta from the SDS residues, placentas were washed with distilled water for fifteen minutes and afterwards, with 1% Triton X-100 (Sigma) solution for 30 minutes. Decellularized chorion amnion was then irrigated for 1 hour via Phosphate Buffered Saline (PBS) solution. After all the steps of decellularization, amniotic membranes were isolated from placenta, were cut into 5x5 cm pieces and ultimately, fixated on glass frames. Power Dry PL 6,000 Freeze Dryers were used for the lyophilization of these grafts. Until use, decellularized and lyophilized amniotic membranes (Fig. 1) were kept in aseptic conditions at room temperature.

*Creation of gelatin-coated decellularized and lyophilized human amniotic membrane grafts (GCDLHAM).* The GCDLHAM was prepared through the chemical cross-linking of gelatin solution with glutaraldehyde according to the method described previously [23,24]. For this, the DLHAM was immersed into a mixed solution of gelatin (5.0%) and glutaraldehyde (0.1%), left at 4°C for 15min (repeated three times), and then left at 4°C for 12h. Afterwards, GCDLHAM was placed in 100mM glycine aqueous solution at 37°C for 1h, and then washed three times with double-distilled water. Finally, the GCDLHAM was freeze-dried and sterilized with ethylene oxide gas, stored at -80°C, and thawed as needed.

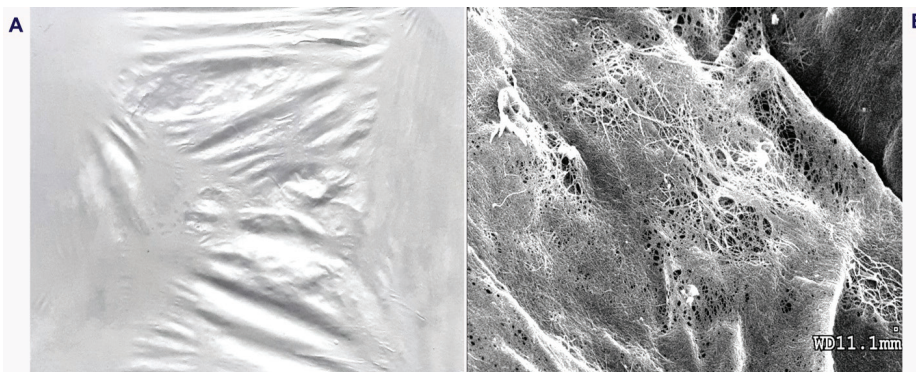


Fig. 1. Human amniotic membrane graft. A) Human amniotic membrane after decellularization and lyophilization; B) Scanning electronic microscopy of decellularized and lyophilized human amniotic membrane

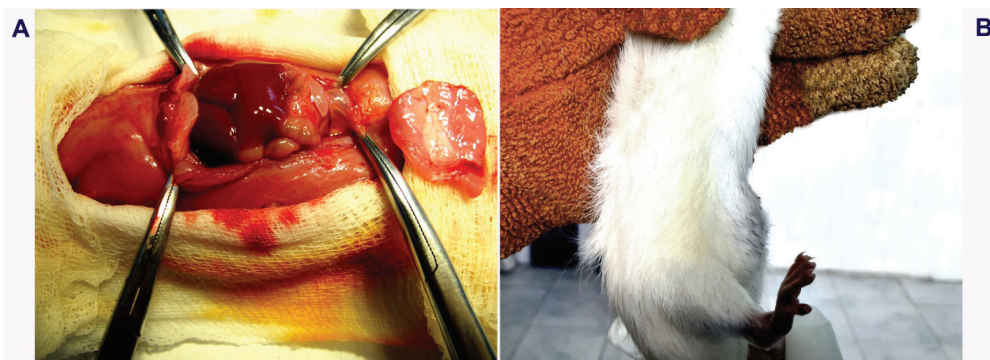


Fig. 2. The creation of abdominal wall defects in rats. A) Defect of the abdominal wall created in the mesogastric region; B) Three weeks after the creation of the anterior abdominal wall defect model

**Surgical procedures.** The creation of abdominal wall defects in rats. After anesthesia, defect of the abdominal wall was created in the mesogastric region in all animals, through the resection of a 1.0 cm diameter fragment of muscle-aponeurotic layer and the parietal peritoneum (Fig. 2A). Three weeks after the creation of the anterior abdominal wall defect model (Fig. 2B). Reconstruction was performed in all experimental animals.

**Reconstruction of the abdominal wall.** Animals were divided into four equivalent groups. In first group (n=10), the defects of the abdominal wall were repaired using ULTRAPRO™ mesh placed in intra-abdominal position. In second group (n=10), defects of the abdominal wall were reconstructed with ULTRAPRO™ mesh located in intra-abdominal position which was covered by DLHAM from both sides. In third group (n=10), defects of the abdominal wall were reconstructed with biological mesh from GCDLHAM placed in intra-abdominal position. In fourth group (n=10), defects of the abdominal wall were repaired with biological surgical mesh XI-S+® (Colorado Therapeutics Denver, USA) placed in intra-abdominal position. XI-S+® represents a product derived from xenogenic (porcine) pericardium that goes through cross-linking procedure which is produced by Colorado Therapeutics providing biocompatibility, durability of the material and consists of significantly low DNA and glutaraldehyde (GA) residuals.

All implants were fixed to the edges of the defect of the abdominal wall with the help of 7/0 monofilament polypropylene sutures (Prolene®, Ethicon). Further, the skin and subcutaneous fatty tissue were sutured tightly using 4/0 monofilament polypropylene sutures (Prolene®, Ethicon).

After surgical operations, all animals were kept under standard vivarium conditions. The animals were taken out of the

experiment on 3rd, 5th, 7th, 14th, 30th, 60th and 90 days after surgery by an intra peritoneal injection of a lethal dose of a 0.5% sodium thiopental solution.

During autopsy, the abdominal cavity was subjected to a U-shaped laparotomy around the sides and bottom edges of the prosthesis. The abdominal cavity was macroscopically inspected and the presence of suture dehiscence, the occurrence and quality of adhesions, fistulas and intra-abdominal complications were determined.

The transplanted mesh fragments with surrounding abdominal tissue were removed and fixed in 10% formalin and subjected to histological preparation, with dehydration in alcohol and xylene, and embedded in paraffin blocks. Histological samples were made on microtome and slides were prepared with standard hematoxylin and eosin (H/E), Masson's Trichrome stains. These slides were submitted to pathological examination to verify the type and degree of inflammation, inflammatory cells, fibroblasts, collagen, and neovascularization in the regions.

**Results and discussion.** In the first group, on the twentieth day after implantation, one case of skin suture stratification was observed. In other cases, skin wounds were successfully closed without any macroscopic signs of inflammatory and infectious processes in the soft tissues of animals (Fig. 3).

Three months after implantation, in the animals of the second group, we observed adhesions involving only the omentum, which were easily separated. In the animals of the first group, the adhesions between the implant, omentum and intestines were denser and stronger (Fig. 4 A-B). In order to free the intestines and omentum from adhesions, they had to be dissected. One case of mesh retraction was observed in the animal of the fourth group (Fig. 4C). It should be noted that animals of the first

group had more newly formed blood vessels (Fig. 4D) compared to other groups of animals. The animals treated with GCDLHAM and XI-S+® grafts had nearly 100% adhesion reduction, compared to the animals of the first group that were treated with ULTRAPRO™ mesh.

Two weeks after implantation, histological studies showed inflammatory cell infiltrations in all groups (Fig. 5 A-H). Significant infiltrations of the inflammatory cells were mainly expressed in the first and second groups. Three weeks later, in animals of the second and third group, the onset of remodeling processes were noted, which consisted of a gradual degradation of the amniotic membrane, the formation of new blood vessels and the deposition

of new collagen. A month after implantation, inflammatory reactions gradually decreased in the animals of the first group and was completely absent in other animal groups. At the same time, in the animals of the second and third group, a large number of ordered collagen fibers were observed that were incorporated in the host tissue (Fig. 5 I-L). Three months after implantation, GCDLHAM graft was integrated with the host tissues so that it was difficult to distinguish it from the surrounding tissues. In the second group, ULTRAPRO™ mesh was still detectable through the decellularized amniotic membrane. In animals of the fourth group, the XI-S+® graft was surrounded by a well-defined connective tissue capsule and was tightly fixed to the host tissues.

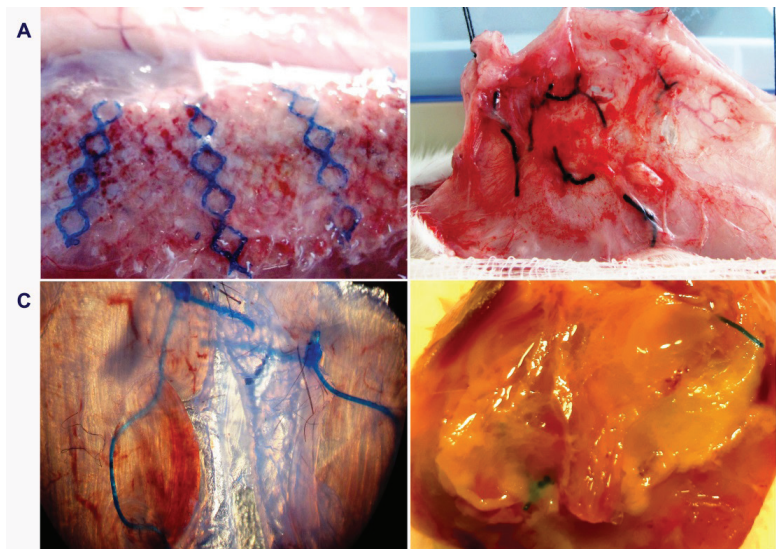


Fig. 3. Macroscopic samples. A) ULTRAPRO™; B) ULTRAPRO™ mesh covered by decellularized and lyophilized human amniotic membrane; C) Gelatin-coated decellularized and lyophilized human amniotic membrane; D) Biological surgical mesh XI-S+®. All grafts are surrounded by host tissues. Three weeks after implantation

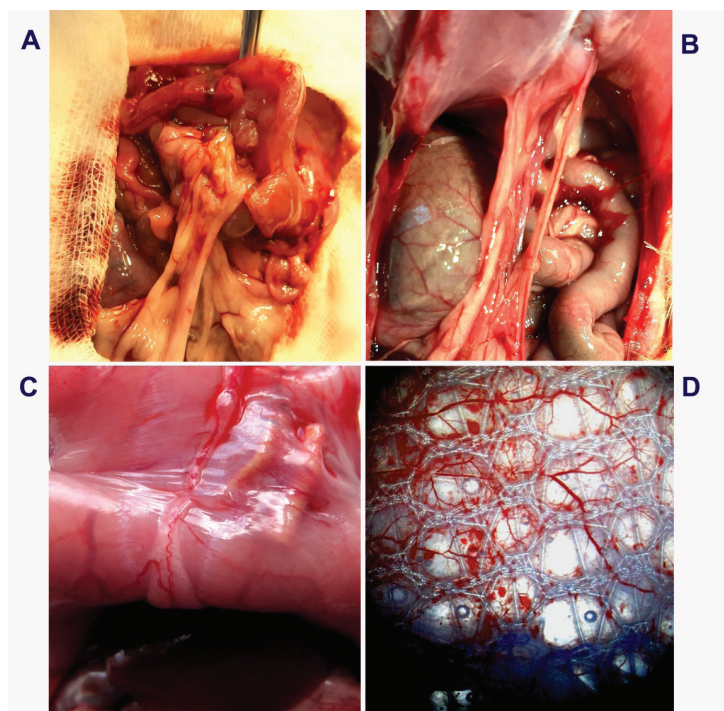


Fig. 4. Postoperative findings. A) Adhesions between the implant, omentum and intestines in the animals of the first group; B) Adhesions involving only the omentum in the animals of the second group. C) Mesh retraction in the animal of the fourth group D) Newly formed blood vessels in the animals of the first group

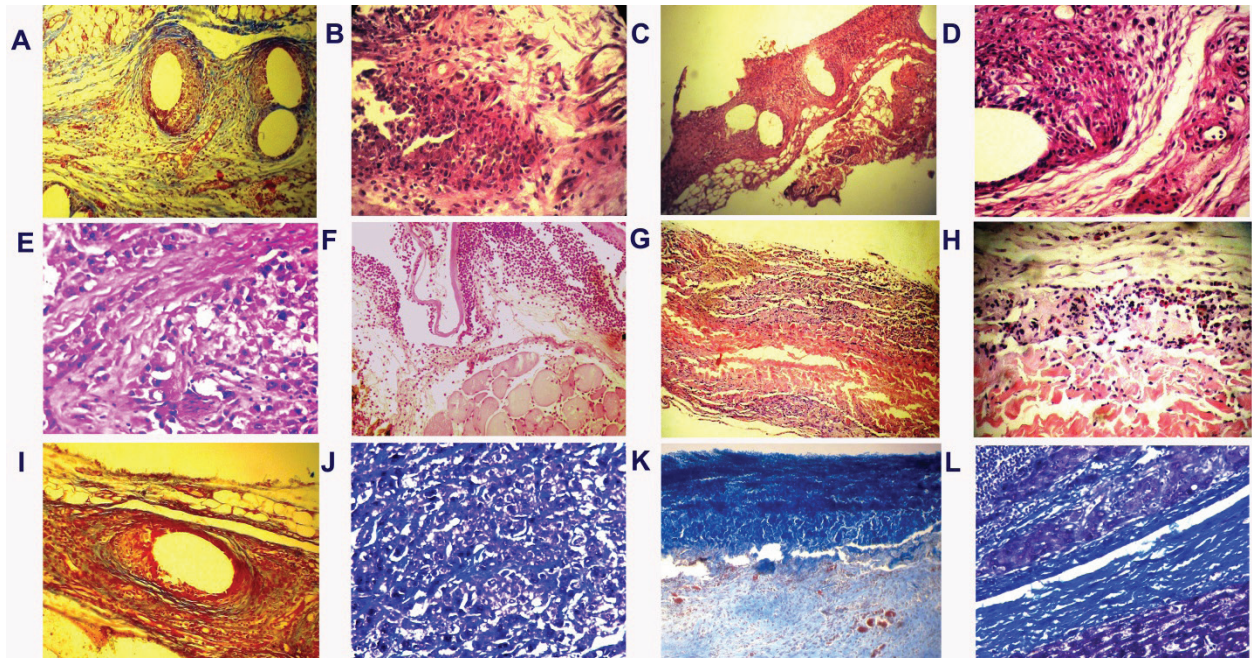


Fig. 5. Evaluation of histological images of the grafts. A and B) ULTRAPRO™; HE staining, one month,  $\times 400$  ; C and D) ULTRAPRO™ mesh covered by decellularized and lyophilized human amniotic membrane; HE staining, one month,  $\times 200/400$ ; E and F) Gelatin-coated decellularized and lyophilized human amniotic membrane; HE staining, one month,  $\times 400/200$ ; G and H) Biological surgical mesh XI-S+®; HE staining, one month,  $\times 200/400$ ; I) ULTRAPRO™; Masson's Trichrome staining, one month,  $\times 200$ ; J) ULTRAPRO™ mesh covered by decellularized and lyophilized human amniotic membrane; Masson's Trichrome staining, one month,  $\times 400$ ; K) Gelatin-coated decellularized and lyophilized human amniotic membrane; Masson's Trichrome staining, one month,  $\times 200$ ; L) Biological surgical mesh XI-S+®; Masson's Trichrome staining, one month,  $\times 400$

One of the main strategies of tissue engineering is to restore, maintain or improve damaged tissue functions using various biomaterials. In recent years, many works related to the development of potentially applicable scaffold materials for tissue engineering have been presented in the literature. Of particular interest in these works was scaffolding in the form of three-dimensional porous biomaterials. Scaffold plays a significant role in tissue repair and regeneration.

The amniotic membrane and the possibility of its use as a scaffold for reconstruction of the anterior abdominal wall attracted our attention. There are many reports about the usage of amniotic membrane for burns varicose ulcers [25,26-28], urinary bladder reconstructions [25,29], nerve and tendon damage [25,30], adhesions control and early healing of peritoneal lesions [25,31], dural repair and transphenoidal surgeries [32], ophthalmic surgery [33], vestibuloplasty [34], periodontal surgical procedures [35], gastric mucosal defect repairs [35], treatment of meningomyelocele and spinal cord malformations [36].

Our previously described report [37] has shown that decellularized human amniotic membrane can be effectively used as a non-invasive treatment for pharyngocutaneous fistula after total laryngectomy. Immunohistochemical and histological studies described in report has revealed five distinct layers of the normal human amniotic membrane: epithelium, basement membrane, fibroblast layer, compact layer and intermediate (sponge) layer. The basement layer was formed by glycoproteins such as nidogen, laminin and fibronectin, as well as by type III and IV collagens. Next was the compact layer, forming the main fiber structure of the amnion, which was represented by I, III, IV, and V collagen types and fibronectin. In addition, we detected that after decellularization human amniotic membrane contained numerous growth factors, such as Epidermal

Growth Factor (EGF), basic Fibroblast Growth Factor (bFGF), Keratinocyte Growth Factor (KGF), Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor alpha (TGF $\alpha$ ), Transforming Growth Factor beta (TGF $\beta$ ), Platelet-Derived Growth Factor (PDGF) and other.

Reports in recent years recommend the use of human amniotic membrane for the cover of the peritoneal cavity as reinforcement in the reconstruction of the abdominal wall with the help of polypropylene mesh [31]. Authors note that human amniotic membrane, as a biological coverage of the abdominal cavity in the abdominal wall reconstruction using polypropylene prosthesis, can be an alternative in cases where there is no viable peritoneum. They also report that the association of the amniotic membrane with the polypropylene mesh in the treatment of abdominal wall defects of Wistar rats did not alter the formation of adhesions after the first week of operation. However, the amniotic membrane was associated with a marked increased inflammation and angiogenesis activity and the predominance of mature collagen fibers, regardless of the anatomical plane in which it was inserted, accelerating healing.

There are also reports about the usage of Amniotic Membrane-Coated Polypropylene Mesh for the repair of incisional hernia [38]. Authors note that the use of polypropylene mesh coated with fresh amniotic membrane provides the advantage of decreasing postoperative intra-abdominal adhesions along with less inflammation and higher epithelialization after abdominal wall repair.

The positive results obtained by the authors are primarily associated with the fact that human amniotic membrane has a low Immunogenicity. These characteristics of human amniotic membrane reduce the chance of transplant rejection, which

represents an essential advantage when selecting materials for the application in regenerative medicine [39,40]. There are reports according to which we find that human amniotic membrane has anti-inflammatory, antifibrotic, antimicrobial, angiogenic properties, low immunogenicity and can also promote epithelization [41]. While using GCDLHAM graft for the reconstruction of the anterior abdominal wall defects, we found that three weeks after operation, in the animals of the second and third group, the onset of remodeling processes was noted, which consisted of a gradual degradation of the amniotic membrane, the formation of new blood vessels and the deposition of new collagen. Three months after implantation GCDLHAM graft was integrated with host tissues so that it was difficult to distinguish it from surrounding tissues. However, in the second group, ULTRAPRO™ mesh was still detectable through the decellularized amniotic membrane. Encouraging results were also noted when using a XI-S+® graft. Three months after implantation, XI-S+® graft was surrounded by a well-defined connective tissue capsule and was tightly fixed to the host tissues.

**Conclusion.** While using GCDLHAM and XI-S+® grafts, all the defects were repaired successfully and none of the rats in these groups showed any evidence of bulging, herniation, development of wound rupture and infection, or fistula formation in postoperative period. Gelatin-Coated decellularized human amniotic membrane can be used as anti-adhesive barrier in abdominal and pelvic surgery, as well as the repair of the abdominal wall hernia.

**Acknowledgement.** This work was supported by Shota Rustaveli National Science Foundation (SRNSF) [PHDF-18-2192; Reconstruction of anterolateral abdominal wall defect with the use of biological three-dimensional membranes]”.

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## SUMMARY

### RECONSTRUCTION OF THE ABDOMINAL WALL DEFECTS USING GELATIN-COATED DECELLULARIZED AND LYOPHILIZED HUMAN AMNIOTIC MEMBRANE

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Ventral hernias, with the incidence of reherniation nearly as high as 50%, still remain to be a real challenge for surgeons

worldwide. The use of mesh in the repair of abdominal wall defects reduces the incidence of reherniation; however, using a prosthetic mesh can lead to complications like wound infection, hematoma, seroma, enterocutaneous fistula, small bowel obstruction, recurrent herniation and erosion into adjacent structures including the intestine. The aim of the study was to develop a method for producing gelatin-coated decellularized and lyophilized human amniotic membrane graft and to determine its effectiveness for the reconstruction of the anterior abdominal wall defects.

Experiments were conducted on 40 Lewis white laboratory rats. Animals were divided into four equivalent groups. Abdominal wall defects were created in all rats and repaired using the ULTRAPRO™ mesh (group I), ULTRAPRO™ mesh which was covered by decellularized and lyophilized human amniotic membrane from both sides (group II), mesh from gelatin-coated decellularized and lyophilized human amniotic membrane (group III) and biological surgical mesh XI-S+® (group IV).

Three months after implantation, meshes from gelatin-coated decellularized and lyophilized human amniotic membrane were integrated with host tissues so that it was difficult to distinguish it from the surrounding tissues. However, in the second group, ULTRAPRO™ mesh was still detectable through the decellularized amniotic membrane. Encouraging results were also observed when using a XI-S+® graft. Three months after implantation, XI-S+® graft was surrounded by a well-defined connective tissue capsule and was tightly fixed to the host tissues.

While using gelatin-coated decellularized and lyophilized human amniotic membrane grafts and XI-S+® grafts, all the defects were repaired successfully and none of the rats in these groups showed any evidence of bulging or herniation, development of wound rupture, wound infection or fistula formation in postoperative period. Gelatin-coated Decellularized human amniotic membrane can be used as anti-adhesive barrier in abdominal and pelvic surgery, as well as for the repair of the abdominal wall hernia.

**Keywords:** tissue engineering, abdominal wall, decellularized human amniotic membrane, ventral hernia repair.

## РЕЗЮМЕ

### РЕКОНСТРУКЦИЯ ДЕФЕКТА БРЮШНОЙ СТЕНКИ С ИСПОЛЬЗОВАНИЕМ ДЕЦЕЛЛЮЛЯРИЗОВАННОЙ И ЛИОФИЛИЗИРОВАННОЙ АМНИОТИЧЕСКОЙ МЕМБРАНЫ ЧЕЛОВЕКА, ПОКРЫТОЙ ЖЕЛАТИНОМ

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Послеоперационные вентральные грыжи, рецидив которых достигает 50%, по-прежнему остаются серьезной проблемой для хирургов во всем мире. Использование сетки при реконструкции дефектов брюшной стенки снижает частоту рецидива; однако использование протезной сетки может привести к таким осложнениям, как инфекция раны, гематома, серома, кожно-кишечный свищ и непроходимость кишечника.

Цель исследования - разработать эффективный метод лечения вентральных грыж с использованием децеллюляри-

зованной и лиофилизированной амниотической мембраны человека, покрытой желатином.

Эксперименты проведены на 40 белых лабораторных крысах линии Lewis. Животные разделены на четыре эквивалентные группы. Всем животным предварительно создана модель дефекта передней брюшной стенки. Животным первой группы дефект передней брюшной стенки восстанавливали с помощью сетки ULTRAPRO™ (ETHICON™); животным второй группы - с помощью сетки ULTRAPRO™ (ETHICON™), которая предварительно была покрыта децеллюляризованной и лиофилизированной амниотической мембраной человека с обеих сторон; животным третьей группы дефект передней брюшной стенки восстанавливали с помощью децеллюляризованной и лиофилизированной амниотической мембраны человека, покрытой желатином; животным четвертой группы - с помощью биологического трансплантата XI-S + ® (США).

У животных первой группы спустя три месяца после имплантации сетки ULTRAPRO™ в брюшной полости наблюдали спаечный процесс. Сетка была замурована в плотных спайках, в которую были включены сальник и петли тонкого кишечника. Во второй группе животных в

эти же сроки спаечный процесс в брюшной полости был незначительным. Однако, сетка ULTRAPRO™ все еще обнаруживалась через децеллюляризованную амниотическую мембрану. У животных третьей группы децеллюляризованная и лиофилизированная амниотическая мембрана человека, покрытая желатином, была интегрирована с тканями хозяина, так что ее трудно было отличить от окружающих тканей. Обнадеживающие результаты наблюдались также при использовании трансплантата XI-S+. Спустя три месяца после реконструкции дефекта передней брюшной стенки трансплантат XI-S+® был окружен соединительнотканной капсулой и плотно прикреплен к тканям хозяина.

При использовании децеллюляризованных и лиофилизированных трансплантатов амниотической мембраны человека с желатиновым покрытием и трансплантатов XI-S+® спаек в брюшной полости, признаков грыжи, раневой инфекции или образования свищей не обнаружено. Децеллюляризованная человеческая амниотическая мембрана может быть использована в качестве антиадгезивного барьера при абдоминальной и тазовой хирургии, а также для восстановления грыжи брюшной стенки.

### რეზიუმე

მუცლის კედლის დეფექტების რეკონსტრუქცია ქელატინით დაფარული დეცელულარიზებული და ლიოფილიზირებული ადამიანის ამნიონური მემბრანის გამოყენებით

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

ვენტრალური თიაქრები, რომელთა განვითარების რეციდივი, დაახლოებით, 50%-ია, ქირურგებისათვის დღესაც უდიდეს გამოწვევას წარმოადგენს. მიუხედავად იმისა, რომ ბადეების გამოყენებამ შეამცირა თიაქრის რეციდივის სიხშირე, სინთეტიკური ბადეების გამოყენებამ შესაძლოა მაინც გამოიწვიოს ისეთი გართულებები, როგორც არის ინფექცია, ჰერნიაცია, სერომა, ენტეროკუტანური ფისტულა, წერილი ნაწლავის ობსტრუქცია, თიაქრის რეციდივი და ახლო მდებარე ქსოვილების ეროზია, მათ შორის ნაწლავებისაც.

კვლევის მიზანს წარმოადგენდა ქელატინით დაფარული დეცელულარიზებული და ლიოფილიზირებული ადამიანის ამნიონური მემბრანის შექმნა და შემდგომ მისი ეფექტურობის განსაზღვრა მუცლის წინა გვერდითი კედლის რეკონსტრუქციის დროს.

ექპერიმენტები ჩატარდა Lewis-ის ჯიშის 40 თეთრ ლაბორატორიულ ვირთავაზე. ცხოველები დაყოფილი იყო 4 ჯგუფად. მას შემდეგ, რაც ყველა ცხოველს შეექმნა მუცლის წინა გვერდითი კედლის დეფექტი, რეკონსტრუქცია ჩატარდა ULTRAPRO™-ის ბადის (ჯგუფი I), დეცელულარიზებული და ლიოფილიზირებული ადამიანის ამნიონური მემბრანით დაფარული ULTRAPRO™-ის ბადის (ჯგუფი II), ქელატინით დაფარული დეცელულარიზებული და ლიოფილიზირებული ადამიანის ამნიონური მემბრანის (ჯგუფი III) და ბიოლოგიური ქირურგიული XI-S+® ბადის (ჯგუფი IV) დახმარებით.

იმპლანტაციიდან სამი თვის შემდეგ ქელატინით დაფარული დეცელულარიზებული და ლიოფილიზირებული ადამიანის ამნიონური მემბრანა კარგად იყო ინტეგრირებული ქსოვილებთან და მისი გარჩევა რთული იყო ახლო მდებარე ქსოვილებისაგან. თუმცა, მეორე ჯგუფში, ULTRAPRO™-ის ბადე დეცელულარიზებული ამნიონური მემბრანის საშუალებით კვლავ შესამჩნევად იყო. კარგი შედეგები გამოვლინდა XI-S+® ბადის გამოყენების შემდეგაც. იმპლანტაციიდან სამი თვის შემდეგ XI-S+® ბადე იყო შემოფარგლული კარგად გამოკვეთილი შემაერთებელქსოვილოვანი კაფსულით და მჭიდროდ ფიქსირებული მიმდებარე ქსოვილებთან.

ქელატინით დაფარული დეცელულარიზებული და ლიოფილიზირებული ადამიანის ამნიონური მემბრანის და XI-S+® ბადის გამოყენების შედეგად ყველა დეფექტის მკურნალობა ეფექტურად დასრულდა; პოსტოპერაციულ პერიოდში არცერთ ვირთავას არ აღენიშნა თიაქრის განვითარება, ჭრილობის მიდამოში რუპტურა, ინფექციის და ფისტულის არსებობა. ქელატინით დაფარული დეცელულარიზებული და ლიოფილიზირებული ადამიანის ამნიონური მემბრანა შესაძლოა გამოყენებულ იქნას როგორც ანტი-ადჰეზიური ბარიერი აბდომინურ ქირურგიაში და თიაქრების რეკონსტრუქციაში.

## THYROID STATUS: IS IT POSSIBLE TO RESTORE MYELIN?

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Currently, there is an increase in the number of diseases accompanied by demyelinating lesions of the central nervous system. The most socially significant and least studied among other diseases of the nervous system is multiple sclerosis (MS), which occurs most often in young and middle age and has an autoimmune nature of the course of the disease. MS simultaneously affects several parts of the central nervous system, which leads to patient disability, worsening of their quality of life, and also complicates diagnosis. With this disease, not only white, but also gray matter suffers, and demyelination of the gray matter is associated with the clinical condition of patients.

To date, drugs for the treatment of MS are aimed at relieving symptoms, alleviating the manifestation of the disease and prolonging the period of remission, but they alone do not restore the affected parts of the brain and do not completely cure the disease. The search for compounds that would prevent demyelination or enhance the process of remyelination is urgent [1].

Thyroid hormones play a significant role in the development and functioning of the structures of the nervous system. Thyroid hormones promote the development of the cerebral cortex and cerebellum in the fetus, stimulate the growth of forebrain neurons, axons, dendrites, and their myelination [2,3]. When a deficiency of triiodothyronine occurs, scientists note violations in the formation of the extracellular matrix, which leads to disorders of neuronal cell migration during brain development [4]. In the course of many experiments, the influence of thyroid hormones on the processes of differentiation and maturation of various subtypes of oligodendrocytes and astrocytes has been established [10,11]. These effects are realized through nuclear receptors for triiodothyronine. They are present in high concentrations in the neurons of the amygdala and hippocampus, as well as in the cerebral cortex, to a lesser extent in the brainstem and cerebellum.

Some scientists consider the process of myelination as T3-mediated activation of glia [2]. Triiodothyronine, in their opinion, regulates not only the differentiation of oligodendrocytes, but also the synthesis of myelin through nuclear receptors to thyroid hormones. It is assumed that hypofunction of the thyroid gland inhibits the expression of genes encoding the synthesis of structural myelin proteins: myelin basic protein, proteolipid protein, myelin-associated glycoprotein, which leads to a decrease in myelin production and the number of myelinated axons [2,10,11].

Animal models help to understand the complex interactions between different CNS cell types and to reveal the general mechanisms of damage and repair of myelin sheaths. There are four well-characterized experimental approaches to inducing CNS demyelination in rodents:

1. genetic mutations of myelin;
2. autoimmune inflammatory demyelination (experimental autoimmune encephalomyelitis);
3. viral demyelination;
4. toxic demyelination.

3. viral demyelination;

4. toxic demyelination.

Cuprizone-induced lesion has attracted much attention and recognition in recent years. This model is a toxic model of demyelination of white and gray matter in the central nervous system, which lacks an autoimmune component. Cuprizone induces apoptosis of mature oligodendrocytes, resulting in sustained demyelination and activation of astrocytes and microglia with regional heterogeneity between different regions of gray and white matter. This model is extremely useful for clarifying the mechanisms during de- and especially remyelination, regardless of interaction with peripheral autoimmune cells. With regular administration of cuprizone, remyelination is interrupted and demyelination persists until the end of the diet (chronic demyelination) [2].

The aim of the study was to study the effect of thyroid hormones on remyelination processes in rats in the cuprizone model of multiple sclerosis in comparison with the process of hypothyroidism.

Tasks: 1) reproduction of the model of multiple sclerosis in rats by means of cuprizone; 2) study of the effect of thyroid preparations on remyelination processes; 3) study of the influence of hypothyroid pathology in the cuprizone model of multiple sclerosis.

**Material and methods.** The object of the study was sexually mature male rats (4-4.5 months) weighing 180-300 g of the Wistar line (n=35). The experiment was carried out on the basis of the Department of Pharmacology and Pharmacy, North-Western State Medical University named after I.I. Mechnikov of the Ministry of Health of Russia. All experimental procedures were carried out in accordance with the rules of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes.

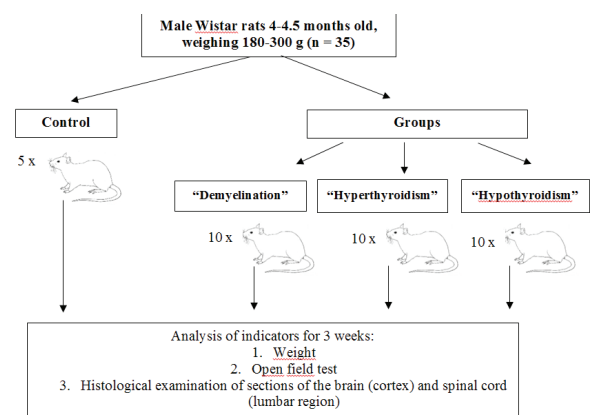


Fig. 1. Study research

Table 1. Study groups

Group	n	Specification
“Control” (I)	5	animals receiving regular normal water
“Demyelination”(II)	10	animals receiving 0.3% cuprizone solution instead of drinking
“Hyperthyroidism”(III)	10	animals receiving 0.3% cuprizone solution instead of drinking, which were injected intraperitoneally with L-thyroxine at a dose of 1.5 µg/kg
“Hyperthyroidism”(IV)	10	animals receiving, instead of drinking, 0.02% aqueous solution of propylthiouracil

The animals were divided into 4 groups (Table 1): group I - "Control" (n=5); group II - "Demyelination" (only cuprizone, n=10); group III - "Hyperthyroidism" (cuprizone + L-thyroxine, n=10); group IV - "Hypothyroidism" (cuprizone + propylthiouracil, n=10).

During the experiment, the animals were kept on a standard vivarium diet with free access to water and food under a 12/12 light regime.

Demyelination was induced by chronic oral administration of a 0.3% aqueous solution of cuprizone, which was given to the rats instead of drinking for 3 weeks. To assess the effect of thyroid hormones, group III animals received L-thyroxine at a dose of 1.5 µg/kg. To create experimental hypothyroidism, we used the propylthiouracil model. Propylthiouracil (PTU) was used as a 0.02% aqueous solution. According to the calculated data, each animal received approximately 0.78 mg PTU per 100 g of body weight per day.

The experimental animals were weighed before the start of the study and 7, 14 and 21 days after the start of Cuprizone intake, since weight loss is one of the manifestations of the toxic effect of Cuprizone on the animal body. Control rats were weighed at the same time. It was found that after the completion of the cuprizone intake, the rats of all the studied groups lost weight ( $p < 0.05$ ).

To study the behavioral response in animals, we used the "open field" test, which is one of the adequate criteria for assessing motor disorders when using neurotoxins, including cuprizone [4].

The test also makes it possible to assess exploratory and emotional activity in animals. In rats, the number of crossed squares (horizontal locomotor activity, HLA), vertical stands with support and without support on the wall (vertical locomotor activity, VLA), mink reflex, and emotional behavior were recorded for three minutes. The mink reflex, together with VLA, characterizes the research activity of the animal. Behavior was assessed before and three weeks after cuprizone consumption.

For morphological studies of the central nervous system, histological sections of the brain (cortex) and spinal cord (lumbar region) with toluidine blue (according to Nissl) were used. This dye binds to membrane structures, which allows at the level of light microscopy to diagnose the state of the nucleus and cytoplasm of neurons, namely the chromatophilic substance. In this analysis, we determined the proportion of unchanged neurons and the proportion of neurons with various structural changes, which manifested themselves in the form of changes in the shape of the body and nucleus of the neuron, the peculiarities of the placement of the chromatophilic substance.

All structural changes can be subdivided into moderate and pronounced. Moderate disorders are characterized by displacement of the nucleolus to the nuclear envelope and an increase in the size of the nucleus, hypochromic cytoplasm, the chromatophilic substance is not detected. Severe neuronal disorders are destructive changes characterized by a decrease in the size of the nucleus with irregular contours, without a visualized nucleolus.

Morphological studies in the studied groups of rats were carried out three weeks after the start of the experiment.

Student's t-test was used for statistical analysis of the results.

**Results and discussion.** In the rats of the main study groups, deviations of the initial behavior from the control group were revealed. After taking cuprizone in rats of the "Demyelination" and "Hypothyroidism" groups, practically all studied behavioral reactions (horizontal activity, vertical activity, research and emotional activity) were inhibited. The decrease was especially pronounced in the "Hypothyroidism" group (Fig. 2-4).

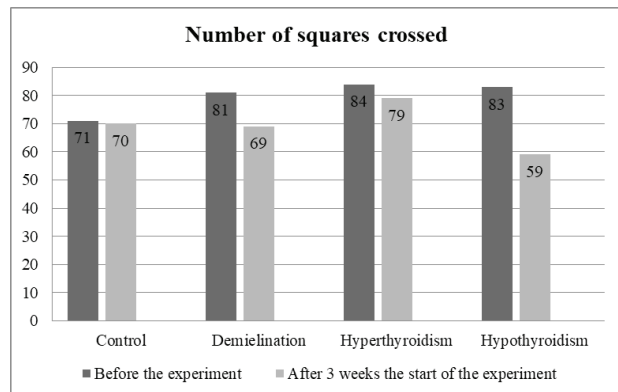


Fig. 2. Influence of cuprizone on the number of squares crossed in the open field test

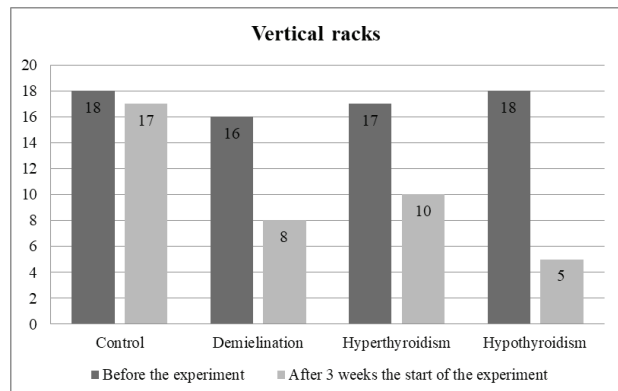


Fig. 3. Influence of cuprizone on the "vertical racks" index in the open field test

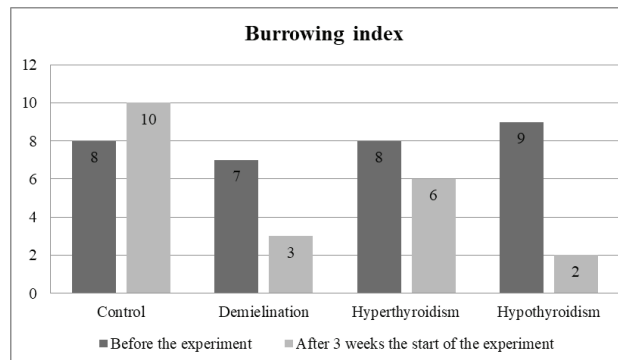


Fig. 4. Influence of cuprizone on the "burrowing" index in the open field test

According to many studies, it is believed that hypofunction of the thyroid gland inhibits the expression of genes encoding the synthesis of structural myelin proteins: myelin basic protein, proteolipid protein, myelin-associated glycoprotein, which leads to a decrease in myelin production and the number of myelinated axons. In this regard, such changes may be associated with rats in the "Hypothyroidism" group.

After taking cuprizone in the gray matter of the brain and spinal cord of rats in the groups "Demyelination", "Hyperthyroidism" and "Hypothyroidism", structural changes in neurons were revealed. The most pronounced changes were found in the "Hypothyroidism" group, the least - in the "Hyperthyroidism" group. During morphometric analysis, it was found that the structural changes in the CNS neurons in the experimental rats were of a different nature - from moderate to pronounced (destructive) (Table 2).

Table 2. Morphological changes in the cortex and lumbar spinal cord in rats after 3 weeks the start of the experiment

Group	Unchanged neurons, %	Neurons with moderate changes, %	Neurons with destructive changes, %
Cortex			
“Control” (I)	95	5	0
“Demyelination”(II)	55	40	5
“Hyperthyroidism”(III)	68	31	1
“Hyperthyroidism”(IV)	43	50	7
Lumbar spinal cord			
“Control” (I)	95	5	0
“Demyelination”(II)	78	20	2
“Hyperthyroidism”(III)	80	20	0
“Hyperthyroidism”(IV)	60	35	5

We observed significant neuronal damage, which characterizes apoptosis, in the “Hypothyroidism” group, which indicates deeper pathological changes in cells. In this case, neuronal degeneration may be associated with the activation of microglia, which secretes pro-inflammatory cytokines, which are the pathogenetic link in multiple sclerosis. There is also the development of oxidative stress in the nervous system.

The results of morphological studies in rats are largely consistent with the data on the assessment of behavioral reactions, which is associated with the physiological characteristics of those parts of the central nervous system that were studied in this work. In providing motor activity, motor neurons of the spinal cord interact with the cerebral cortex. The results of disturbed functioning of the cerebral cortex are changes in HLA and VLA. Also, the cerebral cortex, together with the hypothalamus and the limbic system, is the main component of the emotional manifestation of behavioral reactions. We can assume that the manifestations of motor disorders and emotional behavior that develop in conditions of taking cuprizone are the result of not only demyelination of the central nervous system, but are also associated with damage to the neurons of the brain and spinal cord.

In this work, we saw that rats receiving both cuprizone and L-thyroxine had higher rates in behavioral responses and had fewer morphological changes in the brain and spinal cord compared to the Demyelination and Hypothyroidism groups. This fact may indicate the myelin and axonoprotective properties of this substance.

**Conclusion.** In rats, under the influence of cuprizone, behavioral reactions are inhibited and changes in the structures of neurons in the cerebral cortex and lumbar spinal cord are noted. The severity of these disorders also depends on the thyroid status of the rat organism. In the normal hormonal balance, less significant changes are noted, when in a state of hypofunction these disorders are more pronounced. The Cuprizone model of demyelination is an adequate experimental model of neurodegeneration and behavior disorders, and thyroid hormones can be considered as one of the components of new drugs aimed at treating multiple sclerosis.

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## SUMMARY

### THYROID STATUS: IS IT POSSIBLE TO RESTORE MYELIN?

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The number of demyelinating diseases of central nervous system are prone to grow nowadays. The most socially significant and well studied one is multiple sclerosis. The search of substances that would stop demyelination or reinforce the process of remyelination is in great request. Thyroid gland hormones play a sufficient role in nervous system functioning and developing. Some studies show, that triiodothyronine regulates myelin synthesis through thyroid-sensitive nuclear receptors. In our study process of demyelination were modelled via cuprizone model, which appears to be an optimal method, since it allows to witness the process of demyelination without an autoimmune component. Results of the study show effectiveness of thyroid hormones for myelin and axon protection. In rats, under the influence of cuprizone, behavioral reactions are inhibited and changes in the structures of neurons in the cerebral cortex and lumbar spinal cord are noted. The severity of these disorders also depends on the thyroid status of the rat organism. In the normal hormonal balance, less significant changes are noted, when in a state of hypofunction these disorders are more pronounced. The cuprizone model of demyelination is an adequate experimental model of neurodegeneration and behavior disorders, and thyroid hormones can be considered as one of the components of new drugs aimed at treating multiple sclerosis.

**Keywords:** thyroid status, demyelination, cuprizone, multiple sclerosis.

## РЕЗЮМЕ

### ТИРЕОИДНЫЙ СТАТУС ЩИТОВИДНОЙ ЖЕЛЕЗЫ: МОЖНО ЛИ ВОССТАНОВИТЬ МИЕЛИН?

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В настоящее время наблюдается увеличение числа заболеваний, сопровождающихся демиелинизирующими поражениями ЦНС. Наиболее социально значимым и наименее изученным среди них является рассеянный склероз.

Цель исследования - изучить влияние гормонов щитовидной железы на процессы ремиелинизации у крыс на купризонной модели рассеянного склероза в сравнении с процессом гипотиреоза.

Объектом исследования служили половозрелые крысы-самцы (4-4,5 мес.) линии Вистар массой 180-300 г (n=35).

Эксперимент проводился на базе кафедры фармакологии и фармации Северо-Западного государственного медицинского университета им. И.И. Мечникова Минздрава России. Животные разделены на 4 группы: I группа - «контроль» (n=5); II группа - «демиелинизация» (только купризон, n=10); III группа - «гипертиреоз» (купризон + L-тироксин, n=10); IV группа - «гипотиреоз» (купризон + пропилтиоурацил, n=10).

Ряд исследователей считают, что трийодтиронин регулирует синтез миелина через ядерные рецепторы к тиреоидным гормонам. В проведенном исследовании процессы демиелинизации смоделированы с помощью купризонной модели, которая представляется наиболее оптимальным методом, так как позволяет рассмотреть процесс демиелинизации в отсутствии аутоиммунного компонента.

Результаты исследования показали высокие миелино- и аксонопотективные свойства гормональных препаратов щитовидной железы.

## რეზიუმე

ფარისებრი ჯირკვლის თიროიდული სტატუსი: შესაძლებელია მიელინის აღდგენა?

დ.კაჩანოვი, გ.ატანგულოვი, ს.უსოვი, ა.ბოროდინი, ზ.გაჯიბრაგიმოვა

ი.მეჩნიკოვის სახ. ჩრდილო-დასავლეთის სახელმწიფო სამედიცინო უნივერსიტეტი, სანკტ-პეტერბურგი, რუსეთის ფედერაცია

კვლევის მიზანს წარმოადგენდა ფარისებრი ჯირკვლის ჰორმონების გავლენის შეფასება რემიელინიზაციის პროცესებზე ვირთავებში გაფანტული სკლეროზის კუპრიზონული მოდელით ჰიპოთირეოზის პროცესთან შედარებით.

კვლევის ობიექტებს წარმოადგენდა Wistar-ის ხაზის ზრდასრული, 180-300 გრ მასის, მამრი ვირთავები (4-4.5 თვის ასაკის; n=35). ექსპერიმენტები ჩატარდა ი.მეჩნიკოვის სახ. ჩრდილო-დასავლეთის სახელმწიფო სამედიცინო უნივერსიტეტის ფარმაკოლოგიისა და ფარმაციის კათედრის ბაზაზე. ცხოველები დაიყო 4 ჯგუფად: I - საკონტროლო (n=5), II - "დემიელინიზაცია" (მარტო კუპრიზონი, n=10), III - "ჰიპერთირეოზი" (კუპრიზონი + L-თიროქსინი, n=10), IV - "ჰიპოთირეოზი" (კუპრიზონი + პროპილთიოურაცილი, n=10).

ზოგიერთი მკვლევარი მიიჩნევს, რომ ტრიოიდთირონინი მიელინის სინთეზს არეგულირებს თიროიდული ჰორმონების მიმართ მგრძობიარე ბირთვული რეცეპტორების გზით. ჩატარებულ კვლევაში დემიელინიზაციის პროცესები მოდელირებულია კუპრიზონული მოდელის საშუალებით, რომელიც ყველაზე ოპტიმალურ მეთოდს წარმოადგენს, იძლევა რა დემიელინიზაციური პროცესების კვლევის საშუალებას აუტოიმუნური კომპონენტის არსებობის გარეშე.

კვლევის შედეგებით ნაჩვენებია ფარისებრი ჯირკვლის ჰორმონული პრეპარატების მაღალი მიელინოდა აქსონოპროტექტორული თვისებები.

LOSS OF CAS3 AND INCREASE OF BAX EXPRESSION ASSOCIATED WITH PROGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Apoptosis plays the critical role in the maintenance of tissue homeostasis in human body [1]. In addition, it has been shown that deregulated apoptosis plays the major role in human cancer development, including cervical cancer [1]. Morphologically, apoptosis is characterised with the formation of small, spherical, membrane bound organelles, which are known as apoptotic bodies [2].

Apoptosis represents the tightly regulated process, in which several different families or proteins are involved, including the proteins of Bcl2 and Caspase family [1]. Bcl2 associated X gene, so called BAX gene represents the pro-apoptotic member of Bcl2 family, which is shown to be deregulated during the progression of different cancers [3]. The role of BAX in the progression of cervical intraepithelial neoplasia and cervical cancer less known.

Caspase 3 (Cas3) protein represents, the important member of cysteine-aspartic acid protease family, which plays the major role in the executive phase of apoptosis [4]. It has been suggested that caspase activity is related to the aggressive features of cancer cells, including cervical cancer, which is developed from grade 1 to 3 cervical intraepithelial lesions. It has been shown that Cas3 activity is deregulated during the progression of cervical cancer. Particularly, in 16% of CIN3 cases it is upregulated and in 28% of CIN3 cases it is downregulated, whilst it is gradually decreased in the progression of cervical carcinoma from stage I to stage II-IV [5]. The changes of Cas3 in cervical intraepithelial lesions is not very well studied.

The aim of our study was to evaluate the apoptotic activity the progression of cervical intraepithelial neoplasia, using Cas3 and BAX proteins and to decipher their association with the expression of proliferation marker Ki67 and ER.

**Material and methods.** Formalin fixed and paraffin embedded tissue material was retrieved from the Research, Diagnostic and Teaching Laboratory of Tbilisi State Medical University, Georgia. Study included altogether 140 tissue samples, divided into two major groups: cases without co-infections (n=54) and cases with co-infections (n=86). Co-infections included *bacte-*

*rial vaginosis, chlamydia trachomatis and candida albicans.* Cases without co-infections were divided into following subgroups: normal cervix (10 cases), CINI (18 cases), CINII (14 cases), CINIII (7 cases), invasive carcinoma (5 cases); Cases with co-infections were divided into following subgroups: cervix with only infections (15 cases), CINI (29 cases), CINII (19 cases), CINIII (15 cases), invasive carcinoma (8 cases).

4µ FFPE tissue sections were deparaffinized in xylene, rehydrated by using serial dilutions of ethanol (96%, 80%, 70%) and heat mediated antigen retrieval has been performed. Ready to use antibodies against the following antigens were used: Ki67, Cas3, BAX and ER. Staining and visualisation has been performed using Bond polymer refine detection system. The expression of all markers was evaluated as the percentage of marker positive cells.

Comparisons between groups were made using Kruskal-Wallis test. The Kruskal-Wallis test is a nonparametric (distribution free) test, and is used when the assumptions of one-way ANOVA are not met. The Kruskal-Wallis test can be used for both continuous and ordinal-level dependent variables. Correlations were assessed using Spearman's rank correlation. The Spearman's rank correlation is also used when data is non-parametrically distributed. P values <0.05 were considered as significant. All statistical tests were performed using SPSS software V20.00.

**Results and discussion.** The study of Cas3 in specimens without co-infections indicated that, the average pro-apoptotic index was 56±10.2 in normal cervix, 44±4.9 in CINI, 31±5.6 in CINII, 22±4.4 in CINIII and 9±2.3 in cervical invasive carcinoma. The study of BAX indicated that the average BAX index in normal cervix was 7±2.2, in CINI it was 16±3.9, in CINII it was 19±5.2, in CINIII it was 24±7.6 and in cervical invasive carcinoma it was 55±9.8. The proliferation index measured as Ki67 labelling index was following: 4±1.2 in normal cervix, 13±5.2 in CINI, 15±6.9 in CINII, 20±5.1 in CINIII and 35±10.6 in invasive carcinoma. The average ER distribution was 19±2.2 in normal cervix, 21±5.7 in CINI, 24±5.7 in CINII, 11±3.4 in CINIII and 6±1.1 in invasive carcinoma of the cervix.

Table 1. Distribution apoptotic, proliferation and ER markers in cervical lesions without co-infections. CA, carcinoma









































	Without co-infection			
	Cas3	Bax	Ki67	ER
Normal cervix	 56	 7	 4	 19
CINI	 44	 16	 13	 21
CINII	 31	 19	 15	 24
CINIII	 22	 24	 20	 11
Invasive CA	 9	 55	 35	 6

Table 2. Distribution of apoptotic, proliferation and ER markers in cervical lesions with co-infections. CA, carcinoma

	With Co-infection			
	Cas3	Bax	Ki67	ER
<b>Cervix with Infection</b>	 52	 9	 6	 20
<b>CINI</b>	 43	 21	 17	 22
<b>CINII</b>	 29	 25	 21	 27
<b>CINIII</b>	 18	 30	 26	 14
<b>Invasive CA</b>	 5	 61	 42	 8

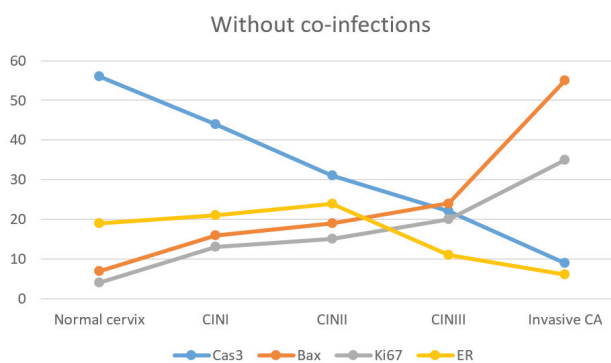
The study of pro-apoptotic marker Cas3 in specimens with co-infections indicated that, the average pro-apoptotic index was  $52 \pm 3.2$  in cervix with infections only,  $43 \pm 6.9$  in CINI,  $29 \pm 2.2$  in CINII,  $18 \pm 3.6$  in CINIII and  $5 \pm 4.1$  in cervical invasive carcinoma. The study of BAX indicated that the average BAX index in normal cervix was  $9 \pm 3.3$ , in CINI it was  $21 \pm 5.8$ , in CINII it was  $25 \pm 5.5$ , in CINIII it was  $30 \pm 6.7$  and in cervical invasive carcinoma it was  $61 \pm 10.8$ . The proliferation index measured as Ki67 labelling index was following:  $6 \pm 1.9$  in normal cervix,  $17 \pm 6.3$  in CINI,  $21 \pm 7.8$  in CINII,  $26 \pm 8.2$  in CINIII and  $42 \pm 10.7$  in invasive carcinoma. The average ER distribution was  $20 \pm 2.4$  in normal cervix,  $22 \pm 3.6$  in CINI,  $27 \pm 4.4$  in CINII,  $14 \pm 2.8$  in CINIII and  $8 \pm 3.6$  in invasive carcinoma of the cervix.

The analysis of the results indicated that the expression of pro-apoptotic protein Cas3 is progressively lost during the progression of cervical intraepithelial neoplasia in the group of without co-infections. Particularly, the expression of Cas3 is almost two-times lower in CINI and CINII compared to normal cervix and it is 3 times lower in CINIII and almost 6 times lower in cervical carcinoma. On the other hand, the expression of BAX is progressively increased during the progression of cervical intraepithelial lesions in the same group. Particularly, the expression of BAX is almost 2-times higher in CINI and CINII compared to normal cervix, 4-times higher in CINIII and almost 6-times higher in cervical CA. The distribution of Ki67 proliferation marker, it is also progressively increased during the progression of CIN. With regards to the expression of ER, the weak expression was seen in normal cervix. The expression of ER was moderate in CINI and CINII lesions, whilst it was again decreased to weak expression in

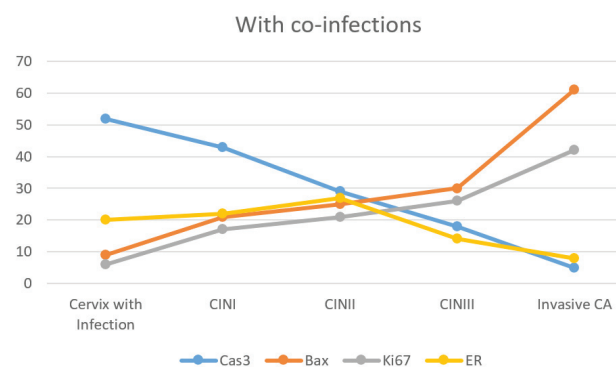
CINIII and almost negativity to cervical carcinoma. The distribution patterns of mentioned markers were similar in the groups with co-infections. However, the loss of Cas3, as well as high expression of Ki67 and the loss of ER was more pronounced in specimens with co-infections. Which might indicate that co-infections further modulate the expression of these markers and therefore playing a role during the CIN progression.

Correlation analysis, in all specimens, indicated that the expression of BAX negatively correlates with the expression of Cas3 ( $r = -42.4$ ,  $p < 0.05$ ) and ER ( $r = -33.4$ ,  $p < 0.05$ ) and positively correlates with the expression of proliferation marker Ki67 ( $r = 56.3$ ,  $p < 0.05$ ).

Cervical cancer is developed from cervical pre-cancerous lesions called cervical intraepithelial neoplasia. There are three grades of CIN, including CINI, CINII and CINIII. Interestingly not all CIN lesions progress to cervical cancer and many cases of CIN undergo the spontaneous resolution. Particularly, only about 10% of patients with CINI lesion develop cervical cancer, whilst this number reaches up to 40% in case of CINIII lesions. Therefore, only morphological detection and diagnosis of different grades of CIN is not enough to predict the development of cervical carcinoma from pre-cancerous lesions and there is the need to discover the molecular markers of CIN progression. It has been shown that in the process of cervical carcinogenesis there is the deregulation of apoptosis through various mechanisms, including the accumulation of mutations and/or epigenetic changes in tumor suppression genes. In addition, the expression levels of apoptotic proteins reflect the actual status of cells apoptotic ability and it might be used as a marker for



Graph 1. The distribution of Cas3, BAX, Ki67 and ER in CIN and cervical CA without co-infections



Graph 2. The distribution of Cas3, BAX, Ki67 and ER in CIN and cervical CA with co-infections



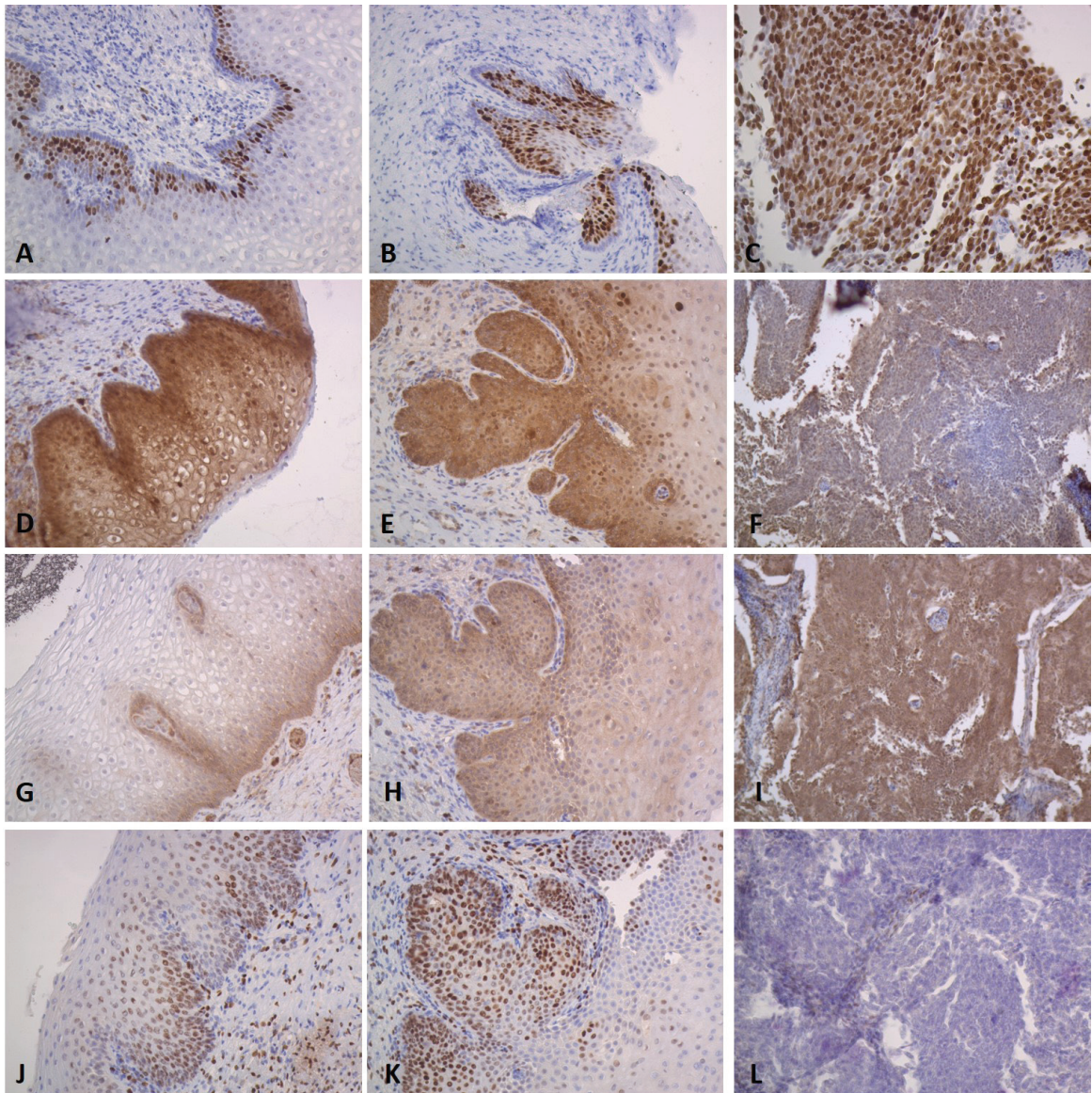


Fig. Expression of Ki67 in A. normal cervix, B. CINIII and C. in cervical CA; expression of Cas3 in D. normal cervix, E. CINIII and F. in cervical CA; expression of BAX in G. normal cervix, H. CINIII and in I. cervical CA; expression of ER in J. normal cervix, K. CINIII and L. cervical carcinoma, IHC, x200

the progression of CIN disease. The measurement of caspase activity is frequently used in experimental studies of apoptosis [6]. Therefore, it has been suggested that the expression of these proteins might also serve as biomarkers on a tissue level [7]. According to the study of Lu et al., the expression of Cas3 was significantly increased in cervical cancer compared to normal tissue [8]. Whilst the others reported that Cas3 expression is decreased in later stages of cervical cancer [5]. Therefore, the existing literature shows the conflicting results. In our study, we have shown that Cas3 is progressively lost during the progression of CIN, showing almost complete loss in cervical cancer. In addition, Cas3 expression is negatively associated with the proliferation marker Ki67 in our study. Hence, we speculate that the expression of Cas3 represents the marker of cells apoptotic potential and therefore the decrease in its expression reflects the decrease of the apoptosis, which is detected as increased proliferation of the cells in CIN and cervical cancer.

To the best of our knowledge, we are first who investigated the expression of BAX in the progression of CIN lesions and in cervical cancer and demonstrated that the expression of BAX is significantly increased at later stages of the disease. Our study is in line with one previous report regarding BAX expression in cytology smears, which showed the increased expression of BAX in abnormal smears, compared to normal smears [9]. In addition, in our study increased BAX expression was correlated to the loss of Cas3. Therefore, we suggest that in cases of Cas3 loss, the increased BAX expression might reflect the over activation of the initiation phase of apoptosis, as a result of decreased ability of cells to execute the final phase of apoptosis.

**Conclusions.** The results indicate that the increased expression of Bax and Cas3 loss, as well as the increase in proliferation index measured as Ki67 expression is significantly related to the progression of CIN into cervical carcinoma. Therefore, the measuring of mentioned protein expression could be used as the markers of the progression of CIN.

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## SUMMARY

### LOSS OF CAS3 AND INCREASE OF BAX EXPRESSION ASSOCIATED WITH PROGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Apoptosis plays one of the major roles in the progression of human cancers including cervical carcinoma. The aim of our study was to analyse the expression of Cas3, Bax and their correlation with the proliferation index and ER expression status during the progression of cervical intraepithelial neoplasia (CIN). Study included altogether 140 specimens, divided into two major groups, such as: cervical lesions without co-infections and with co-infections. Standard immunohistochemistry was used to detect antigens: Ki67, Cas3, Bax and ER. The study results showed that the expression of Cas3 is significantly decreased whilst the expression of Bax is significantly increased during the progression of CIN in both groups with and without co-infections. The expression of Bax negatively correlates with the expression of Cas3 ( $r=-42.4$ ,  $p<0.05$ ) and ER ( $r=-33.4$ ,  $p<0.05$ ) and positively correlates with the expression of proliferation marker Ki67 ( $r=56.3$ ,  $p<0.05$ ). The results indicate that the deregulated apoptosis measured as increased expression of Bax and Cas3 loss, as well as the increase in proliferation index measured as Ki67 expression is significantly related to the progression of CIN into cervical carcinoma. Therefore, the measuring of mentioned protein expression could be used as the markers of the CIN progression.

**Keywords:** CAS3 and BAX proteins; Co-infections; Cervical Lesions.

## РЕЗЮМЕ

### ПОТЕРЯ CAS3 ДОСТОВЕРНО АССОЦИИРУЕТСЯ С ПРОГРЕССИЕЙ ИНТРАЭПИТЕЛИАЛЬНЫХ НЕОПЛАЗИЙ ШЕЙКИ МАТКИ

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Апоптоз играет значимую роль в прогрессии процесса многих видов карцином, в том числе и карцином шейки матки.

Целью исследования явилось изучение экспрессии про-апоптозного белка Cas3 и анти-апоптозного белка Bax в процессах прогрессии интраэпителиальных неоплазий шейки матки и их корреляционных связей с экспрессией маркеров Ki67 и ER. Исследования проведены на 140 образцах тканей, разделенных на 2 основные группы: поражения шейки матки с наличием инфекции ( $n=86$ ) и без инфекции ( $n=54$ ). Стандарным иммуногистохимическим методом изучены молекулярные маркеры Ki67, Cas3, Bax и ER.

Результаты исследования показали, что в процессе прогрессии интраэпителиальных неоплазий шейки матки экспрессия про-апоптозного белка Cas3 значительно уменьшается, а экспрессия анти-апоптозного белка Bax значительно увеличивается в обеих группах. Экспрессия Bax находится в негативной корреляционной связи с экспрессией Cas3 ( $r=-42.4$ ,  $p<0.05$ ) и ER ( $r=-33.4$ ,  $p<0.05$ ) и в позитивной корреляционной связи - с экспрессией Ki67 ( $r=56.3$ ,  $p<0.05$ ).

Результаты исследования выявили увеличение экспрессии Bax и потерю Cas3, также увеличение пролиферативного индекса Ki67, что достоверно связано с процессом прогрессии интраэпителиальных неоплазий шейки матки в карциному. Следовательно, экспрессию данных белков возможно использовать как маркер прогрессии интраэпителиальных неоплазий шейки матки.

## რეზიუმე

Cas3-ის დაკარგვა და BAX-ის მომატებული ექსპრესია სარწმუნოდ ასოცირდება საშვილონოს ყელის ინტრა-ეპითელური ნეოპლაზიების პროგრესიასთან

გ.ფხაკაძე, ზ.ბოხუა, თ.ასათიანი, თ.მუზაშვილი, გ.ბურკაძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

აპოპტოზი მნიშვნელოვან როლს თამაშობს მრავალი ტიპის კარცინომის, მათ შორის საშვილონოს ყელის კარცინომის პროგრესიის პროცესში.

კვლევის მიზანს წარმოადგენდა პრო-აპოპტოზური ცილა Cas3-ის და ანტი-აპოპტოზური ცილა Bax-ის ექსპრესიის შესწავლა საშვილონოს ყელის ინტრა-ეპითელური ნეოპლაზიების პროგრესიის პროცესში და მათი კორელაციური კავშირის დადგენა პროლიფერაციული მარკერების Ki67-ის და ER-ის ექსპრესიასთან.

კვლევაში გამოყენებული იყო ქსოვილის 140 ნიმუში, რომელიც გაყოფილი იყო 2 ჯგუფად: საშვილონოს

ყელის დაზიანებები ინფექციით (n=86) და ინფექციის გარეშე (n=54). სტანდარტული იმუნოჰისტოქიმიური მეთოდით გამოვლენილია მარკერები: Ki67, Cas3, Bax და ER.

კვლევის შედეგებმა აჩვენა, რომ პრო-აპოპტოზური ცილის Cas3-ის ექსპრესია მნიშვნელოვნად მცირდება, ხოლო ანტი-აპოპტოზური ცილის Bax-ის ექსპრესია იზრდება საშვილონოს ყელის ინტრაეპითელური ნეოპლაზიების პროგრესიის პროცესში ორივე საკვლევე ჯგუფში. Bax-ის ექსპრესია ნეგატიურ კორელაციაშია Cas3-ის (r=-42.4, p<0.05) და ER ექსპრესიებთან (r=33.4,

p<0.05) და პოზიტიურ კორელაციაშია პროლიფერაციული მარკერის Ki67-ის ექსპრესიასთან (r=56.3, p<0.05). კვლევის შედეგებმა გამოავლინა, რომ Bax-ის მომატებული ექსპრესია და Cas3-ის დაკარგვა, ისევე როგორც მომატებული Ki67 პროლიფერაციული ინდექსი სარწმუნოდ არის დაკავშირებული საშვილონოს ყელის ინტრაეპითელური ნეოპლაზიების კარცინომად პროგრესიასთან. შესაბამისად, აღნიშნული ცილების ექსპრესია შესაძლებელია გამოყენებული იყოს საშვილონოს ყელის ინტრაეპითელური ნეოპლაზიების პროგრესიის მარკერად.

## MORPHOLOGICAL CHARACTERISTICS OF SMALL INTESTINE MUCOSA IN DYSBIOSIS AND AFTER ITS CORRECTION BY PROBIOTICS AND ENTEROSORBENTS

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Through the recent years, the world medical community has been demonstrating an increasing interest in studying normal human microbiota. Nowadays the term “normal microbiota” is more commonly replaced by the term “microbiome”, proposed in 2001 by an American geneticist Joshua Lederberg [1]. The human microbiome is known to be involved in some essential biological processes: it protects against harmful germs and compounds; it produces considerable impact on the structural and functional state of the internal organs, on the immune system, as well as plays an important role in regulating some vital functions. It should be emphasized that the advance in studying microbiome and its role in maintaining human overall health is considered as one of the key achievement in modern biology and medicine. The editorial board of one of the most significant and authoritative scientific journals, *Science*, has acknowledged the study of the human microbiome as one of the greatest scientific successes in the first decade of the 21st century [2-5].

Considering the importance of the microbiome for human health, the issue of its physiological functioning is attracting a growing attention from researchers and practitioners. Recent scientific reports have convincingly shown that from 70% to 90% of the world population suffers from dysbiosis of varying degrees that, undoubtedly, corroborates their social and environmental significance [6,7]. At present, dysbiosis is defined as a state of imbalance in the microbial ecosystem, i. e. there is simultaneous impairment of the normal functioning and mechanisms of interacting between its major components: a macroorganism and indigenous microbiota associated with the mucous membranes of the cavities and skin [8].

Among the numerous causes of dysbiotic disorders, the use of chemotherapeutic antimicrobials, often of broad-spectrum action and for per-oral administration, is ranking the top position. Especially dangerous in this regard is the use of antibiotics for prophylactic purposes [9]. However, some other groups of medicines can also contribute to the development of dysbiosis by affecting the kinetics of the mucosal epithelium and, accordingly, the mucin composition. This group may include non-steroidal

anti-inflammatory drugs, laxatives, cholagogues, coating agents with adsorbing properties and some others [10]. Irrational, baseless and often uncontrolled use of antibacterial agents in medical practice leads to artificial selection of polyresistant strains of opportunistic microorganisms.

The last decade has been marked by a considerable increase in the interest of healthcare representatives of fields to develop new approaches and to improve existing ones towards the correction of dysbiotic conditions. Among them, the concept of probiotic supplementation is occupying a leading position. According to the WHO definition, probiotics are «microorganisms, which when administered in adequate amounts, confer a health benefit on the host organism» [11]. In recent years, there has been a growing interest in both fundamental and clinical research of probiotics. The mechanisms responsible for various effects produced by probiotics are usually associated with the ability of probiotics to inhibit the development of pathogenic microbes, to demonstrate immunomodulatory properties, to stimulate the proliferation and differentiation of epithelial cells, and to promote the intestinal barrier [12].

At the same time, an imbalance in microbial ecology, as a rule, results from the contamination of the internal body environment with toxic compounds of both exogenous and endogenous nature; therefore, some types of enterosorbents can be attributed to beneficial agents for microflora normalization. The mechanism of their action is largely due to the sanitation of the intestinal lumen resulting in the improved condition for the vital activity of the physiological microbiota. Enterosorption is a non-invasive method of efferent therapy and, when an adequate sorbent selected, can promote effective cleansing the body of allergens, mediators, by-products of allergic or inflammatory processes, metabolites, toxins, viruses and other components. Improvement of biotopes is able to optimize the conditions for normal human microflora functioning [13 - 15]. In the face of increasing resistance to antibacterial agents, the addition of enterosorbents in the integrated therapy of dysbioses is an important and pathogenetic-based approach.

In recent years, much attention has been paid to enterosorbents based on clay minerals, among which bentonite clays have been the most studied. Bentonite itself is a natural clay polymineral by 60-70% composed of minerals of the montmorillonite group. The minerals in this group are characterized by extremely tiny particles, high hydration when moisturized and the ability to form highly viscous sols and gels. Today, bentonites are referred to as so-called «edible» minerals with proven anti-inflammatory, antitoxic and ion-metabolic properties [10].

This study was aimed to determine the effectiveness of the administration of probiotics and enterosorbents for the prophylaxis of morphological and functional changes in the small intestine mucosal layer of mice under the conditions of antibiotic-induced dysbiosis.

**Material and methods.** The study was carried out on *BALB / c* line white laboratory mice (n=100), bred in the vivarium of O. O. Bohomolets National Medical University. The laboratory animals were kept in accordance with the current Sanitary Rules for the organization, equipment and maintenance of experimental and biological clinics (vivaria), on a standard diet consisting of granular compound formula feed for laboratory animals (PKP 1-24 recipe). All the manipulations with the animals were carried out in accordance with the Law of Ukraine “On the Protection of Animals from Cruelty” and in accordance with the “Ethical Rules and Regulations for Working with Laboratory Animals” dated 21.02.2006 No. 3447-IV [16].

All the test animals were divided into 4 groups (20 animals in each group): group 1 (the control one) included 20 mice, who received ordinary tap water (mice in health); group 2 included the animals, which received ampicillin in a dose of 10 mg, metronidazole in a dose of 10 mg, and gentamicin in a dose of 2.9 mg intragastrically with using a tuberculin syringe with thicker needle per day for 5 days; group 3 included the animals, which received ampicillin in a dose of 10 mg, metronidazole in a dose of 10 mg, and gentamicin in a dose of 2.9 mg per day for 5 days and at the same time “SIMBITER® M concentrated”, which contained concentrated biomass of living cells of probiotic microorganisms (lactobacilli -  $1,0 \times 10^{10}$ , bifidobacteria -  $1,0 \times 10^{10}$ , lactic acid streptococci -  $1,0 \times 10^9$ , propionic bacteria -  $1,0 \times 10^8$ , and acetic acid bacteria -  $1,0 \times 10^6$  CFU / g) intragastrically per day for days; group 4 was made up of the animals receiving antibacterials (ampicillin in a dose of 10 mg, metronidazole in a dose of 10 mg and gentamicin in a dose of 2.9 mg intragastrically per day for 5 days in combination with Symbiogel enterosorbent, which contained bentonite (500 mg) and drinking water ( $9.5 \text{ cm}^3$ ).

The course of injecting probiotics and enterosorbents lasted 5 days. The maximum single volume of solution for intragastric administration to the animals was 200  $\mu\text{l}$ , the maximum daily volume of solution for intragastric administration was 400  $\mu\text{l}$ . In addition, these antibiotics were added to the water bowl (1 g of ampicillin, 1 g of metronidazole, and 290 mg of gentamicin per 1000 ml of water).

The animals were euthanized by cervical vertebrae dislocation on the 5<sup>th</sup> day since the beginning of dysbiosis modelling. Samples of the small intestine, liver, and spleen were taken to be processed for electron microscopy. The pieces of these organs sized 1  $\text{mm}^3$  were first fixed in a buffered glutaraldehyde solution for 1 h, then, after washing with buffer, they were fixed in buffered 1% osmium tetroxide solution for 1 h. The samples were dehydrated in ascending ethanol grades; acetone can also be used. Then the materials were embedded into a mixture of epoxy resins (epon and araldite) and being polymerized at +60°C for 36 hours. The sections were obtained by using a glass

knife on ultramicrotome (LKB III Sweden) and examined by using a PEM-125 electron microscope (Ukraine). Before microscopy, sections were contrasted with uranyl acetate and lead citrate according to the standard procedure [17].

To determine qualitative and quantitative composition of intestinal luminal microbiome, animals' faeces were studied. Bacteria were isolated and identified with using appropriate media: Endo, Bifidobacterium agar (Himedia), MRS Agar (Himedia), manufactured in India. Microorganisms were extracted from faecal with sterile saline using a serial dilution method followed by culture inoculation on nutrient media. The cultivation lasted for 24-36 hours at 37 ° C. Anaerobic conditions were created for bifidobacteria using micro-anaerostats with the “Gas Generating Box” system. Reference strains of microorganisms: *Staphylococcus aureus B-918* and *Escherichia coli B-906* were used as the test cultures.

The statistical processing of the findings obtained was carried out with the software for statistical data processing Microsoft Excel 2016 and “Statistica 5.5” (the Vinnytsya National Medical University, licensed number AXXR910A374605FA). Probability analysis was performed by Student's t-test. The difference between the values was considered as statistically significant with a probability of null hypothesis less than 5% ( $p < 0.05$ ).

**Results and discussion.** Through the process of dysbiotic disorder modelling in the control group of animals, bacteriological studies revealed a normal microbiological background (*E. coli* were in the range  $7.6 \times 10^3 - 4,2 \times 10^4$  CFU / g, *Lactobacillus spp.* were in the range  $8,8 \times 10^6 - 2,6 \times 10^7$  CFU / g, and *Bifidobacterium spp.* were in the range  $9.2 \times 10^7 - 2.4 \times 10^8$  CFU / g). However, on the day 5 after the start of antibiotic administration, the mice were found out to have a decrease in the number of all test microorganisms by one or two orders (Fig. 1).

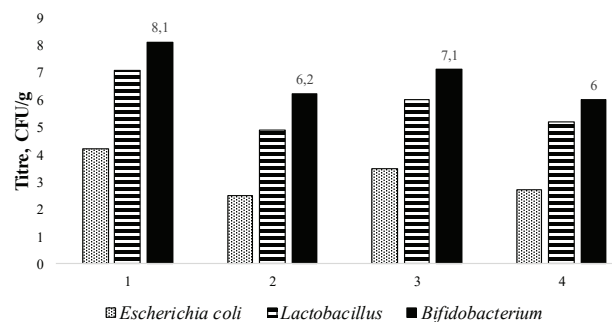


Fig. 1. The composition of the intestinal luminal microflora in the mice in health – control group (1), in the mice with impaired microflora composition induced by antibiotics – group 2 (2), in the mice with impaired microflora composition induced by antibiotics with following probiotic correction – group 3 (3), in the mice with impaired microflora composition induced by antibiotics with following sorbent correction – group 4 (4)

In the test group including the mice, which were administered probiotics, the microbiological parameters also changed, but they were not as pronounced as in the group, which received injected antibiotics alone: *E. coli* were in the range  $1.8 \times 10^3 - 6.2 \times 10^3$  CFU / g, *Lactobacillus spp.* were in the range  $7.4 \times 10^5 - 3.6 \times 10^6$  CFU / g, and *Bifidobacterium spp.* were in the range  $8.2 \times 10^6 - 3.0 \times 10^7$  CFU / g. While in the group of the animals treated with enterosorbents, we recorded more pronounced disturbances in the gut microbiocenosis: *E. coli* were in the range  $4.2 \times 10^2 - 9.3 \times 10^2$  CFU / g, *Lactobacillus spp.* were in the range  $1.2 \times 10^5 - 3.0 \times 10^5$  CFU / g, and *Bifidobacterium spp.* were in the range  $8.4 \times 10^5 - 1.5 \times 10^6$  CFU / g (Fig. 1).

Thus, the described technique of modelling dysbiosis in laboratory animals allows us to obtain well-manifested intestinal dysbiosis and to indirectly detect microecological changes in faecal microflora of the mice. However, the data presented in Fig. 1 suggest the conclusion on the reduction of microecological imbalance during simultaneous administration of antibiotics and probiotics. Instead, the findings obtained following the simultaneous administration of antibiotics and sorbents showed the little difference in microbiological indices for the types of test microorganisms from the findings in the group of animals with artificially modelled dysbiotic changes.

The structural analysis of the morphological changes found in the small intestine of the mice, which received antibacterials only, as early as on the day 5 of their course revealed marked structural alterations: shortening of the microvilli and their partial reduction or destruction with subsequent decomposition (Fig. 2). Total desquamation of the microvilli was characterized by the absence of a brush border, the smoothness of the plasma membrane, the swollen mitochondria, and by the presence of autophagosomes. Some enterocytes developed apoptotic changes accompanied by shifting cells toward the basement membrane, compaction of cytoplasm and organelles, and formation of apoptotic bodies, which shifted towards the basement membrane and moved away from epithelial cells.

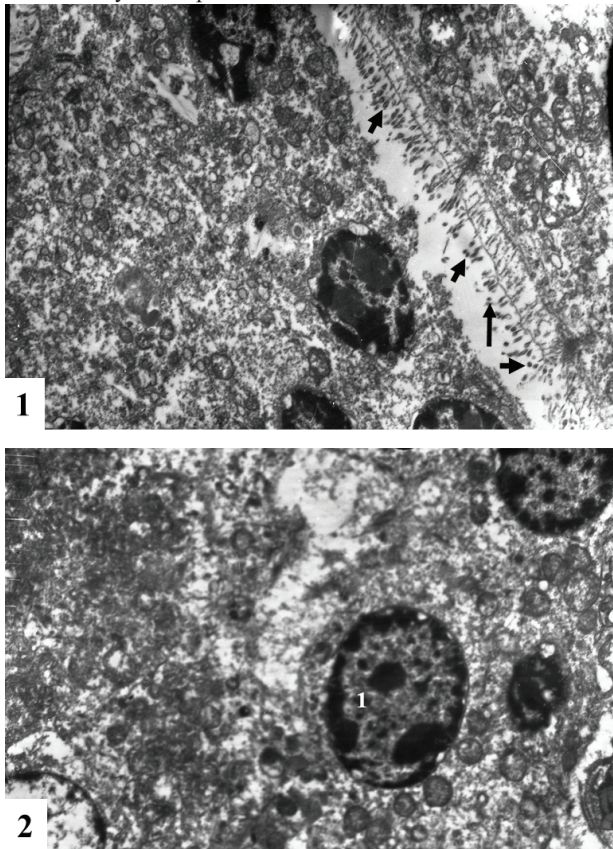


Fig. 2. Electron microphotography. 1 – Local reduction of brush border of small intestinal enterocytes in mice with antibiotic-induced dysbiosis (↑). Magnification 6200×. 2 – Apoptosis of small intestinal enterocyte (1). Magnification 8400×

Moreover, the analysis of electron microphotography showed that in antibiotic-induced dysbiosis the number of eosinophils grew. These cells are known as an indicator of allergic response because they are directly involved in the protective allergic and anaphylactic body responses.

In the mucous membrane of the small intestine in the mice treated with “Multiprobiotic SIMBITER®” (group 3) we observed a visual decrease in the severity of cytodestructive disorders, and, namely, a decrease in the number of desquamated microvilli; the vast majority of enterocytes preserved their brush border compared with the test group 2, which received antibacterials only. In this case, the desquamation of the microvilli had more local character; there was a partial absence of the brush border and no significant smoothing of the plasma membrane. The results of electron microscopy showed the local swelling of the mitochondria, the destruction of crypts and intensive formation of autophagosomes in the enterocytes in mice of the 2<sup>nd</sup> test group compared to the the group 1 (control).

At the same time, no signs of apoptosis, i. e. no shift of cells toward the basement membrane, no compaction of the cytoplasm, organelles and precursors of apoptotic bodies, or any other signs of apoptosis were recorded. The electron microscopy shows the number of Paneth cells detected was statistically higher, but some specific changes were observed in the granules of these cells: granules, which apparently containing defensins, gradually lose their contents and transform into electron-transparent granules, which can be regarded as structures are at different stages of their functional activity and, are more likely proteins. All this is evidence of the ability of probiotics when simultaneously administered with antibiotics to stimulate the body immune response. Moreover, unlike controls, no expansion of the tubules of plasma cells due to their packing with antibodies was recorded. The blood vessels showed no alterations as well (Fig. 3). Furthermore, the analysis of electron microphotographs demonstrated that due to the course of probiotics administration the number of eosinophils and basophils visually reduces.

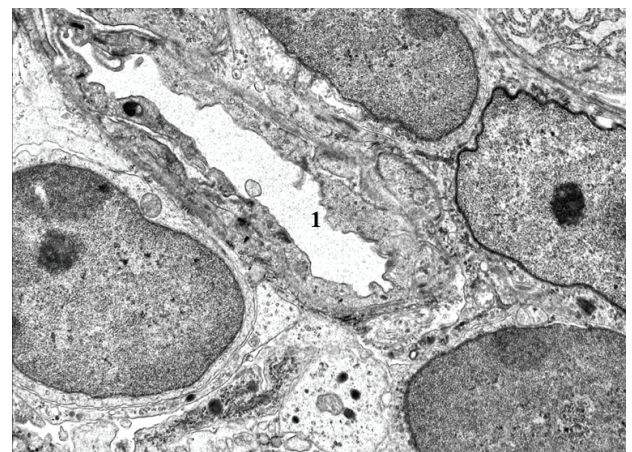


Fig. 3. Electron microphotography. No cytodestructive changes are seen in the blood capillary over the course of probiotics administration (the 6<sup>th</sup> day of the experiment). Magnification 6200×

Thus, based on the data obtained, we can not affirm that the probiotic strains introduced into mice have colonized the intestine. However, the possibility of probiotics when passing through the gastrointestinal tract to release metabolites that positively affect the intestinal barrier function should not be excluded. Nevertheless, after the probiotics administration during the antibiotic-induced dysbiosis the number of test microorganisms was nearly one order of magnitude higher, and the cytodestructive manifestations were less pronounced compared to the group where the animals received antibiotics only.

Regarding the role of enterosorbents in the prevention of dysbiotic intestinal disorders, it should be noted that despite the presence of pronounced microecological disorders developing during the course of simultaneous administration of antibacterials and sorbent, and accompanied by a decrease in the number of *colibacilli*, *lactobacilli*, and *bifidobacteria*, the morphofunctional alterations at the cellular level are specific. The results obtained by analyzing electron microscopic sections of the small intestine of the mice, which received antibacterials and enterosorbent "Symbiogel", demonstrate a less pronounced intensity of structural and morphological impairments compared with the group of animals, which received antibacterials only to induce dysbiotic disorders. Although there was a visual shortening of the length of the microvilli in some areas of the small intestinal mucosa, no cases of their complete reduction or degeneration were observed (Fig. 4).

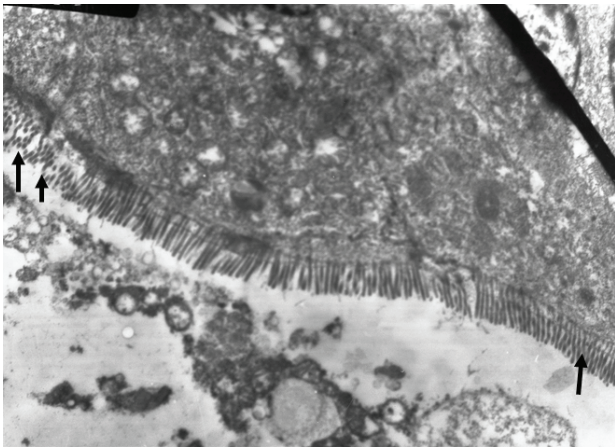


Fig. 4. Electron microphotography. Local desquamation of microvilli with partial absence of microvilli destruction (↑) and slight smoothing of plasma membrane of enterocytes after the administration of Symbiogel. Magnification 8000×

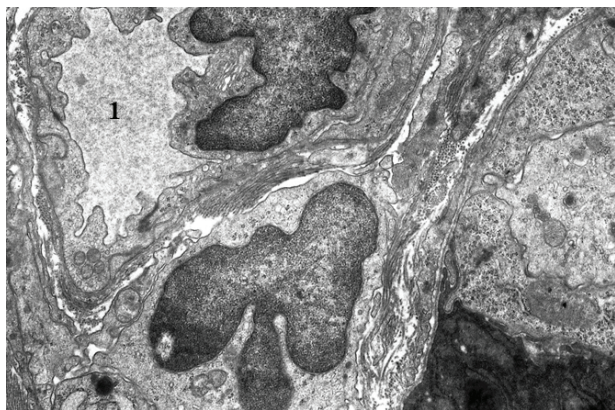


Fig. 5. Electron microphotography. No cytotoxic changes are seen in the blood capillary (1) following the application of sorbents. Magnification 6500×

Based on the data from electron microscopy, we can suggest that the course of enterosorbents results in the activation of plasma cells that is a manifestation of the inflammatory process and the immune system activation. This assumption can be confirmed by the detection of plasma cells with expanded tubules packed with antibodies. In general, it is noteworthy that the use

of sorbents during the course of modelled dysbiosis promotes the activation of the immune response compared to the use of probiotics. However, no changes in the circulatory system have been found out through the course of sorbents administration. It is likely the progression of dysbiotic disorders does not manifest itself on the level of hemomicrocirculatory bed (Fig. 5). There are no direct signs that would be indicative of the regular development of apoptosis with the formation of apoptotic bodies, which shift toward the basement membrane; sometimes pre-apoptotic cells are found. Moreover, it has been found out that following the course of sorbent administration, microbial cells are more frequently detected in the intestinal lumen.

Electron microphotographs demonstrate ultrastructure signs of the presence of proeosinophils and plasma cells in the lamina propria of the small intestinal mucosa. Thus, despite the fact that the simultaneous use of antibiotics and sorbents leads to pronounced microecological disorders of the intestinal microflora accompanied by a decrease in 1-2 orders of magnitude in test microorganisms, we should not exclude the ability of enterosorbents to promote the normalization of immune responses accompanying the progression of dysbiosis. We may suggest that enterosorbents are involved into the extraction, fixation and removal of the bacterial toxins from the gastrointestinal tract, and highly concentrated by-products of natural metabolism, activated enzymes, inflammatory mediators, biologically active substances, opportunistic microorganisms, viruses, etc. Under intestinal dysbiosis, intestinal permeability typically increases, and bacterial translocation exponentially increases.

**Conclusions.** This study has experimentally confirmed the ability of antibacterials to induce dysbiotic conditions in animals that are accompanied by significant shifts in the composition of normal microflora, manifested with cytotoxic disorders in the small intestinal epithelium (**enterocytes**).

We have demonstrated the property of probiotics and, to a lesser extent, of sorbents to reduce the intensity and extension of cytotoxic disorders in the course of antibiotic-induced dysbiosis and to normalize the body immune responses that accompany the development of dysbiotic conditions.

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## SUMMARY

### MORPHOLOGICAL CHARACTERISTICS OF SMALL INTESTINE MUCOSA IN DYSBIOSIS AND AFTER ITS CORRECTION BY PROBIOTICS AND ENTEROSORBENTS

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This study was aimed at investigating morphological and functional changes in the small intestine mucosal layer of mice with antibiotic-induced dysbiosis and following its correction with probiotics and enterosorbents.

The study was carried out on *BALB / c* line white laboratory mice. Samples of the small intestine, liver, and spleen were taken to be processed for electron microscopy. To determine qualitative and quantitative composition of intestinal luminal microbiome, animals' faeces were studied. Bacteria were isolated and identified by standard methods.

This study has experimentally confirmed the ability of anti-

bacterials to induce dysbiotic conditions in animals that are accompanied by significant shifts in the composition of normal microflora, manifested with cytodestructive disorders in the small intestinal epithelium.

We have demonstrated the property of probiotics and, to a lesser extent, of sorbents to reduce the intensity and extension of cytodestructive disorders in the course of antibiotic-induced dysbiosis and to normalize the body immune responses that accompany the development of dysbiotic conditions.

**Keywords:** intestinal mucosa, antibiotic-induced dysbiosis, enterosorbents, probiotics.

## РЕЗЮМЕ

### МОРФОЛОГИЧЕСКИЕ ХАРАКТЕРИСТИКИ СЛИЗИСТОЙ ОБОЛОЧКИ ТОНКОГО КИШЕЧНИКА ПРИ ДИСБИОЗЕ И ПОСЛЕ ЕГО КОРРЕКЦИИ ПРОБИОТИКАМИ И ЭНТЕРОСОРБЕНТАМИ

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Целью исследования явилось определение морфологических и функциональных изменений в слизистой оболочке тонкой кишки мышей с антибиотик-индуцированным дисбиозом и после его коррекции пробиотиками и энтеросорбентами.

Исследование проводилось на белых лабораторных мышках (n=100) линии BALB/c. Образцы тонкой кишки, печени и селезенки взяты для исследования при помощи электронной микроскопии. Для определения качественного и количественного состава микробиоты кишечника изучали фекалии животных. Бактерии выделены и идентифицированы стандартными методами.

Проведенное исследование экспериментально подтвердило способность антибактериальных средств индуцировать дисбиотические состояния у животных, которые сопровождаются значительными сдвигами в составе нормальной микрофлоры, проявляющимися цитодеструктивными нарушениями в тонком эпителии кишечника. Авторы продемонстрировали свойство пробиотиков и, в меньшей степени, сорбентов уменьшать интенсивность и распространять цитодеструктивные нарушения в ходе антибиотик-индуцированного дисбиоза и нормализовать иммунные реакции организма, которые сопровождают развитие дисбиотических состояний.

## რეზიუმე

წვრილი ნაწლავის ლორწოვანი გარსის მორფოლოგიური მახასიათებლები დისბიოზის დროს და მისი კორექციის შემდგომ პრობიოტიკებით და ენტეროსორბენტებით

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კვლევის მიზანს წარმოადგენდა თავგების წვრილი ნაწლავის ლორწოვანი გარსის მორფოლოგიური და ფუნქციური ცვლილებების შეფასება ანტიბიოტიკ-ინდუცირებული დისბიოზის დროს და მისი კორექციის შემდგომ პრობიოტიკებით და ენტეროსორბენტებით.

კვლევა ჩატარდა BALB/c ხაზის თეთრ ლაბორატორიულ თავგებზე (n=100). წვრილი ნაწლავის, ღვიძლის და ელენთის ნიმუშების აღება ხორციელდებოდა ელექტრონული მიკროსკოპიის საშუალებით. ნაწლავის მიკრობიოტის თვისობრივი და რაოდენობრივი განსაზღვრისათვის შესწავლილი იყო ცხოველების ფეკალიები. ბაქტერიების გამოყოფა და იდენტიფიცირება განხორციელდა სტანდარტული მეთოდებით.

ჩატარებული კვლევით ექსპერიმენტულად დადასტურებულია ანტიბაქტერიული საშუალებების უნარი მოახდინოს დისბიოზური ცვლილებების ინდუცირება ცხოველებში, რასაც თან ახლავს ნორმალური მიკროფლორის მნიშვნელოვანი ძვრები, გამოვლენილი წვრილი ნაწლავის ეპითელიუმის ციტოდესტრუქციული დარღვევებით.

ავტორების მიერ დადგენილია პრობიოტიკების და ნაკლები ხარისხით – სორბენტების უნარი შეამციროს ციტოდესტრუქციული დარღვევების ინტენსივობა და გავრცელება ანტიბიოტიკ-ინდუცირებული დისბიოზის დროს და ხელი შეუწყოს ორგანიზმის იმუნური რეაქციების ნორმალიზებას თანმხლები დისბიოზური მდგომარეობების დროს.

## ИСПОЛЬЗОВАНИЕ МОЛЕКУЛЯРНОГО ВОДОРОДА В КОРРЕКЦИИ СИНДРОМА NO-REFLOW НА ПОЛИУРИЧЕСКОЙ СТАДИИ СУЛЕМОВОЙ НЕФРОПАТИИ

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Известно, что молекулярный водород имеет селективные антиокислительные, противовоспалительные и антиапоптозные свойства [10,15], тормозит проявления окислительного стресса [11], подавляет развитие атеросклероза [7], предупреждает расстройства когнитивных нарушений [16], обнаруживает гепатопротекторное влияние [12], защищает от повреждающего воздействия ишемии-реперфузии головной мозг [6], тормозит проявления аллергии [17]. H<sub>2</sub> можно использовать как эффективную антиоксидантную терапию; благодаря способности быстро диффундировать через мембраны, проникать в митохондрии [8], ядро клетки, достигать и реагировать с наиболее опасными цитотоксическими активными формами кислорода, такими как гидроксильный радикал и пероксинитрит, и, тем самым, защищать от окислительных повреждений фосфолипиды мембран, белки, ДНК, воспаления, пироптоза и апоптоза [13].

Известно, что в условиях гипонатриевого рациона питания [5], патогенез сулемовой нефропатии, как модели острого повреждения почек с дисфункцией проксимального отдела нефрона, характеризуется развитием следующих стадий нефропатии спустя 2, 24 и 72 часа, что соответствует началу, периоду олигурии и ранней полиурической стадии острой почечной недостаточности. Наибольший интерес из них представляет стадия ранней полиурии, для которой характерно развитие реперфузионного синдрома no-reflow с невосстановлением почечного кортикального кровотока после ишемии с лавинообразной активацией перекисного окисления липидов, существенным повреждением проксимального канальца, с развитием синдрома потери ионов натрия и выраженным отеком почки [4].

Цель исследования – определить возможность использования молекулярного водорода в коррекции синдрома no-reflow на полиурической стадии острого повреждения



почек спустя 72 часа после введения сулемы у крыс на гипонатриевом рационе питания.

**Материал и методы.** Опыты выполнены на 60 самцах белых нелинейных половозрелых крыс массой 0,16-0,18 кг с исследованием влияния нагрузки водой с насыщением молекулярным водородом. Сулемовую нефропатию моделировали в условиях гипонатриевой диеты путем подкожного введения 0,1% раствора хлорида ртути в дозировке 5 мг/кг с проведением исследования спустя 72 часа, что соответствовало ранней полиурической стадии острого повреждения почек и развитию синдрома *no-reflow* [4,14]. Для насыщения воды молекулярным водородом в концентрации 1,2 ppm и окислительно-восстановительным потенциалом от -100 до -350 мВ использовали генератор H<sub>2</sub> нового поколения Blue Water 900 (Корея), содержащий усовершенствованную протонно-обменную мембрану PEM/SPE, которая одновременно является твердым полимерным электролитом.

Функцию почек изучали в условиях водного индуцированного диуреза обычной водопроводной водой и водой с насыщением молекулярным водородом, для чего исследуемые жидкости в количестве 5% от массы тела с помощью металлического зонда вводили крысам в желудок с дальнейшим сбором мочи в течение 2 часов. Величину диуреза (V) оценивали в мл/2 часа x 100 г. После водной нагрузки с целью получения плазмы крови проводили эвтаназию крыс путем декапитации под легким эфирным наркозом; кровь собирали в пробирки с гепарином. В плазме крови и моче определяли концентрацию креатинина по реакции с пикриновой кислотой, ионов натрия - методом фотометрии пламени на ФПЛ-1. Скорость клубочковой фильтрации (C<sub>cr</sub>) оценивали по клиренсу эндогенного креатинина, которую рассчитывали по формуле:  $C_{cr} = U_{cr} \times V / P_{cr}$ , где U<sub>cr</sub> и P<sub>cr</sub> - концентрация креатинина в моче и плазме крови, соответственно. Экскрецию ионов натрия (ENa<sup>+</sup>) рассчитывали по формуле: ENa<sup>+</sup>=V x UNa<sup>+</sup>, где UNa<sup>+</sup> - концентрация ионов натрия в моче. Исследовали проксимальную реабсорбцию ионов натрия (T<sup>+</sup>Na<sup>+</sup>) по формуле:  $T^{+}Na^{+} = (C_{cr} - V) \times PNa^{+}$ , где PNa<sup>+</sup> - концентрация ионов натрия в плазме крови [1,3].

В корковом веществе почек определяли первичные и вторичные продукты перекисного окисления липидов: диеновые конъюгаты и малоновый альдегид [4,9]. Состояние энергетического обмена оценивали по активности сукцинатдегидрогеназы [14]. В сыворотке крови и моче определяли β2-микроглобулин методом хемиллюминисцентного анализа на автоматическом иммунохемилюминисцентном анализаторе MAGLUMI 1000 с расчетом его проксимальной реабсорбции в % [14]. Тканевой фибринолиз в почках оценивали по определению лизиса азофирина с оценкой суммарной ферментативной активности (СФА), неферментативной активности (НФА) (инкубация проб в присутствии блокатора ферментного фибринолиза ε-аминокапроновой кислоты) и ферментной фибринолитической активности (ФФА), которую рассчитывали по формуле: ФФА=СФА-НФА [4]. Проводили количественную оценку степени отека в 7 исследуемых участках почек после окраски депарафинированных срезов среднего сегмента почек гематоксилин-эозинном: Cortex I, Cortex II - субкапсулярной и юкстамедулярной участках коры почек OSOM, ISOM - внешнем и внутрен-

нем участках мозгового вещества почек IM I, IM II, IM III - участках сосочка почек методом точечного теста по Г.Г.Автандилову [4].

Все исследования выполнены в соответствии с Конвенцией Совета Европы об охране позвоночных животных, которые используются в экспериментах и других научных целях (от 18.03.1986 г.), Директивы ЕЕС №609 (от 24.11.1986 г.), указов МОЗ Украины № 960 от 23.09.2009 г. и № 944 от 14.12.2009 г.

При статистической обработке полученных результатов, соответствующих нормальному (гаусовскому) распределению использовали принятые в медицине методы вариационной статистики и рассчитывались: средняя арифметическая выборка (x), стандартная ошибка средней арифметической (Sx). При оценке достоверности различий между средними величинами вычисляли коэффициент t. Надежность (вероятность «нулевой гипотезы») при данной t и числе степеней свободы рассчитывалась по методу Стьюдента. Для утверждения вероятности разницы учитывалась общепринятая в медикобиологических исследованиях величина уровня вероятности p<0,05. При отклонении типа распределения от нормального, а также в небольших объемах выборки применялись непараметрические критерии (тест Манна-Уитни) с использованием программ “Statgrafics”, “Excel 7.0”, Statistica. Показатель вероятности на рисунках указан только для достоверных различий (p<0,05), которые отмечены соответствующими значками.

**Результаты и обсуждение.** Использование усовершенствованной протонно-обменной мембраны PEM/SPE, которая одновременно является твердым полимерным электролитом в генераторе нового поколения Blue Water 900 (Корея) дает возможность получить антиоксидантный раствор молекулярного водорода с концентрацией H<sub>2</sub>: 0,9-1,2 ppm и окислительно-восстановительным потенциалом от -100 до -350 мВ. H<sub>2</sub> является сильным антиоксидантом, в 170 раз эффективнее аскорбиновой кислоты помогает организму вырабатывать собственные антиоксиданты, в отличие от других антиоксидантов, имеет уникальное свойство проникновения в участки отека, ишемии, внутрь клетки, в митохондрии, клеточное ядро и другие органеллы клетки [11]. Применение молекулярного водорода позволило получить следующие результаты: влияние нагрузки водой с насыщением молекулярным водородом на показатели биохимического состояния коркового вещества почек в полиурическую стадию сулемовой нефропатии при развитии синдрома *no-reflow* характеризовалось антиоксидантным влиянием со снижением уровня диеновых конъюгатов и малонового альдегида (рис. 1), возрастали суммарная и ферментативная фибринолитическая активность, соотношение концентраций ионов калия к ионам натрия и снижалась степень отека.

Отмечено возрастание диуреза, скорости клубочковой фильтрации по клиренсу эндогенного креатинина, проксимальной реабсорбции ионов натрия и бета-2-микроглобулина, выявлено уменьшение проявлений синдрома потерь ионов натрия с мочой и возрастание активности фермента цикла Кребса – сукцинатдегидрогеназы в корковом веществе почек (рис. 2) в условиях влияния нагрузки водой с насыщением молекулярным водородом на полиурической стадии сулемовой нефропатии при развитии синдрома *no-reflow*.

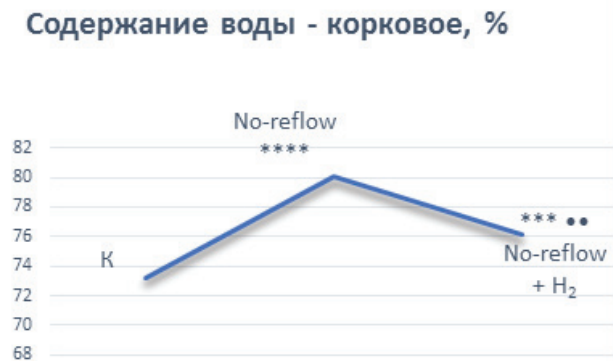
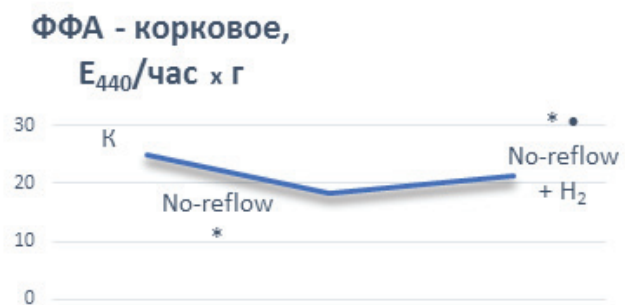
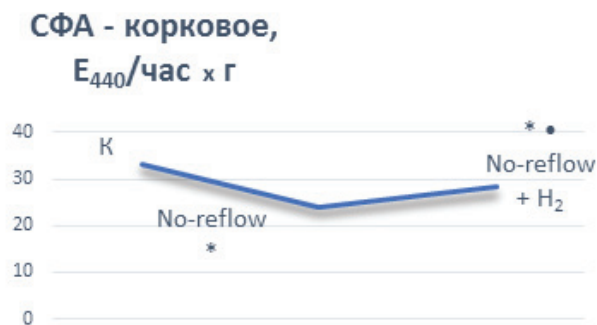
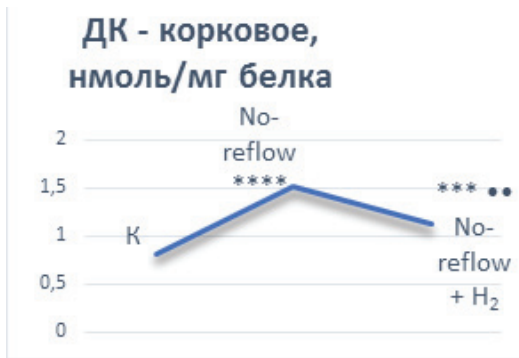


Рис. 1. Влияние водной нагрузки 5% от массы тела с насыщением молекулярным водородом 1.2 ррт на содержание воды, диеновых конъюгатов (ДК), малонового альдегида (МА), суммарную (СФА) и ферментативную (ФФА) фибринолитическую активность, соотношение K<sup>+</sup>/Na<sup>+</sup> в корковом веществе почек в условиях гипонатриевой диеты с регистрацией сбора мочи в течение 2 часов на полиурической стадии острого повреждения почек спустя 72 часа после введения сулемы с развитием синдрома no-reflow у крыс. К - контроль, интактные животные с нагрузкой обычной водопроводной водой, no-reflow – полиурическая стадия сулемовой нефропатии с развитием указанного синдрома при нагрузке обычной водопроводной водой, no-reflow + H<sub>2</sub> – полиурическая стадия сулемовой нефропатии спустя 72 часа после введения сулемы с развитием указанного синдрома при нагрузке водой с насыщением молекулярным водородом 1.2 ррт. Достоверность отличий показана в сравнении с контролем - К: \* - p<0,05; \*\* - p<0,01; \*\*\*\* - p<0,001; в сравнении с полиурической стадией острого повреждения почек спустя 72 часа после введения сулемы с развитием синдрома no-reflow при нагрузке обычной водопроводной водой - с группой no-reflow : • - p<0,05; •• - p<0,02





Рис. 2. Влияние водной нагрузки 5% от массы тела с насыщением молекулярным водородом 1.2 ppm на диурез, скорость клубочковой фильтрации ( $C_{cr}$ ), экскрецию  $Na^+$ , проксимальную реабсорбцию  $Na^+$ ,  $\beta$ -2-микроглобулина, активность сукцинатдегидрогеназы (СДГ) в корковом веществе почек в условиях гипонатриевой диеты с регистрацией сбора мочи в течение 2 часов на полиурической стадии острого повреждения почек спустя 72 часа после введения сулемы с развитием синдрома *no-reflow* у крыс. К - контроль, интактные животные с нагрузкой обычной водопроводной водой, *no-reflow* – полиурическая стадия сулемовой нефропатии с развитием указанного синдрома при нагрузке обычной водопроводной водой, *no-reflow*+ $H_2$  – полиурическая стадия сулемовой нефропатии спустя 72 часа после введения сулемы с развитием указанного синдрома при нагрузке водой с насыщением молекулярным водородом 1.2 ppm. Достоверность отличий показана в сравнении с контролем - К: \* -  $p < 0,05$ ; \*\* -  $p < 0,02$ ; \*\*\* -  $p < 0,01$ ; \*\*\*\* -  $p < 0,001$ ; в сравнении с полиурической стадией острого повреждения почек спустя 72 часа после введения сулемы с развитием синдрома *no-reflow* при нагрузке обычной водопроводной водой - группой *no-reflow* : • -  $p < 0,05$ ; •• -  $p < 0,02$

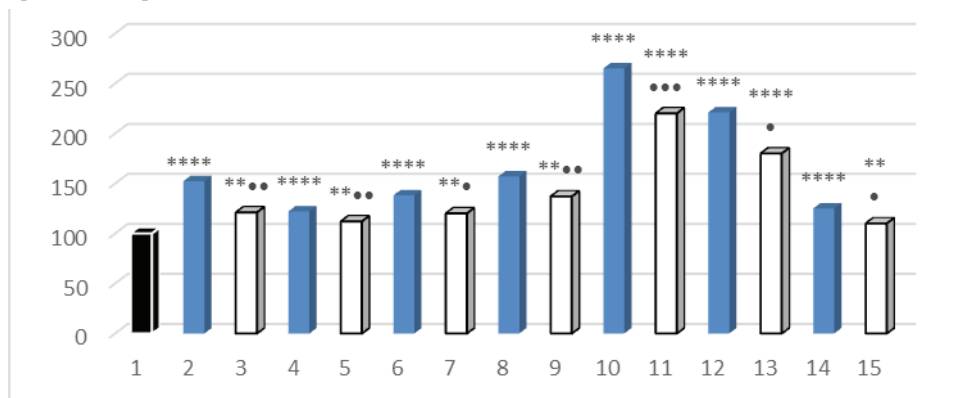


Рис. 3. Влияние водной нагрузки 5% от массы тела с насыщением молекулярным водородом 1.2 ppm на степень отека 7 слоев почки в условиях гипонатриевой диеты с регистрацией сбора мочи в течение 2 часов на полиурической стадии острого повреждения почек спустя 72 часа после введения сулемы с развитием синдрома *no-reflow* у крыс в сравнении с контролем - интактные животные с нагрузкой обычной водопроводной водой (1), принятым за 100%. 2-Cortex I, 3-Cortex I +  $H_2$ ; 4-Cortex II, 5-Cortex II +  $H_2$ ; 6-OSOM, 7-OSOM +  $H_2$ ; 8-ISOM, 9-ISOM +  $H_2$ ; 10-IM-I, 11-IM-I +  $H_2$ ; 12-IM-II, 13-IM-II +  $H_2$ ; 14-IM-III, 15-IM-III +  $H_2$ . Достоверность отличий показана в сравнении с контролем: \*\*\*\*-  $p < 0,001$ ; в сравнении с полиурической стадией острого повреждения почек спустя 72 часа после введения сулемы с развитием синдрома *no-reflow* при нагрузке обычной водопроводной водой: • -  $p < 0,05$ ; •• -  $p < 0,02$ ; ••• -  $p < 0,01$

Выявив противоотечное воздействие молекулярного водорода на уровне коркового вещества почек, определено более детальное его влияние на уровне всех 7 слоев почки, что показало достоверное снижение степени отека в 7 исследуемых участках почек: Cortex I, Cortex II - субкапсулярной и юкстамедулярной участках коры почек, OSOM, ISOM - внешнем и внутреннем участках мозгового слоя почек, IM I, IM II, IM III - участках сосочка почек в условиях влияния нагрузки водой с насыщением молекулярным водородом на полиурической стадии сулемовой нефропатии при развитии синдрома no-reflow (рис. 3).

Полиурическую стадию сулемовой нефропатии можно расценивать как развитие дисрегуляционного патологического процесса [2] с вторичным или даже третичным повреждением проксимального отдела нефрона как следствие избыточного накопления ионов натрия в крови, с развитием гиперосмии, увеличением АДГ и возрастанием влияния факторов с вазодилататорным механизмом, таким как простагландин E2, ВИП, NO,  $\alpha$ -ПНУГ, что приводит к развитию реперфузионного синдрома "no-reflow" в период спустя 72 часа после введения дихлорида ртути в условиях гипонатриевой диеты [4]. В этих условиях антиоксидантное влияние нагрузки водой с насыщением молекулярным водородом приводит к уменьшению потерь ионов натрия за счет улучшения его реабсорбции и  $\beta$ 2-микроглобулина в проксимальном канальце, что обусловлено избирательной антиоксидантной активностью молекулярного водорода по нейтрализации гидроксильного радикала и пероксинитрита [11].

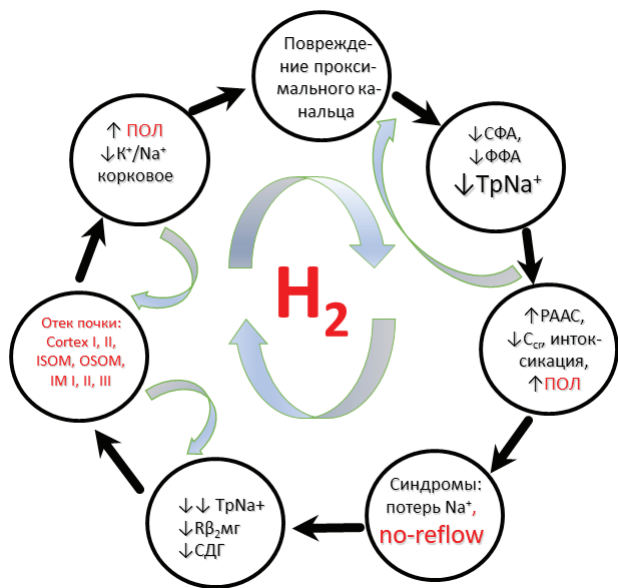


Рис. 4. Разрыв большого и малых порочных кругов повреждения проксимального отдела нефрона на полиурической стадии сулемовой нефропатии спустя 72 часа после введения дихлорида ртути у крыс гипонатриевой группы при развитии синдрома no-reflow с использованием антиоксидантных свойств молекулярного водорода

Вышепредставленными свойствами молекулярного водорода обусловлено снижение перекисного окисления липидов в корковом веществе почек, степени его повреждения по увеличению соотношения  $K^+/Na^+$  и уменьшение степени отека. Улучшение состояния проксимального отдела нефрона с увеличением продукции урокиназы привели к возрас-

танию суммарной, ферментативной фибринолитической активности в корковом веществе почек за счет антиоксидантного влияния нагрузки водой с насыщением молекулярным водородом на полиурической стадии сулемовой нефропатии при развитии синдрома no-reflow. Улучшение активности сукцинатдегидрогеназы в корковом веществе почек обусловлено увеличением доставки электронов за счет отрицательного окислительно-восстановительного потенциала и избирательного антиоксидантного влияния молекулярного водорода. Эффективное противоотечное воздействие молекулярного водорода на уровне 7 слоев почки, кроме вышеперечисленных свойств, обусловлено высокой проникающей способностью и отсутствием заряда  $H_2$ .

В результате проведенных исследований предложены точки влияния  $H_2$  относительно разрыва большого порочного круга (рис. 4).

Повреждение проксимального канальца  $\rightarrow$  снижение суммарной и ферментативной фибринолитической активности, угнетение проксимальной реабсорбции ионов натрия  $\rightarrow$  активация PАС, снижение клубочковой фильтрации, интоксикация, активация ПОЛ (антиоксидантное влияние  $H_2$ )  $\rightarrow$  задержка ионов натрия в организме, возрастание уровня АДГ с увеличением влияния факторов с вазодилататорным механизмом действия ПГЕ2, ВИП,  $\alpha$ -ПНУГ, NO, синдром no-reflow (антиоксидантное действие  $H_2$ )  $\rightarrow$  угнетение проксимальной реабсорбции ионов натрия,  $\beta$ 2-микроглобулина, снижение активности СДГ в корковом веществе почек  $\rightarrow$  отек 7 слоев почки (противоотечное действие  $H_2$ )  $\rightarrow$  активация ПОЛ, снижение соотношения  $K^+/Na^+$  в корковом веществе почки  $\rightarrow$  повреждение проксимального канальца.

Использование  $H_2$  способствует также разрыву сложившихся малых порочных кругов: повреждение проксимального канальца  $\rightarrow$  торможение суммарной и ферментативной фибринолитической активности, снижение проксимальной реабсорбции ионов натрия  $\rightarrow$  активация PАС, торможение клубочковой фильтрации, интоксикация, активация ПОЛ (антиоксидантное действие  $H_2$ )  $\rightarrow$  повреждение проксимального канальца (разрыв первого порочного круга). Торможение проксимальной реабсорбции ионов натрия,  $\beta$ 2-микроглобулина, снижение активности СДГ в корковом веществе почек  $\rightarrow$  отек 7 слоев почки (противоотечное действие  $H_2$ )  $\rightarrow$  торможение проксимальной реабсорбции ионов натрия,  $\beta$ 2-микроглобулина, снижение активности СДГ в корковом веществе почек (разрыв второго порочного круга). Отек 7 участков почки  $\rightarrow$  активация ПОЛ (антиоксидантное действие  $H_2$ ), снижение соотношения  $K^+/Na^+$  в корковом веществе почки  $\rightarrow$  отек 7 слоев почки  $\rightarrow$  (разрыв третьего порочного круга).

**Вывод.** В период формирования синдрома no-reflow у крыс на низконатриевой диете спустя 72 часа после введения сулемы показана возможность разрыва больших и малых порочных кругов антиоксидантным раствором  $H_2$  за счет высокой проницаемости и способности нейтрализовать гидроксильный радикал и пероксинитрит.

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## SUMMARY

### THE USE OF MOLECULAR HYDROGEN IN CORRECTION OF NO-REFLOW SYNDROME IN THE POLYURIC STAGE OF SUBLIMATE NEPHROPATHY

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Objective - to find out the possibility of using molecular hydrogen in the correction of no-reflow syndrome in the polyuric stage of acute kidney injury 72 hours after the administration of mercuric chloride in rats on a hyposodium diet.

The experiments were performed on 60 male white non-linear sexually mature rats weighing 0.16-0.18 kg to study the effect of water loading with saturation with molecular hydrogen. Sublimate nephropathy was modeled under conditions of a hyposodium diet by subcutaneous injection of 0.1% mercury dichloride solution at a dosage of 5 mg/kg with a study after 72 hours, which corresponded to the early polyuric stage of acute kidney injury and the development of no-reflow syndrome. To saturate the water with molecular hydrogen at a concentration of 1.2 ppm and a redox potential from -100 to -350 mV, a new generation H<sub>2</sub> generator Blue Water 900 (Korea) was used, containing an improved proton-exchange membrane PEM/SPE. Used: pathophysiological, biochemical, functional, chemiluminescent, statistical research methods.

The antioxidant effect of loading with water with saturation with molecular hydrogen leads to a decrease in the loss of sodium ions due to an improvement in its reabsorption and β<sub>2</sub>-microglobulin in the proximal tubule, a decrease in lipid peroxidation in the renal cortex was noted, the degree of its damage by an increase in the K<sup>+</sup>/Na<sup>+</sup> ratio and a decrease in degree of edema. Improvement in the condition of the proximal nephron led to an increase in total, enzymatic fibrinolytic activity in the renal cortex. The increase in the activity of succinate dehydrogenase in the renal cortex is due to an increase in the delivery of electrons due to the negative redox potential and the selective antioxidant effect of molecular hydrogen. The anti-edema effect of molecular hydrogen was revealed at the level of 7 layers of the kidney. During the formation of the no-reflow syndrome in rats on a low-sodium diet 72 hours after the introduction of mercuric chloride, the possibility of breaking large and small vicious circles with an antioxidant solution of H<sub>2</sub> was shown due to its high permeability and the ability to neutralize the hydroxyl radical and peroxynitrite.

**Keywords:** sublimate nephropathy, no-reflow syndrome, molecular hydrogen, vicious circles large and small, correction.

## РЕЗЮМЕ

### ИСПОЛЬЗОВАНИЕ МОЛЕКУЛЯРНОГО ВОДОРОДА В КОРРЕКЦИИ СИНДРОМА NO-REFLOW НА ПОЛИУРИЧЕСКОЙ СТАДИИ СУЛЕМОВОЙ НЕФРОПАТИИ

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Цель исследования – определить возможность использования молекулярного водорода в коррекции синдрома

no-reflow на полиурической стадии острого повреждения почек спустя 72 часа после введения сулемы у крыс на гипонатриевом рационе питания.

Опыты выполнены на 60 самцах белых нелинейных половозрелых крыс массой 0,16-0,18 кг с исследованием влияния нагрузки водой с насыщением молекулярным водородом. Сулемовую нефропатию моделировали в условиях гипонатриевой диеты путем подкожного введения 0,1% раствора дихлорида ртути в дозировке 5 мг/кг с проведением исследования спустя 72 часа, что соответствовало ранней полиурической стадии острого повреждения почек и развитию синдрома no-reflow. Для насыщения воды молекулярным водородом в концентрации 1,2 ppm и окислительно-восстановительным потенциалом от -100 до -350 мВ использовали генератор H<sub>2</sub> нового поколения Blue Water 900 (Корея), содержащий усовершенствованную протонно-обменную мембрану PEM/SPE. Использовали патофизиологические, биохимические, функциональные, хемилюминисцентные, статистические методы исследования.

Антиоксидантное влияние нагрузки водой с насыщением

молекулярным водородом приводит к уменьшению потерь ионов натрия за счет улучшения его реабсорбции и β<sub>2</sub>-микроглобулина в проксимальном канальце, отмечено снижение перекисного окисления липидов в корковом веществе почек, степени его повреждения по увеличению соотношения K<sup>+</sup>/Na<sup>+</sup> и уменьшение степени отека. Улучшение состояния проксимального отдела нефрона привело к возрастанию суммарной, ферментативной фибринолитической активности в корковом веществе почек. Повышение активности сукцинатдегидрогеназы в корковом веществе почек обусловлено увеличением доставки электронов за счет отрицательного окислительно-восстановительного потенциала и избирательного антиоксидантного влияния молекулярного водорода. Выявлено противоположное воздействие молекулярного водорода на уровне 7 слоев почки. В период формирования синдрома no-reflow у крыс на низконатриевой диете спустя 72 часа после введения сулемы показана возможность разрыва больших и малых порочных кругов антиоксидантным раствором H<sub>2</sub> за счет высокой проницаемости и способности нейтрализовать гидроксильный радикал и пероксинитрит.

### რეზიუმე

მოლეკულური წყალბადის გამოყენება no-reflow სინდრომის კორექციისათვის სულემური ნეფროპათიის პოლიურიულ სტადიაზე

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კვლევის მიზანს წარმოადგენდა მოლეკულური წყალბადის გამოყენების შესაძლებლობის განსაზღვრა no-reflow სინდრომის კორექციისათვის თირკმლების მწვავე დაზიანების პოლიურიულ სტადიაზე სულემის შეყვანიდან 72 საათის შემდეგ კვების პიპონატრიუმთან რაციონზე მყოფ ვირთაგვებში.

კვლევა ჩატარდა 60 თეთრ არასახოვან ზრდასრულ, 0.16-0.18 კგ მასის ვირთაგვებზე. სულემური ნეფროპათია მოდელირდებოდა პიპონატრიუმის დიეტის პირობებში ვერცხლისწყლის დიქლორიდის 0.1%-იანი ხსნარის კანქვეშ შეყვანით, დოზით 5 მგ/კგ; კვლევა ტარდებოდა 72 საათის შემდეგ, რაც შეესაბამება თირკმლების მწვავე დაზიანების პოლიურიულ სტადიას და no-reflow სინდრომის განვითარებას. წყლის გაჯერებისათვის მოლეკულური წყალბადით, კონცენტრაციით 1,2 ppm და ჟანგვა-აღდგენითი პოტენციალით -100-დან -350 მვ-მდე გამოყენებული იყო ახალი თაობის H<sub>2</sub> გენერატორი Blue Water 900 (კორეა), რომელიც შეიცავს სრულყოფილ პროტონულ-გაცვლით მემბრანას PEM/SPE. გამოყენებულია კვლევის პათოფიზიოლოგიური, ბიოქიმიური, ფუნქციური, ქემილუმინესცენტური, სტატისტიკური მეთოდები.

მოლეკულური ჟანგბადით გაჯერებული წყლით

დატვირთვის ანტიოქსიდაციური გავლენა იწვევს ნატრიუმის იონების კარგვის შემცირებას პროქსიმალურ მილაკებში მისი რეაბსორბციის გაუმჯობესების და β<sub>2</sub>-მიკროგლობულინის ხარჯზე, აღინიშნება ლიპიდების ზეჟანგური ჟანგვის შემცირება თირკმლის ქერქოვან ნივთიერებაში, მისი დაზიანების შემცირება K<sup>+</sup>/Na<sup>+</sup> თანაფარდობის ზრდასთან ერთად და შეშუპების ხარისხის შემცირება. ნეფრონის პროქსიმალური ნაწილის მდგომარეობის გაუმჯობესებამ გამოიწვია ჯამური, ფერმენტული ფიბრინოლიზური აქტივობის ზრდა თირკმლის ქერქოვან ნივთიერებაში.

სუქციანტდეჰიდროგენაზას აქტივობის ზრდა თირკმლის ქერქოვან ნივთიერებაში გამოწვეულია ელექტრონების მიტანის მომატებით უარყოფითი ჟანგვა-აღდგენითი პოტენციალის და მოლეკულური წყალბადის შერწყმით ანტიოქსიდაციური გავლენის ხარჯზე.

No-reflow სინდრომის ფორმირების პერიოდში პიპონატრიუმის დიეტაზე მყოფ ვირთაგვებში, სულემის შეყვანიდან 72 საათის შემდეგ, მაღალი განვლადობისა და ჰიდროქსილური რადიკალის და პეროქსინიტრიტის ნეიტრალიზების უნარის გამო, ნაჩვენებია დიდი და მცირე მანკიერი წრეების გარღვევა ანტიოქსიდაციური ხსნარით H<sub>2</sub>.

## ВЛИЯНИЕ ПИЩЕВЫХ ЖИДКОСТЕЙ НА ЗУБОЧЕЛЮСТНУЮ СИСТЕМУ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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Кариес зубов до настоящего времени относят к числу наиболее распространенных заболеваний. Определение факторов риска, их количественная характеристика позволяют индивидуализировать профилактические меры в зависимости от социально-медицинских, природно-климатических и других условий того или иного региона [1,2].

Факторы риска, влияющие на степень кариесрезистентности твердых тканей зуба и определяющие их стабильность, можно разделить на обеспечивающие локальную противокариозную защиту зубов - эмаль и ее структурные элементы, слюна [1,3,4], иммунитет органов и тканей рта, жизнедеятельность микроорганизмов, состав пищи и воды [2], состояние гигиены рта с учетом естественного самоочищения зубов [3]. Влияние этих факторов на степень кариесрезистентности зубов неодинаково и определяется их количеством, комбинацией, исходным состоянием организма [3,5-7].

В естественных условиях имеет место процесс как деминерализации, так и реминерализации, которые обеспечивают непрерывное обновление минеральных компонентов эмали зубов, в основном, ее поверхностного слоя. Деминерализация является результатом воздействия на поверхность зуба кислот, продуцируемых микроорганизмами зубной бляшки [8-10].

В исследованиях [4,7] отмечено, что бактериальный налет является важнейшим этиологическим фактором для кариеса, пародонтита и периимплантита. Физико-химическое постоянство эмали зубов всецело зависит от состава и химического состояния окружающей ротовой жидкости. Большое значение в патогенезе кариеса придается состоянию ротовой жидкости, которая в зависимости от условий может нести деминерализующий или реминерализующий потенциал [8,10]. Установлено, что изменение состава и свойства слюны, которая обладает высокой пластичностью и чувствительностью к воздействию неблагоприятных факторов, влияет на развитие кариеса зубов [1,4]. Прием углеводов коррелирует с количеством лактобактерий слюны во рту. Повышенное содержание лактобактерий встречается в случаях сниженной секреции слюны и ее низкой буферной емкости даже при наличии в слюне глюкозы [4,7,9].

Среди факторов, способствующих развитию кариеса, все большее значение приобретает употребление напитков с содержанием сахара (НСС), к которым относятся все безалкогольные напитки с сахаром, энергетические, фруктовые и спортивные напитки. Согласно результатам ряда опубликованных исследований [10,11], особенности потребления напитков населением разных стран в последние десятилетия значительно изменились - существенно возросло потребление сладких напитков, однако снизилось потребление воды и молока.

В исследовании Samman M. et al. [6] продемонстрировано, что в США потребление сладких напитков детьми увеличивается, несмотря на усилия общественного здравоохранения по его снижению. В одном из бразильских исследований показано, что прохладительные напитки находятся на втором месте по потреблению после воды, и на их долю приходится до 10% ежедневно потребляемой подростками энергии.

В последние десятилетия актуальность проблемы развития кариеса увеличилась в связи с изменением тенденции потребления напитков [11]. Имеются сообщения о том, что прохладительные напитки практически полностью вытеснили воду из рациона детей школьного возраста, что подтверждается результатами исследования NSW Schools Physical Activity and Nutrition Survey 2010 г., по результатам которого показано, что потребление воды составляет 68,9% в начальной школе и снижается до 63,5% в средней школе [12].

На развитие кариеса и эрозий зубов влияет содержание в напитках как свободных сахаров, так и кислот. Показано наличие тесной корреляции между употреблением в пищу продуктов с высоким содержанием «свободных» сахаров (любые моно- и дисахариды, добавленные в пищу или напиток производителем, поваром или самим потребителем, а также сахара, которые естественным образом содержатся в сиропах, фруктовых соках и мёде) и частотой развития кариеса [13,14]. При этом кислотообразующие бактерии *Streptococci mutans* и *Lactobacilli* преобразуют свободные сахара в молочную кислоту. Молочная кислота, в свою очередь, вызывает деминерализацию зубной эмали, способствуя развитию кариозных поражений [15].

В рамках исследования Radomic B. et al. [16] показано, что степень эрозии эмали прямопропорциональна длительности экспозиции напитка, все исследованные авторами напитки (Coca-Cola, апельсиновый сок, Cedevita и Guarana) обладали эрозивными свойствами за исключением йогурта.

Вышеизложенное свидетельствует о необходимости проведения дальнейших исследований, результаты которых позволят всесторонне оценить влияние пищевых жидкостей на состояние зубочелюстной системы и обосновать научную концепцию проведения профилактических мероприятий, направленных на улучшение состояния здоровья полости рта населения.

Цель исследования - установить влияние потребляемых жидкостей на зубочелюстную систему крыс.

**Материал и методы.** На базе Центра доклинических и клинических исследований Российского университета дружбы народов проведено исследование влияния различных пищевых жидкостей на состояние ротовой полости экспериментальных животных. Эксперименты проведены на 25 белых крысах-самцах из питомника филиала «Кролинфо» Московской области, которые содержались в стандартных условиях вивария. Возраст крыс-3-6 месяцев, вес -150±50 г.

Исследование выполнялось в соответствии с этическими принципами гуманного обращения с животными, согласно действующему законодательству РФ.

Для оценки действия потребляемых жидкостей на зубочелюстную систему крыс использовали группы по 5 животных одного пола (самцы, самки) в каждой. Животные были распределены по группам рандомизированно.

Наблюдение за животными проводили в течение 6 мес., в этот период животные находились в условиях свободного доступа к пище и в качестве питья получали исследуемые жидкости ad libitum.

Экспериментальные группы в течение 3 месяцев получали следующие виды питья: I (контрольная группа) – водопроводная вода; II группа – Кока-кола; III группа – медовая вода; IV группа – дистиллированная вода; V группа – лёгкая вода.

В течение всего эксперимента наблюдение за животными проводили ежедневно с целью выявления влияния характера пищевых жидкостей на зубочелюстную систему. У всех животных 2 раза - спустя 3 и 6 мес. от начала периода наблюдения, оценивали массу тела, гематологические и биохимические показатели.

В конце исследований всех животных подвергали эвтаназии в CO<sub>2</sub>- камере, после чего оценивали показатели микротвердости эмали и дентина моляров.

Определение микротвердости проводили на жевательных зубах фрагментов челюсти экспериментальных животных (крысы) после расчленения челюсти на левую и правую, удаления резцов и мягких тканей, с последующей заливкой фрагментов группы жевательных зубов в блоки самотвердеющей пластмассы (Акродент или Протакрил), рис. 1, 2.



Рис. 1 Вид зубов крыс контрольной группы



Рис. 2. Вид зубов крыс IV группы, получавших дистиллированную воду (образец после шлифовки и испытания на микротвердость)

Определение показателя микротвердости проводили на микротвердомере Duramin-20 («Struers», Дания) по методу отпечатка по Виккерсу в единицах Hv (при нагрузке 50-100 г и времени выдержки под нагрузкой 10-30 с) по формуле:

$$Hv = 0,1891 \frac{F}{d^2}$$

где Hv – значение микротвердости по Виккерсу;

F – нагрузка на испытываемую поверхность, (Н);

d – средняя длина диагонали отпечатка индентора (мм).

Спустя 3 и 6 мес. после начала наблюдения у всех животных, предварительно на ночь лишенных корма, определяли показатели клинической биохимии и гематологии. Забор крови для исследований производился из хвостовой вены в объеме 1,0-2,0 мл.

Кровь объемом 0,9 мл помещали в пробирки с ЭДТА и на автоматическом гематологическом анализаторе PCE 90 VETHTI, ERMA (Япония) определяли гематологические показатели: количество эритроцитов, лейкоцитов, тромбоцитов, уровень гемоглобина, гематокрит, среднее содержание и концентрацию гемоглобина в эритроците, средний объем эритроцитов, ширину распределения эритроцитов по объему.

Для биохимического исследования кровь объемом 1,0-2,0 мл собирали в пробирки без антикоагулянта, центрифугировали после свертывания для получения сыворотки, в которой на автоматическом биохимическом анализаторе крови ILAB 650 (США) при помощи наборов фирмы «Biosystems» (Испания), определяли следующие показатели: общий белок, альбумины, общий холестерин, триглицериды, общий билирубин, глюкозу, мочевины, креатинин, активность щелочной фосфатазы, аланин- и аспаратаминотрансферазу.

Статистическая обработка полученных данных выполнена с использованием программного обеспечения Statsoft. STATISTICA 10 и Microsoft Excel 2016. Непрерывные количественные показатели представлены в виде выборочного среднего значения и стандартной ошибки среднего ( $M \pm m$ ). С учетом непараметрического распределения показателей (проверка на нормальность распределения проводилась с использованием критерия Шапиро-Уилка) и значительных межгрупповых различий по величине дисперсии для межгрупповых сравнений применяли непараметрические статистические методы. Анализ межгрупповых различий по количественным параметрам проводился с применением непараметрического рангового критерия Манна-Уитни. Пороговое значение статистической значимости нулевой гипотезы составило 0,05.

**Результаты и обсуждение.** Результаты наблюдения за экспериментальными животными всех групп межгрупповых различий величины показателя массы тела, изменений в поведении крыс не выявили. Показатели периферической крови крыс всех экспериментальных групп по количественному и качественному составу соответствовали видовой физиологической норме. Влияния потребления животными различных испытуемых жидкостей на основные биохимические показатели крови, активность ферментов плазмы крови и ее электролитный баланс не выявлено.

При потреблении испытуемых жидкостей на слизистых оболочках ротовой полости признаков местно-воспалительной реакции (инфильтрация, покраснение) не зарегистрировано, что подтверждено результатами визуальных осмотров.

Установлено, что значения показателей микротвердости эмали жевательных зубов в группах крыс различались в зависимости от видов потребляемых жидкостей. Из таблицы 1 явствует, что максимальное повышение уровня этого показателя отмечалось в III и V группах, которые пили медовую и легкую воду, соответственно. Уровни этих показателей были статистически значимо выше соответствующих показателей в I группе (водопроводная вода),  $p < 0,001$  для группы 3 и  $p = 0,004$  для группы V. Величина микротвердости эмали жевательных зубов в группе IV (дистиллированная вода) также была существенно больше таковой в I группе ( $p = 0,0083$ ). Уровень микротвердости эмали у животных II группы (Coca-Cola) существенно не отличался от значения показателя в I группе (водопроводная вода). Таким образом, употребление легкой воды повысило микротвердость эмали на 31,8%, дистиллированной воды - на 27,9%, медовой воды - на 33,3%, Coca-Cola – только на 2,1%.



Таблица 1. Показатели микротвердости эмали жевательных зубов крыс ( $M \pm \sigma$ )

Группы животных	Микротвердость 'эмали, Нв
I группа (водопроводная вода)	260,1 $\pm$ 49,0
II группа (Coca-Cola)	265,6 $\pm$ 33,5
III группа (медовая вода)	346,6 $\pm$ 41,1*
IV группа (дистиллированная вода)	332,6 $\pm$ 30,6*
V группа (легкая вода)	342,9 $\pm$ 51,2*

примечание: различия статистически значимы (при  $p < 0,05$ ) в сравнении с группой «Водопроводная вода» по критерию Манна-Уитни

Таблица 2. Показатели микротвердости дентина в группах ( $M \pm \sigma$ )

Группы животных	Микротвердость дентина, Нв
I группа (водопроводная вода)	66,9 $\pm$ 13,0
II группа (Coca-Cola)	60,0 $\pm$ 8,6
III группа (медовая вода)	57,3 $\pm$ 11,4*
IV группа (дистиллированная вода)	74,3 $\pm$ 9,7*
V группа (легкая вода)	77,7 $\pm$ 12,8*

примечание: различия статистически значимы (при  $p < 0,05$ ) в сравнении с группой «Водопроводная вода» по критерию Манна-Уитни

Анализ влияния различных питьевых жидкостей на микротвердость дентина крыс показал, что употребление дистиллированной (IV группа) и легкой (V группа) воды животными приводило к статистически значимому увеличению значений этого показателя в сравнении с его величиной в I группе (соответственно  $p=0,038$  и  $p=0,007$ ), таблица 2.

В то же время отмечено, что во II и III группах значения микротвердости дентина были ниже, чем в I группе, причем у крыс, потреблявших медовую воду, уровень этого показателя был статистически значимо меньше ( $p=0,015$ ), чем у животных, употреблявших водопроводную воду. Таким образом, употребление легкой воды повысило микротвердость дентина на 16,1%, дистиллированной воды - на 11,1%, медовой воды и Coca-Cola - понизило на 14,3% и 10,3%, соответственно.

Согласно современным представлениям, причиной кариеса является длительное воздействие кислот на зубные ткани. На эмаль зуба и изменение кислотности зубного налета большое влияние (в основном опосредованно) оказывает пища, которую употребляет человек. Процессы де- и реминерализации эмали сменяют друг друга при соответствующих значениях кислотности налета. По данным авторов [9,17], в большинстве случаев кислотность среды колеблется в пределах 6,8-7,4. Снижение кислотности ротовой жидкости может способствовать увеличению проницаемости эмали зубов и нарушению минерализации прорезывающихся зубов, а также развитию «окислительного стресса» с внутриклеточным дисбалансом прооксидантной системы [17-19].

Существенным фактором формирования стоматологического здоровья населения следует считать питание [1,12]. Исследования, проведенные *in vitro* на животных и людях, подтверждают широко распространенную точку зрения, что кариес зубов может развиваться только в присутствии сахаров и других рафинированных углеводов, особенно сахарозы. Установлено, что потребление быстрорастворимых углеводов в большом количестве может явиться решающим фактором в сдвиге pH и нарушении процессов минерализации, что приводит к возникновению кариеса зубов. Так, прием 10 граммов сахара ведет к возрастанию молочной

кислоты в слюне в 10-16 раз. Получены убедительные эпидемиологические доказательства того, что распространенность и интенсивность кариеса зубов в группе населения повысится, если большая часть общих энергетических потребностей организма покрывается за счет потребления пищевых продуктов с высоким содержанием глюкозы. Особую роль играет частота употребления глюкозосодержащих продуктов, а не общий их уровень [19,20].

Результаты проведенного исследования показали, что в условиях длительного (6 месяцев) ежедневного применения различных жидкостей (медовая вода, дистиллированная вода, кока-кола, «легкая» вода, водопроводная вода) патологических нарушений гематологических и биохимических показателей крови крыс не выявлено. Употребление этих жидкостей не оказывает негативного воздействия на состояние лабораторных животных. Ежедневное потребление исследуемых растворов не вызывает местного раздражающего действия.

Употребляемые жидкости по-разному влияли на микротвердость эмали и дентина зубов. Установлено, что потребление легкой воды повышает микротвердость эмали на 31,8%, дентина - на 16,1% дистиллированной воды - на 27,9% и 11,1% соответственно. Употребление медовой воды повысило твердость эмали на 33,3%, дентина - понизило на 14,3%, Coca-Cola повысило твердость эмали лишь на 2,1%, а дентина - снизило на 10,3%.

Полученные нами данные согласуются с результатами, представленными другими авторами: Chadwick R.G. et al. [20] проведены экспериментальные исследования по оценке влияния различных напитков на изменение степени шероховатости поверхности зубов. Авторы пришли к выводу, что шероховатость материалов усиливается после воздействия напитка Mirinda и натурального сока манго, которые отличаются высокой кислотностью. По мнению исследователей, выявленные изменения обусловлены способностью кислой среды размягчать пломбировочные материалы [20].

Samman M. et al. [6] провели кросс-секционное исследование, в котором проанализировали данные о питании детей в возрасте от 3 до 10 лет. Авторами использован кластер-

ный анализ для обработки полученных данных. Идентифицированы группы потребления напитков: дети с высоким потреблением газированных напитков; дети с высоким потреблением 100% сока; дети с высоким потреблением соко-содержащих напитков; дети, употребляющие диетические напитки с высоким содержанием молока и большим количеством соды.

Регрессионный анализ показал, что для кластера с высоким содержанием соды была характерна тенденция к увеличению риска развития кариеса: отношение шансов (ОШ)=1,69, 95% доверительный интервал доверительный интервал (ДИ) от 0,9 до 3,1, в то время как кластер с высоким содержанием диетических напитков характеризовался нейтральным влиянием на развитие кариеса: ОШ= 0,94; 95% ДИ 0,5–1,8. Авторами сделан вывод, что диетические напитки не оказывают вредного воздействия на состояние зубов у детей [6].

Сообщения о влиянии содосодержащих напитков на развитие кариеса, в основном, противоречивы. Исследования, проведенные на выборке детей из Айовы, за которыми наблюдали от рождения до стоматологического осмотра в возрасте от 4 до 7 лет, пришли к выводу, что потребление сахаросодержащих напитков увеличивает риск развития кариеса. Авторы сообщили, что регулярное ежедневное потребление газированных напитков в возрасте от 1 до 5 лет удваивает вероятность последующего развития кариеса в возрасте от 4 до 7 лет в сравнении с теми, которые не употребляли газировку или не употребляли ее в небольшом количестве (ОШ=2,2; 95% ДИ 1.4 -3.6) [21]. Подобное состояние наблюдалось и у старших детей.

У третьеклассников (8-9 лет) в Грузии вероятность заболевания кариесом в 1,2 раза были выше при каждой дополнительной ежедневной порции соды (ОШ=1,2; 95% ДИ 1,1–1,3;  $p<0,05$ ) [22]. Кроме того, что потребление соды увеличивает распространенность кариеса, исследования показали, что сода также увеличивает тяжесть кариозных поражений. Marigi B. et al. [23] оценили факторы, выявленные у детей от 4 до 7 лет с тяжелым кариесом, включая различные диетические компоненты, и обнаружили, что увеличение ежедневного потребления обычной газированной воды (унций в день) увеличивает вероятность развития кариеса (ОШ= 1,26; 95% ДИ 1,02- 1,55;  $p=0,04$ ) [23].

Другие авторы не обнаружили взаимосвязи между обычной содой и кариозными поражениями. Ismail A.I. et al. [24] исследующие прогрессирование кариеса на уровне поверхности зубов среди выборки афроамериканских детей дошкольного возраста из малообеспеченных семей пришли к выводу, что скорость прогрессирования кариеса была выше для поверхностей зубов с существующими кариозными поражениями, чем для здоровых поверхностей, независимо от исходного уровня потребления газировки детьми [24].

В исследовании Vargas C.M. et al. [25] показана, 100% взаимосвязь между употреблением сока и развитием кариеса. В связи с этим логично предположить, что потребление сокосодержащих напитков связано с развитием кариеса, поскольку в них добавляется сахар [25].

Karda B. et al. [26] проведено сравнение влияния на зубную эмаль нескольких напитков, при этом показано, что Coca-Cola в сравнении с Nimbooz, Frooti и Yakult обладает наиболее выраженным эрозивным эффектом, так как содержит регулятор кислотности 338 (ортофосфорная кислота), красители, ароматизаторы и кофеин, помимо угольной кис-

лоты производители добавляют в состав фосфорную кислоту для придания напитку характерного вкуса. В связи с наличием этих кислот в составе напитка, Coca-Cola обладает выраженной кислотностью, что способствует развитию эрозии, декальцификации зубной эмали и разрушению различных пломбировочных материалов.

Проведена оценка влияния имеющихся в продаже напитков на эмаль зубов и различные пломбировочные материалы. Исследование проводилось на удаленных зубах, которые разделены на 4 группы в зависимости от преобладающего материала: зубная эмаль, стеклоиономерный цемент, композит и компомер. В исследовании использованы 4 напитка - Coca-Cola, Nimbooz, Frooti и Yakult с измерением pH каждого из напитков. Зубы каждой группы погружались в различные напитки на 14 дней. Эрозивный потенциал каждого напитка оценивался путем расчета изменения средней шероховатости поверхности зубов.

Установлено, что наиболее выраженные изменения шероховатости поверхности зубов наблюдались во II группе (стеклоиономерный цемент), при этом показано, что максимальным эрозивным потенциалом обладает Coca-Cola, минимальным – Yakult. Статистически значимых различий между эрозивной активностью Yakult и Frooti не отмечено [26].

Результаты проведенного нами исследования и данные литературы показали, что среди факторов, которые влияют на состояние зубов, в частности на твердость эмали и дентина, значительную роль играет потребление различных сахаросодержащих напитков, а также продолжительность, количество и частота их потребления. На основании полученных результатов и анализа современных научных источников по изучаемому вопросу авторы рекомендуют для купирования кариесогенности необходима разработка и проведение комплекса профилактических мероприятий, включающих ограничение потребления сладостей и напитков с содержанием сахара наряду с регулярным уходом за зубами и режимом сбалансированного питания.

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## SUMMARY

### INFLUENCE OF BEVERAGES ON THE DENTOALVEOLAR SYSTEM (EXPERIMENTAL STUDY)

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The aim of the study was to determine the influence of various drinking liquids on an the dentoalveolar system in rats.

The study was carried out on 25 white male rats from the nursery of Krolinfo branch of the Moscow region which were kept in standard vivarium conditions. Age of rats-3-6 months, weight - 150-200 grams.

The study was carried out in accordance with the ethical principles of humane treatment of animals, in accordance with the current legislation of the Russian Federation.

To assess the effect of consumed fluids, groups of 5 animals of the same sex (males, females) were used. The animals were randomly assigned to groups. Observation of animals was carried out for 6 months, during this period the animals were in conditions of free access to food and as drink received the studied liquids ad libitum. Experimental groups within 3 months received the following types of drink: I (control group) - tap water; The II group - Coca-Cola; The III group - honey water; The IV group - the distilled water; The V group - light water.

The results obtained by the authors and the data provided in literature confirm that among the factors that affect the teeth condition, in particular the characteristics of the hardness of enamel and dentin, the use of various sugar-containing drinks, as well as the duration, quantity, and frequency of their use, can play a significant role. These factors remain largely unexplored at present. It is obvious that in order to stop caries, it is necessary to develop and carry out a set of preventive measures, including limiting the consumption of sweets and beverages containing sugar, along with regular dental care and a balanced diet.

**Keywords:** drinking liquids, duration, quantity, and frequency of use of sugar-containing drinks, caries, preventive measures.

## РЕЗЮМЕ

### ВЛИЯНИЕ ПИЩЕВЫХ ЖИДКОСТЕЙ НА ЗУБОЧЕЛЮСТНУЮ СИСТЕМУ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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Цель исследования - установление влияния потребляемых жидкостей на зубочелюстную систему крыс.

Проведено исследование влияния различных питьевых

жидкостей на состояние ротовой полости 25 белых крыс-самцах из питомника филиала «Кролинфо» Московской области, которые содержались в стандартных условиях вивария. Возраст крыс - 3-6 месяцев, вес -  $150 \pm 50$  г.

Исследование выполнялось в соответствии с этическими принципами гуманного обращения с животными, согласно действующему законодательству РФ.

Для оценки действия потребляемых жидкостей на зубочелюстную систему крыс использовали группы по 5 животных одного пола (самцы, самки) в каждой группе. Животные распределены по группам рандомизированно.

Наблюдение за животными проводили в течение 6 мес., в этот период животные находились в условиях свободного доступа к пище и в качестве питья получали исследуемые жидкости *ad libitum*. Экспериментальные группы в течение 3 месяцев получали следующие виды питья: I (контрольная

группа) – водопроводная вода; II группа – Кока-кола; III группа – медовая вода; IV группа – дистиллированная вода; V группа – лёгкая вода.

Полученные авторами результаты и данные литературы подтверждают, что среди факторов, которые влияют на состояние зубов, в частности на твердость эмали и дентина, значительную роль играет употребление различных сахаросодержащих напитков, продолжительность, количество и частота их потребления. На основании полученных результатов и анализа современных научных источников по изучаемому вопросу авторы рекомендуют для купирования кариеогенности разработку и проведение комплекса профилактических мероприятий, включающих ограничение потребления сладостей и напитков с содержанием сахара, наряду с регулярным уходом за зубами и режимом сбалансированного питания.

### რეზიუმე

საკვები სითხეების გავლენა ორგანიზმსა და ყბა-კბილთა სისტემაზე (ექსპერიმენტული კვლევა)

ტ.კოსირევა, კ.აბაკელია, იმად კატბეხი, ნ.ტუტუროვი, ა.ხასანი

რუსეთის ხალხთა მეგობრობის უნივერსიტეტი, ბაჟუთა ასაკის სტომატოლოგიისა და ორთოდონტიის კათედრა, მოსკოვი, რუსეთი

კვლევის მიზანს წარმოადგენდა მიღებული სითხეების გავლენის შეფასება ყბა-კბილთა სისტემაზე.

ჩატარებულია სხვადასხვა საკვები სითხის გავლენის კვლევა 3-6 თვის,  $150 \pm 50$  გრ წონის ვირთაგვების პირის ღრუს მდგომარეობაზე ( $n=25$ ), მოსკოვის ოლქის ცხოველების სანაშენე მეურნეობიდან “კროლინფო”. ცხოველები იმყოფებოდნენ ვივარიუმის სტანდარტულ პირობებში. კვლევა ჩატარდა ცხოველებთან ჰუმანური მოპყრობის ეთიკური პრინციპების დაცვით, რუსეთის ფედერაციის მოქმედი კანონმდებლობის შესაბამისად.

მიღებული სითხეების ორგანიზმზე მოქმედების შეფასებისათვის გამოყენებული იყო ცხოველების ჯგუფები, თითოეულში ერთი სქესის (მამრი ან მდედრი) 5 ცხოველით. ცხოველები ჯგუფებში განაწილდა რანდომულად.

დაკვირვება ცხოველებზე მიმდინარეობდა 6 თვის განმავლობაში; ამ პერიოდში ცხოველები იმყოფებოდნენ საკვებზე თავისუფალი წვდომის პირობებში,

სასმელად კი საკვლევი სითხეებს იღებდნენ *ad libitum*. ჯგუფებს სამი თვის განმავლობაში მიეწოდებოდა შემდეგი სითხეები: I (საკონტროლო) ჯგუფს – სასმელი წყალი; II – კოკა-კოლა; III – თაფლის წყალი; IV – დისტილირებული წყალი; V – მსუბუქი წყალი.

მიღებული შედეგები და ლიტერატურაში არსებული მონაცემები ადასტურებს, რომ კბილების მდგომარეობაზე (მინანქრის და დენტინის სიმტკიცე) მოქმედ ფაქტორებს შორის მნიშვნელოვანია შაქრის შემცველი სხვადასხვა სასმელის მოხმარება, მათ შორის – მათი მოხმარების ხანგრძლივობა, რაოდენობა და სისშირე. ეს ფაქტორები დღემდე პრაქტიკულად შეუსწავლელია. ამასთან, ნათელია, რომ კარიესის კუპირებისათვის აუცილებელია პროფილაქტიკური ღონისძიებების შემუშავება და გატარება, რაც, კბილების რეგულარულ მოვლასა და დაბალანსებული კვების რეჟიმთან ერთად, მოიცავს ტეხნიკის და შაქრის შემცველი სასმელის მიღების შემცირებას.

## ЭФФЕКТ ПРОПРАНОЛОЛА НА ПРОФИЛЬ ЦИТОКИНОВ В ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ Т-ЛИМФОЦИТОВ ЧЕЛОВЕКА (КЛЕТКИ JURKAT) *IN VITRO*

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Цитокины, продуцируемые иммунными клетками играют ключевую роль в иммунопатогенезе различных заболеваний (воспалительные заболевания кишечника, пародонит, синдром Шегрена, атеросклероз, вирусная инфекция) [7,9,10,19,21,23,25]. Регуляция цитокинового баланса способствует улучшению состояния пациента при лечении таких заболеваний, как лейкемия и инфаркт миокарда [11,15], подавление секреции провоспалительных цитокинов способствует улучшению функции сердца [16,21].

Функционирование иммунной системы в значительной мере зависит от баланса лимфоцитов, их функциональной активности, пролиферации и гибели. Регуляция функциональной активности лимфоцитов осуществляется посредством ауторегуляторных механизмов, подразумевающих взаимодействие иммунных клеток с медиаторами нервной и эндокринной систем [4,13,14], модуляции активности рецепторов, экспрессируемых на поверхности клеток, в частности β-адренергических рецепторов, сопряженных с аденилатциклазной системой, генерирующей сАМР.

Многочисленные фармакологические исследования с использованием различных бета-агонистов и антагонистов указывают на значимую регуляторную роль бета-адренорецепторной системы мембраны лимфоцитов в патогенезе различных заболеваний. Блокаторы бета-адренорецепторов широко используются в лечении сердечно-сосудистых (артериальная гипертензия, ишемическая болезнь сердца) заболеваний. Имеются данные об противоопухолевых и противовоспалительных эффектах бета-адреноблокаторов, их ингибирующем действии на экспрессию фактора роста эндотелия сосудов (VEGF) в жировой ткани [8,28]. Катехоламины снижают LPS-индуцированную продукцию TNF-α, IL-6, IL-1β, IL-10; блокаторы бета-адренорецепторов могут обеспечить защиту Т-лимфоцитов от апоптоза [26].

В данной статье с целью установления роли нейроэндокринных механизмов в процессах иммуномодуляции, исследовался эффект пропранолола на профиль цитокинов в экспериментальной модели человеческих Т-лимфоцитов (клетки Jurkat) *in vitro*.

**Материал и методы.** Культура лейкоцит-трансформированных Т-клеток (Jurkat) широко применяется для изучения воздействия различных препаратов на активность Т-клеток.

Клетки Jurkat (DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen, Germania) инкубировали в биоактивной среде RPMI 1640 (GIBSO), содержащей инактивированную эмбрионную телячью сыворотку (Sigma), L-глутамин (4 мМ), пенициллин (100 ед/мл) и стрептомицин (100 ед/мл) при температуре 37°C и 5% концентрации CO<sub>2</sub>. Эксперименты проводились при концентрации клеток 0,3-0,6×10<sup>6</sup> в 1 мл среды.

С целью активации клеток Jurkat 4×10<sup>5</sup> клеток/мл инкубировали с фитогемагглютинином (РНА) 50 мкг/мл в присутствии пропранолола (10<sup>-4</sup> М) и без него при 37°C в течение 24 часов.

**Имуноферментный анализ.** Цитокиновый профиль (IL-2, IL-10, IFN-γ) в супернатанте интактных и РНА-стимулированных клеток Jurkat, инкубированных с антагонистом β-адренорецепторов, пропранололом и без него исследовали посредством иммуноферментного анализа ELISA непосредственно после инкубации.

Статистическая обработка полученных результатов проводилась по программе SPSS v.16.0. Для анализа различий между средними значениями использовали t-критерий Стьюдента, а изменение со значением p<0,05 считалось статистически значимым.

**Результаты и обсуждение.** Продукция IL-2 и IL-10 в интактных клетках Jurkat была очень низкой; в РНА-стимулированных клетках Jurkat продукция IL-2 и IL-10 заметно увеличивалась (P<0,05) (рис. 1 А, В). Пропранолол значительно снижал продукцию IL-2 и IL-10 в РНА-стимулированных клетках Jurkat (P<0,05) (рис. 1 А, В).

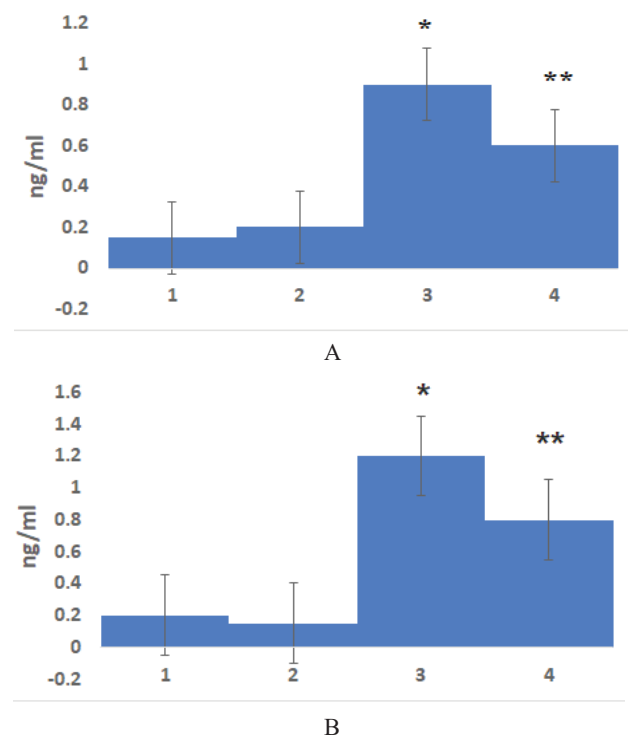


Рис. 1. Продукция IL-2 (А) и IL-10 (В) в интактных и РНА-стимулированных клетках Jurkat в присутствии пропранолола и без него (1 – интактные клетки Jurkat, 2 – интактные клетки Jurkat + пропранолол, 3 – Jurkat+РНА, 4 – Jurkat+РНА+ пропранолол)

Продукция IFN-γ была довольно низкой в интактных клетках Jurkat, а в РНА-стимулированных клетках - заметно увеличилась (P<0,05), пропранолол значительно снижал продукцию IFN-γ в РНА-стимулированных клетках Jurkat (P<0,05) (рис. 2).

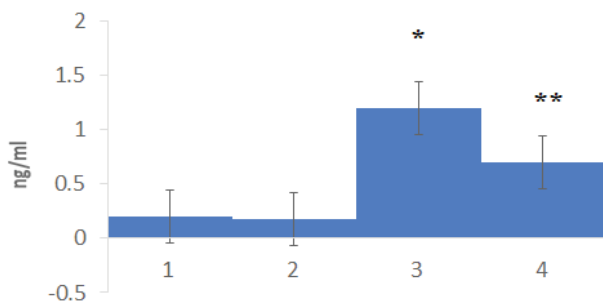


Рис. 2. Продукция IFN-γ в интактных и РНА-стимулированных клетках Jurkat в присутствии пропранолола и без него (1 – интактные клетки Jurkat, 2 – интактные клетки Jurkat + пропранолол, 3 – Jurkat+РНА, 4 – Jurkat+РНА+ пропранолол)

Продукция цитокинов (IL-2, IL-10, IFN-γ) менялась незначительно после воздействия пропранолола на интактные клетки Jurkat, что совпадает с результатами наших предыдущих исследований [17,18] и указывает, что пропранолол не оказывает цитотоксического действия на Т-клетки. Следовательно, ингибирующее действие пропранолола на секрецию IL-2, IL-10 и IFN-γ в РНА-стимулированных клетках Jurkat не является следствием цитотоксического эффекта пропранолола на клетки, а результатом его специфической ингибирующей активности.

Результаты наших исследований, указывающие на ингибирующий эффект пропранолола на РНА-индуцированную секрецию IL-2, IL-10 и IFN-γ человеческими Т-клетками (Jurkat), согласуются с данными литературы, свидетельствующими о снижении секреции IL-2, IL-10 и IFN-γ в лимфоцитах под действием пропранолола *in vivo* и *in vitro* [5,8,24,28]. Следует отметить, что некоторые расхождения между нашими результатами и результатами других исследователей [5,8,24], по всей вероятности, вызваны различиями в условиях экспериментов, включая тип и количество клеток, концентрацию РНА и пропранолола и время инкубации. Необходимо отметить, что используемая нами концентрация пропранолола *in vitro* была намного выше, чем его концентрация, используемая обычно у пациентов с сердечно-сосудистыми заболеваниями [24], тогда как в ситуации *in vivo* пропранолол используется в течение длительного периода времени, что позволяет достичь концентрации лекарства, достаточного для ингибирования воспалительных цитокинов *in vivo* [12].

Учитывая значимую роль IL-2 и IFN-γ в воспалении [2], противовоспалительный эффект пропранолола [28] может быть частично обусловлен его подавляющим действием на продукцию этих воспалительных цитокинов. Действие воспалительных цитокинов обычно регулируется противовоспалительными цитокинами. В ряде исследований у пациентов с сердечно-сосудистыми заболеваниями, на ряду с изменениями содержания воспалительных цитокинов в крови, выявлены также изменения в уровне противовоспалительных цитокинов (IL-10) и рецепторов цитокинов (растворимый TNF-рецептор-2). Считается, что бета-блокаторы могут играть значимую роль в регуляции оптимального уровня IL-10 в крови пациентов с сердечно-сосудистыми заболеваниями [20].

Пропранолол, как неселективный блокатор бета-адренорецепторов, широко используется для лечения многих

сердечно-сосудистых заболеваний, таких как ишемическая болезнь сердца, аритмии, гипертензия, сердечная недостаточность [1,2,3,6,27]; кроме того, пропранолол оказывает противовоспалительное и антиангиогенное действие [8,28]. Выявлен регулирующий эффект пропранолола на продукцию цитокинов в лимфоцитах, инфильтрирующих опухоль, и мононуклеарные клетки периферической крови (РВМС) пациентов с колоректальным раком [8]. Положительный эффект пропранолола в лечении множества заболеваний частично объясняется его регуляторной активностью на секрецию воспалительных (IL-2 и IFN-γ) и противовоспалительных цитокинов (IL-10).

Таким образом, следует заключить, что с целью регуляции функциональной активности лимфоцитов, протекторного и повреждающего действия цитокинов Т-клеток при различных заболеваниях необходимо учитывать ряд ауторегуляторных механизмов, обеспечивающих взаимодействие иммунных клеток с медиаторами нервной и эндокринной систем, поддержание гомеостаза этих систем и регуляцию иммунного ответа.

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## SUMMARY

### EFFECT OF PROPRANOLOL ON CYTOKINE PROFILE IN AN EXPERIMENTAL MODEL OF HUMAN T LYMPHOCYTES (JURKAT CELLS) IN VITRO

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In this research, in order to establish the role of neuroendocrine mechanisms in the processes of immunomodulation, the effect of propranolol on the cytokine profile in an experimental model of human T lymphocytes (Jurkat cells) in vitro was investigated.

Jurkat cells were incubated under standard conditions. Stimulation of the Jurkat cells was performed by incubation with Phytohemagglutinin (PHA) (50  $\mu$ g/ml) in the presence of propranolol (10<sup>-4</sup> M) and without it at 37<sup>o</sup> for 24 hours. The cytokine profile (IL-2, IL-10, IFN- $\gamma$ ) in intact and PHA-stimulated Jurkat cells, incubated with and without  $\beta$ -adrenergic receptor antagonist propranolol, was examined by ELISA.

The production of IL-2, IL-10 and IFN- $\gamma$  in intact Jurkat cells was very low; in PHA-stimulated Jurkat cells, the production of IL-2, IL-10 and IFN- $\gamma$  was markedly increased ( $p < 0.05$ ). Propranolol significantly reduced the production of IL-2, IL-10 and IFN- $\gamma$  in PHA-stimulated Jurkat cells ( $p < 0.05$ ).

Cytokine production (IL-2, IL-10, IFN- $\gamma$ ) did not change significantly after exposure to propranolol on intact Jurkat cells, which indicates that the inhibitory effect of propranolol on cytokine secretion in PHA-stimulated Jurkat cells is not due to the cytotoxic effect of propranolol on cells, but the result of its specific inhibitory activity.

The results of the study allow us to conclude that in order to regulate the functional activity of lymphocytes during various diseases, it is necessary to take into account an autoregulatory mechanisms that ensure the interaction of immune cells with the mediators of the nervous and endocrine systems, maintaining the homeostasis of these systems and regulating the immune response.

**Keywords:** propranolol, cytokine profile, neuroendocrine regulatory mechanisms, T lymphocytes.

## РЕЗЮМЕ

### ЭФФЕКТ ПРОПРАНОЛОЛА НА ПРОФИЛЬ ЦИТОКИНОВ В ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ Т-ЛИМФОЦИТОВ ЧЕЛОВЕКА (КЛЕТКИ JURKAT) IN VITRO

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В статье с целью установления роли нейроэндокринных механизмов в процессах иммуномодуляции, исследо-

ვალსა ეფექტ პროპრონოლოლა ნა პროფილ ციტოკინოვ ნ ექსპერიმენტალური მონელი T-ლიმფოციტოვ ჩელოვეკი (კლეთკი Jurkat) *in vitro*.

კლეთკი Jurkat ინკუბიროვალ ნ სტანდარტური სოფიური. ს ქელეო აქტივაციი კლეთკი Jurkat ინკუბიროვალ ს ფიტოგემაგლუტინინო (PHA), 50 მკგ/მლ, ნ პრისუტსვიი პროპრონოლოლა ( $10^{-4}$  M) ნ ბეზ ნეო პრი 37°C ნ ტეჩენე 24 კოლო. ციტოკინოვი პროფილ (IL-2, IL-10, IFN- $\gamma$ ) ნ ინტაქტური ნ PHA-სტიმულირეული კლეთკი Jurkat, ინკუბირეული ს ანტაგონისტი  $\beta$ -ადრენორეცეპტოროვ პროპრონოლოლი ნ ბეზ ნეო, ისსედოვალ პოსედრსტოვი იმუნოფერმენტური ანალიზი ELISA.

პროდუქციი IL-2, IL-10 ნ IFN- $\gamma$  ნ ინტაქტური კლეთკი Jurkat ბელა იქონი ნიკოვი; ნ PHA-სტიმულირეული კლეთკი Jurkat - ზემოთ იზელევილას (p<0,05). პროპრონოლოლი ზნიკოთ ისსედოვალ პროდუქციი IL-2, IL-10 ნ IFN- $\gamma$  ნ PHA-

სტიმულირეული კლეთკი Jurkat (P<0,05). პროდუქციი ციტოკინოვ (IL-2, IL-10, IFN- $\gamma$ ) პოსლე ზოდიქსტივიი პროპრონოლოლა ნ ინტაქტური კლეთკი Jurkat მენელას ნეზნიკოთელეო, იკოზივალ, ქო ინგიბირეული ქოდიქსტივიი პროპრონოლოლა ნ სეკრეციი ციტოკინოვ ნ PHA-სტიმულირეული კლეთკი Jurkat ნ ელელას სედსტივიი ციტოტოქსიკური ეფექტი პროპრონოლოლა ნ კლეთკი, ა რეზულტოტი იეო სეპეციფიკური ინგიბირეული აქტივოტი.

რეზულტოტი ისსედოვანი პოვოლიოთ ზკლეთოქი, ქო ს ქელეო რეგულიაციი ფუნქციონალური აქტივოტი ლიმფოციტოვ პრი რალიკური ზოხოლევიანი ნეობოხოვიოთ იქოთივალ რეოთ აოთრეგულირეული მექანიზმოვ, იბესნიქივალური ვეოოდიქსტივიი იმუნური კლეთკი ს მედიოტორი ნერვიი ნ ენდოქრინური სისტიემი, პოდერზიანი გეოეოსტოზი ეთი სისტიემი ნ რეგულიაციი იმუნური ქოდიქსტივიი.

### რეზიუმე

პროპრონოლოლის მოქმედება ციტოკინების პროფილზე ადამიანის T-ლიმფოციტების (Jurkat უჯრედები) ექსპერიმენტულ მოდელში *in vitro*

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კვლევაში, იმუნომოდულაციის პროცესებში ნეიროენდოკრინული მექანიზმების როლის დასადგენად, შესწავლილია პროპრონოლოლის მოქმედება ციტოკინების პროფილზე ადამიანის T-ლიმფოციტების (Jurkat უჯრედები) ექსპერიმენტულ მოდელში *in vitro*.

Jurkat უჯრედების ინკუბაცია ხდებოდა სტანდარტულ პირობებში. Jurkat უჯრედების სტიმულირება განხორციელდა ფიტოჰემაგლუტინინთან (PHA) 50 მკგ/მლ ინკუბაციით, 37°C-ზე, 24 საათის განმავლობაში, პროპრონოლოლის ( $10^{-4}$  M) თანაობისა და მის გარეშე ციტოკინების პროფილი (IL-2, IL-10, IFN- $\gamma$ ) ინტაქტურ და PHA-სტიმულირეულ Jurkat უჯრედებში, ინკუბირებულ  $\beta$ -ადრენორეცეპტორების ანტაგონისტთან, პროპრონოლოლთან და მის გარეშე, განისაზღვრა იმუნოფერმენტული მეთოდის ELISA-ს საშუალებით.

IL-2, IL-10 და IFN- $\gamma$  დონე ინტაქტურ Jurkat უჯრედებში ძალიან დაბალი იყო, ხოლო PHA-სტიმულირეულ Jurkat უჯრედებში მათი დონე მკვეთრად გაიზარდა (P<0,05). პროპრონოლოლი მნიშვნელოვნად შეამცირა

IL-2, IL-10 და IFN- $\gamma$  წარმოქმნის დონე PHA-სტიმულირებულ Jurkat უჯრედებში (p<0,05).

ციტოკინების (IL-2, IL-10, IFN- $\gamma$ ) წარმოება პროპრონოლოლის ზემოქმედების ფონზე ინტაქტურ Jurkat უჯრედებში მნიშვნელოვნად არ შეცვლილა, რაც მიუთითებს, რომ პროპრონოლოლის ინიჰიბიტორული მოქმედება ციტოკინის სეკრეციაზე PHA-სტიმულირებულ Jurkat უჯრედებში არ არის გამოწვეული პროპრონოლოლის უჯრედებზე ციტოტოქსიკური მოქმედებით, არამედ მისი სპეციფიკური ინიჰიბიტორული მოქმედების შედეგია.

ავტორებს კვლევის შედეგებზე დაყრდნობით გამოტანილი აქვთ დასკვნა, რომ ლიმფოციტების ფუნქციური აქტივობის დასარეგულირებლად სხვადასხვა დაავადებების დროს აუცილებელია გათვალისწინებულ იყოს აუტორეგულაციური მექანიზმები, რომლებიც უზრუნველყოფენ იმუნური უჯრედების ურთიერთქმედებას ნერვული და ენდოკრინული სისტემების მედიატორებთან, ამ სისტემების ჰომეოსტაზის შენარჩუნებას და იმუნური პასუხის რეგულაციას.



## BIOPHARMACEUTICAL UNDERSTANDING OF FORMULATION PREPARATION VARIABILITY OF PLGA NANOPARTICLES LOADED WITH ERYSIMUM EXTRACT

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Polymeric nanoparticles (PNPs) are a nanotechnology-based system fabricated for pharmaceutical purposes [2,3]. In recent years interest towards polymer nanoparticles has been especially increased due to their favorable characteristics in terms of simple elaboration and good biocompatibility. PNPs have a marked role since they can bring therapeutic agents in the human body with excellent efficiency [4,5]. In addition, they transport active ingredients to intended position at the specified concentration and impart stability and longer duration. Thus, PNPs are considered one of the ideal candidates for drug delivery systems [6]. The design of a PNP delivery system requires efficient control of quality characteristics. Moreover, the development of an unstable nanocomposition results in the uncontrolled and unpredictable behavior of nanoparticles in a complex biological environment [4]. That is why it is critically important to develop nanoparticles with stable, reproducible properties. The properties of polymeric nanoparticles depends on various factors, such as polymer nature, physical-chemical properties of active substance and target characteristics of nanoparticles. Accordingly, understanding process and formulation variables influencing the nanoparticles properties is very important. Though, most of the nanoparticles preparation methods need to be developed and optimized [7,8]. Various process variables influence the characteristics of nanoparticles prepared, which needs to be determined and strictly adjusted during nanoparticle fabrication process. The purpose of this study was to evaluate the effect of process and formulation variables on the preparation of biodegradable polymeric nanoparticles. Poly-lactide-co-glycolide (PLGA) was selected as the most widely used biodegradable polymers [2], which protects active pharmaceutical ingredient from human defence system. Also, PLGA as a nanocarrier, is good candidate to insure sustained release of active ingredient. PLGA based nanoparticles were prepared by modified emulsification method [4,7]. During experiment we studied impact of various biopharmaceutical factors on colloidal characteristics of nanoparticles.

**Material and methods.** Biodegradable polymer PLGA, Poly(D,L-Lactide-co-Glycolide, (LA:GA 50:50, MW 7000-17000), Surfactants: polysorbates-Tween 80, tween 20, Sorbitan monooleate (MW 1310), polyvinyl alcohol (PVA, Mowiol 8-88, MW 67,000), Kolliphor P188 (Poloxamer 188) were purchased from Sigma-Aldrich (Germany). Organic solvents: acetone, chloroform, 1,2-dichloroethane were provided by Tbilisi State Medical University. Freeze-dried crude extract of *Erysimum contractum* Somm. Et Levier was obtained from Neopharmi LTD, Tbilisi, Georgia. Crude extract of *Erysimum contractum* Somm. etLevier is rich with of flavanoids and indole, pyridine alkaloids. Cytotoxic activity of crude extract of *Erysimum contractum* Somm. etLevier is also evaluated by Dr. Dali Beridze.

*Preparation of the NPs (General Procedure).* The polymer NPs were prepared according to the modified emulsification-solvent evaporation method. All experiments of NPs formulation were performed at room temperature. In a typical procedure, a definite amount of PLGA was dissolved in an organic solvent. The organic phase was added to the aqueous phase containing

surfactant and stirred on the magnetic stirrer at 2500 rpm. Evaporation of organic phase takes place at room temperature. Particles are washed three times with 20 ml distilled water. Nanoparticles are washed and collected by centrifuging (15 000 g, 15 min). The influence of the different factors such as organic solvents, surfactants, as well as a polymer concentration in the organic phase, surfactant concentration in the aqueous phase, the organic/water phase ratio on the NPs fabrication process was studied.

*NPs Size and size distribution.* The mean particle diameter of NPs was characterized by size and size distribution (Polydispersity Index, PDI). Measurement was performed by dynamic light scattering (DLS) using a Zetasizer Nano ZS (Malvern Instruments, U.K.) at 25°C. The MPD and PDI are presented as an average of three individual measurements± standard deviation (SD).

*Entrapment efficiency.* The amount of entrapped active pharmaceutical ingredient (crude extract of *Erysimum contractum* Somm. etLevier) was calculated by dissolving the nanoparticle sediment into DMSO (dimethyl sulfoxide) and entrapment efficiency was calculated according to the equation: EE%= amount of extract determined in sediment x100%/applied amount of extract. The absorbance was measured at 425 nm.

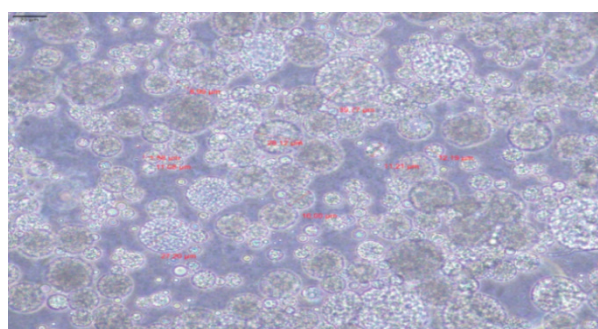
**Results and discussion.** *Influence of surface active substances on particle size and size distribution.* Surface active substances (surfactant) are used to reduce the surface tension and stabilize the droplet phase during emulsification process. The nature and concentration of the surfactant influence on particle size, polydispersity index and their colloidal stability [5].

Low concentration of the surfactant results in colloidal instability of the nanocomposites. While at high concentration, as surfactant acts as a solubilizing agent, the active substance diffuse in aqueous medium and is dissolved in the form of micelles, thus entrapment efficiency is decreased. This phenomenon also reduces surfactant concentration in aqueous medium, which results in colloidal instability of system [9]. Thus, determination of optimal concentration of the surfactant is one of the critical parameters during nanoparticle fabrication. Different non-ionic surfactants were used in nanoparticle preparation process: poloxamer 188, sorbitan monooleate (Span 80), polysorbate 20 (tween 20), polysorbate 80 (tween 80), polyvinyl alcohol (PVA). The NPs were prepared according to the general procedure described above. The parameters of the NPs fabrication process are given below: concentration of the polymer in organic phase 50 mg/ml, organic solvent - 1,2 dichloroethane, organic phase/ water phase ratio – 1:20. Fifteen composition was developed to study influence of surfactants.

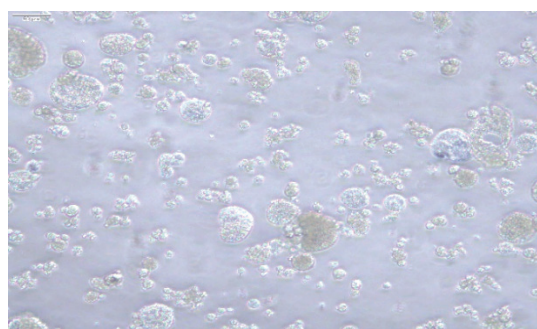
Empirical screening of the prepared nanocomposites was implemented by visual evaluation of nanoemulsion. Exclusion criteria was phase separation and formation large aggregates. In nanocomposites where no large aggregates are visually observed, biological microscope and dynamic light scattering (DLS) are used to characterize size distribution of nanoparticles. List of the formulations, as well as their visual evaluation results are given in the Table 1.

Table 1. The influence of surfactant concentration on PNPs formation

Formulation №	Type of Surfactant	Surfactant concentration, %	Visual evaluation
1	Poloxamer 188	0.1	Complete aggregation
2	Poloxamer 188	0.5	Complete aggregation
3	Poloxamer 188	1,0	Complete aggregation
4	Poloxamer 188	2.5	Aggregation after washing step, difficult resuspendability
5	Poloxamer 188	5	Aggregation after washing step, difficult resuspendability
6	Tween 20	0.5	Complete aggregation
7	Tween 80	0.5	Complete aggregation
8	Span 80	0.5	Complete aggregation
9	Tween 80	2.5	Coalescence, flocculation
10	Tween20	2.5	NPs sedimentation problem
11	Tween 80	2.5	NPs sedimentation problem
12	Polyvinyl alcohol	5	gelatinization of aqueous phase
131	Polyvinyl alcohol	2,5	No aggregation, easily resuspendable
14	Polyvinyl alcohol	1,0	Separate aggregates after resuspension
15	Polyvinyl alcohol	0,5	Separate aggregates after resuspension

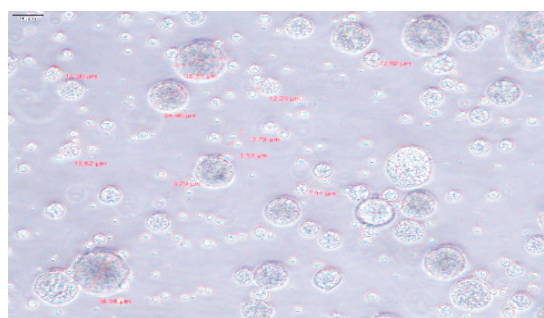


a

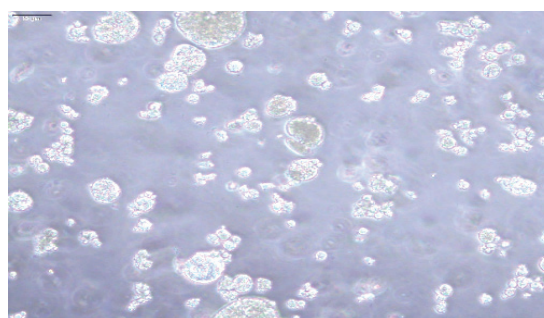


b

Fig. 1. Microscopic images of nanocompositions prepared with poloxamer 188 (2.5%)



a



b

Fig. 2. Microscopic images of nanocompositions prepared with 2.8 % tween 80 (a), 2.5% tween 20 (b)

Considering the surfactant structure, we tried to assess the mechanism of their influence on the properties of nanoparticles. Investigations carried out by us proved that in compositions with low poloxamer 188 concentration (<1%), complete aggregation of polymer occurred instantly (composition 1,2,3, Table 2). While at high concentration of poloxamer 188 (2-5%) composite loses colloidal stability only at purification stage. Evaluation by microscope figures (Fig. 1a,b) clearly shows the colloidal instability mechanisms of the emulsion systems, such as coalescence and flocculation.

The above stated phenomenon can be explained by chemical structure of poloxamers. Chemical structure of poloxam-

ers contain hydrophilic polyethylene oxide blocks (PEO) and hydrophobic polypropylene oxide blocks (PPO), all poloxamers have similar structure, but they differ by molecular weight and PEO/PPO ratio. Hydrophobic (PPO) blocks in poloxamer 188 is less, which results in weak interaction between the hydrophobic polymer (PLGA) particles and the poloxamer. This is the reason why most of the surfactant is removed at washing step and aggregates are formed. The same mechanism explains the colloidal instability of nanocomposites prepared with low concentration (0.5%) of polysorbates (Tween 20, Tween 80) and sorbitan monooleate (span 80), formulations № 6,7,8 respectively (Table 1). Low concentration of the above stated surfac-

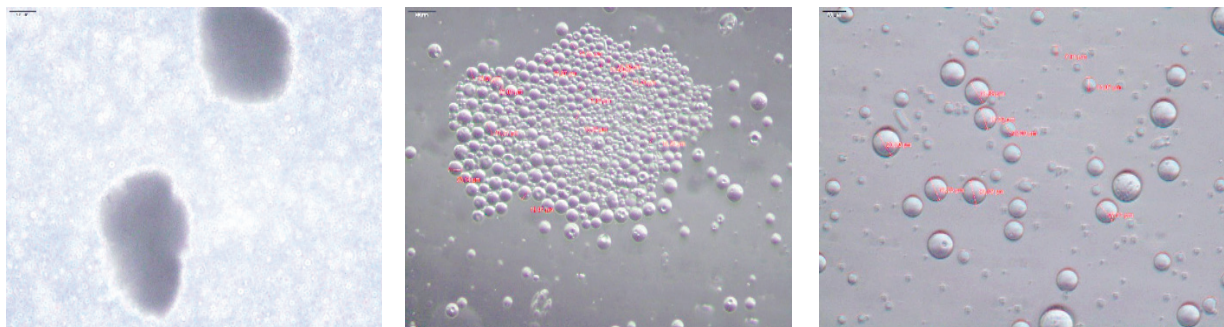


Fig. 3a - PVA 2.5% Fig. 3b. - PVA 0.5% Fig. 3c. PVA 0.1%

tants (Tween 20, Tween 80, span 80) are not sufficient to ensure colloidal stability of composite, visible aggregates are formed instantly. The reason is excess of hydrophilic blocks in their structure, which prevents from strong interaction of surfactant and polymer particle surface. But, in case high concentration ( $\leq 2.5\%$ ) no visually detectable aggregates are formed, although microscopic images prove colloidal instability, such as coalescence, flocculation (Fig. 2a,b).

When high concentration of sorbitan monooleate (span 80) was used nanoparticle sedimentation problem occurred independence of centrifugation speed and duration. The reason of this problem was also in the structure of surfactant. The so-called netlike positioning of hydrophobic blocks of sorbitan monooleate (SPAN 80) in water phase prevents sedimentation of nanoparticles (especially of small size particles).

During our experiments polyvinyl alcohol was used as a surfactant. There are partially hydrolyzed and fully hydrolyzed polyvinyl alcohols. Amount of residual acetyl group in fully hydrolyzed polyvinyl alcohol is approximately 1.5% which provides weak interconnection between the surfactant and PLGA particle surface. Partially hydrolyzed polyvinyl alcohol contains more hydrophobic acetyl groups (10%), that provides stronger interaction of polyvinyl alcohol to the surface of PLGA particles. That is why partially hydrolyzed polyvinyl alcohol is preferred for nanoparticle fabrication.

The above stated hypothesis was proved by the experiments too, in the formulation (№12, 13, 14, 15), where partially hydrolyzed polyvinyl alcohol was used no aggregation of particles was detected. Influence of polyvinyl alcohol concentration is also interesting. In particular, in the experiment we used various concentrations of the surfactant (Table 2). In case of 5% concentration (formulation-12) increased viscosity of water phase prevented further separation of phases and sedimentation of NPs. Microscopic images (Fig. 3a,b,c) clearly show that the particle

size is not homogeneous and they are of micro scale size (within 10-40 micrometer).

Re-suspension of nanocomposites prepared with low concentration of PVA (0.1-0.5%) doesn't occur completely. At the stage of washing, because of removal of a surfactant, the composite loses its stability and collected particles are hardly re-suspended. This is proved microscopically by the presence of single aggregates (Fig. 3a,b,c). Thus, application of 2.5% partially hydrolyzed polyvinyl alcohol provided formation of relatively stable nanocomposites (Fig. 3a). Nanoparticles are easily re-suspendable, particles are of micro-size, with non-homogeneous distribution, although microscopic images do not prove presence of single aggregates. Thereafter, size and poly-dispersion degree of formulation №12 were evaluated by DLS, the size and polydispersity index were  $731.5 \pm 71.02$  and  $0.786 \pm 0.022$ , respectively. Results demonstrate that particles at nanoscale are obtained with broad size distribution. At the next stage, influence of other formulation variables was studied to obtain nanoparticles with narrow size distribution.

*Influence of organic solvent on NPs sizes and size distribution.* Selection criteria of organic phase for nanoparticle preparation was solubility of PLGA polymer. As usual, selection of organic solvent is made empirically. Mechanism of organic solvent influence on particle size is not clearly known. According to one of the hypotheses, organic solvent diffusion coefficient in water can be used as an indicator of particle sizes and distribution degree. Organic solvent with high diffusion factor provides relatively small size and monodisperse particles, while organic solvent with low diffusion factor works on the contrary. The following organic solvents were used in study: chloroform, 1,2 dichloroethane and acetone, formulations are given in Table 2.

Particle size and polydispersity index in composites were evaluated by DLS. Results are given in Table 3.

Table 2. Compositions with different organic phase

Formulation №	Organic phase				Aqueous Phase	
	PLGA, mg	1,2 dichloroethane, ml	Chloroform, ml	Acetone, ml	Polyvinyl alcohol, %	Water, ml
13	50	1	-	-	2,5	20
16	50	-	1	-	2,5	20
17	50	-	-	1	2,5	20

Table 3. Influence of organic solvent on NPs size and size distribution

Formulation №	Z-Ave (nm)	Polydispersity index (PDI)
13	$731 \pm 71$	$0.786 \pm 0.022$
16	$1299 \pm 308$	$0.663 \pm 0.114$
17	$571 \pm 53$	$0.337 \pm 0.12$

Table 4. Impact of aqueous and organic phase ratio on the particle size and entrapment efficiency

Composition № F	Z-Ave (nm)	Polydispersity index (PDI)	Entrapment efficiency (%)
17 (1:20)	571±53	0.337±0.12	25
18 (1:10)	27 ±5	0.228±0.012	48
19 (1:5)	232±3.25	0.18±0.004	73

The obtained results demonstrates (Table 3) that organic solvent greatly influence on NPs size and size distribution. The obtained results proved the hypothesis regarding organic solvent mentioned above. Improved size distribution was obtained in the formulation prepared with water miscible organic solvent, acetone (formulation F17). According to the literature data, nature of organic solvents can influence on interaction of surfactant with polymeric nanoparticles, which itself impactson thecolloidal stability. Apparently, in case water miscible organic solvent is applied, number of surfactants associated with (formulation-17). Therefore, acetone was selected as an organic solvent.

*Influence of polymer concentration on nanoparticle sizes and size distribution.* To determine impact of polymer concentration on particle size we used 50 and 100 mg PLGA. The condition of the NPs fabrication process is: polyvinyl alcohol – 2.5%, organic solvent – acetone, organic phase/ water phase ratio – 1:20. Variable parameters: polymer concentration- 50 mg/ml, 100 mg/ml. By increasing polymer concentration from 50 mg to 100 ml NPs size was increased from 571 nm to 882 nm, respectively. Polydispersity index was also increased from 0.33 to 0.68. By increasing polymer concentration, the viscosity of the organic phase is rised. This increases viscosity force and decreases homogeneous distribution of emulsion drops, which contributes to formation of big size particles. Thus, 50 mg PLGA was considered as an optimal concentration of polymer.

*Influence of aqueous and organic phase ratio on the entrapment efficiency.* Ratio of aqueous and organic phase mainly influences on the entrapment efficiency of active substances in the nanoparticles, especially when organic solvent (acetone) is water miscible.

Alongside with it, ratio of aqueous and organic phase influence on the particles meophology as well. Increase of aqueous phase ensures rapid solidification of nanoparticles, their surface is smoother with a smaller number of pores. By decreasing ratio of aqueous and organic phase the number of pores increases, which in its turn results in high speed of drug release.

Therefore, to achieve high entrapment efficiency of active substance we studied the impact of aqueous and organic phase ratio. The condition of the NPs fabrication process is: polyvinyl alcohol – 2.5%, organic solvent – acetone, amount of PLGA- 50 mg. Variable parameters: organic phase/ water phase ratio- 1:20, 1:10, 1:5.

Impact of aqueous and organic phase ratio on the particle size and entrapment efficiency is given in Table 4.

The obtained results (Tables 4) proved the above referred theoretical hypothesis: decrease of aqueous medium increases the entrapment efficiency. This is explained by the fact that, increasing volume of aqueous phase, more active substances migrate from organic phase to aqueous phase. This process is more intensive when water miscible organic solvent (acetone) is used in the formulation. This is the explanation, that in formulations № 17 and 18 entrapment efficiency is low, 25% and 48% respectively. Decrease of aqueous and organic phase ratio posi-

tively influences on the particles size distribution as well. This is explained by the fact that mixing in small volume is much more intense and homogenous, than in case of big volume. According to the results optimal ratio of aqueous medium and organic phase is considered to be 1:5. This condition obtained smaller nanoparticles (232 nm) with narrow size distribution (0.18) and 73% of entrapment efficiency.

In summary, based on the performed experiments optimal formulation of nanocomposite is suggested: polyvinyl alcohol – 2.5%, organic solvent – acetone, amount of PLGA- 50 mg, organic phase/ water phase ratio 1:5.

**Conclusion.** The result of the study demonstrates that the formulation variables could be effectively altered to achieve the desired characteristics of polymeric nanoparticles. The influence of the various biopharmaceutical factors such as type of organic solvent, surfactant, as well as surfactant concentration in the aqueous phase, polymer concentration in the organic phase, the organicphase/water phase ratio on the NPs size, size distribution and entrapment efficiency were studied. The influence mechanism of different biopharmaceutical factors on the colloidal characteristics of polymer nanoparticles has been theoretically explained and experimentally confirmed. Based on performed study optimal formulation and preparation method of nanocomposite is provided.

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## SUMMARY

### BIOPHARMACEUTICAL UNDERSTANDING OF FORMULATION PREPARATION VARIABILITY OF PLGA NANOPARTICLES LOADED WITH ERYSIMUM EXTRACT

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The purpose of this study was to evaluate effect of process and formulation variables on the preparation of Erysimum extract loaded PLGA nanoparticles.

The influence of the various biopharmaceutical factors such as type of organic solvent, type and concentration of surfactant, polymer concentration in the organic phase, ratio of organic phase and water phase were studied. Modified emulsification solvent evaporation method was used for preparation of nanoparticles. Based on the performed experiments optimal formulation of nanocomposite is suggested. Nanoparticle size, size distribution and entrapment efficiency were determined. Among five non-ionic surfactants polyvinyl alcohol provided more stable nanocomposite. Influence mechanisms of different surfactants on nanoparticle formation are provided. Water miscible organic solvent, acetone obtained 232 nm nanoparticles with improved size distribution. Entrapment efficiency was increased to 73% by reducing ratio of organic and water phases. Based on experiments nanoparticles with stable, reproducible properties are fabricated.

**Keywords:** polymeric nanoparticle, PLGA, formulation variables, endemic plant species.

## РЕЗЮМЕ

### ОЦЕНКА ВЛИЯНИЯ БИОФАРМАЦЕВТИЧЕСКИХ ФАКТОРОВ НА СВОЙСТВА НАНОЧАСТИЦ PLGA, СОДЕРЖАЩИХ ЭКСТРАКТ ERYSIMUM CONTRACTUM SOMM

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Целью исследования явилась оценка влияния биофармацевтических факторов на свойства наночастиц PLGA, содержащих экстракт *Erysimum contractum Somm*.

Изучено влияние различных биофармацевтических факторов: органический растворитель, тип и концентрация поверхностно-активного вещества, тип и концентрация полимера в органической фазе, соотношение водной и органической фаз. Исследовано влияние пяти неионных поверхностно-активных веществ на свойства наночастиц. Теоретически обоснован и экспериментально подтвержден механизм влияния различных биофармацевтических факторов на коллоидные характеристики полимерных наночастиц. Экспериментально установлено, что полугидролизированный поливиниловый спирт обеспечивает коллоидную стабильность наноконпозиции.

Для приготовления наночастиц использовали модифицированный эмульсионный метод. Предложено оптимальное содержание наноконпозиции: поливиниловый спирт - 2,5%, соотношение водной и органической фаз - 1:5, полимер (PLGA) - 50 мг, органический растворитель - ацетон, активное вещество - 5 мг. Определены размер частиц, индекс полидисперсности и инкапсулирование активного вещества. Использование смешиваемых с водой органических растворителей обеспечивает образование наночастиц 232 нм и значительно улучшает степень диспергирования частиц. Уменьшение соотношения водной и органической фаз обеспечило увеличение степени инкапсулирования активного вещества до 73%. Результаты исследования показали, что, изменяя параметры, можно получить наночастицы с желаемыми характеристиками.

## რეზიუმე

ბიოფარმაცევტული ფაქტორების გავლენის შეფასება *Erysimum contractum Somm*-ის შემცველი პოლიმერული ნანონაწილაკების მახასიათებლებზე

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, <sup>1</sup>ფარმაციის ფაკულტეტი, ფარმაცევტული ტექნოლოგიის დეპარტამენტი; <sup>2</sup>ფარმაცოგნოზისა და ფარმაცევტული ბოტანიკის მიმართულება, საქართველო

კვლევის მიზანს წარმოადგენდა ბიოფარმაცევტული ფაქტორების გავლენის შეფასება შეჯგუფებული ერიზიმუმის ექსტრაქტის შემცველი PLGA ნანონაწილაკების მახასიათებლებზე.

შესწავლილია სხვადასხვა ბიოფარმაცევტული ფაქტორების გავლენა, როგორცაა ორგანული გამხსნელი, სურფაქტანტის ტიპი და კონცენტრაცია, პოლიმერის კონცენტრაცია ორგანულ ფაზაში, ორგანულ ფაზისა და წყლის ფაზის თანაფარდობა.

ნანონაწილაკების მოსამზადებლად გამოყენებული იყო მოდიფიცირებული ემულგირება - გამხსნელის აორთქლების მეთოდი. ჩატარებული ექსპერიმენტების საფუძველზე შემოთავაზებულია ნანოკომპოზიციის ოპტიმალური რეცეპტურა. განსაზღვრულია ნანონაწილაკების ზომა, ზომის განაწილება და ჩართულობის ხარისხი. შესწავლილია სუთი არაიონური სურფაქტანტის გავლენა ნანონაწილაკების მახასიათებლებზე. ექსპერიმენტულად დადგენილია, რომ ნახევრადპიდროლიზებული პოლივინილის სპირტი უზრუნველყოფს ნანოკომპოზიციის კოლოიდურ სტაბილურობას. ასევე მოწოდებულია სხვადასხვა ზედაპირულად აქტიური ნივთიერებების გავლენის თეორიული საფუძველები ნანონაწილაკების მახასიათებლებზე. წყალთან შერევადი ორგანული გამხსნელის გამოყენება უზრუნველყოფს 232 ნმ ზომის ნანონაწილაკების ფორმირებას და მკვეთრად აუმჯობესებს ნაწილაკების განაწილების ხარისხს. წყლიანი და ორგანული ფაზის თანაფარდობის შემცირებამ უზრუნველყო მოქმედი ნივთიერების ჩართულობის ხარისხის 73%-მდე გაზრდა. კვლევის შედეგები ცხადყოფს, რომ სხვადასხვა პარამეტრის ცვლილებით შესაძლებელია სასურველი მახასიათებლების მქონე კომპოზიციის მიღება.

## THE BOUNDARIES OF GENDER TOLERANCE IN THE MODERN SOCIETY AND LEGAL STATE (REVIEW)

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For several decades, personal human rights have taken a prominent place in legal science. However, by virtue of their specificity, such rights have always had a particular perception on the part of the legislator, as well as society and its moral and ethical values. The development of gender identity should not affect the ability to enjoy such a fundamental human right as state recognition. The issue of normative consolidation of basic human rights arising from gender self-identification of an individual is currently relevant to modern democratic states, whose main focus in development are human beings, their rights and freedoms. This is related not only to the interests of an individual, but it is also a condition for the progressive development of the modern state itself, since appropriate regulatory regulation of emerging social relations is an effective tool for the state's response to changes in traditional perceptions of society and transformation of its values.

### **The social concept of «gender» in the modern state**

*Breaking a taboo always stirs quick emotions  
although attempts to rationalize may follow.  
The forces of nature, however, know nothing  
of this taboo, and facts remain facts.*

*H. Benjamin<sup>1</sup>*

Gender differentiation between people defined as «man» and «woman» occurs at different levels. In fact, there are seven aspects of sex: chromosomal, gonadal (gender of the sex glands), anatomical, hormonal sex, as well as psychological, erotic-emotional and social sex. Unlike the past society, in which the existence of intermediate categories – often referred to as «hermaphrodites» – still seemed self-evident, a strictly binary concept had spread since the beginning of the 19<sup>th</sup> century. It declared the single perfect congruent orientation of all seven levels of gender as «male» or «female», and any divergence from it was considered deviant and undesirable [12].

Based on the «Chicago Consensus 2005» previously used medical terms such as Hermaphrodite or Pseudo-hermaphrodite, who were perceived as stigmatizing by the victims, have been replaced by the neutral term DSD – the disorder of sex development. Since then, medicine has used DSD as a generic term for a large number of diagnoses with different causes, development processes and manifestations that apply to persons who cannot clearly identify female or male to become, genetically and/ or anatomically or hormonally [12].

The 11th Revision of ICD is presented to the World Health Assembly in May 2019 for adoption and to replace all earlier Revisions from 1 January 2022. The new ICD-11 uses the term Gender incongruence to replace all species of Gender dysphoria and Gender identity disorders that have been removed from the list of mental and behavioural disorders and transferred to the section «Conditions related to sexual health».

Gender incongruence of Adolescence and Adulthood is characterised by a marked and persistent incongruence between an

individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender [38]. The incongruence of childhood must have persisted for about 2 years [39].

However, the more humanity evolves and develops, the more conflicts between science and morality are inherently incompatible [43]. We believe that the conflict arises not only between science and morality, but also between morality and genetics (in particular, the recognition of equal rights of intersexual people<sup>2</sup>), morality and the right to respect for privacy (for example, regarding the issue of sexual rights such as prostitution, same-sex marriage, as well as the right to gender identity).

At present, there is a conflict between sex and gender, namely, between biological sex and social gender in the modern society.

As to the issue of sex, it should be noted that it is socially defined and is the result of the interaction of factors and processes that operate at different biological and psychosexual levels. These include the anatomical and hormonal constitution of a person, the psychological development and resulting identity, as well as social biography (upbringing). Sex also refers to the role of man in society. As a rule, it corresponds to the biological sex, yet sometimes conflicting with it. The sex of a child's upbringing describes the role of a child in the family and society. When a person's sex is registered in the Civil Status Register, the respective sex is recorded administratively and used for other statutory purposes as a distinguishing feature. So far, this has hindered the adoption of intersexual positions in many practical life situations [16].

At present, gender debates have become too dangerous to discuss the differences between what is «real» and what is our social construction. This is too polarized an issue to allow it to develop further and safely support the moral and psychological aspects of children or adults. However, there is a category of people who have repeatedly asked to stop engaging in gender debates – a person's intersex or intersexual people (intersexuality is a simultaneous presence of both male and female characteristics in an individual; intersex is a bisexual person [45]).

Such separation of intersex persons from gender discussions is due to the fact that their gender identity is primarily characterized not by social, psychological (though not excluded) or erotic-emotional sex, but by genetic (anatomical) one. H. Benjamin points out that intersexual people exist both in the body and in the mind. And their disapproval affects far more morality than science [6] (as opposed to transgender or transsexual people).

Medical or social categorization of a person as belonging to one of the two genders or not related to either of them make a neutral diagnosis but affect the self-perception and identity of

<sup>1</sup>Benjamin H. *The transsexual phenomenon* New-York: The Julian Press, Inc. Publishers; 1966.

<sup>2</sup>The conceptual clarification of the medical definition of intersexuality is an ambiguity in the classification of an individual as such, which refers to the male or female sex, as the distinctive features reflect the atypical development of the chromosome, anatomical or hormonal sex. These sexual variants may appear during pregnancy, immediately after birth or at a later age.

such a person. Conflict can arise if a person with an intersex phenotype is identified as belonging to a gender that person does not want or cannot accept. And conversely, conflict is also possible if a person is classified as intersex on the basis of physical characteristics, despite the fact that he is subjectively uniquely related to a particular sex and does not consider physical differences to be significant [16].

In this respect, it may be appropriate to group all intersex persons into one new collective category, such as the «third gender» or «X» gender, parallel to female and male. Such a classification would be incorrect because of the large diversity of intersex people and the fact that many identify themselves as women or men, while others identify themselves as both male and female – that is, the third gender itself. Although there is a group of people who do not refer to either the male, female or third gender, while identifying themselves as a neutral gender that does not belong to any of the above (though, we note that this problem is thus related to the problem of only psychological dysfunction, not physiological). Hence, the selection of gender for persons with Gender Incongruence should, in the presence of anatomical features, be exclusively dispositive at the state level.

Consequently, it is about gender identity. It is a social construction, while sex is a concept that exists whether we perceive it as real or not [37].

The German Ethics Council also defines sexual identity as a general term for self-categorization of people according to their body, hormonal abilities, feelings and biography (including how they were brought up as a child). Sexual identity does not necessarily correspond to a person's physical sex and may conflict with it [16].

Thus, we consider it necessary to highlight in more detail the individual aspects of gender identity in the light of European human rights guarantees.

Therefore, the «real instrument» that must be interpreted in the light of current conditions is the Convention for the Protection of Human Rights and Fundamental Freedoms (the European Convention) [35]. The European Court of Human Rights also defines gender identity and personal development as a fundamental aspect of the right to respect for privacy guaranteed by Article 8 (clause 1) of the European Convention [1], where freedom to determine one's sexual identity is one of the most fundamental elements of this article in general, and the definition of personal autonomy in particular [32]. However, the court interpretation of the rules is general and does not reveal the exact scope of the State's obligations in this area [41].

Hence, private life is a broad term that is beyond exhaustive definition. It includes not only the physical and psychological inviolability of a person, but sometimes it can also cover aspects of his physical and social identity. The right to respect for privacy under Article 8 of the European Convention fully extends to gender identity as a component of personal identity. This applies to all persons. Elements such as gender identification, name, sexual orientation and sexual life are within the personal sphere that is protected by this article [33]. The European Court of Human Rights also provides that serious interference with privacy can occur when the law of a country conflicts with an important aspect of an individual [7], since respect for fundamental human rights cannot meet the requirement that a person has concealed any aspect of his or her personality.

Particular attention should be paid to the opinion of the judges in the case «X and Others v. Austria», which concerned the violation of the right to respect for privacy and discrimination on the basis of gender, where priority to the adoption of a child

was given to the unmarried mixed-sex couple. «The limits of the evolutive interpretation: «present-day conditions» or those of the future». The point of the evolutive interpretation, as conceived by the Court, is to accompany and even channel change; it is not to anticipate change, still less to try to impose it. Without in any way ruling out the possibility that the situation in Europe in the future will evolve in the direction apparently wished for by the majority, this does not seem to be the case, as we have seen, at present. We therefore believe that the majority went beyond the usual limits of the evolutive method of interpretation [40].

At present, most discussion is about legal approval of the change of sex in official documents of a person. The case law of the European Court of Human Rights states that the practice of a general register of civil status acts is to use only biological criteria of sex, namely: chromosomal, gonadal and sexual. The fact that it subsequently becomes apparent that a person's psychological gender is incompatible with these biological criteria does not mean that initially the entry in the acts of civil status is a factual mistake. Only in the case of a clerical error, or when the explicit sex of the child has been incorrectly identified, or if there is a biological criterion for intersexuality, that is, when biological criteria do not match, will changes to the original record be considered and then medical evidence should be provided that the original entry was incorrect. However, there is no error in the birth record of a person who has undergone medical and / or surgical treatment to allow that person to assume the role of the opposite sex [21].

In the case «S.V. v. Italy» the European Court of Justice has stated that the refusal to grant a transgender person's application for a change of name before completing the process of transition to sex through surgery was based on purely formal arguments that did not take into account the particular circumstances of a person. In particular, the authorities did not take into account the fact that a person had been in the process of transition to sex for several years and that his appearance and social identity had long been female. In the instant case, the Court did not see what reasons in the public interest could justify a delay of more than two years and half in changing the name given in an applicant's official documents in order to reflect the reality of her social situation, which, moreover, was recognized by the national court. The person was given 10,000 euros in compensation [32].

The arbitrary change in gender has its inherent and negative aspects. For example, the case of 2020 in the Russian Federation is noteworthy. Thus, according to the Office of the Federal Service of Bailiffs in the Kursk region, the debtor through alimony IN SIZE of 800,000 rubles (about 11,500 euros) was wanted. As it turned out, the man changed his gender and his passport in order to avoid alimony [47]. A similar case occurred in Moscow in 2013 [48].

However, such neglect of parental responsibilities cannot be acknowledged by gender reassignment of abuse of the right to gender identity. Such a question depends on the other moral and ethical qualities inherent in an individual. In this case, changing the sex does not automatically entail changing the legal status of a person.

In our study, we consider it necessary to pay attention to the positive aspect of modern democratic states that have deviated from the binary concept of gender. Thus, in Germany since 2013, in case the children «cannot be assigned to female or male», they must be registered in the birth register without gender [23]. In October 2017, referring to the decision of the Supreme Court, the Federal Constitutional Court of Germany declared unconstitutional a norm according to which, at birth registration, in the column «gender» it reflects only «female» and «male» [25]. In August 2018, the Cabinet of Ministers of Germany adopted a

bill amending the Law «On Civil Status», according to which, if upon the birth of a child, it could not be attributed to either a male or female gender, then legal documents can be filled in the column «third gender», instead of leaving the columns unfilled following the permission made in 2013 [8].

The Law on the Legal Status of Persons with Sexual Disabilities in Iceland provides for passive gender registration, marked «X» [26].

In 2018, the court in the Netherlands, in dealing with the case of protection of intersexual rights, stated in its decision that due to «social and legal changes it is time to recognize the third gender» [4]. In June 2018, the Austrian court approved a third gender identity in legal acts [5]. It is believed that such gender legalization was facilitated by the recognition of the famous Belgian model Hannah Gabi Odell in her gender affiliation with intersexual people, as she had said, to «break the taboo» [28].

The problem of protecting gender-diverse individuals has already been the subject of our scientific research, where we have come to the conclusion that personal human rights, such as the right to gender identity, have already been realized. However, sometimes the legislator does not want to take responsibility for developing a mechanism for their practical implementation, due to the fact that the legalization of such rights at the legislative level of a country requires a certain leap in the public consciousness, the size of which depends on the mentality of the people of each individual country [42]. It is also inadmissible to recognize human rights in the rule of law only after they have been found guilty by a court. Sometimes, in exceptional circumstances, such a state of affairs can be justified in the constant development of social relations, when the law simply does not have time to adjust to such relations. Although in most states there is a legislative provision that, in cases provided by law, allows a person to change their gender in official documents upon application, we consider it a positive manifestation of democratic states that most of them have officially recognized the third gender.

One of these countries was France, where as early as 2012 it was proposed not to label women with different names depending on their marital status as appropriate, but to use a neutral designation [14]. However, the country «slowed down» this process [15]. We believe that this may be due to the French policy aimed at excluding gender-neutral language in the official texts [3].

The Netherlands has gone much further in this regard. In particular, in various institutions of the country, official advertisements do not distinguish between men and women at all, but use common terms to define and refer to any gender [13]. For example, instead of the official address «ladies and gentlemen», phrases «dear Amsterdammers», «dear visitors», etc. are used.

#### **Manifestations of gender identity in various aspects of public life**

*«If I didn't define myself for myself,  
I would be crunched into other people's  
fantasies for me and eaten alive»  
A.G. Lorde*

The problems of the legal protection of human rights must be recognized by the world community, and such recognition can be achieved by the state and society in which they live, provided that their security is real in the context of human progress [46].

In recent years, there has been an increasing spread of «gender neutrality» policies in the international arena in various aspects of public life. However, whatever psychological or emotional-erotic sex is not inherent in the DSD person (Since 2022 according to ICD-11 – Gender Incongruence), in particular, the tran-

sitional person (transgender), both male and female sexes still have features that are not medically and surgically eliminated.

For example, this issue refers to the category of men's and women's sports. The issue under consideration came as a result of a lawsuit filed by intersexual runner Caster Semenya against the International Association of Athletics Federation in the Court of Arbitration. Under the new rules for women established by the Association, some runners were forced to lower their testosterone levels to be allowed to compete. Such DSD rules require that Caster Semenya and other athletes with different sexual development artificially lower their testosterone levels to participate in competitions, in particular in which Caster Semenya has won many medals [29]. The Court of Arbitration for Sport dismissed C. Semenya's claim for the actions of such rules of the Association for women.

In the court's ruling on the legality of testosterone levels for DSD athletes, individual trans-lobby groups require that this should be applied to all athletes, and that the biological sex should be replaced by an «athletic gender». For example, J. Harper argues that the sex assigned at birth does not determine the athletic potential of future adults and should not be the sole criterion for the division of athletes into male and female categories. The author states that gender identity alone should not be used to determine the sport category appropriate for that person. As an alternative to the strict use of a sexually identifiable or gender-specific athlete, an athletic gender may be used to separate gender in other arenas from the appropriate category of competition for athletes. The athletic gender can be spoken about in much the same way as other aspects of gender in the sense that it is one of its aspects – it is separate and potentially either identical or different from a legal or sex-specific gender. If fair competition is assessed, then gender should be determined using a scientifically sound metrics, based on performance. If it is recognized that athletic gender differs from social gender, then it follows that the placement of an athlete in the sport category of both men and women does not affect their self-identifying social gender and, therefore, the way that an athlete lives separately from each other, from sport. Thus, the concept of athletic gender can be a powerful idea that resolves many of the conflicts mentioned earlier. For example, the argument that intersexual athletes or transgenders are bound to be stigmatized if they are unable to compete in the female category due to high testosterone levels loses its validity if the athletic gender is clearly different from the social gender. The concept of athletic gender can also be an effective contraindication for passing the required tests. If athletes can be divided on the basis of a standard physiological test, such as testosterone levels, then there is no longer any need to resort to an Allen test-based methodology. This suggests that testosterone levels are the single and best factor in sports performance [18]. Although some scholars believe this statement is false and unscientific. For example, A. Lee points out that trans activists never confirm their position with evidence by appealing to calm, rational negotiations with informed people. In particular: 1) what about testosterone during the period of growth and maturation? 2) how about cellular male muscle memory? 3) what about the obvious physical and biomechanical differences between men and women? There are many very compelling reasons why sport has always been divided into gender (non-gender) categories for justice [24].

Unfortunately, some trans-activist organizations do not want to be aware of such differences. For example, the introduction of gender neutral restrooms, i.e. shared restrooms for boys, girls and DSDs, has been widely publicized in the UK. This deci-



sion was made contrary to the opinions of parents and teachers, as the result of it the girls were skipping school, «because of fear of further ridicule by the boys». The issue was also raised because a representative of the Transgender Trend parental election group later stated that «trans-activist» organizations misinformed schools that they were violating equality laws if they did not make the toilets unisex. It was noted that there are clear exceptions in the current equality laws which mean that having same-sex (provided for each sex) restrooms is absolutely legal [27]. Following another «splash» of transgender workers, British schools have also begun to introduce gender neutral uniforms, including skirts for boys [22].

Gender education has also influenced another private school, St. Paul's, where in 2017 students were allowed to use names and wear the opposite sex uniform in case they determined their gender. The former head of the private school says some students are transgender just to be cool and «cause turbulence» [31]. We believe that this tendency may have a negative impact on the psychological stability of other students who, in virtue of their age, do not realize the difference and see no boundaries between psychological gender and self-integration into society.

Gender issues have also touched the business sector. Thus, the Victoria's Secret global brand, which annually broadcasts its fashion shows around the world, has been criticized for not including «plus» or transgender models, as the fact that the company is a leader in its industry, it must at least try to keep up with the times and show some support for diversity. In 2017, Ed Razek, the marketing executive of the parent company, was interviewed by Vogue, stating that transgender individuals will not be involved in the show, as traditional beauty standards are a marketing strategy for the company and its focus is specialized («We market to who we sell to, and we don't market to the whole world») [30]. The result of this interview was a call from trans activists to publicly boycott the purchase of branded goods as well as the resignation of manager E. Razek [19].

We agree with the view that social life is regulated both by law and different types of social rules. In many areas, social self-regulation can produce better results than legal norms [41].

However, despite the somewhat aggressive tactics of individual trans groups in promoting gender equality in all aspects of public life, there are positive developments in the dissemination of gender-neutral language in the international arena.

Thus, we can see an increasing spread of a «gender neutrality» policy. For example, the introduction of gender-neutral languages is positive. Yet, in 2008, the European Parliament adopted a Gender-neutral language recommendation in the European Parliament [10], which provided for the use of gender-neutral common phrases to eliminate discrimination. In 2018, this document was updated and supplemented, in particular defining the concept of gender-neutral language, as well as another objective of implementing such a language policy by states recognizing the reduction of gender stereotypes, the impetus for social change and the achievement of gender equality [11]. In addition, in February 2019, the European Commission adopted the «English Style Guide», where the section «Inclusive Languages» envisages the use of gender-neutral language for men and women, as well as for LGBT people [9].

However, few countries recognize such language policy. One of these countries is France, which suggests not to label women with different names depending on their marital status as appropriate, but to use a neutral designation [14].

Besides, in 2016, the House of Commons of Canada overwhelmingly passed a private member's bill that would alter the

national anthem by replacing «in all thy sons command» with «in all of us command» as part of a push to strike gendered language from O Canada [34].

This gender-based tolerance has also affected the film industry. The Berlin International Film Festival has opted to make its acting awards gender-neutral, meaning the prizes for Best Actor and Best Actress will be condensed into a Silver Bear for Best Leading Performance. And the supporting awards will become a Silver Bear for Best Supporting Performance [17].

In 2019, the Merriam-Webster dictionary added «they» as a pronoun for «a single person whose gender identity is not two-fold» [36]. The gender-neutral pronoun «hen» was also introduced by the official Swedish dictionary [2].

Ukraine is moving in the opposite direction, where in 2019 new rules of the Ukrainian spelling were adopted, which, on the contrary, determine the formation of nouns from masculine nouns to identify women (*авторка, редакторка, майстриня, патронеса*) [44,49].

P. Jakiela and O. Ozier argue for a strong negative link between gender languages and women's participation in the workforce. Such results are consistent with research in psychology, linguistics, and anthropology, suggesting that languages form thinking patterns in a subtle and subconscious way. Languages are an important part of our cultural heritage, and it would be inappropriate to assume that some languages are detrimental to women's development or rights. However, languages develop over time; the direction of their evolution is determined both by individual choices (for example, whether to use pronouns such as «he» or «she»), and gender-neutral alternatives such as «they») and conscious decisions by public authorities and other thought leaders (such as major newspapers and magazines). As a result, people have to think about the social implications of their language choices, because the nature of the language we speak shapes the way we think as well as the way our children will think in the future [20].

Thus, the recognition of gender neutrality as one of the stages for further recognition of human rights of the fourth generation has long been widely known in the international community (although it has an advisory character). However, sometimes the legislator does not want to take responsibility for developing a mechanism for the practical realization of individual human rights of the fourth generation, which is explained by the fact that the legalization of such rights at the legislative level of a country requires significant changes in the social consciousness, the extent of which depends on the mentality of the people of each country. As for Ukraine, its own established mentality casts doubt on its further development in this direction (in particular, it concerns the legalization of LGBT rights, which is now quite relevant in the territory of European countries).

**Conclusion.** Summarizing our research, we note that the legislation of most democratic states adapts to the requirements of the present, in particular in terms of recognizing the gender identity of a person through the legislative enshrining of the third gender in official documents. Thus, individuals with a Gender incongruence can finally emerge from the shadows by self-identifying themselves in society as full members.

These positive measures have mostly been interfered with by intersexual people, who also differ in their unwillingness to engage in global gender discussions between society and transgender and transsexual representatives. Such passivity of intersexuals has shown a real result in the development of a society whose traditional ideas are «ready» for their acceptance into society as full members with the gender of men and women.

However, some trans-activist groups believe that this is not sufficient to reject all rules of gender tolerance and ethics. The latter do not take into account the fact that society also needs to adapt to the changes that are currently taking place in the established traditions of the world. This is especially true of the socialization of persons whose psychological gender differs from the physiological one. It takes time to reach the true goal, namely, the equality of male, female and «X» gender, while preserving the moral values of humanity.

Based on a case law study of the European Court of Human Rights, we state that components such as gender identification, first name, sexual orientation and sexual life belong to a person's private life. Violation in this area by the state most often occurs in relation to the legal recognition of gender identification of transitional persons who are at the intermediate stage between the initial phase and the absolute transition. This may refer to both the lack of legislation in the absence of appropriate legal regulation of the issue and the categorical attitude of the authorities to this issue if the law submits its decision to such bodies.

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## SUMMARY

### THE BOUNDARIES OF GENDER TOLERANCE IN THE MODERN SOCIETY AND LEGAL STATE (REVIEW)

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The paper highlights the features of differentiation of the following concepts: «sex», «gender», DSD and Gender incongruence. Such criteria of a person's sex as psychological and social gender in the aspect of a person's right to gender self-identification are distinguished. The case law of the European Court of Human Rights on guaranteeing the right to gender identity is under study. The second part deals with the international experience of gender policy outcomes in various aspects of public life, in particular sports, education and business. Emphasis is placed on the positive aspects of gender-neutral (inclusive) language in the world as a key feature of a gender-tolerant democratic state.

**Keywords:** gender, sex, intersex, gender neutrality, gender language.

## РЕЗЮМЕ

### ГРАНИЦЫ ГЕНДЕРНОЙ ТОЛЕРАНТНОСТИ В СОВРЕМЕННОМ ОБЩЕСТВЕ И ПРАВОВОМ ГОСУДАРСТВЕ (ОБЗОР)

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В статье освещены особенности разграничения следующих понятий: «пол», «гендер», расстройство полового развития и гендерное несоответствие. Выделены такие критерии пола человека, как психологический и социальный пол в аспекте права человека на гендерную самоидентификацию. Изучено прецедентное право Европейского суда по правам человека о гарантиях права на гендерную идентичность. Проанализирован международный опыт достижения результатов гендерной политики в различных сферах общественной жизни, в частности в спорте, образовании и бизнесе. Делается акцент на позитивные аспекты гендерно-нейтрального (инклюзивного) языка в мире как на ключевую особенность гендерно-толерантного демократического государства.

## რეზიუმე

გენდერული ტოლერანტობის საზღვრები თანამედროვე საზოგადოებაში და იურიდიულ სახელმწიფოში

ვ.ზაბოროვსკი, რ.ფრიდმანსკი, ვ.მანზიუკი, ვ.ვაშკოვიჩი, ა.სტოიკა

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სტატიაში საზგასმულია შემდეგი ცნებების დიფერენცირების თავისებურებები: "გენდერი", "სქესი", სექსუალური განვითარების დარღვევა და გენდერული

შეუსაბამობა. ადამიანის უფლებების ასპექტში გენდერული თვითიდენტიფიკაციის თვალსაზრისით გამოყოფილია სქესის ისეთი კრიტერიუმები, როგორცაა ფსიქოლოგიური და სოციალური სქესი. სტატიაში განხილულია ადამიანის უფლებათა ევროპული სასამართლოს პრეცედენტული სამართალი გენდერული იდენტურობის უფლების გარანტიების შესახებ. გაანალიზებულია საერთაშორისო გამოცდილება

საზოგადოებრივი ცხოვრების სხვადასხვა სფეროში გენდერული პოლიტიკის შედეგების მისაღწევად, განსაკუთრებით სპორტში, განათლებასა და ბიზნესში. აქცენტი გაკეთებულია მსოფლიოში გენდერულად ნეიტრალური (ინკლუზიური) ენის პოზიტიურ ასპექტებზე, როგორც გენდერულად ტოლერანტული დემოკრატიული სახელმწიფოს ძირითადი მახასიათებლის შესახებ.

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