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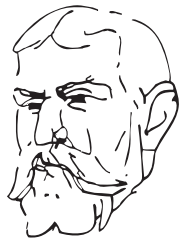

Memory of
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Biegański

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ORIGINAL ARTICLE

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ABSTRACT

The aim: To determine the clinical, instrumental and biochemical factors associated with the degree of physical recovery in patients suffered from acute coronary syndrome (ACS) at the completion of in-hospital rehabilitation period.

Materials and methods: We enrolled 88 patients (all were males); 77 patients had ACS/STEMI and 11 with ACS/unstable angina. The mean age was (median, interquartile range) was 58 (49-64) years. We analyzed clinical, laboratory (including the circulating proprotein convertase subtilisin/kexin type 9 (PSK9) level in blood serum), transthoracic echocardiography and (urgent or delayed) coronary angiography data. Symptom-limited exercise tolerance (ET) test was performed predominantly at the second week of in-hospital stay. According to ET-test results, patients were subdivided into the groups with low (G1; 43 [48,9 %]) and high ET (G2; n=45 [51,1 %]).

Results: G1 (vs. G2) was characterized by older age, lower estimated glomerular filtration rate (eGFR) and higher left atrial (LA) dimension. The cases of any left anterior descending artery (LAD) lesion were more frequent in G1 (25 % vs. 2 % in G2, respectively; p=0,004). We revealed a decrease in PSK9 level after ET-test (pre-ET vs. post-ET: 824,0 (371,0-1073,0) vs. 676,0 (441,9-995,9) ng/ml, respectively; p=0,004 [N=35]).

Conclusions: At the completion of in-hospital rehabilitation period, the insufficient physical recovery in patients suffered from ACS associated with older age, lower eGFR, higher LA dimension, and more frequent any LDA lesion cases. Physical exercises favored the decrease in PCSK9 levels in blood serum.

KEY WORDS: acute coronary syndrome, rehabilitation, exercise tolerance, PCSK9

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INTRODUCTION

The wide usage of the early reperfusion method in cases of acute coronary syndrome (ACS) helped to significantly decrease mortality rate and to improve survival of the patients with myocardial infarction (MI). Although, not least important tool for improving highly advanced interventions in coronary artery disease (CAD) cases, also including recovery improvement, is the process of cardiac rehabilitation through the use of graded exercises, which decelerates the cardiac remodeling process [1-5].

The studies performed during the last decade it was determined that the most valuable qualities of endothelial tissue are recovering and preserving the structural-functional integrity and its reparative activity, which are directly associated with circulating endothelial progenitor cells (EPCs). The results of the recent studies attest to EPCs levels increase in peripheral blood being considered as compensatory reaction of the body in response to endothelial dysfunction development, while increasing of desquamated endotheliocytes percentage is related to endothelial lesion. Moreover, an important enough factor of decreasing endothelial dysfunction risk is the bone marrow's ability to produce EPCs in response to lesion or ischemia, thus scientists use graded exercises to indicate the reserve function of the bone marrow – the ability to produce EPCs [6-8].

Taking into account the significant role of dyslipidemia in the atherosclerosis progression, new groups of pharmaceuticals developed over the last few years to reduce the atherogenic lipid fraction – low-density lipoprotein (LDL) cholesterol. With proven clinical effi-

ciency these pharmaceuticals include the circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. It is well known that PCSK9 plays an essential role in the LDL receptors regulation [9-13]. The additional influence of physical rehabilitation over lipids and lipoproteins metabolism optimization, which is able to keep down the progression of atherosclerotic lesion in coronary arteries according to the new biochemical markers (PCSK9 level, and estimation of endothelial function recovery according to EPCs count data) is a novel, promising and unexplored topic of cardiac rehabilitation, and this is what became the basis for conducting the current research.

THE AIM

The aim of the study was to determine the clinical, instrumental and biochemical factors associated with the degree of physical recovery (by the exertion level during symptom-limited exercise test) in patients suffered from ACS (ST-elevation MI (STEMI) or unstable angina [UA]) at the completion of in-hospital rehabilitation period.

MATERIALS AND METHODS

We enrolled 88 patients (all were males), 77 of which had ACS/STEMI and 11 with ACS/UA. The exclusion criteria were as follows: age ≥76 years; heart failure (HF) stage D; left ventricular (LV) ejection fraction (EF) <35 %; acute LV thrombosed aneurism; the history of stroke and/or transient ischemic attack; orthopedic contraindications to the graded physical exercises; early post-infarction angina; uncontrolled arterial hypertension; atrial fibrillation; atrioventricular block ≥II degree; bundle branch block; the lack of informed consent.

A Q-wave MI (Q-MI) developed in 63 out of 77 (81,8 %) patients with ACS/STEMI, non-Q-wave MI (non-Q-MI) – in 14 out of 77 (18,2 %) patients. Anterior MI occurred in 50 of 77 (64,9 %) patients, inferior-posterior MI – 26 (33,8 %) patients, circular MI – 1 patient. Seven patients with ACS/UA had the history of Q-MI, 1 patient had non-Q-MI, 3 patients had no history of MI. Among the examined patients there were 61 smokers (69,3 %). The mean age of the patients was (hereinafter – median (Me) and interquartile range [IQR]) 58 (49-64) years. The body mass index (BMI) was 28,3 (25,3-31,1) kg/m^2. Twenty-six (29,5%) patients had obesity (BMI >30 kg/m^2). The essential hypertension was diagnosed in 86 patients (98 %). The mean systolic blood pressure (SBP) was 160 (160-170) mm Hg. Chronic HF stage B was present in 24 (27,3 %) patients, stage C – in 64 (72,7 %). Diabetes mellitus (DM) type 2 was present in 23 patients (26,1 %).

Fifty-nine patients out of 77 with ACS/STEMI underwent urgent coronary angiography (CAG) and stent placement into culprit artery, 5 – percutaneous transluminal coronary angioplasty, 13 – delayed CAG and stent placement. CAG was performed to ACS/STEMI patients within 2 hours – 9 patients (12 %), between 2-6 hours – 36 patients (46,8 %) and after 6 hours – 32 patients (41,6 %). We assessed the lesions in three main coronary arteries` territories, namely the left anterior descending artery (LAD) (the branch of left coronary artery [LCA]), circumflex artery (Cx) (the LCA branch), and right coronary artery (RCA). Single-vessel lesion among 88 patients was found in 19 (21,6 %) patients, 2-vessel – in 29 (33,0 %), 3 and more vessels – in 40 (45,5 %). Hemodynamically significant lesions (≥50 %) of a single coronary artery was found in 30 (34,1 %) patients, of two arteries – 30 (34,1 %), three arteries – 27 (30,7 %) patients. Left main coronary artery disease was found in 2 (2,3 %) patients.

The mean serum fasting glucose level was 5,8 (5,0-7,1) mmol/L, total serum cholesterol level – 4,5 (3,6-5,4) mmol/L, serum creatinine level – 104 (89-120) μmol/L. The mean estimated glomerular filtration rate (eGFR) was 66,5 (56,6-79,7) ml/min/1.73 m^2. Eleven (12,5 %) patients had eGFR >90 ml/min/1.73 m^2, 50 (56,8 %) – within 60-89 ml/min/1.73 m^2, in 22 (25,0 %) – within 45-59 ml/min/1.73 m^2, and 5 (5,7 %) – within 30-44 ml/min/1.73 m^2.

The transthoracic echocardiography was performed according to the standard protocol. The average LV EF was 50 (45-55) %. Five (5,7 %) patients had LV EF <40 %, 37 (42,0 %) patients – 40-49 %, and 46 (52,3 %) patients – ≥50 %.

The exercise tolerance test in the form of graded physical exercises was performed in all the patients after 10-15 days since ACS/MI onset, and after 7-10 days after stabilization in ACS/UA patients, with the use of Ergoline ergometric bicycle. The symptom-limited stress-test was performed according to the stepwise-increasing scheme, beginning from 25 W workload with further increase of each exercise level by 25 W until there are ischemic ECG changes or/and pain developed. The duration of the graduated exercise on cycle ergometry lasted 5 minutes at each level.

Under the condition of graded exercise test (GXT) performed on cycle ergometer, the EPCs count in blood was measured before and 60 minutes after the test was done. Blood samples was taken after 10-15 days since ACS/STEMI development, and after 7-10 days (at stabilization) in UA patients. The EPCs count (CD45+/CD34+ phenotype) in peripheral blood was measured by flow cytometry method using reagents for the determination of CD34 and CD45 markers made by «Beckman Coulter Inc.»: 100 μl of peripheral blood was incubated within 15-20 minutes with a mixture of PC7-conjugated monoclonal antibodies against CD45 and PE-conjugated monoclonal antibodies against CD34 (Beckman Coulter Inc.) in a place protected from light. Next, erythrocyte lysis was performed using 500 μl of OptiLyse lytic solution within ten minutes, followed by adding 500 μl

Table I. The main clinical and laboratory values in the groups of patients with low and high GXT levels

Parameters		Group 1 (low tolerance) n=43	Group 2 (high tolerance) n=45	p
Age, years		62 (52-67)	54 (47-60)	0,004
BMI, kg/m^2		27,8 (25-31)	28,0 (25,9-31,2)	0,435
Obesity, n (%)		12(28)	18 (40)	0,266
SBP, mm Hg		160 (160-170)	160 (160-170)	1,000
Smoking, n (%)		32 (74)	29 (64)	0,314
ACS type, n (%)	UA	1 (2)	2 (4)	0,131
	Q	38 (89)	32 (71)	
	Non-Q	4 (9)	11 (25)	
ACS/MI (localization), n/N (%)	Anterior MI	25/42 (60)	29/43 (67)	0,492
	Inferior-posterior MI	16/42 (38)	14/43 (33)	
	Circular MI	1/42 (2)	0/43	
HF stage, n (%)	B	11 (26)	13 (29)	0,129
	C	32 (74)	32 (71)	
DM type 2, n (%)		11(26)	12 (27)	1,000
Blood glucose, mmol/L		5,8 (4,9-7,0)	5,8 (5,0-7,0)	0,501
Glycated hemoglobin, %		5,8 (5,15-6,75)	5,4 (5,1-6,7)	0,253
Creatinine, µmol/L		106 (95-125)	100 (88-114)	0,136
eGFR, ml/min x 1,73 m^2		63 (54-72)	69 (62-84)	0,035
AST, u/L		48 (24-98)	34 (25-42)	0,215
ALT, u/L		47 (29-61)	36 (28-61)	0,298
CPK, u/L		125 (74-860)	164 (97-389)	0,696
De Ritis ratio (AST/ALT)		0,97 (0,72-2,07)	0,93 (0,70-1,33)	0,533
Total serum cholesterol, mmol/L		4,4 (3,5-5,4)	4,5 (4-5,4)	0,258
LDL, mmol/L		2,39 (1,6-3,1)	2,56 (1,99-3,35)	0,287
HDL, mmol/L		1,3 (1,0-1,56)	1,28 (1,05-1,45)	0,927

Notes: AST – aspartate aminotransferase; ALT – alanine aminotransferase; CPK – creatine phosphokinase; HDL – high-density lipoprotein cholesterol

of phosphate-buffer saline. For estimation a number of cells per µL, 100 µL of FlowCount fluorosphere was added to the cells suspension. Calculation of the results was performed using NAVIOS («Beckman Coulter Inc.») device, receiving an absolute quantities of the cells per 1 ml of blood.

Determination of PCSK9 level in blood serum of the patients before and 60 minutes after cycle ergometer exercises was performed using a system for automatic conduction of enzyme multiplied immunoassay. Thunder Bolt with the aid of Storm Software Suite system software using Human PCSK9 ELISA Kit test kit for enzyme multiplied immunoassay made by Elabscience Biotechnology Inc., USA.

According to the results of symptom-limited exercise tolerance test, the enrolled sample of patients was subdivided into two groups: group 1 (low physical tolerance; the exercise level achieved 25-50 W; n=43 [48,9 %]) and group 2 (high physical tolerance; the exercise level achieved 75-125 W; n=45 [51,1 %]).

The data analysis was performed by the use of the following statistical software: Statistica v. 14.0.015 (TIBCO Software Inc., USA); IBM SPSS Statistics v. 27 (Armonk, NY: IBM Corp., USA); and MedCalc v. 22.009 (MedCalc Software Ltd, Belgium). The studied variables were presented as Me (IQR) (continuous ones), and absolute and relative (%) frequency (categorical ones). To compare the parameters between the independent groups, we used Mann-Whitney U-test (for continuous variables) and χ^2 test (with z-test when needed) and Fisher`s exact test (for categorical variables). We used the Wilcoxon test for paired samples to compare the continuous variables at baseline and after GXT. The presented results included the Hodges-Lehmann median difference (the Hodges-Lehmann estimate of location shift) and its 95% confidence interval (CI). A 2-tailed p<0,05 was considered statistically significant.

RESULTS

The clinical-anamnestic characteristic of the two studied groups is depicted in Table I. The groups significantly differed in terms of age, particularly the patients from the

Table II. Instrumental measurements in patients of low and high GXT levels

Parameters		Group 1 (low tolerance) n=43	Group 2 (high tolerance) n=45	p
CAD complexity (significant coronary stenosis), n (%)	No significant stenosis	0	1 (2)	0,467
	1-vessel	14 (33)	16 (36)	
	2-vessel	13 (30)	17 (38)	
	3-vessel	16 (37)	11 (24)	
LAD (LCA) territory lesions, n (%)	No lesions[z]	1 (2,3)	11 (25)	0,016
	<50 %	4 (9,3)	2 (4)	
	50-99 %	22 (51,2)	22 (49)	
	100 %	16 (37,2)	10 (22)	
Significant LAD (LCA) territory stenosis (≥50 %), n (%)		38 (88)	32 (71)	0,064
Cx (LCA) territory lesions, n (%)	No lesions	13 (30)	18 (40)	0,653
	<50 %	5 (12)	4 (9)	
	50-99 %	19 (44)	15 (33)	
	100 %	6 (14)	8 (18)	
Significant Cx (LCA) territory stenosis (≥50 %), n (%)		25 (58)	23 (51)	0,529
RCA territory lesions, n (%)	No lesions	13 (30)	19 (42)	0,325
	<50 %	5 (12)	2 (4)	
	50-99 %	19 (44)	21 (47)	
	100 %	6 (14)	3 (7)	
Significant RCA territory stenosis (≥50 %), n (%)		25 (58)	24 (53)	0,674
Complete revascularization, n (%)		26 (60)	27 (60)	1,000
Number of implanted stents, n,%	No stents	3 (7)	6 (13)	0,419
	1 stent	25 (58)	28 (62)	
	≥2 stents	15 (35)	11 (24)	

Note: [z] – statistically significant difference by z-test

1st group being older than from the 2nd one: 62 (52-67) versus 54 (47-60) years (p=0,004). Both groups of patients did not differ significantly by the majority of clinical parameters. Also, the studied groups were comparable by the frequency of Q-MI, non-Q-MI and UA, as well as by different MI localization patterns. We did not reveal any significant differences in basic biochemical measurements between the compared groups, however the eGFR in the group 1 (low GXT level) was significantly lower, than in the group 2 patients (high GXT level) (Table I).

Regarding the CAG findings, the studied groups were comparable by the total number of affected vessels. At the same time, the 1st group was characterized by the higher frequency of patients with any LAD territory stenosis (25,0 % vs. 2,3 % in the 2nd group, respectively; p=0,004). In particular, the significant LAD lesions tended to be higher in case of low physical tolerance. Besides, we did not observe any significant differences between the studied groups with respect to Cx LCA and RCA territory lesions patterns, as well as the coverage of complete revascularization and the number of implanted coronary stents (Table II).

The 1st group, as compared to the alternative one, was characterized by the higher LA size, and slightly lower LV EF and higher LV posterior wall (PW) thickness (both numerically, but non-significantly) (Table III).

The studied groups were comparable by the EPCs count in blood serum at baseline and after GXT. We did not reveal any significant difference in the EPCs count after the stress-test as compared to baseline in both groups of patients. Near half of patients in both groups presented with the increase of EPCs count after physical exercises, being numerically comparable in case of low and high physical tolerance (Table IV).

The dynamics of PCSK9 level in patients examined under the conditions of GXT on cycle ergometer in presented on Figure 1. We revealed a statistically significant decrease in its level after performing GXT (676,0

Table III. Echocardiography parameters in patients of low and high GXT levels

Parameters	Group 1 (low tolerance) n=43	Group 2 (high tolerance) n=45	p
LA, cm	4,3 (4,04-4,5)	4,1 (3,8-4,2)	0,040
LV EDV, ml	127 (110-150)	128 (110-141)	0,829
LV ESV, ml	61 (52-75)	61 (47-75)	0,612
LV EF, %	49 (43-54)	51 (47-56)	0,055
IVS, cm	1,17 (1,1- 1,25)	1,2 (1,08-1,25)	0,993
LV PW, cm	1,13 (1,07-1,20)	1,09 (1,03-1,16)	0,066
E/A, c.u.	0,97 (0,65-1,17)	0,89 (0,73-1,10)	0,702
IVRT, ms	105 (95-119)	105 (50-120)	0,544
DT, ms	155 (130-200)	140 (120-190)	0,652

Notes: LA – left atrium (anteroposterior dimension); EDV – end-diastolic volume; ESV – end-systolic volume; IVS – interventricular septum; E/A – the ratio of peak velocity blood flow from LV relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave); IVRT – LV isovolumic relaxation time; DT – LV deceleration time

Table IV. EPCs count (per ml) in blood serum at baseline and after physical exercises in patients of low and high GXT levels

Parameters		Group 1 (low tolerance) n=30	Group 2 (high tolerance) n=45	p_1
$EPCs_1$/ml	Me	3491	2796	0,274
	IQR	1931…5245	2057…3793	
	95 % CI	2252…4645	2305…3366	
$EPCs_2$/ml	Me	3389	2987	0,229
	IQR	2228…6455	2196…3855	
	95 % CI	2454…5307	2691…3642	
ΔMe (95 % CI)*		64 (–376…617)	115 (–214…424)	-
p_2		0,781	0,481	-
(+)$\Delta EPCs_{1-2}$/ml, n (%)		14 (47)	24 (53)	0,572
$\Delta EPCs_{1-2}$/ml, n (%)**		1015 (317…1970) n=14	607 (355…1268) n=24	0,428

Notes: $EPCs_1$ – EPCs count at baseline; $EPCs_2$ – EPCs count after GXT; $\Delta EPCs_{1-2}$ – the difference between $EPCs_2$ and $EPCs_1$; (+)$\Delta EPCs_{1-2}$ – any EPCs count increase after GXT; * – Hodges-Lehmann Me difference; ** – in (+)$\Delta EPCs_{1-2}$ patients; p_1 – the significance of difference between groups 1 and 2; p_2 – the significance of difference between $EPCs_1$ and $EPCs_2$ in groups 1 and 2

(441,9…995,9) ng/ml vs. 824,0 (371,0…1073,0) ng/ml at baseline; Hodges-Lehmann Me difference: –63,1 (–138,8…–19,3) ng/ml; p=0,004 [N=35]).

DISCUSSION

Patient's recovery after ACS (MI or UA) needs proper condition assessment, timely intervention and its efficacy evaluation. The main parameter that reflects recovery efficiency after previous ACS is graded exercise test. In our study we separated the patients by GXT level and indicated the aspects with associated with low or high GXT level. Our study shows that the patients with low (25-50 W) GXT were older, and presented with lower eGFR and more frequent any LAD territory lesions. According to transthoracic echocardiography data, patients with low GXT appeared to have larger LA size and slightly (non-significantly) lower LV EF. At the same time, the studied groups did not differ significantly by the rates of complete and incomplete revascularization.

The aim of our study was to determine new biological markers that may be estimated on the stage of recovery in a patient after ACS (estimation of endothelial function recovery, PCSK9 level), when performing GXT. The EPCs count in peripheral blood and its functional state reflect endogenous reserve of endothelial tissue, and can be used as biomarkers of vascular function and predictive indexes of vascular lesions. There are many experimental data demonstrating that the circulating EPCs and resident stem cells facilitate recovery of ventricles and reconstruction after acute ischemic

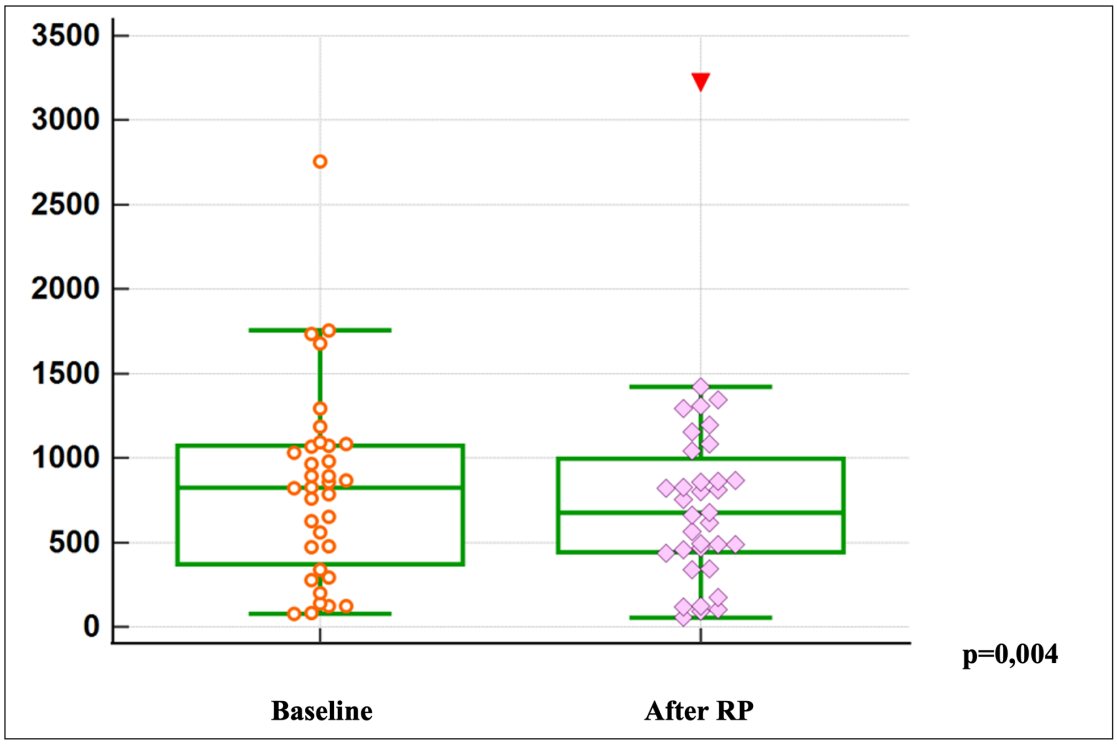

Fig. 1. PCSK9 level (ng/ml) dynamics before and after physical exercises (box-and-whisker and dot plots (all the available data from 35 patients). RP – (in-hospital) rehabilitation period

event. Circulating endothelial progenitor cells can take part in regeneration of vessels and myocardium [6-8]. The prospective incidence study was performed which involved 454 patients with stable CAD aiming to investigate an interrelation between the changes in EPCs count in blood while performing graded exercise test and the risk of developing adverse cardiovascular events [14]. The observations made during the following 3 years showed that the patients having EPCs level decrease after graded exercise test had a higher risk of developing acute MI and cardiac death. The authors concluded that it might be related to the decrease of bone marrow`s reserve function to produce the EPCs in response to ischemia, which is the basis of endothelial dysfunction development.

The results of the recent studies suggest that the EPCs levels increase in peripheral blood could be considered as compensatory reaction of the body in response to endothelial dysfunction development [15-18]. Moreover, an important factor of decreasing endothelial dysfunction risk is the bone marrow's ability to produce EPCs in response to lesion or ischemia, thus scientists use graded exercises to enhance the reserve function of the bone marrow – the ability to produce EPCs. However, both groups of patients in our study were comparable by the EPCs count – either at baseline or after the graded exercise test. Additionally, patients with low and high physical tolerance did not demonstrate any significant post-test EPCs count dynamics, as compared to its pre-test level.

Dyslipidemia is a widely accepted risk factor for atherosclerosis development and progression, and physical exercises are seen as one of the components of non-drug treatment of the patients after ACS. It is known that PCSK9 plays an important role in LDL receptors regulation in volunteers depending on the level of physical activity [9]. Particularly, 67 healthy hospital employees were taking part in the study during six months, they had been using stairs instead of elevators for three months, then the next three months – by their discretion. When determining PCSK9 levels in blood serum after three months, their significant decrease was observed from 403,6 to 324,3 ng/ml (p=0,001), and LDL – from 5,0 to 3.3 mmol/L (p=0,01) [9]. We observed a statistically significant decrease of PCSK9 level decrease in the patients after performing GXT, which befits the data received in the published studies [10-13].

The limitations of the present study include the modest sample size, exclusion of patients with the contraindications to GXT, and the lack of significant differences in the baseline and post-GXT inter and intragroup EPCs count. Taking into account currently available evidence, suggesting the prognostic value of the assessment of EPCs count in response to physical exercise, it seems promising to assess this parameter at follow-up after the completing of in-hospital rehabilitation period (at 3 months, 12 months follow-up etc.). It could be also valuable to study the associations of EPCs count with clinical, laboratory and instrumental data by the use of non-linear models.

CONCLUSIONS

At the completion of in-hospital rehabilitation period, the insufficient physical recovery in patients suffered from ACS associated with older age, lower eGFR, more frequent any LDA (LCA) lesion cases, and higher LA size. Patients with low and high physical tolerance were comparable by the EPCs count in blood at baseline and after graded physical exercise, and by the EPCs count post-test dynamics, as compared to its pre-test values. Physical exercises facilitated a significant decrease of PCSK9 level, which might be one of the ways to affect lipid metabolism and atherosclerotic process progression.

REFERENCES

1. Collet J, Thiele H, Barbato E et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289-1367. doi: 10.1093/eurheartj/ehaa575.
2. Grochulska A, Glowinski S, Bryndal A. Cardiac Rehabilitation and Physical Performance in Patients after Myocardial Infarction: Preliminary Research. J Clin Med. 2021; 10(11): 2253. doi: 10.3390/jcm10112253.
3. Bryndal A, Glowinski S, Grochulska A. Influence of Risk Factors on Exercise Tolerance in Patients after Myocardial Infarction-Early Cardiac Rehabilitation in Poland . J Clin Med. 2022;11(19):5597. doi: 10.3390/jcm11195597.
4. Bjarnason-Wehrens B, McGee H, Zwisler A-D et al. Cardiac rehabilitation in Europe: Results from the European Cardiac Rehabilitation Inventory Survey. Eur. J. Cardiovasc. Prev. Rehabil. 2010;17:410-418. doi: 10.1097/HJR.0b013e328334f42d.
5. Ekblom-Bak E, Halldin M, Vikstrom M et al. Physical activity attenuates cardiovascular risk and mortality in men and women with and without the metabolic syndrome - a 20-year follow-up of a population-based cohort of 60-year-olds. Eur J Prev Cardiol. 2021;28:1376-1385. doi: 10.1177/2047487320916596.
6. Bakogiannis C, Tousoulis D, Androulakis E et al. Circulationg Endothelial Progenitor Cells as Biomarkers for Prediction of Cardiovascular Outcomes. Current Medicinal Chemistry. 2012;19(16):2597-2604. doi: 10.2174/092986712800492995.
7. Kawamoto A, Iwasaki H, Kusano K et al. CD34-positive cells exhibit increased potency and safety for therapeutic neovascularization after myocardial infarction compared with total mononuclear cells. Circulation. 2006;114(20):2163-2169. doi: 10.1161/CIRCULATIONAHA.106.644518.
8. Karaahmet F, Kocaman S. Endothelial Progenitor Cells and Mesenchymal Stem Cells to Overcome Vascular Deterioration and Cytokine Storm in Critical Patients with COVID-19. Med Hypotheses. 2020;144:109973. doi: 10.1016/j.mehy.2020.109973.
9. Kamani C, Gencer B, Montecucco F et al. Stairs instead of elevators at the workplace decreases PCSK9 levels in a healthy population. Eur J Clin Invest. 2015;45(10):1017-1024. doi: 10.1111/eci.12480.
10. Tirandi A, Montecucco F, Liberale L. Physical activity to reduce PCSK9 levels. Front Cardiovasc Med. 2022;9:988698. doi: 10.3389/fcvm.2022.988698.
11. Mäkelä K, Leppäluoto J, Jokelainen J et al. Effect of Physical Activity on Plasma PCSK9 in Subjects With High Risk for Type 2 Diabetes. Front Physiol. 2019;10:456. doi: 10.3389/fphys.2019.00456.
12. Sponder M, Campean I, Dalos D et al. Effect of long-term physical activity on PCSK9, high- and low-density lipoprotein cholesterol, and lipoprotein(a) levels: a prospective observational trial. Pol Arch Intern Med. 2017;127:506–511. doi: 10.1093/eurheartj/ehx502.P1516.
13. Ding Z, Pothineni N, Goel A et al. PCSK9 and inflammation: role of shear stress, pro-inflammatory cytokines, and LOX-1. Cardiovasc Res. 2020;116(5):908-915. doi: 10.1093/cvr/cvz313.
14. Moazzami K, Lima B, Hammadah M et al. Association Between Change in Circulating Progenitor Cells During Exercise Stress and Risk of Adverse Cardiovascular Events in Patients With Coronary Artery Disease. JAMA Cardiol. 2020;5(2):147-155. doi: 10.1001/jamacardio.2019.4528.
15. Uemura R, Xu M, Ahmad N et al. Bone marrow stem cells prevent left ventricular remodeling of ischemic heart through paracrin esignaling. Circ Res. 2006; 98:1414–1421. doi: 10.1161/01.RES.0000225952.61196.39.
16. Asahara T, Masuda H, Takahashi T et al. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. Circulation Research. 1999;85(3):221-228. doi: 10.1161/01.res.85.3.221.
17. Rakic M, Persic V, Kehler T et al. Possible role of circulating endothelial cells in patients after acute myocardial infarction. Med Hypotheses. 2018;117:42-46. doi: 10.1016/j.mehy.2018.06.005.
18. Urbich C, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. Circ Res. 2004;95(4):343-353. doi: 10.1161/01.RES.0000137877.89448.78.

The present study was conducted in accordance with the basic principles of the Council of Europe Convention on Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current Ukrainian regulations. The study protocol was approved by the local ethics committee. The written informed consent to participate in the study was obtained from all the patients.

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ORIGINAL ARTICLE

PREDICTION OF THE RISKS OF THE DEVELOPMENT OF COMORBIDITY OF CORONARY HEART DISEASE AND OBESITY IN THE BACKGROUND OF MILITARY ACTIONS

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ABSTRACT

The aim: Study of prognostic possibilities of batokine complexes (fibroblast growth factor (FGF-21) and vascular endothelial growth factor A (VEGF-A)) in determining the risks of developing coronary heart disease (CHD) and obesity (especially in case of their comorbidity).

Materials and methods: 105 patients aged 25–85 were examined: 70 (main group) –with CHD on the background of obesity and 35 – with isolated CHD (comparison group).

Results: Probable associations with increased risks of comorbidity of CHD and obesity were: increased systolic blood pressure (SBP) (OR = 0.844 [95.0% CI 0.735–0.970], $p = 0.017$), FGF-21 (OR = 1.701 [95.0 % CI 1.219–2.375], $p = 0.002$), VEGF-A (OR = 1.725 [95.0% CI 1.213–2.372], $p = 0.005$), low-density lipoprotein (LDL) (OR = 4.419 [95.0% CI 1.351–14.469], $p = 0.014$). Probable associations were also established for lesions of the left anterior descending artery (LADA) (OR = 1.117 [95.0% CI 0.987–1.263], $p = 0.078$), intermediate branch of the left coronary artery (IBLCA) (OR = 1.336 [95.0% CI 1.099–1.624], $p = 0.004$).

Conclusions: The values of the characteristics of batokine metabolism (FGF-21 and VEGF-A levels) can be used as a significant predictor of the development of obesity in CHD. Increased levels of FGF-21 and VEGF-A in blood serum characterize a significant relationship with the development of such comorbidity, which indicates a significant influence of batokine complexes on the pathogenesis of comorbidity of CHD and obesity.

KEY WORDS: coronary heart disease, obesity, FGF-21, VEGF-A, comorbidity

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INTRODUCTION

Recently, the development of a real epidemic of chronic non-communicable diseases (NCDs) [1] has been determined, which is provoked by the significant prevalence of an unhealthy lifestyle, low physical activity, abuse of alcohol and alcohol-containing substances, significant spread of tobacco smoking, unhealthy diet etc. [2]. Among all NCDs, cardiovascular diseases (CVD) [3, 4], which cause more than 70% of all global deaths, are the leading cause of death in the population [5]. It is precisely because of CVD, according to many scientists, that NCDs are considered threatening and epidemic, because CVD have a significant prevalence and provoke the maximum number of cases of disability and mortality [6, 7].

Thus, conducted studies [8] indicate that CVDs are the cause of more than 17.5 million global deaths annually, causing 17.8 million such cases in 2017 [9, 10], and in 2019 – more than 6,2 million [9]. In Ukraine, mortality due to CVD also occupies the first positions, causing more than 67.0% of all deaths which is 801.6 cases per 100,000 population [11].

Moreover, among all CVDs, the first place in terms of prevalence and causes of death is coronary heart disease (CHD), especially against the background of hyperlipidemia and obesity [3, 4].

The development of CVDs (primarily CHD) is significantly influenced by such negative risk factors as depression and obesity, the occurrence and development of which are associated with the effect of significant psychophysiological and psychoemotional overloads, which are widespread both among the entire world community and in Ukraine (especially in the conditions of today's active hostilities in our country) [12] and provoke a significant number of NCDs [13], among which CVD (most often CHD) and obesity are noted. At the same time, conducted global studies also determined that more than 23% of participants in active military operations experience the impact of over-normal psycho-traumatic overloads [14] (which is quite relevant for our country), because of which there are high risks of the occurrence and development of depression and obesity [15].

At the same time, early diagnosis, and the possibility of predicting the risks of developing CVD (primarily

coronary heart disease) both in the case of monohypertension and against the background of obesity (especially taking into account the increased risks of the development of cardiogenic pathology against the background of active hostilities in Ukraine) become a rather urgent issue. To determine this question, leading scientists are studying the prognostic possibilities of inflammatory mediators, which are produced against the background of pathogenetic changes observed in the background of coronary artery disease and obesity. Among these substances, batokine complexes are of primary importance: fibroblast growth factor (FGF-21) and vascular endothelial growth factor A (VEGF-A), which are mediators of metabolic disorders observed in CHD and obesity (especially in their comorbidity) and have a good cardioprotective effect (due to a reduction in the manifestations of oxidative stress) [16, 17].

Therefore, the study of the prognostic capabilities of batokine complexes (FGF-21 and VEGF-A) in determining the risks of developing CHD and obesity (especially in the case of their comorbidity) is a very relevant and significant problem (primarily in view of the increased risks of the occurrence and development of these diseases against the background of conducting active combat actions in Ukraine), the solution of which requires close attention of researchers and scientists.

THE AIM

The purpose of our study was to study the prognostic capabilities of batokine complexes (FGF-21 and VEGF-A) in determining the risks of developing CHD and obesity (especially in case of their comorbidity).

MATERIALS AND METHODS

We enrolled 105 patients aged 25-85, who were divided into 2 study groups: 70 patients (main group) with CHD on the background of obesity and 35 respondents with isolated coronary artery disease (comparison group). In the main ($n = 70$) group, the average age was 63.6 ± 8.8 years, most of them (72.9 %) were female compared to respondents (27.1 %) who were male; and in the comparison group, the average age was 69.7 ± 7.9 years and, on the contrary, the majority (68.6 %) were men compared to women (31.4 %).

The diagnosis of CHD was established according to current guidelines [18, 19]. The diagnosis of obesity was determined according to the recommendations EASO (2017) [20] and NIH (2000) [21].

Inclusion criteria: age ≥18 years, presence of comorbid CHD and obesity (main group) and isolated CHD (comparison group), consent to participate in the study. Exclusion criteria: age < 18 years, absence of comorbid CHD and obesity (main group) and isolated CHD (comparison group), diffuse and focal diseases, endocrine pathology, allergic reactions, systemic diseases of connective tissue, acute and chronic diseases of internal organs (except CHD and obesity), severe decompensated somatic pathology, mental and oncological diseases, acute cardiovascular disorder, acute and significant decompensation of carbohydrate metabolism, unsatisfactory physical condition, pregnancy and breastfeeding, chronic alcoholism, refusal to participate in the study.

All patients underwent measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP), characteristics of lipid and batokine metabolism. We performed coronary angiography in all the patients to determine the stenosis of the main coronary arteries.

We considered a coronary lesion to be significant in case of stenosis of ≥50%. Among the enrolled patients, significant left anterior descending artery (LADA) (of the left coronary artery [LCA]) lesions were detected in 51 (48,6 %) patients, intermediate branch of LCA (IBLCA) – 12 (11,4 %), right coronary artery (RCA) – 16 (15,2 %), and circumflex artery – in 1 (1,0 %) case. There were no cases of left main disease among the enrolled patients.

Medical-statistical calculation: We calculated the mean value and standard deviation (M ± SD) for continuous variables. Differences between unrelated samples were calculated using Mann-Whitney U-test. Categorical variables were presented in absolute and percent values (with 95 % confidence interval [CI]). Pearson's Chi-squared test was used to assess differences between groups.

Associations of the obtained indicators with the binomial dependent variable were determined using multiple logistic regression analysis with the calculation of standardized β coefficients (odds ratio (OR); and their 95.0% CI). The quality of the obtained models was carried out by calculating the Nagelkerke R^2. For the final model, a multiple binomial regression equation was made to calculate the percentage probability of the desired event. In the regression analysis, we used univariate and multivariate analysis, enter and Backward Wald exclusion of variables in the mathematical model to obtain the most likely independent predictors.

Coding of groups in regression models was as follows: isolated CHD (comparison group) – reference group; comorbid CHD and obesity (main group) – comparison group.

Significance level (p) in the study was taken as lower than 0.05. Statistical calculations were performed in IBM SPSS 25.0 (trial version) for Windows.

Table I. Characteristics of SBP and DBP in patients with CHD and obesity, M ± SD

Characteristics of SBP and DBP	Research groups		p
	main (n = 70)	comparison (n = 35)	
SBP, mm Hg	156.9 ± 14.7	158.0 ± 16.4	0,801
DBP, mm Hg	91.7 ± 7.8	89.3 ± 9.1	0,167

Table II. Characteristics of batokin levels, M ± SD

Batokin levels	Research groups		p
	main (n = 70)	comparison (n = 35)	
FGF-21, pg/ml	241.1 ± 27.1	209.0 ± 13.8	< 0,001
VEGF-A, pg/ml	222.9 ± 7.3	206.0 ± 8.3	< 0,001

Table III. Significant coronary lesions, N (% [95 % CI])

Parameters	Research groups		p
	main (n = 70)	comparison (n = 35)	
LADA lesions	41 (59 [47-70])	10 (29 [15-45])	0,004
IBLCA lesions	12 (17 [9-27])	0 [0-5]	0,009
RCA lesions	16 (23 [14-34])	0 [0-5]	0,002

Table IV. Lipid profile characteristics, M ± SD

Lipid profile characteristics	Research groups		p
	main (n = 70)	comparison (n = 35)	
HDL, mmol/l	1,53 ± 0,29	1,36 ± 0,32	0,009
TG, mmol/l	2,00 ± 1,00	1,53 ± 0,81	0,010
LDL, mmol/l	3,37 ± 1,15	2,57 ± 1,35	< 0,001
VLDL, mmol/l	0,90 ± 0,45	0,70 ± 0,37	0,017
AC, c.u.	2,87 ± 0,83	2,42 ± 0,95	0,008

Table V. Associations of batokine complexes with comorbidity of CHD and obesity

Batokine complexes	Univariate analysis		Multivariate analysis	
	OR (95,0 % CI)	p	OR (95,0 % CI)	p
FGF-21	1,317 (1,182–1,468)	< 0,001	1,265 (1,132–1,414)	< 0,001
VEGF-A	1,095 (1,056–1,136)	< 0,001	1,080 (1,028–1,135)	0,002

Table VI. Associations of significant clinical-laboratory and clinical-instrumental characteristics with comorbidity of CHD and obesity

Reliable characteristics	B-coefficient	OR (95,0 % CI)	p
SBP*	–0,169	0,844 (0,735–0,970)	0,017
FGF-21**	0,531	1,701 (1,219–2,375)	0,002
VEGF-A***	0,542	1,725 (1,213–2,372)	0,005
LADA#	0,111	1,117 (0,987–1,263)	0,078
IBLCA##	0,290	1,336 (1,099–1,624)	0,004
LDL###	1,486	4,419 (1,351–14,469)	0,014

Notes: * – the range: 130-180 mm Hg (n=105); ** – the range: 205.37-241.29 pg/ml (n=105); *** – the range: 199.16-289.08 pg/ml (n=105); # – the range: 20-70 % (n=105); ## – the range: 10-60 % (n=105); ### – the range: 1.17-6.81 mmol/l (n=105)

RESULTS

The characteristics of SBP and DBP in patients with CHD and obesity were analyzed – Table I. There were no statistically significant differences in the levels of SBP and DBP in patients with CHD and obesity. – Table I.

The levels of batokines (FGF-21 and VEGF-A) significantly exceeded the normative values for CHD both in

the main (respectively 241.1 ± 27.1 and 222.9 ± 7.3 pg/ml) and in the comparison group (respectively 209,0 ± 13.8 and 206.0 ± 8.3 pg/ml). In CHD with obesity, the levels of both batokines were probably ($p < 0.001$) higher than the indicators of patients with isolated CHD – Table II.

The group of CHD and obesity was characterized by the higher frequency of significant LADA, IBLCA and RCA lesions, as compared to CHD alone (Table III).

The peculiarities of the lipid profile in CHD and obesity were determined: the levels of high-density lipoproteins (HDL) were within the normative limits, but significantly ($p = 0.009$) prevailed in CHD and obesity compared to isolated CHD (respectively, 1.53 ± 0.29 and 1.36 ± 0.32 mmol/l); the levels of triglycerides (TG) probably ($p = 0.010$) exceeded the normative values in the main group significantly outweighing the indicators of the comparison group (2.00 ± 1.00 and 1.53 ± 0.81 mmol/l, respectively); the levels of low-density lipoprotein (LDL) in all groups were within the normative limits, probably ($p < 0.001$) prevailing among the subjects of the main group compared to the comparison group (3.37 ± 1.15 and 2.57 ± 1.35 mmol/l, respectively), as well as the levels of very low-density lipoproteins (VLDL) (respectively 0.90 ± 0.45 and 0.70 ± 0.37 mmol/l; $p = 0.017$) and the atherogenic coefficient (AC) (respectively, 2.87 ± 0.83 and 2.42 ± 0.95 c.u.; $p = 0.008$) – Table IV.

Determination of associations of batokine levels with the comorbidity of CHD and obesity by both univariate and multivariate logistic regression analysis established significant predictive effects on the development of the combined course of CHD and obesity as an increase in FGF-21 indicators (respectively OR = 1.317 [95.0% CI 1.182– 1.468]; $p < 0.001$ and OR = 1.265 [95.0% CI 1.132–1.414]; $p < 0.001$) and VEGF-A (respectively OR = 1.095 [95.0% CI 1.056–1.136]; $p < 0.001$ and OR = 1.080 [95.0% CI 1.028–1.135]; $p = 0.002$).

In this way, significantly increased chances for the development of comorbid development of CHD and obesity were determined, both by univariate and multivariate analysis, when the levels of FGF-21 increased above the normative indicators (the corresponding increase in the chances by 1.317 and 1.265 times) and VEGF-A (respectively by 1.095 and in 1.080 times) – Table V.

When adding other clinical-laboratory and clinical-instrumental indicators (for which their probable associations with the comorbidity of CHD and obesity were previously obtained) according to multivariate analysis, the final result was determined the influence of all significant characteristics (SBP), lesions of the LADA and the IBLCA and LDL levels) of examined patients with the significant development of comorbidity of coronary artery disease and obesity – Table VI.

Significant associations with increased risks of comorbidity of CHD and obesity were: increased SBP (OR = 0.844 [95.0% CI 0.735–0.970]; $p = 0.017$), FGF-21 (OR = 1.701 [95.0% CI 1.219–2.375]; $p = 0.002$), VEGF-A (OR = 1.725 [95.0% CI 1.213–2.372]; $p = 0.005$) and LDL (OR = 4.419 [95.0% CI 1.351–14.469]; $p = 0.014$). Probable associations were also established for lesions of the LADA (OR = 1.117 [95.0% CI 0.987–1.263]; $p = 0.078$) and IBLCA (OR = 1.336 [95.0% CI 1.099–1.624]; $p = 0.004$). These results indicate a decrease in the odds (by 15.6%) of developing comorbidity of IBLCA and obesity when SBP levels increase above the normal values. Also, an increase in such chances was determined when the levels of FGF-21 (1.701-fold increased odds), VEGF-A (1.725-fold increased odds) and LDL (4.419-fold increased odds) increased above the norm. Increased chances of comorbidity of CHD and obesity with a lesion of 1.0% of LADA (1.117–fold increase in chances) and IBLCA (1.336-fold increase in chances) were also determined – Table VI.

DISCUSSION

Our results regarding the significant associations and effects of the levels of batokin complexes on the risks of developing CHD and obesity and their comorbid combination are completely consistent with other conducted studies. Thus, Zheng X. [22] evaluated the relationships between FGF-21 and the development of negative clinical outcomes (combination of death or severe disability (on the modified Rankin scale ≥ 3) within 1 year after a stroke) in 3412 patients from China with acute ischemic stroke. They established the development of negative clinical consequences in 745 (21.83%) patients (550 developed severe disability and 195 died). After multivariate adjustment, a higher level of FGF-21 in the plasma of patients was highly associated with an increased risk of negative clinical outcomes (OR = 1.52; 95.0% CI 1.11–1.29). At the same time, each 1-SD increase in the logarithmic transformation of FGF-21 (by 0.67 pg/ml) had a probable association with 19.0%; 3.0% and 33.0% increased risks of overall negative clinical outcomes, severe disability and death, respectively. Adding FGF-21 to other risk factors significantly improved the prediction of adverse clinical outcomes in patients with ischemic stroke (net reclassification index = 10.8%; $p = 0.011$; integrated improvement in discrimination = 0.3%; $p = 0.038$).

At the same time, Lee C.H. [23] determined the possibility of predicting the development of CHD using serum FGF-21 in 3528 Chinese patients with type 2 diabetes mellitus (determining increased risks of developing obesity) and CHD. They determined that

serum FGF-21 levels are an independent predictor of CHD and can be used as a biomarker to identify an increased risk of CHD.

They established that, baseline serum log-transformed FGF-21 levels were significantly higher in CHD than those who did not CHD (222.7 pg/mL [92.8–438.4] versus 151.1 pg/mL [75.6–274.6]; $p < 0.001$). On multivariable Cox regression analysis, baseline serum FGF-21 levels, independently predicted incident CHD (hazard ratio = 1.55; 95,0 % CI 1.10–2.19; $p = 0.013$).

In turn, Palmer B.R. [24], found that determination of serum VEGF-A levels has value as a prognostic biomarker in patients with CHD; and Hrovat K. et al. [25] in the study of patients with coronary artery disease noted the importance of determining VEGF-A in CHD.

CONCLUSIONS

Based on the research, it was determined that the values of the characteristics of batokine metabolism (FGF-21 and VEGF-A levels) can be used as a significant predictor of the development of obesity in CHD. Increased levels of FGF-21 and VEGF-A in blood serum characterize a significant relationship with the development of such comorbidity, which indicates a significant influence of batokine complexes on the pathogenesis of comorbidity of CHD and obesity. In addition, the results indicate a direct relationship between the pathogenesis of the comorbidity of CHD and obesity with SBP values, LDL levels, and lesions of LDL and PGLC damage, which should be taken into account to ensure therapeutic and preventive measures.

REFERENCES

1. Gheorghe A, Griffiths U, Murphy A et al. The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. BMC Public Health. 2018;18:975. doi: 10.1186/s12889-018-5806-x.
2. Dziuba OM., Pazynych LM, Sytenko OR, Kryvenko YeM. Shchodo pytannia hlobalnoho tiaharia khvorob v Ukraini [Regarding the issue of the global burden of diseases in Ukraine]. Visn. sotsialnoi hihiieny ta orhanizatsii okhorony zdorovia Ukrainy [Visn. of social hygiene and health care organizations of Ukraine]. 2017;2(72):8–13. doi: 10.11603/1681-2786.2017.2.8101. (In Ukrainian).
3. Yuyun MF, Sliwa K, Kengne AP et al. Cardiovascular Diseases in Sub-Saharan Africa Compared to High-Income Countries: An Epidemiological Perspective. Glob Heart. 2020;12;15(1):15. doi: 10.5334/gh.403.
4. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;10;392(10159):1736–1788. doi: 10.1016/S0140-6736(18)32203-7.
5. Shaposhnikov DI, Radomskyi OV. Analiz epidemiolohichnoi sytuatsii shchodo khvorob systemy krovoobihu v Ukraini ta Pakystani [Analysis of the epidemiological situation regarding diseases of the circulatory system in Ukraine and Pakistan]. Tezy dopovidei 75-yi Vseukrainskoi studentskoi naukovoi konferentsii «Medical students conference in Poltava» (MEDSCOP 2019), m. Poltava, 28–29 bereznia 2019 r. Poltava [Abstracts of reports of the 75th All-Ukrainian student scientific conference «Medical students' conference in Poltava» (MEDSCOP 2019), Poltava, March 28-29, 2019, Poltava]. Poltava. 2019, p.107. (In Ukrainian).
6. Yusuf S, Joseph P, Rangarajan S et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. The Lancet. 2020; 395(10226): 795–808. doi: 10.1016/S0140-6736(19)32008-2.
7. Liu S, Li Y, Zeng X et al. Burden of Cardiovascular Diseases in China, 1990-2016: Findings From the 2016 Global Burden of Disease Study. JAMA Cardiol. 2019; 4(4):342–352. doi: 10.1001/jamacardio.2019.0295.
8. Tilz RR, Lenarczyk R, Scherr D et al. Management of ventricular tachycardia in the ablation era: results of the European Heart Rhythm Association Survey. EP Europace. 2018; 20(1):209–213. doi: 10.1093/europace/eux332.
9. Mensah GA, Roth GA, Fuster V. The Global Burden of Cardiovascular Diseases and Risk Factors: 2020 and Beyond. J. of the American College of Cardiology. 2019; 74(20):2529–2532. doi: 10.1016/j.jacc.2019.10.009.
10. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;10;392(10159):1859–1922. doi: 10.1016/S0140-6736(18)32335-3.
11. Andonieva NM, Berezin OYe, Berezin OO et al. Arterialna hipertenziia ta komorbidnist: monohrafiia [Arterial hypertension and comorbidity: monograph]. Kharkiv: KhNMU. 2020, p.176. (In Ukrainian).
12. Betancourt JA, Stigler GP, Pacheco GJ et al. Obesity and Morbidity Risk in the U.S. Veteran. Healthcare. 2020;8(3):191. doi: 10.3390/healthcare8030191.
13. Buttorff C, Ruder T, Bauman M. Multiple chronic conditions in the United States. 2017. https://www.rand.org/pubs/tools/TL221.html [date access 23.01.2023]
14. Fink DS, Calabrese JR, Liberzon I et al. Retrospective age-of-onset and projected lifetime prevalence of psychiatric disorders among U.S. Army National Guard soldiers. J. Affect. Disord. 2016;202:171–7. doi: 10.1016/j.jad.2016.05.025.

15. Censin JC, Peters SAE, Bovijn J et al. Causal relationships between obesity and the leading causes of death in women and men. PLoS Genet. 2019;15(10):e1008405. doi: 10.1371/journal.pgen.1008405.
16. Aaldijk AS, Verzijl CRC, Jonker JW, Struik D. Biological and pharmacological functions of the FGF19- and FGF21-coreceptor beta klotho. Front Endocrinol (Lausanne). 2023;14:1150222. doi: 10.3389/fendo.2023.1150222.
17. Planavila A, Redondo-Angulo I, Ribas F et al. Fibroblast growth factor 21 protects the heart from oxidative stress. Cardiovasc Res. 2015;1;106(1):19–31. doi: 10.1093/cvr/cvu263.
18. Knuuti J, Wijns W, Saraste A et. al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–477. doi: 10.1093/eurheartj/ehz425.
19. Gulati M, Levy PD, Mukherjee D et. al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;144(22):e368–e454. doi: 10.1161/CIR.0000000000001029.
20. Hebebrand J, Holm JC, Woodward E et. al. Proposal of the European Association for the Study of Obesity to Improve the ICD-11 Diagnostic Criteria for Obesity Based on the Three Dimensions Etiology, Degree of Adiposity and Health Risk. Obes Facts. 2017;10(4):284–307. doi: 10.1159/000479208.
21. National Institutes of Health, NHLBI Obesity Education Initiative, National Heart, Lung, and Blood Institute, North American Association for the Study of Obesity. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. 2000, p.94. https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf [date access 25.01.2023]
22. Zheng X, Zhu Z, Guo D et. al. Prognostic value of plasma fibroblast growth factor 21 among patients with acute ischemic stroke. European Journal of Neurology. 2021;28(3):844–851. doi: 10.1111/ene.14683.
23. Lee CH, Woo Y C, Chow WS et. al. Role of Circulating Fibroblast Growth Factor 21 Measurement in Primary Prevention of Coronary Heart Disease Among Chinese Patients With Type 2 Diabetes Mellitus. J. Am. Heart. Assoc. 2017;6;6(6):e005344. doi: 10.1161/JAHA.116.005344.
24. Palmer BR, Paterson MA, Frampton CM et. al. Vascular endothelial growth factor-A promoter polymorphisms, circulating VEGF-A and survival in acute coronary syndromes. PLoS One. 2021;14;16(7):e0254206. doi: 10.1371/journal.pone.0254206.
25. Hrovat K, Rehberger Likozar A et al. Gene Expression Profiling of Markers of Inflammation, Angiogenesis, Coagulation and Fibrinolysis in Patients with Coronary Artery Disease with Very High Lipoprotein(a) Levels Treated with PCSK9 Inhibitors. J. Cardiovasc. Dev. Dis. 2022;1;9(7):211. doi: 10.3390/jcdd9070211.

The ethical approval was obtained from Bioethics Committee of the Kharkiv National Medical University. All patients provided written consent to participate in research in accordance with the recommendations of the Ethics Committees for Biomedical Research, Ukrainian Health Legislation and the Declaration of Helsinki of 2000, European Community Directive 86/609 On Human Participation in Biomedical Research.

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ORIGINAL ARTICLE

FEATURES OF FUNCTIONING DISORDERS IN PATIENTS WITH STABLE ISCHEMIC HEART DISEASE

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ABSTRACT

The aim: To reveal the peculiarities of functioning disorders in everyday life and the need for rehabilitation in the patients with stable ischemic heart disease (IHD).

Materials and methods: Used 346 medical cards of inpatients with stable (IHD), Department of Cardiology and Cardiorehabilitation, Kyiv City Clinical Hospital No. 4. Research methods: collection, grouping, analysis and generalization of data from doctors' records, medical-statistical, graphical.

Results: It was established that the structure of hospitalized morbidity cases of IHD consisted of 34.7% of angina pectoris and 65.3% of cardiosclerosis. IHD was accompanied by other diseases in 92.8% of cases. It has been proven that among all cases, those with a moderate severity of functional impairment prevail (25.0-49.0%). 28.9% of the patients have contraindications to physical cardiorehabilitation. The remaining the patients need a complex of rehabilitation measures, including physical rehabilitation, and patients with contraindications may use other components of cardiorehabilitation programs.

Conclusions: It has been proven that patients with coronary heart disease, with or without comorbidities, experience impaired functions, reduced activity and participation in everyday life, as well as pain syndromes and painful sensations. This indicates the need for cardiac rehabilitation in the acute and post-acute periods.

KEY WORDS: Patient; diseases of the circulatory system, disorders of functions, structures, activity and participation; needs for rehabilitation; classification

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INTRODUCTION

The current global epidemic situation regarding the prevalence, disability, and mortality caused by diseases of the circulatory system remains unfavorable. In 2017, there were 485,620.9 thousand registered cases of these diseases, with 72,721.2 thousand cases being newly registered that year. Moreover, the number of years people lived with disabilities due to these diseases increased by 4.5% from 2007 to 2017 [1]. This problem continues to be significant in various countries and among different age groups of the population [2].

Ischemic heart disease (IHD) is a major contributor to the overall mortality rates worldwide, causing around 17.5 million deaths annually, and this number is projected to increase to 23.3 million by 2030. More than 75.0% of IHD-related deaths occur in low- and middle-income countries, including Ukraine [3].

Globally, IHD affects approximately 126 million people (1,655 per 100,000), making up about 1.72% of the world population. There were nine million deaths attributed to IHD worldwide. Men are more commonly affected than women, and the incidence usually starts in the fourth decade of life, increasing with age. By 2030, the prevalence rate is expected to exceed 1,845 per 100,000 people. Eastern European countries, including Ukraine, have the highest prevalence of IHD [4].

Ukraine lost 408,721 people from cardio-vascular diseases (CVD) in 2020. IHD caused the death of 284,997 people, which is equal to 69.7% in the structure of causes of death from CVD [5].

The high prevalence of CVD imposes a significant burden on healthcare systems and economies of countries. For instance, the estimated direct costs related to CVD in the United States reached 213.8 billion US dollars in 2014-2015, with projected indirect costs of 237 billion dollars per year, expected to rise to 368 billion dollars by 2035 [6]. Additionally, CVD cost the economies of the European Union 210 billion euros annually, according to estimates [7].

In response to these challenges, healthcare systems, in collaboration with other sectors of economic activity and the population, must prioritize health promotion and prevention of CVD, as well as fulfill their specific functions, including treatment and rehabilitation. Rehabilitation is defined as a set of measures aimed at reducing the level of disability and improving the func-

tioning of individuals with health disorders in everyday life and their interactions with the environment [8, 9]. Therefore, the study of the peculiarities of functioning disorders becomes necessary to determine the rehabilitation needs of the selected population, followed by the development and implementation of appropriate measures into healthcare practice at the individual level.

Modern approaches to rehabilitation involve the use by doctors involved in rehabilitation of two classifications - International Classification of Diseases, Tenth Revision (ICD-10) and International Classification of Functioning, Disability and Health (ICF). These classifications are intended to better understand the patient's health status and obtain information about his functional status by unifying the data, regardless of the country where the clinical activity takes place. For medical organizations, this means an opportunity to improve the planning of rehabilitation services, their resource provision and monitoring of implementation [10].

THE AIM

The aim of the study was to reveal the peculiarities of functioning disorders in everyday life and the need for rehabilitation in patients with stable ischemic heart disease (IHD). The task was to determine the nosological forms of IHD, concomitant diseases, and to obtain data on complaints about limitations of functions, activity, and participation in everyday life among a certain contingent of patients.

MATERIALS AND METHODS

The research materials included medical charts of inpatients with stable IHD from the Department of Cardiology and Cardiorehabilitation at Kyiv City Clinical Hospital No. 4. This institution is representative of the city of Kyiv and serves as a hospital for specialized medical care for adults, where patients with various pathologies, including cardiovascular diseases, receive specialized medical care.

346 medical records of inpatients with IHD were selected for 2019. In 2019, the number of hospitalizations of patients with IHD to Kyiv City Clinical Hospital No. 4 was 1,730. The number of medical cards of inpatients was calculated according to the formula [11]

n=, where: n – volume of the sample population; t – coefficient of normalized deviation (2); p – is the probability of the presence of the feature (0.5); q –is the probability of the absence of a feature (0.5); N – volume of the general population (1730 people); Δ – is the permissible error in medical and sociological research (the maximum permissible error is ± 5.0%).

The volume of the sample set of medical records of inpatients hospitalized for IHD was 324 units, according to the results of the calculations. 346 units were used, therefore, the number of research materials represented the general population at a representative level. All materials were obtained for research with the permission of the management of Kyiv City Clinical Hospital No. 4.

ICD-10 and ICF classifiers were used for the purpose of analyzing and summarizing data on nosological forms of IHD, accompanying IHD and functional disorders.

Research methods included the collection, grouping, analysis, and generalization of data from medical records of inpatients with IHD, which were recorded by doctors during the collection of patients' medical history and observation. For quantitative data, the medical-statistical method was used, and calculations were performed using licensed Microsoft Office Word software. The data was processed to calculate relative values in percentages, averages, and standard deviations for the sample. Additionally, the reliability of differences in indicators between groups of patients based on age and gender criteria was assessed. The researchers also utilized a graphic method to present and visualize the data.

The principles of bioethics were observed during the preparation of the article in accordance with the requirements of the Declaration of Helsinki and the legislation of Ukraine, which was confirmed by the conclusion of the commission on bioethics dated 06.05.2023 (protocol No. 6). Personal data of patients from retrospective records of medical cards were not disclosed.

RESULTS

The general characteristics of the sample showed that there were 219 (63.3%) women; there were 127 (36.7%) men, which differed at a significantly different level ($p<0.05$). The average age of patients was 71.1±10.3 years, in particular, men – 68.7±10.3 years, women – 72.3±10.0 years. The older age of women was significantly different from the age of men ($p\leq0.05$). 305 (88.2%) patients of the sample were unemployed, respectively, only 41 (11.8%) persons worked in various spheres of economic activity; differences in employment status are reliably confirmed ($p<0.05$). In particular, among persons who did not work, 288 (94.4%) patients were pensioners by age. Among persons of retirement age, 50 (17.4%) patients had a disability due to a general disease, namely, due to diseases of CVD.

Analysis of the nosological structure of IHD cases according to ICD-10 by separate nosological forms showed that cardiosclerosis was the leading place - 226

Table I. Violations of functions, structure, activity and participation in patients with IHD were detected, determined on the basis of ICD-10, according to the principle of grouping defined by ICF

Types of violations	Reasons for violations	Clinical symptoms, nosological forms
Violation of functions	Violation of the contractile force of the myocardium	Signs of chronic heart failure
	Violation of coronary blood circulation	Symptoms of angina pectoris
	Violation of functions related to the regulation of heart contractions	Arrhythmias
	Violation of functions related to the regulation of vascular tone	High blood pressure, acute cerebrovascular accident (history), neurocirculatory disorders
	Violations of the functions related to the regulation of the vestibular apparatus	Vestibulo-ataxic syndrome
	Violation of functions of carbohydrate metabolism	Diabetes mellitus, polyneuropathy of the lower extremities
	Violations of thyroid hormone exchange functions	Euthyroidism, hypothyroidism
	Violation of respiratory functions	Chronic obstructive pulmonary disease, chronic bronchitis
	Violation of the function of maintaining body weight	Obesity
	Disorders of neuromuscular, skeletal and movement-related functions	Signs of osteochondrosis
Violation of the structure	Sclerotic lesions of the vessels of the brain, heart, limbs	-
	Edemas of different localization	-
	Anomalies of the valvular apparatus of the heart	-
	Aneurysms of the aorta, walls of the heart ventricle	-
	Stents Aorto-coronary shunts Implants	-
	The structure of the bronchial tree	-
	The structure of the pancreas	-
	The structure of the thyroid gland	-
	Structures related to movement	-
Activity and participation	-	Decreased ability to walk, exercise, move down the street, climb stairs, manage a household, maintain a diet, and physical comfort
Feeling	-	General weakness, palpitations, heart failure, suffocation, shortness of breath, dizziness, vertigo
Pain	-	Headache; pain behind the sternum, in the area of the heart, in the ribcage, in the lumbar region of the spine

(65.3%) cases, including diffuse - 201 (58.1%) cases, post-infarction - 25 (7.2%) of the total number of cases; 37 (10.7%) cases of postinfarction cardiosclerosis and 47 (13.6%) cases of diffuse were combined with angina pectoris. In general, postinfarction cardiosclerosis was diagnosed in 62 (17.9%) cases from the total number of hospitalizations, and diffuse - in 248 (71.7%) cases.

Angina was detected in 120 (34.7%) cases of ICD, including 101 (29.2%) cases of stable angina pectoris, 17 (4.9%) cases of unstable angina pectoris. Cases of stable angina pectoris were registered in the number of 18 (17.8%) with II functional class (FC) of this form of the disease, and 83 (82.2%) – with III FC of angina. All cases of unstable angina were transferred to a stable state by means of drug correction, of which 4 (23.5%) cases – with II FC, 13 cases (74.5%) – with III FC of angina. Progressive angina (angina at rest) with IV FC was registered in only two cases, which was 0.6% of the total number of patients.

154 (44.5%) cases with the presence of arrhythmias were identified. Of these, 64 (41.6%) cases – with persistent atrial fibrillation, 27 (17.5%) – with a persistent form of atrial fibrillation. In 42 (27.3%) cases, a paroxysmal form of atrial fibrillation was diagnosed with medical restoration of heart rhythm. 21 (13.6%) cases of other types of arrhythmias were detected, 8 (2.3%) of

them with ventricular arrhythmia from the total number of cases in the sample. In general, in 91 (26.3%) cases, uncontrolled forms of supraventricular arrhythmias and in 8 (2.3%) cases – ventricular arrhythmias were detected.

It was established that in 24 (6.9%) of the studied cases, patients had stents installed, in 15 (4.3%) cases - shunts, and in four cases (1.2%) - implants as a result of cardiosurgical interventions.

28 (8.1%) cases of IHD with chronic heart failure (CHF) of the 1st degree, 223 (64.5%) cases with CHF 2A degree and 51 (14.7%) cases with CHF 2B degree were identified. In one case, which was only (0.3%) of the total number, grade 4 CHF was determined.

Cases of IHD in the number of 321 (92.8%) units was accompanied by other diseases, of which 316 (98.4%) cases were associated with Hypertensive heart disease (HHD) and other concomitant diseases (consequences of acute cerebrovascular accident, diabetes, neurocirculatory dystonia, chronic obstructive pulmonary disease, chronic bronchitis, anemia, lumbar osteochondrosis spine, obesity, diseases of the thyroid gland, diseases of the autonomic nervous system, etc.).

Different types of complaints were identified and grouped, and the percentage values of their occurrence were determined based on the total number of cases in the sample. The results showed that headache was reported in 154 (44.5%) cases, general weakness in 153 (44.2%) cases, pain behind the sternum or in the chest cavity in 124 (35.8%) cases, and palpitations or interruptions in heart rhythm in 110 (31.8%) cases.

Furthermore, 102 (29.5%) cases of patients reported suffering from suffocation and shortness of breath at different times of the day, depending on physical exertion, and 98 (28.3%) cases reported dizziness and vertigo. Swelling of the extremities was observed in 26 (7.5%) cases, and decreased ability to walk or perform physical exertion was reported in 99 (28.6%) cases.

It has been proven that the use of the ICF codifier by the doctors of the institution where the study was conducted was not carried out, which is confirmed by records in the patients' medical records. In this regard, the authors used a methodical approach to grouping data on the state of health, determined by doctors on the basis of ICD-10, according to the principle of grouping data indicating violations of functions, structure, activity and participation, sensations and pain syndrome, determined by the ICF (Table I).

Based on the available data and the assessment by doctors of the severity of the clinical condition of the patients, as presented in the diagnoses according to the ICD-10, it was determined that the range of size and severity of disorders varied from minor (0-4.0%) to severe (high, intense) (50.0-95.0%). The highest concentration of cases was observed with moderate severity (25.0-49.0%) according to the general ICF qualifier with a negative scale.

DISCUSSION

The results of the study have shown that the objectives were achieved as they provided answers to the research questions. The study revealed the features of functional disorders in patients with stable coronary artery disease, which included a complex of functional disorders in the cardiovascular system (such as clinical signs of chronic heart failure, angina pectoris, various types of arrhythmias, increased blood pressure, and manifestations of neurocirculatory disorders), as well as in other organs and systems (including nervous, endocrine, respiratory, musculoskeletal systems), and disorders of structural components (such as the valvular apparatus of the heart, vessels of the brain, heart and limbs, aorta, walls of the ventricles of the heart, bronchial tree, pancreas, thyroid gland, musculoskeletal and vestibular apparatus).

In everyday life, this leads to restrictions on the patients' vital activities due to a decrease in the ability to walk, exercise, move on the street, climb stairs, manage the household, maintain a diet, and physical comfort. Patients experience general weakness, palpitations, interruptions in the work of the heart, suffocation, shortness of breath, dizziness, dizziness, headache, behind the sternum, in the area of the heart, ribcage, lumbar spine.

The ICF codifier allows obtaining quantitative indicators of functions, structure, activity, and participation at the personal level, covering all functions, types of activities, and participation of a person in everyday life and/or their violations [12]. However, the lack of use of this classification by doctors at the personal level did not allow for the quantitative determination of the magnitude and severity of violations by applying the principles of ICF in the contingent of hospitalized patients.

Established violations of functions, structure, activity and participation, sensations and pain syndromes indicated the need for measures to rehabilitate patients with coronary heart disease, which is confirmed by numerous studies of the feasibility of rehabilitation in chronic non-infectious diseases, in particular, in IHD [13-17]. Multiple concomitant diseases confirmed the need for comprehensive cardiorehabilitation, which should make appropriate adjustments when doctors develop personal rehabilitation programs, as the authors of the studies pointed out [18-19].

Contraindications to physical rehabilitation of patients with coronary artery disease include: unstable angina pectoris; uncontrolled supraventricular and ventricular arrhythmia; uncontrolled heart failure; high-level blockade without an artificial pacemaker; pulmonary embolism, recently experienced thrombophlebitis; other causes not related to heart disease [20]. As revealed by the results of the study, patients with contraindications to physical rehabilitation make up a group of 100 (28.9%) people, or about a third of the sample, but these patients can undergo other cardiorehabilitation measures.

METHODOLOGICAL LIMITATIONS

The main methodological limitation of the work should be considered the lack of data on the personal assessment of patients' functioning by doctors using the ICF codifier, which allowed to obtain only probable results and requires additional prospective research after the introduction of ICF into everyday clinical practice.

CONCLUSIONS

The study has provided evidence that patients with IHD, with or without concomitant diseases, experience impaired functions, activity, and participation in everyday life, along with pain syndromes and painful sensations. These findings underscore the importance of cardiorehabilitation for patients during both acute and post-acute periods.

Among patients hospitalized for coronary artery disease, the majority showed cases with a moderate severity of functional impairment (25.0-49.0%), and 28.9% of patients had contraindications to physical cardiorehabilitation. The remaining 71.1% of patients require a comprehensive rehabilitation approach, including physical rehabilitation, while those with contraindications can benefit from other components of cardiorehabilitation programs.

The introduction of impairment assessment in everyday medical practice will make it possible to conduct an objective assessment of impairments in the vital activities of patients with IHD, to develop appropriate organizational measures and to allocate personnel, infrastructure, technological, technical, informational, financial and organizational resources for their implementation.

REFERENCES

1. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. The Lancet. 2018;392(10159):1789-1858. doi: 10.1016/S0140-6736(18)32279-7.
2. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-1222. doi: 10.1016/S0140-6736(20)30925-9.
3. World Health Organization. Cardiovascular diseases. https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1 [date access 16.05.2023]
4. Khan MA, Hashim MJ, Mustafa H et al. Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. Cureus. 2020;12(7):e9349. doi: 10.7759/cureus.9349.
5. Kilkist pomerlykh za okremymy prychynamy smerti [The number of deaths by individual causes of death]. Derzhavna sluzhba statystyky Ukrayiny. http://www.ukrstat.gov.ua/operativ/operativ2020/ds/kpops/kpops_u/arh_kpops2020_u.html, [date access 16.05.2023] (In Ukrainian).
6. Dunbar SB, Khavjou OA, Bakas T et al. Projected Costs of Informal Caregiving for Cardiovascular Disease: 2015 to 2035: A Policy Statement From the American Heart Association. Circulation. 2018;137(19):e558-e577. doi: 10.1161/CIR.0000000000000570.
7. OECD and The King's Fund Workshop Proceedings. Is Cardiovascular Disease Slowing Improvements in Life Expectancy? Paris. 2020, p.82. doi:10.1787/47a04a11-en.
8. World Health Organization. Access to rehabilitation in primary health care: an ongoing challenge. https://apps.who.int/iris/handle/10665/325522 [date access 16.06.2023]
9. World Health Organization. Region Office for Europe. Rehabilitation. FACTSHEET. Sustainable Development Goals: health targets. https://apps.who.int/iris/handle/10665/340896 [date access 16.05.2023]
10. Prodinger B, Stucki G, Coenen M et al. The measurement of functioning using the International Classification of Functioning, Disability and Health: comparing qualifier ratings with existing health status instruments. Disabil Rehabil. 2019;41(5):541-548. doi: 10.1080/09638288.2017.1381186.
11. Hruzieva TS, Biostatystyka U, Hruzieva TS et al. Biostatystyka [Biostatistics]. Kyiv. 2020, p.384. (In Ukrainian).
12. Leonardi M, Lee H, Kostanjsek N et al. 20 Years of ICF-International Classification of Functioning, Disability and Health: Uses and Applications around the World. Int J Environ Res Public Health. 2022;19(18):11321. doi: 10.3390/ijerph191811321.
13. Cieza A. Rehabilitation the Health Strategy of the 21st Century, Really? Arch Phys Med Rehabil. 2019;100(11):2212-2214. doi: 10.1016/j.apmr.2019.05.019.

14. Heinemann AW, Feuerstein M, Frontera WR et al. Rehabilitation Is a Global Health Priority. Arch Phys Med Rehabil. 2020;101(4):728-729. doi: 10.1016/j.apmr.2019.08.468.
15. Jesus TS, Landry MD, Hoenig H. Global Need for Physical Rehabilitation: Systematic Analysis from the Global Burden of Disease Study 2017. Int J Environ Res Public Health. 2019;16(6):980. doi: 10.3390/ijerph16060980.
16. McMahon SR, Ades PA, Thompson PD. The role of cardiac rehabilitation in patients with heart disease. Trends Cardiovasc Med. 2017;6:420-425. doi: 10.1016/j.tcm.2017.02.005.
17. Servey JT, Stephens M. Cardiac Rehabilitation: Improving Function and Reducing Risk. Am Fam Physician. 2016;94(1):37-43. https://pubmed.ncbi.nlm.nih.gov/27386722/ [date access 16.05.2023]
18. Jegier A, Szalewska D, Mawlichanów A et al. Comprehensive cardiac rehabilitation as the keystone in the secondary prevention of cardiovascular disease. Kardiol Pol. 2021;79(7-8):901-916. doi: 10.33963/KP.a2021.0066.
19. Ghisi GLM, Chaves GSS, Ribeiro AL et al. Comprehensive Cardiac Rehabilitation Effectiveness in a Middle-Income Setting: a randomized controlled trial. J Cardiopulm Rehabil Prev. 2020;40(6):399-406. doi: 10.1097/HCR.0000000000000512.
20. British Association for Cardiovascular Prevention and Rehabilitation. BACPR standards and core components for cardiovascular disease prevention and rehabilitation 2017. 3rd ed. UKBACPR. 2017. https://www.researchgate.net/publication/321676829_British_Association_for_Cardiovascular_Prevention_and_Rehabilitation_Standards_and_Core_Components_3rd_Edtion_2017 [date access 16.05.2023]

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ORIGINAL ARTICLE

CATHETER DIRECTED THROMBOLYSIS IN ACUTE LIMB ISCHEMIA PATIENTS. A SINGLE CENTER'S EXPERIENCE

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ABSTRACT

The aim: This study evaluates catheter-directed thrombolysis (CDT) outcomes in patients with acute lower limb arterial thrombosis and acute limb ischemia.
Materials and methods: 53 patients (17 females, 36 males, aged 53-76) were studied. 57% had femoropopliteal and below-the-knee (BTK) thromboocclusion, 43% had BTK thromboocclusion. Symptoms included pain, pallor, edema, and cyanosis.
Exclusions criteria: contracture, recent surgeries, bleeding.
Results: In 29 (97%) patients regression of lower-limb ischemia rate by 1-2 stages according to the Rutherford classification were observed. One patient (3%) did not exhibit any regression in the degree of lower-limb ischemia, experiencing increasing pain and decreased sensitivity in the lower limb, leading to the development of contracture in the ankle joint and subsequent lower limb amputation over 7 days. Among 12 (40%) patients, after performing follow-up arteriography of the lower limb, angioplasty was performed on the diagnosed steno-occlusive lesions in the revascularized segment with secondary angioplasty. Within a year, one (3%) patient experienced recurrent thrombosis of the lower limb arteries with subsequent revascularization.
Conclusions: CDT is recommended for ALI Patients with arterial thrombooclusion.

KEY WORDS: myocardial infarction (MI), arterial hypertension, revascularization, limb surviving, anticoagulant therapy

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INTRODUCTION

Catheter-directed thrombolysis is a treatment option in patients with Acute Limb Ischemia (ALI). According to the literature [1], this method has shown a high technical success rate and a high percentage of patients who survived. ALI manifests as a sudden occurrence of lower limb ischemia, posing a significant risk of limb loss unless timely and proper interventions are initiated. It not only threatens limb viability but also impacts overall survival. Typically, ALI progresses to advanced limb ischemia within a span of two weeks from the acute onset [2], and the reported mortality rate is approximately 15%-20%, often worsened by concurrent conditions such as cardiovascular or cerebrovascular disease, as well as ischemia-reperfusion injury. Consequently, ALI necessitates not only localized treatment but also stringent systemic management [3].

THE AIM

This study aims to evaluate the results of catheter-directed thrombolysis (CDT) in patients with acute lower limb arterial thrombosis and acute limb ischemia.

MATERIALS AND METHODS

A total of 53 patients with acute lower limb arterial thrombosis and ALI were examined. Among the patients, 17 (32%) were females and 36 (68%) were males, aged between 53 and 76 years. Among the patients, 22 (42%) with diabetes, 11 (21%) patients with a history of myocardial infarction, 8 (15%) patients with persistent atrial fibrillation, and 43 (81%) patients with hypertension. All patients underwent DUS of the lower limb arteries. In 30 (57%) patients, DUS revealed thrombooclusion affecting the femoropopliteal and below-the-knee (BTK) arterial segments. Additionally, 23 (43%) patients were diagnosed with thrombooclusion of the BTK arterial segments. The onset of symptoms was reported by all patients within 3-21 days prior to examination. ALI symptoms were evident in all cases, including pain at rest and during ambulation, pallor, and edema of the lower limb, as well as cyanosis of the foot and tibia. Among the patients, 18 (34%) exhibited contracture of the ankle joint, of which 8 (15%) had contracture of the knee joint. Patients with contracture, with intracranial haemorrhage in anamnesis within the past 2 months, recent open surgical interventions

within the last 30 days, or an active source of bleeding were excluded from the study. The study included 30 patients with IIA-IIB categories (IIA – 12 (40%) patients, IIB – 18 (60%) patients) of ALI according to Rutherford 2 classification.

During the planning of surgical interventions for arterial thrombosis, a patient evaluation algorithm was followed, which involved DUS using Mindray M5 and Samsung Medison R3 ultrasound machines. A linear probe with a variable ultrasound frequency of 9-15 MHz was used for the evaluation of blood flow velocity. Diagnostic angiography and interventions were performed using the Philips Alura F920 system.

Thirty patients underwent CDT with femoral artery puncture using the Seldinger technique, followed by the insertion of a 6F introducer and angiography of the lower limb. Angiography revealed thrombooclusion in the femoropopliteal arterial segment without outflow (no tibial or pedal contrasting) in 18 (60%) patients and thrombosis in the below-the-knee (BTK) arterial segments without outflow in 12 (40%) patients. After angiography a volumetric infusion pump was connected to the introducer for thrombolytic agent infusion.

In this study, we employed recombinant tissue plasminogen activator II (rtPA) with the following dosage: an initial bolus injection of 10 mg intraprocedurally within the first 15 minutes, followed by a continuous infusion of 10 mg per hour for 4 hours, along with a subsequent heparin infusion at a rate of 1000 units per hour for 12 hours. During the thrombolytic therapy and heparin infusion, patients underwent vital monitoring, continuous monitoring of the puncture site, and ultrasound control of the lower limb arteries, with clinical assessment performed every 30 minutes.

The study was providing with compliance of Council of Europe Convention on Human Rights and Biomedicine principles, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current regulations of the Ministry of Health of Ukraine. All patients signed an informed consent to participate in the study. The study protocol was approved by the local ethics committee.

This study presents a limited patient cohort, with the data presented as absolute and relative (%) frequency.

RESULTS

In 29 out of 30 patients (97%), regression of lower-limb ischemia by 1-2 stages, as per the Rutherford classification, was observed. Among the patients, 22 (73%) showed recanalization of the femoropopliteal segment (Fig. 1). Complete contrasting of the arterial contour was achieved in 12 patients (40%), while eight patients (27%) exhibited heterogeneity of contrasted arteries due to mural thrombotic masses. In addition, two patients (7%) had an absence of contrast enhancement in the thrombosed segment, but significant collateral vessels were observed, which were absent in the baseline angiography.

During the first 2-3 hours of thrombolytic therapy, 26 (87%) patients reported paresthesia in the lower limb, along with pain along the surface of the tibia and foot. Reduced pain within 4-7 hours after the initiation of thrombolytic therapy occurred in 28 (93%) patients. In CDT patients group no cases of major (intracranial and gastrointestinal) bleedingwere observed. Complications during the procedure are listed in Fig. 1.

In the previous ultrasound examination, all patients (100%) in our study showed no blood flow in the BTK artery segment of the lower limb. After 12 hours following thrombolytic therapy, 29 (97%) patients had bi-phase or three-phase flow rate form in the popliteal artery and tibia arteries. After heparin infusion, patients underwent angiography of the lower limb arteries for evaluaton. Before and after CDT arteriography are listed in Fig. 2.

One (3%) patient did not show any regression in the degree of lower-limb ischemia, experiencing increasing pain and decreased sensitivity in the lower limb, leading to the development of contracture in the ankle joint and subsequent lower limb amputation over 7 days. Among 12 (40%) patients, after performing follow-up arteriography of the lower limb, angioplasty was performed on the diagnosed steno-occlusive lesions in the revascularized segment with secondary angioplasty.

Anticoagulant therapy according to VOYAGER PAD [4] was prescribed to 29 (97%) patients with scheduled follow-up ultrasound examinations at 1, 4, 12, and 24 weeks. Within a year, one (3%) patient experienced recurrent thrombosis of the lower limb arteries with subsequent revascularization.

DISCUSSION

The results showed promising outcomes with a high rate of successful revascularization and regression of ALI. The majority of patients exhibited an improvement of 1-2 stages according to the Rutherford 2 classification, indicating a positive response to the CDT intervention.

The CDT procedure was performed using rtPA as the thrombolytic agent, administered through a volumetric infusion pump. The majority of patients reported reduced pain and no major bleeding complications were observed during the procedure. This indicates that CDT can be safely performed in patients with ALI and can effectively restore blood flow.

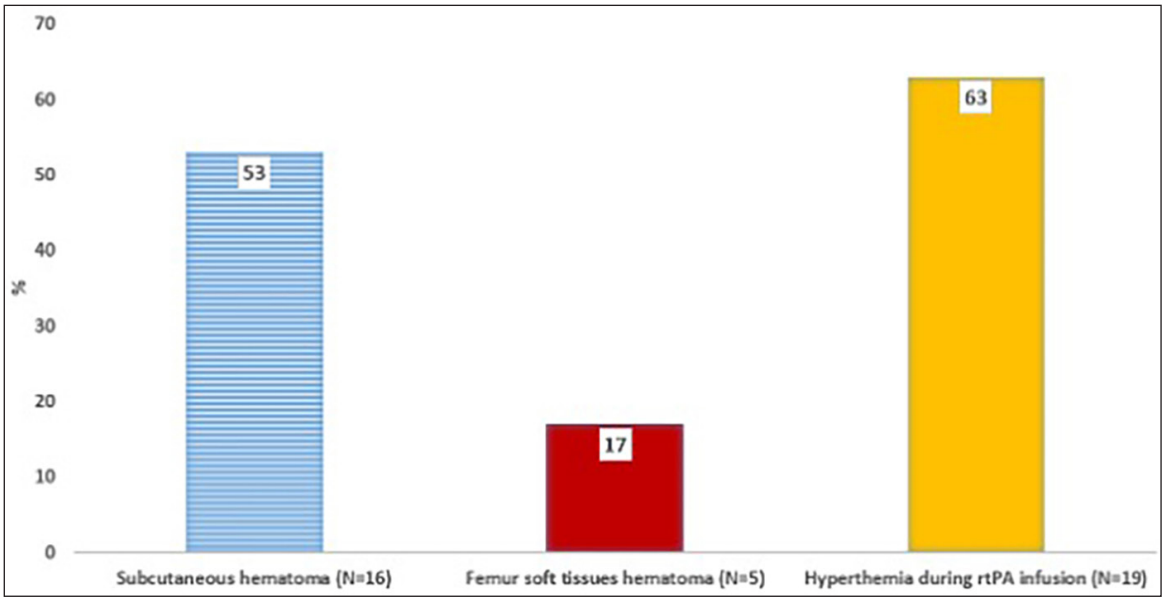

Fig. 1. Periprocedural CDT complications.

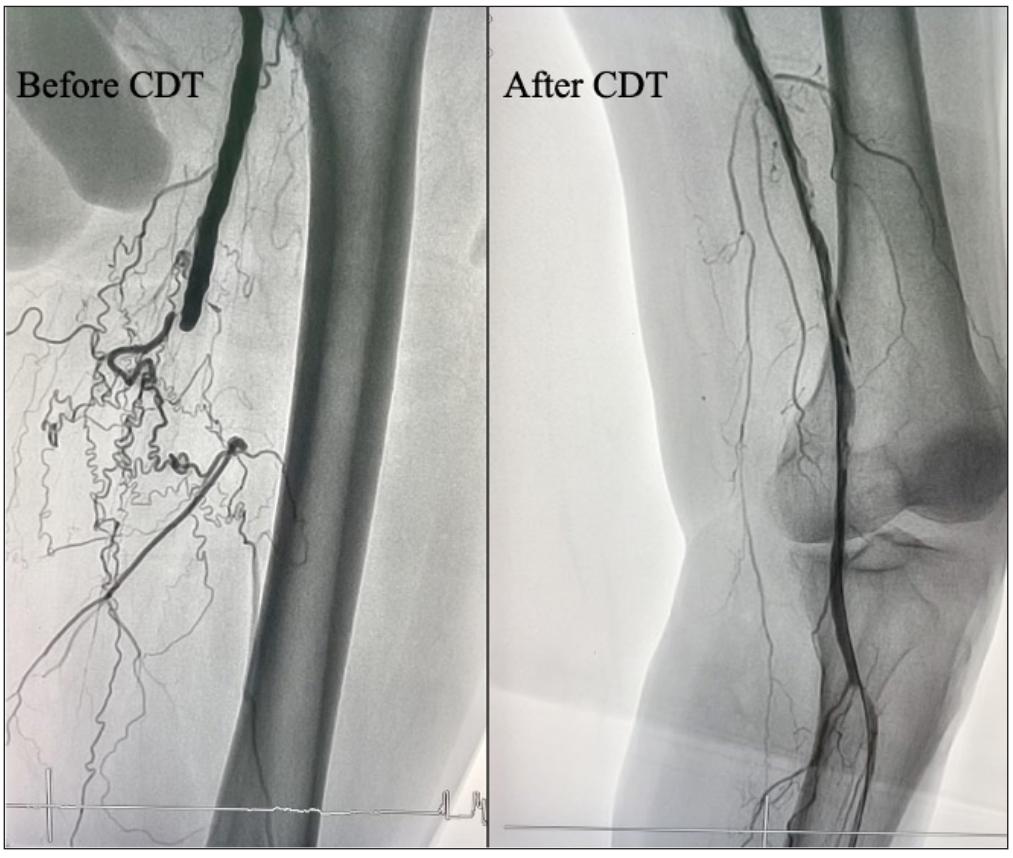

Fig. 2. Before and after CDT arteriography (femoro-popliteal segment)

While the overall success rate of CDT was high, this case highlights the importance of careful patient selection and ongoing monitoring to identify patients who may require alternative treatment approaches.

Follow-up arteriography and angioplasty were performed in some patients to address steno-occlusive lesions, further improving the outcomes of the intervention. This combination of CDT and secondary angioplasty showcases the maximizing patient outcomes compared with intraoperation intraarterial thrombolysis [5].

The long term outcomes in CDT patients group were relatively good, with high rate of secondary angioplasty compared to CDT without secondary angioplasty in short-term [6].

Due to the catheter-directed scheme of thrombolytic therapy with the indicated severity, no critical haemorrhagic complications were observed in our sample of patients. Low risk of critical haemorrhagic complications are described in other researches of CTD [7].

Due to the standardized protocol of thrombolytic therapy dosage and heparin therapy, we did not observe significant disparities in coagulogram indices within the CDT patients group. However, routine analysis of plasma fibrinogen levels was not conducted [8].

Anticoagulant therapy according to VOYAGER PAD was prescribed to the majority of patients, and scheduled follow-up ultrasound examinations were conducted at various time points. This long-term follow-up allowed for the monitoring of recurrences and provided valuable insights into the efficacy of the CDT intervention over time.

CONCLUSIONS

1. The results of this study suggest that CDT is a recommended treatment option for patients with acute lower limb arterial thrombosis and ALI. CDT showed a high success rate in revascularizing the affected arteries and improving the degree of lower-limb ischemia, as evidenced by regression according to the Rutherford classification. The procedure was generally safe, with no major bleeding complications observed.

However, it is important to carefully select patients for CDT and closely monitor their progress to identify cases that may require alternative interventions. Additionally, the combination of CDT with secondary angioplasty proved beneficial in some patients, highlighting the potential for a multidisciplinary approach to managing ALI.

2. Long-term follow-up and anticoagulant therapy played a crucial role in maintaining the efficacy of CDT and preventing recurrent thrombosis in the majority of patients.

In conclusion, CDT represents a valuable and effective treatment option for patients with acute lower limb arterial thrombosis and ALI, offering the potential for successful revascularization and improved clinical outcomes.

REFERENCES

1. Theodoridis PG, Davos CH, Dodos I et al. Thrombolysis in Acute Lower Limb Ischemia: Review of the Current Literature. Ann Vasc Surg. 2018;52:255-262. doi:10.1016/j.avsg.2018.02.030.
2. Luan TMB, Bang HT, Tan NM et al. Catheter-directed intra-arterial thrombolysis in the treatment of acute thrombosis of below-the-knee arteries. Radiol Case Rep. 2021;16(8):2086-2090. doi:10.1016/j.radcr.2021.05.012.
3. Norgren L, Hiatt WR, Dormandy JA et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45(S):S5-S67. doi:10.1016/j.jvs.2006.12.037.
4. Hiatt WR, Bonaca MP, Patel MR et al. Rivaroxaban and Aspirin in Peripheral Artery Disease Lower Extremity Revascularization: Impact of Concomitant Clopidogrel on Efficacy and Safety. Circulation. 2020;142(23):2219-2230. doi:10.1161/CIRCULATIONAHA.120.050465.
5. Dragas M, Zlatanovic P, Koncar I et al. Effect of Intra-operative Intra-arterial Thrombolysis on Long Term Clinical Outcomes in Patients with Acute Popliteal Artery Aneurysm Thrombosis. Eur J Vasc Endovasc Surg. 2020;59(2):255-264. doi:10.1016/j.ejvs.2019.10.013.
6. Doelare SAN, Koedam TWA, Ebben HP et al. Catheter Directed Thrombolysis for Not Immediately Threatening Acute Limb Ischaemia: Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg. 2023;65(4):537-545. doi:10.1016/j.ejvs.2022.12.030.
7. Zatykó DZ, Pomozi E, Pataki Á, Szeberin Z. Akut, kritikus alsó végtagi ischaemia kezelése katéteres thrombolysissel [Catheter-directed thrombolysis in acute critical limb ischemia]. Orv Hetil. 2022;163(11):424-430. doi:10.1556/650.2022.32376.
8. Poorthuis MHF, Brand EC, Hazenberg CEVB et al. Plasma fibrinogen level as a potential predictor of hemorrhagic complications after catheter-directed thrombolysis for peripheral arterial occlusions. J Vasc Surg. 2017;65(5):1519-1527.e26. doi:10.1016/j.jvs.2016.11.025.

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ORIGINAL ARTICLE

CONCEPTUAL, FUNCTIONAL-ORGANISATIONAL MODEL OF THE REGIONAL CENTRE FOR CARDIOLOGY AND CARDIAC SURGERY BASED ON PUBLIC-PRIVATE PARTNERSHIP

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ABSTRACT

The aim: To substantiate the model of the Regional Center for Cardiology and Cardiac Surgery (RCCCS) based on the principles of public-private partnership (PPP).
Materials and methods: A systematic approach and analysis, medical-statistical and sociological method, expert assessment and method of conceptual modelling.
Results: A comprehensive medical and social study of the morbidity rate of the population of the Kyiv region (Ukraine) with circulatory system diseases (CSD), as well as an analysis of the activities of the cardiological service of the Kyiv region in 2010-2019, have been made. Deficiencies in the organisation of medical care were identified, and strategic directions for its improvement were substantiated. The results of a sociological survey of CSD patients, cardiologists and experts – health care organisers have been analysed. According to the results of the expert assessment, health care institutions (HCI) providing cardiac care to the population in the Kyiv region are not ready to work under the conditions of the market economy; there is no appropriate regulatory framework, economic and legal independence of HCI, there is no market strategy for the development of HCI.
Conclusions: The model of RCCCS, based on the principles of PPP being a medical institution of a new organisational and legal form, is capable of providing high-quality and affordable highly specialised medical care of the third level to the population with diseases of the circulatory system at the regional level.

KEY WORDS: cardiology, healthcare organisation, doctors, patients

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INTRODUCTION

In world practice, the academic understanding of the interaction between the state and the private sector contributed to the appearance of the concept of "public-private partnership" and its mechanism, which is now used in more than 150 countries of the world [1].

From the point of view of the Commission WHO on Intellectual Property Rights, Innovation and Public Health, public-private partnership is an effective way to profitably use the opportunities of the public and private sectors to solve health problems that neither side alone can adequately solve [2]. World history is rich in examples of organising such an alternative form of financing business projects as public-private partnership (Panova T.V., 2015; Shevchuk Yu.V., 2017; Alonso J. M. et al., 2017; Torchia M., 2015). [3-6].

In Ukraine, the system of state cardiac care is insufficiently effective due to its underfunding and the lack of a modern model based on PPP principles, in connection with which it becomes evident that it requires modernisation through the integration of the interests of the state, business and patients (Volk S.M., 2016; Adjienko V. L., 2017) [7, 8]. For this, the country has a legislative framework that allows the use of PPP mechanisms in the social sphere: the Law of Ukraine from 01.07. 2010 No. 2404-VI "On public-private partnership", Law of Ukraine dated November 24, 2015 No. 817-VIII "On amendments to some laws of Ukraine regarding the elimination of regulatory barriers to the development of public-private partnerships and stimulating investment in Ukraine" [9, 10].

The need for further development of cardiac care in Ukraine is based on functional models of PPP determined the relevance of this study, its aims and objectives.

THE AIM

To substantiate the conceptual functional and organisational model of the Regional Centre for Cardiology and

Cardiac Surgery based on the principles of public-private partnership as a new independent administrative and legal form of a healthcare institution to provide high-quality specialised and highly specialised medical care to the population with diseases of the circulatory system at the regional level.

MATERIALS AND METHODS

A set of methods is used in the study: a systematic approach and analysis, medical-statistical and sociological method, expert assessment and method of conceptual modelling.

The method of a systematic approach and analysis made it possible to substantiate the concept of organising a cardiological centre on PPP principles and to carry out modelling of a Regional Centre for Cardiology and Cardiac Surgery;

The medical-statistical method was used to collect, process and analyse the data obtained in the research using the methods of descriptive and analytical statistics based on Microsoft Excel and Statistica 8.0 package.

With the help of the sociological method, the point of view of doctors - cardiologists and cardiac surgeons, as well as patients with CSD regarding the problems and ways of improving the organisation of cardiac care, provided in the network of municipal and state institutions of the Kyiv region, was studied. No invasive or non-invasive interventions were performed on the patients during the study, as well as sensitive issues were not the subject of our research [11].

The conceptual modelling method was used to substantiate the conceptual approaches to forming a model and to develop an innovative one for a Regional Centre for Cardiology and Cardiac Surgery based on PPP principles.

The method of expert assessments made it possible to obtain an expert assessment of the organisational aspects of the developed RCCCS model based on PPP principles.

The primary sources of information in this study were statistical data from the State Statistics Committee of Ukraine, materials of state and sectoral statistical reports of the Ministry of Health of Ukraine for 2014-2019. (f. No. 14, 20, 17, 47), as well as materials from a sociological survey of 352 cardiologists and 829 patients and a survey of 31 experts (highly qualified healthcare organisers), which were carried out according to specially developed programs).

RESULTS

Diseases of the circulatory system (DCS) continue to be the leading medical and social problem in Ukraine. In 2019, they accounted for every third (33.4%) of deaths of working-age persons. The likelihood of dying from DCS at working age in Ukraine is twice higher than the average in Europe and 4.6 times higher than in the EU countries. During 2014-2019, the mortality rate of the working-age population from DCS in Ukraine increased by 10% from 142.2 to 157.7 per 100,000 population.

The population of the Kyiv region is losing the largest number of years of life potential in Ukraine due to circulatory system diseases, which determines their special medico-social significance in this region.

In the Kyiv region, more than a million residents suffer from circulatory system diseases. In 2019, DCS accounted for 37.7% of all disorders registered among the adult population of Kyiv; their incidence rate was 446.2, and the prevalence of DCS was 7114.8 per 10 thousand adults. Hypertension (36.7%), ischemic heart disease (IHD, 28.0%) and cerebrovascular diseases (18.7%) occupy the leading places in the structure of the morbidity rate. Their share is 42.9%, 42.6% and 8.6% in the structure of the prevalence of DCS, respectively.

The incidence and prevalence levels of DCS among rural residents are, on average, 1.2 times higher than among urban residents of the region, and the epidemic situation regarding DCS in the Kyiv region is more tense than the average one in Ukraine. Myocardial infarction in the region is diagnosed 1.2 times, and strokes 1.5 times more often than in the country as a whole. The prevalence of coronary heart disease is 1.5 times higher than in Ukraine.

A comprehensive medical and social analysis of the organisation of cardiac care for the population of the Kyiv region revealed several problems that require immediate solutions, taking into account the unfavourable epidemiology of the pathology under study in this region.

So, according to the results of a sociological survey of 829 patients who applied to the Kyiv region's cardiologic units, only 32.9±1.6% of the respondents are fully satisfied with the quality of the local cardiologist examination. According to the same survey, it was revealed that 51.4±1.7% of the respondents were dissatisfied with the organisation of patient reception (accessibility), 41.9±1.9% of the respondents were dissatisfied with the state of equipping the units with medical equipment, 47.1±1.7% by the waiting time for diagnostic examinations, 34.6±1.7% were dissatisfied with the attitude of the medical staff to the patients, 29.7±1.6% were dissatisfied with the effectiveness of the further treatment.

An analysis of the results of a sociological survey of 352 cardiologists of communal health care institutions showed that the main directions of improving the or-

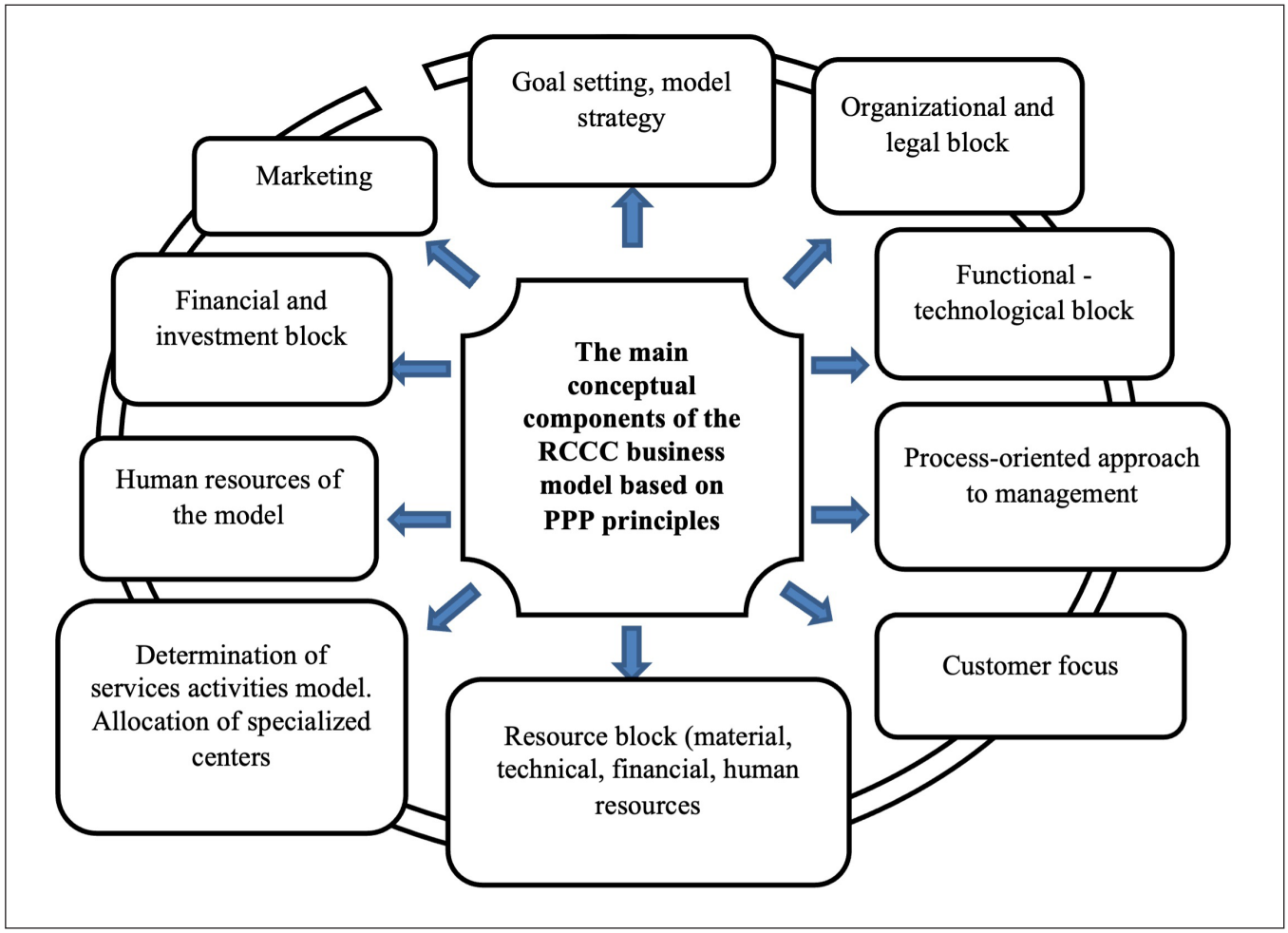

Fig. 1. Conceptual organizational directions of the formation of a model of a regional center for cardiology and cardiac surgery based on PPP principles

ganisation of cardiac care for the rural population are to increase the health care funding (91.5±1.5%) and salaries of medical personnel (87.2±1.8%), the introduction of compulsory medical insurance (81.8±2.1%) and mechanisms of economic motivation of personnel (89.8±1.6%). 73.9±2.3% of cardiologists under the survey pointed out the necessity of equipping healthcare facilities with modern medical and diagnostic equipment, improving the quality of postgraduate training of doctors-cardiologists (78.2±1.9%), introducing public-private partnership mechanisms with preservation of HCI in ownership of the state (79.3±2.2%).

The results of the expert assessment conducted by 31 experts confirmed the existence of the material and technical support problems and the state of cardiac care organisation in the Kyiv region. The equipment of HCI with modern therapeutic and diagnostic medical equipment was assessed by experts only at 2.5±0.16 points on a 5-point scale, the availability of modern medical and information technologies that increase the quality and safety of medical care – 2.2±0.13 points, the presence of medical and economic standards for the quality of medical care – 3.8±0.13 points, the organisation of the work of medical and diagnostic services – 3.6±0.16 points, the patients' possibility to receive the necessary diagnostic examination – 3.3±0.15 points, ensuring the availability and quality of medical care for patients – 3.7±0.14 points. The presence of a regulatory and legislative framework for the development of HCI was assessed by experts at 3.3±0.1 points, economic and legal independence – 3.2±0.1 points, financing of HCI – 2.9±0.1 points, the level of remuneration of medical workers – 3.3±0.15 points, economic motivation of personnel – 2.2±0.13 points.

Thus, a comprehensive study of the prevalence of DCS and the organisation of cardiac care for the population of the Kyiv region indicate the need to develop a regional program for the prevention of DCS and improve cardiologic aid, cardiac surgery and interventional care, as well as increase its availability for the most vulnerable groups, including the rural population of the region, which can be achieved by creating a Regional Centre for Cardiology and Cardiac Surgery.

Analysing the results of the study, determining social, economic, organisational and legal prerequisites, priority

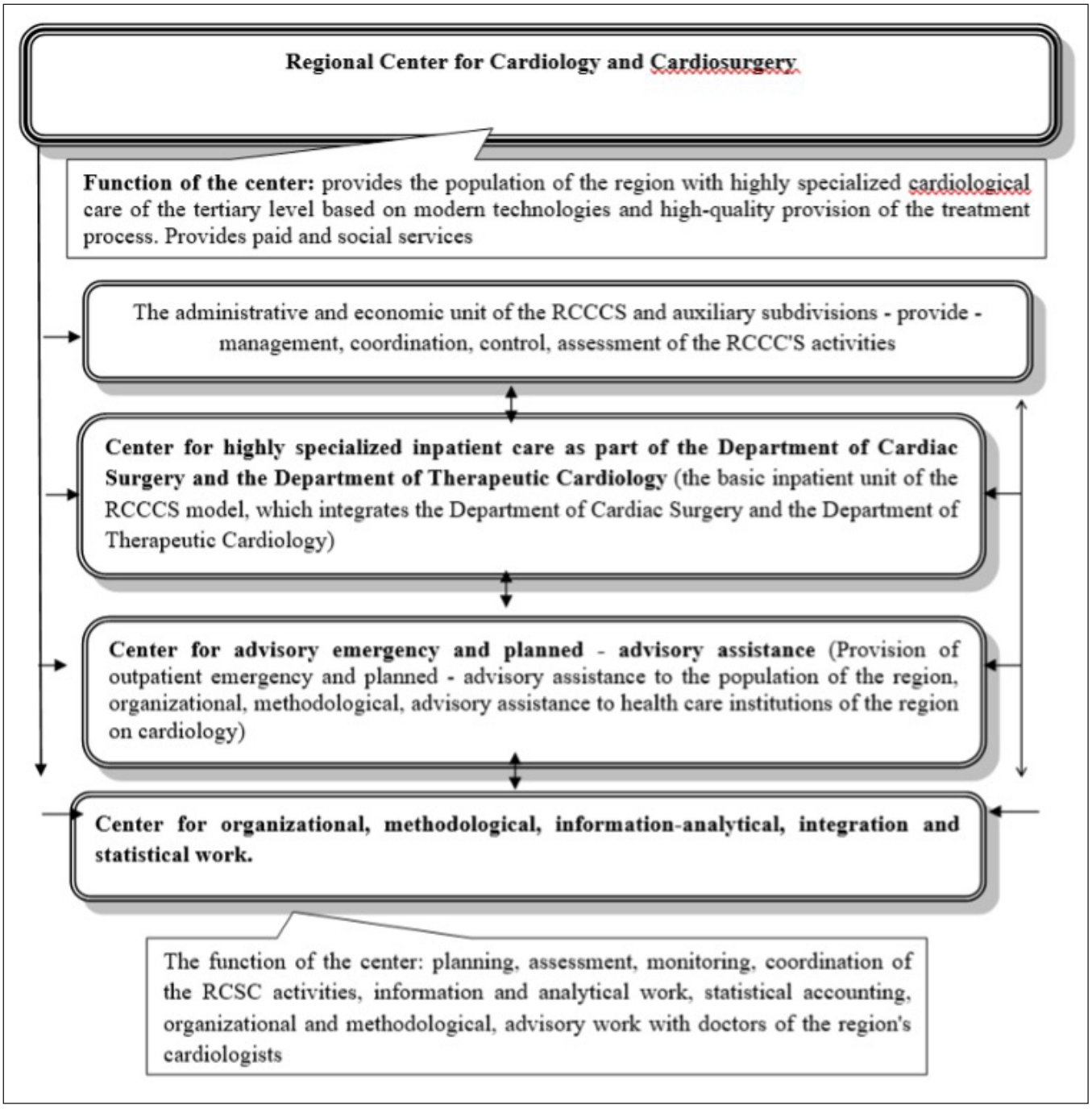

Fig. 2. Scheme of the structure of the conceptual functional-organizational model of the RCSC on the principles of DPP

directions of the state policy of Ukraine in health care sector, recommendations of WHO Regional Office for Europe, the conceptual directions of the formation of the RCCCS model were substantiated. They include ten modern aspects that form a conceptual model of a present-day regional cardiac surgery complex based on PPP principles (Fig. 1).

The RCCCS model based on PPP principles is a regional specialised clinical institution for cardiology, surgery of the heart and great vessels, X-ray endovascular diagnostics and treatment with the most expensive third-level cardiologic medical care (Fig. 2).

The therapeutic and prophylactic function of the RCCCS is provided by two centres: a Centre for Highly Specialised Inpatient Care and a Centre for Advisory Polyclinic Emergency and Planned-Advisory Assistance.

The Centre for Highly Specialised Inpatient Care is the basic inpatient unit of the Centre, which integrates the departments of cardiac surgery and the departments of therapeutic cardiology.

The activity of the Department of Cardiac Surgery determines a number of highly specialised areas: surgery for acquired and congenital heart defects, surgery for

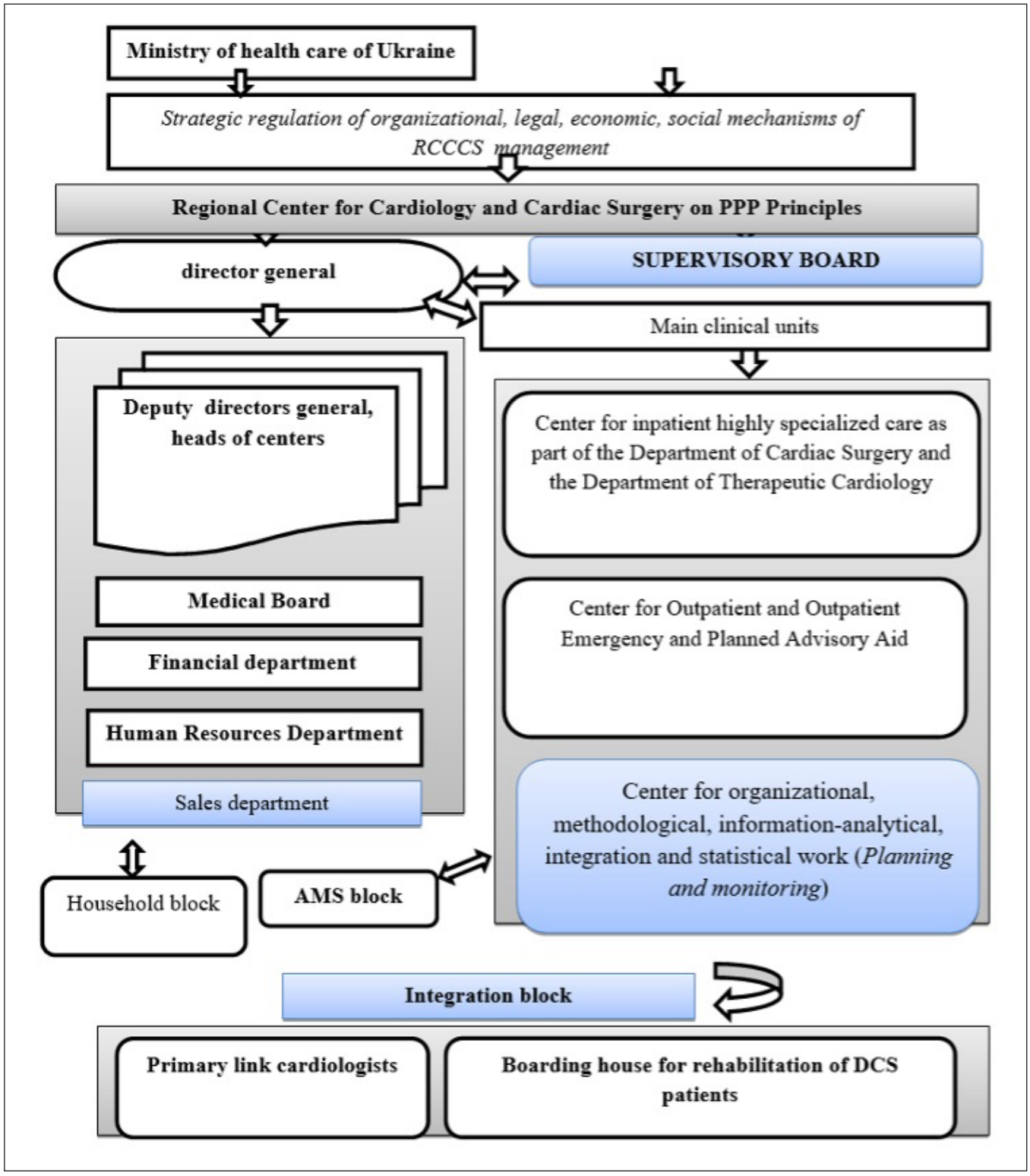

Fig. 3. The functional organizational structure of RCCCS management based on PPP principles.

coronary heart disease, surgery for cardiac arrhythmias, surgery for aortic pathology, and surgery for myocardial pathology.

The Department of Therapeutic Cardiology monitors patients with cardiac disorders for hypertension, ischemic heart disease, acute myocardial infarction, various arrhythmic manifestations, and congenital and acquired heart defects. The subjects of activity of the Centre for Advisory Emergency and Planned-advisory Assistance are the implementation of a complex of outpatient emergency and planned-advisory assistance to the region's population, reduction of cardiac morbidity, disability, and premature mortality. They provide advisory, organisational and methodological services

to HCI in the region on cardiology, X-ray endovascular diagnostics and treatment, heart and great vessels surgery, vascular surgery and transplantology.

To manage the model, a functional organisational structure of the RCCCS model on PPP principles was formed (Fig. 3).

The innovative element in the model's management is the control structure. It includes an authorised body for control over the activities of the Centre from the regional state administration - the supervisory board, Centre for organisational, methodological, information and analytical, integration and statistical work. The Supervisory Board coordinates the organisational and functional structure of the RCCCS and approves strategy for its development.

An expert assessment of the developed conceptual model of the RCCCS on PPP principles of PPP was carried out, and its predictive efficiency was confirmed.

The experts rated the model at 9.75±0.09 points. Individual components of the model received high marks:

- a public-private form of ownership, legal and economic independence of the model, preservation of the object (model) in the ownership of the state was assessed at 9.83±0.07 points;
- the existence of a mechanism for economic incentives for medical workers for the quality of services provided – 9.77±0.07 points;
- the presence of a mechanism of state control over the activities of the model – 9.77±0.08 points;
- the scheme of the functional and organisational model of the RCCCS on PPP principles – 9.67±0.09 points;
- the model orientation to ensure the availability of highly specialised cardiac care for different categories of the region's population within the framework of paid medical services and social state programs – 9.73±0.08 points.

DISCUSSION

The findings allowed us to reveal significant healthcare problems in the field of cardiology pertinent to the Kyiv region and establish apparent interconnections between the patient's point of view and the doctors' and experts' standpoints.

51.4±1.7% of the patients were dissatisfied with the organisation of possibilities to receive appropriate medical cardiological assistance, which is sounded by the opinion of the doctors in the way of necessity in introducing public-private partnership mechanisms with preservation of HCI in ownership of the state (79.3±2.2%) and confirmed by the experts who gave just 3.7±0.14 points in assessment of ensuring the availability and quality of medical care for patients.

The second direction of cardiological healthcare improvement lies in improving cardiology healthcare facilities' equipment. This was confirmed by the strong agreement of doctors and experts. 73.9±2.3% of cardiologists under the survey pointed out the necessity of equipping healthcare facilities with modern medical and diagnostic equipment; the equipment of HCI with modern therapeutic and diagnostic medical equipment was assessed by experts only at 2.5±0.16 points on a 5-point scale. Almost half of the patients complained about the same issue (41.9±1.9% of the respondents were dissatisfied with equipping the units with medical equipment). Comparing the state of provision of medical cardiology institutions in the capital of our country with the provision of similar facilities in developed countries, we find this state of affairs even more alarming. After all, the development and provision of cardiac care have reached significant heights in these countries. Thus, telemedicine, machine learning, programming and artificial intelligence tools, etc., are being actively implemented in cardiology departments [12-15].

The main suggestion to improve this state was described in the model as a public-private form of ownership, legal and economic independence of the model, and preservation of the object (model) in the ownership of the state, which was assessed at 9.83±0.07 points of sufficiency.

Other interconnected problems voiced both by patients and the specialists were:

- the waiting time for diagnostic examinations (47.1±1.7% of dissatisfied patients and the patients' possibility to receive the necessary diagnostic examination – 3.3±0.15 points assessed by the experts);
- the effectiveness of further treatment (29.7±1.6% of patients were dissatisfied, and this is supported by experts evaluating the presence of medical and economic standards for the quality of medical care at 3.8±0.13 points, the availability of modern medical and information technologies that increase the quality and safety of medical care at 2.2±0.13 points);
- the attitude of the medical staff to the patients (34.6±1.7%) which can be mirrored as the absence of proper mechanisms of economic motivation of personnel (89.8±1.6% by doctors/2.2±0.13 points by experts).

CONCLUSIONS

The unfavourable trends in mortality and prevalence of DCS among the population of the Kyiv region indicate the need to improve the system of medical care organisation for patients with DCS.

An analysis of the network, staffing and activities of the cardiologic service of the Kyiv region, the results

of a sociological survey of patients with DCS and cardiologists also confirm the need for its reorganisation.

The results of the expert assessment (conducted by 31 experts) confirmed the existence of problems in the material and technical support and the state of the organisation of cardiac care in the Kyiv region. The presence of a regulatory and legislative framework for the development of HCI was assessed by experts at 3.3±0.1 points, economic and legal independence – 3.2±0.1 points, financing of HCI - 2.9±0.1 points, the level of remuneration of medical workers – 3.3±0.15 points, financial motivation of staff work - 2.2±0.13 points.

The results of the sociological research and expert assessment served as the evidence base to substantiate the need and directions for improving the activities of the health care system, which provides medical care to patients with DCS.

Conceptual directions for the formation of the RCCCS model on PPP principles in the form of ten organisational positions for the formation of the structure of the model, which became the basis for modelling the RCCCS and the strategic directions of long-term interaction between the state and business have been developed.

The developed conceptual functional and organisational model of the Centre based on PPP principles is an investment project for the development of cardiac care for the population of the region, a self-governing, economically and legally independent subject of medical activity with an optimal combination of state regulation and market self-regulation. For the RCCCS model based on PPP principles, a functional organisational management structure has been developed.

The developed model received experts' positive assessment (9.6-9.8 points with a 10-point assessment of individual components of the model).

Prospects for further research are to use the results organisation of medical care for patients with DCS at the regional level.

REFERENCES

1. Varnavskiy V et al. Osnovyi gosudarstvenno-chastnogo partnerstva (teoriya, metodologiya, praktika). [Varnavsky VG et al. [Fundamentals of public-private partnership (theory, methodology, practice)] M: Ankil. 2015, p.252. (In Russian).
2. Derzhavno-pryvatne partnerstvo v sferi okhorony zdorov'ya. Mizhnarodnyy dosvid. [Public-private partnership in the field of health. International experience]. 2021. https://www.apteka.ua/article/423444 [date access 05.04.2023] (In Russian).
3. Panova TV. Opyit razvityih evropeyskih stran v ispolzovanii form i modeley GChP v zdravoohranenii [Experience of developed European countries in the use of forms and models of PPP in health care]. Voprosy ekonomiki i prava. 2015; 11: 99-102. (in Russian).
4. Shevchuk YuV. Rozvytok derzhavno-pryvatnoho partnerstva u konteksti udoskonalennya finansovoho zabezpechennya sfery okhorony zdorov'ya [Development of public-private partnership in the context of improving the financial security of health care]. Ekonomichnyy visnyk universytetu. 2017; 33(1): 416-428 (In Ukrainian).
5. Clifton J, Díaz-Fuentes D et al. (Public private partnerships for hospitals: Does privatization affect employment? Journal of Strategic Contracting and Negotiation. 2016; 2(4): 313–325. doi:10.1177/2055563617710619.
6. Torchia M, Calabrò A, Morner M. Public–Private Partnerships in the Health Care Sector: A Systematic Review of the Literature. Public Management Review. 2015;17:236-261. doi:10.1080/14719037.2013.792380.
7. Vovk SM. Instytutsiyni definitsiyi rozuminnya derzhavno-pryvatnoho partnerstva u medytsyni [Institutional definitions of understanding public-private partnership in medicine]. Derzhava ta rehiony. Seriya: Derzhavne upravlinnya. 2016; 3(55): 23-27 (In Ukrainian).
8. Adzhiyenko VL, Kosinova NM. Stratehichnyy analiz instytutu derzhavno-pryvatnoho partnerstva u sferi okhorony zdorov'ya [Strategic analysis of the institute of public-private partnership in the field of health]. Farmatsiya ta farmakolohiya. 2017; 5 (4): 380-400 (In Russian).
9. Zakon Ukrayiny vid 1 lypnya 2010 roku № 2404-VI - Pro derzhavno – pryvatne partnerstvo iz zminamy, vnesenymy zhidno iz Zakonamy VVR N 5007-VI (5007-17) vid 21.06.2012, 16.10.2012 [Law of Ukraine of July 1, 2010 № 2404-VI - On public-private partnership with changes made in accordance with the Laws of the Supreme Administrative Court No. 5007-VI (5007-17) of June 21, 2012, October 16, 2012]. https://www.apteka.ua/article/423444 [date access 10.04.2023] (In Ukrainian)
10. Zakon Ukrayiny vid 24.11.2015 № 817-VIII «Pro vnesennya zmin do deyakykh zakoniv Ukrayiny shcho do usunennya rehulyatornykh bar'yeriv dlya rozvytku derzhavno-pryvatnoho partnerstva ta stymulyuvannya investytsiy v Ukrayini» [Law of Ukraine of 24.11.2015 № 817-VIII "On Amendments to Certain Laws of Ukraine on Elimination of Regulatory Barriers to the Development of Public-Private Partnerships and Stimulation of Investments in Ukraine"]. http://zakon2.rada.gov. ua / laws / show / 817-19 [date access 10.04.2023] (In Ukrainian).
11. UCL – University College London. Sensitive research, Research Integrity. 2023. https://www.ucl.ac.uk/research/integrity/sensitive-research [date access 10.04.2023]
12. Chowdhury D, Hope KD, Arthur LC et al. Telehealth for Pediatric Cardiology Practitioners in the Time of COVID-19. Pediatr Cardiol. 2020;41(6):1081-1091. doi: 10.1007/s00246-020-02411-1.

13. Leclercq C, Witt H, Hindricks G et al. Wearables, telemedicine, and artificial intelligence in arrhythmias and heart failure: Proceedings of the European Society of Cardiology Cardiovascular Round Table. Europace. 2022;24(9):1372-1383. doi: 10.1093/europace/euac052.
14. Stremmel C, Breitschwerdt R. Digital Transformation in the Diagnostics and Therapy of Cardiovascular Diseases: Comprehensive Literature Review. JMIR Cardio. 2023;7:e44983. doi:10.2196/44983.
15. Svennberg E, Caiani EG, Bruining N et al. The digital journey: 25 years of digital development in electrophysiology from an Europace perspective. Europace. 2023;25(8):euad176. doi: 10.1093/europace/euad176.

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ORIGINAL ARTICLE

ANALYSIS OF THE RESULTS OF GP-FM QUESTIONNAIRE REGARDING TRAINING IN THE SPECIALIZATION «OTOLARYNGOLOGY» BOTH AT THE UNDERGRADUATE AND POSTGRADUATE LEVELS

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ABSTRACT

The aim: To research the degree of satisfaction with the training of general practitioners-family medicine (GP-FM) in the specialization "Otorhinolaryngology" in the leading higher educational institutions (HEIs) of Ukraine at undergraduate and postgraduate levels.

Materials and methods: A questionnaire was conducted of 51 GP-FM doctors.

Results: The duration of otorhinolaryngology training at a medical HEI was indicated by: 49% of respondents about weeks of training, 19.6% - about months. 31.37% received separate training on ENT examination. 56.9% of people were trained in ENT departments. 76.5% of people were not satisfied with the quality of theoretical knowledge, 52.9% of respondents of practical skills at the undergraduate level. 72.6% of doctors not satisfied with the quality of theoretical knowledge, 56.8% of respondents of practical skills at the post-graduate level. 41.2% of respondents received post-graduate training in otorhinolaryngology at the GP-FM specialization cycle, 72.55% of them in a lecture format. 86.3% of people want to deepen their knowledge of otolaryngology and need to understand the etiopathogenetic mechanisms of ENT pathology.

Conclusions. The dissonance with the dissatisfaction of the doctors of the GPFM with the quality of the received theoretical knowledge in ENT pathology and the availability of their practical skills was revealed. It is important for GPFM doctors to undergo separate training in ENT examination and pathology with mandatory study and conscious use of etiopathogenetic mechanisms of ENT pathology, especially in inflammatory diseases.

KEY WORDS: general practice-family medicine, otolaryngology, ENT- pathology, postgraduate training

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INTRODUCTION

Over the past decades, the enhancement of quality and the coverage of primary health care have provided important public health improvements around the whole world [1-7]. The most vulnerable area of general practice is the provision of the same high quality of care by doctors of general practice - family medicine (FP-FM) to patients with various pathology [8]. The main goal of medical education is to provide that each doctor develops and continues improving the basic clinical skills necessary to provide competent medical care throughout their professional life [9,-11]. Otorhinolaryngological problems form a significant part of primary health care visits [12]. Approximately 20% to 40% of consultations of adult general practice are related to otolaryngological complaints [13, 14]. While general practice physician successfully evaluate and treat the majority of ENT diseases, the third largest group of patients referred to clinics for specialized care, has ENT-organs patology [15, 16]. In order to confidently manage with ENT diseases, general practitioners have to have a sufficient level of knowledge, gained in the process of training specialists [17-20].

Less than half of general practitioners receive high-quality postgraduate training in otorhinolaryngology, and most of whom would welcome further training in this specialization at the postgraduate level [21-25]. Taking into account the problem of insufficient training in the specialization "Otolaryngology" in medical universities of a number of leading countries, a questionnaire, for those who graduated from medical universities in Ukraine, completed an internship in the specialization of general practice - family medicine (GP-FM) and work as a GP-FM doctor, was offered by us, on the subject of specialization training "Otorhinolaryngology" as at the university and as after the postgraduate level.

THE AIM

The aim of the research was to study the degree of satisfaction with the training in the specialization "Otorhinolaryngology" in the leading higher educational institutions (HEIs) of Ukraine, as at the undergraduate and as the postgraduate levels, of GP-FM doctors.

MATERIALS AND METHODS

The questionnaire was conducted of 51 GP-FM doctors, who graduated from various medical higher educational institutions of Ukraine, completed internships in the specialization of GP-FM, and work in primary health care centers in Kyiv.

The questionnaire was distributed using Google Forms and processed using the Excel program. The principles of bioethics were followed, as the survey was conducted voluntarily through Google Forms and anonymously.

The following questions were presented in the questionnaire:

1. Year of graduation from medical Higher Educational Institution (HEI)?
2. Name of the medical Higher Educational Institution?
3. What is your work experience?
4. The time allotted for otolaryngology at a medical Higher Educational Institution?
5. Did you undergo separate training in ENT examination?
6. Did you undergo training in ENT departments?
7. If you were trained in the ENT department, how long was it?
8. Are you satisfied with the quality of theoretical knowledge obtained at the undergraduate level, related to otorhinolaryngology training?
9. Are you satisfied with the quality of practical skills obtained at the undergraduate level, related to otorhinolaryngology training?
10. Did you undergo post-graduate training in otorhinolaryngology during the specialization cycle of GP-FM?
11. In which format was the post-graduate study conducted?
12. Are you satisfied with the quality of theoretical knowledge obtained at the post-graduate, related to otorhinolaryngology training?
13. Are you satisfied with the quality of practical skills obtained at the postgraduate level, related to otorhinolaryngology training?
14. Would you like to deepen your knowledge of otorhinolaryngology?15. In which area of ENT-pathology with the quality of practical skills obtained at the undergraduate level, related to otorhinolaryngology training?
15. In which area of ENT-pathology would you like to improve your knowledge?
16. Which etiopathogenetic mechanisms of ENT-pathology should be given more attention in the process of training otorhinolaryngology in an internship?

Statistical processing of data was carried out using the method of non-parametric statistics to establish differences between unrelated groups (Pearson's χ^2). The differences were considered to be statistically significant at $p<0,05$.

RESULTS

Doctors who graduated from university in 1978 were the most trained, and the youngest graduated from university in 2020. The interviewed studied at various higher educational institutions in Ukraine and out of its border: (60.78%) 31 - people graduated from O.O. Bogomolets National Medical University, (3.92%) 2 – people graduated from M.I. Pirogov National Medical University, (9.8%) 5 persons – D. Halytsky National Medical University, (5.9%) 3 doctors – Donetsk NMU, (11.76%) 6 people – Dnipro SMU, (3.92%) 2 – Leninhrad SMU, (1.96%) 1 – Stavropol SMU, and (1.96%) 1 – Nizhnygorodsk SMU.

The distribution of respondents by work experience is shown in Table I.

Regarding the question of the allotted time for otorhinolaryngology at the medical university, 49% (25) of the respondents indicated weeks of studies, 19.6% (10) of the respondents - about months, 31.4% (16) did not remember.

For the 5th question related to separate training in ENT-examination, 68.63% (35) answered that they did not have such study. 31.37%(16) confirmed about separate study of ENT-examination.

Regarding the question about underging of training in ENT-departments, 29 (56.9%) persons had such training, 20 (39.2%) did not confirm, and 2 (3.9%) did not remember.

Regarding the duration of training in the ENT-department, only 40 respondents answered. Among them, 16 (40%) did not remember, 8 (20%) persons indicated a few days, 12 (30%) answered weeks of study and 4 (10%) respondents answered as months of studing.

The interviewed doctors conducted a self-assessment of the received theoretical and practical ENT knowledge at the undergraduate level. The respondents' answers on the 8th question were distributed as shown in Fig. 1.

The group of dissatisfied doctors unite people who are dissatisfied and very dissatisfied with the quality of the received theoretical knowledge regarding the

Table I. Distribution of respondents by length of service.

№	Work experience	amount	Percentage
1.	1 – 5 years	10	19.6%
2.	6 – 10 years	6	11.8%
3.	11 – 20 years	12	23.5%
4.	21 – 30 years	4	7.8%
5.	More than 30 years	19	37.3%

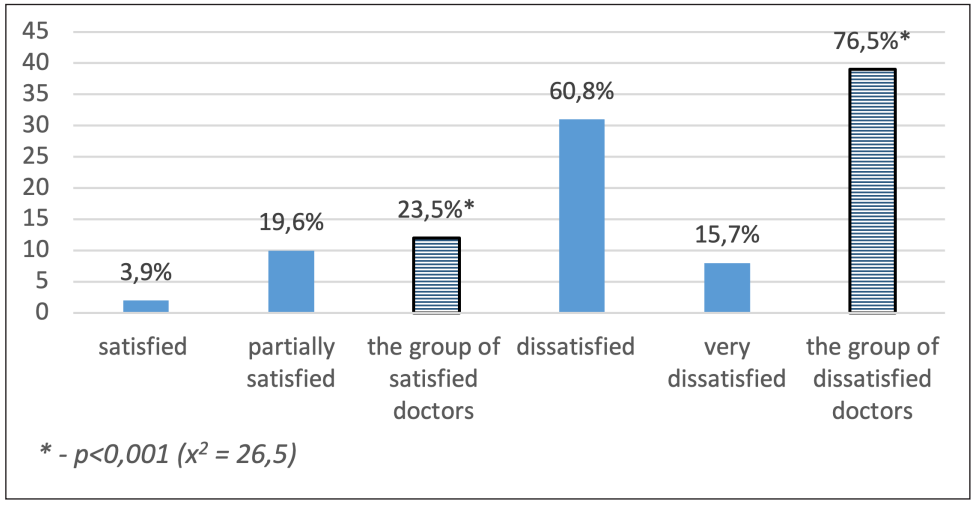

Fig. 1. The level of satisfaction with the quality of received theoretical knowledge regarding the study of otolaryngology at the undergraduate level.

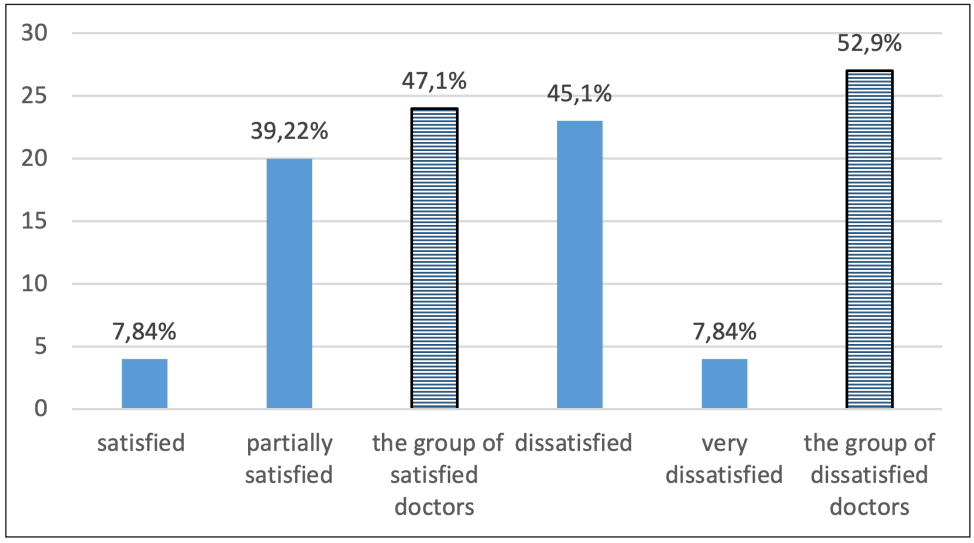

Fig. 2. The level of satisfaction with the quality of received practical skills regarding the study of otolaryngology at the undergraduate level.

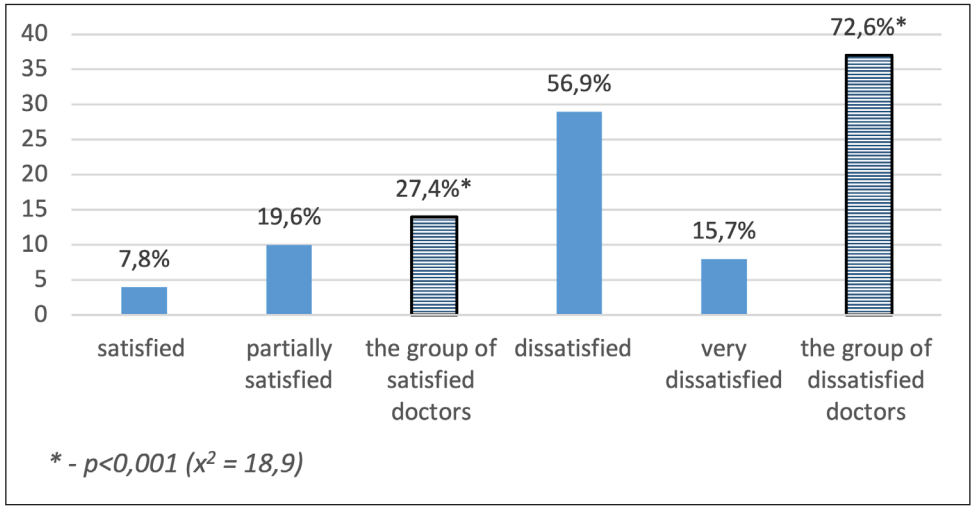

Fig. 3. Respondents' level of satisfaction with the quality of the obtained theoretical knowledge of otolaryngology education at the post-diploma level.

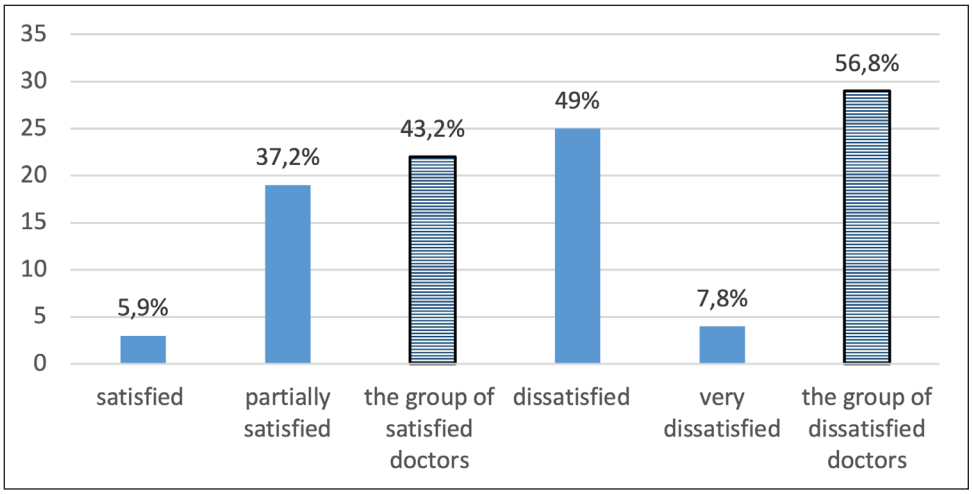

Fig. 4. The level of respondents' satisfaction with the quality of the acquired practical skills regarding the training of otolaryngology at the postgraduate level.

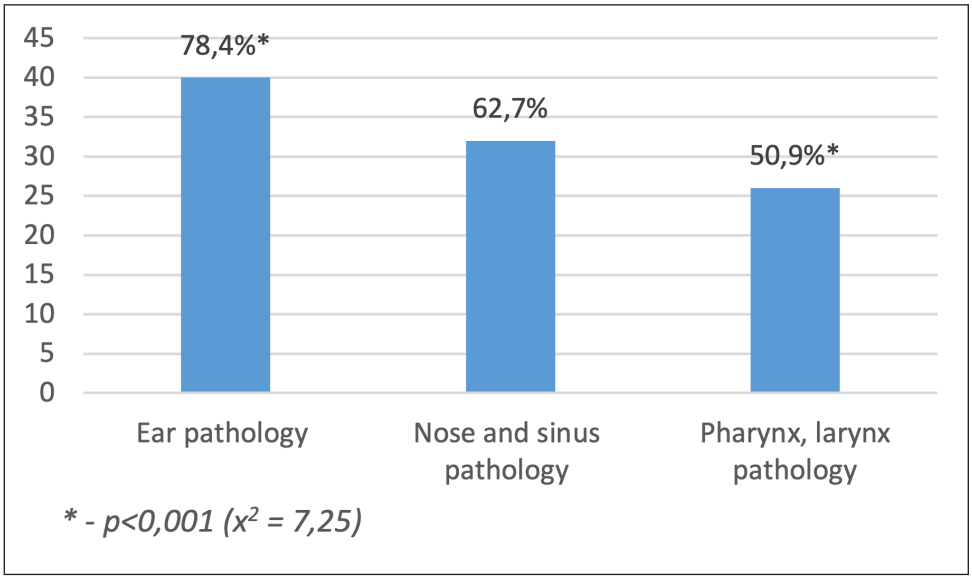

Fig. 5. List of pathological conditions of ENT pathology in which respondents need additional knowledge and skills.

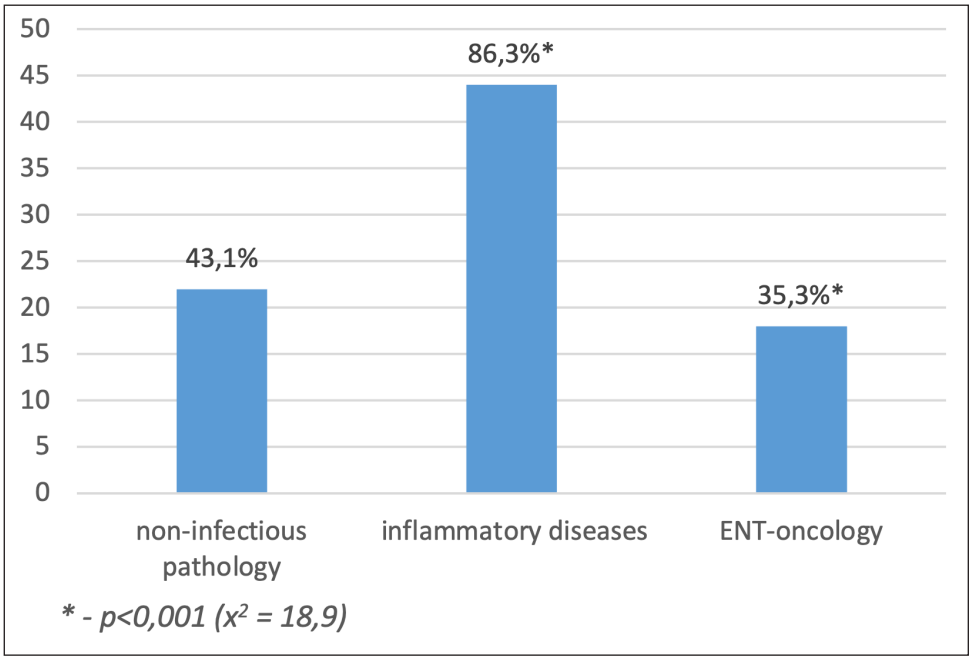

Fig. 6. List of etiopathogenetic mechanisms of ENT pathology, in which respondents need additional knowledge and skills during internship.

study of otolaryngology at the undergraduate and postgraduate levels. The group of satisfied doctors unite people who are satisfied and partially satisfied with the quality of the received theoretical knowledge regarding the study of otolaryngology at the undergraduate and postgraduate levels.

Doctors' answers to the 9th question were distributed as shown in Fig. 2.

For the question related to undergoing of post-graduate training in otorhinolaryngology at the specialization cycle of GP-F, 30 (58.8%) answered that they did have such training. (41.2%) people confirmed about undergoing of training in otorhinolaryngology.

On the question related to the format of post-graduate study, 37 (72.55%) responded as lectures 14 (27.45%) respondents informed abount practical classes.

The respondents were also evaluated of the received theoretical and practical ENT knowledge at the postgraduate level. Respondents' answers to the 12th question were distributed as shown in Fig. 3.

Doctors' answers to the 13th question were distributed as shown in Fig. 4.

The 86.3% (44) of doctors expressed a desire to undergo further training in otolaryngology, 13.7% (7) of respondents had no desire to deepen their knowledge.

Information on areas of ENT pathology in which doctors would like to improve their knowledge is shown in Fig. 5. This indicates that the number of doctors who need knowledge and skills to examine ear pathology is significantly ($p<0.001$; $\chi^2=7.25$) higher than the number of doctors who indicated a lack of knowledge and skills to examine the throat.

Figure 6 shows the identification of the need for doctors to understand the etiopathogenetic mechanisms of ENT pathology in the process of studying otolaryngology at the intership. The number of doctors (86.3%) who need additional knowledge about the causes and pathogenesis of inflammatory pathological processes at various stages of development significantly ($p<0.001$; $\chi^2=18.9$) outnumbers the number of respondents (35.3%) who wished for more knowledge of ENT oncology.

DISCUSSION

Summarizing the data of questionnaire, we come to the following: the interviewed doctors had a work experience from 2 to 45 years. The respondents studied at higher educational institutions in different regions of Ukraine, which indicates a similarity in the style of professional qualification. The term of study of otorhinolaryngology at the undergraduate level was not clearly recorded in the memory of the respondents. Among the interviewed of 56.9% underwent this study in ENT departments, the duration of training in ENT Department lasted one week for 30% of people,40% of the interviewed doctors did not remember the term of study in ENT department. Along with that, 68.6% of respondents indicated that they had not have a separate training related to the examination of ENT organs. This may indicate insufficient professional training in otorhinolaryngology, taking into account the practical needs of doctors of the GP-FM.

The results of the self-assessment of the interviewed doctors regarding the satisfaction with the quality of the theoretical and practical skills received at the undergraduate and postgraduate levels in the examination and pathology of the ENT organs showed: the quality of the theoretical knowledge received at the undergraduate level did not reliably satisfy ($p<0.001$) a larger number of the interviewed doctors (76.5%), while the number of doctors satisfied with the quality of acquired practical skills (47.1%) did not reliably differ from the number of respondents dissatisfied with the quality of practical training at the undergraduate level (Fig. 1, 2). The quality of the received theoretical knowledge at the post-graduate level also did not reliably satisfy ($p<0.001$) a larger number of interviewed doctors (72.6%), regarding the quality of practical skills of the group of satisfied (56.8%) and satisfied doctors (43.2%) reliably not differed (Fig. 3, 4).

Concerning the post-graduate training in otorhinolaryngology in the cycle of specialization in GP-FM, 58.8% of respondents indicated that they did not undergo such training. Among the respondents (41.2%), who were trained in otorhinolaryngology at the postgraduate level, the most doctors (72.55%) indicated that they studied in a lecture format, and only 27.45% of respondents had practical classes. This shows the insufficiently effective level and quality of practical training of doctors of the GP – FM in ENT pathology. The same trends are also found in other countries, 70% of interviewed general practitioners in the south-west of England have undergone some form of post-graduate training in otorhinolaryngology, either in the form of stationary otorhinolaryngology positions, or post-graduate training, it is significantly higher than the previous results in Trento in 1992, only 39% of general practitioners received similar training [24, 26].

The insufficient level of training in otolaryngology is confirmed by the desire of 86.3% of respondents to undergo further training. Which correlates with the data of a number of researchers, who also cite research data, and indicate that three-quarters of general practitioners would like to continue their education [24]. Respondents want to improve their knowledge in fact, in all areas of ENT pathology, it was found that doctors who need to deepen their knowledge of ear pathology (78.4%) significantly ($p<0.001$) exceed the number of doctors who would like to improve their knowledge and skills regarding pharynx and larynx pathology

(50.9%). Also, 62.7% of doctors need to deepen their knowledge of the pathology of the nose and paranasal sinuses. A large group of interviewed doctors (86.3%) expressed the need to deepen their knowledge of the etiopathogenetic mechanisms of ENT pathology, with a significant advantage ($p<0.001$ ($\chi^2=18.9$)) of inflammatory diseases as the most frequent pathology encountered in the primary health care system. It can be researching the pathology of several specialists at the same time. This intersects with the data of a number of researchers that ENT pathology is the third largest group of patients referred to specialized clinics at hospitals [24, 27].

CONCLUSIONS

The dissonance with the dissatisfaction of the doctors of the GPFM with the quality of the received theoretical knowledge in ENT pathology and the availability of their practical skills was revealed.

It is important for GPFM doctors to undergo separate training in ENT examination and pathology with mandatory study and conscious use of etiopathogenetic mechanisms of ENT pathology, especially in inflammatory diseases.

There is a need to develop a program for post-graduate training in ENT pathology specifically for GPFM doctors in the form of training that will combine theoretical knowledge and practical skills.

REFERENCES

1. Allen N, Barkley S, Maeseneer J et al. Unfulfilled potential of primary care in Europe BMJ. 2018. doi: 10.1136/bmj.k4469.
2. Caley M. Remember Barbara Starfield: primary care is the health system's bedrock. BMJ. 2013;347:f4627. doi: 10.1136/bmj.f4627 23900532.
3. Lember M, Cartier T, Bourgueil Y, Dedeu T. Structure and organization of primary care. Building primary care in a changing Europe. (Observatory Studies Series 38). Eur Obs Heal Syst Policies. 2015,p.172. http://apps.who.int/iris/bitstream/handle/10665/154350/9789289050319-eng.pdf [date access 03.04.2023]
4. Macinko J, Starfield B, Shi L. The contribution of primary care systems to health outcomes within Organization for Economic Cooperation and Development (OECD) countries, 1970-1998. Health Serv Res. 2003;38:831-65. doi: 10.1111/1475-6773.00149 12822915.
5. Rohde J, Cousens S, Chopra M et al. 30 years after Alma-Ata: has primary health care worked in countries? Lancet. 2008;372:950-61. doi: 10.1016/S0140-6736(08)61405-1 18790318.
6. Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. Milbank Q. 2005;83:457-502. doi: 10.1111/j.1468-0009.2005.00409.x 16202000.
7. van Weel C, Kassai R, Qidwai W et al. Primary healthcare policy implementation in South Asia. BMJ Glob Health. 2016;1:e000057. doi:10.1136/bmjgh-2016-000057 28588938.
8. Richard B. King's Fund report on improving the quality of care in general practice. BMJ. 2011; 342. doi: 10.1136/bmj.d1932.
9. Fung K. ENT--head and neck surgery in undergraduate medical education: advances and innovations. Laryngoscope. 2015;125(2):S1-14. doi: 10.1002/lary.24875.
10. Margaret CM, Arielle T, Andrew DS, Philip EZ. Using Computer-Assisted Instruction to Increase Otolaryngology Education During Medical School. MedEdPORTAL. 2021;17:11065. doi: 10.15766/mep_2374-8265.11065.
11. Luke JP, Daniel B, Philip Z et al. Assessing Medical Student Basic Otolaryngology Knowledge: A Multi-Institutional Study. Ear Nose Throat J. 2019;98(1):44-49. doi: 10.1177/0145561318823369.
12. Hu A, Sardesai MG, Meyer TK. A need for ENT education among primary care providers. Med Educ Online. 2012;17(1). doi: 10.3402/meo.v17i0.17350.
13. Campisi P, Asaria J, Brown D. Undergraduate ENT education in Canadian medical schools. Laryngoscope. 2008;118(11):1941–50. doi: 10.1097/MLG.0b013e31818208e7.
14. Donnelly MJ, Quraishi MS, McShane DP. ENT and general practice: a study of paediatric ENT problems seen in general practice and recommendations for general practioner training in ENT in Ireland. Ir J Med Sci. 1995;164:209–211. doi:10.1007/BF02967831.
15. Kristine AS, Ashley VH, James B et al An Evaluation of On-Call Otolaryngology Consultations: Assessing an Increasing Workload. Ann Otol Rhinol Laryngol. 2018;127(7):450-455. doi: 10.1177/0003489418776670.
16. Ellen T, Adam RS, John TL et al. Gaps in Training: Misunderstandings of Airway Management in Medical Students and Internal Medicine Residents. Otolaryngol Head Neck Surg. 2021;164(5):938-943. doi: 10.1177/0194599820949528.
17. Zachary S, Kevin F, Elaine L et al. Interprofessional education day - an evaluation of an introductory experience for first-year students. J Interprof Care. 2018;32(3):399-402. doi: 10.1080/13561820.2018.1433641.
18. Matt M, Colin B, Michael F et al. Consultation Intervention Rates for the Otolaryngology Service: A Large Metropolitan Hospital Experience. Spartan Med Res J. 2020;4(2):11596. doi: 10.51894/001c.11596.
19. Abdullah NA, Ashokkumar T, Abdulhakeem A et al. Knowledge and Attitude towards Obstructive Sleep Apnea among Primary Care Physicians in Northern Regions of Saudi Arabia: A Multicenter Study. Healthcare (Basel). 2022;10(12):2369. doi: 10.3390/healthcare10122369.

20. Brendan DS, Julie P. et al. High frequency of otolaryngology/ENT encounters in Canadian primary care despite low medical undergraduate experiences. Canadian medical education journal. 2022; 13(1): 86–89. doi: 10.36834/cmej.72328.
21. Daniel CO, Lane DS, Aaron DR et al. A Multicenter, Cross-Sectional Assessment of Otolaryngology Knowledge Among Primary Care Trainees. Ann Otol Rhinol Laryngol. 2018;127(9):631-636. doi: 10.1177/0003489418784615.
22. Kastley M, Paige B, Matthew WK, Art AA. Effectiveness of an Advanced Airway Training "Boot Camp" for Family Medicine Physician Trainees. Otolaryngol Head Neck Surg. 2020;163(2):204-208. doi: 10.1177/0194599820902065.
23. Ambreen AU, Muhammad HD, Muhammad SA et al. Otorhinolaryngology consultations in a multidisciplinary hospital - their effects on residents training on floor. J Pak Med Assoc. 2022;72(1)(2):S44-S48. doi: 10.47391/JPMA.AKU-20.
24. Clamp PJ, Gunasekaran S, Pothier DD et al. ENT in general practice: Training, experience and referral rates. J Laryngol Otol. 2007;121(6):580–3. doi: 10.1017/S0022215106003495.
25. Vikas A, Matthew H, Naomi K et al. Does focused and dedicated teaching improve the confidence of GP trainees to diagnose and manage common acute ENT pathologies in primary care? Adv Med Educ Pract. 2018;9:335-343. doi: 10.2147/AMEP.S155424.
26. Veitch D, Lewis M, Gibbin K. General practitioner training in the Trent Region. Journal of the Royal Society of Medicine. 1992; 85: 156-158.
27. Coulter A, Noone A, Goldacre M. General practitioners' referrals to specialist outpatient clinics. I. Why general practitioners refer patients to specialist outpatient clinics. BMJ. 1989; 299:304–6. doi: 10.1136/bmj.299.6694.304.

The study is performed on the topic of scientific research work of the multidisciplinary Department of Family Medicine and Outpatient Care, with a dedicated fragment: «Optimization of early diagnosis ways and prevention of the ENT organs diseases in patients with comorbid pathology» (registration number: 0122U002416; term: 2022-2026).

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ORIGINAL ARTICLE

OPTIMIZATION OF POWER-ASSISTED ADENOIDECTOMY IN CHILDREN USING SHAVER TIPS OF VARIOUS MODIFICATION

DOI: 10.36740/WLek202310107

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ABSTRACT

The aim: To study the efficacy of surgical treatment of patients with adenoid vegetations by implementing a differential method for choosing a tip for endoscopic power-assisted adenoidectomy in children depending on dentition.

Materials and methods: We investigated the presence of nasal air emissions in 127 children (2-12 years old) before and after the operation. We excluded 12 patients due to the presence of nasal air emission before the operation. All patients were divided in 2 groups: I – children with aging primary dentition (55 children), II- children with mixed dentition (60 children). Depending on tips, that were used for the operation, we divided patients into two subgroups: A - 40˚ and B- 60 ˚.

Results: In 9,4% of patients have the presence of nasal air emissions before the operation. The use of 40˚ tips does not allow removal of lymphoid tissue in "hard-to-reach" areas of the nasopharynx (perichoanal and peritubular sections) in 30% of children with aging primary dentition and 42.9% with mixed dentition.

Conclusions: The use 40˚ tips for the adenoidectomy is accompanied by a higher risk of velopharyngeal insufficiency in children with mixed dentition compared to children who underwent the intervention with a tip with a larger bending angle and a longer working part (60°). In patients with temporary dentition, it is recommended to use a standard tip for adenoidectomy, except when correction of tubal lymphoid tissue is planned (it is necessary to use a tip with a rotating window). In patients with mixed dentition, it is recommended to use a 60° tip.

KEY WORDS: Adenoidectomy, endoscopic power-assisted adenoidectomy, inflammation of the upper respiratory tract, velopharyngeal inadequacy

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INTRODUCTION

Adenoidectomy (AT) is the most common surgical intervention in pediatric otolaryngology [1, 2]. One of its complications is velopharyngeal inadequacy (VPI) [3-5], which is characterized by hypernasal speech, nasal air emission, and liquid regurgitation [14]. It occurs rather often, but, fortunately, it's mostly temporary with a duration of up to 5-12 months [4, 6]. The frequency of persistent VPI after AT is from 1:1200 to 1:100000 [4].

The factors contributing to the development of VPI involve overt or hidden palatal cleft, short palate, cranial nerve dysfunction, genetic disorders, and hypernasal speech before surgery [7, 8]. However, in 30-77% of VPI occurring after AT, the cause of the latter cannot be identified [3, 8].

In recent years, endoscopic power-assisted adenoidectomy (EPAA) is becoming increasingly popular, which is associated with its significant advantages compared to the classical method [9]. To perform EPAA in children, the manufacturers offer a standard tip of 40° and a length of the working part of 18 mm with a fixed working window on the inner surface [10]. The application of such a tip does not allow doctors to remove the adenoid tissue in the hard-to-reach areas of the nasopharynx [11]. In this case, Pagella recommend using a 60° version of the blade from the line proposed for sinus surgery, which significantly increases the cost of intervention [11], and this is particularly relevant today due to martial law. The attempts to remove adenoid vegetations using a tip with insufficient bending angle an be accompanied by excessive impact on the soft palate during the intervention.

The hypothesis of our research is that a less aggressive impact on the soft palate during AT reduces the risk of VPI development. In our opinion, the selection of the most complementary tool to the structure of the nasopharynx will make it possible to effectively manipulate when removing lymphoid tissue from the vault of the nasopharynx and adjacent areas without creating pressure on the soft palate. We published the

results of designing the configuration of such a tool in a previous publication [12].

To test our hypothesis, we compared the frequency of the development and severity of signs of VPI after AT in children with different dentition when using a tip recommended for powered AT in children, that is a 40° tip with a length of its working end after bending of 18 mm (20 mm along the outer bend)-4 mm RADenoid™ blade (Medtronic, USA) with a fixed working window, and a 60° tip with a length of its working end after bending of 18 mm (33 mm along the outer bend)-4 mm RAD™ 60 blade (Medtronic, USA) and a rotator window, which is recommended for sinus surgery (Figure 1) [10] and meets the specified calculation saving criteria for all groups of children.

THE AIM

The aim was to study the efficacy of surgical treatment of patients with adenoid vegetations by implementing a differential method for choosing a tip for EPAA in children depending on dentition.

MATERIALS AND METHODS

The study involved 127 children (81 boys and 46 girls) aged 4-12 years, who were treated for adenoid vegetations at children's hospital of the State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administration Department.

The study was performed in compliance with bioethical principles. Ethical approval No.15 of 21.12.2020 from the Ethics Commission of Shupyk National Healthcare University of Ukraine was obtained to carry out the research. Informed consent for the research was obtained from the parents.

All patients underwent EPAA. Indications for AT (inclusion criteria) were as follows: nasal breathing disorder, apnea, chronic adenoiditis, as well as a combination of hypertrophy of the pharyngeal tonsil with accompanying pathology, such as chronic secretory otitis media, recurrent acute otitis media, recurrent acute rhinosinusitis. Exclusion criteria were the child's inability to follow the instructions (due to age restrictions or features of mental development), the presence of concomitant pathology of the maxillofacial area, injuries, or operative interventions of the maxillofacial area in past medical history. Exclusion criteria during the study involved nasal air emission (NAE) during preoperative examination.

Among the patients studied, 58 children had APD and 69 children had MD. A study was not conducted in children with deciduous dentition, since patients aged 2-4 years are not always able to perform speech therapy tests.

The assessment of the traumatic nature of AT in relation to the soft palate was carried out based on the analysis of articulation (nasal twang) and determination of NAE presence. The mirror-fogging test was used for this, which is recommended as a screening tool for this purpose [4;13]. The test was performed before surgical intervention and 6-8 hours after AT. In case of a positive result (NAE) at discharge, it was repeated in 1 week, and if the result remained positive, supervision of an otolaryngologist and a speech therapist in the home area was advised.

Due to the presence of NAE before surgical intervention, 12 out of 127 patients were excluded from the study, therefore 115 children (73 boys and 42 girls, average age 6.5±2.24 years) took part in the further study.

As a result, the children were divided into the following groups: group 1 included 55 children with APD (32 boys and 23 girls, average age 4.8±0.79 years), group 2 consisted of 60 children with MD (41 boys and 19 girls, average age 8.15±1.94 years). In addition to EPAA, 67 patients underwent tonsillotomy, 6 patients underwent tympanocentesis. The distribution into groups by gender and concurrent interventions was uniform, and the distribution by age was marked by a significant difference ($p<0.05$, Table I).

Depending on the type of tips used during the intervention, each group was divided into subgroups: subgroup A included children who underwent EPAA using a standard blade for AT (40°), and subgroup B included children who underwent surgical intervention using a tip from the line proposed for sinus surgery (60°). Subgroup A also involved children who underwent primary AT with the use of a 40° tip, but when it was impossible to completely remove lymphoid tissue in the nasopharynx, a 60° tip for sinus surgery was additionally used (12 children from group 1 and 18 children from group 2) (Table II).

The reason for changing the tip during AT was failure to remove lymphoid tissue from the choanal vault and in the peritubular areas. The criterion for changing to a tip with a larger bending angle was the surgeon's subjective feeling of excessive tissue resistance when the palate was stretched, and in case of the need to work in the peritubular areas – the inaccessibility of lymphoid tissue due to insufficient width of the standard working window of the tip and its fixed position relative to the axis of the tip (the need for rotation to remove tissues located laterally).

Statistical processing of the data was carried out using the Statistica version 13.5.0.17 program. Basic statistical indicators were determined, and two-sided Fisher's exact test, Mann-Whitney test for quantitative indicators, and relative risk with a confidence interval (CI) of 95% were calculated.

Table I. Distribution of children into groups

Indicator	n	Group 1 (n=55)		Group 2 (n=60)		P
		%	n	%		
Gender	Male	32	58.2	41	68.3	>0.05
	Female	23	41.8	19	31.4	>0.05
Simultaneous interventions	Tonsillotomy	33	60	34	56.7	>0.05
	Tympanocentesis	4	7.3	2	3.3	>0.05

Table II. Distribution of children into subgroups depending on the type of tips used for EPAA

Indicator	Subgroup A (40° tip), (n=55)		Subgroup B (60° tip), (n=60)	
	Abs.	%	Abs.	%
Group 1 (children with APD)	40*	72.7	15	27.3
Group 2 (children with MD)	42**	70	18	30
p	>0.05		>0.05	

Note:* - in 12 children (30.0%) a microdebrider tip was changed in the course of AT; ** - in 18 children (42.9%) a microdebrider tip was changed during the intervention.

Table III. NAE detection rate in the postoperative period after AT

Indicator	Group 1 (n=55)		Group 2 (n=60)		p_1
	Presence of NAE	Absence of NAE	Presence of NAE	Absence of NAE	
A 40° tip application (subgroup A)	4	36	31	11	<0.05
A 60° tip application (subgroup B)	3	12	6	12	>0.05
p_2	>0.05		<0.05		-
Relative risk (95% confidence interval)	0.50 (0.13-1.98) p>0.05		2.21 (1.12-4.36) p<0.05		-

Notes: p_1 – the significance of difference between the groups 1 and 2; p_2 – the significance of the difference in the corresponding group (either 1 or 2).

RESULTS

The preoperative screening showed that 3 (5.2%) patients with APD and 9 (13.0%) patients with MD had signs of NAE, and the indicated sign was found with the same frequency in children of the groups (p>0.05).

When performing EPAA with a standard tip for AT in subgroup A, it was possible to completely remove all planned lymphoid tissue in 28 (70%) children of group 1 and 24 (57.1%) children of group 2. In the rest of the children of subgroup A, there was a need to use a 60° tip of a microdebrider with a rotating working end in 12 (30%) patients of group 1 and in 18 (42.9%) patients of group 2. The reason for changing the tip in 11 children (27.5%) with APD was a failure to remove lymphoid tissue in the peritubular areas, and only in 1 patient (2.5%) it was hard to reach the choanal vault. In children with MD, the predominant reason for changing the tip was a failure to thoroughly remove the tissue from the nasopharyngeal vault in 12 cases (28.6%), including with spread to the choana in 9 cases, and inaccessibility of peritubular areas in 3 cases (7.15%), as well as a combination of both reasons in 3 cases (7.15%). The results obtained during the study of NAE in the postoperative period are presented in Table III.

One child from subgroup A of group 2 had a nasal twang that disappeared within 1 month.

The data presented in Table III demonstrate that the development of NAE in the postoperative period occurs with the same frequency in both subgroups of children with APD when EPAA is performed (both when using a standard tip for AT and a tip for sinus surgery), while in children with MD, there is a significant difference in the frequency of the development of this symptom in different subgroups. In addition, when comparing subgroups A of both groups (the use of a standard tip for AT), a significantly higher frequency of NAE in the postoperative period was found in children with MD compared to those with APD. When using a tip for sinus surgery (subgroup B) in children of both groups, no difference was found.

DISCUSSION

At the stage of patient selection for our study, it was found that 12 (9.4%) patients, who were scheduled to undergo AT, had signs of NAE in the preoperative period. The analysis of the frequency of cases of hypernasal speech in the postoperative period among all patients showed that 47 (25.5%) children (44 patients without NAE, who underwent

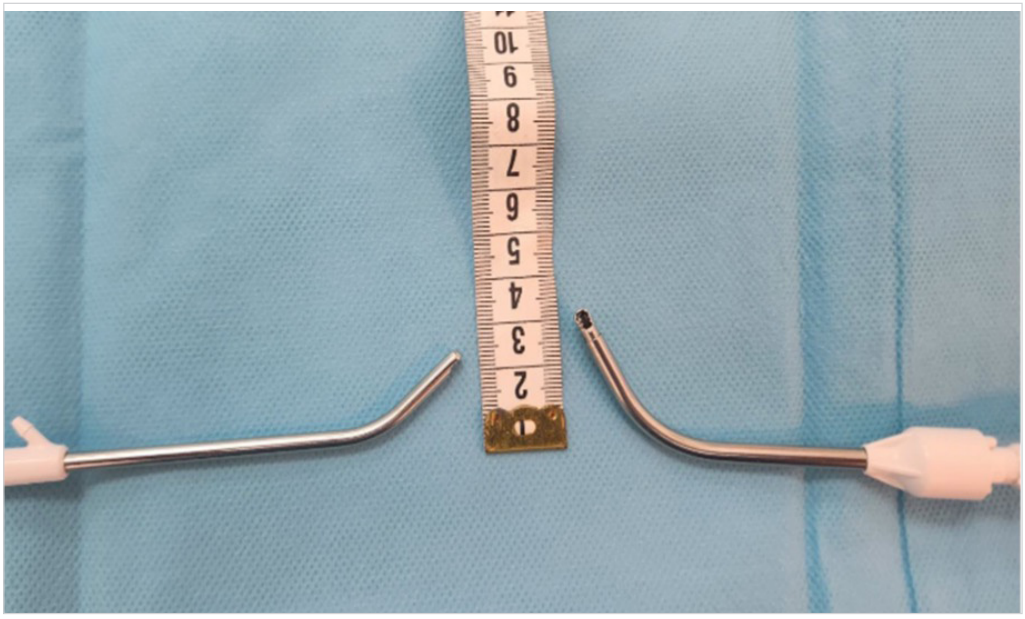

Fig. 1. Tips of various modification
Notice: According to catalog Medtronic®: left – 40° angled blade, length 18 mm, right - 60° angled blade, length 18 mm. Picture represent the difference of length along the outer bend (20 mm and 33 mm respectively).

the intervention using a standard tip, and 12 patients, who were excluded from the study) had this feature in the preoperative period. The obtained result coincides with the research of Lambert (2021), according to which in 34% of patients, who had hypernasal speech after AT, these speech features were noted even before the intervention, and they became more manifestative after it [14].

It was found that in 36.6% of patients (30.0% of children with APD and 42.9% of children with MD) the use of a standard tip did not allow surgeons to remove lymphoid tissue in the hard-to-reach areas, namely peritubular and perichoanal sections. Among them, in 15 patients (18.3%) the inaccessibility of the perichoanal sections was the reason for changing the tip, which coincides with the previously published data on the failure to remove adenoid tissue with a standard adenectomy in the indicated place in 18% of patients [11]. Taking into account the fact that the most frequent sites of residual lymphoid tissue in primary AT and the site of clinically significant recurrence of symptoms of adenoid vegetations are both the nasopharyngeal vault (perichoanal) and the peritubular sections [15], the reachability of both localizations was evaluated in the study.

The analysis of the frequency of NAE development in the group of patients who underwent AT using a tip for sinus surgery (60°), which does not have an impact on the soft palate, showed no difference in the study groups: 3 children (20.0%) in group 1 and 6 children (33.3%) in group 2. It is worth pointing out that the literature indicates the important role of lymphoid tissue in the function of closing the nasopharynx with the soft palate, the removal of which during AT can often lead to insufficiency, which is more often compensated by stretching the palate, as occurs with age-related involution of the pharyngeal tonsil [4, 16]. Therefore, it is believed that patients after AT performed for nasal breathing disorders are more likely to develop VPI compared to those who underwent intervention due to recurrent inflammatory diseases of the upper respiratory tract [14], which are more relevant in older children [17]. In this case, since hypertrophy of the pharyngeal tonsil is a more frequent indication for AT in children of group 1 (average age 4.8±0.79 years), the frequency of NAE detection in the preoperative period should be lower compared to children of group 2 (average age 8.15±1.94 years), which was not found in our study ($p>0.05$). Moreover, if this judgment is correct, then the signs of transient NAE should develop in children of group 1, not due to an impact on the soft palate, but due to a sharp decrease in the lymphoid tissue of the nasopharynx even when using a sparing tip (subgroup B), but in this study, we did not observe such changes. In contrast, a significant difference in the frequency of NAE after surgery in children in subgroup A was found between groups 1 and 2, as well as between subgroups A and B in children with MD. The obtained data indicate that the combination of signs – group 2 (MD) and subgroup A (the use of a standard tip for AT) increases the probability of VPI development. That is why, to prevent the occurrence of this complication, the use of a 60° tip for sinus surgery is recommended in this group of patients.

The results of studying the development of NAE, as an indicator of the impact on the soft palate, confirm our hypothesis that in different groups of children, divided by the dentition, the complementary tip has a different con-

figuration. The division into groups based not on the age from birth certificate, but on the dentition, is determined by the fact that the driving force behind the growth and development of the frontal part of the skull is the process of dentalization. At the same time, the changes in the structures of this area are uneven and multidirectional, which leads to a change not only in linear dimensions but also in the angles between the structures of the facial area, which was proved in our previous publication [12]. Therefore, in most cases, in children with APD, the use of a standard tip (40°) for AT is sufficient (except when eustachian cushion reconstruction is planned), which is reflected in the absence of a reliable difference in the development of NAE between 2 subgroups. In children with MD, the use of this tool is too aggressive in relation to the soft palate and does not allow thorough removal of lymphoid tissue in the vault of the nasopharynx in a significant number of patients.

We focus attention on the fact that the calculated angle and length of the tip after its bending for children of group 1 is 47.18±12.21° and 21.0±7.1 mm, and for children of group 2 – 59.45±13.72° and 30.9±10.2 mm, which in both cases exceeds the angle and length of the working part of a standard tip for AT (40° and 20 mm), but in a real situation, it often allows doctors to perform planned intervention. However, it is necessary to remember that the possibility of working in the perichoanal area (as the most difficult to access) is achieved by stretching the soft palate, which is not critical in children of group 1, but has negative consequences in children of group 2, as the findings show, and requires a change in the approach to the choice of tip.

STUDY LIMITATIONS

A small sample of patients (127 children) does not allow for a wide multivariate analysis of factors in the development of VPI and requires further research. The significant difference in age between the groups does not allow us to exclude the influence of other factors (except dental age) on the results of the study.

CONCLUSIONS

1. In children with adenoid vegetations, who are indicated for AT, signs of NAE are detected before surgical intervention in 9.4% of cases.
2. The use of a standard tip for AT does not allow the removal of lymphoid tissue in the hard-to-reach areas of the nasopharynx (perichoanal and peritubular sections) in 30% of children with APD and 42.9% of children with MD.
3. Removal of adenoid vegetations by EPAA method using only a standard tip for AT (40°) is accompanied by a higher risk of VPI in children with MD compared to those who underwent the intervention using a tip with a larger bending angle and a longer working part along the outer bend (60°).
4. In patients with APD, it is recommended to use a standard microdebrider tip for AT, except when eustachian cushion reconstruction is planned (it is necessary to use a tip with a rotating window). In patients with MD, it is recommended to use a 60° tip for EPAA.

REFERENCES

1. Arambula A et al. Anatomy and physiology of the palatine tonsils, adenoids, and lingual tonsils. World Journal of Otorhinolaryngology-Head and Neck Surgery. 2021;7:155e160. doi:10.1016/j.wjorl.2021.04.003.
2. Karaer IC, Çimen Özaydogdu A. Effect of montelukast treatment on adenoid hypertrophy and sleep quality in pediatric patients. Medicine Science. 2021;10(1):36-9.
3. Kassem F, Ebner Y, Nageris B et al. Cephalometric findings among children with velopharyngeal dysfunction following adenoidectomy - a retrospective study. Clin Otolaryngol. 2017;42(6):1289-1294.
4. Khami M, Tan S, Glicksman JT, Husein M. Incidence and Risk Factors of Velopharyngeal Insufficiency Postadenotonsillectomy. Otolaryngol Head Neck Surg. 2015;153(6): 1051-1055. doi: 10.1177/0194599815596494.
5. Dimatosa C, Nevesa LR, Beltrameb JM et al. Impact of adenotonsillectomy on vocal emission in children. Braz J Otorhinolaryngol. 2016;82(2):151-8. doi: 10.1016/j.bjorl.2015.11.005.
6. Tuzuner A, Demirci S, Akkoc A et al. Nasalance scores in pediatric patients after adenoidectomy. International Journal of Pediatric Otorhinolaryngology. 2014;78(4):610-3. doi: 10.1016/j.ijporl.2014.01.010.
7. Al Shujairi JFS. Causes of nasal obstruction after adenoidectomy. International journal of current research. 2019; 11(06):4533-4537. doi: 10.24941/ijcr.35549.06.2019.
8. Mushi E, Mahdi N, Upile N et al. Velopharyngeal insufficiency in patients without a cleft palate: important considerations for the ENT surgeon. J Laryngol Otol. 2020;134(3):252-255. doi: 10.1017/S002221512000047X.
9. Saibene AM et al. Endoscopic adenoidectomy: a systematic analysis of outcomes and complications in 1006 patients. Acta Otorhinolaryngol Ital. 2020; 40(1): 79–86. doi: 10.14639/0392-100X-N0150.
10. ENT product catalog. 2023. https://www.medtronic.com/content/dam/medtronic-com/products/ear-nose-throat/documents/ent-product-catalog.pdf [date access 08.05.2023]

11. Pagella F, Lizzio R, Pusateri A et al. Adenoidectomy: Anatomical variables as predictive factors of intraoperative adenoid residues. Int J Pediatr Otorhinolaryngol. 2021;140:110493. doi: 10.1016/j.ijporl.2020.110493.
12. Liakh K, Shkorbotun Ya. Anatomical rationale for choosing a blade for power-assisted adenoidectomy in children depending on dentition. Wiad Lek. 2022;75 (9)1:2070-2075.
13. Chow W, Brandt MG, Dworschak-Stokan A et al. Validation of the mirror-fogging test as a screening tool for velopharyngeal insufficiency. Open Otorhinolaryngology Journal. 2015;8:15-21. doi: 10.2174/1874428101508010015.
14. Lambert EM, You P, Kacmarynski DS, Rosenberg TL. Adenoidectomy and persistent velopharyngeal insufficiency: Considerations, risk factors, and treatment. International Journal of Pediatric Otorhinolaryngology. 2021;149:110846. doi: 10.1016/j.ijporl.2021.110846.
15. Singh R, Gupta M. To study the role of endoscopic evaluation of nasopharynx and microdebrider assisted residual tissue removal following conventional adenoidectomy. Indian Journal of research. 2019;8(1):480-483. doi:10.13140/RG.2.2.26259.12324.
16. Bohoroditskaia AV, Sarafanova ME, Golovaneva KD et al. Taktika vedenia detei s raznymi formami rhinophonii [Tactics of managing children with different forms of rhinophony]. Consilium Medicum Pediatrics. 2016;2:37-40. (in Russian)
17. Torun MT. Neutrophil-to-lymphocyte and basophil-to-lymphocyte ratios in children with adenoid vegetation: Can they be prognostic markers? Annals of Medical Research. 2020;27(7):1844-8. doi: 10.5455/annalsmedres.2020.04.376.

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ORIGINAL ARTICLE

HEMODYNAMIC FEATURES IN THE PATIENTS AFTER STROKE SUFFERED FROM CHRONIC PAIN

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ABSTRACT

The aim: To study the hemodynamic parameters in patients with post-stroke pain syndromes.

Materials and methods: We examined the hemodynamic parametrs of 74 patients who were treated at the Departments of General Neurology, Vascular Neurology and Pain Center in the Clinical Hospital «Feofania» State Administrative Department. Main group (44 patients) had stroke in anamnesis and chronic pain (headache, back pain, joint pain). The control group (30 patients) suffered from pain but had no stroke in anamnesis. Relationships between hemodynamic parameters and quantitative characteristics of chronic pain (visual analogue scale – VAS) were studied with help of linear Pearson correlation in different stroke periods and between the patients of Main and Control group.

Results: Strong correlations were found between decreasing in a.vertebralis blood flow and intensity of post-stroke pain. Strong correlations were found between intensivity of joint pain and a.vertebralis hemodynamic parameters in the patients in residual period up to 10 years. In the residual period over 10 years, in addition to the connections with hemodynamics in the VB, there was a correlation with the linear rapidly existing parameters of *a.cerebri media, a.carotis communis*.

Conclusions: Studying of hemodynamic parameters in patients with post-stroke pain syndromes can serve as a basis for a deeper understanding of pain mechanisms and the development of effective preventive and curative measures.

KEY WORDS: Stroke, hemodynamics, headache, back pain

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INTRODUCTION

It is known that the autoregulatory capabilities of the brain is quite high and they are largely associated with the state of cerebral blood flow. The issue of compensation of cerebral functions in patients after stroke is especially relevant, because the state of hemodynamics differs in each case and is associated with neurological deficits [1-4].

Along with neurological focal and cognitive deficits, patients after stroke have painful manifestations often [5-8]. According to A. Hansen [9], a post-stroke pain occurs in patients in 45.8% of cases and often remains in the shadow of motor, speech and cognitive deficits.

Not many works have been devoted to the study of hemodynamic parameters in patients with chronic pain. However, D. Smith et al. [10] note the difficulty of early detection of vertebrobasilar insufficiency (VBI), which is masked by pain syndromes, including headache and cervicalgia. The study by A. Rodrigues et al. [11] showed significant changes in cerebral hemodynamics, namely changes of linear blood flow velocities for a. cerebri anterior and a.cerebri media bilaterally in chronic fibromyalgia patients.

It is known that nociceptive afferents terminate on neurons in the posterior horn and give rise to the pathways of the anterolateral cords (*tr. spinotalamicus etc.*). Ascending to the brain stem, they attach nociceptive afferents from the head - mainly from the trigeminal nerve system.

Blood supply to the brainstem, in which *n.trigemini nuclei* are located, provided by the *vertebrobasilar (VB)* system. In addition, *reticular formation (RF)* is involved in the work of these centrifugal systems. It is known that RF is the area of adjacent blood supply, the most vulnerable in the case of dyscirculation in comparison with the cranial nerves nuclei [12, 13].

The most powerful antinociceptive systems (ANS) are also located in VB blood supply area. In contrast to the nociceptive system (NS), the effect of ANS is more pronounced at the central level than at the peripheral one. Of course, the functional insufficiency of the brainstem ANS, which occurs as a result of impaired VB blood supply, is also crucial. It is also known that in the absence of pain stimulus, the activity of ANSs is low enough but at different levels, they are included in the work only in cases of pain (nociceptive) stimulus. Of course, an inadequate centripetal nociceptive signal cannot activate an already affected ANS. Indeed, in case of insufficiency of brainstem structures blood supply there is a depletion or distortion of a signal both ANS and NS. With the depletion of the nociception at the stem formations level, there is probably a sensitization of the nociceptors - lowering the thresholds, sometimes so much that even light stimuli can cause pain. It was determined that the greater degree of dyscirculation in VB were found the less manifestations of acute cervicalgia and cervicocranialgia had been observed. Over time, chronic pain in the neck lost its delineated zonal and independent character. Cervicalgia and headache which had expressive chronic neuropathic pain type, often of pseudotumorous (hypertensive) nature due to venous insufficiency, came to the fore; the cortical component became prominent. Thus, the change in pain is based on the mechanisms of depletion of ANS and NS, as phylogenetically appropriate protective systems, at the level of afferent structures in the brainstem and upper cervical structures, RF, due to the formation of slowly progressive circulatory failure in VB [14].

Ultrasound research methods are modern non-invasive methods of cerebral blood condition verification [12-16], their indicators can provide interesting information in comparison with the other studies results. Thus, the study of hemodynamic parameters in patients with post-stroke pain syndromes can serve as a basis for a deeper understanding of pain mechanisms and the development of effective preventive and curative measures.

THE AIM

The aim was to study the hemodynamic parameters of patients with post-stroke pain syndromes.

MATERIALS AND METHODS

To address this aim, we examined the hemodynamic parameters of 74 patients whom were treated at the Departments of General Neurology, Vascular Neurology and Pain Center in the Clinical Hospital «Feofania» State Administrative Department.

The study was conducted in compliance with the basic principles of the Council of Europe Convention on Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current national regulations. The study protocol was approved by the local ethics committee. All the patients provided written informed consent.

The inclusion criteria were as follows: patients who had a history of stroke and chronic pain. The exclusion criteria were: patients with aphasia, cognitive function according to the Mini-Mental State Examination test (MMSE) below 20 scores, and patients taking antidepressants. The diagnosis of stroke and its severity were verified by standard methods (neurological examination and MRI). Pain was assessed using questionnaires and visual analogue scales (VAS) and neuropathic pain (NPS) scales.

The main group (n=44) included patients who had stroke in anamnesis and suffered from chronic pain. They were in different periods after stroke: early recovery, late recovery and residual which had been divided on two subgroups – up to 10 years and over 10 years. The control group (n=30) included patients with pain but without stroke in anamnesis. The mean age of main group was 70±8,0 years, among them 18 females (mean age – 68±8,1 years), males – 26 (mean age was 71±6,6). The mean age of control group was 57±6,6 years, among them 12 females (mean age 54±6,6 years) and males – 6 (mean age was 62±3,2).

A duplex ultrasound Doppler imaging of extracranial brachiocephalic vessels, as well as transcranial duplex scans of vessels, was performed on an ultrasonic premium class "HI VISION Ascendus" (Hitachi, Japan) with linear transducer L73S (9,0-4,0 MHz) and cardiovascular transducer S70 (5,0-1,0 MHz) and S50A (4,0-2,0 MHz). Blood flow parameters were included in an approved local protocol prepared in accordance with international recommendations [11-13]. The following calculations were used to determine the hemodynamic parameters at each site: vessel diameter, mm; cross-sectional area (CSA) = $(D/2)2 \times \pi$, mm^2; peak systolic velocity (Vps), cm/s; end diastolic velocity (Ved), cm/s; resistive index (RI), pulsatility index (PI), mean flow velocity (Tamx) cm/s.

Statistical data was processed by the use of the statistical packages «Microsoft Office Excel 2007» and «Statistica for Windows 6.0». The relationship between the studied variables was determined by the use of Pearson's coefficient of correlation (r). A statistically significant correlation was considered at $p<0,05$.

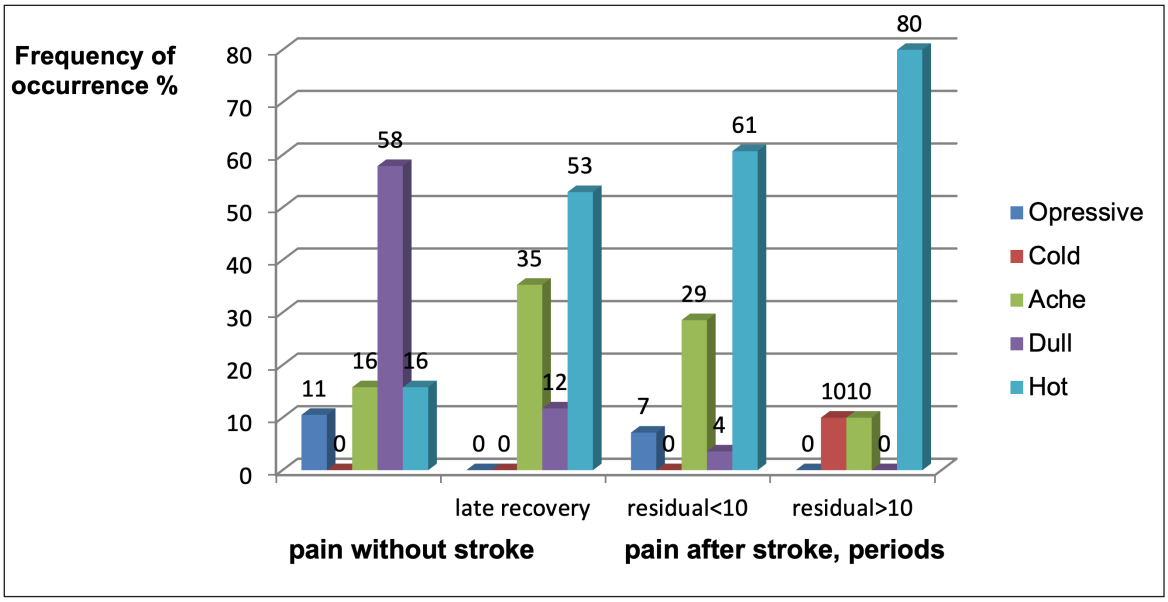

Fig. 1. The variety of neuropathic manifestations of chronic pain in patients after stroke and without stroke ones

RESULTS

By the use of Pearson's linear correlation, the following relationships were obtained between quantitative characteristics of pain (VAS) and hemodynamic parameters in patients of the main (Table I) and control (Table II) groups.

Therefore, medium-strength correlations were observed between headache and % stenosis of *a.carotis communis* (0,66) and between headache and RI (0,58) and PI (0,54) of a.carotis communis, strong correlations were absent.

Medium-strength correlations were observed between headache and *a.carotis communis* % stenosis (0,67), a.cerebri media RI (0,54). We also observed a medium strength correlation between back pain and *a.cerebri media* blood flow rates, namely Tamx (0,56) and Vps (0,52). There were no strong correlations.

Examining the correlations between hemodynamic parameters and the level of quantitative indicators of chronic pain (headache, back pain and joint pain, which were most common in the study group), we found certain correlations depending on the periods of stroke (Tables III-V).

We found differences in the correlation for joint pain depending on the period of stroke. Thus, in the late recovery and residual periods up to 10 years, the intensity of joint pain was associated with a strong correlation with blood flow in *a.vertebralis*, which can be explained by depletion of NS and ANS in the brainstem.

In the residual period of over 10 years, in addition to connections with hemodynamics in VB, there is a correlation with linear blood velocity on *a.carotis communis* and *a.cerebri media*, which can be explained by the severity and progression of hemiparesis, depending on the degree of atherosclerotic lesions of the above vessels. Correlations between hemodynamic parameters and back pain occurred only in the late recovery period (VB and carotid pool) and were not observed in the residual period in the study group, indicating the influence of other mechanisms on the intensity of dorsalgia: common to all patients - restrictions mobility due to neurological deficit.

The presence of strong correlations between the intensity of chronic pain and decrease in blood flow to the *a.vertebralis*, once again confirms the results of a study by O. Kovalenko, who proved that in the basis of pain feeling changes are the mechanisms of depletion of NS- and ANS at the level of afferent structures in the brainstem and upper cervical structures, RF, due to the formation of slowly progressive circulatory failure in VB [10]. Thus, by influencing the circulatory system in VB, it is possible to influence the degree of pain perception in patients with post-stroke pain.

We also found that the neuropathic color of chronic pain determined with NPS scale had some differences in different periods of stroke (Fig. 1).

As we can see from Figure 1, post-stroke pain has differences in the characteristics of neuropathic pain compared to non-stroke one. Mainly we observed dull pain in non-stroke patients. In patients after stroke, neuropathic coloration differed in different periods of disease. Thus, the share of burning pain (hot) in the overall structure of the pain syndrome increased from late recovery to residual period over 10 years. The feeling of cold was more characteristic of patients in the residual period over 10 years than in patients in other periods of stroke. That is, the increase in the duration of the disease in patients was observed in the most pronounced neuropathic manifestations, such as heartburn and cold. Patients did not perceive that as pain

Table I. Relationships between hemodynamic parameters and quantitative characteristics of chronic pain syndromes in main group (n=44) by linear Pearson correlation

Paremeters	r	p
Headache – a.carotis communis (% stenosis)	0,66	0,01
Headache – a.carotis communis (PI)	0,54	0,01
Headache – a.cerebri posterior (Ved)	-0,40	0,01
Joint pain – a.carotis communis (diametr)	-0,45	0,02
Joint pain – a.carotis interna (Ved)	-0,45	0,02
Joint pain – a.vertebralis V2 (Ved)	-0,45	0,02
Joint pain – a.vertebralis V4 (Vps, Ved)	-0,41	0,04
Joint pain – a.carotis externa (VpS)	-0,44	0,03

Table II. Relationships between hemodynamic parameters and quantitative characteristics of chronic pain syndromes in Control group (n=30) by linear Pearson correlation.

Paremeters	r	p
Headache - a.carotis communis (% stenosis)	0,67	0,03
Headache – a.cerebri media (RI)	-0,54	0,04
Headache – a.vertebralis V2 (Ved)	-0,5	0,03
Joint pain – a.cerebri media (PI)	-0,55	0,02
Back pain – a.cerebri media (Tamx)	-0,56	0,03
Back pain – a.cerebri media (Vps)	-0,52	0,04

Table III. Relationships between hemodynamic parameters and quantitative characteristics of chronic pain syndromes in main group patients in late recovery period of stroke (n=14) by linear Pearson correlation

Paremeters	r	p
Headache – a.cerebri media (Tamx)	0,89	0,01
Headache – a. vertebralis V4 (Ved)	0,85	0,01
Headache – a.cerebri media (Ved)	0,78	0,01
Headache - a.cerebri posterior (Ved)	0,79	0,01
Headache - a.carotis interna (Ved)	0,72	0,02
Headache – v.Rosenthal	0,64	0,04
Joint pain – a.vertebralis V2 (Ved)	0,89	0,04
Joint pain – a.vertebralis V4 (Ved)	0,89	0,04
Back pain – a.vertebralis (diametr)	-0,88	0,01
Back pain – a.cerebri media (RI)	0,75	0,002
Back pain – a.cerebri media (Vps)	0,72	0,004
Back pain – a.carotis interna (Ved)	0,60	0,01
Back pain – a.cerebri media (PI)	0,57	0,03
Back pain – a.vertebralis V4 (Vps)	0,56	0,04
Back pain – a.vertebralis V4 (Ved)	0,50	0,02

at all. This phenomenon may be associated with changes in the cerebral NS system due to chronic ischemia and aging of the brain.

DISCUSSION

The presence of strong correlations between the intensity of chronic pain and decrease in blood flow to the *a. vertebralis*, once again confirms the results of the studies [14-17], demonstrated that in the basis of pain feeling changes were the mechanisms of depletion of NS- and ANS at the level of afferent structures in the brainstem and upper cervical structures, RF, due to the formation of slowly progressive circulatory failure in VB [3, 5]. Thus, by influencing the circulatory system in VB, it is possible to influence the degree of pain perception in patients with post-stroke pain.

Table IV. Relationships between hemodynamic parameters and quantitative characteristics of chronic pain syndromes in main group patients in residual period of stroke up to 10 years (n=21) by linear Pearson correlation.

Paremeters	r	p
Headache - a. carotis communis (% stenosis)	0,75	0,01
Headache – a.vertebralis (diametr)	-0,72	0,01
Headache - a. carotis communis (PI)	-0,66	0,01
Headache - a. carotis communis (diametr)	-0,58	0,01
Headache - a. a.cerebri media (PI)	-0,57	0,03
Joint pain – v.Rosenthal	0,80	<0,05
Joint pain – a.carotis communis (diametr)	0,76	0,01
Joint pain – a.vertebralis V4 (Vps)	0,70	0,01
Joint pain – a.vertebralis V4 (Ved)	0,72	0,01
Joint pain – a.vertebralis (diametr)	-0,63	0,03

Table V. Relationships between hemodynamic parameters and quantitative characteristics of chronic pain syndromes in main group patients in residual period of stroke over 10 years (n=9) by linear Pearson correlation

Paremeters	r	p
Headache - a. carotis interna (Vps)	0,87	0,02
Joint pain – a.carotis communis (Ved)	0,74	0,04
Joint pain – a.vertebralis (diametr)	-0,94	0,01
Joint pain – a.cerebri media (VpS)	-0,87	0,01
Joint pain – a.cerebri media (Tamx)	-0,83	0,01
Joint pain – a.vertebralis (Vps)	-0,74	0,04
Back pain – a.carotis comunis (RI)	0,65	0,04

Thus, we found that in the late recovery and residual periods up to 10 years, the intensity of joint pain was associated with a strong correlation with blood flow in *a. vertebralis*, which can be explained by depletion of NS and ANS in the brainstem.

In the residual period over 10 years, in addition to connections with hemodynamics in VB, there is a correlation with linear blood velocity on *a. carotis communis* and *a. cerebri media*, which can be explained by the severity and progression of hemiparesis, depending on the degree of atherosclerotic lesions of the above vessels.

Correlations between hemodynamic parameters and back pain occurred only in the late recovery period (VB and carotid pool) and were not observed in the residual period in the study group, indicating the influence of other mechanisms on the intensity of dorsalgia: common to all patients - restrictions mobility due to neurological deficit.

Regarding of neuropathic manifestations, the share of burning pain (hot) in the overall structure of the pain syndrome increased from late recovery to residual period over 10 years. The feeling of cold was more characteristic of patients in the residual period over 10 years than in patients in other periods of stroke. That is, the increase in the duration of the disease in patients was observed in the most pronounced neuropathic manifestations, such as heartburn and cold. Patients did not perceive that as pain at all. This phenomenon may be associated with changes in the cerebral NS system due to chronic ischemia and aging of the brain [14].

CONCLUSIONS

1. Strong correlations were found between the decrease in *a.vertebralis* blood flow and intensity of poststroke pain (headache, back and joint pain).
2. Strong correlations were found between intensivity of joint pain and *a.vertebralis* hemodynamic parameters in the patients in residual period up to 10 years. In the residual period over 10 years, in addition to the connections with hemodynamics in the VB, there was a correlation with the linear rapidly existing parameters of *a.cerebri media, a.carotis communis*.
3. Correlations between hemodynamic parameters and back pain occurred only in the late recovery period (VB and carotid pool) and were not observed in the residual period in the study group, indicating the influence of other mechanisms on the intensity.

4. Neuropathic characteristics showed differences between post-stroke and non-stroke patients: the predominance of aching pain in the former and the feeling of heartburn and cold in the latter, which were not treated as pain at all. This phenomenon might be associated with changes in the cerebral nociceptive system due to chronic ischemia and aging of the brain.

REFERENCES

1. Castro P, Azevedo E, Sorond F. Cerebral Autoregulation in Stroke. Curr Atheroscler Rep. 2018;20(8):37. doi: 10.1007/s11883-018-0739-5.
2. Nogueira R, Aries M, Minhas J et al. Review of studies on dynamic cerebral autoregulation in the acute phase of stroke and the relationship with clinical outcomeю. Journal of Cerebral Blood Flow & Metabolism. 2022;42(3):430-453. doi: 10.1177/0271678X211045222.
3. Yehorova M, Kondratiuk V, Kuznetsova S, Komissarova O. Ateroskleroz i strukturno-funkcional'noe sostojanie sosudov karotidnogo i vertebro-bazilljarnogo bassejnov. [Atherosclerosis and the structural and functional state of the vessels of the carotid and vertebro-basilar basins]. Family Medicine. 2019;4(84):83-89. doi: 10.30841/2307-5112.4.2019.185054. (In Russian).
4. Siebert J, Gutknecht P, Molisz A et al. Hemodynamic findings in patients with brain stroke. Arch Med Sci. 2012;8(2):371-374. doi: 10.5114/aoms.2012.28567.
5. Cheren'ko T, Heletyuk Yu. Characteristics of acute ischemic stroke depending on the structure of gravity and the duration of arterial hypertension. Simeyna medytsyna. 2018;1(75):81-85. doi:10.30841/2307-5112.1.2018.135313.
6. Westerlind E, Singh R, Persson H, Sunnerhagen K. Experienced pain after stroke: a cross-sectional 5-year follow-up study. BMC Neurol. 2020;20(1):4. doi: 10.1186/s12883-019-1584-z.
7. Plecash A, Chebini A, Ip A et al. Curr Neurol Neurosci Rep. 2019;19(11):86. doi: 10.1007/s11910-019-1003-2.
8. Anwer S, Alghadir A. Incidence, Prevalence, and Risk Factors of Hemiplegic Shoulder Pain. A Systematic Review. Int J Environ Res Public Health. 2020;17(14):4962. doi: 10.3390/ijerph17144962.
9. Hansen A, Marcussen N, Klit H et al. Pain following stroke: a prospective study. Eur J Pain. 2012;16(8):1128-1136. doi: 10.1002/j.1532-2149.2012.00123.x.
10. Smith D, Pyatigorskaya S, Tran N. Delay in diagnosis of vertebrobasilar insufficiency: the masking effect of headache and coexisting pain syndrome. J Anesth Perioper Med 2017; 4:231-236. doi:10.24015/ JAPM.2017.0019.
11. Rodrigues A, Tembl J, Mesa-Gresa P et al. Alteral cerebral blood flow velocity features in fibromyalgia patients in resting-state conditions. PLoS One. 2017;12(7):e0180253. doi: 10.1371/journal.pone.0180253.
12. Osborn A, Hedlund G, Salzman K. Osborn's Brain: Imaging, Pathology, and Anatomy. 2nd Ed. Elsevier. 2017, p.1300.
13. Hall J, Hall M. Guyton and Hall Textbook of Medical Physiology. 14th Ed. Elsevier; 2020, p.1152.
14. Kovalenko O, Chizhykova M, Dzhura N. Evaluation of the Effects of Acupuncture on Cerebral Hemodynamics in Patients Suffering from Cerebrovascular Pathology with Duplex Ultrasound Doppler Imaging. Journal of US-China Medical Science. 2018;15:1-9. doi: 10.17265/1548-6648/2018.01.001.
15. Lau V, Jaidka A, Wiskar K et al. Better With Ultrasound: Transcranial Doppler. Chest. 2020;157(1):142-150. doi: 10.1016/j.chest.2019.08.2204.
16. Csiba L, Baracchini C. Manual of Neurosonology. Cambridge University Press. 2016, p 330.
17. Kovalenko O, Chizhykova M. Effectiveness of acupuncture for headache in post-stroke patients. Psychosomatic Medicine and General Practice. 2018;3(2):e0302107. doi: 10.26766/pmgp.v3i2.107.

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ORIGINAL ARTICLE

ACTIVITY OF PHOSPHATASES IN THE ORAL LIQUID OF PATIENTS FROM POLLUTED AREAS WHO ARE DIAGNOSED WITH GENERALIZED PERIODONTITIS AND RHEUMATOID ARTHRITIS

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ABSTRACT

The aim: To study the activity of acid and alkaline phosphatases as markers of bone metabolism in patients from bad environmental areas who are diagnosed with rheumatoid arthritis and are affected by generalized periodontitis.

Materials and methods: A total of 137 residents from Kalush district of the Ivano-Frankivsk region, Ukraine were enrolled in this investigation. There were 105 patients aged between 18 and 60 years with generalized periodontitis of the I-II degree severity selected for further research. Among them were 70 patients diagnosed with rheumatoid arthritis at the stage of remission. The research comprised the study of oral fluid of the examined individuals in order to assess the bone metabolism based on activity of the acid and alkaline phosphatases.

Results: The results of the conducted studies testify an increase of acid phosphatase in subgroups of patients diagnosed with rheumatoid arthritis and affected by generalized chronic periodontitis. On the other hand, the obtained results of alkaline phosphatase activity demonstrated a decrease of this indicator in all subgroups.

Conclusions: The results of biochemical studies suggest that there is a significant violation of bone tissue metabolism observed in patients from environmentally unfavorable areas affected by generalized periodontitis and diagnosed with rheumatoid arthritis.

KEY WORDS: periodontitis, rheumatoid arthritis, phosphatase

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INTRODUCTION

Periodontal disorders have been one of the main problems of dental science and practice for many decades. In the past decade, this issue becomes especially important as the number of young patients affected by periodontal disorders is on the growth. A number of researchers indicate the negative impact of a bad environment on the dental health of the population [1, 2]. Advances in scientific and technical progress have brought benefits, but have significally worsened the ecology in most industrial regions.

Furthermore, the ecological situation in many regions of Ukraine has become even more threatening and unpredictable with the beginning of military aggression, the full-scale war of russia against Ukraine as many objects of industrial infrastructure are destroyed; toxic, chemical compounds enter the environment, greatly polluting the territory and affecting the health of not only the current inhabitants , but the health of future generations.

Environmentalists claim that Ukraine is currently the most "ecologically polluted" country in Europe.

Unfortunately, there were many bad ecological regions in Ukraine even before the war, and one of the most revealing is the Kalush mining and industrial district of the Ivano-Frankivsk region, where the emergence and development of negative man-made factors is due to the production and procession of potash ores, as well as the location of the mine - chemical enterprises and facilities for disposal of toxic waste.

Kalush mining and industrial district has been recognized as a zone of "emergency" ecological situation since 2010. A prominent place among the most common environmental pollutants is occupied by heavy metals that can accumulate in the human body. Heavy metals are characterized by high toxicity and biochemical activity, which allows them to be classified as ecocidal and biocidal toxicants, in case if their concentration exceeds the maximum permissible standards.

The sources of heavy metals of the Kalush industrial region are and were the chemical and energy projects. There is a change in the characteristics of the microbiome, which often acquires pathogenic properties under the influence of heavy metals [1].

Many studies have established a close relationship between periodontitis and somatic diseases, among which is rheumatoid arthritis [3-11]. Investigations suggest that adverse environmental factors also affect the further prognosis of rheumatoid arthritis [12], which confirmed the relevance of our study.

That is why, we chose to examine the residents of Kalush district in order to analyze the peculiarities of the clinical course, treatment and prevention of periodontitis in patients with rheumatoid arthritis as rheumatoid arthritis may predispose to periodontitis and they may interact. The mutual negative influence of periodontitis and rheumatoid arthritis is also taken into account [3-11].

Xenobiotics are also considered as being important in the assessment of environmental impact together with the body's response to them. In conditions of man-made polluted environment is formed a syndrome of non-specific hypersensitivity. This is an established factor that impairs the multifunctional disorders of various organs and systems, including the bone metabolism.

It can be testified that the oral tissues along with other organs are targets for exogenous and endogenous damaging factors that determine the medical problem.

THE AIM

The aim of the research: to study the activity of acid and alkaline phosphatases as markers of bone metabolism in patients from environmentally bad areas which are diagnosed with rheumatoid arthritis and generalized periodontitis.

MATERIALS AND METHODS

We examined 137 residents from Kalush district of the Ivano-Frankivsk region.

For further research, 105 patients with generalized periodontitis of the I-II degree of severity, aged from 18 to 60 years were selected. Among them were 70 patients with rheumatoid arthritis at remission.

Patients affected by generalized periodontitis and diagnosed with rheumatoid arthritis (70 people) were further divided into two groups. Group I - 35 patients from ecologically unfavorable areas (inhabitants of the Kalush district - "zone of an ecological emergency") and Group II - 35 patients who live in relatively ecologically favorable territories (Ivano-Frankivsk).

Group III consisted of 35 people with generalized periodontitis not diagnosed with rheumatoid arthritis.

Each of the groups was divided into subgroups depending on the severity of generalized periodontitis: A – generalized periodontitis of the first degree; B – generalized periodontitis of the II degree of severity.

The control group consisted of 18 healthy individuals with an intact periodontium with preserved dentition (K). The diagnosis of periodontitis was established based on the results of clinical and laboratory examinations, according to the classification introduced by M.F. Danylevskyy.

Diagnosis "Rheumatoid arthritis" was established by a rheumatologist based on clinical, laboratory and X-ray data according to the unified clinical protocol "Rheumatoid Arthritis". Clinical studies were conducted in accordance with the legislation of Ukraine and the principles of the Helsinki Declaration on Human Rights.

Clinical examination of patients with generalized periodontitis was carried out at Postgraduate Dentistry Department (Head of the Department - Doctor of Medicine, Professor I.V. Paliichuk) and at Therapeutic Department of the dentistry center of Ivano-Frankivsk National Medical University (Head of the center - phD, Assoc. Kryvenkyy T.P.).

Determination of the activity of acid and alkaline phosphatases were carried out at the "Center of Bioelementology" of the Ivano-Frankivsk National Medical University (Director, Doctor of Biology, Professor Erstenyuk H.M).

Each patient provided written consent for the examination. Clinical examination of patients was carried out according to unified clinical protocols. Subjective methods of examination included the presentation of complaints, medical and life anamnesis, comprehensive case history and assessments of the general somatic status.

When questioning patients, attention was paid to the duration of the disease, its course, the frequency of exacerbations - both of generalized periodontitis and rheumatoid arthritis. Also, information was gathered about hereditary anamnesis and social history.

The general investigation included the head and face examination with an assessment of the facial symmetry, proportionality, color, and presence of any lesions. During the intraoral examination, attention was paid to the tongue, palate, and cheeks, recording any pathology and checking abnormal frenal attachment. During the inspection of the gingival tissues, the presence of color changes, swelling, shape, size, spontaneous bleeding, and recession were noted.

When examining the dental arches, we recorded their integrity, the overhanging edges of restorations and presence of orthopedic bridges.

Oral liquid is considered to be one of the main factors that affect the condition of periodontium and is an indicator of impaired resistance of oral tissues. Analysis of oral

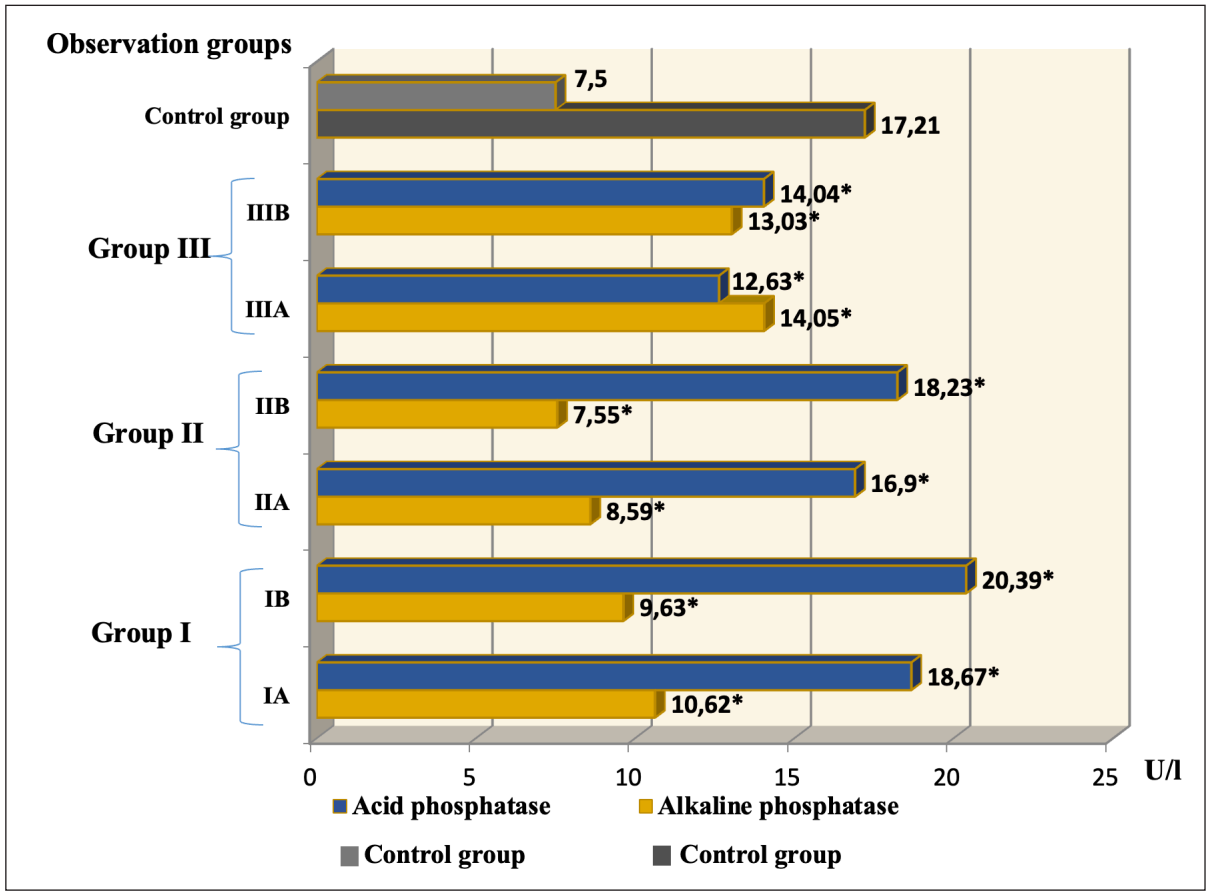

Fig.1. Activities of acid phosphatase and alkaline phosphatase in the oral liquid of examined patients with generalized periodontitis of the I-II degrees and rheumatoid arthritis

Note: * – probability of difference from the control group: pIA-K<0,05, pIB-K<0,05, pIIA-K<0,05, pIIB-K<0,05, pIIIA-K<0,05, pIIIB-K<0,05.

liquid is a non-invasive and safe method of examination. Oral fluid was collected in the morning, before breakfast. The obtained portions of oral liquid we were kept frozen at a temperature of no more than minus 40°C. Frozen samples were thawed and thoroughly mixed to a homogeneous consistency. The samples were not subjected to repeated cycles of freezing and thawing.

We used biochemical methods to study osteoclastic bone resorption (acid phosphatase) and osteoblastic bone formation (alkaline phosphatase) as the mineral composition of oral liquid reflects the general metabolism of the body.

The activity of acid phosphatase (AcP) was determined according to the modified Hillman method with the reagents of SpL LLC (Ukraine). The principle of the method is that the titrate is used as a specific agent for the prostatic fraction of acid phosphatase. The increase of light absorption at a wavelength of 405 nm is proportional to the activity of total acid phosphatase in the sample. Thus, its activity can be determined indirectly (through the determination of non-prostatic acid phosphatase) and by calculating the difference between the activity of total and non-prostatic acid phosphatase.

Alkaline phosphatase (AlP) activity was determined with SpL LLC reagents (Ukraine). The principle of the method is that alkaline phosphatase catalyzes the hydrolysis of p-nitrophenyl phosphate at pH = 10.04, releasing p-nitrophenol to phosphate. The rate of formation of p-nitrophenol is proportional to the catalytic activity of alkaline phosphatase in the sample and is measured on a photometer.

To assess the degree of reliability of the results obtained, their analysis was performed by using the application program for working with electronic spreadsheets "Microsoft Excel 2000" and "Statistica 7.0".

During the statistical processing of the research results, the average arithmetic value (M), mean square deviation (б) was calculated. Paired factor correlation analysis was conducted with the calculation of the Pearson correlation coefficient (r).

RESULTS

The results of the conducted studies testify to the increase in the activity of acid phosphatase in the oral liquid observed in patients of all subgroups diagnosed with

generalized periodontitis and rheumatoid arthritis. The analysis of the gained statistic also showed that in the case of generalized periodontitis of the II degree, these deviations were more significant than in the case of the degree I. Among those with generalized periodontitis of the II degree, the highest activity of acid phosphatase was detected in the IB subgroup - (20.39±0.74) Units/l, which is in 2.72 times higher than the result of the control group ($p_{IB-K}<0,05$). In patients with IIB and IIIB subgroups, the activity of acid phosphatase significantly exceeded the indicators of the control group in 2.43 and 1.87 times, respectively ($p_{IIB-K}<0,05$, $p_{IIIB-K}<0,05$) (Fig. 1).

Considering those from all subgroups with the 1st degree of generalized periodontitis, it can be assumed that the highest value of acid phosphatase activity was recorded in the IA subgroup, which is in 2.49 times higher than the result of the control group($p_{IA-K}<0,05$). The lowest acid phosphatase activity was found in the IIIA subgroup - (12.63±0.41) units/l, which is in 1.68 times more than the result of the control group ($p_{IIIA-K}<0,05$).

The data of determining the activity of alkaline phosphatase in the oral liquid showed a decrease in the activity of the studied indicator in all subgroups (Fig. 1). The greatest fall in the activity of alkaline phosphatase was observed in the IIB subgroup, namely in 2.28 times comparing to the value of the control group ($p_{IIB-K}<0,05$).

Somewhat higher activity of this indicator was found in subgroups IB and IIIB, which is in 1.78 and 1.32 times lower than the results of the control group ($p_{IB-K}<0,05$, $p_{IIIB-K}<0,05$). Similar dynamics of alkaline phosphatase activity is observed in all subgroups with the 1st degree of generalized periodontitis.

In particular, in the IIA subgroup, the value of the activity of the studied indicator was significantly lower in 2 times, in the IA subgroup 1.62 times and in the IIIA subgroup 1.22 times compared to the obtained results of the control group ($p_{IA-K}<0,05$, $p_{IIA-K}<0,05$, $p_{IIIA-K}<0,05$.

The gained results confirm an increase of the pathological destruction in periodontal tissues recorded in all sub-groups. Moreover, these changes are more pronounced in patients who live in anthropogenically burdened areas and are diagnosed with rheumatoid arthritis. Obviously, as the severity of generalized periodontitis increases, the more exact the pathological changes become.

DISCUSSION

Periodontal disorders are the most prevalent stomatological diseases and rank second after dental caries. Besides, they lead to the tooth loss that is in 2-3 times more than by caries. There are relationships between periodontitis and somatic diseases, rheumatoid arthritis in particular, which causes deep changes in the internal environment of the body, and as a result leads to the structural destructions in periodonrtium. Furthermore, if the damage to the periodontal tissues becomes greater, the more severe and longer the course of rheumatoid arthritis is [3-5, 9, 10].

The results of our study revealed that there is a connection between generalized periodontitis, rheumatoid arthritis and ecological living conditions. This is confirmed also by researches of other scientists [3-11], which proved a higher frequency of periodontal tissue diseases in patients with rheumatoid arthritis and their mutual effect.

Generalized periodontitis increases a risk for development of rheumatoid arthritis and may predispose to it. This is an important factor considering the high prevalence of generalized periodontitis. The latter may have significant clinical and social implications for public health in general.

Destructive processes in periodontal tissues, and bone metabolism of the alveolar process are closely related to the structural and functional state of the bone system, the activity of metabolic processes, and the intensity of skeletal bone remodeling.

It should be noted that in the last decade, there has been an upward trend in the number of patients diagnosed with generalized periodontitis and also affected with structural and functional bone disorders.

The state of bone tissue is assessed by markers of bone tissue metabolism, which reflect the intensity of bone resorption and bone formation [13-16].

The analysis of phosphatases activity indicates a raise of pathological resorption in the periodontal tissues in all observation subgroups. Pathological changes are expressed to a greater extent in patients with rheumatoid arthritis from polluted areas.

Rheumatoid arthritis and adverse environmental factors lead to an imbalance of osteogenesis and osteoresorption, which accelerates the progression of generalized periodontitis.

CONCLUSIONS

The results of biochemical studies show an indicative violation of the bone metabolism (Calcium-Phosphorus exchange) in patients diagnosed with generalized periodontitis and rheumatoid arthritis who live in polluted areas.

This is confirmed by elevated activity of acid phosphatase and a lower concentration of Calcium and Phosphorus in the oral liquid. The activity of alkaline phosphatase decreases with the progression of periodontitis, which may be associated with adverse environmental effects.

REFERENCES

1. Buduneli N. Environmental factors and periodontal microbiome. Periodontol 2000. 2021;85(1):112-125. doi: 10.1111/prd.12355.
2. Popovych Z, Rozhko M, Ostapyak I et al. Biochemical indexes of mineral metabolism in patients from the polluted region affected by chronic periodontitis. Pharmacia 2020; 67(1): 23–28. doi:10.3897/PHARMACIA.67.E36150.
3. Rajkarnikar J, Thomas B, Rao S. Inter-Relationship Between Rheumatoid Arthritis and Periodontitis. Kathmandu University Medical Journal. 2013; 41(1):22-26. doi: 10.3126/kumj.v11i1.11018.
4. González-Febles J, Sanz M. Periodontitis and rheumatoid arthritis: What have we learned about their connection and their treatment?. Periodontology 2000. 2021; 87 :181-203. doi:10.1111/prd.12385.
5. Bello-Gualtero J, Lafaurie G, Hoyos L et al. Periodontal Disease in Individuals With a Genetic Risk of Developing Arthritis and Early Rheumatoid Arthritis: A Cross-Sectional Study. Journal of Periodontology. 2016;87(4):346-356 doi:10.1902/jop.2015.150455.
6. Jajoo N, Shelke A, Bajaj R et al. Correction to: Periodontitis and Rheumatoid Arthritis: The Common Thread. Clinical Reviews in Bone and Mineral Metabolism . 2021; 19: 50–62. doi:10.1007/s12018-021-09280-z.
7. Kaur S, White S, Bartold P. Periodontal disease and rheumatoid arthritis: A systematic review. J Dent Res. 2013; 92: 399– 408. doi: 10.1177/0022034513483142.
8. Mikuls T, Payne J, Yu F et al. Periodontitis and Porphyromonas gingivalis in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66(5):1090-100. doi: 10.1002/art.38348.
9. Marotte H, Farge P, Gaudin P et al. The association between periodontal disease and joint destruction in rheumatoid arthritis extends the link between the HLA-DR shared epitope and severity of bone destruction. Ann Rheum Dis. 2006;65(7):905-9. doi: 10.1136/ard.2005.036913.
10. De Pablo P, Chapple I, Buckley C et al. Periodontitis in systemic rheumatic diseases. Nat Rev Rheumatol. 2009;5(4):218-24. doi: 10.1038/nrrheum.2009.28.
11. Serban S, Dietrich T, Lopez-Oliva I et al. Attitudes towards Oral Health in Patients with Rheumatoid Arthritis: A Qualitative Study Nested within a Randomized Controlled Trial. JDR Clinical and Translation. 2019;4(4):360-70. doi:10.1177%2F2380084419833694.
12. Bilozets'kyy I. Suchasni vyyavlennya pro vzayemozv''yazky heneralizovanoho parodontytu, revmatoyidnoho artrytu y osteoporozu. [Modern ideas about the relationship between generalized periodontitis, rheumatoid arthritis and osteoporosis]. Problemy osteolohiyi. 2015; 2 (18): 51-63. (in Ukraine).
13. Song L. Chapter One - Calcium and Bone Metabolism Indices. Advances in Clinical Chemistry. 2017;82: 1-46. doi:10.1016/bs.acc.2017.06.005.
14. López-Lacomba D, Roa-López A, González-Jaranay M et al. Periodontal and biochemical bone metabolism assessment on a chronic oral anticoagulation population treated with dicoumarins. Med Oral Patol Oral Cir Bucal. 2017;22(2):e258-e263. doi: 10.4317/medoral.21567.
15. Schulze-Späte U, Turner R, Wang Y et al. Relationship of Bone Metabolism Biomarkers and Periodontal Disease: The Osteoporotic Fractures in Men (MrOS) Study. J Clin Endocrinol Metab. 2015;100(6):2425-33. doi: 10.1210/jc.2014-4180.
16. Zachariadou C, Hart T, Hooper D et al. Molecular characteristics of periodontal health: Collagens. Journal of Periodontology. 2023; 94 (6): 606-615. doi:10.1002/JPER.22-0415.

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ORIGINAL ARTICLE

CLINICAL AND PATHOHISTOLOGICAL MANIFESTATIONS OF ACUTE KIDNEY INJURY AMONG PATIENTS WITH ACUTE DRUG POISONING (OVERDOSE)

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ABSTRACT

The aim: To investigate clinical and pathohistological manifestations of acute kidney injury among patients with drug poisoning (overdose).

Materials and methods: A cohort retrospective analysis of medical data of 86 patients treated in 2017-2021 with a diagnosis of "acute drug poisoning" complicated by the development of acute kidney injury syndrome was conducted. A forensic medical examination of deceased patients (7 persons) was carried out. Histological samples were examined using an microscope OPTON Axioskop (Germany) in transmitted light, at magnifications of 100 and 400 times. Statistical analysis of the obtained data was carried out using the IBM SPSS Statistics 29.0.0.0 program, Pearson's correlation analysis was used, $p \leq 0.05$.

Results: Acute renal failure in drug poisoning occurs under the influence of prerenal (hypoxia, r=0,66, p=0,0021; hypovolemia, r=0,61, p=0,0333) and renal factors (toxic effect of chemical components of the drug and rhabdomyolysis, r=0,743, p=0,0034). In the tissue samples, erythrocyte stasis in the capillaries, general fullness of blood vessels, signs of the sludge effect and small diapedesis hemorrhages were found; vasculitis and perivascular sclerosis are noted; foci of mononuclear infiltration of the stroma, focal edema, necrosis and interstitial fibrosis; desquamation, degenerative-dystrophic changes of the nephrothelium, tubular atrophy were found; hyaline casts in separate tubules; focal glomerular changes with segmental increase of the mesangial matrix and proliferation of endothelial cells, atrophy and hyalinosis of individual glomeruli were noted.

Conclusions: The multifactorial effect of opioids is confirmed by microcirculation disorders, vascular, interstitial, tubular and glomerular changes in the kidneys.

KEY WORDS: opioids, drug poisoning (overdose), nephrotoxicity

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INTRODUCTION

The spread of new drugs from the group of synthetic opioids has led to an increase in the number of cases of acute kidney injury (AKI). At the same time, the combined consumption of narcotic and psychotropic substances, including alcohol, plays a significant role in the development of the most severe form of acute renal failure (ARF).

ARF in acute drug poisoning (overdose) has a multifactorial nature, for example, nephrotoxicity of drugs can be a consequence of the direct action of chemical components or their metabolites on the kidneys, due to the effect on hemodynamics and acid-base status, or due to the massive formation of products of the destruction of cellular elements (hemolysis, rhabdomyolysis), which block the tubular apparatus of the kidneys.

Today, the true incidence of opioid-induced kidney failure is not fully understood. However, it is known that the mechanism of development of acute kidney damage with the consumption of opioids consists in multi-organ disorders arising as a result of respiratory depression, hypoxia and hypovolemia, which in addition can be accompanied by rhabdomyolysis. The high risk of kidney damage due to drug poisoning requires vigilance from intensive care physicians and readiness for timely use of hemodialysis, ultrafiltration and other methods of efferent therapy.

THE AIM

To investigate clinical and pathohistological manifestations of acute kidney injury syndrome in patients with narcotic poisoning (overdoses).

MATERIALS AND METHODS

A cohort retrospective analysis of the medical data of 86 patients who were brought to the department of intensive care and extracorporeal detoxification of the "Kyiv City Clinical Hospital of Emergency Medical Care" in the period 2017-2021 with a diagnosis of "Acute narcotic poisoning" (MCD-10:T40. 0-T40.3), complicated by the development of AKI and ARF. The assessment of ARF syndrome was carried out according to the recommendations of Clinical Practice Guideline for Acute Kidney Injury (KDIGO, 2012): an increase in serum creatinine concentration of ≥0.3 mg/dL (26.5 mmol/L) within 48 hours, or a ≥1.5-fold increase during the last 7 days, or diuresis <0.5 ml/kg/h for 6 h [1].

In cases of death of patients, a forensic medical examination was conducted (7 cases). The study of the biological environment of patients for the content of drugs was carried out by the method of immunochromatographic analysis (express testing); research of alcohol content - by gas chromatography (GC - Chrom-5). Forensic medical examinations of the tissues and fluids of the deceased for drug content were carried out by the method of liquid chromatography and mass spectrometry (device - Aligent 6850/5973N, column - HP-5MS). Pathohistological studies were performed in the Department of Forensic Histology of the Municipal Institution of the Kyiv Regional Council "Kyiv Regional Bureau of Forensic Medical Examination". After formalin fixation, alcohol wiring, and paraffin embedding, the sections were stained with hematoxylin and eosin. The preparations were examined using a microscope OPTON Axioskop (Germany) in transmitted light, at magnifications of 100 and 400 times. Statistical analysis of the obtained data was carried out using the Microsoft Excel 2019 package, and Pearson's correlation analysis was used, at $p \leq 0.05$.

RESULTS

According to international drug monitoring services, the practice of simultaneous use of several narcotic substances and/or psychotropic substances, for example: opioids and ethanol, is widespread in the world; opioids, cocaine, and ethanol; opioids and marijuana, as well as other various combinations involving amphetamine, methamphetamine, hallucinogens and analgesics [2-4].

It is known that certain combinations of drugs significantly increase the risk not only of overdose but also contribute to the damage of target organs, which is manifested by the development of neuro-, nephro-, cardio-, hepato-, immuno-, and other organotoxic effects. Despite the fact that opioids are not nephrotoxic, their combination with alcohol, cocaine, or other psychotropic substances causes the development of functional changes in many organs and systems of the body, which leads to the development of ARF [5-7].

ARF is characterized by a wide range of disorders - from a temporary increase in the concentration of biological markers of kidney damage to severe metabolic and clinical disorders - ARF, which require the use of hemodialysis, or other forms of renal replacement therapy and other methods of extracorporeal detoxification. Thus, the analysis of 86 cases of the development of acute respiratory distress syndrome in patients with an overdose of narcotic substances, including in combination with alcohol (57 cases, 66.28%) revealed that upon admission to the intensive care unit, the patients had the following clinical signs: deep depression of consciousness, coma (100%), hypovolemia (100%), apnea (90.7%), muscle atony (62.8%), electrolyte disturbances (75.6%), heart rhythm disturbances (40.7%), signs of positional compression of soft tissues (13.9%) and hypothermia (17.4%).

A direct correlation was established between clinical parameters and the development of ARF: deep cerebral coma ($r=0.86$, $p=0,0043$) and apnea ($r=0.66$, $p=0,0021$), heart rhythm disturbances ($r=0.76$, $p=0,0487$), hypovolemia ($r=0.61$, $p=0,0333$), signs of soft tissue compression syndrome ($r=0.58$, $p=0,0241$), hyperkalemia ($r=0.55$, $p=0,0017$), hemoconcentration, Ht>0.58 ($r=0.52$, $p=0,0131$), increased level of creatine phosphokinase (CPK) in blood serum > 5000 units/l ($r=0.743$, $p=0,0034$).

During the pathohistological examination of kidney preparations in patients who died as a result of narcotic poisoning, manifestations characteristic of the AKI syndrome were revealed: microcirculation disorders, vascular, interstitial, tubular, and glomerular changes (Fig. 1).

In the tissue samples, erythrocyte stasis in the capillaries, general fullness of blood vessels, signs of the sludge effect and small diapedesis hemorrhages were found; vasculitis and perivascular sclerosis are noted; foci of mononuclear infiltration of the stroma, focal edema, necrosis and interstitial fibrosis (Fig. 1 a-b); desquamation, degenerative-dystrophic changes of the nephrothelium, tubular atrophy were found; hyaline casts in separate tubules (Fig. 1 c-d); focal glomerular changes with segmental increase of the mesangial matrix and proliferation of endothelial cells, atrophy and hyalinosis of individual glomeruli were noted (Fig. 1 e-f).

In our opinion, the pathogenetic basis for the development of ARF was: dehydration with signs of a significant decrease in the volume of circulating blood, which was manifested by hypotension, a decrease in total cardiac output and average arterial pressure; hypoxia, which in turn led to a decrease in renal blood flow and glomerular filtration rate and led to damage to renal

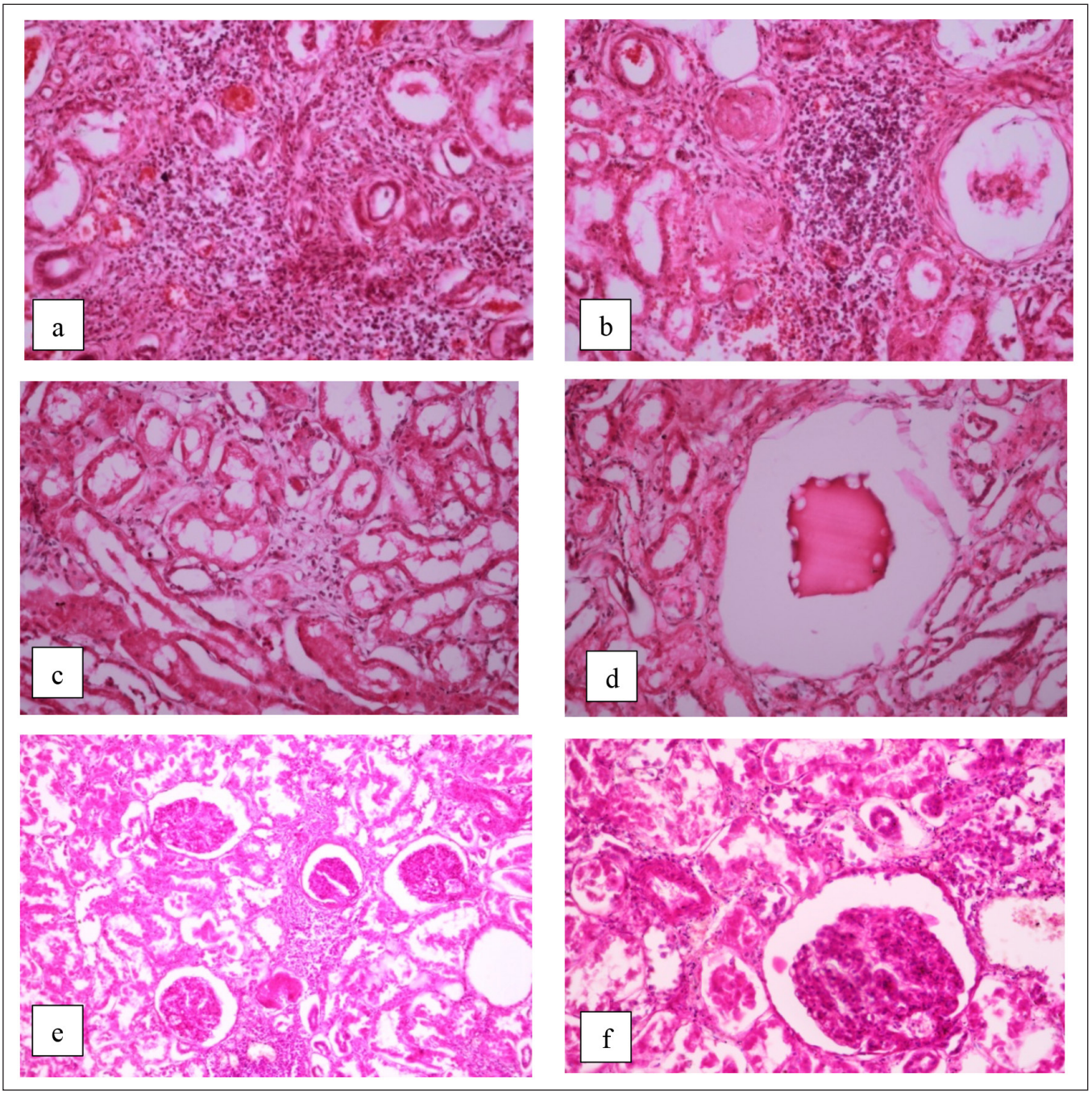

Fig 1. Microcirculatory, vascular, interstitial, tubular and glomerular changes in kidney samples of patients who died as a result of drug poisoning (overdose): vasculitis and perivascular sclerosis (a); focal edema, necrosis and interstitial fibrosis (b); tubular atrophy (c); hyaline casts in separate tubules (d); segmental increase of the mesangial matrix and proliferation of endothelial cells (e), atrophy and hyalinosis of glomeruli (f). Hematoxylin-eosin.

tubules. At the same time, the decrease in renal blood flow activated the sympathetic tone of the kidney, increasing the effect of ischemia and tubule damage, which was confirmed during pathohistological studies.

DISCUSSION

Most often, opioids lead to ARF due to a decrease in the glomerular filtration rate (GFR), which occurs as a result of dehydration and/or rhabdomyolysis [8-10]. The clinical picture of the opioid syndrome is well known, but an important element of the diagnosis is palpation of the abdomen and careful examination and palpation of the muscles. The only symptom in a comatose patient may be muscle swelling, which may reflect the onset of muscle necrosis. Abdominal palpation will reveal a distended bladder due to urinary retention. Serum chemistry can reveal markers of myocyte damage and the expulsion of normal intracellular components into the serum, such as potassium, uric acid, and phospho-

rus. The biggest threat is hyperkalemia, which requires immediate hemodialysis treatment. In addition to myoglobin breakdown products, the level of CPK may be elevated. A urine test shows a positive blood test (myoglobin) without erythrocytes since there is no bleeding. Evidence of severe renal impairment is a low fractional sodium excretion, a change in the color of urine (dark urine) due to myoglobinuria, and tubular necrosis, accompanied by a rapid rise in creatinine and eventually leading to anuria.

The development of AKI in poisonings accompanied by opioid syndrome is based on several mechanisms, which is confirmed by previous clinical and experimental studies [11, 12].

1. Opioids decrease GFR and urine output by causing complex changes in the body's neuroendocrine system, including changes in the autonomic nervous system (sympathetic and parasympathetic), the renin-angiotensin-aldosterone system, and antidiuretic hormone. Autoregulation of blood flow together with renal oxygenation control GFR. Opioids lead to activation of the central opioid peptide receptor and increase renal sympathetic tone, leading to vasoconstriction and renal ischemia, which further promote sympathetic activity and may subsequently lead to ischemic renal injury. These effects can be attenuated by the administration of naloxone (a central opioid antagonist).
2. Opioids provoke a decrease in fluid intake, which leads to acute kidney damage.
3. Opioids can cause urinary retention due to their anticholinergic properties.
4. Prolonged hypoxia and immobility lead to muscle damage, leading to increased intracellular calcium concentration and myocyte destruction. Muscle breakdown products and other intracellular components enter the bloodstream, including myoglobin, phosphate, potassium, and other markers such as CPK. At the same time, vasoconstriction contributes to the damage of renal tubules and the development of acidosis, which in turn causes precipitation of proteins in the tubules in the form of casts that cause tubule obstruction. Hyperuricemia causes uric acid nephropathy; hyperphosphatemia leads to the effects of extravascular phosphate deposition, while hyperkalemia leads to instability of cell membranes with the development of systemic effects.
5. Long-term use of opioids can lead to the development of chronic kidney failure. Chronic infections and exposure to various toxins included in street drugs (heroin, methadone, etc.) contribute to the development of heroin-associated nephropathy (focal and segmental glomerulosclerosis) and secondary kidney amyloidosis.

CONCLUSIONS

Acute renal failure in drug poisoning occurs under the influence of prerenal (hypoxia, hypovolemia, neuroendocrine disorders) and renal factors (toxic effect of chemical components of the drug, rhabdomyolysis). The multifactorial effect of opioids is confirmed by various pathohistological manifestations, which confirm microcirculation disorders, and vascular, interstitial, tubular, and glomerular changes in the kidneys.

REFERENCES

1. KDIGO guidelines focus on topics related to the prevention or management of individuals with kidney diseases. https://kdigo.org/guidelines/acute-kidney-injury. [date access 08.04.2023]
2. European Monitoring Center for Drugs and Drug Addiction (EMCDDA). European Drug Report 2021: Trends and Developments. https://www.emcdda.europa.eu/publications/edr/trends-developments/2021_en. [date access 08.04.2023]
3. Looking back on 25 years of annual reporting on the drug problem in Europe. European Monitoring Centre for Drugs and Drug Addiction. 2020 https://www.emcdda.europa.eu/publications/brochures/25-years-annual-reporting_en. doi:10.2810/199193. [date access 08.04.2023]
4. Decuyper I, Armentia A, Martín-Armentia B et al. Adverse Reactions to Illicit Drugs (Marijuana, Opioids, Cocaine) and Alcohol. J Allergy Clin Immunol Pract. 2021;9(8):3006-3014. doi: 10.1016/j.jaip.2021.04.061.
5. Paik JM. Introduction: Opioids and the Kidney. Semin Nephrol. 2021;41(1):1. doi: 10.1016/j.semnephrol.2021.03.001.
6. Khokhar S, Garcia D, Thirumaran R. A rare case of renal infarction due to heroin and amphetamine abuse: case report. BMC Nephrol. 2022;23(1):28. doi: 10.1186/s12882-021-02642-1.
7. Alinejad S, Ghaemi K, Abdollahi M, Mehrpour O. Nephrotoxicity of methadone: a systematic review. Springerplus. 2016;5(1):2087. doi: 10.1186/s40064-016-3757-1.
8. Long B, Koyfman A, Gottlieb M. Anevidence-based narrative review of the emergency department evaluation and management of rhabdomyolysis. Am J Emerg Med. 2019;37(3):518-523. doi: 10.1016/j.ajem.2018.12.061.
9. Kamal F, Snook L, Saikumar JH. Rhabdomyolysis-associated acute kidney injury with normal creatinephosphokinase. Am J Med Sci. 2018;355(1):84-87. doi: 10.1016/j.amjms.2017.04.014.

10. O'Carroll C, Fenwick R. Rhabdomyolysis: a case-based critical reflection on its causes and diagnosis. Emerg Nurse. 2020;28(3):24-28. doi: 10.7748/en.2020.e2004.
11. Mallappallil M, Sabu J, Friedman EA et al. What Do We Know about Opioids and the Kidney? Int J Mol Sci. 2017; 18(1): 223. doi: 10.3390/ijms18010223.
12. Milroy M C, Parai J-L. The histopathology of drugs of abuse. Histopathology. 2011;59(4):579-593. doi:10.1111/j.1365-2559.2010.03728.x.

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ORIGINAL ARTICLE

EFFECTIVENESS OF HORMONAL MONOTHERAPY BEFORE SURGICAL TREATMENT IN PATIENTS WITH EXTERNAL GENITAL ENDOMETRIOSIS

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ABSTRACT

The aim: Evaluation of the effectiveness of hormone therapy before and after surgical treatment in patients with external genital endometriosis (HRT).

Materials and methods: Bibliographic, information-analytical, clinical-instrumental, laboratory, histomorphological methods were used in the work. The sources of information were data from the scientific literature on the topic of the study, modern guidelines, a review of randomized controlled studies.

Results: All women involved in the study received hormone therapy before and after surgery for 3-6-9 months: 45.0% - only COCs, 25.0% - courses of a-GnRH drugs; 30.0% - only progestogens. Comparative evaluation of the function of the relapse-free course of UHD using the Kaplan-Meier method showed that when using a-GnRH in patients with UHD, the duration of the relapse-free period is higher than for other groups of drugs: the indicator of the function of maintaining remission before surgical treatment decreases from 100% to 0% during the first 6 months in 89.0%, and during 9 months - in 66.0% of patients. Progression of the disease, after surgery and withdrawal of a-GnRH, with a 3-month course occurred - after 3 months - in 45.0%, with a 6-month course - after 9 months - in 33.0%, with a 9-month course - after 12 months - in 12.0% of people. Thus, the average median of the recurrence-free course was ±11.6 months.

Conclusions: The most effective hormone therapy in patients with HRT before and after surgical treatment is therapy with drugs of the α-¬HnRH group, courses of at least 6 months.

KEY WORDS: external genital endometriosis, reproductive health, effectiveness of medical care, quality of life

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INTRODUCTION

The prevalence of endometriosis varies from 2 to 10% in the general female population, while among infertile women it is almost 50%, among people with dysmenorrhea - 40-60%, and in patients with chronic pelvic pain - 70-80% [1-6].

The main indicator of the effectiveness of treatment for various forms of endometriosis is the duration of the disease-free period. The recurrence-free period is considered as the time interval from the beginning of the primary treatment to the date of the documented recurrence of the disease [4,7,8].

THE AIM

Evaluation of the effectiveness of hormonal monotherapy (HMT) before and after surgical treatment in patients with external genital endometriosis (HRT).

MATERIALS AND METHODS

Scientific work was carried out during 2020-2021. On the basis scientific Department of minimally invasive surgery State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administrative Department (SIS «RPC PCM» SAD, Kyiv, Ukraine). In working with patients, we followed the ethical principles of the Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 2000), EU Directive No. 609 (1986), the main provisions of the "Rules of Ethical Principles of Scientific Medical Research with Human Participation" approved by the ICHGCP (1996) and orders of the Ministry of Health of Ukraine No. 690 dated September 23, 2009, No. 944 dated 14.12.2009, No. 616 dated 03.08.2012. Each patient signed a voluntary informed consent to the processing of personal data of medical records and to participate in a scientific study.

Table I. The results of studying the anamnesis data (n=100)(hormonal therapy was carried out before surgical treatment)

Previous treatment	Number of patients	
	Absolute	%
Hormone therapy		
Short courses (3-6 months)	25	25,0
Long courses (6-12 months)	30	30,0
In total	55	55,0

Note: significant differences relative to 3 groups (p<0,05)

Table II. The results of studying data on types of therapy before surgical treatment

Drug group	Number of patients					
	Short courses n=25		Long courses n=30		In total n=55	
	Absolute	%	Absolute	%	Absolute	%
a-GnRH	5	20	12	40,0	17	30,0
COC (combined oral contracepives)	9	36	-	-	9	16,0
Gestogen	11	44	-	-	11	54,0

Table III. The results of studying data on therapy in the postoperative period

Drug group	The number of patients					
	Short- courses a-GnRH ≤ 3 mon. n=40		Long courses a-GnRH ≤ 6 mon. n=60		In total n=100	
	Absolute	%	Absolute	%	Absolute	%
Did not receive therapy	25	62,5	40	63,3	65	65,0
a-GnRH	8	20,0	10	16,7	18	18,0
COC	3	7,5	8	13,3	11	11,0
Gestogen	4	10,0	6	10,0	10	10,0

Table IV. Dependence of indicators of the recurrence-free course of endometriosis on the duration of hormonal therapy in patients with UTI

Bibliographic, information-analytical, clinical-instrumental, laboratory, histomorphological methods were used in the work.

Statistical analysis of the duration of the recurrence-free course of UTI without and against the background of the use of various types of hormonal therapy was performed using the method of data analysis of lifetime (Survival analysis) and life tables (Life table) to display the characteristics of the studied parameter in time intervals specified by the user. The function of maintaining remission was described using the Weibull model. Comparative analysis of the remission maintenance function in two groups was performed using the Gehan-Wilcoxon test and was presented using Kaplan-Meier curves. To build a life table based on the available data, an interval width of 1 month was adopted. At the same time, the duration of remission was equated with the time of absence of symptoms characteristic of the disease, and the interruption of remission (relapse) - with its appearance. Statistical assessment of the influence of qualitative binomial characteristics was performed using Cox's F-test, qualitative characteristics with a number of levels greater than 2 - using Pearson's %2. The following parameters were analyzed: median survival in the compared groups, the average value of the recurrence-free period, the total number of observations, and the level of significance of the difference). The influence of the duration of drug therapy on the duration of the recurrence-free course of endometriosis was considered statistically significant (F- test of Cox=2.36; p<0.001).

RESULTS

The 55.0% of 100 examined women received anti-relapse hormone therapy (HMT) before surgery, 25.0% of them received one or two (3-6 month) courses, 30.0% - longer courses (6-12 months) (Table I).

In patients with UTI who received HMT before surgical treatment, a temporary effect was noted during the treatment period - pain and the volume of blood loss during menstruation decreased, and then the symptoms returned. The number of relapses was maximum at 12 months of observation (18.0% of patients), the

Type of therapy	Short- courses a-GnRH ≤ 3 mon.	Long courses a-GnRH ≥ 6 mon.
Median disease-free course (months)	9,0	10,0
The average value of the relapse-free course of the disease (months)	8,8	10,1
Number of uncensored cases	31	25
Number of censored cases	0	0
The total number of observations	31	25
The level of significance according to the F-criterion, R	<0,001	

Table V. Dependence of indicators of the recurrence-free course of endometriosis on the type and duration of hormonal monotherapy after surgical treatment

Type of therapy	Short- courses a-GnRH ≤ 3 mon.	Short- courses COC ≤ 3 mon.	Short- courses Gestogen≤ 3 mon.	Long courses a-GnRH ≤ 6 mon.	Long courses COC≤ 6 mon.	Long courses Gestogens ≤ 6 mon.
Median disease-free course (months)	9,0	7,0	5,0	12,0	6,5	8,0
The average value of the relapse-free course of the disease (months)	8,4	7,0	5,8	11,5	6,8	8,1
Number of uncensored cases	10	4	8	9	10	20
Number of censored cases	5	1	0	4	2	1
Total number of observations	15	5	8	13	12	21
The level of significance according to the Chi-square, P	<0,001					

lowest number of relapses (2.0%) was observed at 3 months.

Detailed characteristics of hormonal therapy for HRT patients at the stage before surgical treatment are presented in Table II.

The relative value of the frequency of relapses in the interval was different in the analyzed time periods: the minimum (from 0.004 to 0.15) in the first six months of observation and the maximum (0.16 to 0.80) in the second six months of the study. The proportion of relapses was maximal after 12 months of observation and was 0.80 (80.0%).

The function of maintaining remission in patients with UHD is graphically presented, demonstrating its decrease from 100% to 0% in patients with UHD who received HMT before surgical treatment, during the observation period of 14 months (Fig. 1).

Of the total number of subjects, 3 months after the end of HMT, disease progression was noted in 3.0%, after 6 months - in 38.0%, and after 9 months - in 59.0% of female patients. The duration of the relapse-free period of more than 10 months was observed only in 8.0% of people.

As can be seen from the graph, the indicators of the intensity of relapse (the proportion of cases of relapse, which is calculated for one month of observation) were different: in the interval from the 3rd to the 8th month - fluctuations in the intensity of the progress of the disease were in the range from 0 to 0.2, and at 10 months, there was a sharp increase in this parameter to 1.0 (Fig. 2).

Antirelapse therapy after surgical treatment was received from 100 examined women - 39.0%, of them 37.5% - one-two (3-6 month) courses, 40.0% - long courses (6-12 months) (Table III).

A comparison of the recurrence-free period in female patients revealed a number of patterns: firstly, drugs of the a-GnRH group for UTI are more effective than other types of hormonal therapy (monotherapy with drugs of the a-GnRH group, COCs, Gestogens), secondly, when using a long course of taking drugs a-GnRH - the duration of the relapse-free period is higher than when using a short course a-GnRH. The median duration of the recurrence-free course of endometriosis in patients who received this option of therapy reaches 10 months (Tables IV and V).

A comparison of the time of the recurrence-free period in patients receiving one or another type of hormonal therapy (monotherapy with drugs of the a-GnRH, group, COCs, gestogen) revealed a number of

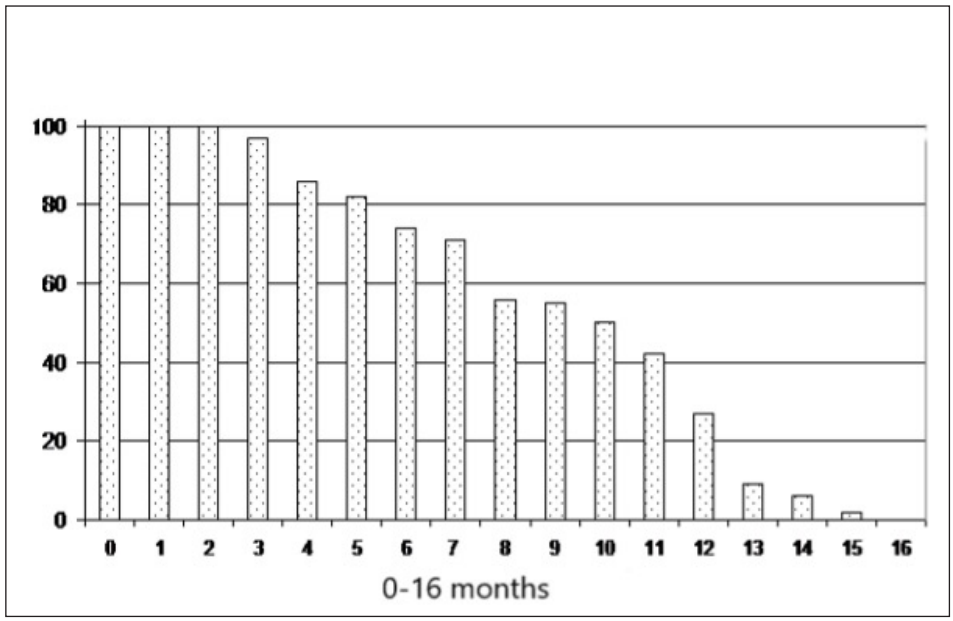

Fig. 1. The function of maintaining remission in patients with UTI who received hormonal monotherapy before surgical treatment(in months; 0-16 months)

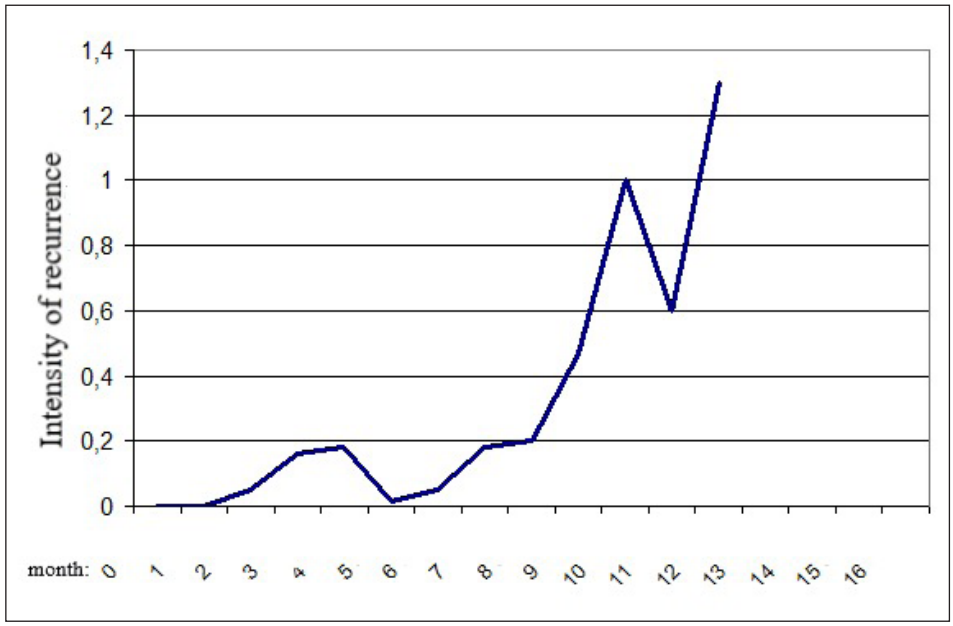

Fig. 2. Intensity of recurrence in patients with endometriosis who received hormonal monotherapy before surgical treatment (in months; 0-16 months)

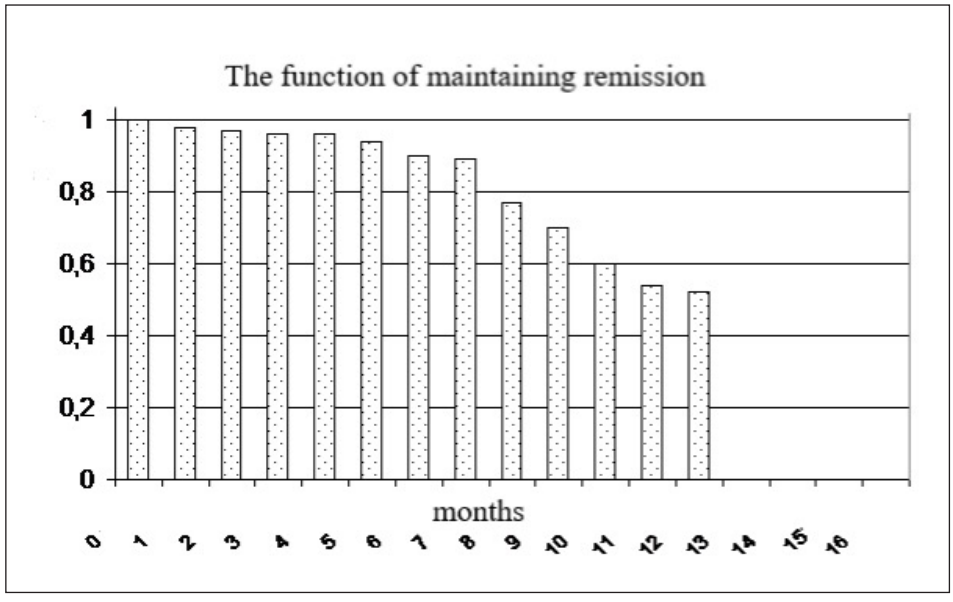

Fig. 3. The function of maintaining remission in patients with UTI who received hormonal monotherapy after surgical treatment (in months; 0-16 months)

patterns: when using a long course of taking a-GnRH drugs, the duration of the recurrence-free period is higher than when using a short course. In Tables IVand V show quantitative estimates of the duration of the relapse-free course for these groups of patients.

As can be seen from the table (TableV), the number of relapses was the maximum in the 12th month of observation (33.0% of patients), the lowest number of relapses was observed in the first five months of registration. At the same time, in the first four months after surgical treatment, relapses were not observed at all, and only in 5 months there were 3.0% of relapses. According to the relative value of the frequency of relapses in the interval, two parts can be conditionally distinguished: in the first half-year of observation, this indicator did not rise above 0.08, in the second half-year, the indicator rose to 0.14 (month 8), and even to 0.98 (month 12 of observation).

Figure 3 graphically presents the function of maintaining remission in patients with UTI who received hormonal monotherapy after surgical treatment.

When analyzing the graph (Fig. 3.), it can be concluded that the index of preservation function of maintaining remission in patients with UTI who received hormonal monotherapy after surgical treatment during the observation period of 13 months decreases from 100% to 0%.

DISCUSSION

Our study demonstrates results that are consistent with the pan-European trend outlined in the ESHRE (European Society of Human Reproduction and Embryology) guidelines and in the recommendations of the European Society of Human Reproduction and Embryology (2019) on the management of women with endometriosis (2016). It is recommended to offer surgery as one of the options to reduce endometriosis-associated pain. Women with endometriosis if not desiring immediate pregnancy may be offered postoperative hormone treatment as it does not negatively impact their fertility and improves the immediate outcome of surgery for pain. It is also not recommended to prescribe preoperative hormone treatment to improve the immediate outcome of surgery for pain in women with endometriosis, as according to guidelines and our study the most effective is the appointment of drugs of the α-GnRH group after surgical treatment [9-11]. However, at the same time, the analysis of our obtained data does not completely correspond to the recommendations of the Ukrainian Unified Clinical Protocol «Tactics of management of patients with genital endometriosis», the order of the Ministry of Health of Ukraine dated April 6, 2016 No. 319, which recommends the use of RH agonists only after surgical treatment when establishing histological diagnosis of endometriosis. In our opinion, in this context, adjuvant therapy in the postoperative period can be a prognostic factor regarding the duration of the recurrence-free course of the disease [12-16].

Undoubtedly, surgical treatment today is the «gold standard» for the radical removal of endometriosis foci, but, unfortunately, the surgical method in most cases negatively affects the state of the ovarian reserve, worsening the quality of oogenesis [9,17-20]. And the therapeutic effect of hormone therapy is that it is aimed primarily at preventing the progression of the disease or relapses of the disease, as well as for preparation before surgical intervention or programs of assisted reproductive technologies (ART), precisely to preserve the reproductive potential of a woman. Thus, to date, there is no single tactic for the treatment of endometriosis and, in our opinion, there is only an individual approach with a comprehensive solution to the problem regarding the age of the woman, the localization and degree of prevalence of the process, the severity of symptoms, the state of fertility and the need to restore reproductive function [9, 21-23].

CONCLUSIONS

All women involved in the study received hormone therapy before and after surgery for 3-6-9 months: 45.0% - only COCs, 25.0% - courses of a-GnRH drugs; 30.0% - only Gestogens. Progression of the disease, after surgery and withdrawal of a-GnRH, with a 3-month course occurred - after 3 months - in 45.0%, with a 6-month course - after 9 months - in 33.0%, with a 9-month course - after 12 months - in 12.0% of people. Thus, the average median of the recurrence-free course was ±11.6 months. A comparative evaluation of the function of the recurrence-free course of UTI shows that the use of a-GnRH increases the duration of the recurrence-free period compared to other groups of drugs, with the longest duration of remission when prescribed in courses of at least 6 months. The median duration of a relapse-free course in patients who received this option of therapy reaches 12 months. The minimum duration of the recurrence-free period was observed in patients receiving short-course progestogens and was 5 months.

REFERENCES

1. Ghiasi M, Kulkarni MT, Missmer SA. Is Endometriosis More Common and More Severe Than It Was 30 Years Ago? J. Minim. Invasive Gynecol. 2020; 27: 452–461. doi: 10.1016/j.jmig.2019.11.018.
2. Eisenberg VH, Weil C, Chodick G et al. Epidemiology of endometriosis: A large population-based database study from a healthcare provider with 2 million members. BJOG. 2018; 125: 55–62. doi: 10.1111/1471-0528.14711.
3. Grandi G, Barra F, Ferrero S et al. Hormonal contraception in women with endometriosis: a systematic review. Eur J Contracept Reprod Health Care. 2019;24(1):61-70. doi: 10.1080/13625187.2018.1550576.
4. Giudice LC, Kao LC. Endometriosis. Lancet. 2004; 364: 1789–1799. doi: 10.1016/S0140-6736(04)17403-5.
5. Vercellini P, Vigano P, Somigliana E et al. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10:261–275. doi: 10.1038/nrendo.20132.55.
6. Meuleman C, Vandenabeele B, Fieuws S et al. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril. 2009;92:68–74. doi: 10.1016/j.fertnstert.2008.04.056.
7. Somigliana E, Garcia-Velasco JA. Treatment of infertility associated with deep endometriosis. Fertility and Sterility. 2015;104(4):764–770. doi: 10.1016/j.fertnstert.2015.08.003.
8. Bedaiwy MA, Alfaraj S, Yong P et al. New developments in the medical treatment of endometriosis. Fertility and Sterility. 2017;107(3):555–565. doi: 10.1016/j.fertnstert.2016.12.025.
9. Guideline of the European Society of Human Reproduction and Embryology. Ovarian stimulation f BP IVF/ICSI. October 2019, ESHRE Reproductive Endocrinology Guideline Group. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI. [date access 20.03.2023]
10. Dunselman GA, Vermeulen N, Becker C et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29(3):400–12. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Endometriosis-guideline [date access 20.03.2023]
11. ASRM. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. Fertil Steril. 2008;90 (5):S260-9. doi: 10.1016/j.fertnstert.2014.02.012.
12. Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care Prevention of mother-to-child transmission. Order of the Ministry of Health of Ukraine 16.05.2016 № 449.
13. Lysenko BM. Henital'nyy endometrioz u zhinok z hipotyreozom: patohenez, taktyka likuvannya ta profilaktyka retsydyviv [Genital endometriosis in women with hypothyroidism: pathogenesis, treatment tactics and prevention of relapses]. Women's health. 2017; 2: 88-92.
14. Struk TA, Hordiychuk OA, Nikitina OA et al. Osoblyvosti klinichnoyi kharakterystyky patsiyentok z henital'nym endometriozom na tli hipotyreozuv perioperatsiynomu periodi [Peculiarities of the clinical characteristics of patients with genital endometriosis against the background of hypothyroidism in the perioperative period]. Clinical and preventive medicine. 2020; 1(11):40-50. doi: 10.31612/2616-4868.1(11).2020.05.
15. Lysenko B, Khabrat B, GordejchukA et al. Nonspecific protection and features of autoimmune processes in patients with external genital endometriosis against the background of hypothyroidis. Endocrinology. 2019; 24(4): 323-330. doi:10.31793/1680-1466.2019.24-4.324.
16. Khmil' SV, Pidhayna IYA, Kulyk II et al. Endometrioz: dosyahnennya ta pytannya v svitovykh doslidzhennyakh [Endometriosis: achievements and issues in global research]. Herald of social hygiene and health care organization of Ukraine. 2019; 4 (82):84-93. doi:10.11603/1681-2786.2019.4.10953.
17. Becker CM, Gattrell WT, Gude K et al. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertility and Sterility. 2017; 108 (1): 125–136. doi: 10.1016/j.fertnstert.2017.05.004.
18. Muhaidat N, Saleh S et al. Prevalence of endometriosis in women undergoing laparoscopic surgery for various gynaecological indications at a Jordanian referral centre: Gaining insight into the epidemiology of an important women's health problem. BMC Women's Health. 2021; 21: 381. doi: 10.1186/s12905-021-01530-y.
19. Bedaiwy MA, Alfaraj S, Yong P et al. New developments in the medical treatment of endometriosis. Fertility and Sterility. 2017;107(3):555–565. doi: 10.1016/j.fertnstert.2016.12.025.
20. Soares SR, Martínez-Varea A, Hidalgo-Mora JJ et al. Pharmacologic therapies in endometriosis: a systematic review. Fertility and Sterility. 2012; 98(3):529–55. doi: 10.1016/j.fertnstert.2012.07.1120.
21. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. Nat. Rev. Endocrinol. 2019; 15:666–682. doi: 10.1038/s41574-019-0245-z.
22. Allen C, Hopewell S, Prentice A et al. Non steroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Data base of Systematic Reviews. 2017. https://api.repository.cam.ac.uk/server/api/core/bitstreams/ca05cfe2-f1bc-442c-abf8-66c21f9de824/content [date access 06.04.2023]
23. Estes SJ, Soliman AM et al. National trends in inpatient endometriosis admissions: Patients, procedures and outcomes, 2006—2015. PLoS ONE. 2019; 14:e0222889. doi: 10.1371/journal.pone.0222889.

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ORIGINAL ARTICLE

PERSONIFICATION OF VISUAL DIAGNOSTIC METHODS IN WOMEN WITH SUBMUCOSAL UTERINE FIBROIDS: A RETROSPECTIVE CLINICAL ANALYSIS

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ABSTRACT

The aim: To determine the parameters of perioperative application of radiographic methods for visual diagnosis in women with submucous uterine fibroids.
Materials and methods: We conducted a retrospective analysis of the data from 200 medical records of women with submucous uterine fibroids (SUF).
Results: Preoperatively, nodes were diagnosed by ultrasound as follows: solitary nodes - SM0 type - 65 (46%) near the fundus; SMI - 41 (29%) on the anterior or posterior wall; SMII - 35 (25%) on the lateral walls of the uterus and in the cornual areas of the fallopian tubes; multiple in combinations: O3-4 / SMI - 16 (27.0%) and O3-6 / SMII - 14 (24.0%); with localization: O3-4 / SM0 - mainly in the fundus - 49%, O3-4 / SMI and O3-4 / SMII on the posterior and lateral - 25.0%, 28.0%; O5-6 / SM0 - posterior and fundus - 38.0%, 49.0%; O5-6 / SMI and O5-6 / SMII - posterior and lateral - 45.0% and 37.5%. The maximum average diameter was 20-30 mm, with a quantity of ≤ 3 per individual. When comparing ultrasound and MRI data, discrepancies in the number and localization of nodes were observed in cases of isolated SMI / SMII (on the lateral walls and in the cornual areas of the uterus) at 29.0%; as well as in cases involving combinations of nodes of types O 3-4 / SMI at 39.0% and O 3-4 / SMII at 23.0% ($p<0.05$). During hysteroscopy, in the group without intraoperative sonography, there were 30% more conversions from
hysteroscopic to laparoscopic myomectomy, and 25% more combinations of hysteroscopic myomectomy with laparoscopic monitoring.
Conclusions: Hysteroscopic myomectomy with intraoperative sonography is an effective method of treatment for isolated and multiple fibroids of types SMI/SMII and O3-4/SMI as well as O3-4/SMII.

KEY WORDS: uterine fibroids, hysteroscopy, sonography, magnetic resonance imaging, reproductive health, effectiveness of medical care

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INTRODUCTION

In the current conditions, the main principles of individualized selection of surgical approach and extent of surgical intervention in patients with uterine fibroids (UF) are based on the expansion of preoperative diagnostic methods such as ultrasound (US) and magnetic resonance imaging (MRI). This allows reducing the high frequency of disease recurrence and increasing the likelihood of achieving desired pregnancies [1, 2].

However, in cases of multiple uterine fibroids (UF), preoperative ultrasound (US) may not be able to provide a clear navigation for performing the surgery, especially when dealing with difficult-to-access locations of myomatous nodes for hysteroscopic myomectomy. Therefore, this clinical challenge is addressed by using MRI in preoperative diagnostic assessment or by applying intraoperative sonography [3-4].

THE AIM

The aim of the study was to determine the parameters of perioperative application of radiological visual diagnostic methods in women with submucous uterine fibroids.

To achieve this aim, the following objectives were set:

1) To conduct a retrospective analysis of the effectiveness of radiological preoperative diagnostic methods in patients with submucous uterine fibroids;
2) To study the structure of surgical interventions depending on the applied methods of preoperative visual diagnostics;
3) To determine the parameters of perioperative application of radiological visual diagnostic methods in women with submucous uterine fibroids, including intraoperative sonography.

MATERIALS AND METHODS

During the scientific work from 2021 to 2023, the first stage involved a retrospective analysis of the effectiveness of preoperative diagnostic radiological methods. The second stage focused on studying the surgical intervention structure based on the applied preoperative visual diagnostic methods using the data from 200 medical records of women with submucous uterine fibroids (SMF). Out of these 200 records, two groups were distinguished during the first stage: the first group consisted of 120 individuals who were solely examined using ultrasound (US) method, and the second group included 80 women who utilized both US and magnetic resonance imaging (MRI) methods. During the second stage, the data was further divided into two groups: Group A (n=60) - solely sonographic method; Group B (n=60) - intraoperative sonography.

All subjects provided informed consent to participate in the scientific research. Treatment was free of charge for all study participants. All surgical interventions were performed using endoscopic methods on equipment by Karl Storz GmbH Co (hysteroscope with a diameter of 8.6 mm with a single operative channel for introducing a monopolar electrode loop with a diameter of 5 mm) from Germany, during the first phase of the menstrual cycle.

All treatment methods and types of surgical interventions were approved by the sectorial standards of the Ministry of Health of Ukraine dated December 31, 2004, No. 676 and December 27, 2006, No. 905 "On Approval of Clinical Protocols for Obstetric and Gynecological Care", as well as approved local protocols and based on the PALM-COEIN and STEP-W classification recommended by the International Federation of Gynecology and Obstetrics (FIGO) and included in international clinical protocols for managing patients with the studied pathology. There is no additional health risk to patients associated with conducting the research within the framework of the scientific work.

Exclusion criteria included radiological evidence of adenomyosis or uterine fibroids with transmural nodes, a history of malignant neoplasms of the pelvic organs or cervical dysplasia, previous surgical or endovascular treatment of uterine fibroids (uterine artery embolization (UAE)), and any contraindications to abdominal surgery or anesthesia that would preclude participation in the research.

Statistical data collection of the research results was carried out on a PC using Microsoft Excel software. Mathematical processing was performed using standard statistical packages (SPSS version 12). Quantitative data were presented as mean ± standard deviation, qualitative data – as absolute and relative (%) frequency. Quantitative parameters in the independent groups were compared by the use of the t-Student`s criterion or Mann-Whitney U-test. To compare qualitative variables, we used the $\chi^2$ test and Fisher`s exact test. A 2-tailed $p<0,05$ was considered statistically significant.

RESULTS

The main complaint of the patients was heavy cyclic menstrual bleeding (from ≥ 160 ml to ≤ 500 ml), confirmed by alkaline hematin analysis and with a minimum of a three-month history within 6 months from the time of inclusion in the study. The overall structure of complaints in both groups of patients was as follows: infertility in 60%, polymenorrhea in 54%, menometrorrhagia in 46%, and algomenorrhea in 30.0%. Mild and moderate anemia was present in 36.0% of the patients. The average duration of follow-up for patients with uterine fibroids was 3.5±0.7 years, and the duration of treatment was 3.6±0.3 years.

During the retrospective assessment of the reproductive history in the research groups, primary infertility was diagnosed in 60.0% of cases, and secondary infertility in 40.0% of cases. Primary infertility was significantly more common in the group of patients with multiple uterine fibroids (65.0%), while among patients with solitary fibroids, the frequency of primary infertility was 38.0% ($p<0.05$). The frequency of secondary infertility was 49.0% in cases of single fibroids and 51.0% in cases of multiple fibroids ($p<0.05$) [1].

At the end of the first stage, based on the data from the ultrasound examinations of 200 patients, predominantly solitary submucous fibroids (SM) were identified, with a mean diameter of 23.1±0.9 mm in 141 cases (70.5%), and multiple fibroids in 59 cases (29.5%), with a mean diameter of 23.5±0.5 mm and an average of 2.5±0.5 fibroids per person. The structure of solitary fibroids was characterized as follows: SM0 type - 65 (46%), SMI - 41 (29%), and SMII - 35 (25%) types. In our study, solitary fibroids were predominantly located as follows: SM0 - near the fundus, SMI - at the anterior or posterior walls, and SMII - at the lateral walls of the uterus and in the cornual areas of the fallopian tubes (Table I).

In the presence of multiple fibroids, the diameter of submucosal nodes in combination with type O and SM nodes ranged up to 30 mm, while intramural or serosal nodes had an average size ranging from (Tables I and II). According to the obtained results, the most frequent combinations of nodes in multiple fibroids were: O3-4 / SMI (16 cases, 27.0%) and O3-6 / SMII (14 cases, 24.0%), with the maximum mean diameter of submucosal and intramural nodes ranging from 20 to 30 mm and a maximum of 3 nodes in one individual. Among patients with multiple fibroids in both subgroups, the dominant node types were: O3 in 10 cases (29.4%), O4 in 12 cases (35.3%), O5 in 7 cases (2.5%), O6 in 3 cases (9.0%), and SM in 2 cases (5.8%). In cases of multiple fibroids, the combinations of nodes were evaluated based on the local-

Table I. Characterization of uterine fibroids based on the results of sonography

The type of nodes	The number of examined individuals, n = 200 (100%)								
	SM, n=141 (70,5 %)			Combinations SM and O, n = 59 (29,5%)					
	0	1	2	O 3-4 / SM0	O3-4 / SMI	O3-4 / SMII	O5-6 / SM0	O5-6 / SM I	O5-6 / SM II
Number	65 (46,0%)	41 (29,0%)	35 (25,0%)	6 (10,0%)	16 (27,0%)	14 (24,0 %)	6 (10,0%)	9 (15,0 %)	8 (14,0 %)
Size(mm)									
≤ 20	40 (62,0%)	10 (24,9%)	15 (43,0%)	34,0%	25,0%	23,0%	17,0%	21,0%	25,0%
20-30	15 (23,0%)	23 (56,3%)	16 (45,7%)	49,0%	45,0%	49,0%	34,0%	34,0%	37,5%
≥30	10 (15%)	8 (18,8%)	4 (11,3%)	17,0%	30,0%	28,0%	49,0%	45,0%	37,5%

Table II. Characteristics of MM nodes based on sonography data (%)

The type of nodes	The number of examined individuals n = 200 (100%)								
	SM n=141			Combinations SM and O n = 59					
	0	1	2	O 3-4 / SM0	O3-4 / SMI	O3-4 / SMII	O5-6 / SM0	O5-6 / SM I	O5-6 / SM II
Number	65 (100%)	41 (100%)	35 (100%)	6 (100%)	16 (100%)	14 (100 %)	6 (100%)	9 (100 %)	8 (100 %)
Uterine walls:									
Anterior (front)	12,0%	30,0%	16,0%	17,0%	18,0%	15,0%	-	-	-
Posterior (back)	11,0%	24,4%	15,0%	34,0%	25,0%	21,0%	34,0%	34,0%	37,5%
Uterine fundus (top part of the uterus)	77,0%	-	-	49,0%	18,0%	15,0%	49,0%	-	-
Ribs of the uterus	-	32,0%	43,0%	-	25,0%	28,0%	17,0%	45,0%	25,0%
Fimbrial ends of the fallopian tubes	-	13,6%	26,0%	-	14,0%	21,0%	-	21,0%	37,5%

ization of the clinically significant node (causing symptoms) relative to the uterine walls: O3-4 / SM0 – predominantly in the fundus (49%), O3-4 / SMI and O3-4 / SMII at the posterior and lateral walls (25.0%, 28.0%); O5-6 / SM0 – at the posterior and fundal walls (38.0%, 49.0%); O5-6 / SMI and O5-6 / SMII at the posterior and lateral walls (45.0% and 37.5%, respectively) (Table II).

In the comparative analysis of the results, it was determined that the highest incidence of discrepancies between ultrasound and MRI data, in terms of the number and location of myometrial nodes, was observed in isolated MM in 29.0% (mainly SMI/SMII type, with localization along the lateral walls of the uterus and in the areas of the fallopian tubes); in multinodular MM in 39.0% of clinical situations (among combinations of nodes of types O 3-4/SMI and O 3-4/SMII in 23.0%) ($p<0.05$).

At the second stage of scientific work, the results of the study of the data on the volume of surgical intervention showed significant differences between patients of the study groups depending on the type of visual diagnostics used.

The duration of hysteroscopic myomectomy was largely dependent on the diameter of the myomatous nodule and its depth of invasion into the myometrium. For solitary nodules of types SM0/I/II with a mean diameter of 23.5±0.5 mm, the duration of hysteroscopic myomectomy was 35.2±0.3 minutes in both groups. Data from Group A indicated that in 15% of clinical cases, during hysteroscopy with the presence of nodules of types SM/I/II located in the areas of uterine tube cornua, hysteroscopic myomectomy with laparoscopic control was performed, with an average duration of 57.2±0.3 minutes. Conversion from hysteroscopic to laparoscopic myomectomy was observed in 17% of patients with solitary nodules of types SM/I/II and in 25% of patients with multiple myomatous nodules, especially in cases of nodule combinations such as O3-4 SM/I/II and localization along the lateral walls of the uterus. The occurrence of biological infeasibility to continue hys-

teroscopic myomectomy due to high intraoperative risks in these clinical cases was attributed to the discrepancy of the nodule diameter of SM/I/II during hysteroscopic visualization, which was 25% higher than the preoperative sonography results, and the average duration was 42.1±0.3 minutes. During the surgical procedure, the total blood loss in subgroup A ranged from 50 ml to 750.0 ml (average 570.2±50.3 ml).

Thus, in Group A, the average duration of the surgical procedure was 60.1±0.3 minutes, which was likely longer than in the comparison Group B, where the operation time was 24.2±0.3 minutes ($p<0.05$). The average diameter of clinically significant nodules of types SM0/I/II was 20.8±0.42 mm, as determined by both preoperative MRI and intraoperative assessment, allowing for radical removal of the nodules within 20-30 minutes. Intraoperative blood loss did not exceed 50 ml in any of the subgroups. The indicators for average hemoglobin levels and duration of hospitalization did not significantly differ between the groups. The analysis of clinical symptoms in patients from both research groups at 6 months after myomectomy showed no significant difference between Groups A and B. The duration of hospitalization (in days) was likely longer in patients of subgroup A, primarily due to those patients who underwent a combination of hystero-laparoscopy or experienced conversion from hysteroscopic to laparoscopic access during myomectomy. On average, the duration of hospitalization in Group A was 2.5±0.5 days, while in Group B, it was 1.0±0.5 days.

According to the results of our study, the effectiveness of radical hysteroscopic removal of SM nodules was 75% and 100% in groups A and B, respectively. The analysis of the dynamic changes in clinical symptoms over 12 months after myomectomy in patients of both research groups revealed that at 3 months and 6 months after the operation, women in Group A experienced pain syndrome, dysmenorrhea, dysuria, and hypermenorrhea approximately 2.5±1.5 times more frequently than in Group B. However, complete restoration of the menstrual cycle occurred within 3 months in all 120 (100%) patients.

DISCUSSION

The management of patients with benign uterine pathologies involves a wide range of diagnostic, therapeutic, and surgical methods. Accurate diagnosis of various pathological conditions of the internal genital organs is of great practical importance, especially during the planning and implementation of surgical interventions. In recent years, there have been studies in the international literature dedicated to intraoperative laparoscopic/hystero-echography, which highlight its high informativeness. For instance, W.T. Yang et al., comparing preoperative and intraoperative echography with computer or magnetic resonance tomography, radiographic hysterosalpingography, endoscopy, and echography, concluded that its accuracy was 10% higher compared to the above-mentioned visual diagnostic methods during the preoperative stage, which is in full agreement with our research results [7,8].

However, many researchers also note that despite hystero-laparoscopy providing a panoramic view of the pelvic organs, it is limited to two-dimensional visualization of organs on the monitor. In cases of small isolated myomatous nodules with a diameter of up to 25 mm, primarily located within the thick walls of the uterus or conglomerate of small-sized nodules within the myometrium, with unclear deformation of the uterine cavity contour - which were precisely represented in our study - an unfavorable intraoperative clinical situation may arise. In such cases, the surgeon can only determine the localization of tumor-like formations through intraoperative palpation, which were not diagnosed during preoperative echography, and subsequently remove them [1-5,8].

Therefore, as demonstrated in our research, the refinement of minimally invasive surgical technologies in the treatment of submucous uterine myoma through the personalization of preoperative and intraoperative echography application can significantly reduce intraoperative risks and operative interventions in reproductive-aged women [4,5].

CONCLUSIONS

1. The use of preoperative ultrasound (US) is a highly informative method of visual diagnostics for the majority of myomatous nodules, both isolated and multiple, except for SMI-SMII types with a predominant localization along the lateral walls of the uterus and in the regions of the uterine tubes.
2. The application of hysteroscopic myomectomy with intraoperative sonographic assistance in cases of isolated myomatous nodules, predominantly of SMI/SMII types, with localization along the lateral walls of the uterus and in the regions of the uterine tubes, as well as in cases of multiple myomatous nodules of O3-4/SMI and O3-4/SMII types, allows for the radical one-step removal of the myomatous nodule or timely correction of the surgical technique to avoid repeat surgery or conversions to laparoscopic myomectomy. This approach helps reduce intraoperative blood loss, minimize the volume of infusion therapy, and preserve the functional tissue of the endometrium in the altered area, which is crucial for the reproductive purposes and overall quality of life for the patients.

REFERENCES

1. Lytvak OO, Khabrat BV, Lysenko BM, Khabrat AB. Optymizatsiya khirurhichnoho likuvannya zhinok reproduktyvnoho viku khvorykh na miomu matky [Optimization of surgical treatment of women of reproductive age with uterine fibroids]. Clinical and preventive medicine. 2017; 3:48-55 (In Ukrainian).
2. Turocy JM, Rackow BW. Uterine factor in recurrent pregnancy loss. Semin Perinatol. 2019;43(2):74-79. doi: 10.1053/j.semperi.2018.12.003.
3. Vellone V, Paudice M, Biatta Ch et al. Surgical Pathology of Uterine Myomas: From Usual Forms to Differential Diagnosis. 2019. https://www.researchgate.net/publication/331791248_Surgical_Pathology_of_Uterine_Myomas_From_Usual_Forms_to_Differential_Diagnosis [date access 09.04.2023]
4. Lytvak OO, Khabrat BV, Lysenko BM et al. Dyferentsiyne zastosuvannya maloinvazyvnykh metodiv khirurhichnoho likuvannya submukoznoyi miomy matky u zhinok reproduktyvnoho viku. [Differential use of minimally invasive methods of surgical treatment of submucous uterine fibroids in women of reproductive age]. Actual problems of modern medicine: Bulletin of the Ukrainian Medical Stomatological Academy 2016;16(4-1)(56): 155-159 (In Ukrainian).
5. Piecak K, Milart P. Hysteroscopic myomectomy. Prz Menopauzalny. 2017;16(4):126-128. doi: 10.5114/pm.2017.72757.
6. Loffer FD. Management of Submucosal Myomas Not Completely Resected. J Minim Invasive Gynecol. 2019;26(5):787-788. doi: 10.1016/j.jmig.2019.02.006.
7. Akita S. Wound repair and regeneration: Mechanisms, signaling. Int. J. Mol. Sci. 2019;20(24):6328. doi: 10.3390/ijms20246328.
8. Grewal K, Jones B, L'Heveder A, Jindal S. The use of intra-operative ultrasound in gynecological surgery: a review. Future Science. 2020; 7: 3. doi:10.2144/fsoa-2020-0172.

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ORIGINAL ARTICLE

HEART RATE VARIABILITY AS AN OBJECTIVE CRITERION FOR THE PSYCHO-EMOTIONAL STATE OF COMBATANTS

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ABSTRACT

The aim: To evaluate the functioning of the autonomic nervous system in combatants, the relationship between the heat rate variability (HRV) and questionnaire indicators, to improve the diagnosis of post-traumatic stress disorder (PTSD) and to evaluate the effectiveness of Transcendental Meditation (TM).

Materials and methods: 57 combatants and 30 civilians, with registering ECG and HRV-analysis, self-questionnaire testing.

Results: The combatants' group showed an increase in heart rate, in the degree of centralisation of heart rate control and the R. Bayevsky stress index, a decrease in the total HRV value. PTSD score was negatively correlated with pNN50. The indicator «Stress» (by DASS-21), revealed negative relationships with the TP, (LF+HF), RMSSD, HF, HFn. The effects of TM on HRV are to save the work of the cardiovascular system (reduced heart rate), reduce the level of nervous and emotional stress, increase the overall adaptation reserve. After TM, the HRV spectrum retains the same proportions of very low, low, and high frequencies as in the baseline state.

Conclusions: The study objectively proved the presence of neuro-emotional stress and depletion of autonomic regulation reserves in combatants, both by questionnaire surveys and HRV analysis. The high level of correlation between HRV and questionnaire indicators gives grounds for the introduction of HRV analysis for the initial assessment of the psycho-emotional state and tracking its dynamics, as well as for assessing the effectiveness of its correction. Our use of TM has confirmed its effectiveness in correcting the psycho-emotional state.

KEY WORDS: heart rate variability, combatants, post-traumatic stress disorder, autonomic dysfunction, Transcendental Meditation

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INTRODUCTION

In times of war, the largest risk group for the development of stress disorders, including post-traumatic stress disorder (PTSD), consists of military personnel who are directly involved in combat operations [1, 2]. The impact of stress factors on the body is usually manifested by emotional arousal, which is somatically reflected in the tension of the autonomic nervous system (ANS), with increase in tone of sympathetic part of ANS, with its subsequent negative impact on the functioning of the cardiovascular, nervous, endocrine, immune and other systems of the body [3, 4]. Detection and correction, at early stages, of autonomic imbalance observed in individuals after suffering distress is an important task of preventing not only functional disorders of the ANS, but also the development of somatic diseases. Psychological distress is usually assessed using subjective questionnaires. However, this method has disadvantages, such as patients' bias towards their own self-esteem, as well as impaired ability to realize their condition, which is often observed in people with mine-blast trauma. The working hypothesis of our study was that the level of autonomic dysfunction, determined by heart rate variability (HRV), is associated with the severity of PTSD in military personnel after exposure to combat, and can be corrected with Transcendental Meditation (TM).

THE AIM

The aim of the study was to evaluate the functional state of the ANS in combatants, to investigate the relationship between HRV and questionnaire indicators

of psycho-emotional state, to improve the diagnosis of its disorders and to evaluate the effectiveness of the corrective effect of TM using HRV analysis.

MATERIALS AND METHODS

We examined 57 servicemen (men, average age 41.5±1.2 years) who participated in combat operations with an average stay on the front line of more than 3 months (90 days). The control group consisted of 30 people (men, average age 38.5±1.6 years) who did not participate in hostilities. Among the combatant soldiers who underwent rehabilitation at the State Institution «Veteran Mental Health and Rehabilitation Center «Forest Glade» Ministry Of Health Of Ukraine», Kyiv, Ukraine, 37 people had shrapnel wounds, and all of the subjects reportedly suffered contusions. The main complaints of the combatants were headaches, irritability, sleep disturbances, pain at the level of 4-5 points on a 10-point visual analog scale, depression and anxiety. No acute or focal pathology was detected in the objective status of the combatants at the time of the examination. The psycho-emotional state was studied using the DASS-21 questionnaire [1], PTSD screening questionnaire [3, 5], questionnaire for detection of autonomic dysfunction by A.M. Wayne [6].

The study of heart rate variability was performed by recording the ECG in 6 leads using a portable digital ECG recorder DiaCard 06000.1 (Solvaig, Ukraine) in a sitting position for 3 minutes. The ECG and HRV were analyzed using the Finnish-Ukrainian cloud service CardioLyse (www.cardiolyse.com) and the Oracul ECG signal recording and analysis software (AC No. 95334, AC No. 47857, V.M. Glushkov Institute of Cybernetics of the National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine. Some combatants underwent heart rate variability studies before and after treatment, which consisted of training and application of TM. TM training was conducted in 11 people (men, mean age 42.3±2.2 years). HRV was assessed before and after the TM session, in a sitting position, for three minutes. Statistical data processing was carried out using SPSS-21.0 software.

We used the standard HRV parameters [7 - 10]:

- mRR, ms - mean value of R-R intervals; HR, bpm - Heart Rate;
- SDNN, ms - Square Deviation of N-N intervals. The measure of total HRV.
- RMSSD, ms - the square root of the mean of the squares of the successive differences between adjacent NNs. The measure of parasympathetic (vagal) activity.
- pNN50,% the proportion of pairs of successive NNs that differ by more than 50 ms divided by total number of NNs. The measure of parasympathetic (vagal) activity.
- TP, ms^2 - Total Power of HRV spectrum. The measure of total HRV.
- VLF, ms^2 - The spectral power of very low frequency (0,04 - 0,003(3) Hz). The measure of activity of subcortical sympathetic ergotropic nervous centers. Provides sympathetic influences on the heart.
- LF, ms^2 - The spectral power of low frequency (0,15 - 0,04 Hz). The measure of activity of the baroreflex center of medulla oblongata. Provides sympathetic influences on the heart.
- HF, ms^2 The spectral power of high frequency (0,4 - 0,15 Hz). The measure of parasympathetic (vagal) activity. Provides vagal influences on the heart.
- LF/HF - ratio - reflects sympatho-vagal balance
- VLF/HF - ratio, the index of activation of subcortical nervous centers
- IC = (VLF+LF)/HF , - the index of centralization of the management of heart rhythm
- VLFn,% - partial spectral power in VLF range
- LFn,% - partial spectral power in LF range
- HFn,% - partial spectral power in HF range
- SI (Bayevskyi Stress-index) - the index of neuro-emotional tension; SI = AMo/(2*Mo*(RRmax-RRmin); Mo (sec) - the Mode of R-R interval; AMo (%) - the Amplitude of Mode; AMo = n/N*100%; n - the number of R-R intervals included into Mode range (the width of pocket of histogram of R-R intervals is 50 ms); N - total number of R-R - intervals.

The average values of the indicators (M) and their errors (m) were calculated. The reliability of differences in mean values when comparing the experimental and control groups was assessed using Student's T-test for two independent samples. The reliability of the magnitude of the shift in HRV indices after the TM session was assessed using a one-sample Student's T-test. For correlation analysis, Pearson's linear correlation coefficients (R) and Spearman's rank correlation (R Sp) were used.

RESULTS

COMPARISON OF HRV AND PARAMETERS OF SUBJECTIVE ASSESSMENT IN COMBATANTS WITH THE CONTROL GROUP

According to all the indicators of psycho-emotional state assessed in the study, both according to the questionnaire (Table I) and HRV (Table II), the combatant group significantly differed from the control group. The combatants' scores on the PTSD, DASS-21, and Wayne tests were significantly higher than those of the control group.

While estimating the results, it can be noted that, compared to the control group, the following changes in HRV were observed in combatants. Heart rate was 9% higher than in the control group. The value of total HRV was significantly lower than in the control group (30% lower for SDNN and 49% lower for TP). The value of the absolute activity of

Table I. Indicators for assessing the psycho-emotional state

Indicator	Combatants, M±m, n=57	Control group, M±m, n= 30
PTSD	4,23±0,24*	1,83±0,27
DASS-21	35,84±1,89*	16,13±1,70
D (Depression)	9,85±0,73*	4,7±0,63
A (Anxiety)	11,71±0,67*	3,33±0,42
S (Stress)	14,28±0,70*	8,10±0,88
Wayne	43,72±1,84*	18,28±2,40

Notes: * - Reliability of differences in mean values with the control group at the level of p<0,001.

Table II. Indicators of HRV

Indicator	Combatants, M±m, n=57	Control group, M±m, n= 30
mRR, ms	756±16*	839±36
HR, bpm	81,4±1,7*	74,9±2,8
SDNN, ms	27,4±1,5***	39,0±2,6
RMSSD, ms	16,9±1,5**	26,6±2,8
pNN50,%	1,94±0,66**	8,97±2,41
TP, ms^2	731±90**	1430±203
VLF, ms^2	280±34*	467±83
LF, ms^2	325±47**	658±113
HF, ms^2	126±31**	306±53
LF/HF	5,06±0,66	3,84±0,58
VLF/HF	5,47±0,79*	3,04±0,72
IC	10,53±1,26*	6,88±1,15
VLFn,%	42,31±2,38*	32,51±2,93
LFn,%	42,05±2,18	46,21±3,06
HFn,%	15,64±1,59	21,29±2,59
SI	480±48**	264±45

Notes: * - Reliability of differences in mean values with the control group at the level of 0,01<p<0,05 ; ** - at the level of 0,001<p<0,01 ; *** - at the level of p<0,001.

Table III. Grouping people by anxiety levels

Group	n	Anxiety level by frequency distribution in the sample	The value of the anxiety index according to the DASS-21 test	Qualitative assessment
1	20	< Q1	0 - 3 points	Normal (no anxiety)
2	21	Q1 - Me	4 - 7 points	Mild to moderate anxiety
3	18	Me – Q3	8 - 12 points	Severe and very severe anxiety
4	26	> Q3	>= 13 points	Very severe anxiety

parasympathetic modulation was significantly lower than in the control group (by 36% lower, according to RMSSD, by 78% lower, according to pNN50, by 59% lower, according to HF). At the same time, the specific activity of parasympathetic modulation, measured by the specific spectral power in the high frequency range, HFn, in the combatant group was 27% lower than in the control group (at the level of a strong trend, p=0.053). The autonomous balance index, assessed by the LF/HF ratio, was 32% higher in the military group than in the control group (at the level of a weak trend, p=0.166). The index of activation of subcortical nerve centers, assessed by the VLF/HF ratio, was significantly higher in combatants, by 80%, compared to the control group.

The index of centralisation of heart rate control, assessed by the ratio (VLF+LF)/HF, was also significantly higher in combatants, by 53%, compared to the control group. The specific activity of subcortical ergotropic sympathetic nerve centers, according to the VLFn index, in combatants was

Table IV. Significant correlations between HRV-indices and indices of psycho-emotional state in the group of highly anxious individuals (n=44).

index	DASS-21	D (depression)	S (stress)
RMSSD	no significant correlations	no significant correlations	R = -0,356*
HF	no significant correlations	no significant correlations	R = -0,403*; $R_{Sp.}$ = -0,348*
VLF	no significant correlations	$R_{Sp.}$ = -0,316*	no significant correlations
VLFn	R = -0,319*; $R_{Sp.}$ = -0,310*	no significant correlations	R = 0,354*
VLF/HF	R = 0,343*	R = 0,343*	no significant correlations

Notes: * - The significance of the coefficient of correlation at the level of p<0,05.

Table V. Significant correlations between HRV-indices and indices of psycho-emotional state in the group with an anxiety level of more than 13 points.

Index	PTSD	S (stress)
TP	no significant correlations	R = -0,450*
LF+HF	no significant correlations	R = -0,511*
RMSSD	no significant correlations	R = -0,563**
pNN50	R = -0,451*; $R_{Sp.}$ = -0,422*	no significant correlations
HF	no significant correlations	R = -0,643**
HFn	no significant correlations	R = -0,559**

Notes: * - The significance of the coefficient of correlation at the level of p<0,05 ; ** - at the level of p<0,01.

30% higher than in the control group. The specific activity of the baroreflex (vasomotor) center of the medulla oblongata, according to the LFn index, in military personnel did not differ from the control. The stress index of regulatory systems (Roman Baevsky's stress index) in combatants was significantly higher by 82% than in the control group. Thus, according to the HRV indicators, the combatants' group showed such signs of nervous and emotional stress as an increase in heart rate, a decrease in the total HRV value, an increase in the degree of centralisation of heart rate control and the R. Bayevsky stress index. These data characterizing HRV are fully consistent with the results of our psychological questionnaire testing of combatants.

CORRELATIONS BETWEEN HRV INDICES AND PSYCHO-EMOTIONAL STATE IN INDIVIDUALS WITH DIFFERENT LEVELS OF ANXIETY (ACCORDING TO THE DASS-21 TEST)

The total sample (combatants and controls) was divided into 4 groups, according to the frequency distribution of anxiety (Table III).

Our main focus was on the group of highly anxious individuals (n=44) whose DASS-21 anxiety score exceeded the median of the distribution of the total sample, i.e., was higher than 7 points (see Table IV).

To further study the peculiarities of correlations, the group of highly anxious individuals (n=44) was divided into two groups according to the median level of anxiety calculated for this group, which was 13 points. In the first group, with an anxiety level of up to 13 points, there was a positive correlation between the Baevsky stress index and anxiety (R=0,484; p<0,05). In the second group, with an anxiety level of more than 13 points, the following significant correlations were found (Table V).

It was shown that the PTSD score was negatively correlated with the parasympathetic activity marker pNN50. At the same time, the indicator «Stress», according to the DASS-21 questionnaire, revealed negative relationships with both the total power of the HRV spectrum (TP), the total spectral power in the high and low frequency domains (LF+HF), and the indicators of absolute (RMSSD, HF) and specific (HFn) parasympathetic activity.

THE ASSESSMENT OF THE IMPACT OF TM ON HRV

Changes in HRV indices in our study with combatants after TM were as follows (Table VI). Heart rate significantly decreased by 8 beats per minute (by 9.6% of the baseline). Overall HRV, which includes SDNN and TP, showed a significant increase. There was a significant increase in RMSSD, the index of parasympathetic activity, by 29% compared to the baseline. However, the spectral power in the high frequency (HF) range, which is also a measure of parasympathetic activity, did not show a significant shift. The activity index of the subcortical sympathetic ergotropic nerve centers VLF increased by 90%, and the activity index of the baroreflex center of the medulla oblongata LF increased by 84% compared to the baseline.

Table VI. HRV indicators before and after TM

Indicators of HRV	Before TM, M± m	After TM, M± m	Average individual shift in the indicator after TM (M±m)
HR, bpm	82,4±4,8	74,5±3,4	-7,91±2,02**
mRR, ms	761±56	826±45	65,6±17,8**
SDNN, ms^2	29,8±3,5	37,7±4,0	7,91±1,50***
RMSSD, ms	18,3±4,2	23,6±3,3	5,36±1,80*
SI, conv. units	437,0±100,8	260,7±50,1	-176±65*
TP, ms^2	831±170	1395±263	564±161**
VLF, ms^2	338±98	643±161	305±103*
LF, ms^2	275±39	505±108	230±93*
HF, ms^2	218±82	247±64	29±43
VLF/HF	3,62±1,13	4,50±1,60	0,88±0,96
LF/HF	3,92±1,04	3,85±0,90	-0,07±1,15
IC	7,54±1,85	8,34±2,36	0,81±2,04
VLFn, %	37,20±5,37	41,31±5,31	4,11±3,72
LFn, %	41,85±5,63	40,62±5,19	-1,23±2,96
HFn, %	20,95±4,96	18,07±3,72	-2,88±5,08

Note: * - reliability of the average value of the indicator shift at the level of $p< 0,05$; ** - at the level of $p< 0,01$; *** - at the level of $p< 0,001$.

Thus, the effects of TM on HRV are to save the work of the cardiovascular system (reduced heart rate), reduce the level of nervous and emotional stress, increase the overall adaptation reserve. At the same time, the overall adaptation reserve increases due mainly to an increase in the activity of subcortical sympathetic ergotropic centers and the baroreflex center of the medulla oblongata.

DISCUSSION

The analysis of HRV occupies an important place among the methods of objective comprehensive assessment of the functional state of the human body, it allows to objectively assess the activity of different levels of autonomic regulation, balance of sympathetic and parasympathetic activity, the degree of centralization of heart rate control, which are markers of nervous and emotional stress, and also reflect the ability of a person to adaptively cope with stress [7-11]. Low heart rate variability (HRV) is associated with an increased risk of developing post-traumatic stress disorder (PTSD) in individuals who have participated in combat [4].

According to the HRV indicators, the combatants' group showed such signs of nervous and emotional stress as an increase in heart rate, a decrease in the total HRV value, an increase in the degree of centralisation of heart rate control and the R. Bayevsky stress index. These data characterizing HRV are fully consistent with the results of our psychological questionnaire testing of combatants. In the two subgroups of combatants who differ in their level of anxiety, different patterns of correlation between HRV and indicators of psycho-emotional state (anxiety, PTSD, stress) were found. The common features of these correlations for both groups are that the severity of pathological signs of the psycho-emotional state according to the questionnaires positively correlated with the degree of tension of regulatory systems (with tension of the sympathetic part of ANS) and negatively correlated with the total HRV (TP), absolute activity of all three levels of autonomic regulation of the heart rate. In combatants with more severe nervous system injuries, who, accordingly, have a higher level of anxiety, there is an increase in the number of significant correlations between HRV and indices of psycho-emotional state. This fact provides the basis for the hypothesis that models of adaptation to neuro-emotional distress differ depending on the severity of its components, one of which is increased anxiety. Thus, on the basis of our data, it can be argued that the role of autonomic regulation, its individual components, in the adaptation of the body of highly anxious individuals, compared to low-anxious individuals, is strengthened, which is a strong argument for using mathematical analysis of HRV to assess the psycho-emotional state of individuals in a state of distress, in particular, combatants with PTSD, in order to objectively monitor and predict it at the stages of rehabilitation. The purpose of our next research may be to clarify the role of individual components of the ANS in the implementation of adaptation. Another approach, which indicates the possibility of using the method of HRV determination to assess the state of ANS in combatants, was to study the effect of Transcendental Meditation (TM) on the dynamics of the main HRV indicators in the process of its application. TM is a simple mental technique that is practiced 2 times a day for 15-20 minutes, sitting in a comfortable

position with eyes closed. The practice of TM itself does not involve concentration or contemplation, is not a religion or philosophy, and does not require a change in lifestyle [12].

TM is a method that achieves a unique state of deep relaxation. There are scientific papers in which the TM method has proven to be one of the most effective for overcoming PTSD in combatants [13]. Studies of TM practices have revealed patterns of increased parasympathetic response and autonomic stability. Numerous studies have also found that TM can help alleviate the symptoms of depression in various populations. Early research on TM for PTSD in military and veterans has shown promising effects for TM as a treatment for PTSD symptoms. Recently conducted randomized controlled trial involving 203 veterans and found that TM practice is not inferior to prolonged exposure therapy, which is considered the gold standard of first-line psychotherapy, in the treatment of PTSD [13]. Interestingly, after TM, the HRV spectrum retains the same proportions of very low, low, and high frequencies as in the baseline state. That is, TM does not change the ratio of activity of different levels of heart rate regulation. Such changes in HRV during TM may reflect a state of «awakened calm» where, against the background of deep physical relaxation, fully awakened mental activity and concentration remain, i.e. this state is not similar to falling asleep, trance or hypnosis. The fact that we observe an increase in RMSSD and no increase in HF may be evidence of a change in the respiratory pattern during TM described by various authors [14-16]. This pattern change is characterized, in particular, by a decrease in the frequency of respiratory movements. Accordingly, this suggests the need to introduce individual correction of the high frequency (HF) spectral range limit at each cardiac rhythmogram recording in the following developments of telemedicine systems that analyze ECG and HRV. TM reduces the R. Baevsky stress index, and therefore reduces nervous and emotional tension and the degree of tension of regulatory systems. After TM practice, an increase in Total power (TP) is noted, which indicates an improvement in the body's adaptive reserves.

CONCLUSIONS

The study objectively proved the presence of neuro-emotional stress and depletion of autonomic regulation reserves in combatants, both by questionnaire surveys and HRV analysis. The high level of correlation between HRV indicators and questionnaire indicators of subjective assessment of the psycho-emotional state revealed in the study gives grounds for the introduction of the method of mathematical analysis of HRV for the initial assessment of the psycho-emotional state and tracking its dynamics, as well as for assessing the effectiveness of its correction by various methods. Our use of TM has confirmed its effectiveness in correcting the psycho-emotional state, based on the data obtained from the HRV analysis (decrease in heart rate, increase in total HRV and parasympathetic activity).

REFERENCES

1. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales. 2nd. Ed. Sydney: Psychology Foundation. 1995. https://www.worldcat.org/title/Manual-for-the-depression-anxiety-stress-scales/oclc/222009504 [date access 05.04.2023]
2. Post-traumatic stress disorder. Order of the Ministry of Health of Ukraine of 1995. 23.02.2016. No. 121. https://www.dec.gov.ua/wp-content/uploads/2019/11/2016_121_ykpmd_ptsr.pdf [date access 05.04.2023]
3. Schneider M, Schwerdtfeger A. Autonomic dysfunction in posttraumatic stress disorder indexed by heart rate variability: a meta-analysis. Psychol Med. 2020 ;50(12):1937-1948. doi: 10.1017/S003329172000207X.
4. Minassian A, Maihofer A, Baker D. Association of Predeployment Heart Rate Variability With Risk of Postdeployment Posttraumatic Stress Disorder in Active-DutyMarines. JAMA Psychiatry. 2015;72(10):979-986. doi:10.1001/jamapsychiatry.2015.0922.
5. Pisaruk A, Shatilo V, Chyzhova V et al. Posttraumatic stress disorder: online poll of people who experienced war stress in Ukraine in 2022. Ageing and Longevity. 2022; 3(2): 57-62. http://www.aging-longevity.org.ua/index.php/journal-description/article/view/53/60 [date access 05.04.2023]
6. Wayne AM. Vegetative disorders: clinic, diagnosis, treatment. Moscow: LLC «Medical Information Agency». 2003, p.752.
7. Yabluchanskiy NI, Martyinenko AV, Isaeva AS. Osnovyi prakticheskogo primeneniya neinvazivnoy tehnologii issledovaniya regulyatornyih sistem cheloveka. Kharkov: Osnova. 2000, p.88.
8. Apykhtin KO, Drozdovska SB, Gurenko OO et al. Heart rate variability in people with metabolic syndrome. Ageing and Longevity. 2023; 1(1):1– 7. http://aging-longevity.org.ua/index.php/journal-description/article/view/88/74. [date access 05.04.2023]
9. Pisaruk A, Mekhova L, Antoniuk-Shchegloval et al. Estimating biological age of the autonomic regulation cardio-vascular system. Ageing and Longevity. 2022; 3 (2): 1-7. http://www.aging-longevity.org.ua/index.php/journal-description/article/view/42/51. [date access 05.04.2023]
10. Lisun Y, Uhlev Y. Heart rate variability, applying and methods of analysis. Pain, Anaesthesia & intensive care. 2020; 4: 83-89. doi:10.25284/2519-2078.4(93).2020.22069.
11. Cheng Yi-Ch, Huang Yu-Ch, Huang W-Li. Heart rate variability in patients with somatic symptom disorders and functional somatic syndromes: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2020;112:336-344. doi:10.1016/j.neubiorev.2020.02.007.

12. Bellehsen M, Stoycheva V, Cohen B et al. A Pilot Randomized Controlled Trial of Transcendental Meditation as Treatment for Posttraumatic Stress Disorder in Veterans. J Trauma Stress. 2022;35(1):22-31. doi: 10.1002/jts.22665.
13. Nidich SI, Mills PJ, Rainforth M et al. Non-trauma-focused meditation versus exposure therapy in veterans with post-traumatic stress disorder: A randomized controlled trial. The Lancet. Psychiatry. 2018;5(12): 975-986. doi:10.1016/S2215-0366(18)30384-5.
14. Farrowand J, Hebert R. Breath Suspension During the Transcendental Meditation Technique. Psychosom Med. 1982;44(2):133-53. doi: 10.1097/00006842-198205000-00001.
15. Gallois P. Neurophysiological and Respiratory Changes During the Practice of Relaxation Techniques. L'Encephale (The Encephalon). 1984; 10: 139-144.
16. Badawi K, Wallace RK, Orme-Johnson DW et al. Electrophysiologic characteristics of respiratory suspension periods occurring during the practice of the Transcendental Meditation program. Psychosomatic Medicine. 1984;46(3):267-276. doi: 10.1097/00006842-198405000-00008.

The authors adhere to the standards of the Helsinki Declaration of the World Health Organization. The submitted manuscripts relate to the work patients and are prepared in accordance with ethical standards.
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ORIGINAL ARTICLE

PREVALENCE AND INCIDENCE OF BREAST CANCER IN UKRAINE

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ABSTRACT

The aim: To analyze the prevalence of breast cancer from 2014 to 2022 and the incidence rate in the population of Ukraine.

Materials and methods: The methods used in the research include historical-biographical analysis, content analysis, and a systemic approach.

Results: According to the National Cancer Registry of Ukraine, from 2014 to 2020, there were stable figures of malignant neoplasms (MN) with a 1% increase in morbidity. The lowest rate was observed in 2014, with 135.307 new cases of MN, showing a slight increase until 2019 with 138.509 new cases. Starting from 2020, there has been a decrease in the registration of new MN cases, such as 113.368 new cases in 2020, in 2021-120.055, and 93.276 in 2022. The decrease in new MN cases is attributed to limited access to medical services for the population residing in annexed territories and areas affected by ongoing military actions.

Conclusions: A relatively stable increase in breast cancer incidence is observed from 2014 to 2020, within a 1% range, followed by a sharp decrease from 2020 to 2022. This decrease could be attributed to limited access to medical services due to the pandemic and ongoing military actions.

KEY WORDS: breast cancer, National Cancer Registry of Ukraine, electronic health system, new case of malignant neoplasm (MN)

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INTRODUCTION

The development of healthcare in Ukraine is an integral part of the modern state policy and directly impacts both the overall demographics and the well-being of families and individual citizens. One of the most significant issues of contemporary society is the problem of oncological diseases. Ukraine's prevalence of this pathology follows similar trends to global patterns, and in terms of the spread of cancer, it ranks second in Europe. Indeed, over the past 10 years, oncological diseases have been newly diagnosed annually in more than 160,000 Ukrainians. According to the data from the National Health Service of Ukraine (NHSU), the main prevalent oncological diseases for which medical assistance was provided within healthcare packages in 2022 include malignancies of the breast, prostate gland, rectum, ovaries, sigmoid colon, upper lobe of the bronchus or lung, and endometrium [1, 2].

The number of detected cancer cases in Ukraine decreased by 27.1 thousand cases in 2020 compared to the average number of cases detected during 2014-2019. In 2021, the incidence of cancer in Ukraine increased by 6.0% compared to 2020, but it was lower by 13.3% compared to 2019. In 2022, the widespread military actions on the territory of Ukraine had a negative impact on healthcare facilities and the system of cancer disease tracking. The number of detected cancer cases in Ukraine decreased by 27.1 thousand cases in 2020 compared to the average number of cases detected during 2014-2019. In 2021, the incidence of cancer in Ukraine increased by 6.0% compared to 2020, but it was lower by 13.3% compared to 2019. In 2022, the widespread military actions on the territory of Ukraine had a negative impact on healthcare facilities and the system of cancer disease tracking. During 2022, there were 26.8 thousand (22.3%) fewer detected cancer cases in Ukraine compared to 2021. However, it is known that according to the practices of cancer registries in European and American countries, data collected for the previous year may be incomplete and therefore may not reflect 100% of cancer prevalence in the studied population due to the impossibility of obtaining data on registration completeness for the majority (≥95%) of cases. To ensure data completeness, cancer registries establish a data refinement period (usually two years or more) during which information about at least 95% of cancer cases is collected. Indeed, it is important to consider this aspect when analyzing operational data for previous years and to pay more attention to the data processing for the year 2022, taking into account the challenges posed by military actions, occupation of certain regions, and other factors associated with these events [1, 3-12].

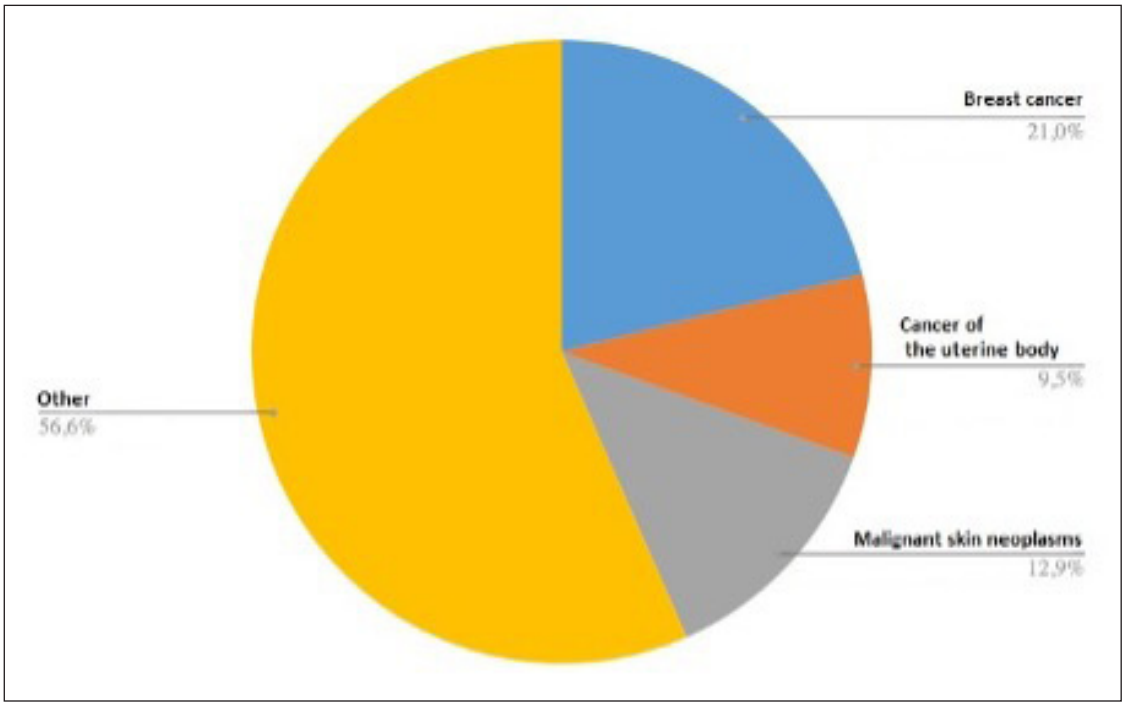

Fig 1. Structure of morbidity by the most common nosological forms of malignant neoplasms

THE AIM

The aim of the study was to analyze the prevalence of breast cancer (BC) from 2014 to 2022 and the incidence rate in the population of Ukraine.

MATERIALS AND METHODS

The methods used in the research include historical-biographical analysis, content analysis, and a systemic approach. For quantitative data, the medical-statistical method was used, and calculations were performed using licensed Microsoft Office Word software. The data was processed to calculate relative values in percentages (%). We also utilized a graphic method to present and visualize the data.

RESULTS

In Ukraine, among the overall incidence of malignant neoplasms, the proportion of BC among women accounts for approximately 52.8%, ranking first (Figure 1) [1, 3, 4].

Among the morbidity of oncological diseases in women, breast, skin, body and cervix uteri, and sigmoid colon malignancies continued to dominate, accounting for 54.5% of the detected diseases [1].

Over the past nine years, the prevalence of BC among the female population of the country has shown a tendency to increase, from 60.6 per 1000 population in 2014 to 62.4 per 1000 female population in 2021. The mortality rate from BC among the female population of the country over the last nine years has shown a tendency to decrease, from 24.6 per 1000 population in 2014 to 20.4 per 1000 female population in 2021 [5, 11].

Ukraine exhibits significant variability in regional BC prevalence rates among women (Table I). The highest prevalence rates of BC in women in 2022 were observed in Kyiv city (82.1 per 1000 female population), Dnipropetrovsk (66.4 per 1000 female population), Zaporizhzhia (65.8 per 1000 female population), and Kyiv (65.6 per 1000 female population) regions. Conversely, the lowest rates were seen in Chernivtsi (44.1 per 1000 female population), Ivano-Frankivsk (48.6 per 1000 female population), and Zakarpattia (49.1 per 1000 female population) regions [5-12].

The analysis of the dynamics of changes in the prevalence of BC among the female population in the administrative regions of Ukraine over the past nine years (2014-2022) indicates the impossibility of making unequivocal statements regarding overall trends in the dynamics of BC prevalence among the female population of the country. Despite the fact that over the past nine years, the overall incidence rate of BC among the female population in the country has increased slightly by 0.2%, from 60.6 (in 2014) to 62.4 (in 2022) per 1000 corresponding population, there is still an increase in the growth rate of the overall BC prevalence in some regions of Ukraine [5-12].

An increase in the prevalence rate of BC among women (over the past nine years, 2014-2022) is observed in Chernihiv region (by 1.09% - from 1.65 to 4.45 per 1000 female population), Zhytomyr region (by 0.73% - from 1.05 to 2.5 per 1000 female population), Lviv region (by 0.64% - from 2.35 to 3.8 per 1000 female population),

Table I. Breast cancer prevalence dynamics, 2014-2022

Names of regions	Years									Increase 2014/2022, %
	2014	2015	2016	2017	2018	2019	2020	2021	2022	
Ukraine	60,6	63,7	63,7	63,8	71,4	65,9	65	56,9	62,4	0,2
Autonomous Republic of Crimea	-	-	-	-	-	-	-	-	-	-
Vinnytsia	57,4	60,1	57,6	66,6	68,7	61,9	63,1	50,8	55,2	-0,24
Volyn	54,6	47,4	46	58	54,3	53,9	53,5	54,1	55,8	0,13
Dnipropetrovsk	64,9	66,3	67,2	66,4	82,9	69,9	68,7	65,4	66,4	0,16
Donetsk	-	-	-	-	-	-	-	-	-	-
Zhytomyr	51,2	56,2	63,1	57,4	68,9	61,9	57,8	53,9	58	0,73
Zakarpattia	48,9	48,2	48,4	49,9	47	51,3	46	42,6	49,1	0,02
Zaporizhzhia	64	67,8	70,6	66,3	73	68,6	71,3	56,9	65,8	0,2
Ivano-Frankivsk	46	44	43,9	45,3	50,4	49,4	47,5	41,7	48,6	0,28
Kyiv	62,7	65,1	73,8	73	79,6	74,4	75,9	66,1	65,6	0,32
Kirovohrad	59	65,1	61,9	70,4	84,1	67,4	67,6	57,5	64	0,55
Luhansk	-	-	-	-	-	-	-	-	-	-
Lviv	54,4	62	61,2	58	70	69,2	63,8	53,5	60,2	0,64
Mykolaiv	68,9	68,2	63,5	68,3	81,2	70,9	67,1	59,4	62	-0,77
Odesa	67,9	75,6	67,6	66,9	64,6	66,2	65,2	60,6	64	-0,43
Poltava	61,9	57,1	61	62	71,8	59,7	64,3	53,3	64,5	-0,73
Rivne	56,2	52,7	61,2	47,8	52,7	53,9	55,1	52,2	57,5	0,14
Sumy	64,4	64,4	67,7	59,4	77	62,8	67,9	54,2	63,9	-0,06
Ternopil	47,4	51,1	49	46,7	55,2	49,7	56,5	41,6	53	0,62
Kharkiv	62	69,4	67,9	68,1	70,8	67,8	63,6	57,8	64,6	0,29
Kherson	66,5	61,1	68	69,1	75,7	66,6	64,5	61,9	62	-0,5
Khmelnytskyi	56	62,9	62	62,2	71,4	63,5	65	54,2	60,8	0,55
Cherkasy	58,5	64,7	61,8	63	70	61,7	58,1	51,5	63,6	0,57
Chernivtsi	49,3	47,8	50,8	51,2	47,9	46,5	44,5	40,7	44,1	-0,58
Chernihiv	50,2	53,5	57,3	56,6	71,4	60,5	60,5	51,1	60	1,09
Kyiv city	80,2	89,2	83,2	85,7	97,6	92,6	91,4	76,7	82,1	0,21
Sevastopol	-	-	-	-	-	-	-	-	-	-

Ternopil region (by 0.62% - from 1.65 to 2.96 per 1000 female population), Cherkasy region (by 0.57% - from 3.1 to 5.08 per 1000 female population), Khmelnytskyi region (by 0.55% - from 3.03 to 4.87 per 1000 female population), Kirovohrad region (by 0.55% - from 3.05 to 3.95 per 1000 female population), Kyiv region (by 0.32% - from 0.85 to 1.2 per 1000 female population), Kharkiv region (by 0.29% - from 3.4 to 3.9 per 1000 female population), Ivano-Frankivsk region (by 0.28% - from 1.0 to 1.45 per 1000 female population), Kyiv city (by 0.21% - from 2.7 to 3.2 per 1000 female population), and Zaporizhzhia region (by 0.2% - from 1.9 to 2.45 per 1000 female population).

A significant decrease in the prevalence rate of BC among the female population is observed in Poltava region (by 2.3 times - from 5.6 to 2.4 per 1000 female population), Chernivtsi region (by 2.1 times - from 1.7 to 0.75 per 1000 female population), Kherson region (almost 6 times - from 2.7 to 0.5 per 1000 female population), and Odessa region (by 2.03 times - from 3.85 to 1.7 per 1000 female population) [5-12].

DISCUSSION

According to the research findings, the prevalence rate of BC in the population of Ukraine remains relatively

stable, with an average annual growth of less than 1% during 2014-2020. In 2020, there was a significant decrease in the prevalence rate by 18.2%, which can be attributed to a decrease in hospital visits due to the COVID-19 pandemic. It has been established that during 2022, due to military actions and emigration of a portion of the female population abroad, there were 26.8 thousand (22.3%) fewer detected cases of malignant neoplasms registered in comparison to 2021. It is important to emphasize that in the practical context of cancer registries in the country, the collection and processing of statistical data are considerably complicated due to military operations, occupation of specific areas, and other related factors. Furthermore, the consequences of the war have also influenced the data refinement process, particularly regarding the collection of deferred data for 2022 [5-13].

Differences in the prevalence and incidence rates of BC among the female population across administrative regions of Ukraine can be attributed to regional socio-cultural and behavioral characteristics, as well as their influence on the behaviors and lifestyles of women and the families in which they are raised. Based on statistical reports of recent years (2014-2022), a conclusion can be drawn for the female population of Ukraine that the highest prevalence of BC is observed in central regions of the country, while the lowest prevalence is observed in western regions [5-12].

According to the updated data from the National Cancer Registry of Ukraine, in 2021, there were 120,055 new cases of malignant neoplasms registered in Ukraine (56,781 in males and 63,274 in females), with 53,009 deaths from malignant neoplasms (29,534 in males and 23,475 in females). The level of neglect of malignant neoplasms recorded in Ukraine in 2022 was 22.4%, which increased by 1.4% compared to 2021. This is associated with limited access to medical services for the population due to the pandemic and active military actions during the armed conflict [1].

CONCLUSIONS

1. BC constitutes a significant proportion of the overall structure of oncological diseases (52.8%) and accounts for a high prevalence (21%) among the female population of Ukraine. In the period from 2014 to 2022, the trend in the incidence of BC in the Ukrainian population remains relatively stable, with an average annual growth of less than 1%. A sharp decline in the incidence rate by 18.2% occurred in 2020, which can be attributed to a reduction in hospital visits. The reduction in BC incidence among women may be associated with the impact of the COVID-19 pandemic and military actions during times of conflict, which led to restricted access to medical services.
2. The most reliable way to address the issue of registering the vital status of cancer patients would be obtaining this data through an electronic healthcare system.

REFERENCES

1. The National Cancer Registry of Ukraine: annual bulletins and other publications of the National Cancer Registry of Ukraine. http://www.ncru.inf.ua/ [date access 19.03.2023]
2. Budget of the Medical Guarantees Program (2022). NHSU. Available from: https://nszu.gov.ua/novini/byudzhetprogrami-medichnih-garantij-2022-na-338-milyarda-bi-684 [date access 19.03.2023]
3. Europe's Beating Cancer Plan: Implementation Roadmap. Health and Food Safety Directorate General. 2021. https://ec.europa.eu/newsroom/sante/newsletter-archives/35593 [date access 19.03.2023]
4. National cancer control strategy until 2030. Draft Resolution of the Cabinet of Ministers of Ukraine dated January 28, 2021. https://moz.gov.ua/article/publicdiscussions-archive/proekt-postanovi-kabinetu-ministriv-ukraini-pro-zatverdzhennja-nacionalnoi-strategiikontrolju-onkologichnih-zahvorjuvan-do-2030-roku [date access 19.03.2023]
5. Bulletin of the national cancer registry of Ukraine. No. 17. http://www.ncru.inf.ua/publications/BULL_17/PDF/BULL_17.pdf [date access 19.03.2023]
6. Bulletin of the national cancer registry of Ukraine. No. 18. http://www.ncru.inf.ua/publications/BULL_18/PDF/BULL_18.pdf [date access 19.03.2023]
7. Bulletin of the national cancer registry of Ukraine. No. 19. http://www.ncru.inf.ua/publications/BULL_19/PDF/Bull_19full.pdf [date access 19.03.2023]
8. Bulletin of the national cancer registry of Ukraine. No. 20. http://www.ncru.inf.ua/publications/BULL_20/index.htm [date access 19.03.2023]
9. Bulletin of the national cancer registry of Ukraine. No. 21. http://www.ncru.inf.ua/publications/BULL_21/PDF/BULL_21.pdf [date access 19.03.2023]

10. Bulletin of the national cancer registry of Ukraine. No. 22. http://www.ncru.inf.ua/publications/BULL_22/PDF/BULL_22.pdf [date access 19.03.2023]
11. Bulletin of the national cancer registry of Ukraine. No. 23. http://www.ncru.inf.ua/publications/BULL_23/PDF/BULL_23.pdf [date access 19.03.2023]
12. Bulletin of the national cancer registry of Ukraine. No. 24. http://www.ncru.inf.ua/publications/BULL_24/PDF/BULL_24.pdf [date access 19.03.2023]
13. The plan for the recovery of the health care system of Ukraine from the consequences of the war for 2022 – 2032. https://moz.gov.ua/uploads/ckeditor/%D0%9D%D0%BE%D0%B2%D0%B8%D0%BD%D0%B8/21-07- 2022-Draft-Ukraine%20HC%20System%20Recovery%20Plan-2022-2032_UKR.pdf [date access 19.03.2023]

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ORIGINAL ARTICLE

MICROCIRCULATORY ALTERATIONS IN STABLE CORONARY ARTERY DISEASE PATIENTS WITH CONCOMITANT COVID-19

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ABSTRACT

The aim: To evaluate the alterations in microcirculation of stable coronary artery disease (SCAD) patients with concomitant COVID-19.

Materials and methods: The cross-sectional study analyzed the data from 80 patients, being subdivided as follows: group 1 (G_1) – SCAD without COVID-19 (n=30); group 2 (G_2) – SCAD with concomitant COVID-19 (n=25); group 3 (G_3) – COVID-19 without SCAD (n=25). The control group included 30 relatively healthy volunteers. The state of microcirculation was assessed by nailfold videocapillaroscopy (NVC) and laser Doppler flowmetry (LDF).

Results: NVC data from G_2 revealed the sings of capillary bed remodeling, along with the most pronounced decrease in capillary (arteriolar part of the loop) blood flow velocity (vs. G_1 and G_3). LDF data from G_2 were evident for the alterations in both endothelium-dependent and -independent mechanisms of microvascular flow regulation. The 72 % of G_2 constituted the cases of microcirculatory hemodynamic «congestion-stasis» (MHCS) type (characterized by the decreased laser Doppler perfusion index and reduced endothelium-dependent microvascular reactivity [MVR]), and the cases of mixed type with reduced MVR. The pooled hyporeactive profile (of both MHCS type and a mixed type with reduced MVR) demonstrated the higher frequency of G_2 patients (40 %), as against 11 % in the pooled alternative hemodynamic group (p<0,001) (included 80 % of cases with preserved MVR).

Conclusions: G_2 profile demonstrated the predomination of patients, possessing a MHCS type or a mixed type with reduced MVR. The pooled microcirculatory hyporeactive profile was presented with G_2 cases to a greater extent, than in the pooled profile with predominantly preserved MVR.

KEY WORDS: SARS-CoV-2 infection, COVID-19, myocardial ischemia, microcirculation

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INTRODUCTION

To date, it has been clearly established, that the coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), mostly affecting a respiratory system, simultaneously induces a multi-organ damage, which, in its turn, is associated with an increased risk of severe complicated course of SARS-CoV-2 infection [1].

While discussing a COVID-19 as a multifaceted systemic disorder, it is worth mentioning that SARS-CoV-2 negatively impacts on the microcirculation, involving the series of underlying pathomechanisms, particularly the endothelial damage, microthrombosis and microvascular occlusion [2, 3]. Of note, the microvascular alterations are considered not only as a pathophysiological aspect within the framework of acute SARS-CoV-2 infection, but also as a factor associated with the increased risk of long-term postinfection sequelae in COVID-19 convalescents [4].

The growing body of evidence suggests that the patients with pre-existing cardiovascular comorbidities are more prone to COVID-19-related complications and subjected to higher associated mortality [5]. In particular, the coronary artery disease is linked to SARS-CoV-2 infection in a manner of mutually aggravation [5-7]. Moreover, the microvascular alterations, including the endothelial dysfunction and damage, are likely to be the factors, significantly contributing to such a dramatic reciprocal deterioration of both conditions` course [8, 9].

At present, the methodology of non-invasive study of peripheral microcirculation, specifically in COVID-19 patients or convalescents, includes the use of nailfold (video) cappilaroscopy (NVC) [10, 11] and the laser-based tech-

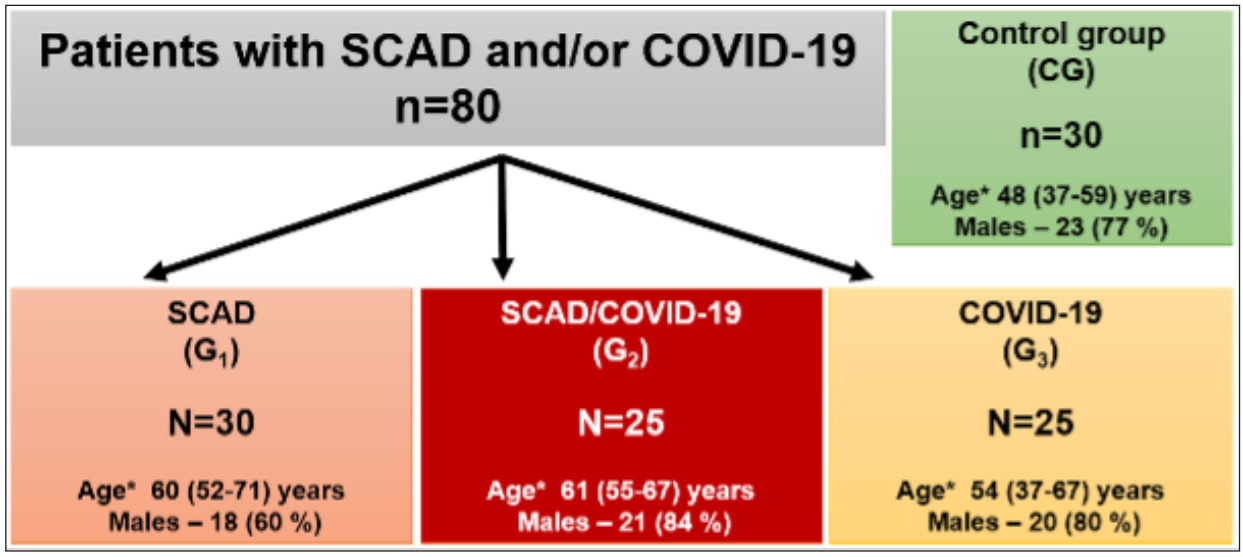
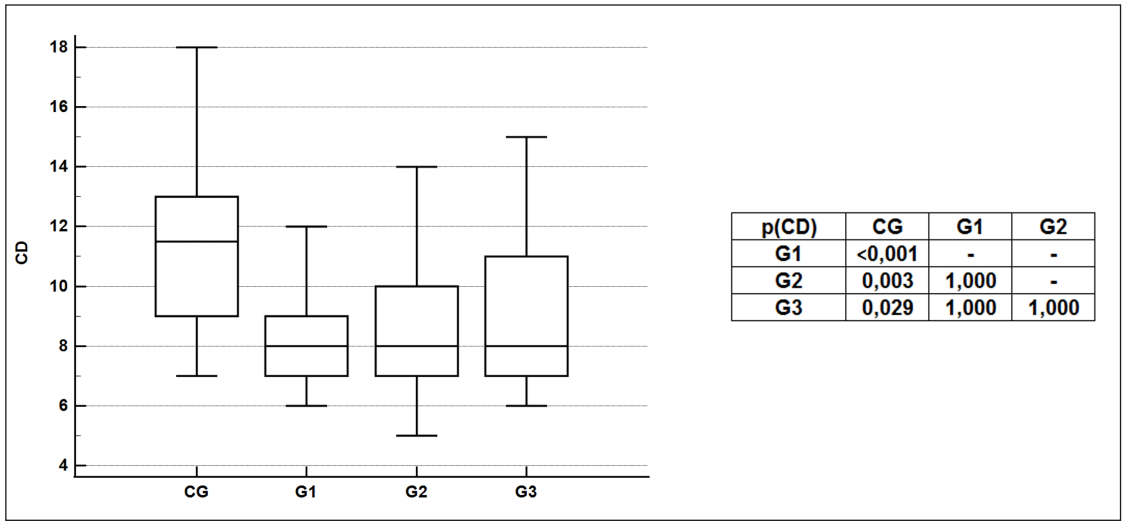
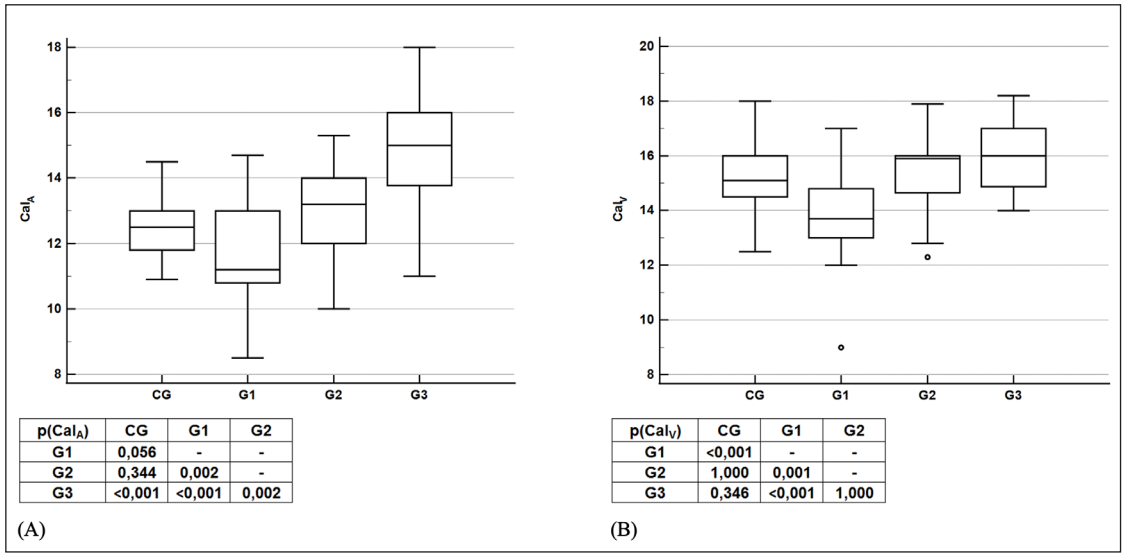


Fig. 1. The present study design. * – Median (Me), interquartile range (IQR).



p(CD)	CG	G1	G2
G1	<0,001	-	-
G2	0,003	1,000	-
G3	0,029	1,000	1,000

Fig. 2. CD (per 1 mm^2) in G_1-G_3 patients and controls (box-and-whiskey plots; the significance of difference (p[CD]) between the studied groups)

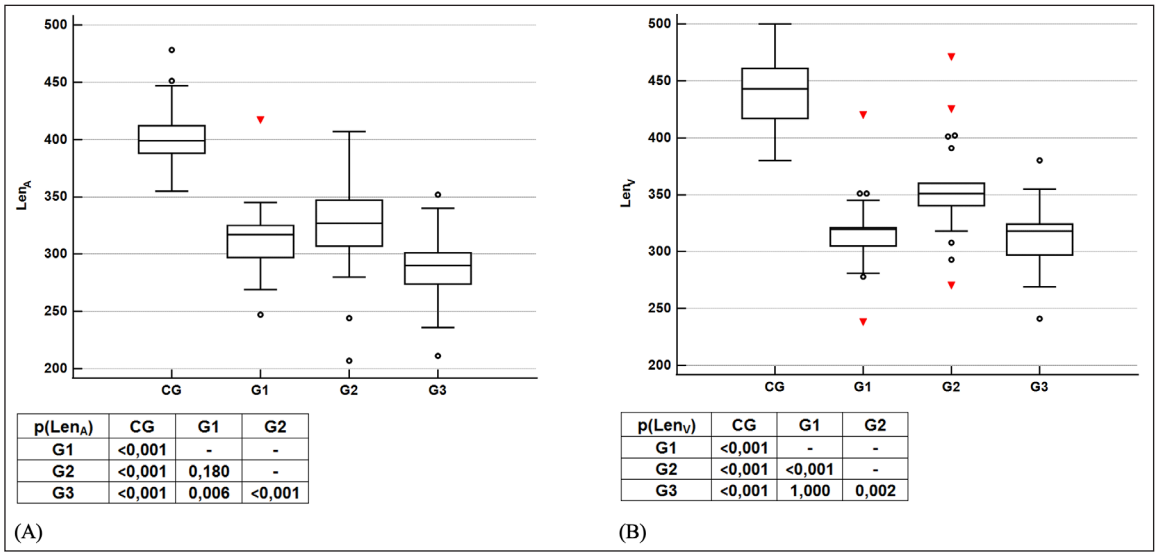


p(CalA)	CG	G1	G2
G1	0,056	-	-
G2	0,344	0,002	-
G3	<0,001	<0,001	0,002

p(CalV)	CG	G1	G2
G1	<0,001	-	-
G2	1,000	0,001	-
G3	0,346	<0,001	1,000

(A) (B)

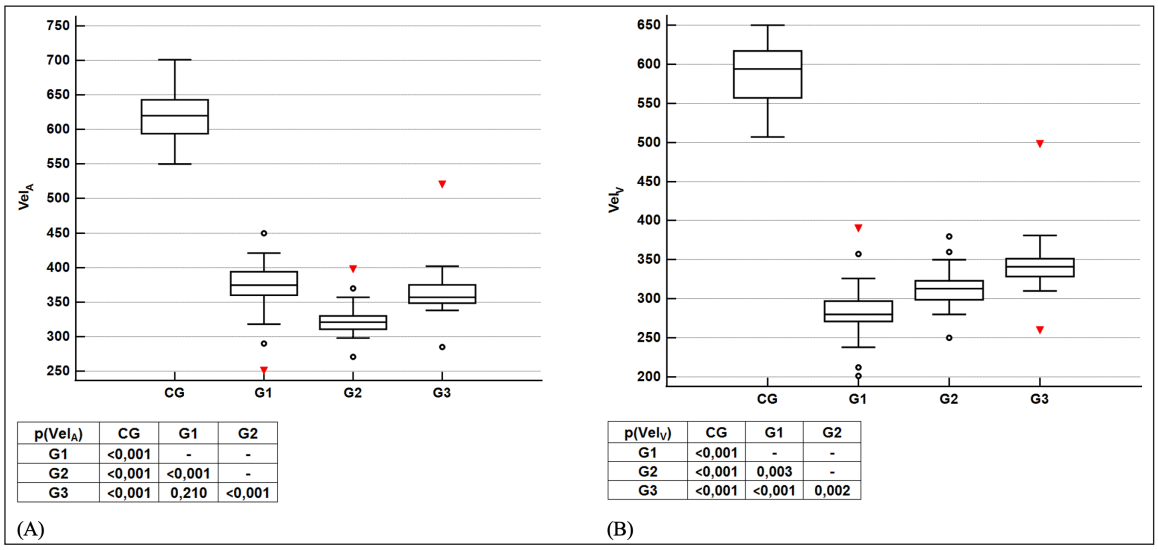
Fig. 3. Cal_A (A) and Cal_V (μm) (B) in G_1-G_3 patients and CG (box-and-whiskey plots; the significance of difference (p[Cal_A] and p[Cal_V], respectively) between the studied groups)



p(Len$_A$)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	0,180	-
G3	<0,001	0,006	<0,001

p(Len$_V$)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	<0,001	-
G3	<0,001	1,000	0,002

Fig. 4. Len$_A$ (A) and Len$_V$ (μm) (B) in G$_1$-G$_3$ patients and CG (box-and-whiskey plots; the significance of difference (p[Len$_A$] and p[Len$_V$], respectively) between the studied groups)



p(Vel$_A$)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	<0,001	-
G3	<0,001	0,210	<0,001

p(Vel$_V$)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	0,003	-
G3	<0,001	<0,001	0,002

Fig. 5. Vel$_A$ (A) and Vel$_V$ (μm/s) (B) in G$_1$-G$_3$ patients and CG (box-and-whiskey plots; the significance of difference (p[Vel$_A$] and p[Vel$_V$], respectively) between the studied groups)

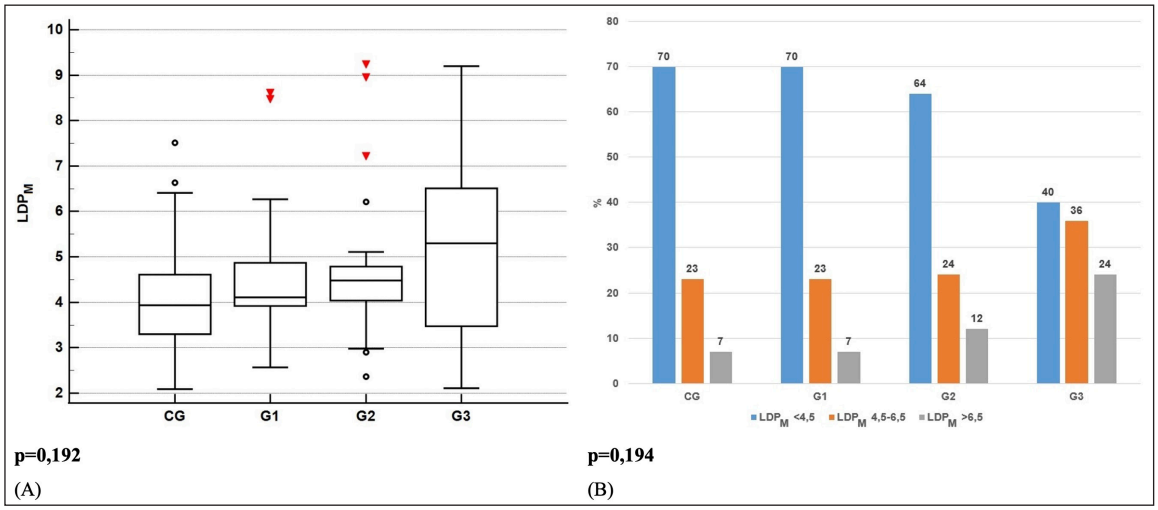
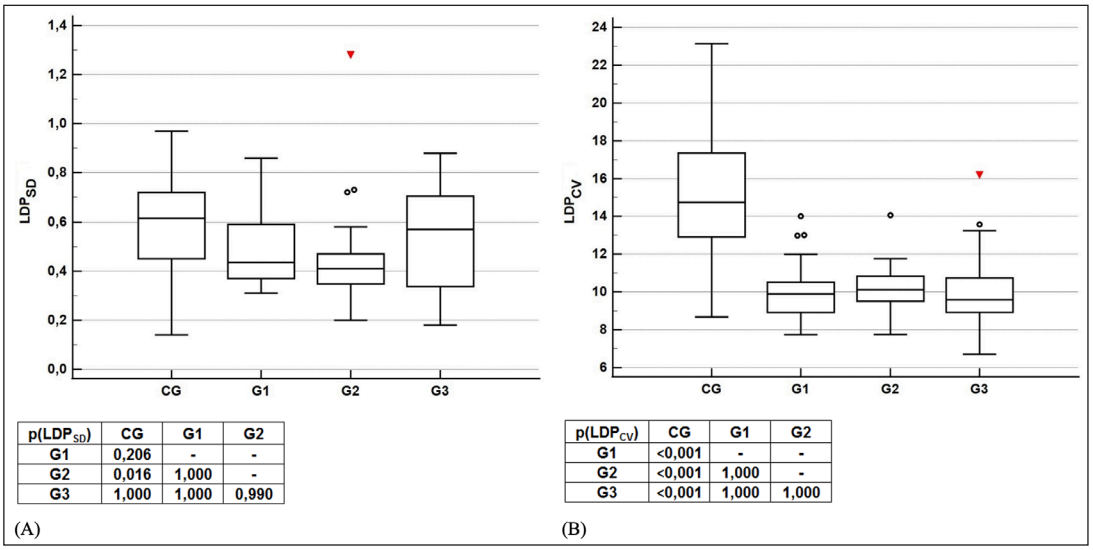


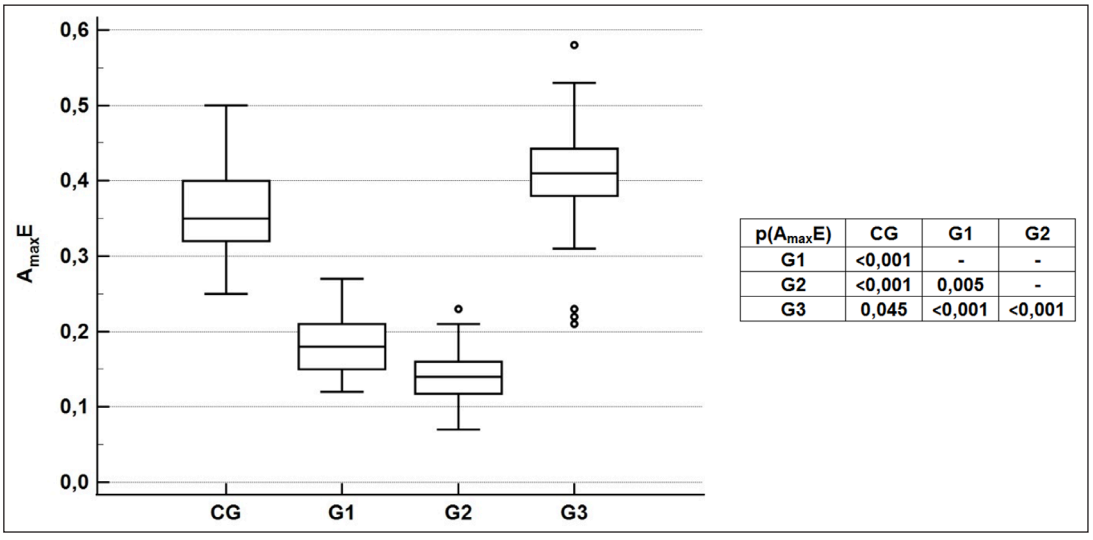
Fig. 6. Baseline LDP$_M$ (a.u.) in G$_1$-G$_3$ patients and controls (A – box-and-whiskey plots; B – the structure of LDP$_M$ patterns (a.u.) in the studied groups).



p(LDP$_{SD}$)	CG	G1	G2
G1	0,206	-	-
G2	0,016	1,000	-
G3	1,000	1,000	0,990

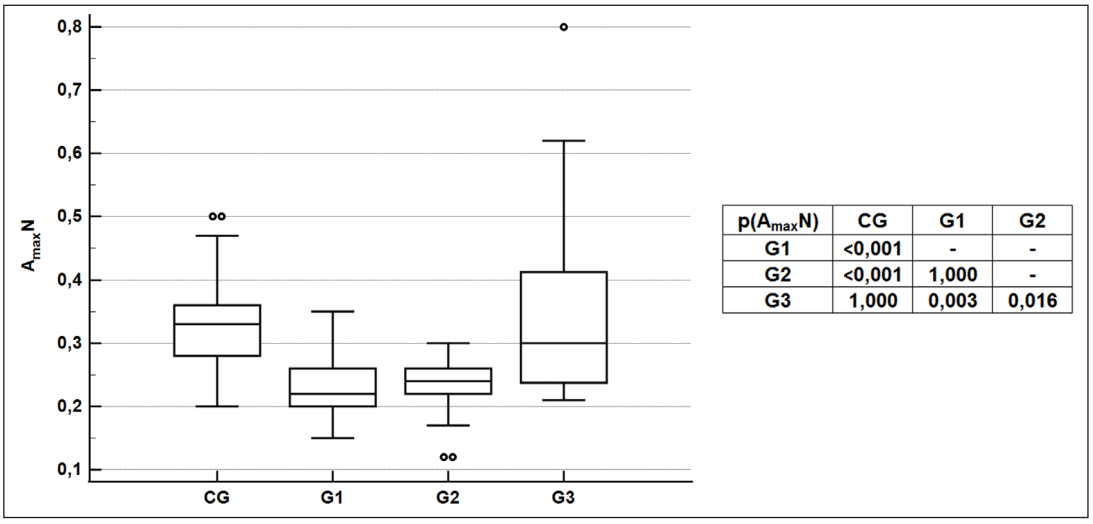
p(LDP$_{CV}$)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	1,000	-
G3	<0,001	1,000	1,000

Fig. 7. Baseline LDP variability in G_1-G_3 patients and controls (A – SD (a.u.); box-and-whiskey plots; the significance of difference (p[LDP_{SD}]) between the studied groups; B – CV (%); box-and-whiskey plots; the significance of difference (p[LDP_{CV}]) between the studied groups).



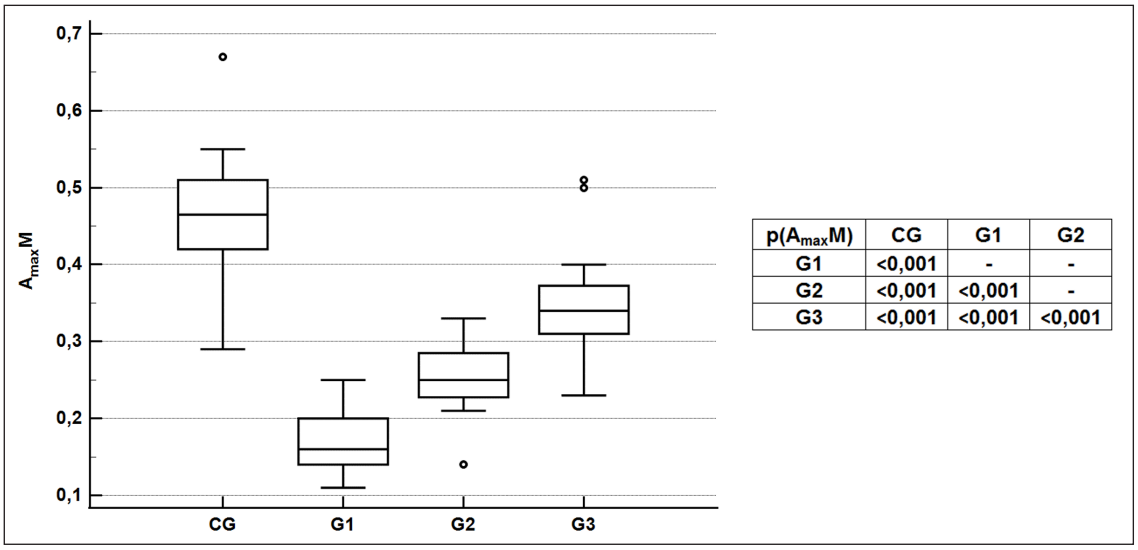
p(A_{max}E)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	0,005	-
G3	0,045	<0,001	<0,001

Fig. 8. A_{max}E (Hz) in G_1-G_3 patients and CG (box-and-whiskey plots; the significance of difference (p[A_{max}E]) between the studied groups)



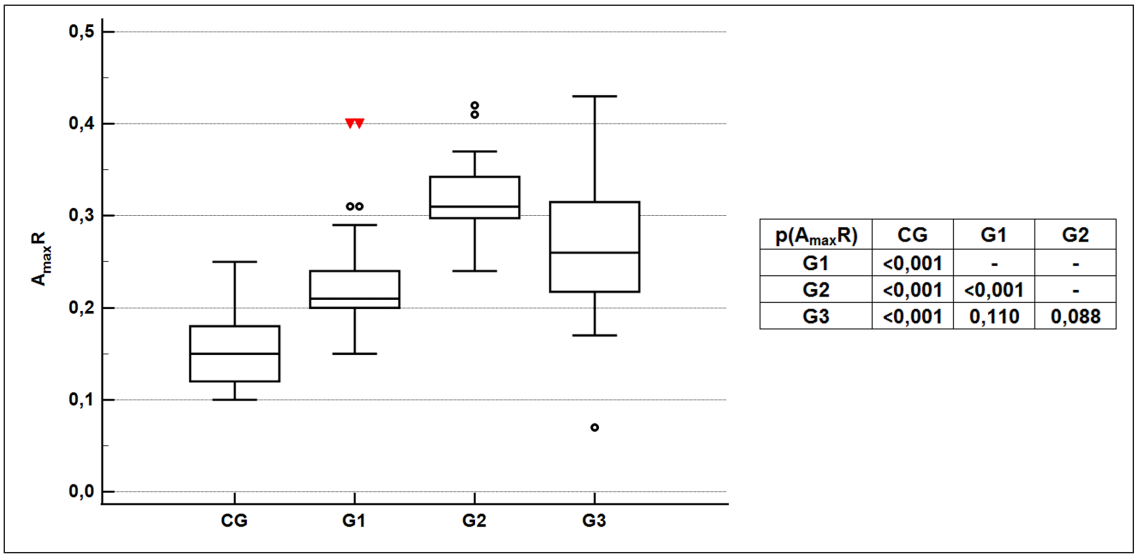
p(A_{max}N)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	1,000	-
G3	1,000	0,003	0,016

Fig. 9. A_{max}N (Hz) in G_1-G_3 patients and CG (box-and-whiskey plots; the significance of difference (p[A_{max}N]) between the studied groups)



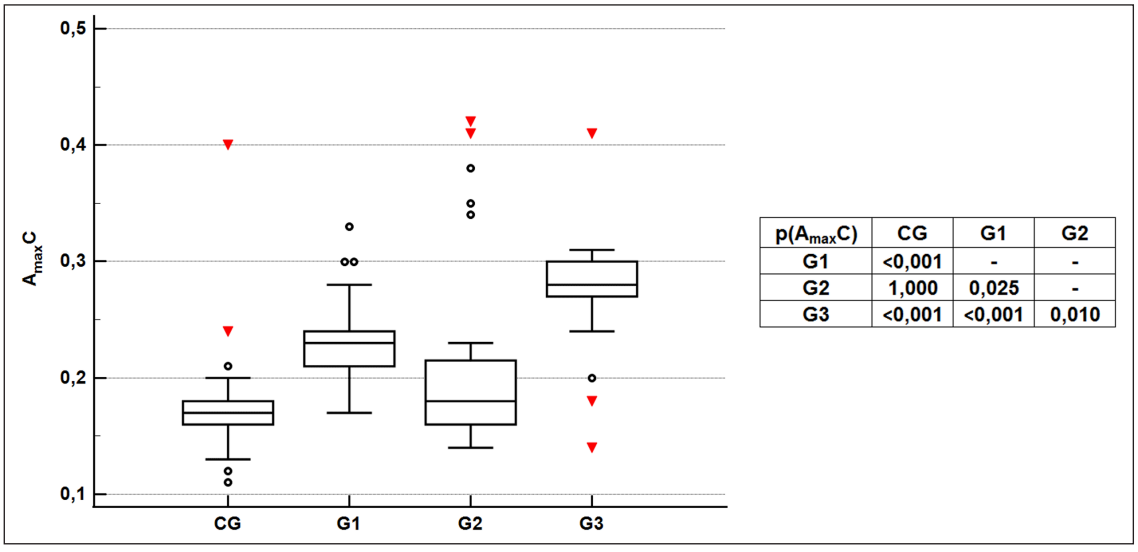
p(A_{max}M)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	<0,001	-
G3	<0,001	<0,001	<0,001

Fig. 10. A_{max}M (Hz) in G_1-G_3 patients and CG (box-and-whiskey plots; the significance of difference (p[A_{max}M]) between the studied groups)



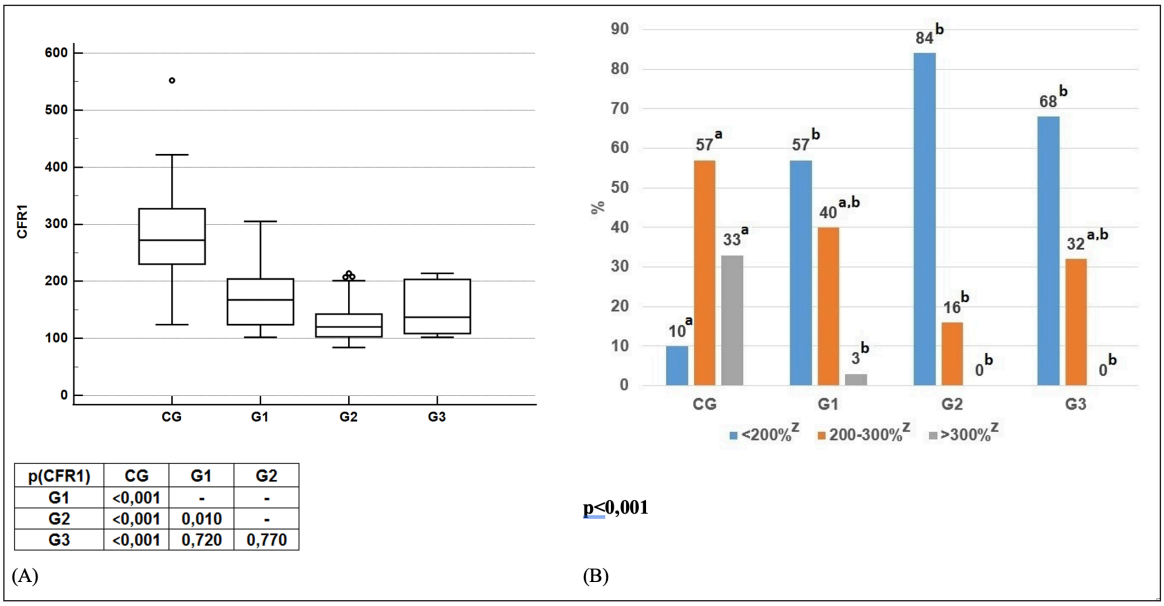
p(A_{max}R)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	<0,001	-
G3	<0,001	0,110	0,088

Fig. 11. A_{max}R (Hz) in G_1-G_3 patients and CG (box-and-whiskey plots; the significance of difference (p[A_{max}R]) between the studied groups)



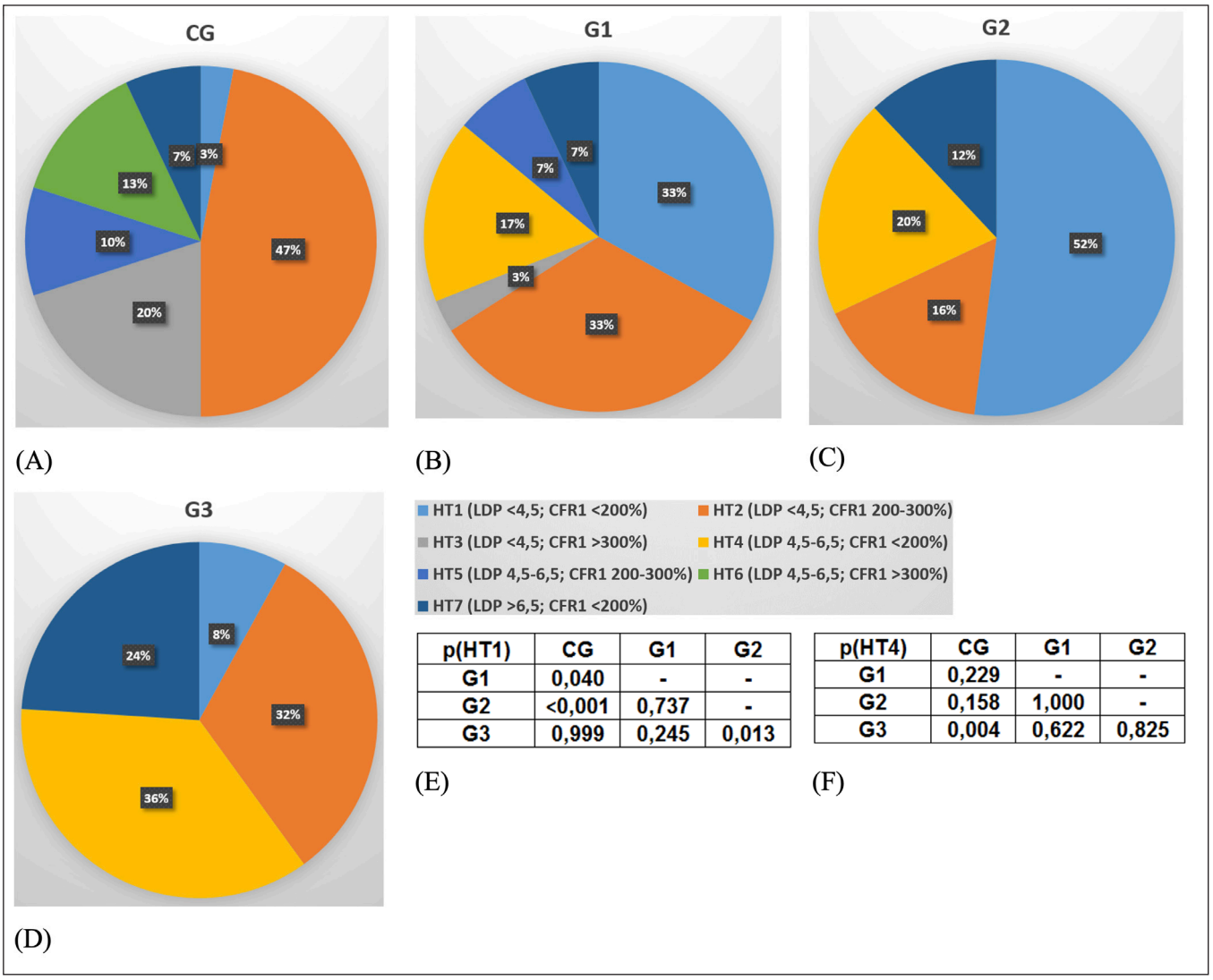
p(A_{max}C)	CG	G1	G2
G1	<0,001	-	-
G2	1,000	0,025	-
G3	<0,001	<0,001	0,010

Fig. 12. A_{max}C (Hz) in G_1-G_3 patients and CG (box-and-whiskey plots; the significance of difference (p[A_{max}C]) between the studied groups)



p(CFR1)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	0,010	-
G3	<0,001	0,720	0,770

Fig. 13. CFR1 (%) in G_1-G_3 patients and controls (A – box-and-whiskey plots and the significance of difference (p[CFR1]) between the studied groups; B – the structure of CFR1 patterns in the studied groups). [z] – Statistically significant difference by z-test. [a, b] – Each subscript letter denotes the subsets of the corresponding studied groups, whose column proportions do not differ significantly from each other at p<0,05.



p(HT1)	CG	G1	G2
G1	0,040	-	-
G2	<0,001	0,737	-
G3	0,999	0,245	0,013

(E)

p(HT4)	CG	G1	G2
G1	0,229	-	-
G2	0,158	1,000	-
G3	0,004	0,622	0,825

(F)

Fig. 14. Hemodynamic types (HTs) of microcirculation in G_1-G_3 patients and controls (A-D: the structure of HTs (%) in CG and G_1-G_3; E – the significance of difference (p[HT1]) between the studied groups by HT1 frequency; F – the significance of difference (p[HT4]) between the studied groups by HT4 frequency)

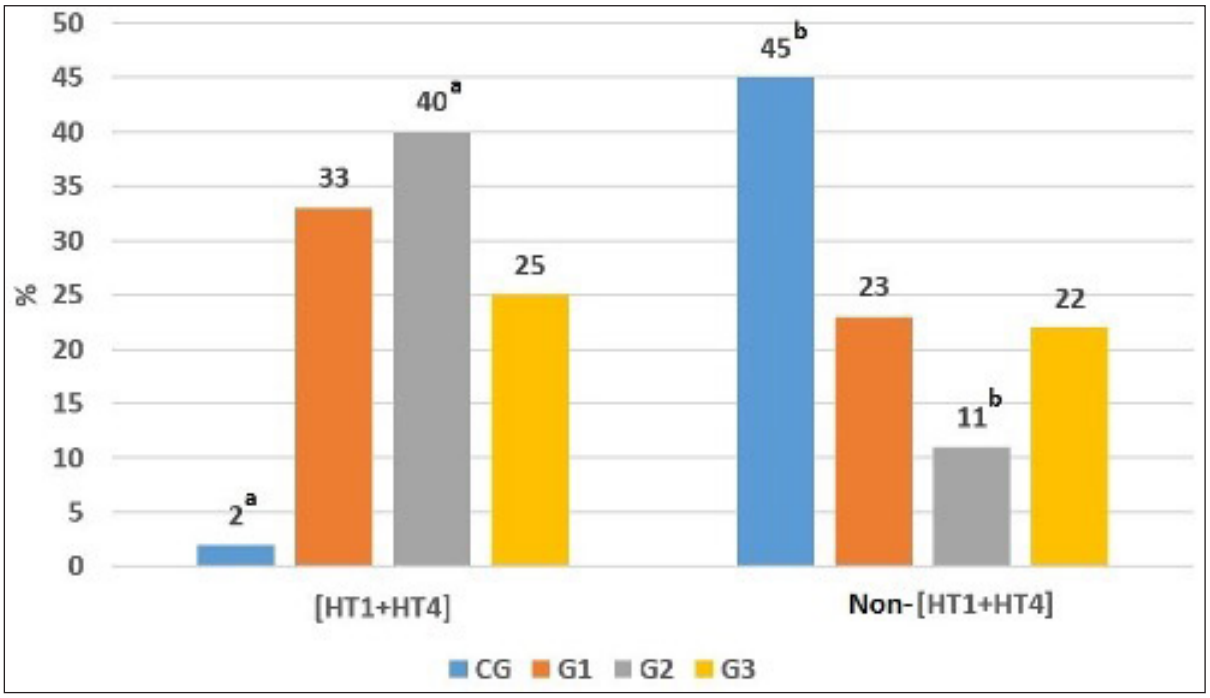
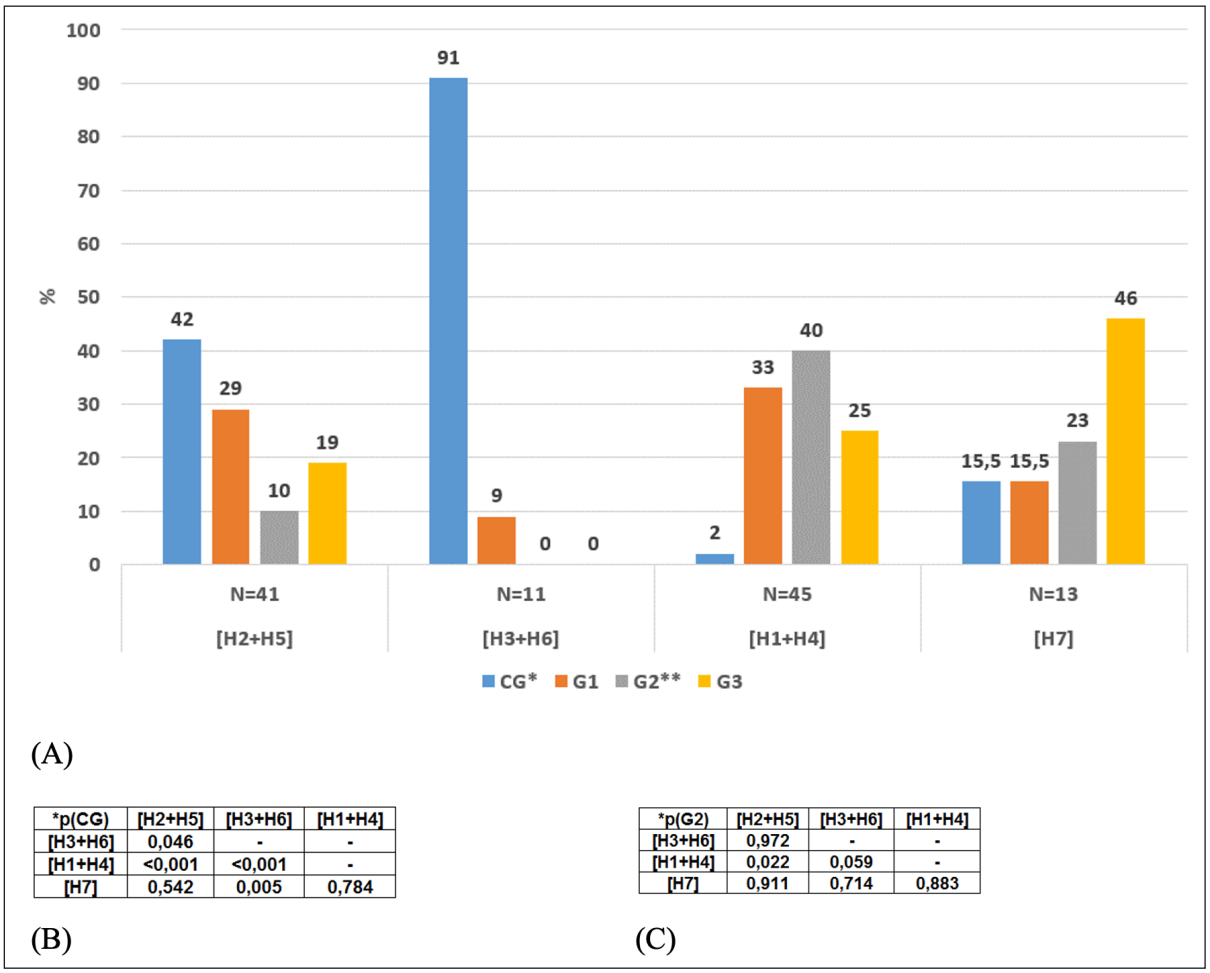


Fig. 15. The clinical status structure (%) of the pooled group [HT1+HT4] (N=45) and the non-[HT1+HT4] group (N=65). [a,b] – Each subscript letter denotes the subsets of the corresponding studied groups, whose column proportions do not differ significantly from each other at p<0,05 (z-test).



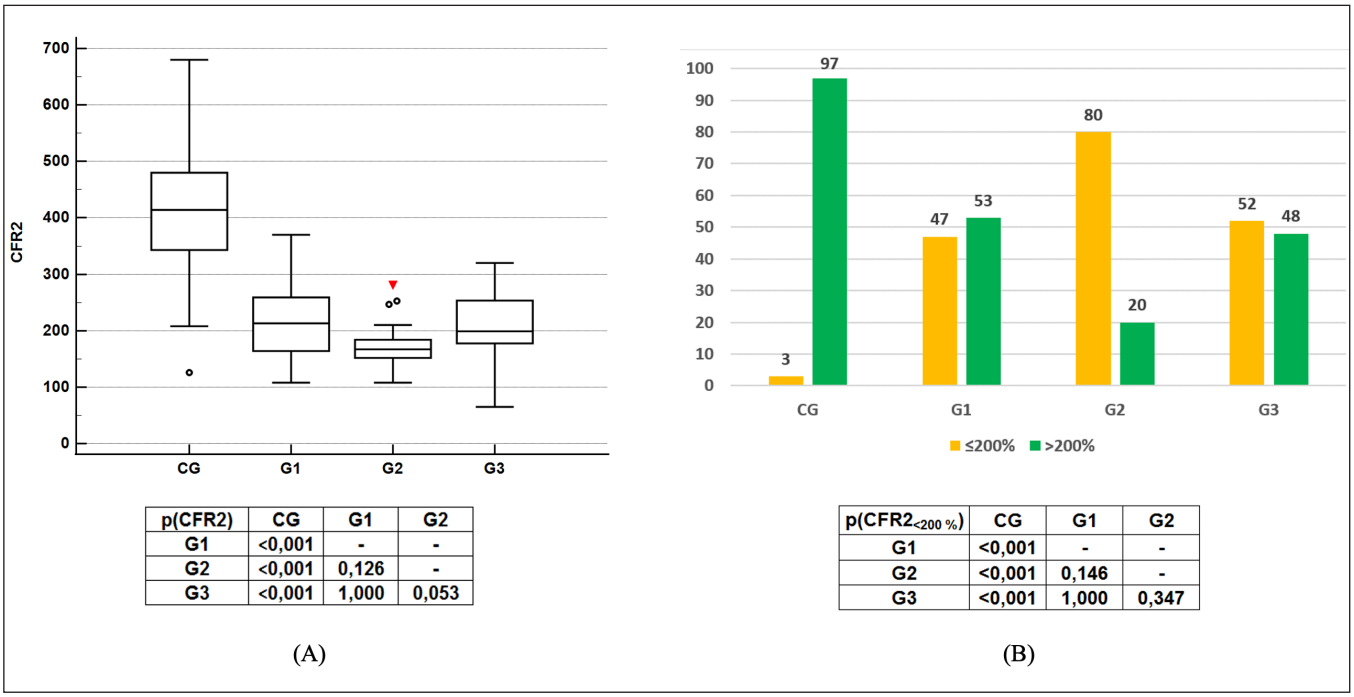
*p(CG)	[H2+H5]	[H3+H6]	[H1+H4]
[H3+H6]	0,046	-	-
[H1+H4]	<0,001	<0,001	-
[H7]	0,542	0,005	0,784

(B)

*p(G2)	[H2+H5]	[H3+H6]	[H1+H4]
[H3+H6]	0,972	-	-
[H1+H4]	0,022	0,059	-
[H7]	0,911	0,714	0,883

(C)

Fig. 16. The clinical status structure (%) of the pooled groups [HT2+HT5], [HT3+HT6], [HT1+HT4], and [H7] (A). The significance of difference between the groups by CG (B) and G2 (C) frequency.



p(CFR2)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	0,126	-
G3	<0,001	1,000	0,053

(A)

p(CFR2$_{<200\,\%}$)	CG	G1	G2
G1	<0,001	-	-
G2	<0,001	0,146	-
G3	<0,001	1,000	0,347

(B)

Fig. 17. CFR2 (%) (A) and the frequency of CFR2$_{<200\,\%}$ (B) in G_1-G_3 patients and controls (box-and-whiskey plots; the significance of difference (p[CFR2] and p[CFR2$_{<200\,\%}$], respectively) between the studied groups)

Parameters	CD	CalA	CalV	LenA	LenV	VelA	VelV
LDP (M)	-0,048	0,116	0,002	-0,115	-0,100	-0,162	-0,120
LDP (SD)	**0,204**	-0,057	-0,004	**0,289**	**0,263**	**0,217**	**0,224**
LDP (CV)	**0,281**	**-0,210**	-0,004	**0,468**	**0,491**	**0,410**	**0,495**
CFR1	**0,562**	**-0,197**	0,005	**0,439**	**0,392**	**0,637**	**0,513**
CFR2	**0,513**	-0,029	0,064	**0,431**	**0,428**	**0,635**	**0,572**
AmaxE	**0,313**	**0,261**	**0,202**	0,053	0,124	**0,479**	**0,588**
AmaxN	0,065	**0,204**	0,109	**0,225**	**0,329**	**0,291**	**0,419**
AmaxM	**0,388**	**0,296**	**0,340**	**0,432**	**0,558**	**0,470**	**0,782**
AmaxR	**-0,226**	**0,227**	0,070	**-0,387**	**-0,359**	**-0,759**	**-0,470**
AmaxC	-0,181	**0,215**	0,075	**-0,434**	**-0,429**	**-0,237**	**-0,269**

Fig. 18. The correlations of LDF and NFC parameters. All the significant correlations are bold (at p<0,05).

niques, particularly laser Doppler flowmetry (LDF) [12, 13]. In addition, there are data on the purposeful assessment of coronary microvascular dysfunction in COVID-19 patients and post-COVID-19 survivors [14-16], being, however, of limited availability to be obtained in routine clinical settings.

At the same time, one should be concerned over the lacking of data regarding the use of non-invasive tests for the assessment of peripheral microvascular flow and morphology, in particular NVC/LDF, in stable coronary artery disease (SCAD) patients with concomitant COVID-19. Therefore, there is an obvious need to extend our knowledge as to the clinical application of such more accessible technologies in the routine management of SCAD patients in the acute phase of SARS-CoV-2 infection, and those recovered from COVID-19.

THE AIM

The aim of the study was to evaluate the alterations in microcirculation of SCAD patients with concomitant COVID-19.

MATERIALS AND METHODS

The present cross-sectional study consecutively enrolled and analyzed the data from 55 patients with SCAD (including those with concomitant COVID-19 [n=25]), and 25 patients with SARS-CoV-2 infection without SCAD, during the period 10 Dec 2019 – 31 Dec 2022. We also enrolled 30 relatively healthy volunteers, being free from previous SARS-CoV-2 infection, and non-vaccinated against COVID-19 prior to the study (Fig. 1). The principal aspects of the study design, particularly the exclusion criteria, and the clinical and certain instrumental characteristics of the enrolled persons have been presented earlier [17].

NVC was performed by the use of a digital biomicroscope, with a dedicated software for image analysis, according to the standardized procedures [18, 19]. Following the application of maple oil, the right index finger (the eponychium) was examined. Other fingers (except the thumbs) bilaterally could be also examined, as required. The following static parameters were assessed: capillary density (CD) per 1 mm^2; the caliber

Table I. The hemodynamic microcirculatory types in the enrolled sample (N=110) (adapted from [23, 24])

HT	LDP_M (a.u.)	Basal MF	CFR1 (%)	MVR	Description (type)	n (%)
HT1	<4,5	↓	<200	↓*	Congestion-stasis (CS)	26 (23,6)
HT2	<4,5	↓	200-300	N	Mixed	36 (32,7)
HT3	<4,5	↓	>300	↑**	Spastic	7 (6,4)
HT4	4,5-6,5	N	<200	↓*	Mixed	19 (17,3)
HT5	4,5-6,5	N	200-300	N	Normal	5 (4,6)
HT6	4,5-6,5	N	>300	↑**	Mixed	4 (3,6)
HT7	>6,5	↑	<200	↓*	Hyperemic	13 (11,8)

Note: MF – microvascular flow; MVR – microvascular reactivity; N – normal; ↓ – reduced; ↑ – increased; * – hyporeactivity; ** – hyperreactivity

(diameter) of the arteriolar and venular parts of the capillary loop (Cal_A and Cal_V, respectively); and the length of the arteriolar and venular parts of the capillary loop (Len_A and Len_V, respectively). In addition, the dynamic parameters were assessed, namely the blood flow (red blood cells (RBC) movement) velocity in the arteriolar and venular parts of the capillary loop (Vel_A and Vel_V, respectively).

LDF, being an optical technique for estimation of microcirculation, based on the Doppler principle [20], has been performed by the use of computerized laser Doppler flowmeter in accordance with the available principles and guidelines [20-24]. The laser probe was applied on the left extensor side forearm skin (in the midline, 4 cm above the basis of styloid processes, perpendicular to the skin surface), known to be lack of arterio-venous (AV) anastomoses, and the LDF signal was recorded for 10 minutes.

At the first step, we measured the parameters characterizing the average basal cutaneous microvascular flow (per patient or control): the mean value of (laser Doppler) perfusion (LDP) index (LDP_M; in arbitrary units [a.u.]); the standard deviation of LDP (LDP_{SD}; a.u); and the coefficient of variation of LDP (LDP_{CV}; %), calculated as a ratio (LDP_M/LDP_{SD}) x 100 %.

At the second step, we performed the wavelet analysis of the basal LDF signal and measured the (maximal) amplitude of blood flow oscillations of different frequency bands, reflecting the series of mechanisms related to the microcirculatory blood flow regulation, namely the following: the endothelial oscillations ($A_{max}E$) (0,005-0,021 Hz), representing the endothelium activity in terms of both nitric oxide (II) (NO)-dependent and -independent ways of vascular tone regulation; the neurogenic oscillations ($A_{max}N$) (0,021-0,052 Hz), reflecting the impact of neural (sympathetic) innervation on cutaneous blood flow; the myogenic oscillations ($A_{max}M$) (0,052-0,145 Hz), corresponding to (precapillary) vascular smooth muscles activity; the respiratory ($A_{max}R$) (0,145-0,6 Hz) and cardiac (pulse) ($A_{max}C$) (0,6-2 Hz) oscillations, representing, respectively, the influence of macrohemodynamics (heart rate, pulse wave) and movement of the thorax («respiratory pump») on the microvascular blood flow. The $A_{max}E$, $A_{max}N$ and $A_{max}M$ characterize the active mechanisms of microcirculatory flow modulation, whereas $A_{max}R$ and $A_{max}C$ are considered as passive ones [22-24].

After the measurement of basal microvascular flow, the occlusion functional test was performed. A pressure cuff was placed on the upper left, with the following steps of the test: the basal flow recording (for 1 minute); then the pneumatic cuff rapid inflation up to 200 mm Hg (or 50 mm Hg higher than the value of systolic blood pressure indicated by the participant) and holding for 3 minutes; and, finally, the cuff rapid deflation with continuous blood flow recording for the next 6 minutes [20, 23]. After the cuff release, one can observe a short period of the rise of perfusion, reflecting the maximum filling of microcirculatory bed with blood, referred to as «post-occlusive reactive hyperemia» (PORH). PORH, in general, characterizes the whole microcirculatory blood filling capacity, being also an accepted parameter of the endothelium function, namely the endothelium-dependent mechanisms of microvascular relaxation [23, 25]. According to the occlusion test results, we measured the capillary flow reserve (CFR1) as a ratio of the maximal flow (during the PORH period) to the basal flow (in %). The normal CFR1 was considered to be >200 % [23, 24].

The pharmacological provocative test (1 % nitroglycerin iontophoresis protocol) was performed 15 minutes after the occlusion test according to previously described principles [23, 26], with the following steps: the basal flow recording (for 1 minute); then the flow recording during the iontophoresis for 3 minutes; and, finally, the continuous blood flow recording after the stop of iontophoresis for the next 6 minutes. The nitroglycerin iontophoresis test is purposed to assess the endothelium-independent microvascular relaxation, induced by the direct effect of exogenous NO upon the

capillary smooth myocytes [23]. According to the pharmacological provocative test results, we measured the capillary flow reserve (CFR2) as a ratio of the maximal flow (on the top of nitroglycerin iontophoresis) to the basal flow (in %). The normal CFR2 was conventionally considered to be >200 %.

According to the proposed LDP_M grades (<4,5; 4,5-6,5; and ≥6,5 a.u.; LDPM <4,5 a.u. referred to as «reduced flow») [24], and considering the proposed CFR1 patterns (<200 %; 200-300 %; and >300 % [$CFR1_{<200\%}$, $CFR1_{200-300\%}$ and $CFR1_{>300\%}$, respectively]) [23, 24], the 7 microcirculatory hemodynamic types (HTs) were identified and summarized in Table I.

We used the certain statistical software programs for the data analysis, namely Statistica v. 14.0.0.15 (TIBCO Software Inc., USA), IBM SPSS Statistics v. 27.0 (Armonk, NY: IBM Corp., USA), MedCalc v. 22.001 (MedCalc Software Ltd., Belgium), MedStat v. 5.0 and EZR v. 1.61. Quantitative variables were presented as Me (IQR), and qualitative ones – as absolute and relative (%) frequency (with 95 % confidence interval (CI), as required). To compare the quantitative variables, we used Kruskal-Wallis H test with the following *post hoc* Mann-Whitney U-test (considering the Bonferroni correction). To compare the qualitative variables, we used the χ^2 test with the following z-test, as required, or with *post hoc* Marascuilo-Liakh-Gurianov procedure, and Fisher`s exact test (for «2x2» tables). The relationship between the quantitative variables was determined by the use of Spearman`s rank coefficient of correlation (ρ). A 2-tailed p<0,05 was considered statistically significant (considering the Bonferroni correction) (Table I).

RESULTS

The description of participants` profiles and comparison of clinical characteristics between the studied groups have been presented earlier [17].

The results of NFC were indicative for the capillary rarefaction in G_1-G_3, as compared to controls (Fig. 2).

The Cal_A tended to be lower in G_1 (vs. CG), and was the highest in G_3 (vs. CG, G_1 and G_2). Besides, G_1-G_2-G_3 demonstrated a trend towards the increase in Cal_A (Fig. 3A). In addition, the Cal_V was lower in G_1 (vs. CG), being, however, comparable between CG, G_2 and G_3 (Fig. 3B).

All three groups of patients demonstrated the decrease of Len_A and Len_V (vs. CG) (Fig. 4), with the lowest Len_A value observed in G_3 (Fig. 4A).

Moreover, G_1-G_3 demonstrated the drop of Vel_A and Vel_V, in contrast to controls (Fig. 5), with the lowest Vel_A value observed in G_2 (Fig. 5A) and Vel_V – in G_1 patients (Fig. 5B). Finally, G_1-G_2-G_3 demonstrated a trend towards the increase in Vel_V (Fig. 5B).

The studied groups were comparable in terms of LDP_M, as well as regarding the frequency of LDP_M patterns (Fig. 6). However, G_3, in contrast to CG and G_1-G_2, was characterized by numerically, bot non-significantly lower frequency of LDP_M <4,5 a.u. pattern, and higher of LDP_M >6,5 a.u. category, being more «harmonized» by the presence of all three LDP_M patterns (Fig. 6). Moreover, the LDP variability was reduced in all the groups of patients, as compared to controls (in G_1-G_3 – by LDP_{CV}, and G_2 – by LDP_{SD} also) (Fig. 7).

The $A_{max}E$ was reduced in G_1 and G_2, in comparison with controls, with the lowest value observed in G_2. At the same time, we did not observe a decrease of $A_{max}E$ in G_3, which was even slightly higher than that in CG (Fig. 8). In addition, G_1 and G_2 demonstrated a drop in $A_{max}N$ (vs. CG and G_3), which was comparable between controls and «isolated» COVID-19 patients (G_3) (Fig. 9). Patients from G_1-G_3 presented with a decrease of $A_{max}M$ (vs. CG), with the lowest value registered in G_1 (Fig. 10). We detected a rise of $A_{max}R$ in G_1-G_3 (vs. CG), which tended to be the most pronounced in G_2 (Fig. 11). Finally, despite the increase of $A_{max}C$ in G_1 and G_3 (vs. CG), G_2 did not present such a tendency (Fig. 12).

The results of the occlusion test were evident for the decrease of CFR1 in all three groups of patients, as compared to CG (Fig. 13A). The $CFR1_{200-300\%}$ pattern was the most prevalent among controls, being more frequent in comparison to G_2, where it constituted the minority of cases (57 % vs. 16 %, respectively; p=0,035) (Fig. 13B). On the contrary, the frequency $CFR1_{<200\%}$ pattern was higher in all three groups of patients, as opposed to CG, where it constituted the minority of cases (10 % vs. 57 % in G_1 (p=0,003); 84 % in G_2 (p<0,001); and 68 % in G_3 [p<0,001]). In addition, the $CFR1_{<200\%}$ pattern was the most prevalent (numerically, but non-significantly) in G_2, in comparison to G_1 and G_3 (Fig. 13B). At last, the $CFR1_{>300\%}$ pattern constituted one-third of the controls (33 % [95 **%** CI 17-52 %]), being significantly higher vs. G_1 (3 % [95 % CI 0-13 %]; p=0,040), G_2 (0 [95 % CI 0-7 %]; p=0,010) and G_3 (0 [95 % CI 0-7 %]; p=0,010) (Fig. 13B).

According to the HTs distribution in the studied groups (Fig. 14), CG was characterized by the prevalence of HT2 (mixed type with LDP_M <4,5 a.u. and preserved endothelium-dependent microcirculatory reactivity) and HT3 (spastic type) (67 % in total). In turn, the half of patients with «isolated» SCAD presented with a pattern of LDP_M ≤6,5 a.u. and impaired microvascular reactivity (including CS-type (HT1) and mixed HT4), and one-third – with HT2. Moreover, HT1 and HT4 altogether prevailed in G_2 and constituted 72 % of the cases. At last, patients with «isolated» COVID-19 (G_3) presented with 3 major HTs, namely H2, H4 and HT7 (the hyperemic one) (Fig. 14).

The studied groups differed significantly in terms of the frequency of HT1 and HT4 cases. In particular, HT1 was more prevalent in G_1 (33 %) and G_2 (52 %), as compared to CG (3 %; p=0,040 and p<0,001, respectively). And the frequency of HT4 was higher in G_3 (36 % [95 % CI 18-56 %]), in contrast to CG (0 [95 % CI 0-6 %]; p=0,004) (Fig. 14).

Importantly, the group of patients with the pooled pattern [HT1+HT4], being characterized, as previously mentioned, by LDP ≤6,5 a.u. and impaired microvascular reactivity ($CFR1_{<200\%}$), demonstrated the higher frequency of SCAD and COVID-19 constellation (40 %), as against 11 % in the pooled non-[HT1+HT4] group (p<0,001), including, predominantly, the cases of LDP ≤6,5 a.u. with preserved microvascular reactivity ($CFR1_{200\text{-}300\ \%}$ and $CFR1_{>300\ \%}$) (52 of 65 [80 %]). Of note, the controls constituted only 2 % in the pooled group [HT1+HT4] (vs. 45 % in non-[HT1+HT4] group [p<0,001]) (Fig. 15).

Furthermore, while pooling H2 and H5 (based on the presence of normal microvascular reactivity [$CFR1_{200\text{-}300\ \%}$]), and combining H3 and H6 (based on LDP ≤6,5 a.u. and microvascular «hyperreactivity» [$CFR1_{>300\ \%}$]), as well as considering HT7 as a separate (hyperemic) type, the frequency of G_2 was higher in the pooled [H1+H4] group vs. the pooled [H2+H5] pattern, and tended to be higher vs. H7 (Fig. 16). In addition, the pooled group [H3+H6] was represented almost entirely by the controls (10 of 11 cases).

The results of the pharmacologic provocation test (nitroglycerin iontophoresis) demonstrated the decrease of CFR2 in G_1-G_3, as opposed to CG (Fig. 17A). Furthermore, G_2 was characterized by the predominance of $CFR2_{<200\ \%}$ cases, which were more frequent as opposed to CG (significantly), G_1 and G_3 (numerically, but non-significantly) (Fig. 17B).

The NFC data, characterizing the capillary remodeling and blood velocity (in arterial and venous parts of the capillary loop), in general, correlated with microvascular flow parameters, obtained by means of LDF (Fig. 18). In particular, the moderate (or close to moderate) positive correlations were observed between CD and CFR1/CFR2; Len_A and LDP_{CV}; Len_V and $LDP_{CV}/A_{max}M$; Vel_A and $CFR1/CFR2/A_{max}E/A_{max}M$; Vel_V and $LDP_{CV}/CFR1/CFR2/A_{max}E$; and negative – between Vel_V and $A_{max}R$ (Fig. 18). In addition, we identified a strong positive correlation of Vel_V with $A_{max}M$; and negative – between Vel_A and $A_{max}R$ (Fig. 18).

DISCUSSION

Currently available data have given us a new set of insights on the impact of SARS-CoV-2 on the structural and functional aspects of microcirculation [10-13], raising further questions regarding the alterations in the active and passive mechanisms of microvascular blood flow regulation, and their comprehensive evaluation in the management of COVID-19 patients, including those with SCAD. These issues could be, at least partly, bypassed by the use of laser-based technologies, particularly LDF, for non-invasive assessment of microcirculatory perfusion, bringing the valuable data in addition to NVC [20-24].

The presently obtained NVC results were evident for the changes in capillary bed, namely its remodeling (the capillary rarefication, along with dilation, narrowing or shortening of the capillary loops` parts) and functional alterations (the drop in blood flow in both loop compartments), occurred universally across the entire spectrum of the enrolled patients [2, 11, 12, 18, 19, 27, 28]. In particular, patients with «isolated» COVID-19 presented with the most advanced dilation and shortening of the arteriolar part of the capillary loop, along with the least slowing of the venular flow, corresponding with currently available data regarding the impact of SARS-CoV-2 infection upon the capillaries [2, 11, 12, 27, 28]. In contrast, «isolated» SCAD patients demonstrated the narrowest arteriolar part and the lowest Vel_V among the enrolled subjects. At last, the slowest RBC motion in the arteriolar part of the capillary loop was inherent to SCAD patients with concomitant COVID-19.

Despite the fact that presently studied groups of controls and patients were comparable by the average perfusion index value, we observed the decrease in LDP variability in G_1-G_3, suggesting the deterioration of the dynamic component of microvascular flow regulation in both SCAD and COVID-19, as well as their constellation [22-24].

The wavelet analysis revealed a decrease of $A_{max}E$ in both G_1 and G_2, indicating not only the microvascular endothelium to be functionally compromised in both non-infected and infected SCAD patients, but also assuming the SARS-CoV-2 infection to be superimposed on the preexisting endothelial dysfunction, that would probably provide a basis for its further aggravation in SCAD patients with concomitant COVID-19. At the same time, patients with «isolated» COVID-19 did not demonstrate a depressed $A_{max}E$ value, as compared to controls and SCAD groups, suggesting the more advanced «plasticity» of endothelial barrier function regulation and its higher compensatory ability to adapt itself to the homeostasis disruption in the case of lesser comorbidity burdened COVID-19 patients [3, 8, 9].

A drop in $A_{max}N$ and $A_{max}M$, being detected in both G_1 and G_2, and considering the registration skin site lacking of AV-anastomoses, reflects the rise of sympathetic ac-

tivity, and microvascular resistance (the increase in precapillary smooth muscles tone), with the consequent decrease in the nutritive blood flow. In turn, the increase of $A_{max}R$ in G_1-G_3 could be the sign of venular outflow impairment and, therefore, microcirculatory congestion, tended to be the most pronounced in SCAD patients with concomitant SARS-CoV-2 infection. Moreover, the sympathetic overactivity, along with presumably decreased arterial wall compliance, could underlie the rise in $A_{max}C$ in SCAD patients [22-24]. However, patients with SCAD and concomitant COVID-19 did not present the increase in $A_{max}C$, as compared to controls, that could be, at least partly, related to the most pronounced left ventricular (LV) contractility decline in G_2, in contrast to G_1 and G_3 (see [17]). Finally, as of G_3, numerically (but non-significantly) more prevalent LDP >6,5 a.u. pattern, along with comparable $A_{max}N$, the least decreased $A_{max}M$ and the increased $A_{max}C$ (all three parameters vs. CG), indicate the increased perfusion due to the lower (as compared to SCAD) precapillary resistance [22-24], being presently observed in «isolated» SARS-CoV-2 infection, and probably linked to the COVID-19-related hyperproduction of proinflammatory cytokines [29].

Facing the evidence on the multifaceted nature of microcirculatory alterations [20-24], and accounting for the presently obtained data, the patients with SCAD, COVID-19 and their constellation are supposed to demonstrate the various patterns of microvascular flow disturbances, being characterized by the presence of «spastic», «congestive» and «hyperemic» properties. However, a more comprehensive approach to the evaluation of microvascular flow disturbances requires the series of functional tests to be additionally performed [20, 23, 24].

The presently obtained results of the vascular occlusion test and pharmacologic provocation test (nitroglycerin iontophoresis) demonstrated the decrease of CFR1 and CFR2 in G_1-G_3 (vs. CG), suggesting both endothelium-dependent and -independent mechanisms of microcirculatory reactivity to be universally affected in all the studied conditions [3, 8, 9, 23, 24, 30].

The combined analysis of both LDP and CFR1 patterns revealed the predomination of HT2 (mixed type reduced perfusion and preserved microcirculatory reactivity) and HT3 (spastic type) among controls, reflecting, at least partly, the known fact regarding the vasculature to be normally in a relatively constricted state [21].

At the same time, the **«**isolated**»** COVID-19 group was characterized by the presence of HTs with the wide spectrum of properties, being likely related to the multifaceted pathophysiology of SARS-CoV-2 infection [1, 4, 29, 30]. In particular, interleukin (IL)-6 is known to promote a vascular remodeling via the increased transforming growth factor-β_1-mediated matrix metalloproteinases (MMPs) (2 and 3 types) signaling. In turn, the activation of MMPs contributes to the disruption in endothelial vasodilatory function, which is tightly linked to the stability of endothelial glycocalyx. The pro-inflammatory and pro-oxidative conditions, being clearly evident in COVID-19, are associated with the endothelial glycocalyx structural alterations, and its damage by pro-inflammatory cytokines (such as IL-1 and IL-6) leads to the increased vascular permeability with the consequent interstitial fluid shift and generalized edema [31, 32].

Finally, the SCAD patients with concomitant COVID-19 presented with the predomination of pooled «congestion-like**»** [HT1+HT4] pattern, being more frequent than in **«**isolated**»** SCAD group. In addition, the combined SCAD/COVID-19 cases occurred more often in the pooled [HT1+HT4] group, as compared to other HTs, namely the group with pooled [HT2+HT5] pattern. These data prompt us to make an assumption that the shift towards congestive or **«**congestive-like**»** microvascular alterations in SCAD patients with concomitant SARS-CoV-2 infection is supposed to be the result of a dramatic additive effect of COVID-19-related pathomechanisms of vascular remodeling *per se*, along with the superimposition of coronavirus infection on the preexisting SCAD-associated endothelial dysfunction, and the probable myocardial damage leading to a more advanced decrease in LV contractility, being also demonstrated in our previous work [17].

Generally, the deterioration of the capillary bed structural and functional properties, detected by NVC, correlated with the alterations in the active mechanisms of microvascular flow regulation, and were associated with the changes in the passive ones. At the same time, the combined analysis of both NVC and LDF data allows us to provide an averaged integral evaluation of the «portraits» of patients with different studied conditions.

In particular, the abovementioned changes in the capillary bed and the LDF signal properties are focused on the shift towards «hyperemic» microcirculatory alterations, being specifically attributed to the «isolated» COVID-19 averaged phenotype.

At the same time, the «isolated» SCAD group represented a phenotype of the «increased arterial resistance», being reflected, *inter alia*, by the narrowing of the arteriolar part of capillary loops. Importantly, such a phenotype included the cases of both reduced and preserved microvascular reactivity. Here, it worth be considered the strong correlation of the reduced myogenic flow oscillations, being the most advanced in «isolated» SCAD patients, and the drop of venular blood flow, suggesting indirectly the reduce of arteri-

olar capillary flow related to the increased precapillary resistance. We surmise also that the reversibility of the observed microcirculatory alterations in SCAD patients seems to depend on the baseline structural and functional properties of the arterial vascular bed, namely the state of endothelium, known to be affected in the setting of atherosclerosis, hypertension, diabetes mellitus etc. [33].

Finally, the potential aggravation of the preexisted endothelial dysfunction in SCAD patients under the impact of SARS-CoV-2 infection seems to contribute to a more frequent and more pronounced microcirculatory congestion, as compared to that in patients with both «isolated» conditions, being evident also by the slowest RBC movement in the arteriolar part of the capillary loops. It should be emphasized the strong correlation of Vel_A with the amplitude of respiratory oscillations, tended to be the highest in SCAD patients with concomitant SARS-CoV-2 infection, which was an additional argument for a shift towards the more advanced congestive microcirculatory alterations in the settings of such an associated pathology. Furthermore, the LV systolic function impairment, observed previously in G_2 [17], due to probable COVID-19-related myocardial damage, could enhance the severity of microcirculatory congestion in an additive manner.

The present study is subjected to several limitations, including its cross-sectional design, modest sample size, and the enrollment of unvaccinated patients and controls. Moreover, the limitations of NVC and LDF should be also considered. In particular, NVC is not the examination of choice for the evaluation of the blood flow, thus requiring to be complemented with other dedicated methods for better peripheral perfusion measurements [10]. Furthermore, the limitations of LDF technique are related to the standardization issues and the necessity of the control group enrollment [20-24].

Because of the partial overlapping between the studied groups in terms of different HTs, further research is highly necessary to provide an advanced phenotyping of such a specific pattern of SCAD patients with concomitant COVID-19. This issue could be, at least partly, resolved by the study of microcirculatory data relationships with the broad spectrum of patients` characteristics, including the parameters of central hemodynamics, and considering the applied pharmacotherapy, at baseline and follow-up. Such an approach to the data analysis is justified considering the purpose to improve the management of SCAD patients, suffering from SARS-CoV-2 infection, particularly regarding the better risk stratification for COVID-19-related complications (including the thromboembolic events) and post-COVID sequelae, with the following personalization of treatment and preventive strategies.

CONCLUSIONS

SCAD patients with concomitant COVID-19 demonstrated a wide spectrum of microcirculatory disturbances, particularly the remodeling of the capillary bed, the alterations in the active (endothelium-dependent and -independent) mechanisms of microvascular flow regulation, and the drop in arteriolar and venular RBC movement velocity. At the same time, the profile of SCAD and COVID-19 constellation, as opposed to the «isolated» course of both conditions, was characterized by the predomination of patients, possessing a hemodynamic microcirculatory CS-type or a mixed pattern of reduced microvascular reactivity. Furthermore, the pooled microcirculatory hyporeactive profile was presented with the cases of combined SCAD and SARS-CoV-2 infection to a greater extent, than in the pooled profile with predominantly preserved microvascular reactivity. There is a need for the methods of non-invasive evaluation of microcirculatory system properties and the assessment of microvascular reactivity to be broadly applied while management of SCAD patients, suffering from COVID-19.

REFERENCES

1. Rabaan AA, Smajlović S, Tombuloglu H et al. SARS-CoV-2 infection and multi-organ system damage: A review. Biomol Biomed. 2023;23(1):37-52. doi: 10.17305/bjbms.2022.7762.
2. Mondini L, Confalonieri P, Pozzan R et al. Microvascular Alteration in COVID-19 Documented by Nailfold Capillaroscopy. Diagnostics (Basel). 2023;13(11):1905. doi: 10.3390/diagnostics13111905.
3. Xu SW, Ilyas I, Weng JP. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacol Sin. 2023;44(4):695-709. doi: 10.1038/s41401-022-00998-0.
4. Nicolai L, Kaiser R, Stark K. Thromboinflammation in long COVID-the elusive key to postinfection sequelae? J Thromb Haemost. 2023;21(8):2020-2031. doi: 10.1016/j.jtha.2023.04.039.
5. Yousefimoghaddam F, Goudarzi E, Ramandi A, Khaheshi I. Coronary artery calcium score as a prognostic factor of adverse outcomes in patients with COVID-19: a comprehensive review. Curr Probl Cardiol. 2023;48(8):101175. doi: 10.1016/j.cpcardiol.2022.101175.
6. Szarpak L, Mierzejewska M, Jurek J et al. Effect of Coronary Artery Disease on COVID-19-Prognosis and Risk Assessment: A Systematic Review and Meta-Analysis. Biology (Basel). 2022;11(2):221. doi: 10.3390/biology11020221.

7. Boulos PK, Freeman SV, Henry TD et al. Interaction of COVID-19 With Common Cardiovascular Disorders. Circ Res. 2023;132(10):1259-1271. doi: 10.1161/CIRCRESAHA.122.321952.
8. Kovanen PT, Vuorio A. SARS-CoV-2 reinfection: Adding insult to dysfunctional endothelium in patients with atherosclerotic cardiovascular disease. Atheroscler Plus. 2023;53:1-5. doi: 10.1016/j.athplu.2023.06.002.
9. Passi R, Brittan M, Baker AH. The role of the endothelium in severe acute respiratory syndrome coronavirus 2 infection and pathogenesis. Curr Opin Physiol. 2023;34:100670. doi: 10.1016/j.cophys.2023.100670.
10. Natalello G, De Luca G, Gigante L et al. Nailfold capillaroscopy findings in patients with coronavirus disease 2019: Broadening the spectrum of COVID-19 microvascular involvement. Microvasc Res. 2021;133:104071. doi: 10.1016/j.mvr.2020.104071.
11. Karahan S, Aydin K, Cetinkaya A, Sirakaya HA. Nailfold Videocapillaroscopy in Patients with COVID-19-associated Pneumonia in Intensive Care Units. J Coll Physicians Surg Pak. 2022;32(4):455-460. doi: 10.29271/jcpsp.2022.04.455.
12. Sabioni L, De Lorenzo A, Castro-Faria-Neto HC et al. Long-term assessment of systemic microcirculatory function and plasma cytokines after coronavirus disease 2019 (COVID-19). Braz J Infect Dis. 2023;27(1):102719. doi: 10.1016/j.bjid.2022.102719.
13. Sabioni L, De Lorenzo A, Lamas C et al. Systemic microvascular endothelial dysfunction and disease severity in COVID-19 patients: Evaluation by laser Doppler perfusion monitoring and cytokine/chemokine analysis. Microvasc Res. 2021;134:104119. doi: 10.1016/j.mvr.2020.104119.
14. Malahfji M, Crudo V, Ahmed AI et al. Coronary microvascular dysfunction and COVID-19: implications for long COVID patients. J Nucl Cardiol. 2022;1-3. doi: 10.1007/s12350-022-03073-7.
15. Çalışkan M, Baycan ÖF, Çelik FB et al. Coronary microvascular dysfunction is common in patients hospitalized with COVID-19 infection. Microcirculation. 2022;29(4-5):e12757. doi: 10.1111/micc.12757.
16. Rola P, Włodarczak A, Włodarczak S et al. Invasive assessment of coronary microvascular dysfunction in patients with long COVID: Outcomes of a pilot study. Kardiol Pol. 2022;80(12):1252-1255. doi: 10.33963/KP.a2022.0239.
17. Netiazhenko VZ, Mostovyi SI, Safonova OM et al. Intracardiac hemodynamics, cerebral blood flow and microembolic signal burden in stable coronary artery disease patients with concomitant COVID-19. Wiad Lek. 2023;76(5 pt 2):1205-1215. doi: 10.36740/WLek202305211.
18. Lushchyk UB, Novytskyi VV, Kolosova YuO. Suchasni mozhlyvosti kapiliaroskopii [Current capabilities of capillaroscopy]. Kyiv: MPP «Istyna». 2004. https://www.researchgate.net/publication/318883496_Sucasni_mozlivosti_kapilaroskopii [date access 05.06.2023] (In Ukrainian).
19. Smith V, Herrick AL, Ingegnoli F et al. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev. 2020;19(3):102458. doi: 10.1016/j.autrev.2020.102458.
20. Bircher A, de Boer EM, Agner T et al. Guidelines for measurement of cutaneous blood flow by laser Doppler flowmetry. A report from the Standardization Group of the European Society of Contact Dermatitis. Contact Dermatitis. 1994;30(2):65-72. doi: 10.1111/j.1600-0536.1994.tb00565.x.
21. Fullerton A, Stücker M, Wilhelm KP et al. Guidelines for visualization of cutaneous blood flow by laser Doppler perfusion imaging. A report from the Standardization Group of the European Society of Contact Dermatitis based upon the HIRELADO European community project. Contact Dermatitis. 2002;46(3):129-140. doi: 10.1034/j.1600-0536.2002.460301.x.
22. Saha M, Dremin V, Rafailov I et al. Wearable Laser Doppler Flowmetry Sensor: A Feasibility Study with Smoker and Non-Smoker Volunteers. Biosensors (Basel). 2020;10(12):201. doi: 10.3390/bios10120201.
23. Goltsov A, Anisimova AV, Zakharkina M. Bifurcation in Blood Oscillatory Rhythms for Patients with Ischemic Stroke: A Small Scale Clinical Trial using Laser Doppler Flowmetry and Computational Modeling of Vasomotion. Front Physiol. 2017; 8: 160. doi: 10.3389/fphys.2017.00160.
24. Makolkin V.I., Podzolkov V.I., Bran'ko V.V. Mikrotsirkulyatsiya v kardiologii. [Microcirculation in cardiology]. Moscow: Vizart. 2004 pp.105-110.
25. Horn AG, Schulze KM, Weber RE et al. Post-occlusive reactive hyperemia and skeletal muscle capillary hemodynamics. Microvasc Res. 2022;140:104283. doi: 10.1016/j.mvr.2021.104283.
26. Iredahl F, Sadda V, Ward LJ et al. Modeling Perfusion Dynamics in the Skin During Iontophoresis of Vasoactive Drugs Using Single-Pulse and Multiple-Pulse Protocols. Microcirculation. 2015;22(6):446-53. doi: 10.1111/micc.12211.
27. Osiaevi I, Schulze A, Evers G et al. Persistent capillary rarefication in long COVID syndrome. Angiogenesis. 2023;26(1):53-61. doi: 10.1007/s10456-022-09850-9.
28. Gualtierotti R, Fox SE, Da Silva Lameira F et al. Nailfold Videocapillaroscopic Alterations as Markers of Microangiopathy in COVID-19 Patients. J Clin Med. 2023;12(11):3727. doi: 10.3390/jcm12113727.
29. Dharra R, Kumar Sharma A, Datta S. Emerging aspects of cytokine storm in COVID-19: The role of proinflammatory cytokines and therapeutic prospects. Cytokine. 2023;169:156287. doi: 10.1016/j.cyto.2023.156287.
30. Santoro L, Zaccone V, Falsetti L et al. Role of Endothelium in Cardiovascular Sequelae of Long COVID. Biomedicines. 2023;11(8):2239. doi: 10.3390/biomedicines11082239.

31. Doroszko A, Rola P, Włodarczak S et al. Coronary microvascular dysfunction in the context of long COVID-19: What is the effect of anti-inflammatory treatment? Author's reply. Kardiol Pol. 2023;81(3):320-321. doi: 10.33963/KP.a2023.0040.
32. Okada H, Yoshida S, Hara A et al. Vascular endothelial injury exacerbates coronavirus disease 2019: The role of endothelial glycocalyx protection. Microcirculation. 2021;28(3):e12654. doi: 10.1111/micc.12654.
33. Zhang Z, Li X, He J et al. Molecular mechanisms of endothelial dysfunction in coronary microcirculation dysfunction. J Thromb Thrombolysis. 2023;56(3):388-397. doi: 10.1007/s11239-023-02862-2.

The study was conducted in accordance with the basic principles of the Council of Europe Convention on Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current national regulations. The study protocol was approved by the local ethics committee. All the patients provided written informed consent to participate in the study.

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ORIGINAL ARTICLE

AGE AND GENDER-SPECIFIC FEATURES OF CYTOGENETIC CHANGES IN BUCCAL EPITHELIUM IN INDIVIDUALS RESIDING IN THE «SICK BUILDING»

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ABSTRACT

The aim: The study of cytomorphological and cytogenetic features of the buccal epithelium of residents of apartments who complained of unpleasant odors in their homes.

Materials and methods: The state of buccal epithelium in residents of multi-story buildings was studied. A total of 237 individuals were examined, 117 males and 120 females, aged from 6 to 81 years. Buccal cells were collected using a sterile spatula and stained with a 2.5% solutionofaceto-orcein and 1% light green. The preparations were examined using a light microscope OPTON Axioskop (Germany) with oil immersion at a magnification of x1000. Statistical processing of the data was performed using IBMSPSS Statistics 29.0.0.0 (t-Student criterion; Mann-Whitney; ANOVA: Tukey; T3-Dunnett), with $p \leq 0.05$.

Results: Cytomorphological and cytogenetic abnormalities, compared to physiological limits, were mainly manifested as karyorrhexis, nuclear doubling, the appearance of epitheliocytes with perinuclear vacuoles, or nuclear vacuolization. The frequency of micronuclei was observed in the range of (0.3-2.8 ‰). The highest micronucleus index (per 1000 cells, ‰) was observed among males aged 15-39 years and females over 65 years old. In both sexes, the lowest micronucleus indices were found in the age group of 6-14 years.

Conclusions: in the «sick building» an increase in the frequency of micronucleus occurrence among males and females was observed simultaneously with increasing age.

KEY WORDS: buccal epithelium, micronucleus test, volatile organic compounds, sick building syndrome

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INTRODUCTION

Buccal cells (BC) form the first protective barrier against the entry of xenobiotics during inhalation or ingestion, therefore they are the best target for harmful agents that enter the body and cause the appearance of early genotoxic phenomena. [1, 2]. The research potential of BC lies in the fact that regulatory mechanisms, signaling pathways, and genetic changes can be personalized for the patient at the preclinical stage of the disease. BC provides opportunities not only for early diagnosis but also for a unique model for studying cytological and cytogenetic changes at the level of large cohorts of the population or population, to assess the harmful effects of environmental factors [3, 4].

THE AIM

To investigate age and gender-specific cytological and cytogenetic (by MN-test) changesin buccall epithelial cells among residents of multi-story buildings who are exposed to volatile organic compounds (VOCs) in the conditions of a «sick building».

MATERIALS AND METHODS

A sanitary and hygienic assessment of the air in residential buildings was carried out by the Kyiv City Center for Disease Control and Prevention of the Ministry of Health of Ukraine from 2010 to 2019 based on citizen complaints (126 cases). The analysis revealed that the air

quality in many residential areas did not meet the relevant standards. Concentrations of around 30 pollutants in the air of enclosed spaces exceeded the maximum permissible concentration by 2-34 times. The source of pollutants was found to be building polymer materials (BPM), which are widely used as decorative, sound, and heat insulation materials, paints, furniture, and more.

During the survey of adult residents of residential buildings who complained about the air quality in their homes, the «Questionnaire for the subjective assessment of living conditions of residents of residential premises using polymer materials» was used, which contained 34 evaluation criteria. The following information was recorded: gender, age, weight, height, lifestyle, general health status (self-assessment), consumption of alcohol, coffee, tobacco, and drugs, and dental procedures. Based on the analysis of the questionnaires, 237 individuals were selected, 117 male and 120 female, ranging in age from 6 to 81 years old. All adult respondents provided written consent to participate in the study, and the parents of minor respondents provided consent for their examination. Based on the survey results, «Biomedical Research Protocols» were developed. Respondents most often indicated that a strong odor in the room causes the following conditions: general fatigue, decreased performance, irritation of the mucous membranes of the mouth, eyes, and upper respiratory tract, exacerbation of chronic allergic diseases, respiratory diseases, etc.

Samples of biological material were taken from individuals who did not suffer from obesity, were not exposed to professional genotoxic ants, and did not take anti-tumor drugs, antioxidants, vitamins, and dietary supplements during the study. Preschool children did not participate in the study.

Control group: 16 students from the Department of Social Medicine and Public Health at the Bogomolets National Medical University, under the supervision of Dr. med. Prof. Palamar B.I. Biological material was collected using a sterile medical spatula, transferred to a glass slide, and dried in the open air for 15-20 minutes. Staining was carried out using a 2.5%solution of aceto-orcein and 1% light green. Microscopy of prepared slides was performed using a light microscope OPTON Axioskop (Germany) under oil immersion at a magnification of x1000. Images of the slides were captured using a digital camera Canon EOS 1000D (Japan). Morphometric analysis of parameters and accounting for the percentage ratio of different forms of epithelial cells were carried out using the Excel software package.

The frequency of pathological epithelial cells in the mucous membrane of the mouth in individuals living in a «sick» house was calculated using the methodology approved by the order of the Ministry of Health of Ukraine dated March 13, 2007, No. 116 «On approval of methodological recommendations "Survey and zoning of the territory according to the degree of influence of anthropogenic factors on the state of environmental objects using cytogenetic methods» [5]. Statistical processing was performed using the IBM SPSS Statistics 29.0.0.0 software; comparison of indicators in the study groups was carried out using the following methods: Student's t-test; Mann-Whitney; ANOVA (Tukey; T3-Dunnett), at $p \leq 0.05$.

Table I. Cytomorphological and cytogenetic characteristics of buccal epithelial cells (per 1000 cells, ‰) of male residents (N=117) of multi-story buildings.

Age groups	6-14	15-39	40-64	> 65
Number of attempts	n=19 (16%)	n=45 (38%)	n=29 (25%)	n=24 (21%)
Cytogenetic disorders:				
micronucleus	1,55-2,12	2,12-2.46	1,88-2,31	2,03-2,54
core protrusions	0,60-0,97	1,39-1,76	1,5-2,29	1,23-1,42
absence of nucleus	1,01-1,4	1,35-1,66	1,36-1,74	1,59-2,06
Proliferation indicators:				
double core	0,72-1,05	1,18-1,35	1,08-1,25	1,3-1,53
two cores	1,5-2,07	1,79-2,16	1,762-,17	1,59-2,06
many cores	0,23-0,5	0,38-0,63	0,20-0,41	0,2-0,46
Indicators of the distraction of the nucleus:				
perinuclear vacuole	1,42-1,93	1,31-1,62	1,55-2,02	1,42-1,93
vacuolization of the nucleus	4,31-5,78	4,5-4,45	4,71-6,1	4,31-5,78
chromatin condensation	14-17,25	15,81-17,86	13,99-16,28	14-17,25
karyokinesis	4,5-5,81	4,42-5,25	4,45-5,68	4,5-5,81
karyorrhexis	0,35-0,58	0,52-0,67	0,35-0,54	0,35-0,58
karyolysis	5,52-6,83	5,88-6,87	5,62-6,9	5,52-6,83
apoptosis	2,86-3,55	3,13-3,52	3,2-3,75	2,86-3,55

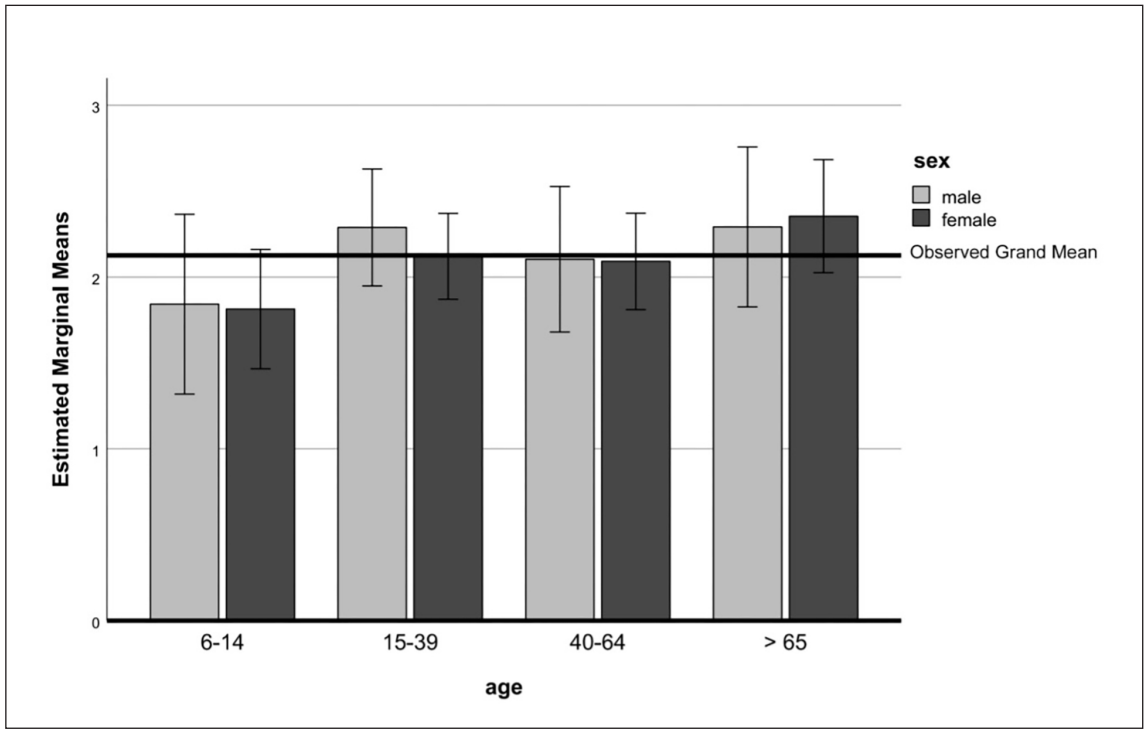

Fig. 1. Indicators of the frequency (and marginal mean) of micronucleus formation in buccal epithelium cells among respondents of different ages (N=237).

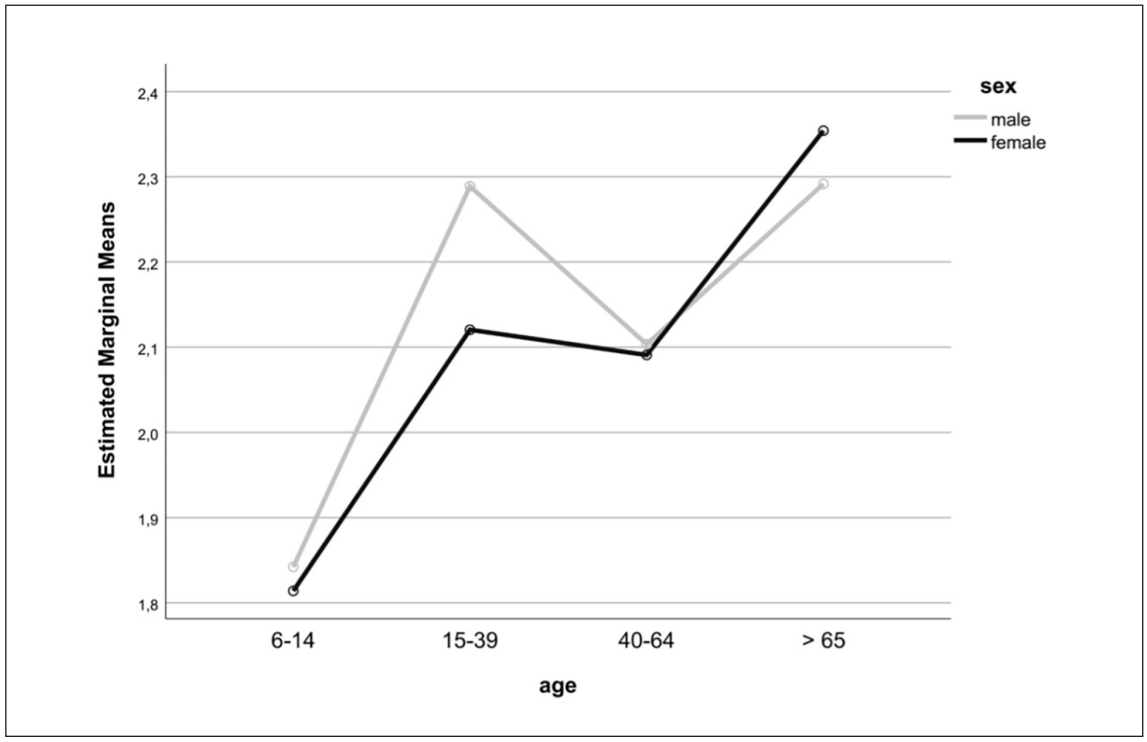

Fig. 2. The average frequency of micronucleus formation in buccal epithelium cells in different age groups among males (n=117) and females (n=120); according to the results of one-factor ANOVA analysis (Tukey; T3-Dunnett).

RESULTS

The cytogenetic characteristics of the buccal epithelial cells identified in the study included the presence of signs of microbial contamination, and the appearance of labrocytes and lymphocytes**.** Cytogenetic abnormalities, proliferation and nuclear destruction indicators were evaluated separately (Tables I and II).

It was found that cytological and cytogenetic abnormalities in buccal epithelial cells mainly manifested as karyorrhexis, nuclear doubling, and vacuolar

Table II. Cytomorphological and cytogenetic characteristics of buccal epithelium cells(per 1000 cells, ‰) of female residents (N=120) of multi-story buildings.

Age groups	6-14	15-39	40-64	> 65
Number of attempts	n=21 (18%)	n=42 (35%)	n=33 (27%)	n=24 (20%)
Cytogenetic disorders:				
micronucleus	1,61-2,00	1,99-2,24	1,96-2,21	2,16-2,53
core protrusions	0,74-0,97	1,92-2,29	1,7-2,17	1,24-1,37
absence of nucleus	1,1-1,35	1,31-1,54	1,28-1,49	1,67-2,02
Proliferation indicators:				
double core	0,8-1,01	1,14-1,29	1,07-1,16	1,33-1,5
two cores	1,58-1,95	1,74-2,03	1,78-2,05	1,66-1,99
many cores	0,31-0,48	0,47-0,69	0,34-0,49	0,23-0,42
Indicators of the distraction of the nucleus:				
perinuclear vacuole	1,5-1,83	1,28-1,51	1,74-2,03	1,21-1,44
vacuolization of the nucleus	4,54-5,49	4,68-5,35	4,71-5,64	3,8-4,45
chromatin condensation	14,41-16,56	16,11-17,52	15,50-17,15	12,54-14,49
karyokinesis	4,86-5,69	4,64-5,25	4,45-5,26	4,6-5,43
karyorrhexis	0,4-0,57	0,66-0,76	0,37-0,5	0,88-0,99
karyolysis	5,64-6,45	6,24-6,97	5,37-6,2	61-6,7
apoptosis	2,8-3,23	3,29-3,56	3,32-3,67	4,85-572

dystrophy (as one of the possible consequences of cytogenetic abnormalities). The frequency of MN was observed in the range of (0.3-2.8 ‰). A comparative analysis of the frequency of micronuclei occurrence was conducted in different age groups of respondents in both studies (Fig. 1).

It was found that the frequency of MN formation in all age groups among males and females is within the same range of frequencies (Fig. 1), not exceeding 3 MN/1000 cells. Similar indicators were obtained in individuals of the control group (1.7-2.3 MN/1000 cells). However, according to the results of one-factor ANOVA analysis (Tukey; T3-Dunnett), it was determined that the average frequency of MN formation in BE cells differs among males (n=117) and females (n=120) (Fig. 3).

Overall, the study demonstrates a frequency of MN formation in buccal epithelial cells that is close to «normal» among individuals who lived in conditions of a «sick building». However, the graph in Fig. 3 shows that the frequency of MN formation among males in the age group of 15-39 years exceeds the corresponding indicators among females of the same age (p=0.00352). In other age groups, no statistically significant differences were observed.

Among females, there was a tendency for an increase in the frequency of MN formation with age, while among males, such a trend was absent. Among individuals of both sexes, the lowest frequency of MN formation was observed in the younger age group, and the highest was among individuals over 65 years old.

Further analysis is required to examine the gender differences in the frequency of MN formation among young individuals (15-39 years old). The excess of this indicator among males (15-39 years old) compared to females of the same age indicates a higher potential risk of genotoxic effects among young males. Our research in this direction is ongoing.

It is not in doubt that prolonged exposure to pollutants in living conditions creates a risk of pre-pathological conditions and diseases, especially for sensitive populations such as children and youth, pregnant women, and individuals with chronic illnesses.

DISCUSSION

According to the World Health Organization, the widespread use of building and construction materials (BCMs) creates a special air environment in residential buildings, the quality of which significantly affects the health of the population [6, 7]. BCMs can be a source of simultaneous presence in the air of 150-280 chemical pollutants belonging to different classes of danger, some of which cause effects such as embryotoxic, gonadotoxic, carcinogenic, allergic diseases, etc. [8, 9].

Over the past 20 years, the micronucleus assay (MN assay) has been widely used to assess the harmful effects of various mutagenic and carcinogenic chemical or physical factors, such as arsenic in drinking water, dioxins, ethylene oxide, formaldehyde, lead oxide, benzene, ozone, polycyclic aromatic hydrocarbons,

toxic gases, pesticides, toluene, hexane, acetone, all types of tobacco, alcohol, and others. Previous studies have shown that inhalation of formaldehyde leads to an increase in the frequency of MN in the cells of the nasal and/or buccal mucosa over a wide range of MN frequencies (0.05-11.5 MN/1000 cells). In many studies, authors have reported a normal range of 0.5-2.5 MN/1000 cells [6-9], or 1-3 MN/1000 cells. However, it has been established that the frequency of MN in adults varies widely according to different data sources [3].

Undoubtedly, buccal epithelial cells are sensitive to various exogenous and endogenous factors, which is reflected in their cytomorphological and cytogenetic features, and these features have a fairlywide range. However, based on our data, it is currently impossible to assess the local and systemic genotoxicity of pollutants present in the air, the source of which is the «sick building». Based on the degree of impact on human health, factors are divided into two main groups: those that directly cause illness and those that exacerbate (worsen) the course of the underlying illness caused by other factors.

The results of the conducted research confirm that changes in epithelial cells have a multi-factorial nature, which is determined by factors such as gender and age of respondents, the presence of acute and chronic comorbidities, belonging to different professional groups, etc. Even though the data obtained in this study do not provide an opportunity to assess the health risk due to staying in a «sick building», they provide a basis for a more detailed study of gender and age peculiarities of the formation of micronuclei in response to a constant source of chemical influence, such as pollutants in the air of residential buildings.

CONCLUSIONS

According to the results of the study of exfoliated cells of the buccal epithelium of residents of residential buildings who complained of discomfort or health problems caused by the odor of volatile organic compounds in the air of their homes, the following was established:

- Cytomorphological disorders in buccal epithelial cells mainly manifested as karyorrhexis, nuclear doubling, and vacuolar dystrophy of the nucleus which can be considered as one of the consequences of cytogenetic disorders.
- The highest frequency of micronuclei formation was observed among males aged 15-39 and females over 65 years old.
- Among both males and females, the lowest frequency of micronuclei formation was observed among children and adolescents (aged 6-14).
- An increase in the frequency of micronuclei formation among females was observed simultaneously with an increase in age, while such a trend was not observed among males.
- The obtained data provide a basis for a more detailed study of gender and age-specific features of micronuclei formation in response to a constant source of chemical exposure, such as pollutants in the air of «sick buildings».

REFERENCES

1. Senel S. An Overview of Physical, Microbiological and Immune Barriers of Oral Mucosa. Int. J. Mol. Sci. 2021;22:7821. doi: 10.3390/ijms22157821.
2. Groeger S, Meyle J. Oral Mucosal Epithelial Cells. Front. Immunol. 2019;10:208. doi: 10.3389/fimmu.2019.00208.
3. Sommer S, Buraczewska I, Kruszewski M. Micronucleus Assay: the state of art, and future directions. International Journal of Molecular Sciences. 2020;21:1534-53. doi: 10.3390/ijms21041534.
4. Wang S-S, Tang Y-L, Pang X et al. The maintenance of an oral epithelial barrier. Life Sci. 2019;227:129–136. doi: 10.1016/j.lfs.2019.04.029.
5. «Pro zatverdzhennya metodychnykh rekomendatsiy «Obstezhennya ta rayonuvannya terytoriyi za stupenem vplyvu antropohennykh chynnykiv na stan ob'yektiv dovkillya z vykorystannyam tsytohenetychnykh metodiv»: Nakaz MOZ Ukrayiny 13.03.2007 №116 ["On approval of methodological recommendations "Survey and zoning of the territory according to the degree of influence of anthropogenic factors on the state of environmental objects using cytogenetic methods : "Order of the Ministry of Health of Ukraine 13.03.2007 No. 116]. https://zakon.rada.gov.ua/rada/show/v0116282-07#Text. [date access 20.04.2023]. (In Ukrainian).
6. WHO. Chemical pollution of indoor air and its risk for children's health: educational course: supplementary publication to the screening tool for assessment of health risks from combined exposure to multiple chemicals in indoor air in public settings for children. https://apps.who.int/iris/handle/10665/341984 [date access 20.04.2023].
7. WHO. Methods for sampling and analysis of chemical pollutants in indoor air: supplementary publication to the screening tool for assessment of health risks from combined exposure to multiple chemicals in indoor air in public settings for children. https://apps.who.int/iris/handle/10665/334389 [date access 20.04.2023].
8. Lin W-T, Chen C-Y, Lee C-C et al. Air Phthalate Emitted from Flooring Building Material by the Micro-Chamber Method: Two-Stage Emission Evaluation and Comparison. Toxics. 2021;9:216. doi: 10.3390/toxics9090216.

9. Kaewrat J, Janta R, Sichum S et al. Indoor Air Quality and Human Health Risk Assessment in the Open-Air Classroom. Sustainability. 2021;13:8302. doi: 10.3390/su13158302.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

CHARACTERISTICS OF MOTORIC ACTIVITY AND FOCUS OF ATTENTION OF STUDENT ATHLETES WITH DIFFERENT INVOLVEMENT IN COMPUTER GAMES

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ABSTRACT

The aim: To investigate the prevalence of computer games among student athletes and the impact of computer game addiction on their lifestyle and cognitive functions.

Materials and methods: 125 students (age 17 to 26) took part in the study. Students were divided into groups: e-sportsmen (12 people), who have played for an average of 4,592 hours; athletes of various sports (31 people), who are fond of computer games; athletes (82 people), who do not play computer games. A lifestyle questionnaire and attention research methods based on Landolt rings (E. Landolt) were used.

Results: We did not set the task of finding reliable differences between groups, but to find out general tendencies. Athletes, who indicated, that they are fond of computer games, show a lower level of weekly motoric activity compared to athletes, who are not fond of computer games. Cyber-sportsmen demonstrated insufficient physical activity in order to maintain physical fitness and a healthy lifestyle, 17% of cyber-sportsmen did not have any physical activity, that lasted for half an hour or more at any time of the week. Cyber-athletes showed a general tendency towards worsening of indicators of quality of life (sleep duration, insomnia, headaches), deterioration of attention, if compared to the athletes of other sports.

Conclusions: Studies have shown that students, who combine computer games with a sufficient amount of motoric activity, have a tendency to better concentration of attention. Studies of the necessary parameters of motoric activity and the alternation of mental, physical activity and rest for e-athletes should be prospective.

KEY WORDS: e-sports, computer games, motoric activity, cognitive functions, focus of attention

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INTRODUCTION

Computer games are gaining more and more popularity in the modern world. The consequence of the growing popularity of this direction is the rapid development of the e-sports market as well as the development of numerous organizations engaged in e-sports [1, 2]. Video games have rapidly entered everyday life and are available to every owner of a game console or a personal computer, and for many it is a way of having a good time and an opportunity to gain new knowledge in the field of computer games and not only. An example of this can be the study by [3], it was found that 2.69 billion of the entire global population play computer games, that is, they are gamers (in this study, all people who play (digital) games on PCs, consoles, mobile device or other digital device), which makes gaming and all its manifestations a popular hobby in the world. It is also a chance for the emergence of new professions and, interestingly, often professions that have not yet been created [1].

Scientific studies of this cultural and social phenomenon are developing as rapidly as e-sports itself. Until quite recently, it was believed that the main contingent of computer gamers are teenage boys and young men. Returning to gender roles and stereotypes, it is worth noting that the gender distribution among all gamers is 59% male to 41% female [4].

«Computer games» refers to a wide class of programs and technical devices on which they are installed. The classification of computer games should take into account the degree of complexity of the game and its content, cognitive and motor skills necessary for game activity [5, 6]. In fact, cyber athletes are often people who show skills that are not exclusively physical, but also logical-mathematical. Therefore among the frequent participants there are also those who cannot practice

traditional sports for different reasons. The introduction of sports rules and clear objectives contributes to the awareness that e-sports can be considered a discipline of body and mind [7]. The role and place of leisure in different types of society are analyzed [8]. From these data, it is obvious, that everyone plays computer games, players cannot be classified as a special sociological group, that differs from the rest of the population in certain demographic parameters.

Selected studies highlight the negative effects of e-sport on health from different perspectives [9]. It is stated that e-sports players are not physically active due to sedentary time for a long time. In some studies, it is claimed that long-term sedentary life will result in obesity [10], this is partly due to their fondness for playing games on gadgets [11]. Therefore, a pathological fascination with computer games is characterized by a significant number of negative consequences. On the other hand, computer games have positive effects on the personality and contribute to development [12] due to the emergence of new skills, operations, and ways of performing actions, new target and motivational and meaningful structures, new forms of mediation and new types of activities [12].

Thus, the authors of one of the earliest studies of the socio-psychological aspects of computer games [13] showed, that intensive computer game experience significantly affects the personal characteristics and self-awareness of players. The socio-psychological features of the formation of health-preserving competencies in the conditions of being in a virtual space are considered [14]. There are presented the research results of the positive impact of video games, that imitated sports actions, on the cognitive functions of a group of healthy elderly people, as well as on a group of people who did aerobic exercises [15]. Based on research, the authors conclude that video games, as well as the practice of physical exercises, can be considered among the possible methods of preserving mental functions and improving cognitive abilities for the elderly [15].

THE AIM

To investigate the prevalence of computer games among student-athletes and the impact of computer game addiction on their lifestyle and cognitive functions.

MATERIALS AND METHODS

From November to December 2022 there was conducted the study based on a questionnaire developed in the Google Form format: «Description of personal qualities and state of health of students». The parameters of attention (E. Landolt) were studied using the hardware and software complex of psychological and psychophysiological diagnostics «BOS-test-Professional». 125 students (age 17 to 26) took part in the study. This sample consisted of students of various sports, such as: e-sports, basketball, volleyball, football, rhythmic gymnastics, sports ballroom dancing, karate, Greco-Roman wrestling, boxing, judo, swimming, strength fitness, tennis. For research on the impact of computer game addiction on lifestyle, motoric activity and cognitive functions, students were divided into groups: e-sportsmen (12 people), who have played for 4,592 hours in average; athletes of various sports (31 people), who are fond of computer games; athletes (82 people), who do not play computer games.

The researchers followed all protocols and procedures required by the Biomedical Research Ethics Committee and conform to the directive of the Ukrainian Legislation on health care, Helsinki Declaration 2000 and European Society Directive 86/609 on human participation in biomedical research to ensure adherence to all standards for adequate protection and well-being of participants. The following statistical parameters were determined: mean, standard deviation SD, median, lower and upper quartiles Me (25%, 75%).

RESULTS

Out of 125 respondents, 31 student-athletes were identified as the ones, who, along with playing other sports, are also fond of computer games; 12 e-athletes, who participated in various competitions and 82 student-athletes, who are not interested in and do not play computer games. So, from our sample, 34.4% of students play computer games, among which the percentage of boys is 77% and girls 23%. Studies related to video games in the field of sports science have included eSport within the framework of traditional games [16]. Typically, cybergames are first-person shooters, real-time strategies, and sports simulations. The genre is determined by the goal of the game. A game can belong to one or several genres. Like regular sports, specific games are called disciplines. The most popular of them are: CounterStrike, Dota 2, FIFA, Halo 2, Heroes of Newerth, League of Legends, Quake, Starcraft, Warcraft, World of Tanks, etc. It was found that most of the students we studied prefer the following games: CounterStrike (CS:GO). Counter-Strike: Global Offensive (CS:GO) is the most popular first-person shooter of the last decade and one of the top esports disciplines – 31%; MOBA – 5%; Survival horror – 7%; Dota 2 – 18%; World

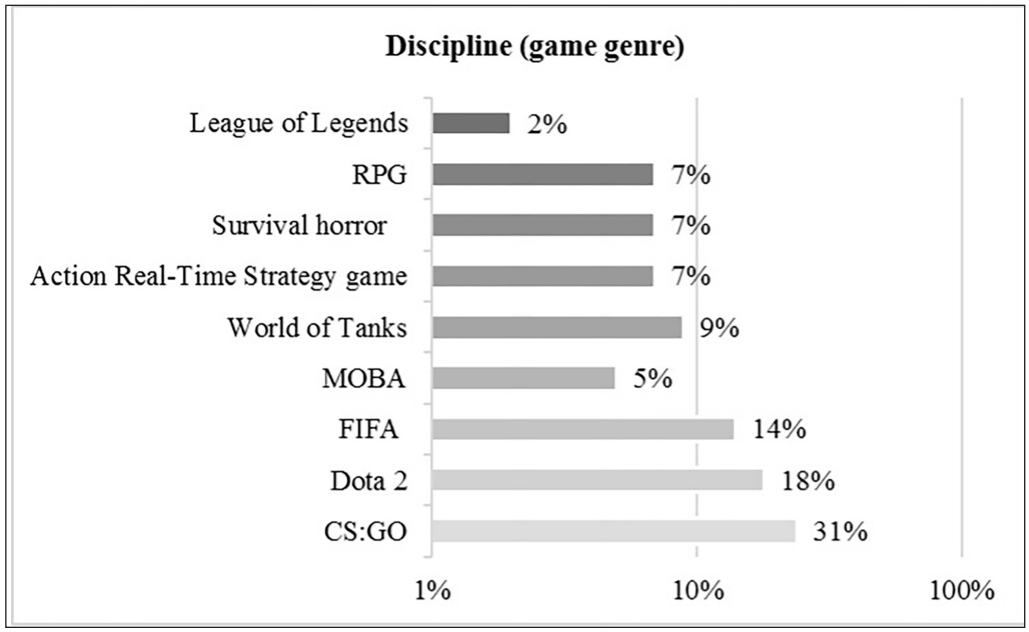

Fig. 1. Enthusiasm for computer games among student-athletes (n=43)

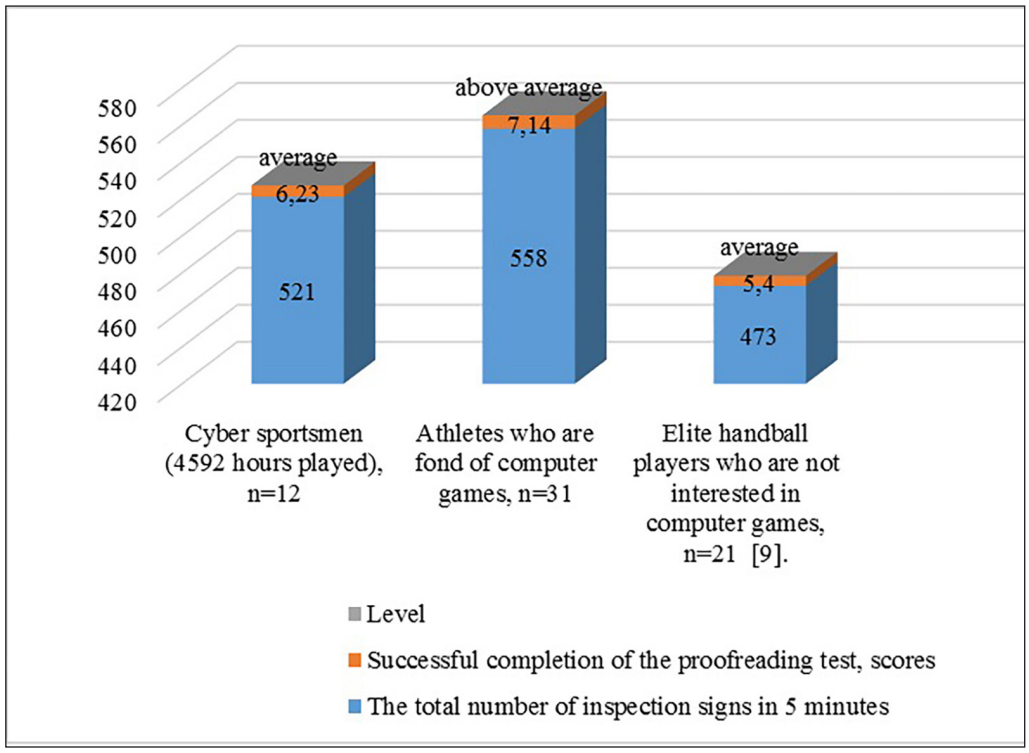

Fig. 2. Indicators of attention properties of student-athletes with different involvement in computer games

of Tanks – 9%; RPG – 7%; FIFA – 14%; Action Rial-Time Strategy game – 7%; League of Legends – 2% (Fig. 1).

The most important indicator of the degree of young people's fascination for computer games is the time spent on them. Moreover, it is the weekly amount of this time that is important, since a significant part of it is falling on days free from studies.

Cyber sportsmen, who took part in the survey, have played for 4,592 hours in average. Most athletes, who specialize in various sports and play computer games in their free time, spend 3 to 40 hours a week on them (Table I). It is indicative, that only 5 people (16%) are qualified athletes in this group of students. At the same time, the group of athletes, who stated, that they are not interested in and do not play computer games, includes 34 (41.5%) qualified athletes from various sports.

To compare the lifestyle, level of motoric activity, and well-being, we analyzed the respondents' answers to the questionnaire developed by us. We were interested in finding out how passion for computer games affects motoric activity and health parameters, such as sleep, nutrition, appetite, and well-being. In the current study, we did not set the task of finding reliable differences between groups, but to find out general tendencies.

Table I. Time spent by students on computer games per week, n=31

Number of hours per week student-athletes spend playing computer games	Number of students in %
Up to 10 hours a week	65%
10-30 hours per week	29%
30-40 hours a week	6%

Table II. Peculiarities of motoric activity of students with different involvement in computer games, n=125

Motor activity that lasts half an hour or more (training, exercises, running, swimming, fitness)	Cyber sportsmen, n=12	Athletes who are fond of computer games, n=31	Athletes who are not interested in computer games, n=82
Once or twice a week	33%	32%	24%
Three or more times a week	50%	68%	76%
Not once a week	17%	0%	0%

To compare the features of motoric activity of student-athletes, we divided the respondents into three groups (Table II).

Athletes, who indicated, that they are fond of computer games, are less physically active compared to athletes who are not fond of them. One of the indicators of a healthy lifestyle is the quality and duration of sleep. 41% of e-athletes, 13% of athletes, who play and 16% of athletes, who do not play computer games, indicated that they sleep less than 7 hours a day. 58% of e-athletes, 26% of athletes, who are fond of computer games, suffer from insomnia from time to time. 42% of e-athletes and 39% of athletes, who play computer games, suffer from headaches more than twice a week.

Eat 3-4 times a day — 58% (cyberathletes), 61% (athletes playing computer games) and have a good appetite: 67% (cyberathletes) and 81% (athletes playing computer games).

DISCUSSION

The impact of computer games on a person has many aspects. One of the visible problems is that gamers and e-sports players spend too much time on the computer, which threatens to cause health problems, that are not directly related to computer games but are a consequence of them. There is a total of 246 e-sports articles published from 2006 to 2020, that sought to understand the motivation, behavior, social implications, and legal aspects of eSports [2]. However, the impact of computer games on the physical and mental health of a person is still a relevant subject of scientific research.

Despite all the advantages and prospects for the development of e-sports [1, 17], an important problem is the sedentary lifestyle of computer game players, who are mostly young people. As the results of our survey showed, 17% of e-athletes do not have any motoric activity sufficient for a healthy lifestyle, although competitive activity in e-sports requires the athlete to develop certain psychological, physical and psychophysical characteristics and requires physical training [17, 18]. Athletes, who indicated that they are fond of computer games, have lower level of wekly motoric activity compared to athletes, who are not fond of tcomputer games. Despite the presence of a large number of studies on the positive impact of computer games on the cognitive abilities and psychological qualities of players [17]; coordination of movements and reactions [19-21], mental and intellectual abilities, our studies showed a tendency to better indicators of focus of attention for students, who combine computer games with a sufficient amount of motoric activity (Fig. 2).

All athletes who play computer games in addition to their chosen sport have average to high concentration scores. At the same time, only 66% of e-athletes showed indicators of concentration of attention in this part. In our study, we investigated the tendency for better indicators of attentional activity (above average) in student-athletes who are fond of computer games, compared to elite-level female handball players [18] who do not play computer games, and female e-athletes with unsatisfactory level motor activity. Therefore, it can be assumed that, just as for the elderly [15], it is possible to increase cognitive abilities for student youth by combining the practice of motor activity with computer games. One's lifestyle plays the crucial role in health maintenance and promotion [22]. The aspects of eSports focused on are mainly psychology [23], issues about athletes' and gamers' health [24]. The conditions for the formation of a healthy lifestyle are: motor activity, balanced and good nutrition, the absence of bad habits, quenching and active rest [25]. Physical activity as a part of human lifestyle, including the physical work and sports, is one of the basic attributes of human life. It improves physical condition and health condition, reduces the risk of emergence of civilizational diseases,

and it is one of the factors extending the human lifespan [26]. Physical activity of young people is inevitable for keeping them both physically and mentally fit [27].

In our opinion, the research of the necessary parameters of motor activity and alternation of mental, physical load and rest for e-athletes should be promising.

CONCLUSIONS

The most common types of computer games among student-athletes are CS:GO and Dota 2. The 65% of student-athletes use computer games from one to ten hours per week, and 35% of students use computer games from ten to forty hours per week. Students, who are athletically qualified, use computer games less than students, who are not athletically qualified.

Student-athletes named the following as the main reasons for their fascination with computer games: a means to distract from current tasks - 58%; receiving adrenaline - 29%; calming - 13%.

Athletes, who indicated, that they are fond of computer games, have a lower level of weekly motor activity compared to athletes, who are not fond of them. 50% of cyber sportsmen had physical activity that lasted more than half an hour three times a week; 68% of sportsmen, who play computer games, had physical activity that lasted more than half an hour three times a week; and 76% of sportsmen, who do not play games, had physical activity that lasted more than half an hour three times a week.

Cyber sportsmen demonstrated insufficient physical activity to maintain fitness and a healthy lifestyle, 17% of whom did not engage in any physical activity per week lasting half an hour or more.

Cyber sportsmen showed a general tendency towards worse quality of life indicators (sleep duration, insomnia, headaches, incidence of viral diseases and colds) compared to athletes of other sports, who enjoy and play computer games.

Studies have shown a tendency to better indicators of attention properties in students who combine computer games with sufficient motor activity. Student-athletes demonstrated the following level of overall success in performing the corrective test according to Landolt's test: cyber sportsmen - average (6.23 points); athletes, who combine sports training with playing computer games, are above average (7.14 points).

It is promising to study the necessary parameters of motor activity and alternation of mental activity, physical activity, and rest of cyber sportsmen.

REFERENCES

1. Jozwiak P. E-sports cities: a study on special legal problems connected with e-sports from the point of view of a local government. Journal of Physical Education and Sport. 2022; 22 (5): 1304-1310. doi:10.7752/jpes.2022.05163.
2. Yamanaka GK, Marcus VS, Roble OJ, Mazze LC. eSport: a state-of-the-art review based on bibliometric analysis. Journal of Physical Education and Sport. 2021; 21 (6): 3547-3555. doi:10.7752/jpes.2021.06480.
3. Newzoo. Global games market report. 2020. 2022_Newzoo_Free_Global_Games_Market_Report.pdf [date access 28.04.2023]
4. Entertainment Software Association. Survey «2020 Essential Facts About the Computer and Video Game Industry». 2020. https://www.theesa.com/resource/2020-essential-facts/ [date access 28.04.2023]
5. Mavrodiy N. Vplyv komp'yuternykh ihor na psykholohichnyy rozvytok osobystosti pidlitka [The influence of computer games on the psychological development of a teenager's personality]. Mykolaiv: CHNU. 2022, p.88. (In Ukrainian).
6. Shinkaruk O, Lut I. Content and structure of technical and tactical training in e-sports. Theory and methodology of physical education and sports. Scientific and theoretical magazine: history, pedagogy, psychology, law, sociology and philosophy in the field of physical education and sports. 2022(2):29-36. doi:10.32652/tmfvs.2022.2.29-36.
7. Viscione I, D'elia F. Augmented reality for learning in distance education: the case of e-sports. Journal of Physical Education and Sport. 2019;19(5): 2047-2050. doi:10.7752/jpes.2019.s5304.
8. Latyshev M, Tropin Yu, Ferenchuk B, Yushina O. Popularity of sports in Ukraine: modern trends. Scientific journal Physical culture and sport. 2023; (1): 98-103. doi: 10.31891/pcs.2023.1.15.
9. Happonen A, Minashkina D. Professionalism in Esports: benefits in skills and health and possible downsides. Lappeenrannan–Lahden Teknillinen Yliopisto LUT. Project Report 90. Slovakia; 2019. doi:10.13140/RG.2.2.28958.59208/2.
10. Bayrakdar A, Yıldız Y, Bayraktar I. Do e-athletes move? A study on physical activity level and body composition in elite e-sports. Physical Education of Students. 2020;24(5):259-264. doi: 10.15561/20755279.2020.0501.
11. Rahayu T, Aprilawati D, Mahmud J et al. Both upper and lower extremity-only video game-based exercises (exergaming) affect blood glucose serum levels and heart rates but not oxygen saturation in teenagers. Journal of Physical Education and Sport. 2019;19(3):802-807. doi:10.7752/jpes.2019.s 3114.
12. Chayka GV. Positive impacts of computer games. The Psychology of Giftedness. 2019;16(4):269-278.

13. Maltseva OI. Kibersotsializatsiya yak osoblyvyy vyd sotsializatsiyi osobystosti [Cyber socialization as a special type of personality socialization]. Visnyk LNU imeni Tarasa Shevchenka. Pedahohichni nauky. 2020; 2 (333): 190-199. doi: 10.12958/2227-2844-2020-2(333)-2-190-199. (In Ukrainian).
14. Condes TV. Socio-psychological features of the formation of health-preserving competencies of future specialists in the socionomic profile [dissertation]. Eastern Ukraine national University named after Volodymyr Dahl. Severodonetsk. 2019, p.244.
15. Guimaraes A, Barbosa A, Meneghini V. Active videogame-based physical activity vs. aerobic exercise and cognitive performance in older adults: a randomized controlled trial. Journal of Physical Education and Sport. 2018; 18 (1): 203-209. doi: 10.7752/jpes.2018.01026.
16. Elasri-Ejjaberi A, Rodriguez-Rodriguez S, Aparicio-Chueca P. Effect of eSport sponsorship on brands: an empirical study applied to youth. Journal of Physical Education and Sport. 2020; 20(2): 852-861. doi:10.7752/jpes.2020.02122.
17. Imas EV, Petrovska TV, Hanaha OYu. E-sports in Ukraine as a modern cultural phenomenon. Theory and methods of physical education and sports. 2021;1: 75-81. doi:10.32652/tmfvs.2021.1.75-81.
18. Fedorchuk S, Petrovska T, Khmelnytska I et al. The influence of motivation to achieve success and avoid failure on the properties of attention of skilled handball players. Sports medicine, physical therapy and occupational therapy. 2022; (2): 33-38. doi: 10.32652/spmed.2022.2.33-38.
19. Nagorsky E. The structure of performance and training in esports. PLoS One. 2020; 15(8): e0237584. doi: 10.1371/journal.pone.0237584.
20. Grabar O, Morozov A. Analysis and modeling of methods for measuring changes in the speed of a person's psychological reaction to moving objects for use in the development of an arcade game. Technical engineering. 2020;1(85):110-114. doi: 10.26642/ten-2020-1(85)-110-114.
21. Hanaha OYu, Petrovska TV, Fedorchuk SV. Psychological and psychophysiological methods for assessing the cognitive resource of e-athletes. Health-saving technologies, rehabilitation and physical therapy. Collection of articles of the XV International Scientific Conference. 2022;3(1). doi: 10.58962/HSTRPT.2022.3.1.19-22.
22. Alexandr I, Fyodorov V, Erlikh V et al. Young students' health attitudes. Journal of Physical Education and Sport. 2019; 19 (4): 2512-2517. doi: 10.7752/jpes.2019.04381.
23. Banyai F, Griffiths MD, Kiraly O, Demetrovics Z. The psychology of ESports: A systematic literature review. Journal of Gambling Studies. 2019;35(2):351-365. doi: 10.1007/s10899-018-9763-1,
24. DiFrancisco-Donoghue J, Balentine J, Schmidt G, Zwibel H. Managing the health of the eSport athlete: an integrated health management model. BMJ Open Sport & exercise medicine. 2019;5(1):1-6. doi: 10.1136/bmjsem-2018-000467.
25. Rybalko L, Yopa T, Hagner-Derengowska M et al. Motor activity as an indicator of a healthy way of life. Journal of Physical Education and Sport. 2021; 21 (5): 2813-2819. doi:10.7752/jpes. 2021.s 5374.
26. Slováková M, Bendíková E, Rozim R, Daubnerová J. The effect of goal-directed extracurricular physical activities on development of physical abilities in children of early school age. Journal of Physical Education and Sport. 2022; 22 (5): 1105-1111. doi: 10.7752/jpes.2022.05139.
27. Rozim R, Daubnerová J, Slováková M, Bendíková E. Changes in somatic characteristics and indicators of physical ability, physical performance and body posture in 10 and 11 years old pupils. 16th International Technology, Education and Development Conference Online. 2022. doi: 10.21125/inted.2022.0207.

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ORIGINAL ARTICLE

CLINICAL PROFILES AND CHARACTERISTICS OF MENSTRUAL DYSFUNCTION IN WOMEN AFTER SUFFERING FROM COVID-19 OR VACCINATION

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ABSTRACT

The aim: To investigate changes in the characteristics of menstrual function in women after suffering from Covid-19 or vaccination against SARS-CoV-2.

Materials and methods: After the retrospective analysis of 378 medical records patients were divided into: Group 1 (177 women) with menstrual function disorders (MFD) after COVID-19, Group 2 (121 women) with MFD after SARS-CoV-2 vaccination, Group C (80 women) without MFD after COVID-19 or vaccination (controls). The study focused on the clinical and hormonal menstrual cycle characteristics and factors influencing MFD.

Results: Dyshormonal thyroid disorders were observed in 63.0% of Group 1 and 45.7% of Group 2 patients; hyperprolactinemia - in 31.0% and 39.4%, hyperestrogenia - in 50% and 21%, and hyperandrogenism - in 39% and 20%. MFD was associated with hyperandrogenism with concurrent hyperprolactinemia, in the context of thyroid dysfunction; and with changes of gonadotropin production, along with normal and elevated estrogen concentrations and worsening of mental health that suggest disruption of central regulatory and feedback mechanisms in the pituitary-thyroid-ovarian system under the stressors influence.

Conclusions: There are changes in the menstrual cycle associated with disruption of the hypothalamus-pituitary-ovary system and thyroid function in women after suffering from Covid-19 or vaccination. To reestablish reproductive homeostasis, employing a personalized diagnostic strategy is recommended, encompassing the evaluation of thyroid gland status, hormonal profiling, and the consideration of psychosocial facets.

KEY WORDS: COVID-19 incidence, menstrual cycle, reproductive health, endocrine pathology, organization of gynecological care, effectiveness of medical care

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INTRODUCTION

As of July 2023, according to WHO data, over 767 million confirmed COVID-19 cases have been registered worldwide, resulting in 6.9 million fatalities. Additionally, more than 13 billion vaccine doses have been administered [1]. The psychological well-being of European populations has been significantly affected by virus-related fears, enforced social isolation, and uncertainties about financial stability and the future. Since stress has its own specific characteristics for the female body and can potentially activate the hypothalamic-pituitary-gonadal axis (HPG) and change the neuroregulation of gonadotropin-releasing hormone (GnRH), this adversely affects women's reproductive system functionality [2,3].

Retrospective observational studies, prospective research, and cases published during the pandemic years have reported thyroid gland function disruptions associated with SARS-CoV-2 infection. Thyroid dysfunctions, including hypothyroidism, subacute thyroiditis, and thyrotoxicosis, can occur both during acute infection and after recovery [4]. Excessive thyroid activity may lead to shortened menstrual duration and reduced bleeding intensity, while decreased thyroid hormone levels can result in prolonged and heavy menstruation or amenorrhea [5].

The menstrual cycle serves as an indicator of health and reproductive potential. Even individuals with regular cycles may experience changes due to inherent variability. When combined with novel factors, such as the potential impact of SARS-CoV-2 infection and COVID-19 vaccination, alterations in menstrual characteristics may become exacerbated, accompanied by cycle irregularities or changes in duration. There are foreign studies to evidence to support these assertions [6,7].

THE AIM

To investigate changes in the characteristics of menstrual function in women after suffering from Covid-19 or vaccination against SARS-CoV-2.

MATERIALS AND METHODS

The research was conducted in accordance with the fundamental principles of the «Rules of Ethical Principles for Conducting Medical Research Involving Human Subjects», as outlined in the Helsinki Declaration (1964-2013), ICH GCP (1996), Directive EEC No. 609 (dated November 24, 1986), and Orders of the Ministry of Health of Ukraine No. 690 dated September 23, 2009, No. 944 dated December 14, 2009, and No. 616 dated August 3, 2012. Each of the female patients provided informed consent to participate in the study.

Inclusion criteria: age 21-40 years; desire to preserve and fulfill reproductive function; presence of ovaries and a uterus functionally capable of supporting pregnancy; history of COVID-19 within the last year or vaccination against SARS-CoV-2.

Exclusion criteria: pregnancy and lactation; urgent gynecological pathology or acute inflammatory processes of any localization; oncopathology; severe somatic and organic central nervous system pathology or current/historical psychiatric disorders; unclear etiology dysfunctional uterine bleeding and atypical hyperplastic processes of the endometrial mucosa; ovarian cysts ≥ 4 cm; uterine developmental anomalies; uterine fibroids presence; genital endometriosis.

To accomplish the stated objectives, a retrospective analysis of medical inpatient and outpatient records of patients seeking assistance during 2020-23 was conducted. A total of 378 women were included and categorized into the following groups: Group 1 – 177 patients with identified menstrual function disorders (MFD) after recovering from Covid-19; Group 2 (comparison) consisted of clinical data from 121 women in whom MFD appeared after vaccination against SARS-CoV-2; Group C (controls) – 80 female individuals without MFD complaints after Covid-19 or vaccination. Patients in the studied groups were matched based on age, duration, clinical manifestations of the disease, and the timing of their occurrence. The average age of examined women was (34.7±2.6 years). A retrospective analysis of the clinical characteristics of the menstrual cycle was conducted, and interdependent and independent statistically significant factors influencing MFD in women before and after Covid-19 or after vaccination against SARS-CoV-2 were determined.

The data analysis was performed by the use of the statistical software programs (Statistica v. 14.0 (TIBCO Software Inc., USA); EZR v. 1.61; and MedStat v. 5.0). Quantitative variables were presented as median (Me) and interquartile range (IQR). Qualitative variables were presented as absolute and relative (%) frequency. To compare quantitative variables between the studied groups, we performed Kruskal-Wallis H test with the following *post hoc* comparisons by the use of Mann-Whitney U-test. To compare qualitative variables, we used Fisher`s exact test (between two independent groups) or the Marascuilo – Liakh – Gurianov (MLG) procedure (between three independent groups). A 2-tailed $p<0,05$ was considered statistically significant (considering the Bonferroni correction).

RESULTS

Analyzing data from medical records, we determined the prevalence of MFD among patients in the studied groups following the onset of the Covid-19 pandemic. One patient could have several of the mentioned disorders at the same time (Table I).

Similar indicators of hypermenorrhea were observed in Group 1 (11.9%) and Group 2 (8.3%), while in Group C (5.9%), this indicator was even lower. However, there was a statistically significant difference between Groups 1 and C ($p_{1-C} = 0.042$). The frequency of metrorrhagia in Group 1 (14.7%) was higher than in Group 2 (8.3%), and no cases were reported in Group C. Statistically significant differences were found between Groups 1 and C ($p_{1-C} < 0.001$), as well as between Groups 2 and C ($p_{2-C} = 0.018$). Menorrhagia rates were similar in Groups 1 (11.3%) and 2 (7.4%), but in Group C (2.5%), this rate was even lower. The difference between Groups 1 and C did not reach statistical significance ($p = 0.055$*), but the difference between the frequency of menorrhagia in the pooled group (1+2): 29/298 (9.7%) was statistically significant compared to the control group ($p=0.038$).

A significant impact of variable factors on polymenorrhea was observed, with Group 2 (45.5%) having the highest frequency compared to Groups 1 (9.6%) and C (5.0%). Statistically significant differences were found among all pairs of groups ($p_{1-2} < 0.001$, $p_{2-C} < 0.001$, $p_{1-C} < 0.001$). Group 1 (15.3%) had the highest frequency of opsomenorrhea, while Groups 2 and C did not have this disorder. Statistically significant differences were found between Groups 1 and 2 ($p_{1-2} < 0.001$), as well as between Groups 1 and C ($p_{1-C} < 0.001$). Changes in the shortening of the menstrual cycle, particularly the luteal phase, were observed in Groups 1 (7.4%) and 2 (17.0%). The difference between Groups 1 and 2 did not reach statistical significance ($p_{1-2} = 0.069$), but it was statistically significant between Groups 2 and C ($p_{2-C} = 0.027$). Group 1 (11.3%) and Group 2 (2.5%) reported cases of secondary amenorrhea, while Group C did not have such cases. Statistically significant differences were found between Groups 1 and 2 ($p_{1-2} = 0.018$), as well as between Groups 1 and C ($p_{1-C} < 0.001$). The frequency of dysmenorrhea was higher in Group 1 (17.5%) compared to Group 2 (6.6%), but lower than in Group C (13.8%).

Table I. The frequency of MFD in the studied groups

Parameters	Group 1 N= 177	Group 2 N = 121	Group C N=80	Total N=378	p
Hypermenorrhea, n (%)	21 (11,9)	10 (8,3)	2 (5,9)	33 (8,7)	p_{1-C}=0,042
Metrorrhagia, n (%)	26 (14,7)	10 (8,3)	0	36 (9,5)	p_{1-C}<0,001 p_{2-C}=0,018
Menorrhagia, n (%)	20 (11,3)	9 (7,4)	2 (2,5)	31 (8,2)	0,055*
Polymenorrhea, n (%)	17 (9,6)	55 (45,5)	4 (5,0)	76 (20,1)	p_{1-2}<0,001 p_{2-C}<0,001
Opsomenorrhoea, n (%)	27 (15,3)	0	0	27 (7,1)	p_{1-2}<0,001 p_{1-C}<0,001
Shortening of the menstrual cycle, n (%)	9 (7,4)	30 (17,0)	4 (5,0)	43 (11,4)	p_{1-2}=0,069 p_{2-C}=0,027
Secondary amenorrhea, n (%)	20 (11,3)	3 (2,5)	0	23 (6,1)	p_{1-2}=0,018 p_{1-C}<0,001
Algodysmenorrhea, n (%)	31 (17,5)	8 (6,6)	11 (13,8)	50 (13,2)	p_{1-2}=0,025

Notes: p_{1-C} – the significance of difference between group 1 and controls; p_{2-C} – the significance of difference between group 2 and controls; p_{1-2} – the significance of difference between the groups 1 and 2; * – MLG procedure; the frequency of menorrhagia in the pooled group [1+2]: 29/298 (9,7 %) (vs. 2/80 (2,5 %) in the control group: p=0,038).

Table II. The parameters of hormonal homeostasis in the studied groups (Me, IQR)

Parameters	Groups			P
	Group 1 N= 177	Group 2 N = 121	Group C N=80	
LH, mIU/ml	8,6 (7,9-9,6)	5,6 (5,3-5,9)	4,8 (4,6-5,0)	p_{1-2}<0,001 p_{1-C}<0,001 p_{2-C}<0,001
FSH, mIU/ml	7,4 (7,1-7,8)	3,7 (3,4-4,1)	3,4 (3,2-3,9)	p_{1-2}<0,001 p_{1-C}<0,001 p_{2-C}=0,002
TSH, µIU/ml	5,9 (5,2-6,3)	4,5 (4,0-5,0)	2,2 (1,9-2,4)	p_{1-2}<0,001 p_{1-C}<0,001 p_{2-C}<0,001
FT4, pg/ml	22,7 (20,9-24,5)	20,3 (19,8-20,7)	19,4 (19,1-19,8)	p_{1-2}<0,001 p_{1-C}<0,001 p_{2-C}<0,001
Prolactin, ng/ml	30,3 (29,6-31,0)	47,9 (46,2-49,8)	8,5 (7,8-8,9)	p_{1-2}<0,001 p_{1-C}<0,001 p_{2-C}<0,001
E2, pg/ml	39,7 (36,6-42,1)	45,5 (44,8-46,5)	46,1 (44,3-48,1)	p_{1-2}<0,001 p_{1-C}<0,001
Progesterone, nmol/l	5,4 (5,1-5,9)	18,2 (17,2-19,2)	25,5 (23,9-26,9)	p_{1-2}<0,001 p_{1-C}<0,001 p_{2-C}<0,001
Index of free testosterone, nmol/l	1,7 (1,5-1,8)	3,2 (2,9-3,4)	1,7 (1,3-1,9)	p_{1-2}<0,001 p_{2-C}<0,001
Cortisol, nmol/l	327,9 (318,5-337,5)	317,7 (307,3-325,2)	247,2 (230,5-262,3)	p_{1-2}<0,001 p_{1-C}<0,001 p_{2-C}<0,001
DHEA-S, µmol/l	158,3 (148,1-168,5)	125,5 (118,5-132,8)	198,1 (193,6-202,9)	p_{1-2}<0,001 p_{1-C}<0,001 p_{2-C}<0,001
17-OHP, nmol/l	2,7 (2,6-2,9)	2,8 (2,6-3,0)	2,8 (2,6-3,0)	p_{1-2}=0,073 p_{1-C}=0,016

Notes: p_{1-C} – the significance of difference between group 1 and controls; p_{2-C} – the significance of difference between group 2 and controls; p_{1-2} – the significance of difference between the groups 1 and 2.

Statistically significant differences were found between Groups 1 and 2 ($p_{1-2} = 0.025$).

Based on the analysis of hormonal homeostasis parameters provided in Table II, several statistically significant changes were identified among the studied groups. Hormone levels were determined during the early follicular phase.

The concentration of LH was highest in Group 1 (8.6 mIU/ml) and lowest in Group C (4.8 mIU/ml). Statistically significant differences were found between all groups ($p_{1-2} < 0.001$; $p_{1-C} < 0.001$; $p_{2-C} < 0.001$). Group 1 had the highest concentration of FSH (7.4 mIU/ml), while Group C had the lowest (3.4 mIU/ml). Statistically significant differences were also found between all studied groups ($p_{1-2} < 0.001$; $p_{1-C} < 0.001$; $p_{2-C} = 0.002$). Group 1 had the highest concentration of TSH (5.9 µIU/ml), while Group C had the lowest (2.2 µIU/ml). Statistically significant differences were found between all groups ($p_{1-2} < 0.001$; $p_{1-C} < 0.001$; $p_{2-C} < 0.001$). The concentration of FT4 was highest in Group 1 (22.7 pg/ml) and lowest in Group C (19.4 pg/ml). Statistically significant differences were found between all groups ($p_{1-2} < 0.001$; $p_{1-C} < 0.001$; $p_{2-C} < 0.001$). Group 2 had the highest concentration of prolactin (47.9 ng/ml), while Group C had the lowest (8.5 ng/ml). Statistically significant differences were found between all groups ($p_{1-2} < 0.001$; $p_{1-C} < 0.001$; $p_{2-C} < 0.001$). Group 2 had the highest concentration of estradiol (45.5 pg/ml), while Group C had the lowest (46.1 pg/ml). Statistically significant differences were found between Groups 1 and 2 (p1-2 < 0.001), as well as between Groups 1 and C ($p_{1-C} < 0.001$). Group 2 had the highest concentration of progesterone (18.2 nmol/L), while Group C had the lowest (25.5 nmol/L). Statistically significant differences were found between all groups ($p_{1-2} < 0.001$; $p_{1-C} < 0.001$; $p_{2-C} < 0.001$). Group 2 had the highest concentration of free testosterone (3.2 nmol/L), while Group C had the lowest (1.7 nmol/L). Statistically significant differences were found between Groups 1 and 2 ($p_{1-2} < 0.001$), as well as between Groups 2 and C ($p_{2-C} < 0.001$). Group 1 had the highest cortisol level (327.9 nmol/L), while Group C had the lowest (247.2 nmol/L). Statistically significant differences were found between Groups 1 and 2 ($p_{1-2} < 0.001$), as well as between Groups 1 and C ($p_{1-C} < 0.001$) and between Groups 2 and C ($p_{2-C} < 0.001$). Group 1 had the highest DHEA-S level (158.3 µmol/L), while Group C had the lowest (198.1 µmol/L). Statistically significant differences were found between Groups 1 and 2 ($p_{1-2} < 0.001$), as well as between Groups 1 and C ($p_{1-C} < 0.001$) and between Groups 2 and C ($p_{2-C} < 0.001$).

Analyzing the cumulative data comparatively, it was determined that the frequency of thyroid dysfunction in women in Group 1 of the study was 63.0%, compared to 45.7% in patients of Group 2. Hyperprolactinemia was observed in 31.0% and 39.4%, respectively. Changes in the LH/FSH ratio – hypogestagenemia – were noted in 48% and 44%, hyperestrogenia in 50% and 21%, and hyperandrogenia in 20% and 34% respectively.

DISCUSSION

According to the comparative analysis of the tables, many hormonal parameters and characteristics of MFD show both statistically and clinically significant differences between Group 1 (those who had COVID-19) and Group 2 (those vaccinated against SARS-CoV-2). Consequently, Group 1 exhibits more pronounced hormonal changes, characterized by a higher frequency of oligomenorrhea, secondary amenorrhea, alterations in several hormones (LH, FSH, TSH, FT4, Prolactin), and indicate more significant thyroid function disruptions. This is consistent with retrospective observational and prospective studies that have reported thyroid function disturbances associated with acute SARS-CoV-2 infection or even several weeks after its resolution. Since the thyroid gland, like the hypothalamus and pituitary gland, expresses angiotensin-converting enzyme 2 (ACE2), the primary protein through which SARS-CoV-2 binds to cells as a receptor [4,12,13], these disruptions are related to the activity of the «cytokine storm» [4,10,11]. However, cases of thyroid disorders have also been reported following the administration of SARS-CoV-2 vaccines.

Considering that the hormonal homeostasis in Group 2 is characterized by polymenorrhea, shortening of the luteal phase, elevated free testosterone index, hyperprolactinemia, and a lower frequency of thyroid dysfunction, these changes suggest a more substantial impact of the stress factor on the development of MFD in this group.

The study demonstrated that having a history of COVID-19 or receiving a vaccination against SARS-CoV-2 could impact the menstrual cycle and be associated with a slight change in cycle length but not menstrual length. Notably, statistically significant differences in menorrhagia indicators were not observed, which is consistent with findings from international studies [6,7].

In the comparative analysis of hormonal screening results among the study groups, it was found that the concentration of LH in patients of Group 1 was nearly twice as high as that in patients of Group 2. Estrogen saturation analysis indicated that in the majority of women from the study groups, estrogen levels were within normal range. Concentrations of DHEA-S and Cortisol likely did not differ significantly among the study groups. The free Testosterone index was

approximately 1.5 times higher in patients of Group 2 compared to the main group and 2.5 times higher than in the control group, which may suggest the role of hyperandrogenemia in the development of MFD and anovulation syndrome, particularly in the context of stress agents [12,13].

Overall, the pathogenetic aspects of MFD in the context of COVID-19 identified in our research align with contemporary trends in pathogenetic studies from various international research centers. These findings reflect dysfunction in the central mechanisms of regulation and feedback in the pituitary-thyroid-ovarian system under the influence of stress factors, characterized by thyroid function disturbances in the presence of normal and elevated estrogen concentrations [4,8-10].

The identified changes in hormonal homeostasis in our study necessitate, in our view, personalized diagnostics and correction aimed at restoring the functional state of the reproductive system in such women. Specifically, evaluating thyroid function in these women is a pertinent step in the diagnostic search algorithm. This includes assessing thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3), as well as determining antibodies to thyroid structures (such as thyroperoxidase antibodies or antibodies to thyroglobulin), which can aid in identifying potential autoimmune gland disorders. Additionally, an important component of the diagnostic algorithm could be considering psychosocial aspects, such as stress levels and psychological states of patients, as well as evaluating prolactin levels and its monomers [14,15].

The utilization of the developed diagnostic algorithm could prove valuable for clinical practice and counseling patients who have experienced COVID-19 or have been vaccinated, with regards to potential changes in their menstrual cycle and reproductive function.

CONCLUSIONS

The overarching trend in the development of MFD in patients after suffering from Covid-19 or vaccination against the SARS-CoV-2 coronavirus is the dysfunction of central regulatory mechanisms in the hypothalamo-pituitary-thyroid-ovarian system and thyroid function disruption under the influence of stress factors. This is characterized by alterations in gonadotropin production amidst normal and elevated estrogen concentrations.

Such changes necessitate personalized diagnosis and correction strategies aimed at restoring the functional state of the reproductive system in these women. Developing a diagnostic algorithm that encompasses thyroid function evaluation (including assessing TSH, fT4, T3, and thyroid structure antibodies) along with the assessment of psychosocial aspects (including prolactin levels and its monomers) could be beneficial for counseling patients regarding potential changes in their menstrual cycle and reproductive function following COVID-19 or SARS-CoV-2 vaccination.

REFERENCES

1. WHO. Coronavirus (COVID-19) Dashboard. https://covid19.who.int/. [date access 17.05.2023]
2. Talic S, Shah S, Wild H et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-nalysis. The British Medical Journal. 2021;375:e068302. doi:10.1136/bmj-2021-068302.
3. McGinty EE, Presskreischer R, Han H et al. Psychological Distress and Loneliness Reported by US Adults in 2018 and April 2020. Journal of the American Medical Association. 2020;324(1):93–4. doi: 10.1001/jama.2020.9740.
4. Rossetti CL, Cazarin J, Hecht F et al. COVID-19 and thyroid function: What do we know so far? Front Endocrinol (Lausanne). 2022;13:1041676. doi: 10.3389/fendo.2022.1041676.
5. Jacobson MH, Howards PP, Darrow LA et al. Thyroid hormones and menstrual cycle function in a longitudinal cohort of premenopausal women. Paediatr Perinat Epidemiol. 2018; 32: 225-234. doi: 10.1111/ppe.12462.
6. Lebar V, Laganà AS, Chiantera V et al. The Effect of COVID-19 on the Menstrual Cycle: A Systematic Review. Journal of Clinical Medicine. 2022;11(13):3800. doi: 10.3390/jcm11133800.
7. Rodríguez Quejada L, Toro Wills MF, Martínez-Ávila MC et al. Menstrual cycle disturbances after COVID-19 vaccination. Womens Health (Lond). 2022;18:17455057221109375. doi: 10.1177/17455057221109375.
8. Pierce M, Hope H, Ford T et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. Lancet Psychiatry. 2020;7(10):883–92. doi: 10.1016/S2215-0366(20)30308-4.
9. Lytvak O, Petruk A. Clinical and morphological aspects of the reproductive system of reproductive age women with menstrual disorders after COVID-19. Clinical and Preventive Medicine. 2022;3(21):4-10. doi: 10.31612/2616-4868.3(21).2022.01.
10. Pan D, Sze S, Minhas JS et al. The impact of ethnicity on clinical outcomes in COVID-19: A systematic review. EClinicalMedicine. 2020;23:100404. doi: 10.1016/j.eclinm.2020.100404.

11. Navarro VM, Kaiser UB. Metabolic influences on neuroendocrine regulation of reproduction. Curr Opin Endocrinol Diabetes Obes. 2013;20(4):335–41. doi: 10.1097/MED.0b013e32836318ce.
12. Ilyaev B, Muminiy SN, Borukh E et al. COVID-Induced Hyperthyroidism in a 30-Year-Old Female: A Case Study. Cureus. 2023;15(6):e40851. doi:10.7759/cureus.40851.
13. Çabuk SA, Cevher AZ, Küçükardalı Y. Thyroid Function During and After COVID-19 Infection: A Review. touch REV Endocrinol. 2022;18(1):58-62. doi: 10.17925/EE.2022.18.1.58.
14. Medina-Perucha L, López-Jiménez T, Holst AS et al. Self-Reported Menstrual Alterations During the COVID-19 Syndemic in Spain: A Cross-Sectional Study. Int J Womens Health. 2022;14:529-544. doi:10.2147/IJWH.S354655.
15. Rahman SA, Grant LK, Gooley JJ et al. Endogenous Circadian Regulation of Female Reproductive Hormones. The Journal of Clinical Endocrinology and Metabolism. 2019;104(12):6049–59. doi: 10.1210/jc.2019-00803.

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ORIGINAL ARTICLE

ASSESSMENT OF THE QUALITY OF LIFE OF PATIENTS WITH PERIODONTAL TISSUE DISEASES (RESULTS OF A PILOT SURVEY)

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ABSTRACT

The aim: To study the quality of life of patients with periodontal disease.

Materials and methods: The study was conducted among 189 patients, including 87 men and 102 women. Research methods – clinical method, questionnaire survey (study of the quality of life related to oral health (oral health-related quality of life – OHRQoL, OHIP-14), medical and statistical analysis using an application package Statistica 10.0 (StatSoft, Inc., USA) and Microsoft Office Excel 2010.

Results: According to the results of periodontal examination, it was found that 29,1% of patients suffer from acute gingivitis, acute periodontitis – 48,1%, chronic periodontitis – 21,7%. According to the results of patients' self-assessment of the quality of life associated with oral health, a good lifestyle can be stated. Almost 50% of patients said that the most tangible problems associated with the health of their oral cavity are functional disorders (31,7%), oral pain, and difficulty eating (16,6%). Psychological problems were reported by 16,3% of respondents, among whom one-third noted a feeling of irritability and tension, dissatisfaction with eating, and also noted limitations in communication with people, and the need to interrupt food intake during its intake due to oral problems.

Conclusions: Periodontal tissue diseases reduce the quality of life of patients. Assessing the quality of life related to oral health is essential to determine the effectiveness of measures aimed at improving and preserving public health.

KEY WORDS: Periodontal tissue diseases, quality of life

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INTRODUCTION

One of the most urgent problems of dentistry today is periodontal disease, which is the main cause of early tooth loss of non-traumatic genesis in middle and older age groups of the population [1]. Periodontal diseases affect not only physical health but also the emotional and social state of a person [2-4]. Patients with periodontal disease often show signs of psycho-emotional stress due to aesthetic dissatisfaction with a smile and agnosia of harmony in their appearance; the presence of discomfort, manifested in the form of symptoms such as pain, bad breath, burning and bleeding gums, lack of teeth, which in the effective aggregate reduces the quality of life of patients [5, 6].

THE AIM

The aim was to study the quality of life of patients with periodontal diseases.

MATERIALS AND METHODS

The study was conducted among 189 patients, including 87 men and 102 women, who are attached for medical care to the State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administrative Department (SIS «RPC PCM» SAD) and underwent a dental examination by a dentist in April-May 2023.

Research methods – clinical method, questionnaire, medical and statistical analysis.

All patients were assessed for the hygienic state of the oral cavity (Green-Vermilion index – OHI-S) and determination of periodontal indices (papillary-marginal-alveolar index in the Parma modification). We studied the regularity of patients' visits to the dentist and the reasons for appeals.

The study used the oral health-related quality of life (OHRQoL) questionnaire OHRQoL, which contains 14 questions with a gradation of expressiveness of sensa-

tions from 1, which is interpreted as «never» to 4 points – «very often» and allows evaluating the following parameters: functional limitations (impaired chewing function); physical pain; psychological discomfort; psychological inferiority; social inferiority; damage. The answers to the questions were evaluated in blocks: dysfunction (1-2 questions), feeling of pain (3-4 questions), psychological discomfort (5-6 questions), physical disability (7-8 questions), psychological maladjustment (9-10 questions), violation of socialization (11-12 questions), damage, inferiority (13-14 questions). The degree of influence on OHRQoL was determined by adding up the sum of all OHIP-14 items (56 points maximum), a high indicator indicating a poor quality of life associated with dental health. Patients filled out questionnaires themselves after the interview and obtained written consent from them to conduct scientific research.

Statistical analysis was carried out after the consolidation of results using the application package Statistica 10.0 (StatSoft, Inc., USA) and Microsoft Office Excel 2010.

To compare quantitative indicators, the arithmetic mean (M), and standard deviation (SD) were calculated and the Student criterion (Pt) was determined. The determination of statistical significance for relative values is carried out by the method of the angular Fisher transform (Pφ). The values of the indicator P below 0,05 were considered as statistically significant.

RESULTS

According to the results of the periodontal examination, it was found that 29,1% of patients suffer from acute gingivitis (K05.0), acute periodontitis (K05.2) – 48,1%, chronic periodontitis (K05.3) – 21,7%. The sex and age composition of patients according to nosological forms of periodontal diseases did not differ (Table I).

The majority of patients, both male and, female, who had periodontal disease were in the age group of 40 years and older (89,7% men and 90,2% women, Pφ>0.05). Acute gingivitis among men of this age group was observed in 21.8% of patients, and among women – in 32,6% (Pφ > 0.05), acute periodontitis – 57,7% and 47,8%, respectively (Pφ > 0,05), chronic periodontitis – 20,5% and 19, 6% (Pφ > 0,05). Men in the age group 18-39 years who had periodontal tissue disease were 8 (9,3%), women – 9 (8,9%).

From the anamnesis data, it was established that during the last year, most patients in the age group over 40 years visited a dentist. The proportion of such patients is 93%. The reasons for treatment were: consultation (22,1%), pain or problems with teeth, gums, oral cavity (19,2%), treatment and/or continuation of treatment (15,1%), and preventive examination (43%).

According to the results of patients' self-assessment of the quality of life associated with oral health, a good lifestyle can be stated. Over the past year, among the majority of respondents, dental problems have sometimes been bothered. The degree of influence on OHRQoL is minimal – the sum of points according to the results of the survey for men was 15,48±1,7 points, for women – 15,31±1,1 points, Pt=0,44. The summarized results of the survey of patients in the age group of 40 years and older are presented in Table II.

Almost 50% of patients said that the most tangible problems related to the health of their oral cavity were functional disorders (31,7%), pain in the oral cavity ,and difficulties in eating food (16,6%). Psychological problems were reported by 16,3% of respondents, among whom one-third noted a feeling of irritability and tension, dissatisfaction with eating, and also noted limitations in communication with people and the need to interrupt food intake during its intake due to oral problems.

DISCUSSION

Disadvantages associated with the prevention of oral diseases, late treatment reduce the quality of life of patients, and the treatment significantly changes its quality depending on age, gender and methods [7-10].

The study of the quality of life related to the state of oral health was conducted among patients with periodontal diseases, who were of the same type according to the main characteristics (gender, age, nosological forms of periodontal tissue diseases, motivation to preserve dental health). Generalization of the results of self-assessment of the profile of the impact of dental problems on the daily life of respondents showed that, in general, the quality of life of the examined patients was good. This may be due to the preservation of the principles of targeted medical examination in the medical care of the attached population to the SIS «RPC PCM» SAD and the possibility of the attached contingent undergoing annual preventive examinations by a dentist, as well as to be monitored by dentists within the framework of programs of dispensary monitoring of patients at risk of developing the most common non-communicable diseases.

Most patients enrolled in the study are motivated to maintain and/or improve their dental health. Every year, more than 60% of patients turned to a dentist for consultation (22,1%) and preventive examination (43%). 15,1% of patients underwent treatment for diseases of the oral cavity and teeth. In general, the coverage of respondents by examinations by dentists over the past year is 93%.

It is known that the severity of clinical manifestations of various pathologies on the part of the oral cavity not only reflect the fact of loss of dental health itself,

Table I. Sex and age composition of patients with periodontal diseases

Nosological form (number of patients)	Men				Women			
	Age group				Age group			
	Over 60 years n (%)	40-49 years n (%)	25-39 years n (%)	18-25 years n (%)	Over 60 years n (%)	40-49 years n (%)	25-39 years n (%)	18-25 years n (%)
Acute gingivitis (55)	11 (50%)	6 (27,3%)	3 (13,6%)	2 (9,1%)	23 (69,7%)	7 (21,2%)	3 (9,1%)	–
Acute periodontitis (91)	42 (93,3%)	3 (6,7%)	–	–	38 (82,6%)	6 (13,0%)	2 (4,4%)	–
Chronic periodontitis (41)	15 (78,9%)	1 (5,3%)	2 (10,5%)	1 (5,3%)	16 (72,7%)	2 (9,1%)	4 (18,2%)	–

Table II. Characteristics of patients' quality of life problems related to dental health and periodontal diseases

The nature of the problem	Problem	Indicator of the impact of dental problems on quality of life (M ± SD)		P_t	Frequently answered questionnaire questions OHIP 14
		Men	Women		
Dysfunction	Difficulty pronouncing / Loss of taste	1,33 ± 0,47	1,31 ± 0,46	> 0,05	Never 68,3% Sometimes 31,7%
Sensation of pain	Oral pain ... / Difficulty eating	1,22 ± 0,52	1,17 ± 0,41	> 0,05	Never 83,4% Sometimes 13,7% Frequently 2,9%
Psychological discomfort	The feeling of limitation when communicating / Feeling of tension	1,08 ± 0,28	1,05 ± 0,22	> 0,05	Never 93,6% Sometimes 6,4%
Physical disability	Dissatisfaction with eating / Interruption of food consumption	1,06 ± 0,26	1,08 ± 0,31	> 0,05	Never 94,8% Sometimes 5,2%
Psychological maladjustment	Inability to relax / Embarrassment	1,04 ± 0,21	1,05 ± 0,22	> 0,05	Never 95,3% Sometimes 4,7%
Violation of socialization	Irritability / Difficulties during normal work	1,00 ± 0,00	1,00 ± 0,00	> 0,05	Never 100%
Damage, inferiority	Dissatisfaction with life / Failure to act normaly in every day activity	1,01 ± 0,08	1,00 ± 0,00	> 0,05	Never 99,7% Sometimes 0,3%

but also significantly affect the patient's quality of life. Periodontal diseases negatively affect the quality of life, with severe periodontitis worsening aspects related to function and aesthetics. Unlike periodontitis, gingivitis is associated with pain and negatively correlates with feeling comfortable [11]. The results of our factor analysis of self-esteem of respondents with various periodontal diseases of quality of life characteristics showed that the most significant problems associated with periodontal health are psychological discomfort – factor 1 (feeling of tension and dissatisfaction with eating due to oral problems), its share in the total variance of the main components of factor analysis is 16,1%. Another problem related to periodontal health is functional disorders (factor 2 – loss of taste, share in the total dispersion 12,5%, factor 3 – difficulties in pronouncing sounds due to oral problems – 12,4%, factor 4 – difficulties in eating, share in total variance 11,8%).

Based on the above data, the quality of life of patients, which is associated with the state of their dental health, is not the last position in the quality of dental care and it must be taken into account in the practice of dentists. Indicators of quality of life are variable depending on the patient's condition, so it is necessary to correct them at all stages of monitoring the patient's health (routine preventive examinations and treatment). The participation of the patient in assessing his condition is a valuable and informative indicator of the state of his dental health [12].

A promising direction of scientific research is the search for methods for formalized assessment of the effective-

ness of dental care, in particular the creation of formulas convenient in daily clinical administration to assess the quality of life of dental patients, as well as the need to search for new criteria for the relationship between clinical objective and subjective indicators of quality of life.

CONCLUSIONS

Periodontal tissue diseases reduce the quality of life of patients as a generalized characteristic of physical, psychological, emotional, and social functioning of a person. Assessing the quality of life related to oral health is essential to determine the effectiveness of measures aimed at improving and preserving public health. Modern approaches to the preservation of dental health should include achieving optimal control over the disease and improving the quality of life of patients, paying attention to the patient with his individual perception of the outside world and his illness.

REFERENCES

1. Vasko M, Tkachenko I, Kovalenko V et al. Clinical assessment of the condition of periodontal tissues in patients with chronic generalized periodontitis class II. Aktualni problemy suchasnoi medytsyny: Visnyk ukrainskoi medychnoi stomatolohichnoi akademii. 2021;21(3(75)):52-57. doi:10.31718/2077-1096.21.3.52.
2. Haag DG, Peres KG, Balasubramanian M, Brennan DS. Oral Conditions and Health-Related Quality of Life: A Systematic Review. Journal of dental research. 2017;96(8):864–874. doi: 10.1177/0022034517709737.
3. Brignardello-Petersen R. Tooth loss, periodontal disease, and dental caries may be associated with decreased oral health-related quality of life, but there is no evidence about the magnitude of this association. Journal of the American Dental Association (1939). 2017;148(10):e150. doi:10.1016/j.adaj.2017.06.049.
4. Wong LB, Yap AU, Allen PF. Periodontal disease and quality of life: Umbrella review of systematic reviews. Journal of periodontal research. 2021;56(1):1–17. doi:10.1111/jre.12805.
5. Su N, van Wijk A, Visscher CM. Psychosocial oral health-related quality of life impact: A systematic review. Journal of oral rehabilitation. 2021;48(3):282–292. doi:10.1111/joor.13064.
6. Kolenko Yu G, Volovyk IA, Myalkivsky KO. The influence of periodont tissue diseases on the quality of life of patients Actual Dentistry. 2021;(2):36-42. doi:10.33295/1992-576X-2021-2-36.
7. Zhachko N, Nespriad'ko-Monborgne T, Skrypnyk I, Zhachko M. Restoration of oral health as one of the important factors improving the quality of life. Actual Dentistry. 2021;(1):78-81. doi:10.33295/1992-576X-2021-1-78.
8. Vodoriz Yalu. Obgruntuvannia vyboru optymalnoho metodu likuvannia patsiientiv z defektamy tverdykh tkanyn zubiv u frontalnii diliantsi. [Substantiation of choice of the optimal treatment method of patients with defects of tooth hard tissues of anterior teeth]. Poltava: Poltavskyi derzhavnyi medychnyi universytet, MOZ; 2021. 2023. http://repository.pdmu.edu.ua/handle/123456789/18231 [date access 17.05.2023] (in Ukrainian)
9. Janishen I, Andrienko K, Pogorila EA, Saliya L. Otsinka éfektyvnosti ortopedychnoho likuvannya patsiyentiv zi znimnymy konstruktsiyamy zubnykh proteziv na pidstavi danykh yakosti zhyttya. [Orthopedic treatment's evaluation of patients using removable dentures based on quality of life]. Experimental and Clinical Dentistry. 2018;4(3):40-45. doi:10.35339/ecd.4.3.40-45 (in Ukrainian).
10. Yanko N, Kaskova L, Pavlenkova O et al. Assessment of impact of oral health parameters on oral health-related quality of life in future dentists. Ukrainian Dental Almanac. 2020;(2):47-52. doi:10.31718/2409-0255.2.2020.07.
11. Ferreira MC, Dias-Pereira AC, Branco-de-Almeida LS et al. Impact of periodontal disease on quality of life: a systematic review. Journal of periodontal research. 2017;52(4):651–665. doi:10.1111/jre.12436.
12. Rawlinson A, Vettore MV, Baker SR, Robinson PG. Periodontal treatment, psychological factors and oral health-related quality of life. Journal of clinical periodontology. 2021;48(2):226–236. doi:10.1111/jcpe.13405.

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ORIGINAL ARTICLE

EBV-ENCEPHALITIS IN CHILDREN: DIAGNOSTIC CRITERIA

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ABSTRACT

The aim: To investigate the clinical characteristics of EBV infection in the pediatric nervous system using laboratory methods and brain MRI data.
Materials and methods: We observed 41 children with EBV encephalitis ranging from 8 months to 17 years old. The diagnosis of EBV-encephalitis was established on the basis of clinical and medical history, laboratory and instrumental (brain MRI) data. The main thing in the diagnosis was clinical symptoms, combining general infection, cerebral syndromes and focal neurological symptoms. The etiology of Epstein-Barr virus was determined using ELISA and PCR.
Results: EBV-encephalitis can be as a manifestation of reactivation of persistent EBV infection (85%), much less often - acute primary EBV infection (15%). By nature, the duration of EBV encephalitis has distinguished two forms of its course: acute (63%) and chronioc (37%). The criteria of differential diagnosis of acute and chronic forms of EBV-encephalitis are proposed, which include the most common anamnesis data, clinical manifestations and changes in brain MRI.
Conclusions: The proposed criteria specifically for acute and chronic forms of EBV-encephalitis can contribute to the timely and more accurate diagnosis of this disease in children.

KEY WORDS: Epstein-Barr virus, EBV-infection, herpesvirus, nervous system, magnetic resonance imaging

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INTRODUCTION

Neuroinfections are the leading pathology in severity of the course and adverse effects. Encephalitis and meningoencephalitis occupy a significant place, the etiological factor of which is most often viruses [1, 2]. More than 20% of all acute encephalitis is caused by herpes viruses because the whole family of herpes viruses (8 types) has tropism to the nervous system. Epstein-Barr virus (EBV) ranks third among herpes viruses in the incidence of encephalitis, after the herpes simplex virus (HSV) and cytomegalovirus (CMV) [3].

A special place among the variety of clinical forms of EBV infection is given to EBV lesions of the nervous system (NS). The frequency of neurological complications of EBV infection is between 0,4–7,5% in the different cases [4]. Neurological manifestations of EBV infection performed by encephalitis, aseptic meningitis, transverse myelitis, acute cerebellar ataxia, optic neuritis, Guillain-Barre syndrome or acute demyelinating encephalomyelitis [5]. There is information about the role of EBV in the development of mental deterioration, reversible Parkinsonism, and coagulation disorders [4]. EBV-lesions can located in the brainstem, cerebellum, thalamus, basal ganglia, optic nerve, or spinal cord [6].

The pathogenesis of neurological diseases caused by EBV infection remains unclear. Three pathways of pathogenesis have been identified so far. The first way involves the development of EBV encephalitis (EEBV) as a primary infection as a result of direct viral invasion into the nervous system. In this case, only neurological symptoms are observed in the absence of other manifestations of EBV infection (such as tonsillitis, lymphadenopathy, hepatosplenomegaly) [7]. The second route involves the development of an im-

mune-mediated infection. The patient's immune system produces autoimmune T-lymphocytes and anti-neuronal antibodies to myelin-oligodendrocyte glycoprotein, which has a similar antigen to EBV. Thus, the immune system, by triggering the mechanisms of destruction of EBV, contributes to the destruction of its own cells [7-10]. The third, perhaps the main mechanism for the development of EBV-related neurological disease is the reactivation of a latent infection. In immunosuppressed patients, specific antibodies to EBV are produced in the nerve sheath, leading to reactivation of EBV infection in the nervous system [7].

Despite the fact that neurological diseases of EBV etiology are continuously attracting the attention of scientists from different countries, EEBV in children is still poorly understood and the diagnosis could be difficult.

THE AIM

The purpose of our work is to investigate the clinical characteristics of EBV infection in the pediatric nervous system using laboratory methods and brain MRI imaging data.

MATERIALS AND METHODS

The study was performed between January 2019 and December 2022. 41 children (25 boys and 16 girls) with EBV- encephalitis, who were hospitalized at the Kharkiv Regional Children's Clinical Hospital, were studied. The patients' ages ranged from 8 months to 17 years old.

The diagnosis of EEBV was established on the basis of clinical and medical history findings, laboratory and instrumental (echoencephaloscopy, MRI of the brain) data. The etiology of Epstein-Barr virus was determined by serological results (the presence of virus-specific antibodies EBV VCA IgM, EBV EA IgG and EBV NA IgG in the blood by enzyme-linked immunosorbent assay (ELISA) and detection of EBV DNA in blood, cerebrospinal fluid by polymerase chain reaction (PCR). The detection of the DNA pathogen in the patient's cerebrospinal fluid by PCR was an indicator of the active replication of the virus in the child's body. The diagnosis of EBV infection was established at least two positive markers for EBV.

Statistical analyses in this study were conducted using MS Excel and STATISTICA 8.0 (Tulsa, OK) software. The mean M for each indicator was used to determine the difference between the values of the indicators in the comparison groups. To compare two independent samples, a non-parametric Mann-Whitney U-test has been used. The difference between groups was considered statistically significant when $p < 0,05$.

RESULTS

Laboratory data allowed us to divide patients into two groups: (1) acute primary EBV infection - 6 (15%) patients, and (2) reactivation of persistent EBV infection - 35 (85%) cases. Acute primary EBV infection was established based on the presence of specific acute phase antibodies (EBV VCA IgM and EBV EA IgG) in the patient's blood serum with the absence of late EBV NA IgG antibodies. Detection of nuclear antibodies (EBV NA IgG) with acute phase markers in the patient's blood indicated reactivation of persistent EBV infection.

The study of anamnestic data, the character of the onset of the disease, and the course of the clinical picture of the disease made it possible to distinguish 2 forms of the duration of EEBV: acute and chronic. In all 6 children with primary EBV infection, the duration of encephalitis was acute. Among 35 children with reactivation of persistent EBV infection, the duration of encephalitis was both acute (20 children) and chronic (15 patients). Acute duration of encephalitis in children with primary and reactivation of EBV infection has no any differences, so we combined these patients into one group with acute duration of EEBV. Thus, acute form of EEBV was diagnosed in 26 (63%) children, chronic - in 15 (27%) patients.

The analysis of anamnesis data made it possible to identify a connection with infectious mononucleosis (IM) in 6 (23,1%) patients with an acute EEBV but was not observed at all in children with the chronic form of this disease ($p<0,05$). A history of neurologic diseases was observed exclusively in patients with the chronic form of encephalitis ($p<0,01$). All patients with a chronic course of EEBV in anamnesis had some neurological disorders, such as vascular dystonia, neurosis of obsessive states - 6 (40,0%) patients, history of seizures - 5 (33,3%) patients, 4 (26,7%) children were previously treated for EEBV.

General infection syndrome is a characteristic of both forms of EEBV and is represented by an increase in body temperature and general malaise. Low-grade fever was typical for both acute and chronic forms of EEBV - 29 (70,7%) cases. However, its duration in patients of different groups varied: in acute form - from 3 to 14 days, in chronic sluggish form - from 3 months to 5 years. In 10 (24,4%) patients exclusively with acute EEBV febrile fever was observed. In 2 (4,9%) patients with a chronic form of EEBV the clinical picture developed against a background of normal body temperature.

Cerebral syndrome was observed in 26 (63,4%) patients and was represented by impaired consciousness of varying severity. A mild degree of impaired consciousness in the form of inhibition occurred in 15 (36,6%) patients with both acute and chronic forms of

Table I. Focal neurological symptoms characteristic of meningoencephalitis

Symptoms	Acute form, n = 26	Subacute form, n = 15	p-value
Hemiparesis (plegia)	12 (46,1%)	3 (20,0%)	p < 0,05
anisoreflexia, changes in muscle tone, pathological signs	14 (53,8%)	10 (66,7%)	NS
Extrapyramidal symptoms (tremor, psychopathological problems)	6 (23,1%)	11 (73,3%)	p <0,01
Damage to the oculomotor nerves	19 (73,1%)	6 (40,0%)	p < 0,05
Facial nerve damage	11 (42,3%)	2 (13,3%)	p < 0,05
Bulbar nerve damage	6 (23,1%)	0 (0%)	p < 0,05
Ataxia	13 (50,0%)	4 (26,7%)	NS

Table II. Pathological changes in the structure of the brain according to MRI

Symptoms	Acute form, n = 26	Subacute form, n = 15	p-value
Hypotrophy of the cerebral cortex	2 (8,9%)	13 (86,7%)	p <0,01
Signs of external hydrocephalus	13 (52,0%)	15 (100%)	p <0,01
Swelling of the mucous membranes of the sinuses	11 (44,0%)	2 (13,3%)	p < 0,05
Damage to the white matter and subcortical nuclei of the brain	18 (72,0%)	1 (6,7%)	p <0,01
Inflammation of the arachnoid membranes	7 (28,0%)	1 (6,7%)	p < 0,05
Brain stem inflammation	6 (24,0%)	0 (0%)	p < 0,05
Ventricular dilatation of the brain	4 (16,0%)	11 (73,3%)	p <0,01
Periventricular gliosis	1 (4,0%)	5 (33,3%)	p< 0,05
Dystrophy of the cerebellum and white matter of the brain	0 (0%)	5 (33,3%)	p <0,01

the disease. A severe degree of impaired consciousness in the form of sopor and coma was characteristic exclusively for the acute form of encephalitis and was observed in 11 (26,8%) patients. In 15 (36,6%) patients, consciousness was preserved.

One of the manifestations of EEBV was convulsive syndrome. It occurred in all patients. Large generalized convulsive seizures were observed in 15 (57,7%) children with acute EEBV and 6 (40,0%) with chronic form. Focal convulsions were observed in 9 (34,6%) patients and 4 (26,7%) cases, respectively. These convulsive manifestations were determined in patients of both groups with almost the same frequency (p>0,05) and cannot serve as indicators of differentiation of acute and chronic forms of EEBV. In contrast, small atonic seizures, myoclonus were characteristic exclusively for the chronic form of encephalitis (8 (53,3%) patients), as p<0,05 reliably indicates.

An analysis of the clinical manifestations of EEBV in children allowed us to identify clinical characteristic features of various forms of this disease (Table I).

Clinical leading of encephalitis was focal neurological symptoms, the analysis of which made it possible to identify the characteristic signs for each of the forms of EEBV.

Pyramidal symptoms were manifested by hemiparesis and were observed in 12 (26,1%) patients with acute form and 3 (20,0%) children with chronic form of encephalitis. Pathology of the oculomotor nerves was detected in 19 (73,1%) patients with acute form and 6 (40,0%) patients with chronic form of encephalitis. Facial nerve damage - in 11 (42,3%) and 2 (13,3%) patients, respectively. Disorders from the bulbar nerves - in 6 (23,1%) children with acute EEBV and were absent in patients with chronic form. Manifestations of extrapyramidal symptoms (tremor, choreoathetosis) were determined in 11 (73,3%) patients with chronic form and 6 (23,1%) children with acute encephalitis.

Neurological symptoms such as anysoreflexia, changes in muscle tone, pathological signs, and ataxia were detected with the same frequency in patients of both groups (p>0,05) and cannot serve as differentiation criteria for any form of EEBV.

The final diagnosis of encephalitis was established on the basis of changes in the brain detected by MRI of the brain (Table II).

Due to the severity of the condition, MRI was not performed for one patient. The main MRI signs of the acute form of EEBV were lesions of the subcortical areas and the white matter of the brain, as p<0,001 reliably

indicates. These changes were observed in 18 (72%) patients with acute EEBV and only in 1 (6,7%) child with chronic form. Characteristics are signs of brain stem damage that were found in 6 (24%) patients exclusively with acute EEBV ($p<0,05$). The involvement of the arachnoid in the inflammatory process indicated the presence of arachnoiditis in 7 (28,0%) patients with an acute form and only 1 (6,7%) child with a chronic form ($p<0,05$). Signs of edema of the mucous membranes of the main and paranasal sinuses were determined in 11 (44,0%) patients with acute encephalitis and only in 2 (13,3%) children with chronic form ($p<0,05$).

DISCUSSION

Considering the variants of the pathogenesis of EBV lesions of the nervous system, EEBV can be a manifestation of primary or reactivation of persistent EBV infection, as well as an immune-mediated reaction [4]. According to our research, EEBV in children is predominantly caused by the first two variants of development (both acute primary (6/41, 15%) and reactivation of persistent EBV infection (35/41, 35%)). So, the leading role in the occurrence of EEBV in children is assigned to the reactivation of persistent EBV infection, which is fully consistent with the data of scientists from Thailand [4].

Taking into account the characteristics of the course, EBV CNS infections we divided into two groups: 1) acute (26/41, 63%) and 2) chronic duration (15/41, 37%). According to research by Japanese scientists, which completely coincided with our data, EBV infection of the NS can be considered as manifestations of two forms: (1) acute duration associated with primary or reactivated EBV infection, (2) chronic course associated with reactivation of EBV-infection only [11]. Our study showed that in most (35/41, 85%) cases EEBV had no any connection with IM, but in some (6/41, 15%) patients EEBV was present in forms simultaneously with the clinical symptoms of IM – 5 cases, or later during the recovery phase – 1 case. Explanation of this fact is based on the pathogenesis of CNS diseases EBV etiology: can be primary EBV-infection, latent reactivation of the virus, or an antibody-mediated post-infection inflammatory reaction, so the clinical symptoms of IM may not necessarily accompany all cases of EEBV [4, 7, 11].

We were able to establish some anamnesis features characteristic of acute and chronic forms of EEBV: association with IM was observed in rare (15% cases) and exclusively in patients with an acute form of EEBV ($p<0,05$), but data of neurologic diseases in past - exclusively in patients with a chronic form of EEBV ($p<0,01$).

Our research revealed convulsive syndrome in 100% of patients with EEBV. Many foreign authors point to manifestations of the convulsive syndrome in patients with EEBV [3, 4, 7, 11, 12]. A possible pathophysiological mechanism for seizures was proposed by Japanese scientists: EBV initially infected and reactivated in astrocytes, leading to astrocyte dysfunction and neuronal hyperexcitability, resulting in seizures [12]. Low-grade fever (29/41, 70,7%), different degrees of consciousness disturbance impaired (26/41, 63,4%), ataxia (17/41, 41,5%) cranial nerve involvement (21/41, 51,2%) were typical for EEBV. Our findings were similar to the results reported by Cheng H. et al. [7]. However these symptoms were determined in patients of both acute and chronic forms of EEBV with almost the same frequency ($p>0,05$) and cannot serve as indicators of differentiation of these groups.

We were able to identify clinical criteria characteristic of acute and chronic forms of EEBV. The acute form of EEBV is characterized by damage to the cranial nerves (pathology of the oculomotor nerves (19/26, 73,1%), facial nerve damage (11/26, 42,3%), bulbar nerves (6/26, 23,1%) and pyramidal symptoms manifested by hemiparesis (12/26, 46,1%), as $p<0.05$ reliably testifies. The chronic form of EEBV was characterized by the presence of extrapyramidal symptoms, as evidenced by $p<0,001$. In most (11/15, 73,3%) patients with chronic form were determined tremors, choreoathetosis, and emotional and psychopathological disorders (hallucinations, fears).

The literature provides different data on brain changes detected on MRI in EEBV. Smith H. et al. [13] revealed such IMR findings in patients with EEBV - multifocal areas of hyperintensity present mainly within the sub-cortical white matter and deep grey nuclei of the brain. According to our data, MRI signs of acute EEBV include damage to the subcortical structures and white matter (18/26, 72,0%), signs of damage of the arachnoid membranes (7/26, 28,0%), brainstem inflammation (6/26, 24,0%). The main MRI signs of the chronic form of EEBV include internal and external hydrocephalus (15/15, 100%), signs of cerebral cortex hypotrophy (13/15, 86,7%), and dystrophy of various brain structures (white matter, cerebellum) (5/15, 33,3%), as evidenced by $p<0,001$.

CONCLUSIONS

One of the manifestations of EBV infection in children is the development of such neurological diseases as EEBV. Using highly sensitive methods of laboratory diagnostics (ELISA, PCR) helped us to find that in 85% of cases, EEBV is a manifestation of reactivation of persistent EBV infection, much less often (15%) is

the result of acute primary EBV infection. In 14.6% of the cases, the connection between the development of acute EEBV and infectious mononucleosis was revealed, but most often (85.4% of patients) EEBV occurs in isolation.

According to the nature of the course of EEBV, two forms has been distinguished: acute and chronic. We proposed criteria for the differential diagnosis of acute and chronic forms of EEBV, which included the most common anamnesis data, clinical manifestations, and changes during brain MRI.

REFERENCES

1. Britton PN, Dale RC, Blyth CC et al. Causes and clinical features of childhood encephalitis: a multicenter, prospective cohort study. Clinical Infectious Diseases. 2020;70(12):2517-2526. doi: 10.1093/cid/ciz685.
2. Krawczuk K, Czupryna P, Pancewicz S et al. Wybrane wirusowe neuroinfekcje u dzieci. Polski Merkuriusz Lekarski. 2019; 46(272):88-93 (In Polish).
3. Rudenko AO, Muravska LV, Dyachenko PA et al. Klinichni osoblywosti urazhen nervovoi systemy u hvoryh z monoinfekcieju EBV i w associaciji z inshymy herpesvirusamy pry jih reactyvaciji i persystenciji [Clinical features of nervous system lesions in patients with EBV monoinfection and in association with other herpesviruses during their reactivation and persistence]. Aktual`naâ infectologiâ 2017; 5(6):260-264. doi: 10.22141/2312-413x.5.6.2017.122136. (In Ukrainian)
4. Pangprasertkul S, Sanguansermsri C, Sudjaritruk T. Epstein-Barr virus meningoencephalitis in a young immunocompetent child: A case report. Heliyon. 2022;8(10):e11150. doi: 10.1016/j.heliyon.2022.e11150.
5. Ganea S-L, Arbune M, Santea D-R et al. Meningo encephalitis with Epstein-Barr virus in an immunocompetent adult patient: case report Ro J Infect Dis. 2023;26(1) doi: 10.37897/RJID.2023.1.3.
6. Huang L, Zhang X, Fang X. Case Report: Epstein-Barr Virus Encephalitis Complicated With Brain Stem Hemorrhage in an Immune-Competent Adult. Front Immunol. 2021;12:618830. doi: 10.3389/fimmu.2021.618830.
7. Cheng H, Chen D, Peng X et al. Clinical characteristics of Epstein-Barr virus infection in the pediatric nervous system. BMC Infect Dis. 2020;20(1):886. 2020;20(1):886. doi: 10.1186/s12879-020-05623-1.
8. Wang H, Munger KL, Reindl M et al. Myelin oligodendrocyte glycoprotein antibodies and multiple sclerosis in healthy young adults. Neurology. 2008;71:1142–6. doi: 10.1212/01.wnl.0000316195.52001.e1.
9. Bien CG, Bien CI. Autoimmune encephalitis in children and adolescents. Neurol Res Pract. 2020;2:4. doi: 10.1186/s42466-019-0047-8.
10. Cellucci T, Van Mater H, Graus F et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurol Neuroimmunol Neuroinflamm. 2020;7(2):e663. doi: 10.1212/NXI.0000000000000663.
11. Fujimoto H, Asaoka K, Imaizumi T et al. Epstein-Barr virus infections of the central nervous system. Intern. Med. 2003;42 (1): 33-40. doi: 10.2169/internalmedicine.42.33.
12. Ohya Yu, Nakamura K, Wakisaka Yo et al. Epstein-Barr Virus-Associated Encephalopathy Presenting with Nonconvulsive Status Epilepticus in an Immunosuppressive State. Case Rep Neurol. 2020;12(2):214-221. doi: 10.1159/000507976.
13. Smith H, Sheikh Y, Sharma R et al. Epstein-Barr virus encephalitis. Reference article, Radiopaedia.org. 2023. doi:10.53347/rID-60636.

The authors adhered to the principles contained in the 1964 Declaration of Helsinki and their latest amendments. All the patients gave oral and written voluntary informed consent for examination, tests, treatment, operation, analgesia and data processing. The work with patients was prepared and carried out in accordance with the principles of ethics. The permission to conduct the study and the study protocol were approved of by the bioethics committee of the institution. The work is a fragment of research work of the Department of Infectious Disease, Children Infectious Disease, Phthisiatry and Pulmonology of Kharkiv National Medical University "Etiopathogenetic and clinical features of meningoencephalitis in children and optimization of their treatment" (№ state registration 017U000586; deadline: 2018-2023).

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ORIGINAL ARTICLE

PREDICTIVE VALUE OF PLATELET COUNT AND PLATELET INDICES IN CERVICAL CANCER PATIENTS WITH EXTERNAL RADIATION THERAPY

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ABSTRACT

The aim: This study aims to assess the role of platelets and platelet indices as a cost-effective predictive marker of the cervical cancer patient's response before, 15th, and 25th external radiation.

Materials and methods: A total of 54 cervical cancer patients at Dr. Kariadi Hospital were divided into good and poor therapeutic response groups. Measurements of platelet count and indices including PDW, P-LCR, and PCT were carried out before, 15th, and 25th external radiation.

Results: There was no difference in platelet counts, MPV, PDW, P-LCR, and PCT in both groups, but patients with decreased MPV and P-LCR values on 15th-25th external radiation had a better therapeutic response (p= 0.005 and 0.007).

Conclusions: MPV and P-LCR values at 15th to 25th external radiation appeared to decrease further in the group that responded better to therapy.

KEY WORDS: Platelet count, MPV, PDW, P-LCR, Plateletcrit, External radiation

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INTRODUCTION

Cervical cancer is the second most common type of cancer and the third leading cause of death among women [1]. In developing countries, more than 80% of women with cervical cancer are diagnosed at an advanced stage [2Brazil. MATERIALS AND METHODS: A retrospective cohort study was performed comprising 865 women newly diagnosed with cervical cancer between 2012 and 2014. Times from diagnosis to treatment initiation (less than or equal to 60 days]. Moreover, besides surgery and chemotherapy, approximately 40% of patients receive radiotherapy as one of the therapeutic modalities for treating cancer [3].

A previous study stated that exposure to ionizing radiation has a lethal effect on blood cells. This is because hematopoietic cells are sensitive to radiation exposure, even at low doses [4]. Blood components that can be affected by radiotherapy are hemoglobin, leukocytes, and platelet cells. Following this, the platelet count is influenced by the condition of malignancy in cervical cancer. Platelet activation plays an important role in tumor growth and metastasis. It was also discovered that elevated platelet counts are associated with poor outcomes in several solid malignant tumors, including cancer of the breast, colon, and Non-Small Cell Lung (NSCLC) and others. Furthermore, platelets have many functions and are also involved in the development of malignancy [5].

Radiotherapy has a lethal effect on blood cells because, at low doses, hematopoietic cells are sensitive to radiation exposure. The pathophysiology of malignancy in patients with cervical cancer also affects platelet values. Therefore, the research problem was formulated, whether the platelet count and indices of cervical cancer patients during external radiation can be used as a predictor of patient outcome.

THE AIM

This study aims to assess the role of platelets and platelet indices as a cost-effective predictive marker of the cervical cancer patient's response before, 15th, and 25th external radiation.

MATERIALS AND METHODS

This is a retrospective observational study involving 54 cervical cancer patients receiving external radiation therapy at the radiotherapy unit of Dr. Kariadi Hospital, Semarang. Subjects who had a history of 25 cycles of interrupted external radiation, blood transfusions during external radiation, blood disorders, coagulation disorders, and any combination with chemotherapy during the cycle were excluded from this study. Outcomes were divided into groups of good and poor responses to therapy according to the guidelines of The National Comprehensive Cancer Network. Patients with signs of further metastases, the need for additional radiation doses, and those who require intensive monitoring every month fall into the "poor" outcome category. Meanwhile, the ethical clearance was obtained from the Medical and Health Research Ethics Committee Institute Dr. Kariadi Hospital with a registration number of 1205/EC/KEPK-RSDK/2022

RESEARCH PERIOD AND LOCATION

This study was conducted from July 2022 – August 2022 at the Dr. Kariadi Hospital (RSDK) Semarang. The parameters and hematological indices of cervical cancer patients at the 0th, 15th, and 25th external radiation were examined at the RSDK Laboratory Installation, Semarang.

DATA COLLECTION

Platelet count, mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR), and plateletcrit were evaluated in a complete hematological examination using the Sysmex XN-1000 hematology analyzer using the impedance method to obtain the values. Plateletcrit and MPV normal values are 150 – 450 x 103/µL and 8.4-12 fL, while that of PDW, P-LCR, and Plateletcrit are 10-18 fL, 10-30%, and 0.22-0.24%, respectively.

RESULTS

A total of 316 cervical cancer patients who went to the radio-oncology polyclinic at Dr. Kariadi Hospital from September 2021 to May 2022 were identified. Based on the reports, 147 patients are receiving combination chemotherapy, 46 patients required transfusions during external radiation cycles and 52 patients with interrupted external radiation cycles. Furthermore, 2 patients are with a history of blood disorders, and 15 have incomplete examination data, making 54 patients that were included in the inclusion criteria. According to the characteristics of subjects as presented in Table I, there was no significant difference between early and advanced stages, as well as a history of comorbidities and previous operations on the outcome.

Early and late stages were differentiated by the platelet cut-off value of $300x10^3$/uL. Generally, thrombocytosis is caused by conditions related to the activation

Table I. Characteristics of subjects

Characteristics	Outcome		p-value
	Poor (n=32)	Good (=22)	
Stadium			
I	6 (75)	2 (25)	0.282£
> 1	26 (56.5)	20 (43.5)	
Comorbidities			
Yes	9 (52.9)	8 (47.1)	0.732¥
No	23 (62.2)	14 (37.8)	
History of prior operation			
Yes	7 (70)	3 (30)	0.347£
No	25 (56.8)	19 (43.2)	

* Significant ($p < 0.05$); £ Fisher's exact; ¥ Yates Correction

Table II. Characteristics of thrombocytosis in the early and late stages.

Stadium	Platelet		p-value
	≤ 300 x 10^3/uL(13)	≤ 300 x 10^3/uL(13)	
I	3 (37.5)	3 (37.5)	
>I	10 (21.7)	10 (21.7)	0.290£

* Significant ($p < 0,05$); £ Fisher's exact

Table III. The comparison between the platelet count and the platelet indices.

Parameter	Outcome		p-value
	Poor (32)	Good (22)	
Platelet (103/uL)			
I	383.22 ± 93.05	373.77 ± 183.56	0.135‡
II	289.31 ± 113.99	262.59 ± 77.31	0.454‡
III	282.03 ± 99.28	293.36 ± 100.17	0.972‡
p-value	0.001†*	0.001†*	
I – II difference	-93.91 ± 114.38	-111.18 ± 154.21	0.616‡
I – III difference	-101.19 ± 97.91	-80.11 ± 128.84	0.154‡
II – III difference	-7.28 ± 74.66	30.77 ± 73.52	0.070§
MPV (fL)			
I	9.52 ± 0.72	9.68 ± 1.05	0.512§
II	9.19 ± 0.66	9.37 ± 0.68	0.508‡
III	9.19 ± 0.72	8.95 ± 0.73	0.177‡
p-value	0.007¶*	<0.001†*	
I – II difference	-0.33 ± 0.55	-0.31 ± 0.56	0.902§
I – III difference	-0.33 ± 0.70	-0.72 ± 0.65	0.122‡
II – III difference	0.003 ± 0.62	-0.41 ± 0.32	0.005§*
PDW (fL)			
I	10.09 ± 1.80	10.58 ± 2.35	0.393‡
II	9.45 ± 1.62	9.52 ± 1.29	0.591‡
III	9.29 ± 1.42	9.03 ± 1.45	0.503‡
p-value	0.001†*	0.001†*	
I – II difference	-0.64 ± 1.43	-1.06 ± 1.72	0.393‡
I – III difference	-0.80 ± 1.62	-1.55 ± 1.37	0.070‡
II – III difference	-0.16 ± 1.16	-0.49 ± 0.77	0.251§
P-LCR (%)			
I	20.79 ± 6.00	22.25 ± 8.40	0.460§
II	18.28 ± 5.38	19.24 ± 5.48	0.523§
III	18.15 ± 5.91	16.43 ± 5.87	0.238‡
p-value	0.007¶*	<0.001†*	
I – II difference	-2.51 ± 4.51	-3.00 ± 4.38	0.692§
I – III difference	-2.64 ± 5.90	-5.81 ± 5.05	0.100‡
II – III difference	-0.13 ± 4.89	-2.81 ± 2.53	0.007§*
Plateletcrit (%)			
I	0.36 ± 0.08	0.35 ± 0.14	0.141‡
II	0.26 ± 0.09	0.24 ± 0.06	0.672‡
III	0.26 ± 0.08	0.26 ± 0.09	0.579‡
p-value	<0.001†*	<0.001†*	
I – II difference	-0.10 ± 0.10	-0.11 ± 0.12	0.402‡
I – III difference	-0.10 ± 0.08	-0.09 ± 0.10	0.220‡
II – III difference	-0.01 ± 0.06	0.02 ± 0.07	0.236§

*Significant ($p < 0.05$); § Independent t; ‡ Mann Whitney; † Friedman; ¶ Repeated Anova; I = (before) external radiation; II = 15th external radiation; III = 25th external radiation

situation, while platelets release granules containing various contents that can inhibit and stimulate plasmatic coagulation, angiogenesis immunosurveillance, or plasma neo-growth [6] In this study, there was no

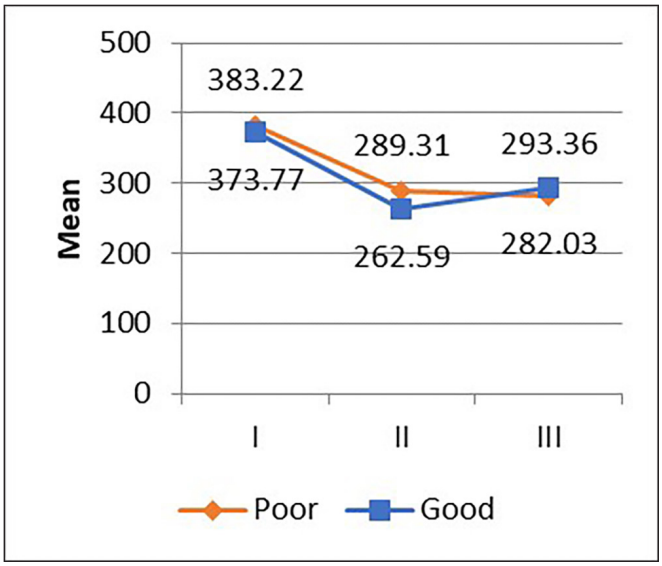

Fig. 1. Platelet graph (103/mL)

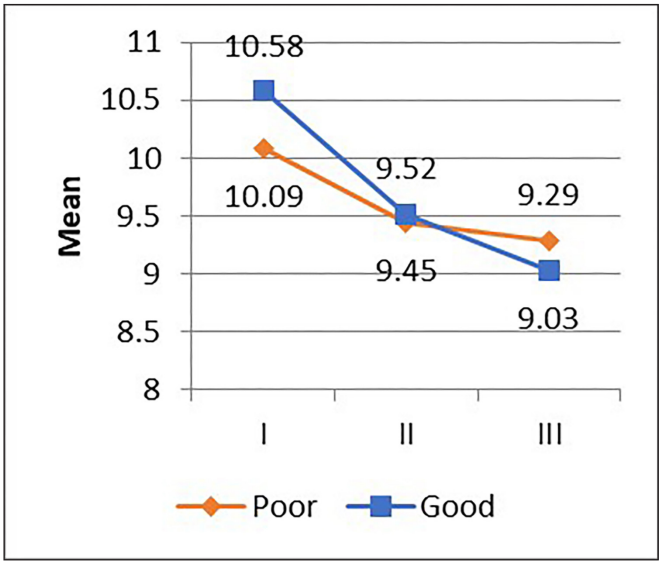

Fig. 3. PDW graph (fL)

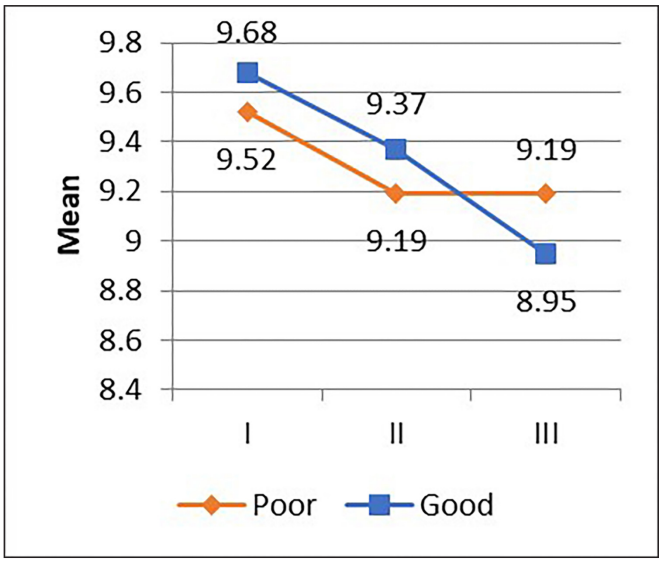

Fig. 2. MPV graph (fL)

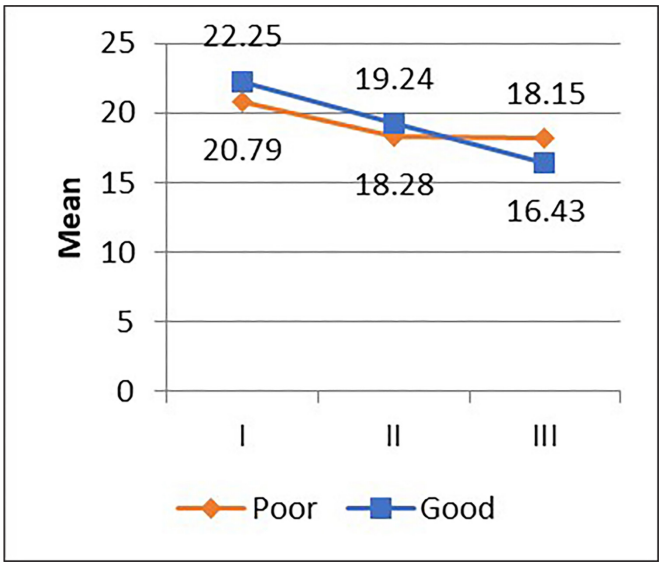

Fig. 4. P-LCR graph (%)

significant difference in the comparison of early and advanced stages of the incidence of thrombocytosis, as shown in Table II.

Platelet count and indices values were recorded on each visit before, the 15th, and 25th external radiation as illustrated in Table III. Based on a comparison of the platelet difference and platelet index was carried out, there is a significant difference in MPV and P-LCR values at the 15th and 25th external radiation. Figure 1-5 depicts the travel curve of platelet values and index before (I), 15th (II), and 25th external radiation (III). The MPV, PDW, and P-LCR graphs show a decrease along the course of the external radiation cycle. However, the PDW did not show any significant difference in those times to the outcome, with p values of I-II 0.393, I-III 0.070, and II-III 0.251.

An overview of the range of differences in the MPV and P-LCR parameters is presented in Figures 6 and 7. From the two graphs, the range of differences in the MPV and P-LCR is larger, which further illustrates the decrease in the value of these parameters in the good outcome group. The cut-off value from the difference in the platelet index results was also identified to assess the Area Under the Curve, and the result is illustrated in Figure 8.

From Table IV, the difference between MPV had the best Area Under the Curve value. According to the Chi-square analysis, there is no significant difference in all parameters for the two groups. Therefore, the above parameters cannot be used as predictors of the outcome of cervical cancer patients who received external radiation therapy as shown in Table V.

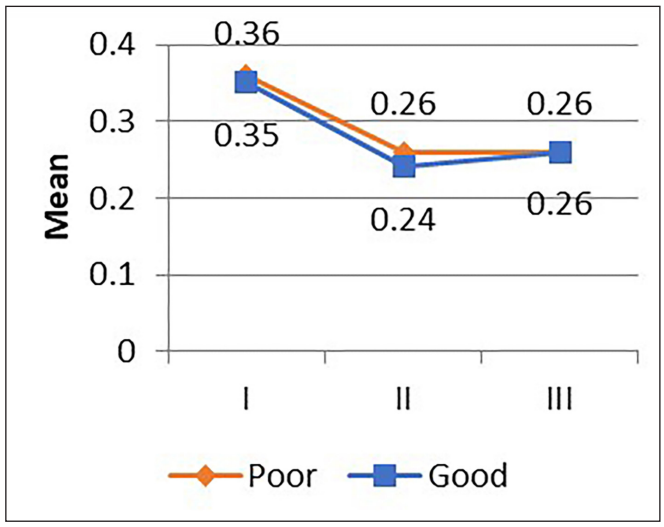

Fig. 5. Plateletcrit graph (%)

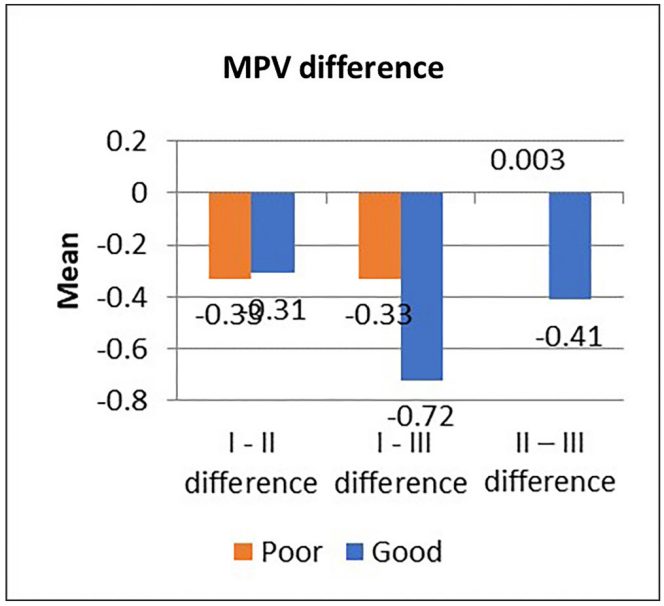

Fig. 6. MPV difference graph (fL)

DISCUSSION

This study showed that patients with decreased MPV and P-LCR values at 15 - 25 external radiation had a better response to therapy (p = 0.005 and 0.007). Generally, the MPV indicates the average size of platelets in the blood. When the MPV value of more than 13 fL tends to occur in hyperdestruction, the platelets become larger, and the activity increases, while a value lower than 8 fL signifies hypoproduction. In a meta-analytic study, it was discovered that MPV has a potential biomarker of patient prognosis due to higher MPV scores obtained with poorer clinical outcomes [7also called thrombocytes, are produced in bone marrow and are the second most numerous blood cells which circulate in blood and play a pivotal role in hemostasis, wound healing, angiogenesis. There is a large body of evidence

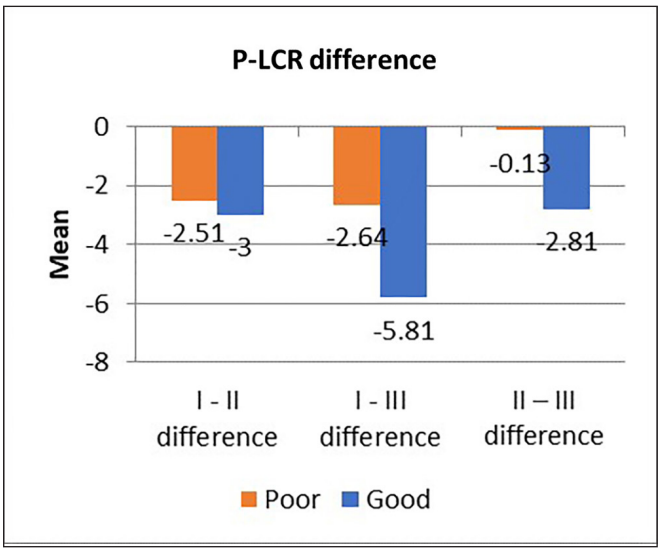

Fig. 7. P-LCR difference graph

that platelets are likely to contribute to inflammation in multiple diseases. Also, recent studies revealed the association between platelet indices (PI]. A study conducted by Lembeck et al. showed a significant relationship between increased MPV, which is often associated with clinical deterioration in pancreatic duct adenocarcinoma patients [8].

The P-LCR is another marker of platelet activity that describes the percentage of platelets in the bloodstream with a volume of more than 12 fL. A previous study discovered a direct relationship between P-LCR with PDW and MPV, as well as an inverse correlation with platelet counts in patients with thrombocytopenia. P-LCR appears to be more susceptible to changes in platelet size than MPV, although there is a correlation [7also called thrombocytes, are produced in bone marrow and are the second most numerous blood cells which circulate in blood and play a pivotal role in hemostasis, wound healing, angiogenesis. There is a large body of evidence that platelets are likely to contribute to inflammation in multiple diseases. Also, recent studies revealed the association between platelet indices (PI]. According to Wei Yang et al, decreased MPV and P-LCR indicated a more severe condition for gynecological tumors with a lower survival rate [9]. However, different results were obtained in this study, where MPV values decreased in patients with good outcomes, as supported by other investigations. There are no studies that explain the character of the P-LCR on the outcome of cervical cancer patients.

Platelets play an important role in the pathophysiological process of tumors, including the development of neoplasms and the metastatic process. In cancer development, various tumor-associated humoral factors and cytokines directly influence megakaryopoiesis and

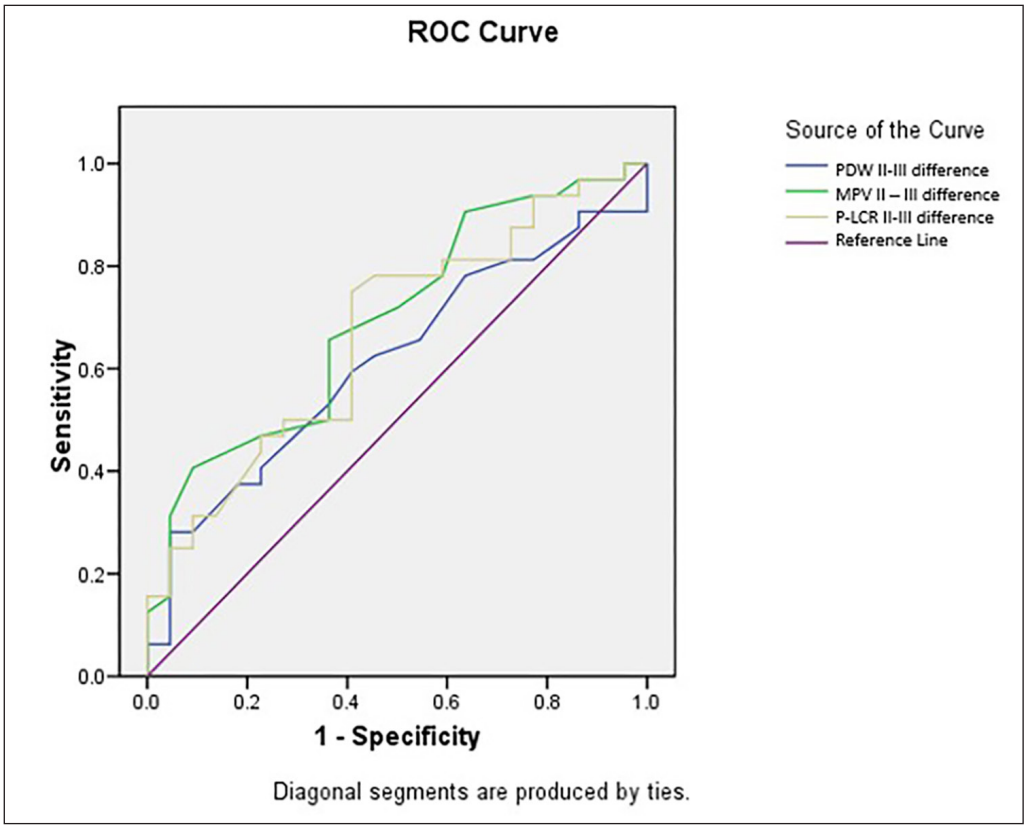

Fig. 8. ROC graph

Table IV. The Area Under the Curve of the difference between the platelet value and indices on the 15th – 25th external radiation based on the outcome.

Variables	AUC	p-value	IK 95%		Cut-off point
II-III difference			Lower	Upper	
Thrombocyte	0.653	0.057	0.505	0.802	11.500
PDW	0.613	0.162	0.463	0.763	-0.350
MPV	0.694	0.016	0.553	0.835	-0.250
P-LCR	0.667	0.039	0.521	0.813	-1.700
PCT	0.563	0.433	0.407	0.719	0.015

II = 15th external radiation, III = 25th external radiation, AUC, Area Under the Curve.

thrombopoiesis. It has been shown that primary tumors can produce and secrete granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) into the bloodstream. This can lead to the stimulation of megakaryopoiesis and subsequent thrombopoiesis, which subsequently causes increased platelet activity [10].

The response to radiation exposure is observed in the induction of apoptosis in bone marrow cells, including hematopoiesis stem cells. Ionizing radiation will activate p53 and induce Puma to block the interaction between antiapoptotic proteins (Bcl-2 and Bcl-xl) and proapoptotic effectors (Bax and Bak). Subsequently, mitochondria will release caspase-activating factors (cytochrome c and Apaf-1), which activate Caspase-3, -6, and -7 and cause apoptosis [4]. The greater the radiation dose absorbed, the more hematopoietic stem cells and precursor cells die, and the less or no more functional mature cells are formed. This effect is most likely to occur with large volumes of radiation, such as to the pelvic area or spine which is the main site of functional bone marrow, with approximately 60% of the total volume [4]. In this study, radiation was administered to the entire pelvic area at a dose of 25x2 Gy.

CONCLUSIONS

The results showed that patients with decreased MPV and P-LCR values at the 15th - 25th external radiation had a better response to therapy (p = 0.005 and 0.007). However, the platelet count and indices cannot be used as predictors of the outcome of cervical cancer patients undergoing external radiation therapy. This makes it necessary to carry out a further investigation

Table V. Chi-square analysis on the platelet count and indices difference to the 15th – 25th external radiation based on the outcome.

Variable	Outcome		p-value	RR (95% CI)
	Poor (32)	Good (22)		
Platelet				
≤ 11.50	20 (71.4)	8 (28.6)	0.107¥	1.55 (0.96 – 2.49)
> 11.50	12 (46.2)	14 (53.8)		
PDW				
≥ -0.35	19 (67.9)	9 (32.1)	0.290¥	1.36 (0.86 – 2.15)
< -0.35	13 (50)	13 (50)		
MPV				
≥ -0.25	21 (72.4)	8 (27.6)	0.066¥	1.65 (1.00 – 2.70)
< -0.25	11 (44)	14 (56)		
P-LCR				
≥ -1.70	19 (67.9)	9 (32.1)	0.290¥	1.36 (0.86 – 2.15)
< -1.70	13 (50)	13 (50)		
PCT				
≤ 0.015	19 (63.3)	11 (36.7)	0.687¥	1.17 (0.74 – 1.84)
> 0.015	13 (54.2)	11 (45.8)		

* Significant ($p < 0.05$); £ Fisher's exact; ¥ Yates Correction

by monitoring hematological parameters with shorter intervals between radiation during exposure to external radiation therapy to determine the point of change in hematological status.

REFERENCES

1. World Health Organisation (WHO). Incidence, Mortality, and Prevalence by Cancer Site. 2020. https://gco.iarc.fr/ today/data/ factsheets/ populations/360-indonesia-fact-sheets.pdf. [date access 20.11.2023]
2. Ferreira da Silva I, Ferreira da Silva I, Koifman RJ. Cervical Cancer Treatment Delays and Associated Factors in a Cohort of Women From a Developing Country. J Glob Oncol. 2019;5:1-11. doi:10.1200/JGO.18.00199.
3. Cancer Research UK. Cervical Cancer for The UK. 2022. https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk#:~:text=There are around 167%2C000 cancer,year (2017-2019). [date access 20.11.2023]
4. Tito Apreza R, Gondhowiardjo SA. The Effect of Bone Radiation on Hematopoiesis: A Literature Review The Effect of Bone Radiation on Hematopoiesis: A Literature Review. 2021:12(2)62-69. doi: 10.32532/jori.v12i2.135.
5. Zhang X, Cui M-M, Fu S et al. Platelet distribution width correlates with prognosis of gastric cancer. Oncotarget. 2017;8(12):20213-20219. doi:10.18632/oncotarget.15561.
6. Rao X-D, Zhang H, Xu Z-S et al. Poor prognostic role of the pretreatment platelet counts in colorectal cancer: A meta-analysis. Medicine (Baltimore). 2018;97(23):e10831. doi:10.1097/MD.0000000000010831.
7. Pogorzelska K, Krętowska A, Krawczuk-Rybak M, Sawicka-Żukowska M. Characteristics of platelet indices and their prognostic significance in selected medical condition - a systematic review. Adv Med Sci. 2020;65(2):310-315. doi:10.1016/j.advms.2020.05.002.
8. Lembeck AL, Posch F, Klocker EV et al. Large platelet size is associated with poor outcome in patients with metastatic pancreatic cancer. Clin Chem Lab Med. 2019;57(5):740-744. doi:10.1515/cclm-2018-0016.
9. Yang W, Chen Y-Y, Bi C et al. Predictive and prognostic values of preoperative platelet parameters in patients with gynecological tumors. J Clin Lab Anal. 2020;34(7):e23295. doi:10.1002/jcla.23295.
10. Plantureux L, Mège D, Crescence L et al. Impacts of Cancer on Platelet Production, Activation and Education and Mechanisms of Cancer-Associated Thrombosis. Cancers (Basel). 2018;10(11). doi:10.3390/cancers10110441.

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ORIGINAL ARTICLE

TREATMENT EXPERIENCE OF CHRONIC LUNG ABSCESSES USING MINI-INVASIVE ELECTROSURGICAL TECHNIQUES

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ABSTRACT

The aim: To increase the efficiency of surgical treatment of patients with chronic lung abscesses by developing mini-invasive methods of surgical treatment using electrosurgical technologies.

Materials and methods: Conducted study of the results of surgical treatment of 78 patients with chronic lung abscesses operated from 2011 to 2021. Patients were divided into two groups: the main group (37 patients who were treated using developed technologies) and a comparison group (41 patients, treated using traditional tactics).

Results: Transthoracic and endobronchial sanitation of the purulent cavity in the lung at the first stage of treatment contributed to the rapid elimination of inflammation and significantly accelerated the regeneration of lung tissue. Clinical effectiveness in the main group was expressed in reducing the phenomena of intoxication, decrease in Leukocyte intoxication index (LII) (early as on day 5 after surgery), on the 10th day, a significant reduction in patients bacterial excretion was noted (in the main group by 18.9%, in the comparison group – by 14.6%), the average time of reducing the abscess cavity by 1/4 of the volume 6 days less, the healing time of the cavity of the AL which is on average 13 and 16 days, respectively, less.

Conclusions: The developed methods of surgical interventions made it possible to significantly positively influence the level of endogenous intoxication indicators, avoid resection surgical interventions, reduce the number of postoperative complications, avoid damage to neighboring organs, reduce the time of patients with achieving a stable positive effect.

KEY WORDS: chronic lung abscess, argon-plasma coagulation, electrosurgery

Wiad Lek. 2023;76(10):2277-2282

INTRODUCTION

Chronic lung abscesses (CAL) are still one of the most severe pathologies in thoracic surgery [1, 2]. Many researchers note that the number of patients with CAL are still remains at a fairly high level and amounts to 49.7% of the total number of purulent and destructive diseases of the chest cavity [3, 4]. It is known that this pathology is characterized by a severe long course, complexity and low effectiveness of known methods of treatment and consistently unfavorable treatment results [5, 6]. The severity of the condition of this contingent of patients, and the need for urgent medical measures create prerequisites for the constant improvement of methods of their diagnosis and treatment [7, 8].

One of the ways to improve the results of treatment of patients with CAL, according to leading experts, is to find new ways to treat this disease, in particular with the help of mini-invasive transthoracic and endobronchial surgical methods, methods of local treatment of the destruction cavity with chemical and physical factors and correction of the activity of the inflammatory process [9, 10].

THE AIM

Is to improve the efficiency of surgical treatment of patients with chronic lung abscesses by developing mini-invasive methods of surgical treatment using electrosurgical technologies.

MATERIALS AND METHODS

We conducted a randomized controlled single-center retro-prospective study, which is based on the analysis of the results of surgical treatment of 78 patients with chronic lung abscesses operated on the basis of SE «Institute of General and Emergency Surgery by V. T. Zaitsev NAMS of Ukraine», Kharkiv from 2011 to 2021.

According to the objectives of the study, patients were divided into two groups: the main group (37 patients who were treated from 2016 to 2021. using developed technologies) and a comparison group (41 patients) (patients treated from 2011–2015 using traditional tactics).

All studied patients underwent a general clinical examination in accordance with the approved medical care procedures and standards of medical care in Ukraine. The definition and conduct of additional methods for examining patients were determined by the features of the clinical course and nature of the disease, as well as the goals and objectives of this study.

Leukocyte intoxication index (LII) and lymphocyte index (LI) were separately evaluated.

To study the cellular composition, quantitative and qualitative composition of pathogenic microflora, as well as its sensitivity to antibacterial drugs, sputum was collected and the contents of purulent cavities, followed by seeding on nutrient media and bacterioscopy. To this end, the study was carried out at the time of admission of the patient, and then after puncture and drainage of the purulent cavity in the lung and on the 5-th, 10-th and 20-th day from the operation. The material for the study was sputum, abscess cavity contents and bronchial washings from patients with chronic lung abscesses.

In the treatment of patients of the main group, the method of argon-plasma coagulation (APC) was used, which is a contactless method of high-frequency electrosurgery. Its principle is the thermal effect of a high frequency current supplied to the tissue by a stream of ionized argon plasma.

We considered the following clinical situations as indications for the use of minimally invasive-draining methods of surgical treatment in 43.5% of patients in the study groups: 1. a blocked, peripherally located chronic lung abscess; 2. a peripherally located chronic abscess that is insufficiently drained through the bronchial tree; 3. peripherally located chronic lung abscesses, whose diameter exceeds 5 cm, regardless of the presence or absence of drainage through the bronchus. These interventions were performed according to preliminary data of polyposition X-ray examination or under the control of fluoroscopy and under the control of ultrasonography.

In the case when the manure drained through the bronchus, we actively used endoscopic methods to sanitize its cavity. In patients with sharp violations of the drainage function of the bronchi, rehabilitation began with urgent therapeutic bronchoscopy. After the evacuation of purulent contents and determination of draining bronchus by us, under X-ray control, catheterization of the orifice of draining bronchus or abscess cavity was carried out wa ith polychlorvinyl catheter, which was left for 7–10 days depending on the rate of elimination of purulent tracheobronchitis and cleaning of the cavity of CAL. If it was impossible to leave the catheter, therapeutic bronchoscopy was performed every other day, a total of 6–12 per course of treatment. Patients who were in serious condition and who could not carry out program bronchoscopies performed micro tracheostomy (MTS), which, in our opinion, was especially important in patients with severe respiratory failure, which occurs as a result of the active withdrawal of purulent sputum and concomitant purulent tracheobronchitis and does not allow for adequate bronchoscopic sanation and can lead to the development of asphyxia. Endobronchial methods of treatment included sanation bronchoscopy with pouring of medicinal mixtures, endoscopic catheterization of draining bronchi with subsequent sanation, and formation of micro tracheostomy with the performance of laryngeal fillings of satisfying solutions.

The reference point to the beginning of the second stage of treatment in patients of the study group was a dynamic bacteriological study. It should be noted that in all patients studied, the microbial number on day 1 of treatment was approximately the same and amounted to $1x10^{8-9}$ CFU/ml. On the 5^{th} day of treatment, the microbial number averaged $1x10^{6}$ CFU/ml. On the 10^{th} day, the microbial number in the vast majority of patients was below the critical level ($1x10^{3}$ CFU/ml).

In patients of the main group, at the second stage of treatment, the abscess capsule was treated with APK, which was used during endobronchial sanation using the working part of the coagulator conducted through the biopsy channel of the bronchoscope in 18 (48.6%) patients. In 17 (45.9%), this manipulation was performed transthoracically by conducting a bronchoscope with a coagulator through earlier drainage into the abscess cavity for visual control of its implementation. (the total number of procedures ranged from 8 to 12 per course of treatment). In 2 (5.4%) cases, due to insufficient patency of the draining pathways, as well as in cases of complete absence of abscess drainage, additional puncture-draining manipulations were used to treat the abscess capsule.

Medical-statistical calculation. The mean value (M) and standard square deviation (SD, σ) were determined: M ± SD. Categorical variables were presented in abso-

Table I. Frequency of intraoperative complications in patients of the study groups

Type of complications	Patient groups		p
	main (n=37)	comparison (n=41)	
Pneumothorax	2 (5.4)	5 (12.2)	0,436
Hemoptysis	1 (2.7)	4 (9.8)	0,362
Pulmonary hemorrhage	0*	7 (17.1**)	0,012
Subcutaneous emphysema	3 (8.1)	7 (17.1)	0,317
Damage to neighboring organs	0*	6 (14.6***)	0,027
Generally	6 (16.2)	29 (70.7)	<0.001

Notes: * – 95 % CI [0-5,1 %]; ** – 95 % CI [7,0-30,4 %]; *** – 95 CI [5,4-27,4 %]

Table II. Dynamics of intoxication indicators in patients of the study groups

Patient groups	LII, c.u.			LI, c.u.		
	Before operation	The 5th day	The 14th day	Before operation	The 5th day	The 14th day
Main (n=37)	4.12 ± 0.23	2.92 ± 0.14	1.78 ± 0.18	0.26 ± 0.04	0.36 ± 0.04	0.41 ± 0.03
Comparison (n=41)	4.05 ± 0.18	3.57 ± 0.18	2.03 ± 0.18	0.25 ± 0.03	0.28 ± 0.03	0.45 ± 0.01
p	0.31	0.034	0.16	0.43	0.001	0.14

Table III. Instrumental monitoring of the effectiveness of treatment of patients with CAL

Indicators of treatment effectiveness	Patient groups		p
	comparison (n=41)	main (n=37)	
Time to reduce the abscess cavity by 1/4 (days)	12.2 ± 0.54	5.5 ± 0.32	**<0.001**
Time for reduction of the abscess cavity by 1/2 (days)	22.3 ± 1.05	12.5 ± 0.57	**<0.001**
Time for complete healing of the destruction cavity (days)	36.07 ± 1.8	19.8 ± 0.62	**<0.001**
Time to clean the destruction cavity from purulent contents (days)	20.9 ± 0.85	7.56 ± 0.62	**<0.001**

lute and percent values (with a 95 % confidence interval [CI]). The probability of differences in the obtained quantitative characteristics in two mutually independent groups was determined using the Mann-Whitney U-test and in mutually dependent groups – the Wilcoxon matched-pairs signed-ranks T-test. Fisher's F-test probability calculation was also used. The significance level (p) in the study was taken as lower than 0.05. Statistical calculations were performed by the use of IBM SPSS 25.0 and MedStat v. 5.0.

RESULTS

Transthoracic and endobronchial sanation of the purulent cavity in the lung at the first stage of treatment contributed to the rapid elimination of inflammation and significantly accelerated the regeneration of lung tissue. Clinical effectiveness was expressed in reducing the phenomena of intoxication – already on the 3-rd–5-th day there was a decrease in hyperthermia and a systematic decrease in leukocytosis.

The indication for the removal of drainage in patients of the comparison group was the cessation of the intake of purulent separable, stable normalization of body temperature, and positive laboratory dynamics of blood parameters. X-ray sign, which was taken into account as a signal to remove drainage – the disappearance of inflammatory infiltration and the reduction in the size of the destruction cavity.

Analysis of postoperative complications is given in Table I.

Before performing draining methods of treatment (transthoracic or endobronchial) in patients of both groups of the study, LII exceeded the level of physiological norms (1.6 ± 0.5 in. units) by 2 times, while no significant intergroup differences were found in this indicator ($p > 0.1$). A statistically significant decrease in LII in the main group compared to the comparison group was observed as early as on day 5 after surgery ($p < 0.05$). On Day 14, the LII value in all study groups did not significantly differ from the reference normal range. The difference between LII scores in all study arms was not significant ($p > 0.1$).

In addition, according to the results of the study, before the mini-invasive intervention for drainage of the purulent cavity, a twofold decrease in LI was noted compared with the norms (0.41 ± 0.03 y. units) in the entire patient pool. This trend of integral indices of the leukocyte formula fully

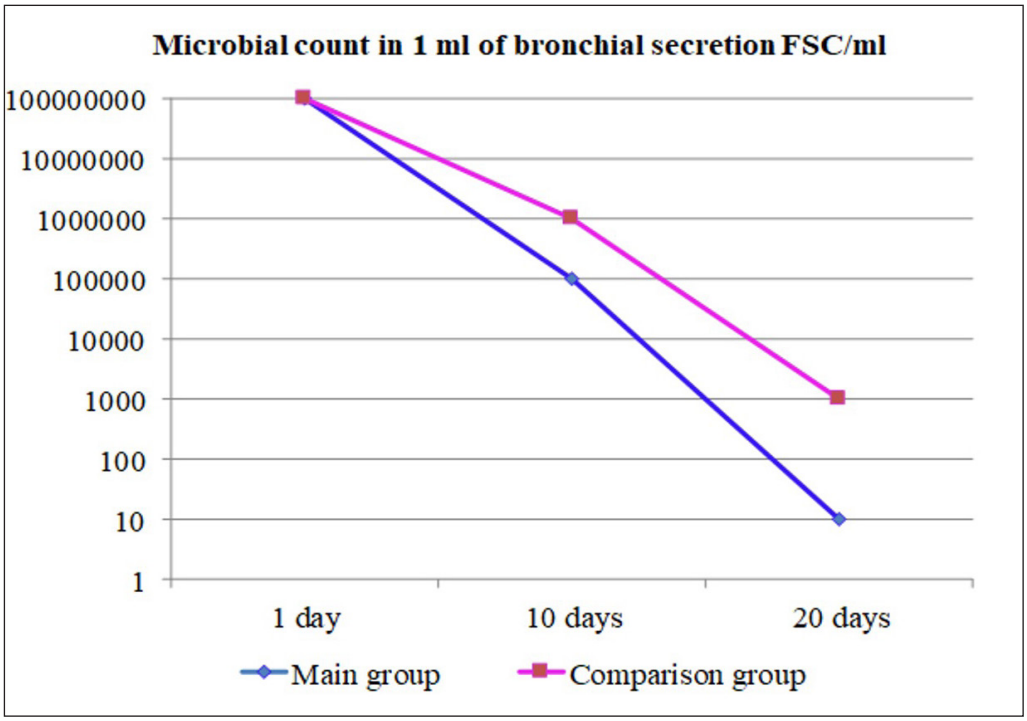

Fig. 1. Microbial number dynamics in the studied patients.

confirms the analytical data of hemograms of transfer blood of patients in the study groups (Table II).

When assessing the results of bacteriological examination before the start of treatment of the entire pool of patients under study, it was possible to establish the presence of microbial associations in 31.5% of cases and the presence of monoculture in 68.5% of observations. When studying the species composition of the microflora, we found that before the operation, strains of gram-positive pathogens prevailed in sputum patients (61.3%). With repeated bacteriological studies of the isolated already on the 10th day, a significant reduction in patients bacterial excretors was noted: in the main group by 18.9%, in the comparison group – by 14.6%, while statistically significant intergroup differences in the qualitative composition of microflora sown from drains were not established in the described period.

Also, to assess the effectiveness of treatment, we conducted a bacteriological study: and the dynamics of treatment in patients with comparison groups, the microbial number in 1 ml of bronchial washings taken during bronchoscopy was studied. The results obtained are graphically shown in Fig 1.

In patients of the main and comparison group, the microbial number on the 1st day of treatment was approximately the same and amounted to $1x10^{8-9}$ CFU/ml (colony-forming units in 1 ml). On the 10th day of treatment, the microbial number in the patients of the main group was $1x10^5$ CFU/ml, which is 10 times less than the microbial number in the comparison group $1x10^6$ CFU/ml at the same time. On the 20th day, the microbial number in patients of the main group reached an average of 1x10 CFU/ml, and in patients of the comparison group at the same time, the microbial number was $1x10^3$ CFU/ml. It should be noted that in 28 (75.7%) cases in the main group, decontamination of the purulent-destructive cavity was achieved. At the same time, the volume of decomposition separated from the cavity decreased systematically from the moment of drainage.

When monitoring the effectiveness of treatment in patients with comparison groups, we evaluated the following indicators over time: the average time to reduce the volume of the destruction cavity by 1/4, 1/2 and its complete healing, the average time to clear the CAL cavity from purulent content. The data obtained by observation are presented in Table III.

Thus, analyzing the data of our dynamic instrumental control over the effectiveness of two fundamentally different methods of treatment of patients with CAL, it is possible to assert that the treatment program proposed in patients of the main group is more effective in comparison with the comparison group. So, in patients of the main group, the average time of reducing the abscess cavity by 1/4 of the volume was 5.5 ± 0.32 days, which is 6 days less ($p < 0,001$) than in patients of the comparison group. The leading indicator we considered the healing time of the cavity of the AL. In patients of the main group, it was 7.56 ± 0.62 days, which is on average 13 and 16 days, respectively, less ($p < 0.05$) than the same indicator in patients of the comparison group.

DISCUSSION

The data obtained by us confirm the opinion of researchers who claim that with the contactless use of argon plasma, antimicrobial properties are noted, a sterilizing effect is created, and the processes of prolifer-

ation and regeneration of tissues are accelerated, which contributes to the optimization of the wound process.

So, Deguchi H. [11] conducted a case–control study in 62 patients (34 men and 28 women, median age; 69 years) who underwent APC after endoscopic injection sclerotherapy (EIS) (main group) for hemorrhagic or risky esophageal varices was compared with that of control patients who did not undergo APC after EIS (control group). They determined that APC after EIS was safe and could significantly prevent the recurrence of esophageal varices. They determined that the 1-year and 2-year recurrence rates of the main group were 9.7% and 11.3%, respectively, and the rates of the control group were 29.0% and 34.7%, respectively. Kaplan–Meier curves showed a significantly lower recurrence rate in the main group ($p = 0.013$, log–rank test).

Loh R. [12] a multi-institutional, retrospective cohort study was conducted, comprising 283 patients who underwent bilateral tonsillectomies. They compare the safety and efficacy of APC and coblation techniques in tonsillectomy. They determined that in the APC group, mean operative time and post-operative hemorrhage rate were significantly reduced, $p = 0.0006$ and $p = 0.003$ respectively.

Nam K. [13] were retrospectively reviewed 109 patients who underwent Endoscopic snare papillectomy (ESP) for ampullary adenoma. Using propensity score matching, Nam K. et. al. compared short- and long-term outcomes between the ESP-with-additional-APC group (ESP + APC group) and the ESP-only group. Bleeding rate was significantly lower in the ESP + APC group than in the ESP-only group (7.3% vs 31.7%, OR = 0.180, $p < 0.01$). However, there were no significant differences in other: pancreatitis (12.2% vs 19.5%, P = 0.365), cholangitis (2.4% vs 9.8%, P = 0.198), and perforation (2.4% vs 2.4%, P = 1.000). Papillary stricture (9.8% vs 4.9%, P = 0.405) and recurrence rates (24.4% vs 24.4%, P = 0.797) were not significantly different between the ESP + APC group and the ESP-only group.

CONCLUSIONS

1. The developed methods of using mini-invasive bronchoscopic and puncture-draining surgical interventions using electrosurgical technologies made it possible to significantly positively affect the level of endogenous intoxication indicators (by 5 days of treatment), reduce the healing time of the abscess cavity from 36.07 ± 1.8 days to 22.6 ± 0.38 with the use of APK ($p < 0.05$), as well as reduce the level of contamination by 63.9% and 64.9%, as well as avoid resection surgical interventions.
2. The use of minimally invasive bronchoscopic technologies (with centrally located HAL) and puncture-draining (with peripheral HAL) surgical interventions using electrosurgical technologies allowed to reduce the number of postoperative complications from 70.7% to 16.2% when using APK, as well as to avoid damage to neighboring organs.
3. Analysis of the results of mini-invasive surgical methods for the treatment of chronic lung abscesses made it possible to establish that the timely use of mini-invasive endobronchial, puncture-draining techniques using electrosurgical devices can significantly reduce the time of clinical and socio-labor rehabilitation of patients (1.2 times) with the achievement of a stable positive effect, as well as avoid resection methods of surgical interventions and deaths in the postoperative period.

REFERENCES

1. Feki W, Ketata W, Bahloul N et al. Lung abscess: Diagnosis and management. Revue des Maladies Respiratoires. 2019;36(6):707–719. doi: 10.1016/j.rmr.2018.07.010.
2. Takaki M, Tsuyama N, Ikeda E et al. The Transbronchial Drainage of a Lung Abscess Using Endobronchial Ultrasonography with a Modified Guide Sheath. Internal Medicine Journal. 2019;58(1):97–100. doi: 10.2169/internalmedicine.9419-17.
3. Churylin RYu, Voronzhev IO, Kolomiychenko YuA et al. Dyferentsiyna renthenodiahnostyka psevdotuberkul'oznoho varianta abstsesu lehen' z porozhnynamy tuberkul'oznoyi etiolohiyi. [Differential x-ray diagnostics of pseudotuberculosis variant of lung abscess with cavities of tuberculous etiology]. Ukrainian Journal of Radiology and Oncology. 2021;29(1):9–20. doi: 10.46879/ukroj.1.2021.9-20. (in Ukrainian)
4. Matarese A, Tamburrini M, Desai U, Zuccon U. Percutaneous lung abscess drainage: revisiting the old gold standard. Monaldi Archives for Chest Disease. 2020;90(1):1214. doi: 10.4081/monaldi.2020.1214.
5. Teng E, Bennett L, Morelli T, Banerjee A. An unusual presentation of pulmonary embolism leading to infarction, cavitation, abscess formation and bronchopleural fistulation. BMJ Case Reports. 2018;2018:bcr2017–222859. doi: 10.1136/bcr-2017-222859.
6. Yun SS, Cho HS, Heo M et al. Lung abscess by Actinomyces odontolyticus and Parvimonas micra co-infection presenting as acute respiratory failure. Medicine. 2019;98(35):e16911. doi: 10.1097/md.0000000000016911.
7. Miki M. Standard and Novel Additional (Optional) Therapy for Lung Abscess by Drainage Using Bronchoscopic Endobronchial Ultrasonography with a Guide Sheath (EBUS-GS). Internal Medicine. 2019;58(1):1–2. doi: 10.2169/ internalmedicine.0968-18.

8. Shivachev H, Pahnev Y, Antonova Z et al. Complex minimally invasive approach for complicated parapneumonic pulmonary abscess with bronchopleural fistula in childhood. European Respiratory Journal. 2019;54:PA2218. doi: 10.1183/13993003.congress-2019.pa2218.
9. Konietzke P, Mueller J, Wuennemann F et al. The value of chest magnetic resonance imaging compared to chest radiographs with and without additional lung ultrasound in children with complicated pneumonia. PLOS ONE. 2020;15(3):e0230252. doi: 10.1371/journal.pone.0230252.
10. Brahmavar M, Joshi D, Raman D. Application of Lung Ultrasound in Critical Care Setting: A Review. Cureus. 2019;11(7):e5233. doi: 10.7759/cureus.5233.
11. Deguchi H, Kato J, Maeda Y et al. Argon plasma coagulation is effective for prevention of recurrent esophageal varices after endoscopic injection sclerotherapy: Single-center case–control study. Dig Endosc. 2016;28(1):42–49. doi: 10.1111/den.12538.
12. Loh R, Stepan L, Zhen E, Shaw CL. Argon plasma coagulation tonsillectomy versus coblation tonsillectomy: a comparison of efficacy and safety. J Laryngol Otol. 2019;133(6):520–525. doi: 10.1017/S0022215119001191.
13. Nam K, Song TJ, Kim RE et. al. Usefulness of argon plasma coagulation ablation subsequent to endoscopic snare papillectomy for ampullary adenoma. Dig Endosc. 2018;30(4):485–492. doi: 10.1111/den.13008.

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ORIGINAL ARTICLE

CONFLICTS OF INTEREST IN THE HEALTHCARE SECTOR: LEGAL ASPECTS

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ABSTRACT

The aim: To study the features of legal regulation of preventing conflicts of interest in the healthcare field in foreign countries in order to propose improvements to national legislation.

Materials and methods: The methodological basis of the article is a set of methods and techniques of scientific knowledge. Methods of theoretical analysis, system-analytical, comparative-legal methods provided us with the opportunity to characterize the features of the legal regulation of preventing conflicts of interest in the area under study.

Results: The common features of preventing conflicts of interest in the healthcare field in foreign countries are: (1) a combination of mandatory, recommendatory, ethical and legal norms that define a number of requirements, restrictions and prohibitions in this area; (2) different levels of legal regulation of conflicts of interest (international, national, regional, local); (3) two approaches to determining the content of conflict of interest: general (the conflict is defined the same for all cases) and differentiated (the conflict of interest is determined by each area, taking into account its specifics). The debatable and problematic issues of conflict prevention in the national healthcare system are analyzed, and amendments to the medical legislation are proposed.

Conclusions: Prevention of conflict of interest in the healthcare field should be considered as a specific group of public legal relations and an independent subject of legal regulation arising from the norms of the legislation of most foreign countries.

KEY WORDS: prevention of corruption, preventing of conflict of interest, healthcare, human rights, legal regulation

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INTRODUCTION

Ensuring proper legal regulation of preventing conflicts of interest in the healthcare sector is a strategic priority for the anti-corruption activities of public authorities and civil society institutions. Reforming anti-corruption legislation and developing the institutional framework for preventing conflicts of interest is normatively defined as an unconditional priority in Ukraine and the member states of the European Union [1]. In accordance with the requirements for the implementation of the provisions of the Association Agreement between Ukraine and the European Union (2014), it is proclaimed that the Parties cooperate in the fight against corruption in public authorities and in private authorities (Art. 22). The UN Convention against Corruption, ratified by Ukraine, determines that each State shall strive to create, maintain and strengthen systems that promote transparency and prevent conflicts of interest [2].

Representatives of civil society also note the continued existence of a high risk of corruption in the healthcare sector in the context of conflicts of interest. Such risks always exist in the exercise of discretionary public powers by healthcare officials authorized to perform the functions of the state or local government. The problem of the lack of effective legal measures to prevent conflicts of interest in the healthcare sector in Ukraine also remains unresolved. To improve the national legislation of Ukraine, we study the features of the legal regulation of preventing conflicts of interest in this area in foreign countries.

THE AIM

The purpose of our work is to study the features of legal regulation to prevent conflicts of interest in the healthcare field in foreign countries in order to propose improvements to national legislation.

MATERIALS AND METHODS

The complexity of the study is ensured by a systematic approach, which made it possible to consider and analyze the problems of preventing conflicts of interest in the healthcare field in the unity of their content, essence and legal form. The methodological basis of the study is a set of methods and techniques of scientific knowledge: formal dogmatic, systemic, semantic, epistemological and axiological, sociological, comparative legal, statistical, systemic and structural analysis.

The use of scientific methods helps to achieve the purpose of the article, substantiate the conclusions of the study and propose suitable solutions to the problem of preventing conflicts of interest in the healthcare field in Ukraine, taking into account foreign experience. Using the method of theoretical analysis, systemic and analytical methods, the features of the legal regulation of preventing conflicts of interest in the healthcare field in foreign countries and the scientific substantiation of the theoretical conclusions in this study are characterized.

RESULTS

According to Art. 1 of the Law of Ukraine «On the Prevention of Corruption», the key features of a conflict of interest are the presence of a person's official/representative powers and private interest. Depending on the ratio of these signs, a potential or real conflict of interest arises [3]. By establishing requirements for preventing the emergence and settlement of an existing conflict of interest in the healthcare field, the state recognizes the inadequacy of not only the moral and ethical standards that are inherent in every society but also establishes legal norms that determine the behavior of official state authorities. This indicates the preventive nature of the legal regulation of the conflict of interest in the healthcare sector [4].

Rodwin M. et al., exploring the conflict of interest in the health sector in the US, France and Japan, note their wide distribution in these countries. The author points out that in order to prevent conflicts of interest in the healthcare sector, appropriate legislative measures are needed, supported by economic, organizational, educational, and moral mechanisms [5].

The conflict of interest in the healthcare sector is one of the factors leading to corruption [4] and affects the efficiency of the entire healthcare organization system. Thus, a conflict of interest can arise in any situation in the field of healthcare. Since the conflict of interest is a corruption risk [6] for the implementation of the principles of the rule of law, legality, social justice, equality, and accessibility of medical care and medical services, these principles of health care in Ukraine are defined and provided by the Constitution of Ukraine.

In foreign countries, measures to prevent conflicts of interest in the healthcare sector are provided for in-laws on the prevention of corruption, laws on public service [7], in separate laws on conflict of interest [8-11], in special medical codes, as well as laws of the medical direction [12]. In particular, at the first General Assembly in Paris, the World Medical Association was created, which implements international standards of medical activity that are mandatory for everyone [13]. This document for the first time indicates the relationship of moral, ethical and legal norms in the regulation of medical activity.

Effective measures to prevent conflicts of interest were among the first to be used in US law. In this country, regulation is carried out in accordance with the rules or codes of «ethical conduct». In the United States, such measures were implemented in 1989 through the adoption of amendments to the Law «On Ethics Services in State Bodies», as well as the development of an appropriate regulatory act of the President of the country [14]. The activities of the executive authorities operating in the United States are regulated by the norms of the law «On rank ethics», adopted in 1978. Legislative acts supplemented the decree of the President of the United States, which approved the principles of ethics [14].

Prevention of conflicts of interest in the healthcare sector is carried out at the interstate, national, regional and local levels. For example, in the province of Ontario in Canada, since 1991, the regulatory legal act No. 114/94 has been in force, which regulates conflicts of interest in the activities of doctors [12]. The French Law on transparency in public life (Act no. 2013-907 on transparency in public life) establishes a separate regulation to prevent such a situation as a conflict of interest. In Art. 2 of this French Law of October 11, 2013, a definition of a conflict of interest is provided as any conflict of public interests or public and private interests that can undermine the independent, impartial and objective performance of any state (administrative) function [15]. In France, on December 29, 2011, Law No. 2011-2012 «On Strengthening the Safety of Medicines and Health Products» was adopted, establishing a fine of 30 thousand euros imposed on an expert who concealed information about his ties with the commercial sphere [16].

In the Portuguese Law governing incompatibility and disqualification applicable to officials (Law no. 28/95), there is a brief explanation of the duration of the conflict of interest, where it is stated that such a problem is the opposite of the implementation of official obligations of an official, which leads to the disappearance of his personal interests [17]. In the Czech Republic, Law No.

159/2006 of March 16, 2006, on Conflict of Interest determines that a public official must refrain from any action in which his personal interests may affect the performance of his functions. According to this Law, «personal interest» means an interest that brings a public official, a person close to a public official, a legal entity controlled by a public official, an increase in property or other benefits [18].

Also, a separate law on conflict of interest was adopted in the Kyrgyz Republic. In particular, in the Law of the Kyrgyz Republic «On Conflict of Interest» dated December 12, 2017 No. 206(11), a conflict of interest is defined as a conflict between public legal obligations and personal (private) interests of persons defined in the norms of this Law, in which their personal (private) interests affect or may affect the performance of their official duties, which leads or may lead to a violation of the rights and interests of citizens, organizations and the state. A conflict of interest can be potential, real and already held [19]. Therefore, the concept of «conflict of interests» is defined at the level of a special legislative act and is detailed in subordinate legal acts.

In the Health Code of the Republic of Tajikistan, the concept of «conflict of interest» is a situation in which the personal interest of medical and pharmaceutical workers in their work for the purpose of making a profit with the help of pharmaceutical companies or through their representative offices can cause dishonest performance of professional activities of healthcare professionals and contradict the interests of the patient [20]. Consequently, the conflict of interest in the field of healthcare is also regulated by special laws, and its concept is also defined there, which covers the activities of medical and pharmaceutical workers.

In Germany, at the beginning of 2015, legislative procedures began under the federal law on combating corruption in the healthcare sector. New types of criminal offenses in the healthcare sector will be introduced [21]. In the UK, the judicial practice has also developed a special test, the essence of which is as follows: a conflict of interest exists if a reasonable person, assessing the actual circumstances of the situation, can indicate that there is a real possibility of such a conflict [22].

The most advanced legal system for the prevention of conflicts of interest is provided by Canadian law. In Canada, conflicts of interest are regulated by the Constitution, a special Conflict of Interest Act, as well as the rules of the Corrupt Practices Act of Canada, bylaws and regulations regarding the healthcare system.

Some EU states have separate rules to prevent conflicts of interest in the activities of public authorities and officials in the field of health. Specialized institutions are provided to prevent conflicts of interest in the healthcare sector among the functions of anti-corruption authorities in government structures, and special measures have already been introduced on the rules of conduct and restrictions on the activities of healthcare officials.

It should be noted that, compared with international standards and norms [23], the national anti-corruption legislation of Ukraine does not define the term «perceived conflict of interest» in the healthcare sector, in the presence of which the requirements for notification and its settlement by healthcare officials would also be established. Therefore, the category of «perceived conflict of interest» should be provided for in Article 1 of the Law of Ukraine «Fundamentals of Ukrainian Legislation on Health Care» dated November 19, 1992 No. 2801-XII. A «perceived conflict of interest» in healthcare occurs when there is an opinion that the private interests of a public official in this area may unduly influence the performance of their official duties, but in reality, this does not happen [23].

At the same time, activities that may give rise to a false appearance of a conflict of interest are also regulated, for example, the existence of a suspicion that the conflict is unresolved among healthcare officials, may provoke doubts about its honesty and undermine public confidence in the state authorities of the healthcare system.

DISCUSSION

There is no common understanding of the term «conflict of interest» in the legal literature. Some scientists understand such a term as a «collision**», [5]** other researchers «as a situation**» [4],** others – «as a contradiction**» [1],** others – «as a contradiction**» [**23], in the presence of private interest and their influence, or the possibility of such influence in a person in the area in which he exercises his official, professional or representative powers, in the event of making decisions or committing or not committing actions in the exercise of official powers.

There is no clear understanding of the content of the categories: «real conflict of interest**»,** «potential conflict of interest**»,** and «private interest**»,** which are defined in the Law of Ukraine «On Prevention of Corruption**» [3].** Problematic for application is such a criterion as the lack of proof of the existence of a contradiction between private interest and the official authority of an official in the healthcare sector in the context of a conflict of interest, which is decisive for the courts when resolving the issue of violation of the requirements of the Law of Ukraine «On the Prevention of Corruption**».** This creates additional obstacles for bringing persons to administrative

responsibility and ensuring the principle of inevitability of responsibility for offenses related to corruption [3]. This situation is one of the factors in the different applications by administrative courts of the grounds for considering cases on bringing to administrative responsibility for violating the requirements for preventing and resolving conflicts of interest in the healthcare sector.

The problematic issue remains that the rules for resolving a conflict of interest in the healthcare sector are not sufficient to ensure it and resolve such situations. There is no algorithm for the actions of the direct head of healthcare in the event that he does not have the authority to apply one or another method of external settlement of a conflict of interest in a subordinate person (for example, transfer and dismissal) [3]. There is an inconsistency between the norms of the Law of Ukraine «On the Prevention of Corruption» regarding the timing of notification of a conflict of interest and the timing of its independent settlement in the healthcare sector. The administrative responsibility of the heads of healthcare institutions for not taking measures to resolve the conflict of interest among subordinates has not been established. There are no requirements regarding the form and procedure for reporting a conflict of interest, which leads to alternative (uncertainty) actions for a person in case of a conflict of interest and may entail bringing the person to responsibility [3] in the field of healthcare.

CONCLUSIONS

It is expedient to consider the prevention of conflicts of interest in the field of health care as a specific group of public relations and an independent subject of legal regulation arising from the norms of the legislation of most foreign countries of the world.

Prevention of conflicts of interest in the field of healthcare in foreign countries is both part of the structural system for combating corruption and a component of a preventive strategy (the existence of regulatory acts to prevent conflicts of interest in the field of healthcare, adopted codes of conduct for doctors, effective legislation is in place to prevent violations of the standards of professional behavior of official healthcare professionals). The presence of rules for refraining from participation in decisions in the context of a conflict of interest is a fairly effective approach to preventing conflicts of interest in this area.

REFERENCES

1. Shevchuk O, Lysodyed O, Matyukhina N et al. Conflict of interest in the activities of judges in Ukraine and the European Union: a comparative legal study. Juridical Tribune Journal. 2023;13(2): 261-282. doi:10.24818/TBJ/2023/13/2.06.
2. United Nations Convention against Corruption: International Document of 31.10.2003 № 995_c16. Official Gazette of Ukraine. 2010. № 10. № 44. 2006, Art. 2938., Art. 506.
3. On the prevention of corruption: Law of Ukraine of 10.14.2014 №. 1700-VII. Information of the Verkhovna Rada of Ukraine. 2014. No. 49. St. 2056
4. Shevchuk O, Yarova A. Prevention and settlement of conflicts of interest in health care of Ukraine as an administrative legal institute. Juridical Tribune. 2022;12 (3): 387-398. doi: 10.24818/TBJ/2022/12/3.05.
5. Rodwin M. Conflicts of Interest and the Future of Medicine: The United States, France, and Japan. Oxford University Press. 2011. Suffolk University Law School Research. https://ssrn.com/abstract=1789751 [date access 14.06.2023]
6. Conflict of Interest Policies and Practices in Nine EU Member States: A Comparative Review. SIGMA OECP. 2005. https://ideas.repec.org/p/oec/govaac/36-en.html [date access 14.06.2023]
7. The management of ethics and conduct in the Public Service Portugal. https://www.oecd.org/gov/ethics/2731886.htm [date access 14.06.2023]
8. Conflict of interest: Law of the Kyrgyz Republic of 12 December 2017 № 206 (11). http://cbd.minjust.gov.kg/act/view/ru-ru/111716 [date access 14.06.2023]
9. Conflict of Interest Act (S.C. 2006, c. 9, s. 2). https://laws-lois.justice.gc.ca/eng/acts/c-36.65/page-1.html#h-92024 [date access 14.06.2023]
10. Zákon č. 159/2006 Sb. Zákon o střetu zájmů. https://www.zakonyprolidi.cz/cs/2006-159 [date access 14.06.2023]
11. Konflikt interesa: Zakon Kyrgyzskoy Federatsii 12 Dekabrya 2017 № 206 (11). [Conflict of interest: Law of the Kyrgyz Republic of 12 December 2017 № 206 (11)]. http://cbd.minjust.gov.kg/act/view/ru-ru/111716 [date access 14.06.2023] (in Russian)
12. Medicine Act, 1991. Ontario regulation 114/94. http://www.elaws.gov.on.ca/html/regs/english/elaws_regs_940114_e.htm [date access 14.06.2023]
13. International code of medical ethics. Adoption by the 3rd General Assembly of the All-World Medical Association (London, June 1949) with further amendments 1968, 1983. https://zakon.rada.gov.ua/laws/show/990_002#Text [date access 14.06.2023]
14. Henry N. Public administration and public affairs. https://handoutset.com/wp-content/uploads/2022/06/Public-Administration-and-Public-Affairs-Nicholas-Henry.pdf [date access 14.06.2023]

15. Act no. 2013-907 French Republic dated 11 October 2013 on transparency in public life. https://www.hatvp.fr/wordpress/wp-content/uploads/2018/01/Act-no.-2013-907-dated-11-October-2013-on-transparency-in-public-life.pdf [date access 14.06.2023]
16. Butler D. France toughens conflict rules. Nature. 2011;478(7368):169. doi: 10.1038/478169a.
17. The management of ethics and conduct in the Public Service Portugal. https://www.oecd.org/gov/ethics/2731886.htm [date access 14.06.2023]
18. Zákon č. 159/2006 Sb. Zákon o střetu zájmů. https://www.zakonyprolidi.cz/cs/2006-159 [date access 14.06.2023]
19. Konflikt interesa: Zakon Kyrgyzskoy Federatsii 12 Dekabrya 2017 № 206 (11). [Conflict of interest: Law of the Kyrgyz Republic of 12 December 2017 № 206 (11)]. http://cbd.minjust.gov.kg/act/view/ru-ru/111716 (in Russian) [date access 14.06.2023]
20. Health Code of the Republic of Tajikistan. https://cis-legislation.com/document.fwx?rgn=97585 [date access 14.06.2023]
21. Moosom K. Internal report on anti-corruption measures in Europe: areas of activity, experience, tools. Ukraine-EU civil society platform. Brussels. https://www.eesc.europa.eu/sites/default/files/resources/docs/reportcorruption_ukr.pdf [date access 14.06.2023]
22. Mortimore S. Company Directors: Duties, Liabilities, and Remedies. Oxford. 2009, p. 306. https://academic.oup.com/book/41770 [date access 14.06.2023]
23. Canadian Institute for Health Research. Government of Canada. Political statement of the three councils. Ethical Behavior for Human Research. https://ethics.gc.ca/eng/tcps2-eptc2_2022_chapter7-chapitre7.html [date access 14.06.2023]

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ORIGINAL ARTICLE

THE IMPACT OF HORMONE-VITAMIN COMPLEX ON FUNCTIONAL ACTIVITY OF THE MUSCLE TISSUE OF DESCENDANTS OF IRRADIATED ANIMALS

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ABSTRACT

The aim: To determine the hormone-vitamin complex impact on the terminal links of glycolysis, the tricarboxylic acids cycle, and the initial stage of gluconeogenesis in the muscle tissue in descendants of irradiated animals.

Materials and methods: Pyruvate kinase, lactate dehydrogenase, malate dehydrogenase, NADP-dependent malate dehydrogenasee and phosphoenolpyruvate carboxykinase activities, the content of lactate, pyruvate, malate and oxaloacetate were determined in the blood, myocardium and thigh muscles of 66 rats after exposure to ionizing gamma-radiation. Rats were injected by a hormone-vitamin complex which efficacy was determined using the abovementioned indexes.

Results: Hormone-vitamin complex administration to descendants of irradiated animals exposed to 1.0 Gy results to pyruvate kinase activity increase in the myocardium and skeletal muscles of descendants from animals irradiated by 0.5 Gy and exposed to 1.0 Gy irradiation.

Blood serum pyruvate kinase activity in descendants from animals irradiated by 1.0 Gy and exposed to 1.0 Gy radiation after the pharmacological correction was higher compared with the same index before pharmacological correction.

The lactate dehydrogenase activity in the myocardium, skeletal muscles and blood in descendants born from animals irradiated by maximal dose exposed to 1.0 Gy radiation was less in these tissues after pharmacological correction.

Conclusions: The hormone-vitamin complex use in the descendants of irradiated animals led to muscle tissue energy resources improvement. Our data are the experimental background for theoriginal hormone-vitamin complex efficacy further evaluation in the aspect of vital organs and body systems functional activity restoration under the influence of ionizing radiation.

KEY WORDS: total irradiation, descendants of irradiated animals, physical working capacity, hormone-vitamin complex, mechanisms of development

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INTRODUCTION

The problem of the biological effect of ionizing radiation, especially in small doses, and protection against it continues to be one of the fundamental problems in the of medical and biological sciences complex in Ukraine [1-3]. The impact of ionizing radiation on the body causes destructive changes that occur at all structural and functional levels of the organization [4-6].

The general state of the body after the effects of ionizing radiation and the changes caused by this radiation largely determine the functioning of muscle tissue [7-10], which plays an important role in ensuring the vital activity of the body, and considering that the descendants of irradiated animals are exposed to physical stress, deeper biochemical changes in the metabolism of muscle tissue should be expected [9]. Of particular importance is the substrate phosphorylation enzymes failure, which plays a leading role in bioenergetics, the weakening of the function of NAD-dependent dehydrogenases of the tricarboxylic acid cycle and the lipid peroxidation intensification which results to biomembranes both structure and function failure [11]. In addition, catabolic processes leading to protein destruction and negative nitrogen balance are enhanced [12].

One of the real ways to improve the health of the population can be the use of agents that have antioxidant properties that increase the body's resistance to adverse factors [13, 14]. The results of previously conducted research and the analysis of data from the scientific literature prove the effectiveness of separate use of anabolic steroid drugs [15], vitamin E [16] and other vitamins [17], in particular, as radioprotective compounds that have protective effects, including increasing of the lifespan of experimental animals. The original idea was the joint introduction of the above-mentioned pharmacological compounds to

test their effectiveness in the descendants of irradiated animals [18].

THE AIM

The aim was to determine the hormone-vitamin complex impact on the terminal links of glycolysis, the tricarboxylic acids cycle and the initial stage of gluconeogenesis in the muscle tissue in descendants of irradiated animals.

MATERIALS AND METHODS

Experimental studies were carried out on 66 mature white Wistar rats kept on a standard vivarium diet. Keeping, processing and manipulation of animals was carried out in accordance with the "General Ethical Principles of Animal Experiments" adopted by the Fifth National Congress on Bioethics (Kyiv, 2013). We used the recommendations of the European Convention on the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1985) and the rules of humane treatment of experimental animals and conditions approved by the Bioethics Commission of the Odessa National Medical University (protocol No. 32D dated 03/17/2016).

The mature rats were exposed to a single total gamma irradiation of ^{60}Co in the morning on an empty stomach on the "Agat" telegammatherapy unit (the distance to the device was 75 cm, the dose rate was 0.54 Gy/min, the absorbed dose was 0.5 Gy and 1.0 Gy).

The animals were randomized in the following way: the 1st group (n=10) – 1-month-old rats born from intact animals; the 2nd and the 3rd groups (n=2x10) – 1-month-old rat pups born from animals once totally irradiated by 0.5 Gy and 1.0 Gy; the 4th and the 5th groups (n=2x10) – 1-month-old rat pups born from animals once totally irradiated by 0.5 Gy and by 1.0 Gy and exposed to a dose of 1.0 Gy; the 6th and the 7th groups (n=2x8) – 1-month-old rat pups born from animals once totally irradiated by 0.5 Gy and by 1.0 Gy and exposed to a dose of 1.0 Gy, which were administered with a hormone-vitamin complex (HVC).

The HVC included tocopherol acetate (i.m., 50 mg/kg, 30 min after irradiation), retabolil (i.m., 2.5 mg/kg, 3 hrs after irradiation), cocarboxylase (s.c., 5 mg /kg) and nicotinamide (s.c., 10 mg/kg), which were administered 1 day after irradiation dissolved in 0.5 ml of saline. The HVC was administered during 12 days [18].

After euthanasia (i.v., propofol, 60 mg/kg) the animals' blood was collected, the heart (2/3 of the heart`s apex) and the frontal group of thigh muscles (mainly quadriceps femoris and sartorius muscle) were removed. Blood was centrifuged at 3000 g for 10 min to obtain serum. The removed cardiac and skeletal muscles were washed with chilled 0.9% physiological NaCl solution, minced and homogenized and subjected to differential centrifugation in a refrigerated centrifuge PC-6.

To detect the biosubstrates content in tissues, they were immersed in liquid nitrogen, deproteinized with 0.6N perchloric acid and homogenized. The protein precipitate was separated by centrifugation for 15 min at 3000 g.

Mitochondria, mitochondrial supernatant of myocardium, thigh muscles frontal group and blood serum were used for biochemical studies. We determined the activity of pyruvate kinase (PK), lactate dehydrogenase (LDH), malate dehydrogenase (MDH), NADP-dependent MDH, phosphoenolpyruvate carboxykinase and the content of lactate, pyruvate, malate, and oxaloacetate [19].

PK activity was determined according to [20] and expressed in μmoles of pyruvate per mg of protein in the sample for 1 min of incubation. LDH activity was determined according to [19] and expressed in nmol of used $NADH+H^+$ per mg of protein in the sample for 1 min of incubation.

MDH activity was determined according to [19] and expressed in μmol of formed NADH per mg of protein in the sample in 1 min. incubation The activity of phosphoenolpyruvate carboxy kinase was determined according to [21] and expressed in nmol of oxidized NADH per mg of protein in the sample for 1 min of incubation.

The content of lactate, pyruvate, malate, and oxaloacetate was determined according to [19] and expressed in μmol per 1 g of tissue and in nmol per 1 g of tissue (for oxaloacetate).

The data obtained were presented as mean (x) and the standard error of the mean (SE). $\chi 2$ criterion was used to detect the significant differences between the investigated groups $p<0.05$ was considered asa statistically significant difference.

RESULTS

The HVC administration to irradiated descendants, which were exposed to a dose of 1.0 Gy, leads to PK activity increase in the myocardium and skeletal muscles of the descendants born from animals once irradiated by 0.5 Gy and exposed to irradiation in a dose of 1.0 g. These indexes are increased by 6.7% in cardiac and 10.9% in skeletal muscles compared to such data in rats that did not receive HVC (in both cases $p>0.05$).

In the muscle tissue of descendants born from animals irradiated at a dose of 1.0 Gy and exposed to irradiation at the same dose, PK activity is reduced. The PK activity is greater by 15.5% and by 21% in cardiac and skeletal

Table I. The influence of the hormone-vitamin complex on the activity of NAD-dependent malatedehydrogenases and the content of reaction metabolites in the tissues of 1-month-old rats born from irradiated animals and exposed to radiation at a dose of 1.0 Gy

N	Enzymes and metabolites	Myocardium		Skeletal muscle		Blood
		Cytoplasm	Mitochondria	Cytoplasm	Mitochondria	
Intact rat pups (the 1st group), n=10						
1	NAD-MDH (direct reaction)	0.582±0.052	0.286±0.023	0.214±0.014	47,37±3,24	1,932±0,164
2	NAD-MDH (reverse reaction)	2.461±0.021	0.216±0.032	1.065±0.026	54,18±3,61	4,372±0,362
3	Malat	0.336±0.029		0.118±0.011		0.107±0.011
4	Oxaloacet	47.43±3.17		39.18±2.84		15.72±1.32
1-month-old rats born from animals once irradiated by 0.5 Gy and exposed to irradiation at a dose of 1.0 Gy (the 4th group), n=10						
Before correction						
1	NAD-MDH (direct reaction)	0.656±0.18	0.236±0.014	0.278±0.008	40,36±2,80	2,244±0,198
2	NAD-MDH (reverse reaction)	2.464±0.152	0.268±0.054	1.448±0.074*	68,24±2,92	4,618±0,314
3	Malat	0.389±0.024		0.164±0.013		0.117±0.014
4	Oxaloacet	43.76±2.75		36.19±2.65		14.82±1.33
After correction						
1	NAD-MDH (direct reaction)	0.632±0.18	0.226±0.01	0.264±0.008	43,28±3,20	1,786±0,178
2	NAD-MDH (reverse reaction)	2.084±0.144	0.248±0.056	1.284±0.056	66,48±2,86	4,282±0,312
3	Malat	0.392±0.026		0.172±0.014		0.124±0.012
4	Oxaloacet	42.68±1.96		34.52±1.74		14.48±1.26
1-month-old rats born from animals once irradiated by 1.0 Gy and exposed to irradiation at a dose of 1.0 Gy (the 5th group), n=10						
Before correction						
1	NAD-MDH (direct reaction)	0.984±0.36	0.178±0.012*	0.314±0.012*	26,56±1,4*	1,246±0,134*
2	NAD-MDH (reverse reaction)	3.814±0.236*	0.296±0.088	1.838±0.096*	78,52±3,64*	5,722±0,386*
3	Malat	0.492±0.084		0.236±0.022*		0.184±0.016*
4	Oxaloacet	59.12±3.96*		55.06±3.48*		19.24±2.16
After correction						
1	NAD-MDH (direct reaction)	0.686±0.20#	0.254±0.016	0.278±0.008	41,94±3,2#	1,924±0,186#
2	NAD-MDH (reverse reaction)	1.998±0.134#	0.278±0.072	1.296±0.068	68,42±2,92	4,546±0,342
3	Malat	0.416±0.032		0.178±0.016		0.128±0.014
4	Oxaloacet	43.62±1.94		35.84±1.76#		15.94±1.28

Notes: group numbers correspond to those given in "Materials and Methods" * - $p<0.05$ - significant differences of the investigated indexes compared with the same in intact rat pups; # - $p<0.05$ – significant differences of the investigated indexes compared with the same before correction.

muscles, respectively, compared to similar data in animals that did not receive HVC ($p>0.05$). The activity of this enzyme is significantly lower in blood serum of descendants born from animals irradiated at a dose of 0.5 Gy and exposed to radiation at a dose of 1.0 Gy ($p<0.05$), and its increase by 1.5 times is observed in the blood serum of descendants born from animals irradiated at a dose of 1.0 Gy and exposed to irradiation at the same dose, to which HVC was administered ($p<0.05$).

The activity of LDH in the myocardium, skeletal muscles and blood of descendants born from animals irradiated with the maximal dose, which were exposed to radiation at a dose of 1.0 Gy, after the HVC injection is characterized by a significant decrease in activity ($p<0.05$).

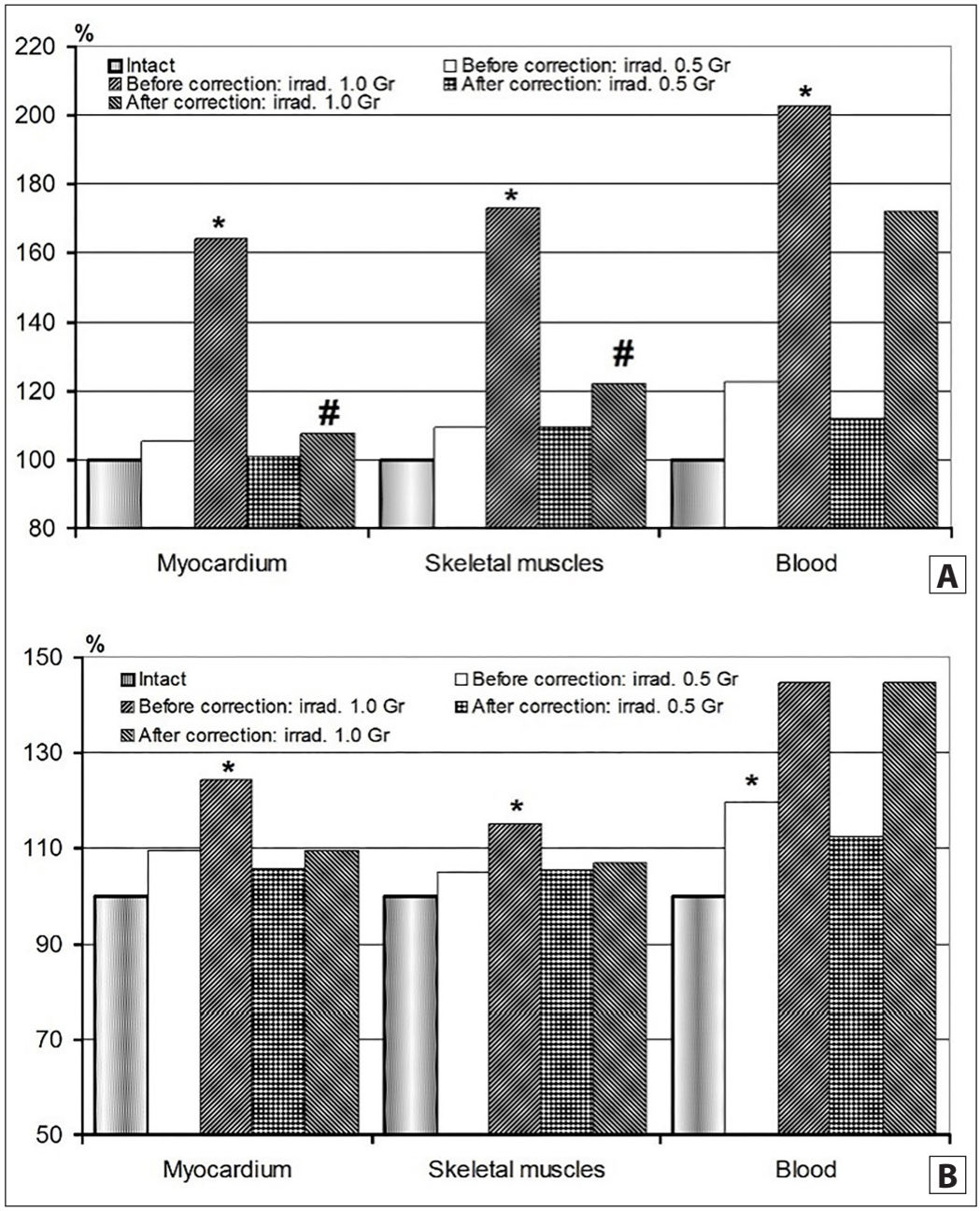

Fig. 1. The influence of the hormone-vitamin complex on the content of glycolysis metabolites (lactate; appendix A); (pyruvate; appendix B) in the investigated tissues of 1-month-old rats born from irradiated animals and exposed to radiation at a dose of 1.0 Gy.
Notes: * - $p<0.05$ – significant differences of the investigated indexes compared with the same in intact rat pups; # - $p<0.05$ – significant differences of the investigated indexes compared with the same before correction.

The pharmacological correction prevents the increase of phosphoenolpyruvate carboxykinase activity in the tissues of irradiated descendants exposed to radiation at a dose of 1.0 Gy.

The pyruvate and lactate content in the investigated tissues of irradiated descendants, which were exposed to radiation at a dose of 1.0 Gy, after the HVC introduction has some parallelism with the same indexes in the same descendants which did not receive HVC therapy ($p>0.05$; Fig. 1).

A slight increase in lactate content was observed in the myocardium and skeletal muscle of 1-month-old rats born from animals once irradiated by 0.5 Gy and exposed to irradiation at a dose of 1.0 Gy after the HVC injection (Fig. 1, A). A more pronounced increase in lactate content in muscle tissue of irradiated descendants by 1.0 Gy and exposed to irradiation at a dose of 1.0 Gy ($p<0.05$). The content of lactate in the blood of the studied rats also exceeds the same control index, and a significantly higher lactate concentration is observed in the blood of irradiated descendants by 1.0 Gy and exposed to irradiation at a dose of 1.0 Gy ($p<0.05$).

The pyruvate content after the HVC introduction exceeds the same index both in the muscle tissue and blood of 1-month-old rats born from animals irradiated by 0.5 Gy and exposed to irradiation at a dose of 1.0 Gy, as well as in all the investigated tissues of descendants born from irradiated animals by of 1.0 Gy and exposed to radiation at a dose of 1.0 Gy ($p>0.05$; Fig. 1, B).).

The activity of NAD-dependent MDH in the cytoplasm of cardiac and skeletal muscles of irradiated descendants exposed to radiation at a dose of 1.0 Gy after the HCV injection is comparable to the corresponding control index. The activity of the direct NAD-dependent MDH reaction in the mitochondria of cardiac and skeletal muscles of irradiated descendants exposed to radiation at a dose of 1.0 Gy after the HVC introduction is reduced, and the lowest values are observed in rats born from animals irradiated at a dose of 1.0 Gy and exposed to irradiation at a dose of 1.0 Gy, however, these indexes are identical to the same in intact rats ($p>0.05$; Table I).

The activity of the direct NAD-dependent MDH reaction in the blood of irradiated descendants exposed to radiation at a dose of 1.0 Gy after the HVC introduction also reduced, and the lowest index is observed in rats born from irradiated animals by 0,5 Gy exposed to radiation at a dose of 1.0 Gy ($p>0.05$).

The activity of NAD-dependent MDH in the myocardium cytoplasm of irradiated descendants exposed to radiation with a dose of 1.0 Gy after the HVC introduction is lower compared to the intact group, and the lowest indicator of its activity is observed in the cytoplasm of the myocardium in rats born from animals irradiated by 1.0 Gy and exposed to irradiation at a dose of 1.0 Gy after PMC introduction ($p>0.05$).

The activity of NAD-dependent MDH (reverse reaction) in the mitochondria of cardiac and skeletal muscles, as well as in the blood of irradiated descendants exposed to radiation at a dose of 1.0 Gy after the HVC introduction is comparable to same control indexes ($p>0.05$).

The malate and oxaloacetate content in the muscle tissue and blood of irradiated descendants exposed to radiation at a dose of 1.0 Gy after the HVC introduction has a multidirectional nature. Against the background of a slightly increased concentration of malate in muscle tissue and blood, the content of oxaloacetate decreases compared to intact rats. As a result, an increase in the ratio of malate to oxaloacetate was observed in the examined tissues of irradiated descendants exposed to radiation at a dose of 1.0 Gy after the HVC introduction compared to irradiated descendants exposed to radiation in a dose of 1.0 Gy which did not receive pharmacological correction.

DISCUSSION

Thus, the obtained results indicate that the HVC introduction to the irradiated of animals, exposed to radiation at a dose of 1.0 Gy, led to an energy resources improvement in muscle tissue both due to the increase in glycolytic substrate phosphorylation, which is of dominant importance for providing energy to skeletal muscles, and due to the increase in the oxidative potential of the tricarboxylic acid cycle not only at the stage of MDH action, but also at the stage that is catalyzed by succinatedehydrogenase. We consider it appropriate to stress the following ideas.

Firstly, we assumed that the pharmacological correction of radiation disorders of energy metabolism in irradiated descendants exposed to radiation at the same doses should be aimed at correcting disorders by the tissues provision with macroergic compounds that occur according to catabolism prevailing over anabolism, anaerobic processes strengthening, metabolic acidosis development in tissues, weakening of substrate phosphorylation and the cycle of tricarboxylic acids, as well as cellular genetic apparatus damage prevention, regeneration processes normalization [4, 11].

Secondly, we suppose to understand the mechanisms of the radioprotective effect realization in the used corrective pharmacological scheme: the improvement of lactate and pyruvate accumulation as the end products of glycolysis in the tissues of the descendants, the weakening of the processes of substrate and oxidative phosphorylation, which leads to malate and oxaloacetate - the final products of the tricarboxylic acid cycle - increase. It is important to understand that in the accumulation of malate, the leading role is played by the activation of the reverse NAD-dependent MDG in the cytoplasm and in the mitochondria of muscle tissue, as well as the predominance of the reverse NADP-dependent MDH reaction, which ensures the pyruvate carboxylation and its transformation into malate [11, 22].

Finally, let us add that glycolytic substrate phosphorylation is of dominant importance for providing energy to skeletal muscles, therefore, based on the results obtained, it can be stated that under the influence of the hormone-vitamin complex, the energy resources of skeletal muscles are improved, which will definitely be reflected in the physical performance of the descendants, born from irradiated animals and exposed to radiation at the same dose [9, 11, 23].

Therefore, the increase in malate and oxaloacetate content in the muscle tissue and blood in the irradiated descendants exposed to radiation by 1.0 Gy after the HVC introduction, according to our ideas, occurs due to malate content increase in both tissues and the oxaloacetate content decrease. Thus, we can talk about

the increase of the oxidation potential of the cycle of tricarboxylic acids not only at the MDG stage but also at the stage catalyzed by succinate dehydrogenase.

CONCLUSIONS

1. Pronounced radioprotective efficacy of the HVC, which includes tocopherol, retabolil, cocarboxylase, and nicotinamide, was proved for the normalizing energy processes in the muscle tissue of the irradiated animals descendants.
2. The radioprotective efficacy of the applied HVC consisted in blood PK activity normalization, LDH muscle tissue, and blood activity normalization as well as in preventing an increase of phosphoenolpyruvate carboxykinase activity in the examined tissues of the irradiated animals descendants.
3. Under the influence of the hormone-vitamin complex, a decrease in the content of lactate in cardiac and skeletal muscles was noted, which improved the energy resources of the muscle tissue of the irradiated animals descendants.

REFERENCES

1. Azarov SI, Eremenko SA, Sydorenko VL et al. Tekhnohenno-ekolohichni naslidky Chornobylskoi katastrofy [Technogenic and ecological consequences of the Chernobyl disaster]. Kyiv: MPBP Hordon. 2019, p.455. (in Ukrainian).
2. Andrushkiv B. Nekhtuvannia problemamy Chornobylskoi trahedii ye naslidkovym lantsiuhom vynyknennia suchasnykh problem povnomasshtabnoi viiny z Rosiieiu [Neglecting the problems of the Chernobyl tragedy is a consequential chain of the emergence of modern problems of a full-scale war with Russia]. Naukovo-informatsiinyi visnyk Natsionalnoi akademii nauk vyshchoi osvity Ukrainy. 2022; 1: 13-18. (in Ukrainian).
3. Buzunov VO, Krasnikova LI, Voychulene YS et al. Epidemiolohichni doslidzhennia kardio- ta tserebrovaskulyarnykh zakhvoriuvan v uchasnykiv likvidatsii naslidkiv avarii na chornobylskii AES: Analiz vplyvu radiatsiinoho i neradiatsiinykh faktoriv [Epidemiological studies of cardiovascular and cerebrovascular diseases in participants in liquidation of the consequences of the accident at the Chernobyl nuclear power plant: Analysis of the influence of radiation and non-radiation factors]. Zhurnal NAMN Ukrainy. 2016; 22(2): 153-162. (in Ukrainian).
4. Burgio E, Piscitelli P, Migliore L. Ionizing Radiation and Human Health: Reviewing Models of Exposure and Mechanisms of Cellular Damage. An Epigenetic Perspective. International journal of environmental research and public health. 2018; 15(9): 1971. doi:10.3390/ijerph15091971.
5. Helm JS, Rudel RA. Adverse outcome pathways for ionizing radiation and breast cancer involve direct and indirect DNA damage, oxidative stress, inflammation, genomic instability, and interaction with hormonal regulation of the breast. Archives of toxicology. 2020; 94(5): 1511-1549. doi:10.1007/s00204-020-02752-z.
6. Shivappa P, Bernhardt GV. Natural Radioprotectors on Current and Future Perspectives: A Mini-Review. Journal of pharmacy & bioallied sciences. 2022; 14(2): 57-71. doi:10.4103/jpbs.jpbs_502_21.
7. Fedirko P, Pilmane M, Babenko TF, Konopecka V. Holovnyi mozok ta orhan zoru yak potentsiini misheni dlia vplyvu ionizuiuchoho vyprominiuvannia. Chastyna IV – Rozlady binokuliarnoho zoru ploda, sprychyneni radiatsiinym vplyvom in utero: pilotne doslidzhennia. imunohistokhimichni zminy neoprominenykh miaziv ochnoho yabluka pry kosookosti. mozhlyvyi mekhanizm rozvytku kosokosti v osib, yaki zaznaly prenatalnoho oprominennia [Brain and eye as potential targets for ionizing radiation impact. Part IV - fetal radiation-induced binocular vision disorders: a pilot study. Immunohistochemical changes of non/irradiated eyeball muscles affected by strabismus. Evidence of a possible mechanism of the strabismus development in persons exposed to fetal radiation]. Problemy radiatsiinoi medytsyny ta radiobiolohii/ Problems of radiation medicine and radiobiology. 2022; 27: 412-422. doi:10.33145/2304-8336-2022-27-412-422. (in Ukrainian).
8. Lumniczky K, Impens N, Armengol G et al. Low dose ionizing radiation effects on the immune system. Environment international. 2021; 149: 106212. doi:10.1016/j.envint.2020.106212.
9. Paithankar JG, Gupta SC, Sharma A. Therapeutic potential of low dose ionizing radiation against cancer, dementia, and diabetes: evidences from epidemiological, clinical, and preclinical studies. Molecular biology reports. 2023;50(3):2823-2834. doi:10.1007/s11033-022-08211-5.
10. Xu P, Yi Y, Luo Y et al. Radiation-induced dysfunction of energy metabolism in the heart results in the fibrosis of cardiac tissues. Molecular medicine reports. 2021;24(6):842. doi:10.3892/mmr.2021.12482.
11. Baynes J, Dominiczak M. Medical Biochemistry. Elsevier; 2023, p. 744.
12. Bondar OI, Vashchenko VM, Azarov SI et al. Chornobyl chetverte desiatylittia [Chernobyl in the fourth decade]. Kyiv: NAIR. 2019, p. 407 (in Ukrainian).
13. Levchenko OE. Viiskova toksykolohiia, radiolohiia, medychnyi zakhyst [Military toxicology, radiology, medical protection]. Kyiv: SPD Chalchynska N.V. 2017, p. 361 (in Ukrainian).
14. Azzam EI, Colangelo NW, Domogauer JD et al. Is Ionizing Radiation Harmful at any Exposure? An Echo That Continues to Vibrate. Health physics. 2016;110(3):249-251. doi:10.1097/HP.0000000000000450.

15. Yamaguchi M, Suzuki M, Funaba M et al. Mitigative efficacy of the clinical dosage administration of granulocyte colony-stimulating factor and romiplostim in mice with severe acute radiation syndrome. Stem cell research & therapy. 2020;11(1):339. doi:10.1186/s13287-020-01861-x.
16. Nukala U, Thakkar S, Krager KJ et al. Antioxidant Tocols as Radiation Countermeasures (Challenges to be Addressed to Use Tocols as Radiation Countermeasures in Humans). Antioxidants (Basel, Switzerland). 2018;7(2):33. doi:10.3390/antiox7020033.
17. Lledó I, Ibáñez B, Melero A et al. Vitamins and Radioprotective Effect: A Review. Antioxidants (Basel, Switzerland). 2023;12(3):611. doi:10.3390/antiox12030611.
18. Mardashko OO, Popyk GS, Storchilo OV. Sposib korektsii homeostazu orhanizmu, yakyi zaznav vplyvu radiatsiinoho urazhennia [A method of correcting the homeostasis of an organism affected by radiation damage]. Ukraine Patent UA 68126. 2004. https://sis.ukrpatent.org/uk/search/detail/378445/ [date access 08.04.2023] (in Ukrainian).
19. Lapovets LE, Lebed GB, Yastremska OO. Klinichna laboratorna diahnostyka [Clinical laboratory diagnostics]. Kyiv: Medytsyna; 2019, p. 472. (in Ukrainian).
20. Nakonechna OA, Bachynskyi RO. Biokhimiia fermentiv. Aspekty medychnoi enzymolohii [Biochemistry of enzymes. Aspects of medical enzymology]. Kharkiv. 2020, p. 48. (in Ukrainian).
21. Fulghum KL, Audam TN, Lorkiewicz PK et al. In vivo deep network tracing reveals phosphofructokinase-mediated coordination of biosynthetic pathway activity in the myocardium. Journal of molecular and cellular cardiology. 2022;162:32-42. doi:10.1016/j.yjmcc.2021.08.013.
22. Fix DK, Hardee JP, Bateman TA, Carson JA. Effect of irradiation on Akt signaling in atrophying skeletal muscle. Journal of applied physiology. 2016;121(4):917-924. doi:10.1152/japplphysiol.00218.2016.
23. Stepanov GF, Vastyanov RS. The peculiarities of low dose ionizing radiation influence on muscles metabolism in experimental animals. World of Medicine and Biology. 2023;2(84):233-238. doi:10.26724/2079-8334-2023-2-84-233-238.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

MATHEMATICAL MODEL FOR PREDICTING FASTING BLOOD GLUCOSE LEVEL IN DIABETES MELLITUS PATIENTS

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ABSTRACT

The aim: To substantiate the use of data on patients' lifestyle, parameters of blood glucose, heart rate, blood pressure and bread units to build a mathematical model for predicting fasting blood glucose level in diabetes mellitus patients to improve existing measures for diabetes prevention.

Materials and methods: An open database consisting of the studied parameters of 359 people was used in the research. The linear regression method was used to predict fasting blood glucose level in diabetes mellitus patients. The statistical software IBM SPSS Statistics Version 23 was chosen for calculations.

Results: To calculate the coefficients of the linear regression equation, stepwise elimination of parameters was chosen. The analysis of the coefficients of influence of independent variables on dependent showed that the greatest effect on the change in glucose level had value of consumed bread units. The model for women diagnosed with type 2 diabetes showed the highest accuracy.

Conclusions: Mathematical modeling made it clear that any malnutrition or health disorders can lead to a significant change in glucose levels. The obtained models consist of a number of parameters, some of which might depend on the presence of concomitant diseases. Further studies should focus on the optimal combination of various parameters taking into account methods of treating comorbidities.

KEY WORDS: prevention of diabetes, lifestyle of patients, linear regression equation

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INTRODUCTION

Diabetes mellitus (DM) is a disease characterized by prolonged excessive plasma glucose, resulting in acute and chronic complications such as hypoglycemia, micro- and macro-vascular disease [1].

The prevalence of DM is steadily increasing [2]. It is reported that the number of patients with DM doubles every 15 years. Mass screening examinations have shown that in developed countries 2-4% of the population have severe diabetes. In addition, another 4-6% have latent or borderline diabetes, which are referred to as impaired glucose tolerance. According to the World Health Organization [3], about 422 million people worldwide have diabetes, and 1.5 million deaths each year are directly attributable to diabetes [4]. DM is the seventh leading cause of death worldwide. More than 420 million people are currently living with diabetes, and this number is estimated to rise to 570 million by 2030 and 700 million by 2045.

The body of a person with diabetes is not able to properly regulate the level of sugar in the blood (glucose level), which is the main source of energy in the body. To maintain blood sugar at a given level and avoid problems with the kidneys, heart, legs and eyes, the patient must control his meals, lead an active lifestyle and take medications. Daily monitoring of not only sugar level, but also such indicators as heart rate (HR), blood pressure (BP) and the amount of carbohydrates is a common practice for people with DM [5]. There is a need for constant recording and analysis of the indicators described above in order to predict the course of the disease and avoid severe complications. Timely detection of deviations of control indicators might help regulate the sugar level: the increase or decrease of glucose in this case occurs with the help of additional injections of insulin or consumption of sugar.

The level of sugar in the blood can decrease or increase during the day, depending on the activity, as well as the time and amount of food consumed by a person. To determine the true level of sugar for monitoring, it is necessary to measure it two hours after eating, since the glucose level can rise sharply even in a healthy person straight

after eating [6]. The analysis of indicators before or after eating can lead to the conclusion about the course of the disease, namely to determine hypo- or hyperglycemia in the patient. If the patient has a constant decrease in the level of glucose after eating for a certain time, then the doctor can conduct additional tests to check the tendency to hypoglycemia, and in case of a constant increase in the sugar level, the tendency to hyperglycemia.

For self-monitoring of sugar level, the patient will need the following devices:

- lancet a very thin needle used for drawing a small amount of blood;
- test-strips pieces of special paper on which the blood taken with a lancet is applied;
- glucometer a device, which reads a test-strip and informs the patient about the level of sugar in the blood;
- diary for recording the value of the sugar level at the appropriate time intervals.

The frequency of monitoring is determined depending on the type of diabetes and should be set by a doctor. In addition to self-monitoring, the patient should undergo regular consultation with an endocrinologist. As a rule, it takes place once every three months. The determination of the level of glycated hemoglobin (HbA1c) is also necessary [7]. This study is used to detect the chemical reaction of hemoglobin (contained in erythrocytes) with glucose. The analysis is used to determine the average content of glucose in the blood during the last 2-3 months. This monitoring is carried out to ensure the stability of glucose levels over time.

A great number of programs are currently under development, both for self-monitoring and for monitoring by doctors. Leading specialists in endocrinology proposed 3 programs for monitoring patients with MD.

THE AIM

The aim of the study is to substantiate the use of data on patients' lifestyle, parameters of blood glucose, heart rate, blood pressure and bread units to build a mathematical model for predicting fasting blood glucose level in diabetes mellitus patients to improve existing measures for diabetes prevention.

MATERIALS AND METHODS

In recent decades, predictive mathematical models have been used for various studies related to DM. For instance, model of DM progression [8, 9], evaluation of diagnostic tests [10, 11], long-term micro- and macro-vascular complications [12, 13], and blood glucose dynamics [14, 15].

Mathematical models have a number of advantages over neural networks [16], which are presented in Table I.

Mathematical models help understand the dynamics of the course of DM. There are various models based on the distribution of glucose and insulin that explain their interaction. All developed models work under certain conditions and assumptions and are very helpful for conducting research. All of them have limitations in predicting blood glucose levels in a real-time clinical situation due to the need for constantly updated information and parameters such as glucose load and insulin availability. The above indicators might be different for different patients.

Regression analysis is used for prediction, time series analysis, hypothesis testing [17], and identifying hidden relationships in data.

Regression analysis is used when the relationship between variables can be expressed quantitatively in the form of some combination of these variables. The resulting combination is used to predict the value that the dependent variable can take, which is calculated on a given set of values of the independent variables. In the simplest case, linear regression is used for this.

A regression model is a function of an independent variable and coefficients with included random variables [18]. The general form of the linear regression equation looks as follows:

$$Y = + + \ldots + \quad (1)$$

where Y – dependent variable, – independent variables, and – variable influence factor.

The main parameters for a self-monitoring diary, which are important when choosing treatment tactics for patients with DM, are glucose level, HR, BP, and bread units.

Glucose level (glycemia), which is sugar content in a patient's blood, is determined using third-party devices, namely glucometers; units are measured in mmol/l.

Table I. Advantages of mathematical model and neural network

No	Factor of comparison	Neural network	Mathematical model
1.	Availability of implementation	Only an experienced person can develop a neural network	Basic knowledge in statistics is enough to develop a mathematical model
2.	Resources for analysis	A database with a large number of patients is required for neural network training. Two large groups are needed: for training and testing the finished network	Only one database with the number of patients is needed, which will be objectively sufficient for the analysis
3.	Implementability in the program	Possible difficulties in embedding the code in the program	Ease of embedding the equation into the program code

Table II. Main parameters of the studied patients

Parameters	Type of diabetes mellitus									
	Gestational		Type 1				Type 2			
Number of subjects	71		91		116		42		39	
Gender	Female		Male		Female		Male		Female	
Parameters	Age	Weight	Age	Weight	Age	Weight	Age	Weight	Age	Weight
Average	32	123.69	53.95	123.05	44.54	123.3	49.24	121.9	45	116.21
Standard deviation	7.3	23.99	14.23	22.57	15.22	24.21	15.53	23.95	15.69	24.51
Minimum	19	83	26	80	19	80	21	83	20	81
Maximum	45	160	82	160	84	160	80	160	83	159

Table III. Measurement of indicators

Indicator	When measured	Program No.1	Program No.2	Program No.3
Glucose level	On an empty stomach	yes	yes	yes
	2 hours after breakfast	no	yes	no
	Before lunch	no	yes	yes
	2 hours after lunch	no	yes	no
	Before dinner	no	yes	yes
	2 hours after dinner	yes	yes	yes
Heart rate	On an empty stomach	yes	yes	yes
	2 hours after breakfast	no	yes	no
	Before lunch	no	yes	yes
	2 hours after lunch	no	yes	no
	Before dinner	no	yes	yes
	2 hours after dinner	yes	yes	no
Blood pressure	On an empty stomach	yes	yes	yes
	2 hours after breakfast	no	yes	no
	Before lunch	no	yes	yes
	2 hours after lunch	no	yes	no
	Before dinner	no	yes	yes
	2 hours after dinner	yes	yes	yes
Bread units	After breakfast	yes	yes	yes
	After the first snack	yes	yes	yes
	For lunch	yes	yes	yes
	After the second snack	yes	yes	yes
	After dinner	yes	yes	yes

HR is the number of pulse waves in 1 minute, determined using the device or by palpation.

BP is measured over the arteries and determines the force of blood pressure on the walls of the arteries during systole and diastole of the heart muscle. Two values are always measured: systolic (SBP, upper) and diastolic (DBP, lower). The determination is made using a tonometer; units are measured in mmHg.

Bread unit (BU) is a unit of measurement for determining the amount of carbohydrates in a product. It increases the blood sugar level by the same amount – 2.8 mmol/l – and requires 2 units of insulin to be absorbed by the body. It is calculated using special tables or a BU calculator; units are measured in grams.

The research database includes: weight indicators, age, gender, program and health status of the patient (women with gestational diabetes, men and women diagnosed with type 1 or type 2 diabetes), data on glucose level, HR, BP (systolic and diastolic), and BU.

The research was conducted on a publicly available database consisting of a study of 359 people, the main data of which are shown in Table II.

Endocrinologists have developed three main programs for the ease of convenience. Program No.1 is

Table IV. Conventional notations in equations

Indicator	When measured	Notation in equations
Age	At the start of the treatment	x1
Weight	At the start of the treatment	x2
Glucose level	On an empty stomach	x3
	2 hours after breakfast	x4
	Before lunch	x5
	2 hours after lunch	x6
	Before dinner	x7
	2 hours after dinner	x8
Heart rate	On an empty stomach	x9
	2 hours after breakfast	x10
	Before lunch	x11
	2 hours after lunch	x12
	Before dinner	x13
	2 hours after dinner	x14
Diastolic blood pressure	On an empty stomach	x15
	2 hours after breakfast	x16
	Before lunch	x17
	2 hours after lunch	x18
	Before dinner	x19
	2 hours after dinner	x20
Systolic blood pressure	On an empty stomach	x21
	2 hours after breakfast	x22
	Before lunch	x23
	2 hours after lunch	x24
	Before dinner	x25
	2 hours after dinner	x26
Bread units	After breakfast	x27
	After the first snack	x28
	For lunch	x29
	After the second snack	x30
	After dinner	x31

intended for pregnant women diagnosed with gestational diabetes. Program No.2 is for patients diagnosed with type 2 diabetes. Program No.3 is for patients diagnosed with type 1 diabetes.

The frequency of measurement of indicators and their relation to a specific monitoring program are shown in Table III.

To predict glucose levels it is convenient to use linear regression. Linear regression is a mathematical modeling method which helps establish the relationship between data described by an equation that determines the value of the dependent coefficient on the contribution of each independent variable.

The statistical software IBM SPSS Statistics Version 23 was chosen for calculations. The package of standard functions contains all necessary database analysis for calculations.

The study was conducted in accordance with the basic principles of the Council of Europe Convention on Human Rights and Biomedicine, World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current national regulations. The study protocol was approved by the local ethics committee. Informed patient consents are available.

RESULTS

To calculate the coefficients of the linear regression equation, stepwise elimination of parameters was chosen. This is a variable selection procedure in which all variables are entered in an equation, and then sequentially excluded

Table V. Quality of predictive models

Type of diabetes	Gender	Equation No.	Quality of the constructed model
Gestational	Female	1	72,4%
Type 1	Male	2	67,8%
	Female	3	78,3%
Type 2	Male	4	81,3%
	Female	5	91,5%

from it. The first candidate for elimination is a variable that has the lowest partial correlation with the dependent variable. If it meets the exclusion criteria, it is eliminated. The next candidate for exclusion is a variable that has a partial correlation with the dependent variable among the remaining ones . The procedure stops when there are no variables remaining that meet the exclusion criterion [19].

All indicators contained in the database have the following notations in equations (Table IV).

To predict morning glucose level in women with gestational diabetes, the main indicators measured on an empty stomach and after dinner were taken into account as independent variables, in addition to the parameter of glucose level, which was measured on an empty stomach, as well as bread units throughout the day, age and weight.

Using the coefficients obtained in the IBM SPSS Statistics Version 23, we will make an equation (2), which will help predict glucose level on the following morning for women with gestational diabetes.

$$y = 14.929 - 0.016*x15 - 0.327*x30 \quad (2)$$

For men diagnosed with type 1 diabetes, a predictive mathematical model was obtained for determining glucose levels the next morning with such independent variables as the values of bread units after breakfast, at lunch, and after the second snack (3):

$$y = 11.153 + 0{,}026*x27 + 0{,}041*x29 - 0{,}571*x30 \quad (3)$$

In women diagnosed with type 1 diabetes, glucose level on the following morning can be calculated using equation (4):

$$y = 11.729 + 0.03*x11 - 0.01*x15 - 0.017*x17 + 0.022*x26 - 0.179*x27 \quad (4)$$

When conducting research with patients diagnosed with type 2 diabetes, the following equations were obtained for determining the glucose level the next morning in men (5) and women (6):

$$y = 13.848 - 0.023*x2 - 0.374*x4 - 0.341*x7 + 0.042*x10 + 0.036*x26 \quad (5)$$

$$y = 14.087 + 0.054*x9 - 0.08*x10 + 0.047*x14 - 0.063*x21 - 0.038*x16 - 0.043*x23 + 0.052*x19 + 0.416*x27 - 0.51*x29 + 0.43*x31 \quad (6)$$

The application of the stepwise elimination of the studied parameters from the model made it possible to investigate the quality of the obtained models (Table V). The model for women diagnosed with type 2 diabetes showed the highest accuracy.

DISCUSSION

There is a lot of research related to the prediction and analysis of blood sugar levels [20-23]. Machine learning methods are most often used in such studies. Most of the algorithms are focused on getting the answer whether the patient has diabetes or not.

In machine learning methods the input data are age, gender, body mass index, insulin, cholesterol, glycated hemoglobin, and several glucose measurements. Blood pressure, heart rate and the number of bread units consumed during the current day were additionally introduced in our investigation.

This research describes the application of multivariate linear regression, which can be used to predict glucose levels the next morning with high prediction accuracy. In particular, the application of the prognostic model for pregnant women showed a prediction accuracy of 72.4%. Predicting glucose levels the next morning in men can be predicted with an accuracy of 67.8% (for type 1 diabetes) and 81.3% (for type 2 diabetes). The best results were obtained for women in predicting type 1 diabetes (78.3%) and type 2 diabetes (91.5%).

The analysis of the coefficients of influence of independent variables on dependent showed that the greatest effect on the change in glucose level had value of consumed bread units.

The use of bread unit indicators in prognostic models is effective for nutritional correction and correction of the patient's health status by a doctor.

Early screening and prediction of the probability of developing gestational diabetes in pregnant women are mandatory for the prevention and treatment of this condition [24]. If the level of glucose in pregnant women with gestational diabetes is poorly controlled, then this can lead to the development of fetal pathologies. After the diagnosis of gestational diabetes, insulin is prescribed and the pregnant woman's diet is monitored. There fore, identifying risk factors and creating a simple practical model for predicting the risk of gestational diabetes, especially in the first trimester of pregnancy, is of great clinical importance.

Patients with type 1 diabetes need insulin. Most patients with type 1 diabetes can be taught to adjust insulin doses based on blood glucose levels and carbohydrate (bread units) intake. Some patients with type 2 diabetes can avoid drug treatment if they are able to maintain plasma glucose

levels through diet, exercise, and normalization of blood pressure and heart rate. For this purpose, learning takes place in the school of self-control. At each visit to the self-monitoring school for patients with diabetes mellitus, nurses and doctors update the knowledge of patients about the pathogenesis and therapy of diabetes mellitus. These measures are quite effective and help to improve the results of diabetes treatment.

The obtained prognostic mathematical models can be used at the beginning of the treatment of patients with type 1 and type 2 diabetes to correct the patient's lifestyle. Also, these models can be embedded in a mobile application or computer software to help doctors predict the development of diabetes in patients in the future and provide the necessary preventive measures.

The obtained models can be improved in the future and studied with other parameters that may influence the progression of diabetes of different types. In medicine, the highest accuracy and the lowest errors are very important, so we will continue to improve glucose prediction. It is planned to classify the progression of the disease using other possible mathematical methods of prediction. After optimizing all algorithms, the best model will be determined. These researches will be interesting for researchers in the area of medicine who use machine learning and mathematical prediction methods.

CONCLUSIONS

Predicting blood glucose levels based on a patient's lifestyle data is of great importance for patients, doctors, and researchers. Such knowledge can help improve existing measures on prevention and treatment of DM.

Mathematical modeling made it clear that any malnutrition or health disturbances can lead to a significant change in glucose levels.

Patients with type 1 diabetes need an effective tool for monitoring glucose levels and making the right decisions about insulin administration and food consumption. Qualitative and accurate prediction of future blood glucose levels several steps ahead benefits patients with diabetes by helping them reduce the risk of glucose extremes, including hypo- and hyperglycemia.

Being able to accurately predict future blood glucose levels will help patients prevent both low and high blood glucose levels, allow them to reach glycemic targets and reduce the risk of long-term complications.

The obtained models consist of a number of parameters, some of which might depend on the presence of concomitant diseases. Further studies should focus on the optimal combination of various parameters taking into account methods of treating comorbidities.

REFERENCES

1. Shamanna P, Dharmalingam M, Sahay R et al. Retrospective study of glycemic variability, BMI, and blood pressure in diabetes patients in the Digital Twin Precision Treatment Program. Sci Rep. 2021;11(1):1-9. doi: 10.1038/s41598-021-94339-6.
2. Hollingshead C, Luttmann K, Georgescu C. Bilateral emphysematous pyelonephritis. ID Cases. 2021;23:e01042. doi: 10.1016/j.idcr.2020.e01042.
3. WHO. Diabetes. https://www.who.int/health-topics/diabetes#tab=tab_1 [date access 07.04.2023]
4. WHO. Diabetes Ukraine 2016 country profile. https://www.who.int/publications/m/item/diabetes-ukr-country-profile-ukraine-2016 [date access 07.04.2023].
5. Fundoiano-Hershcovitz Y, Bacher D, Ritholz MD et al. Blood Pressure Monitoring as a Digital Health Tool for Improving Diabetes Clinical Outcomes: Retrospective Real-world Study. J Med Internet Res. 2022;24(2):e32923. doi: 10.2196/32923.
6. Amante DJ, Harlan DM, Lemon SC et al. Evaluation of a Diabetes Remote Monitoring Program Facilitated by Connected Glucose Meters for Patients With Poorly Controlled Type 2 Diabetes: Randomized Crossover Trial. JMIR Diabetes. 2021;6(1):e25574. doi: 10.2196/25574.
7. Miller KM, Beck RW, Foster NC et al. HbA1c Levels in Type 1 Diabetes from Early Childhood to Older Adults: A Deeper Dive into the Influence of Technology and Socioeconomic Status on HbA1c in the T1D Exchange Clinic Registry Findings. Diabetes Technol Ther. 2020;22(9):645-650. doi: 10.1089/dia.2019.0393.
8. Yang B, Li J, Haller MJ et al. The progression of secondary diabetes: A review of modeling studies. Front Endocrinol (Lausanne). 2022;13:1070979. doi: 10.3389/fendo.2022.1070979.
9. Zavala E, Wedgwood K, Voliotis M et al. Mathematical Modelling of Endocrine Systems. Trends Endocrinol Metab. 2019;30(4):244-257. doi: 10.1016/j.tem.2019.01.008.
10. López-Palau NE, Olais-Govea JM. Mathematical model of blood glucose dynamics by emulating the pathophysiology of glucose metabolism in type 2 diabetes mellitus. Sci Rep. 2020;10(1):12697. doi: 10.1038/s41598-020-69629-0.
11. Vahidi O, Kwok KE, Gopaluni RB et al. Developing a physiological model for type II diabetes mellitus. Bioch Engin Journ. 2011;55(1):7-16. doi: 10.1016/j.bej.2011.02.01.
12. Armengol GD, Hayfron-Benjamin CF, van den Born BH et al. Microvascular and macrovascular complications in type 2 diabetes in a multiethnic population based in Amsterdam. The HELIUS study. Prim Care Diabetes. 2021;15(3):528-534. doi: 10.1016/j.pcd.2021.02.008.
13. Li J, Bao Y, Chen X et al. Decision models in type 2 diabetes mellitus: A systematic review. Acta Diabetol. 2021;58(11):1451-1469. doi:

10.1007/s00592-021-01742-6.
14. Ajmera I, Swat M, Laibe C et al. The impact of mathematical modeling on the understanding of diabetes and related complications. CPT Pharmacometrics Syst Pharmacol. 2013;2(7):e54. doi: 10.1038/psp.2013.30.
15. Banzi W, Kambutse I, Dusabejambo V et al. Mathematical Modelling of Glucose-Insulin System and Test of Abnormalities of Type 2 Diabetic Patients. Int Journ of Mathem and Mathem Sci. 2021;1-12. doi: 10.1155/2021/6660177.
16. Buchaniec S, Gnatowski M, Brus G. Integration of Classical Mathematical Modeling with an Artificial Neural Network for the Problems with Limited Dataset. Energies. 2021;14(16):5127. doi: 10.3390/en14165127.
17. Liu S, Gao Y, Shen Y et al. Application of three statistical models for predicting the risk of diabetes. BMC Endocr Disord. 2019;19(1):126. doi: 10.1186/s12902-019-0456-2.
18. Skiera B, Reiner J, Albers S. Regression Analysis. Handbook of Market Research. Springer, Cham. 2018. doi: 10.1007/978-3-319-05542-8_17-1.
19. Wang X, Zhai M, Ren Z et al. Exploratory study on classification of diabetes mellitus through a combined Random Forest Classifier. BMC Med Inform Decis Mak. 2021;21(1):105. doi: 10.1186/s12911-021-01471-4.
20. Daliya VK, Ramesh TK, Ko S-B. An Optimised Multivariable Regression Model for Predictive Analysis of Diabetic Disease Progression. IEEE Access. 2021;9: 99768–99780. doi: 10.1109/access.2021.3096139.
21. Woldaregay AZ, Årsand E, Walderhaug S et al. Data-driven modeling and prediction of blood glucose dynamics: Machine learning applications in type 1 diabetes. Artif Intell Med. 2019;98:109-134. doi: 10.1016/j.artmed.2019.07.007.
22. Sarker I, Faruque MD, Alqahtani H et al. K-Nearest Neighbor Learning based Diabetes Mellitus Prediction and Analysis for eHealth Services. ICST Transactions on Scalable Inform Syst. 2018;0(0):162737. doi: 10.4108/eai.13-7-2018.162737.
23. Alfian G, Syafrudin M, Rhee J et al. Blood Glucose Prediction Model for Type 1 Diabetes based on Extreme Gradient Boosting. IOP Conf. Ser.: Mater. Sci. Eng. 2020;803(1): 012012. doi: 10.1088/1757-899x/803/1/012012.
24. Modzelewski R, Stefanowicz-Rutkowska MM, Matuszewski W et al. Gestational Diabetes Mellitus-Recent Literature Review. J Clin Med. 2022;11(19):5736. doi: 10.3390/jcm11195736.

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ORIGINAL ARTICLE

CLINICAL AND EPIDEMIOLOGICAL FEATURES OF COVID-19 IN CHILDREN FOR THE PERIOD 2020-2022

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ABSTRACT

The aim: To investigate the epidemiological and clinical characteristics of COVID-19 in children for the period 2020-2022.

Materials and methods: A retrospective analysis of 1144 case histories of children who were hospitalized at the St. Zinaida Children's Clinical Hospital (Sumy, Ukraine) for coronavirus disease for 2020-2022 was carried out. The observed patients were divided into 3 groups corresponding to the 3 waves of the pandemic: group 1 - 120 children, group 2 - 311 children, and group 3 - 713. The diagnosis of COVID-19 was established based on clinical, medical histories, laboratory and instrumental data. The etiology of coronavirus disease was determined based on the detection of antigens of the SARS-CoV-2 virus using PCR reverse transcription of a nasopharyngeal swab.

Results: An analysis of the clinical and epidemiological indicators of children who were treated for COVID-19 during 2020-2022 was conducted, depending on the outbreak of the pandemic. The frequency of lesions in children of different age groups was determined, and the main clinical symptoms and the frequency of complications in the form of pneumonia during different waves of COVID-19 were determined.

Conclusions: The incidence of coronavirus infection was mainly observed in children of the younger group (0-5 years). A more severe course of the disease and a higher frequency of complications in the form of pneumonia in children were determined during the 3rd wave of the COVID-19 pandemic.

KEY WORDS: COVID-19, SARS-CoV-2, coronavirus infection, pneumonia, children

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INTRODUCTION

The COVID-19 pandemic has prompted scientists and practitioners to rethink the epidemic danger of coronavirus infection and its role in the occurrence of diseases of varying severity in adults and children. Compared with adults, the incidence of COVID-19 in children, according to different authors, is 2-5% depending on the country [1]. In Ukraine, the proportion of children with a confirmed diagnosis of COVID-19 in relation to adult patients at the end of August 2023 is 5%, and infant mortality is 0,1% in the overall age structure of mortality [2]. The low incidence rate is explained by the reduced risk of infection in children due to less travel, communication, and movement. Also, children, as a rule, do not have chronic somatic diseases and the resistance of the protective mechanisms of the mucosa is much stronger due to its intactness by negative impact factors (smoking, air pollution). Swedish scientist Ludvigsson J.F. suggested that exposure to the children's mucosa of pathogens of other acute respiratory viral infections activates the local immune response and limits the attachment of coronavirus [1].

According to foreign colleagues, COVID-19 in children is accompanied by the development of a mild course of the disease and only occasionally leads to death, and in 15-35% of cases it is asymptomatic [3-5]. However, it should be noted that the current course of the disease in children has changed, the percentage of severe cases of disease with the possible development of life-threatening conditions has increased (mainly in children with concomitant chronic pathology and infants) [6, 7].

An interesting established fact is the increase in the number of manifest forms of COVID-19, depending on the increase in the age of children. According to WHO data for the period 2019-2021, the incidence of COVID-19 was observed mainly in children of the older age group: children under 5 y.o. – 1,8% (mortality rate 0,1% in the world), from 5 to 14 y.o. – 6,3% (mortality 0,1%), from 15 to 24 years – 14,5% (mortality 0,4%) [8]. The Chinese scientist Dong Y. explains the increase in the number of cases of COVID-19 with increasing patient age by the difference in the functioning and maturity of the immune system of patients of different age categories [7]. Scientist Held L. has a slightly different opinion and sees the reason for the growth according to the age of the viral load on the child's body [9]. Infection of children usually occurs in families.

It is known that the SARS-CoV-2 virus is characterized by the emergence of its new strains, which caused the undulating course of the pandemic. For convenience, variants of SARS-CoV-2 strains are labeled with Greek letters. Depending on the time of occurrence in Ukraine, 3 waves of COVID-19 were identified. The first wave (second half of 2020) was characterized by the circulation of the alpha strain, the second (first half of 2021) by the dominance of the beta and gamma strains, and the third wave (end of 2021-beginning of 2022) by the delta and omicron strains. It was the delta strain that caused the greatest concern of the medical community, since, according to the British scientist Lewis T., it was characterized by 40-60% greater contagiousness and severity of the course, 2,5 times more often led to hospitalization, and complications of the disease [10, 11].

Given the differences in the susceptibility of children to different strains of SARS-CoV-2, the variety of clinical symptoms in different waves of the pandemic, the characteristics of the course of COVID-19 in children need further study and comparison.

THE AIM

The purpose of our work is to investigate the epidemiological and clinical characteristics of COVID-19 in children for the period 2020-2022.

MATERIALS AND METHODS

A retrospective analysis of 1144 case histories of children who were hospitalized at the Children's Clinical Hospital of St. Zinaida (Sumy, Ukraine) for the period from November 2020 to August 2022 was performed. The ages of the patients ranged from 4 months to 17 years. No deaths were registered in 2020 and 2021. In 2022, in 2 children with comorbidities, the disease was complicated by the development of acute respiratory failure and the patients died: (1) Patient N., 15 y.o., diagnosed with COVID-19, acute respiratory failure. Degenerative disease of the nervous system, focal epilepsy. (2) Patient E., 16 y.o., diagnosis: COVID-19, acute respiratory failure. Progressive Duchenne muscular dystrophy).

The diagnosis of COVID-19 was established based on clinical, medical history findings, laboratory and instrumental data. The etiology of coronavirus disease was determined based on the results of the detection of antigens of the SARS-CoV-2 virus by reverse transcription polymerase chain reaction (PCR) (RT-PCR) of a nasopharyngeal swab. Testing was carried out according to clinical and epidemiological indications.

Statistical analyses in this study were conducted using MS Excel and STATISTICA 8.0 (Tulsa, OK) software. The mean M for each indicator was used to determine the difference between the values of the indicators in the comparison groups. The difference between groups was considered statistically significant when $p < 0,05$.

RESULTS

Depending on the time of onset of the coronavirus disease, we divided all patients into 3 groups: Group I (120 children) was hospitalized during the 1st wave of the pandemic (November, and December 2020), Group II (311 patients) belonged to during the 2nd wave of the pandemic (February - August 2021) and group III (713 patients) fell ill during the 3rd wave (September 2021 - May 2022). In most cases, those strains of coronavirus were determined in hospitalized children that corresponded to those circulating in a certain period. Each group of patients, in turn, was divided into 4 age categories (0-12 mo.o., 1-5 y.o, 6-9 y.o. and 10-18 y.o.) (Fig. 1).

During the 1st wave of COVID-19, the following distribution of sick children by age was observed: 0-1 y.o. – 20,7% (25/120), 1-5 y.o. – 29,2% (35/120), 6-9 y.o. – 15,8% (19/120), 10-18 y.o.– 34,3% (41/120). The distribution of the incidence rate of children by age during the 2nd wave of the pandemic: children 0-1 y.o. – 24,1% (75/311), 1-5 y.o. – 43,4% (135/311), 6-9 y.o. - 15, 0% (47/311), 10-18 y.o. – 17,5% (54/311). During 2022, the following age distribution trend was noted: 0-1 y.o. – 24,0% (171/713), 1-5 y.o. – 45,0% (321/713), 6-9 y.o. – 15,0% (107/713), 10-18 y.o. – 16,0% (114/713). As can be seen from Fig. 1, over the course of all 3 years, the incidence of COVID-19 diseases prevailed in the age groups of 0-5 years, and during the 1st wave, also in children aged 10-18.

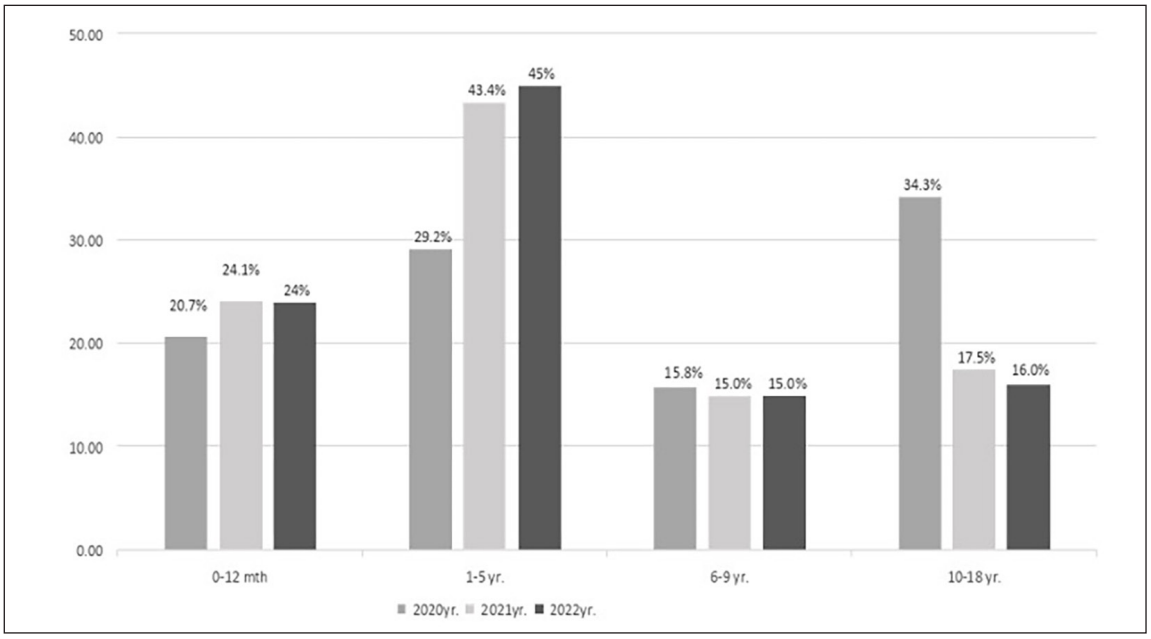

Fig. 1. Distribution of patients with COVID-19 by age during 2020-2022

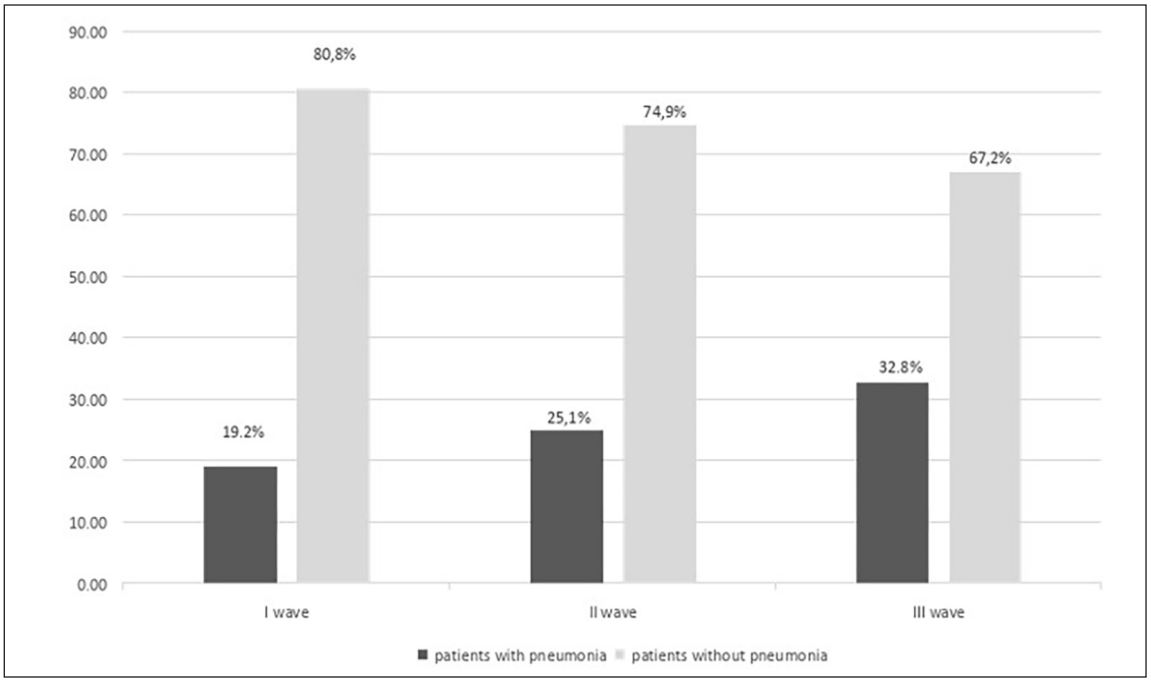

Fig.2. Distribution of children with COVID-19, depending on the fact of pneumonia for the period 2020-2022

For the period 2020-2022, two dominant symptom complexes were determined: upper respiratory tract symptoms (such as acute nasopharyngitis) and lower respiratory tract symptoms with the development of pneumonia. The diagnosis of pneumonia was confirmed by X-ray. Depending on the diagnosis of pneumonia, the patients of each group were divided into 2 subgroups: with and without pneumonia (Fig. 2).

During the first wave of COVID-19, 23 out of 120 children were diagnosed with pneumonia, which accounted for 19,2%, during the second wave - 78 out of 311 (25,1%) children had pneumonia, during the third wave - 234 out of 713 children, which amounted to 32,8%. As can be seen from Fig. 2, the disease COVID-19 predominantly (67-80% of cases) proceeded as an acute respiratory infection with symptoms of damage to the upper respiratory tract, and only 19-33% of children developed pneumonia. Comparing the incidence of pneumonia in 2020-2022, it should be noted that a higher number of pneumonia developments occurred in 2021-2022 when the 2nd and 3rd waves of the pandemic were observed, which is explained by the circulation of more aggressive strains.

Table I. Features of the clinical symptoms of COVID-19 in children for the period 2020-2022

Symptom	2020	I semester of 2021	II semester 2021 – I semestr 2022
Number of children (n)	120	311	713
Fever, abs. (%)	114 (95,0)	305 (98,1)	711 (99,7)
Weakness, abs. (%)	106 (88,3)	303 (97,4)	706 (99,0)
Symptoms of the upper respiratory tract affecting Rhinitis, abs. (%)	58 (48,3)	228 (73,3)	571 (80,1)
Sore throat, abs. (%)	34 (28,3)	93 (29,9)	482 (67,6)
Symptoms of the lower respiratory tract affecting Cough, abs. (%)	78 (65,0)	178 (57,2)	592 (83,0)
Shortness of breath, abs. (%)	6 (5,0)	29 (9,3)	207 (29,0)
Gastrointestinal symptoms			
Decreased appetite, abs. (%)	90 (75,0)	308 (99,0)	706 (99,0)
Abdominal pain, abs. (%)	4 (3,3)	25 (8,0)	53 (7,4)
Diarrhea, abs. (%)	9 (7,5)	26 (8,5)	91 (12,8)
Anosmia, abs. (%)	9 (7,5)	12 (3,9)	62 (8,7)
Skin rash, abs. (%)	6 (5,0)	13 (4,2)	12 (1,7)

The main clinical symptoms of children with coronavirus disease are listed in Table. The main symptoms of children from the general cohort were most often: fever (97.6%), weakness (94,9%), decreased appetite (91,0%), cough (68,4%), symptoms of rhinitis (67,2%), pain or discomfort in the throat (in 41,9%).

During 2020, the leading clinical symptoms of COVID-19 in children were: fever (114/120, 95,0%), weakness (106/120, 88,3%), decreased appetite (90/120, 75,0%), cough (78/120, 65,0%). About half of the patients had symptoms of rhinitis (58/120, 48,3%), less often – pain (discomfort) in the throat (34/120, 28,3%). Dyspnea was observed in only 5,0% (6/120) of patients, which indicated the severity of the course of the respiratory disease. Gastrointestinal symptoms such as diarrhea (9/120, 7,5%) and abdominal pain (4/120, 3,3%) were occasionally noted. Anosmia and skin rash were determined in 7,5% and 5,0% respectively (Table I).

During the first half of 2021 (second wave of coronavirus infection) almost all patients experienced a decreased appetite (308/311, 99,0%), fever (305/311, 98,1%), significant weakness (303/31, 97,4%) and rhinitis phenomena (228/311, 73,3%). Compared to 2020, cough was slightly less common (178/311, 57,2%), but the percentage of dyspnea almost doubled (9,3% vs. 5,0%), indicating an increase in the severity of the disease during the 2nd wave of the pandemic. Compared to 2020, gastrointestinal symptoms were more common: abdominal pain (8,0% vs. 3,3%), diarrhea (8,5% vs. 7,5%), anosmia, and skin rash were determined occasionally and with about the same frequency (3,9% and 4,2%, respectively).

The course of the coronavirus disease for the second half of 2021 - the first half of 2022 was characterized by a predominance of such symptoms as fever (711/713, 99,7%), general weakness, and loss of appetite (706/713, 99,0% in each case). Among the catarrhal symptoms, cough (592/713, 83,0%) and rhinitis (571/713, 80,1%) came to the fore, and sore throat (482/713, 67,6%) gave way to them. The incidence of dyspnea in patients of this group increased (107/713, 15,0%) compared to the previous groups. Signs of damage to the gastrointestinal tract were more common (abdominal pain – 7,4%, diarrhea – 12,8%). The incidence of skin rash has significantly decreased compared to previous years (1,7% versus 5,0% and 4,2%, respectively).

DISCUSSION

The COVID-19 pandemic has been characterized by an undulating course due to the constant mutation of the virus and the emergence of new strains. During the 1st wave of the pandemic, the circulation of the alpha strain was predominantly observed [10]. We found that in the 1st wave of incidence, children of the older age group (10-18 y.o.) and the younger group (0-5 y.o.) were predominantly affected, which correlates with the data of foreign authors [12].

British scientists Erica Molteni et al. also investigated the course of coronavirus infection caused by the alpha strain in children. According to their data, the 1st wave of a pandemic in 80% of cases has an uncomplicated course and is mainly accompanied by the development of fever, general weakness, rhinitis, and sore throat [12]. Our studies have shown that the COVID-19 disease in the 1st wave proceeded as an ARVI in 80.8% of children and was accompanied by the development of pneumonia in only 19.2% of cases, which fully confirms the data of British researchers. According to our results, the leading clinical symptoms of the 1st wave of COVID-19 in children were: fever (95,0%), general weakness (88,3%), loss of appetite (75,0%), and cough (65,0%) .

The 2nd and 3rd waves of the pandemic were characterized by an increase in the incidence of diseases exclusively in children of the first 5 years of age and a significant decrease in the number of affection older children, which coincides with the data of other researchers [10].

The 2nd wave was characterized by a more severe course of the disease and an increase in the number of cases of pneumonia (25,1%). Compared with the patients of the previous group, it can be argued that the symptoms of loss of appetite (99,0%), fever (98,1%), weakness (97,4%), and rhinitis (73,3%) were more common and more pronounced. Cough was observed in more than half of the patients (57.2%), but it was less common than in the previous group. It should be noted that the percentage of dyspnea almost doubled (9,3% vs. 5,0%), indicating an increase in the severity of the disease during the 2тв wave of the pandemic. More often than in the previous group, there were symptoms of GIT lesions: abdominal pain (8,0% vs. 3,3%), and diarrhea (8,5% vs. 7,5%). Our results are consistent with the data of other researchers, who noted a more severe course of the 2nd wave of the pandemic and more frequent development of complications, which is explained by the circulation of more aggressive beta and gamma strains [13].

One of the most severe periods of the incidence of COVID-19 falls on the 3rd wave of the pandemic, due to the circulation of the most aggressive strains of delta and omicron. According to Li B. et al. delta virus is 40–60% more contagious than the alpha variant [14] and is characterized by a more severe course of the disease and the development of complications [15, 16]. We found that the number of pneumonia development was significantly higher during the 3rd wave compared to the previous ones (32.8% in accordance with 19,2% and 25,1%). Also, 2 deaths in older children were observed during the 3rd wave. Clinical symptoms in the form of fever (99,7%), weakness (99,0%), loss of appetite (99,0%), cough (83,0%), and rhinitis (80,1%) were significantly pronounced and were observed almost in all patients. The sore throat was less common (67,6%), but the incidence of shortness of breath (15,0%) in patients of this group increased significantly - 3 times compared with the 1st wave (15,0% and 5,0%, respectively) and almost doubled compared with the 2nd wave (15,0% and 9,5% respectively). It should be noted that during the 2nd and 3rd waves of the disease, signs of GIT damage were more common than during the 1st wave (abdominal pain – 7,4% and 8,0% versus 3,3%, diarrhea – 12,8% and 8,5% versus 7,5%, respectively). The data obtained by us completely coincides with the data of Canadian scientists [15].

CONCLUSIONS

An analysis of the clinical and epidemiological indicators of children with COVID-19 during 2020-2022 was carried. The incidence of coronavirus infection was mainly observed in children of the younger group (0-5 years). A more severe course of the disease and a higher frequency of complications in the form of pneumonia in children were determined during the 3rd wave of the COVID-19 pandemic.

REFERENCES

1. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088-1095. doi 10.1111/apa.15270.
2. Minfin. Operational information on the main indicators of the incidence of COVID-19 in Ukraine. https://index.minfin.com.ua/ua/reference/coronavirus/ukraine/ [date access 15.08.2023]
3. Alsohime F, Temsah M-H, Al-Nemri AM et al. COVID-19 infection prevalence in pediatric population: Etiology, clinical presentation, and outcome. Journal of Infection and Public Health. 2020; 13(12): 1791-1796. doi:10.1016/j.jiph.2020.10.008.
4. Chen ZM, Fu JF, Shu Q et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J. Pediatr. 2020; 16(3): 240- 246. doi: 10.1007/s12519-020-00345-5.
5. Stokes EK, Zambrano LD, Anderson KN et al. Coronavirus disease 2019 case surveillance — United States, January 22 — May 30, 2020. MMWR Morb. Mortal. Wkly. Rep. 2020; 69: 759-765.
6. Mundeep Kainth K, Goenka PK, Williamson KA et al. Early Experience of COVID-19 in a US Children's Hospital Pediatrics. 2020; 146(4): e2020003186. doi: 10.1542/peds.2020-003186.
7. Dong Y, Mo X, Hu Y et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020; 145 (6). doi: 10.1542/peds.2020-0702.
8. WHO. COVID-19 disease in children and adolescents. https://apps.who.int/iris/bitstream/handle/10665/345575/WHO-2019-nCoV-Sci-Brief-Children-and-adolescents-2021.1-rus.pdf [date access 15.08.2023]
9. Held L. A discussion and reanalysis of the results reported in Jones et al. 2020. https://osf.io/bkuar/. [date access 15.08.2023]
10. Kramarev SO, Seriakova IY, Yevtushenko VV et al. Porivnialna kharacterystyka tretioji hvyli koronavirusnoihvoroby v ditej z poperedimy spalachamy zahvoriuvanosti [Comparative characteristics of the third wave of coronavirus infection in children with previous outbreaks]. Modern Pediatrics. 2022; 4: 5-14. http://nbuv.gov.ua/UJRN/Sped_2022_4_3 [date access 15.08.2023] (In Ukrainian).

11. Lewis T. How Dangerous Is the Delta Variant, and Will It Cause a COVID Surge in the U.S.? Scientific American. 2021. https://www.scientificamerican.com/article/how-dangerous- is-the-delta-variant-and-will-it-cause-a-covid-surge-in-the- u-s/. [date access 15.08.2023]
12. Molteni E, Sudre CH, Canas LS et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. The Lancet. Child & adolescent health. 2021; 5(10): 708-718. doi:10.1016/S2352-4642(21)00198-X.
13. Naveca F, Nascimento V, Souza V et al. COVID-19 epidemic in the Brazilian state of Amazonas was driven by long-term persistence of endemic SARS-CoV-2 lineages and the recent emergence of the new Variant of Concern P.1. 2021, PREPRINT (Version 1). doi:b10.21203/rs.3.rs-275494/v1.
14. Li B, Deng A, Li K et al. Viral infection and transmission in a large well-traced outbreak caused by the Delta SARS-CoV-2 variant. Nature Communications. 2022;13(1):460. doi: 10.1038/s41467-022-28089-y.
15. Irfan O, Muttalib F, Tang K et al. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child. 2021; 106(5): 440–448. doi: 10.1136/archdischild-2020-321385.
16. Murillo–Zamor E, Trujillo X, Huerta M et al. Decreased risk of COVID-19 pneumonia in children and adolescents during the Delta variant emergence. Public Health. 2022;204:9-11. doi: 10.1016/j.puhe.2021.12.017.

The authors adhered to the principles contained in the 1964 Declaration of Helsinki and their latest amendments. All the patients gave oral and written voluntary informed consent for examination, tests, treatment, operation, analgesia and data processing. The work with patients was prepared and carried out in accordance with the principles of ethics. The permission to conduct the study and the study protocol were approved of by the bioethics committee of the institution. The work is a fragment of research work of the Pediatrics Department of Academic and Research Medical Institute «Sumy State University» «Infectious and somatic diseases in children: features of the current course and ways to improve their treatment» (№ state registration 0120U102150; deadline: 2020-2025).

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ORIGINAL ARTICLE

THE ROLE OF NEUROHORMONAL FACTORS IN THE FORMATION OF A PATIENT'S CLINICAL PROFILE AND THE IMPACT ON STRUCTURAL CARDIAC AND VASCULAR REMODELING IN PATIENTS WITH MYOCARDIAL INFARCTION AFTER REPERFUSION THERAPY

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ABSTRACT

The aim: To determine the dynamics of galectin-3 in the formation of the patient's clinical profile and the impact on structural cardiac and vascular remodeling in patients with myocardial infarction after reperfusion therapy.

Materials and methods: 140 patients with class II A CHF syndrome according to Vasilenko-Strazhesko FC II-III (NYHA), which occurred in patients with MI, and 22 patients with MI without signs of CHF were examined.

Results: The average serum galectin-3 level of the studied patients was analyzed. The average concentration of galectin-3 in patients with stenting without signs of CHF was (10.87±1.65) ng/ml comparing to (6.57±0.21) ng/ml in healthy subjects ($p<0.05$). An increase in the concentration of this indicator was observed in the group of patients with CHF after MI with reperfusion - (35.2±1.76) ng/ml, which is significantly higher in comparison with practically healthy subjects, and in patients without revascularization it was (38.94±1.97) ng/ml ($p<0.001$). Positive correlations of medium strength were found between left ventricular end-systolic volume (ESV), left ventricular end-diastolic volume (LVEDV) and serum galectin-3 concentration in the examined patients. The correlation coefficient between the abovementioned indicators was 0.60 ($p<0.01$) and 0.53 ($p<0.05$), respectively.

Conclusions: It has been determined that in patients with CHF with postinfarction cardiosclerosis there is a direct correlation of medium strength between the values of indicators of LV myocardial remodeling with plasma galectin-3 concentration, including ESV, EDV, in examined patients. The role of galectin-3 as a marker of postinfarction remodeling in patients with CHF for early diagnosis, prognosis, and risk stratification has been presented.

KEY WORDS: myocardial infarction, heart failure, reperfusion therapy

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INTRODUCTION

Myocardial infarction (MI) is one of the most common pathologies among cardiovascular diseases (CVD) and is a leading cause of overall mortality. According to the GRACE registry, mortality after MI exceeds 10% by the end of the first 6 months and reaches 15% after 12 months. It is becoming increasingly important to look for specific markers for early diagnosis, prognosis of chronic heart failure (CHF), post-infarction period and risk stratification of patients [1]. The discovery of a new biomarker, galectin-3, is one of the achievements of modern medicine. Galectin-3 was included as a marker of stratification of patients at high risk of adverse clinical outcomes (death and re-hospitalization) in the clinical protocol for prevention and treatment of CHF [2,3]. Galectin-3 belongs to the family of β-galactoside-binding proteins and is expressed by many cells, including neutrophils, macrophages, labrocytes, fibroblasts and osteoblasts, and is hardly detected in cardiomyocytes. In recent years, a significant number of clinical trials have been published to evaluate galectin-3 as a biomarker of CVD [4]. Thus, in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study, patients with a level of this marker level lower than or equal to the average showed a 30.4% reduction in the number of cardiovascular complications. Overall, the study of galectin-3 properties was conducted involving more than 16,900 patients. Therefore, this lectin can be considered to be the most studied cardiovascular biomarker after BNP and NT-proBNP [5.6]. However, the possibility of its use in clinical practice remains unclear.

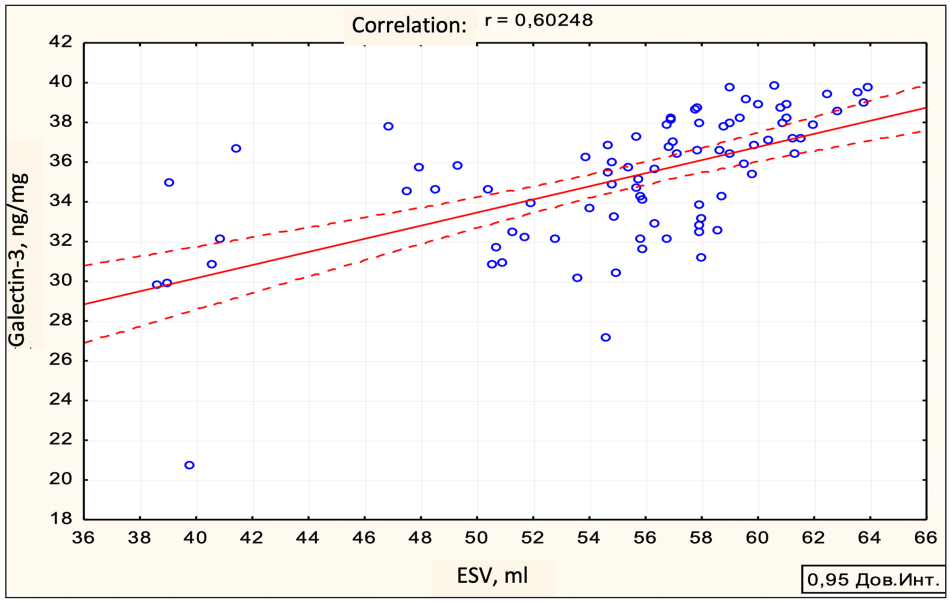

Fig. 1. Correlation between end-systolic volume and plasma galectin-3 concentration in patients with CHF.

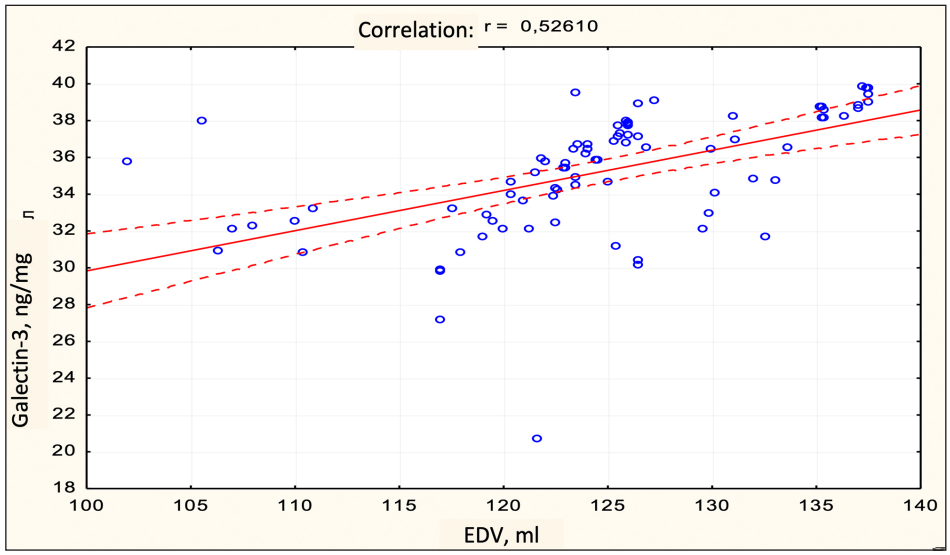

Fig. 2. Correlation between end-diastolic volume and plasma galectin-3 concentration in patients with CHF.

THE AIM

To determine the dynamics of galectin-3 in the formation of the patient's clinical profile and the impact on structural cardiac and vascular remodeling in patients with myocardial infarction after reperfusion therapy

MATERIALS AND METHODS

140 patients with class II A CHF syndrome according to Vasilenko-Strazhesko FC II-III (NYHA), which occurred in patients with MI, and 22 patients with MI without signs of CHF were examined. The diagnosis of CHF was made based on complaints, anamnesis, physical, laboratory, and instrumental examination data, taking into account the guidelines for the diagnosis and treatment of chronic heart failure (2017) of the Association of Cardiologists of Ukraine and the recommendations of the European Society of Cardiology (ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2016) []. The ischemic origin of CHF was verified on the basis of the previous record of MI with a note on the presence of positive biological markers, ECG, echocardiography, coronary angiography in accordance with the Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (2017), draft guidelines of the Association of Cardiologists of Ukraine (2013).

All patients with CHF were randomized into 2 groups, depending on the availability of reperfusion therapy performed with stenting of the infarct-dependent coronary artery (IDCA) during the acute period of MI or in its absence:

I) – patients with class II A CHF, FC II-III after reperfusion therapy in the acute period of MI with stenting of the IDCA (n=84).

Table I. Biomarker levels in patients with heart failure after myocardial infarction depending on the performed stenting

Indicators	Practically healthy (n=15)	Patients with stenting without heart failure (n=22)	Patients with heart failure after myocardial infarction with stenting (n=84)	Patients with heart failure after myocardial infarction without stenting (n=56)
Galectin-3 level (ng/ml)	6.57± 0.21	10.87± 1.65 p<0.05	35.2± 1.76 p<0.001	38.94± 1.97 p<0.001

Note: p - probability of variance of indicators comparing to practically healthy subjects.

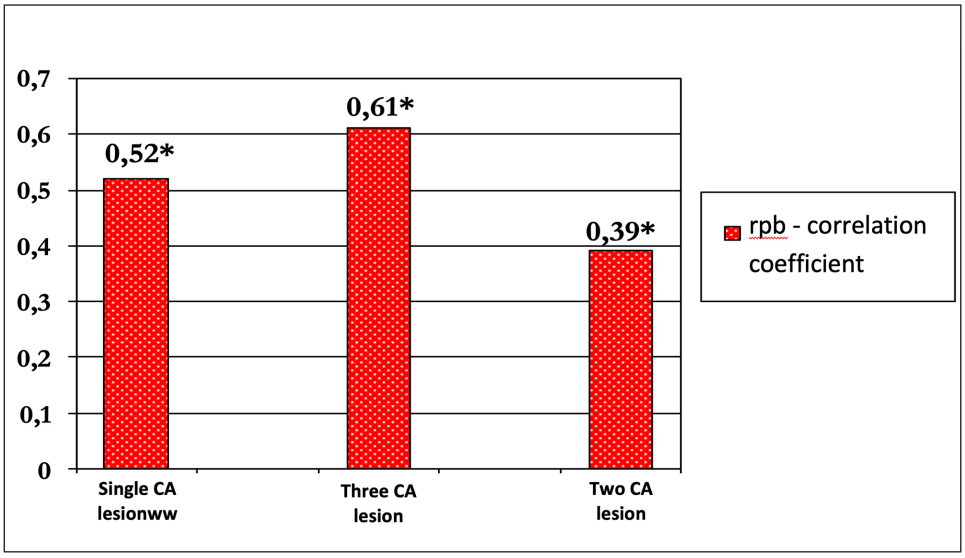

Fig. 3. Point-biserial correlation between the concentration of galectin-3 and the number of affected coronary vessels.
Note. The probability of the difference in average values is *p<0.05.

II) – patients with class II A CHF, FC II-III without reperfusion therapy in acute period of MI (n=56). Patients with no signs of CHF (n=22) were the control group. 15 practically healthy individuals formed the normal control group.

The study did not include patients with acute and chronic inflammatory diseases of the cardiovascular system (endocarditis, myocarditis, pericarditis), unstable angina, in the first 28 days after MI, with severe arrhythmia and conduction disorders, clinical signs of CHF class IIB-III, which correlated to functional class IV according to the New York Heart Association (NYHA) classification, with a stroke and transient ischemic attack (TIA), severe renal failure, high risk of bleeding (thrombocytopenia, traumatic brain injury, gastrointestinal bleeding up to one year ago and any internal bleeding at present), and coronary artery bypass grafting (CABG) in anamnesis.

The average age of patients was (51.8±2.64) years: men – (50.9±1.4), women – (58.3±1.8).

A detailed evaluation of general clinical, as well as special laboratory and instrumental methods of examination was performed.

Traditional clinical methods were applied: study of complaints, medical history and life history, clinical condition of patients was determined by the clinical condition rating scale, general physical examination, ECG. Heart rate, systolic and diastolic blood pressure levels were also measured. The scientific program of patient examination included transthoracic echocardiography using parasternal and apical approaches, ECG Holter test , coronary angiography, and a six-minute walk test. The serum galectin-3 concentration was studied.

RESULTS AND DISCUSSION

The promising biomarkers of heart failure were studied in the study. For this purpose, the average serum galectin-3 level of the studied patients was analyzed.

According to Table I, the average concentration of galectin-3 in patients with stenting without signs of CHF was (10.87±1.65) ng/ml comparing to (6.57±0.21) ng/ml in healthy subjects (p<0.05). An increase in the concentration of this indicator was observed in the group of patients with CHF after MI with reperfusion - (35.2±1.76) ng/ml, which is significantly higher compared with practically healthy patients, while in patients without revascularization it was (38.94±1.97) ng/ml (p<0.001). Thus, there was no dependence of the level of this marker on revascularization with stenting in the acute period of MI (p>0.05). However, when evaluating the dependence of the serum galectin-3 concentration on the number of affected CAs, the presence of increased values of galectin-3 in patients with lesions of three or more coronary vessels (37.42±1.73) ng/ml, in contrast to patients with single-vessel (25.1±1.64) ng/ml (p<0.001)

and two-vessel lesions of the CA (32.8±1.45) ng/ml ($p<0.05$), was determined.

Considering the results of echocardiography and enzyme-linked immunosorbent assay of serum galectin-3 levels in the examined patients, a correlation analysis was performed between the indicators of myocardial remodeling - ESV, EDV and the concentration of this marker.

Positive correlations of medium strength were found between left ventricular end-systolic volume (ESV), left ventricular end-diastolic volume (LVEDV) and serum galectin-3 concentration in the examined patients. The correlation coefficient (r) between the above- mentioned indicators was 0.60 ($p<0.01$) and 0.53 ($p<0.05$) respectively (Figure 1, Figure 2).

The correlations between the concentration of serum galectin-3 and the number of lesions in the coronary arteries in patients with CHF were analyzed. For this purpose, a point-biserial correlation analysis was performed, which allows us to establish a correlation between quantitative and qualitative indicators.

The point-biserial correlation coefficient (rpb) was 0.52 ($p<0.05$). When analyzing the correlation between the serum galectin-3 concentration in the examined patients and the lesions of three or more CAs, a statistically significant correlation of medium strength was found. The point-biserial correlation coefficient (rpb) was 0.61 ($p<0.05$). This indicates a relatively high probability of the influence of single- and three-vessel coronary lesions on the level of serum galectin-3 The correlation of two-vessel lesions with this indicator is weak but significant with rpb=0.39 ($p<0.05$).

CONCLUSIONS

1. The absence of reperfusion therapy with stenting of the IDCA in the acute period of MI leads to a significant deterioration in the course and prognosis of the disease. This has been proved by an increase in the intensity of myocardial ischemia, activation of left ventricular remodeling processes, and deterioration of diastolic myocardial dysfunction in the examined patients with persistent risk factors.
2. The described changes in the functional condition of various organs and systems in patients with CHF after MI without stenting are the cause of unfavorable disease course, in particular, an increased risk of acute coronary syndrome, sudden coronary death, and decompensated heart failure.
3. There is a significant increase in the blood level of galectin-3 in CHF with a previous MI. This indicates the existence of severe cardiac pathological remodeling in the examined patients, the intensity of which depends on the progression of heart failure in the postinfarction period.
4. It has been determined that in patients with CHF with postinfarction cardiosclerosis there is a direct correlation of medium strength between the values of indicators of LV myocardial remodeling with plasma galectin-3 concentration, including ESV, EDV, in examined patients. The role of galectin-3 as a marker of postinfarction remodeling in patients with CHF for early diagnosis, prognosis, and risk stratification has been presented.

REFERENCES

1. Atlas Writing Group, Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, Wilkins E, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. Eur Heart J. 2018 Feb 14;39 (7): 508-79. PMID: 29190377. doi: 10.1093/eurheartj/ehx628
2. Nar G, Aksan G, Gorgulu O, Inci S, Soylu K, Ozdemir M, Sahin M. Galectin-3 as a novel biomarker for the diagnosis of essential hypertension with left ventricular hypertrophy. Journal of Experimental and Clinical Medicine. 2016; 33(3):123-128.
3. He XW, Li WL, Li C, Liu P, Shen YG, Zhu M, Jin XP. Serum levels of galectin-1, galectin-3, and galectin-9 are associated with large artery atherosclerotic stroke. Scientific reports. 2017; 7(1);1-9.
4. Grübler MR, Delgado G, Kleber M, et al. Effect of Galectin-3 on Aldosterone-Associated Risk of Cardiovascular Mortality in Patients Undergoing Coronary Angiography. The American Journal of Cardiology. 2020; Jul, 127:9-15. DOI: 10.1016/j.amjcard .2020.04.017.
5. Ivanov V, Onyshchuk T, Vysochanskyi O. Nature of correlations and dependence of plasma concentrations of galectin-3 and aldosterone on different clinical characteristics in male and female patients with arterial hypertension. Georgian medical news. 2019; 12(297):74-79.
6. Suthahar N, Meijers WC, Silljé HHW, Ho JE, Liu FT, de Boer RA. Galectin-3 Activation and Inhibition in Heart Failure and Cardiovascular Disease: An Update. Theranostics. 2018 Jan 1; 8 (3): 593-609. PMID: 29344292. PMCID: PMC5771079. doi: 10.7150/thno.22196.

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ORIGINAL ARTICLE

HEALTHCARE-ASSOCIATED BACTERIAL VAGINOSIS AFTER GYNECOLOGICAL SURGERIES AND ASSOCIATED ADVERSE PREGNANCY OUTCOME IN UKRAINE

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ABSTRACT

The aim: To determine the prevalence of healthcare-associated bacterial vaginosis after gynecological surgeries and associated adverse pregnancy outcomes in Ukraine.

Materials and methods: Multicenter retrospective cohort study was conducted from January 2019 to December 2021 in eleven medical centers from eight regions of Ukraine. Vaginal cultures were obtained preoperatively from 3,502 women undergoing gynecologic surgery. Diagnosis of Bacterial Vaginosis is based on the Nugent and Amsel criteria.

Results: Healthcare-associated bacterial vaginosis (HA BV) was diagnosed in 1,498 of 3,502 women, giving a prevalence rate of 42.8%. HA BV was significantly associated with preterm birth (risk ratio [RR], 2.68; 95% confidence interval [CI], 1.44–4.98), miscarriage (RR, 6.11; 95% CI, 3.22–14.11), low birth weight (RR, 3.20; 95% CI, 1.29–7.94), and premature rupture of membranes (RR, 6.75; 95% CI, 3.11–14.67).

Conclusions: The HA BV after gynecological surgeries prevalence is high in Ukraine, with a concomitant adverse pregnancy outcome, including preterm birth, low birth weight, premature rupture of membranes, and miscarriage. A significant number of cases of bacterial vaginosis are associated with long-term use of antibiotics to treat post-operative infections.

KEY WORDS: Prevalence, healthcare-associated bacterial vaginosis, gynecological surgery, antibiotic use, pregnancy outcomes

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INTRODUCTION

Improving maternal and perinatal health is one of the biggest medical and public health challenges worldwide. Over the past decades, there have been increasing discussions on whether vaginal dysbiosis, the imbalance of the vaginal commensal bacterial communities (microbiota), influences pregnancy outcomes and should be monitored antenatally. Healthy vaginal microbiota (VMB) is crucial to the lower female reproductive tract. VMB contains a predominance of hydrogen-peroxide-producing *Lactobacillus* species that contribute to an immunological balance and therefore support a healthy reproductive tract.

Bacterial vaginosis (BV) is one of the most common vaginal dysbiotic conditions worldwide. BV constitutes a gynecological condition characterized by an alteration of the vaginal microenvironment and more specifically an alteration of the normal *Lactobacillus*-dominated vaginal flora, to a flora that includes a variety of facultative and obligatory anaerobic bacteria. According to literature, general population prevalence of BV is high globally, ranging from 23% to 29% across regions (Europe and Central Asia, 23%; East Asia and Pacific, 24%; Latin America and Caribbean, 24%; Middle East and North Africa, 25%; sub-Saharan Africa, 25%; North America, 27%; South Asia, 29%). Within North America, black and Hispanic women have significantly higher (33% and 31%, respectively) prevalence compared with other racial groups (white, 23%; Asian, 11%). During pregnancy, the prevalence of BV varies from 11.7% to 49.0% while variability in prevalence exists between different races and/or ethnicities [1]. It remains unclear

whether these findings reflect genetic, socioeconomic, or behavioral discrepancies.

BV has been associated with increased risk of preterm delivery, first-trimester miscarriage in women undergoing in vitro fertilization, preterm premature rupture of membranes, amniotic fluid infections, chorioamnionitis, postpartum and postabortal endomyometritis as well as postabortal pelvic inflammatory disease [2, 3]. The estimated annual global economic burden of treating symptomatic BV is US $4.8 (95% CI, 3.7-6.1) billion. The US economic burden of BV is nearly tripled when including costs of BV-associated preterm births and human immunodeficiency virus cases [1].

The pathogenesis of BV remains largely elusive, although some microorganisms, including *Gardnerella vaginalis*, are suspected of playing a role in the etiology of this disorder. Although various risk factors and pathogenetic mechanisms related to the development of BV have been described, its exact etiology remains unknown. The healthy vaginal flora is inhabited by a variety of *Lactobacillus* spp. (90–95% of total bacteria), such as *L. chrispatus*, *L. iners*, *L. jensenii*, *L. vaginalis*, and *L. gasseri* that maintain a low pH (<4.5), produce bacteriostatic and bactericidal substances and, as a result, impede the occurrence of infection [4]. A decrease in or absence of *Lactobacillus* spp. provokes an increase in the vaginal pH that leads to an overgrowth of anaerobic Gram-negative rods, leading to the development of BV [5]. The vaginal flora responsible for BV can either be transient or of a more permanent nature and consists of various microorganisms including *Gardnerella vaginalis*, *Prevotella* spp., *Porphyromonas* spp., *Bacteroides* spp., *Peptostreptococcus* spp., *Mycoplasma hominis, Ureaplasma urealyticum, Mobiluncus* spp., *Fusobacterium* spp., *Sneathia* spp., *Atopobium vaginae*, and *Clostridium* spp. [6, 7]. A polymicrobial biofilm on the epithelial cells of the vagina is a characteristic feature of BV [8].

Risk factors for BV mainly include hormonal changes, current or prior use of specific medication such as antibiotics and immunosuppressants [9], smoking as well as women's hygiene behavior, i.e., vaginal douching and sexual habits, such as the number of sexual partners [10], age of first sexual encounter, use of an intrauterine device [1, 11]. In Ukraine clinicians often overprescribe antibiotics pre-surgery and post-surgery sometimes for several days after gynecological surgery. However, the number of cases of healthcare-associated infections after gynecological surgeries is not decreasing [12-14]. This is often associated with multidrug-resistant strains of the responsible pathogens [15, 16]. Treatment of post-operative infections include the extended use of antibiotics. Long-term use of antibiotics to treat infections caused by multidrug-resistant pathogens can alter the vaginal flora. Studies evaluating healthcare-associated bacterial vaginosis after gynecological surgeries are currently lacking.

THE AIM

The aim this study to determine the prevalence of healthcare-associated bacterial vaginosis after gynecological surgeries and associated adverse pregnancy outcomes in Ukraine

MATERIALS AND METHODS

DESIGN, SETTINGS AND POPULIATION

Multicenter retrospective cohort study was conducted from January 2019 to December 2021 and recruited 3,502 women (pregnant and non-pregnant) reproductive age, defined as ages 15 to 49 years undergoing gynecologic surgery. We compiled list of the 20 medical centers. However, only eleven medical centers from eight regions of Ukraine agreed to take part in our study. The study population included women had history of gynecological surgery for benign diseases who were local residents. Exclusion criteria included Chlamydial infections, Syphilis or other sexually transmitted bacterial infections, plans to move within the next 12 months, participation in a clinical trial using antibiotics or genital microbicides, and limitations preventing informed consent.

DATA COLLECTION

Data were obtained for the following variables: age, gravidity, parity, diagnosis, surgical procedure, preoperative and postoperative antibiotic use, complications, and postoperative BV. Each patient was identified only by a code to ensure confidentiality. Incident and clinical signs of BV, including cervical motion tenderness, uterine tenderness, and adnexal tenderness, were measured at each visit. As this was a time-to-event data analysis, women not developing BV contributed data until their last study visit. Participants were followed quarterly for approximately 12 months with clinical examinations and surveys. Our study includes interviews, questionnaires, and examinations medical records. Information was collected at baseline and each follow-up visit. Ambulatory medical records and relevant hospital records were reviewed for the all-women's. A data collection form was created to extract demographic, microbiological, and clinical data, and outcome information from routine patient records.

ETHICS

All participants gave written informed consent, and the study was approved by the institutional review boards of the Shupyk National Healthcare University of Ukraine; Ethics Committee approved this study.

MICROBIOLOGICAL METHODS

Vaginal cultures were obtained for nonpregnant patients undergoing gynecologic surgery, which included benign gynecologic, urogynecologic, and gynecologic oncology cases. At each visit, vaginal fluid was collected for vaginal smears. Gram stains were performed and categorized using the Nugent scoring method as low, intermediate, or high (0–3, 4–6, and 7–10, respectively) [17]. High Nugent scores are indicative of BV and for clarity are termed "Nugent-BV" [18]. Additionally, clinical diagnosis of BV was assessed using Amsel criteria (having 3 of the following clinician-assessed signs: thin homogeneous vaginal discharge, vaginal pH >4.5, the presence of a fishy odor upon adding potassium hydroxide solution to vaginal secretions, and/or clue cells on microscopy) [19]. Diagnosis by Amsel criteria has also been recently termed "Amsel-BV" [18]. Clinicians directly questioned women regarding vaginal symptoms (including vaginal discharge, irritation, itching, burning, foul odor, and other), and then coded those that met Amsel criteria for BV as "symptomatic BV" or "asymptomatic BV" based on their clinical judgement [18].

STATISTICAL ANALYSIS

In this study clinical and microbiological data were entered in an Excel (Microsoft Corp., Redmond, WA, USA) database for statistical analysis. We estimated pooled prevalence with a random effects model with inverse variance weights. We adjusted estimates of prevalence obtained by Amsel's criteria using the formula and estimates of sensitivity and specificity relative to Nugent score [18]. We tested risk factors associated with incident Bacterial Vaginosis including Nugent category, Amsel-BV (both symptomatic and asymptomatic), and sociodemographic measures. We used $\chi 2$ and Fisher exact tests for categorical factors, and Cochran–Armitage trend tests for ordinal factors. Cox proportional hazards models were used to test whether Nugent score and Amsel-BV with risk factors behaviors were associated with risk of incident BV. We generated both unadjusted models and models adjusted for all other factors. The proportional hazards assumption was assessed using scaled Schoenfeld residuals for all models. In this study statistical significance was defined as $P<0.05$.

RESULTS

PREVALENCE OF BACTERIAL VAGINOSIS

During the study period (2019-2021), 1,498 of 3,502 women's undergoing gynecologic surgery were found to have healthcare-associated bacterial vaginosis (HA BV). Of the total HA BV cases, 12.8% were asymptomatic. The prevalence of HA BV among participants this study was 42.8% (95% CI: 42.0–43.6). The prevalence of HA BV varied by type of gynecological procedure and antibiotic use. Characteristics of the study sample are summarized in Table I.

Most women (89%) received preoperative or perioperative antibiotics, with ceftriaxone alone (41%) and cefoxitin alone (33%) the most commonly given antibiotics. Forty one percent of the patients with HA BV had *Lactobacillus*-predominant vaginal microflora, 22.3% had an intermediate BV vaginal microflora, and 70.9% had a BV vaginal microflora. There were no statistically significant differences between the three BV groups with respect to age, invasiveness of the surgery, or use of preoperative antibiotics (Table I).

Table I describes relationships between operative characteristics and postoperative HA BV. Although the percentage of patients with HA BV was higher for procedures in which the vagina was entered than for other procedures (20.7% versus 37.7%), this difference was not statistically significant. HA BV was also more common in patients who received preoperative or perioperative antibiotics (89.3% versus 10.7%), but this difference was not statistically significant. The higher rate of HA BV associated with pre/perioperative and postoperative antibiotic use may reflect a tendency to use antibiotics in patients who are at higher risk of postoperative infection. No statistically significant difference was found between ceftriaxone alone, cefoxitin alone, and other antibiotics with respect to the HA BV (Table II). There was a statistically significant difference between the three BV groups with respect to postoperative HA BV ($P= 0.017$). Further significance testing found that the differences between the positive-BV group and the Lactobacillus-predominant group, and between the positive-BV group and the intermediate-BV group, with respect to postoperative HA BV, were statistically significant ($P =0.045$ and $P=0.007$, respectively). The difference between the intermediate BV group and the Lactobacillus-predominant group was not statistically significant ($P= 0.28$).

BACTERIAL VAGINOSIS AND PREGNANCY OUTCOMES

Of the 1,498 women who were positive for HA BV, 24.8% had preterm birth, 14.1% had low birth weight

Table I. Characteristics of women with healthcare-associated Bacterial Vaginosis (HA BV) after gynecological surgeries in Ukraine (2019-2021)

Characteristics	All women's	HA BV				P value
		Yes		No		
	n	%	n	%	n	%	
Age (years)						0.053
15-21	189	5.4	162	8.1	27	1.8	
22-26	311	8.9	297	14.8	14	0.9	
27-31	421	12.0	317	15.8	104	6.9	
32-36	784	22.4	468	23.4	316	21.1	
37-41	936	26.7	486	24.3	450	30.0	
42-49	861	24.6	274	13.7	587	39.2	
Peritoneum entry						0.086
Vaginal only	978	27.9	414	20.7	564	37.7	
Abdominal only	786	22.4	403	20.1	383	25.6	
Vaginal and abdominal	1,738	49.6	1,187	59.2	551	30.8	
Pre/perioperative antibiotics given	3,127	89.3	1,891	94.4	1,236	82.5	
Vagina not entered during procedure	1,480	42.3				0.11
Lactobacillus predominant	386	26.1	175	8.7	211	14.1	
Intermediate BV	311	21.0	194	9.7	117	7.8	
Positive BV	783	52.9	302	15.1	481	32.1	
Vagina entered during procedure	1,960	56.0				0.09
Lactobacillus predominant	684	34.9	273	13.6	211	27.4	
Intermediate BV	379	19.3	162	8.1	217	14.5	
Positive BV	897	45.8	316	15.8	581	38.8	
Preoperative antibiotics not given	375	10.7				0.057
Lactobacillus predominant	146	38.9	95	4.7	51	3.4	
Intermediate BV	68	18.1	31	1.5	37	2.5	
Positive BV	161	42.9	64	4.0	97	6.5	
Preoperative antibiotics given	3,127	89.3				0.024
Lactobacillus predominant	927	29.6	710	35.4	217	14.5	
Intermediate BV	909	29.1	588	29.3	321	21.1	
Positive BV	1,291	41.3	723	36.1	568	37.9	
Post-operative antibiotics given	2,189	62.5				0.0014
Lactobacillus predominant	136	6.2	85	4.2	51	3.4	
Intermediate BV	511	23.3	128	6.4	383	25.6	
Positive BV	1,542	70.4	355	17.7	1,187	79.2	
Total	3,502	100.0	2004	57.2	1498	42.8	0.05

(LBW), and 28.4% had premature rupture of membranes (PROM), and 26.6% had miscarriage. They had 2.7 times the risk of preterm birth (95% confidence interval [CI], 1.44–4.98), 3.2 times the risk of LBW (95% CI, 1.29–7.9), 6.8 times the risk of PROM (95% CI, 3.1–14.7), and 6.1 times the risk of miscarriage (95% CI, 3.22 –14.1) compared with those who were negative (Table II).

DISCUSSION

To our knowledge, no study addressing to the prevalence of HA BV after gynecological surgeries and associated adverse pregnancy and birth outcomes. The present study showed that HA BV after gynecological surgeries is a common vaginal disease in women of reproductive age in Ukraine. The prevalence of HA BV among participants this study was 42.8%. Of the

Table II. Relationship among the presence of healthcare-associated bacterial vaginosis (HA BV) after gynecological surgeries and adverse pregnancy outcomes in Ukraine (2019-2021)

Pregnancy Outcome	HA BV				RR (95% CI)	P value
	Yes (n=1,498)		No (n=2,004)			
	n	%	n	%		
Preterm birth	371	24,8	186	9,3	2.68 (1.44–4.98)	0.002
Miscarriage	398	26,6	76	3,8	6.11 (3.22–14.11)	<.001
LBW	211	14,1	89	4,4	3.2 (1.29–7.94)	0.008
PROM	425	28,4	91	4,5	6.75 (3.11–14.67)	<.001

*BV, bacterial vaginosis; CI, confidence interval; LBW, low birth weight; PROM, premature rupture of membranes; RR, risk ratio.

total HA BV cases, 12.8% were asymptomatic. The prevalence of HA BV varied by type of gynecological procedure and antibiotic use. HA BV was significantly associated with preterm birth, miscarriage, LBW, and PROM. Of the 1,498 women who were positive for HA BV, 24.8% had

The prevalence rate of HA BV of 42,8% among pregnant women in this study is within the range of other recent studies, i.e., from 5.8% to 49% [1, 20–22]. It remains unclear whether these findings reflect genetic, socioeconomic, or behavioral discrepancies.

According to literature, risk factors for BV mainly include hormonal changes, current or prior use of specific medication such as antibiotics and immunosuppressants, and the existence of foreign bodies, such as cloth or toilet tissue in the vagina [9]. In our study a significant number of cases of bacterial vaginosis are associated with long-term use of antibiotics to treat post-operative infections.

Increasing evidence is suggesting that BV is associated with various adverse pregnancy outcomes, such as an increased risk of early and late miscarriage, PROM, LBW, and preterm birth [2, 20, 22–25]. The results of our study supported previous studies.

The treatment of HA BV may prevent post-operative infections after major gynecological surgery or surgical termination of pregnancy. Women undergoing hysterectomy, the surgical termination of pregnancy, should be screened for BV, and those who are positive should be treated. Asymptomatic pregnant women with previous preterm delivery may benefit from treatment, but the screening and treatment of these women remain controversial [2].

Our study showed that post-operative infection remains the common complication after gynecological procedures in Ukraine. Best practices should be established and followed to reduce the risk of post-operative infection associated with gynecologic surgery. Optimizing the antibiotic prophylaxis and empirical antimicrobial therapy may reduce the burden of postoperative infection in gynecological surgeries, but prevention is the key element [12-16].

The high cost of HA BV-associated sequelae highlights the need for research to understand potential causal linkages between HA BV and adverse health outcomes. Further research to determine the etiology of HA BV and corresponding prevention and sustainable treatment strategies are urgently needed to reduce the burden of BV among women.

STRENGTH AND LIMITATION

This is the first epidemiological study that focuses on the prevalence of healthcare-associated bacterial vaginosis after gynecological surgeries and adverse pregnancy and birth outcomes. The results of this study provide useful evidence for prevention efforts to decrease HA BV and its contribution to adverse pregnancy outcomes in Ukraine. The limitations of our study include its retrospective design and including 29.2% regions in Ukraine. Therefore, results this study may not be representative of other Ukrainian regions.

CONCLUSIONS

The present study showed that HA BV after gynecological surgeries prevalence is high in Ukraine, with a concomitant adverse pregnancy outcome, including preterm birth, low birth weight, premature rupture of membranes, and miscarriage. A significant number of cases of bacterial vaginosis are associated with long-term use of antibiotics to treat post-operative infections. The high cost of HA BV-associated sequelae highlights, further research is needed to determine the etiology and understand potential causal linkages between HA BV after gynecological surgeries, and adverse pregnancy and birth outcomes in female.

REFERENCES

1. Peebles K, Velloza J, Balkus JE, et al. High Global Burden and Costs of Bacterial Vaginosis: A Systematic Review and Meta-Analysis. Sex Transm Dis. 2019;46(5):304-311. doi: 10.1097/OLQ.0000000000000972.
2. Ziogou A, Ziogos E, Giannakodimos I et al. Bacterial Vaginosis and Post-Operative Pelvic Infections. Healthcare (Basel). 2023;11(9):1218. doi: 10.3390/healthcare11091218.
3. Lev-Sagie A, De Seta F, Verstraelen H et al. The Vaginal Microbiome: II. Vaginal Dysbiotic Conditions. J Low Genit Tract Dis. 2022;26(1):79-84. doi: 10.1097/LGT.0000000000000644.
4. Johnston C, Magaret A, Srinivasan S et al. P239 Genital HSV-2 Suppression Is Not Associated with Alterations in the Vaginal Microbiome: A One-Way, Cross-over Study. Sex. Transm. Infect. 2019;95:A148. doi:10.1136/sextrans-2019-sti.374.
5. Schwebke JR, Weiss HL. Interrelationships of Bacterial Vaginosis and Cervical Inflammation. Sex. Transm. Dis. 2002;29:59–64. doi: 10.1097/00007435-200201000-00010.
6. Brotman RM, Klebanoff MA, Nansel TR et al. Bacterial vaginosis assessed by gram stain and diminished colonization resistance to incident gonococcal, chlamydial, and trichomonal genital infection. J Infect Dis. 2010;202(12):1907-15. doi: 10.1086/657320.
7. Ling Z, Kong J, Liu F et al. Molecular analysis of the diversity of vaginal microbiota associated with bacterial vaginosis. BMC Genomics. 2010;11:488. doi: 10.1186/1471-2164-11-488.
8. Swidsinski A, Mendling W, Loening-Baucke V et al. Adherent biofilms in bacterial vaginosis. Obstet Gynecol. 2005;106(5 Pt 1):1013-23. doi: 10.1097/01.AOG.0000183594.45524.d2.
9. Tidbury FD, Langhart A, Weidlinger S et al. Non-antibiotic treatment of bacterial vaginosis-a systematic review. Arch Gynecol Obstet. 2021;303(1):37-45. doi: 10.1007/s00404-020-05821-x.
10. Kenyon CR, Buyze J, Klebanoff M et al. Association between bacterial vaginosis and partner concurrency: a longitudinal study. Sex Transm Infect. 2018;94(1):75-77. doi: 10.1136/sextrans-2016-052652.
11. Achilles SL, Austin MN, Meyn LA et al. Impact of contraceptive initiation on vaginal microbiota. Am J Obstet Gynecol. 2018 ;218(6):622.e1-622.e10. doi: 10.1016/j.ajog.2018.02.017.
12. Salmanov AG, Vitiuk AD, Kovalyshyn OA et al. Surgical site infection after laparoscopic hysterectomy for benign gynecological disease in Ukraine. Wiad Lek. 2022;75(1):251-258. 10.36740/WLek202201218.
13. Salmanov AG, Terekhov VA, Voloshynovych NS et al. Healthcare-associated tubo-ovarian infections in Ukraine: Results of a multicenter study (2020-2022). Wiad Lek. 2022;75(8 p2):2003-2009. doi: 10.36740/WLek202208211.
14. Salmanov AG, Baksheev SM, Kuflovskyi DV et al. Healthcare-associated infection after legal induced abortions in Ukraine: results a multicenter study. Wiad Lek. 2021;74(7):1559-1565. doi: 10.36740/WLek202107103.
15. Salmanov A, Shchehlov D, Svyrydiuk O et al. Epidemiology of healthcare-associated infections and mechanisms of antimicrobial resistance of responsible pathogens in Ukraine: a multicentre study. J Hosp Infect. 2023;131:129-138. doi: 10.1016/j.jhin.2022.10.007.
16. Salmanov AG, Koctjuk IM, Ihnatieva OK et al. Prevalence of healthcare-associated cervicitis and antimicrobial resistance of the responsible pathogens in Ukraine: results of a multicenter study (2019-2021). Wiad Lek. 2022;75(9 p2):2189-2197. doi: 10.36740/WLek202209202.
17. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of Gram stain interpretation. J Clin Microbiol 1991;29(2):297-301. doi: 10.1128/jcm.29.2.297-301.1991.
18. McKinnon LR, Achilles SL, Bradshaw CS et al.. The evolving facets of bacterial vaginosis: implications for HIV transmission. AIDS Res Hum Retroviruses 2019;35(3):219-228. doi: 10.1089/AID.2018.0304.
19. Amsel R, Totten PA, Spiegel CA et al. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med 1983;74(1):14-22. doi: 10.1016/0002-9343(83)91112-9.
20. Kenyon C, Colebunders R, Crucitti T. The global epidemiology of bacterial vaginosis: a systematic review. Am J Obstet Gynecol. 2013;209(6):505-23. doi: 10.1016/j.ajog.2013.05.006.
21. Tolosa JE, Chaithongwongwatthana S, Daly S et al. The International Infections in Pregnancy (IIP) study: variations in the prevalence of bacterial vaginosis and distribution of morphotypes in vaginal smears among pregnant women. Am J Obstet Gynecol. 2006;195(5):1198-204. doi: 10.1016/j.ajog.2006.08.016.
22. Dingens AS, Fairfortune TS, Reed S et al. Bacterial vaginosis and adverse outcomes among full-term infants: a cohort study. BMC Pregnancy Childbirth. 2016;16(1):278. doi: 10.1186/s12884-016-1073-y.
23. Svare JA, Schmidt H, Hansen BB et al. Bacterial vaginosis in a cohort of Danish pregnant women: prevalence and relationship with preterm delivery, low birthweight and perinatal infections. BJOG. 2006;113(12):1419-25. doi: 10.1111/j.1471-0528.2006.01087.x.
24. Redelinghuys MJ, Geldenhuys J, Jung H et al. Bacterial Vaginosis: Current Diagnostic Avenues and Future Opportunities. Front Cell Infect Microbiol. 2020;10:354. doi: 10.3389/fcimb.2020.00354.
25. Mohanty T, Doke PP, Khuroo SR. Effect of bacterial vaginosis on preterm birth: a meta-analysis. Arch Gynecol Obstet. 2023;308(4):1247-1255. doi: 10.1007/s00404-022-06817-5.

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REVIEW ARTICLE

FEATURES OF THE PROCESS OF TRAINING IN EDUCATIONAL MEDICAL INSTITUTIONS OF UKRAINE AT THE PRESENT STAGE. PART 2. REACTION OF HIGHER EDUCATIONAL INSTITUTIONS TO DISTANCE LEARNING

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ABSTRACT
Higher education is one of the areas most affected by the Covid-19 pandemic and martial law. Against the backdrop of severe restrictions, universities faced the issue of the existing opportunities for the implementation of educational programs, the need to change the format of the educational process with the transition mainly to electronic educational technologies.
Under these conditions, it was necessary to consolidate all the forces and resources of the university community. The governments of many countries have recognized the need to provide infrastructural and technological support to educational institutions.
Thanks to the institutional support of the state and relevant ministries, universities managed to reduce financial losses and implement initiatives for continuous education. These measures have contributed to the sustainability of universities.
In response to the COVID-19 pandemic, educational institutions all over the world have adopted different approaches and made significant changes to the education system itself in accordance with their resources and capabilities.

KEY WORDS: educational medical institutions, medical students, COVID-19 pandemic, martial law, distance learning

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INTRODUCTION

Medical education in Ukraine, as in most other countries, has experienced major changes caused by the COVID-19 pandemic, and Russian military aggression has further worsened the situation. Universities across the country found themselves in different circumstances: some were destroyed, others suffered significant damage, some faced the issue of temporary relocation to another, safer territory. Both the Ukrainian society and university communities were faced with the question of not only survival, but also the continuation of functioning in extremely difficult circumstances [1-3].

THE AIM

To characterize the learning process in educational medical institutions of Ukraine at the present stage

MATERIALS AND METHODS

This article presents an assessment of more than 70 world literary sources published in the period from 2020 to 2023, which discuss the issues of distance learning process at medical universities. The study involved an evaluation of literary sources included in the PubMed, Google Scholar databases.

The assessment employed data from sociological studies on the attitude of students and teachers of universities to distance learning, conducted by expert organizations during the pandemic, analytical and information materials of universities, bibliographic sources. Secondary analysis and interpretation of the results of sociological surveys, systematization and classification of the theoretical and factual materials used, analysis of management practices and experience of universities in the conditions of extreme transition to remote mode were carried out.

REVIEW AND DISCUSSIONS

Given the current situation, first all over the world, and then aggravation in Ukraine due to the military aggression, a high degree of mobilization of university management teams was required to quickly respond,

search for and implement solutions to non-standard tasks and problems. In the context of the crisis, and especially the martial law in Ukraine, not only administration, but also communication with students, employees and other interested parties, stakeholders became a key task. For Ukrainian students, depending on their place of residence, the Ministry of Education and Science of Ukraine has developed several models of education using its different forms.

The circumstances required continuous communication between members of the university community, exchange of information in order to be aware of changes and be able to act appropriately during disruptions and destabilization [4].

Most universities have created separate sections on the websites of their universities, where they accumulated news, appeals from management, and instructions. Supporting services were also included, namely training materials with recommendations for transferring education to an online format, class schedules, information on how exams will be held and the admission campaign, assistance in temporary employment. A number of universities have actively used social networks to disseminate up-to-date information and recommendations at the present time. Some universities have launched a hotline for students and staff. Most universities have signed contracts with companies such as Microsoft that provide Office resources, Teams, or technology platforms to enhance virtual communication.

The COVID-19 pandemic has highlighted the growing need for broader concepts of academic sustainability that take into account important mental health issues [5-6].

A number of universities have developed effective screening and intervention strategies to build student resilience during their lockdown or any other emergencies in the future.

Mental health and wellness support programs include several means of behavioral assistance: phone support; self-managed mental health care; applications with recommendations for acquiring coping skills; individual therapy services [7].

Some universities have created online communities of students, teachers, administrators, which helped reduce the stress of social isolation. For example, Vanderbilt University School of Medicine has created a Virtual Wellness and Learning Communities (VWLC) program. The VWLC program consists of hour-long virtual events that offer students the opportunity to connect with their peers online through talks, game nights, or self-paced workshops to share interests. After attending a VWLC event, 79% of participants reported increased feelings of connection with peers, 61% felt better, and 55% felt that such activities should be continued regularly [8].

Distance learning has become a way out of a situation where the physical presence in institutions of higher medical education has become limited or impossible, and the usual teaching tools cannot be used due to unpredictable and insurmountable, force majeure circumstances. [9].

Learning management systems (LMS, for example: Google Classroom, Moodle, Blackboard, Canvas); applications for learning based on mobile devices; programs with extended offline functionality; massive open online courses (MOOCs); self-learning services; electronic readers; software for online collaboration (Zoom, Google Meet, WebEX, Skype); means of creating digital educational content and numerous electronic databases of educational materials were used as tools for organizing distance learning, providing social support for participants in educational relations [10].

From the point of view of supporting medical education, the PIVOT MedEd project of the Faculty Development Network of the Association of Medical Faculties of Canada (AFMC) Faculty Development Network is interesting. To support educators, faculty leaders at Canadian Medical Schools (FacDevCanada) co-curated medical education resources in three categories: guides to transitioning to classroom and online clinical programs; discipline-specific learning resources and general resources including basic sciences, patient safety, and others. FacDevCanada members have used crowdsourcing. The project involved communities of educators and authors from 74 countries: Canada (48%), USA (24%), Portugal, UK, Mexico (up to 3%) and others. This open access online resource has become a one-stop place to find materials and resources to support online education [11].

Under normal circumstances, developing an online course involves a process of designing and analyzing student needs and prior experiences, as well as a range of teaching methods and strategy selection, carefully considering the unique characteristics of the target groups and the chosen learning environment. In addition, course development is usually a collaborative effort of the course team (teachers, curriculum developers, technical specialists). The course contains several learning objects (video lectures, assignments, discussions) that meet various criteria set by national or international quality assurance indicators, as well as a number of rules (accessibility, copyright).

One of the fastest and most economical solutions in terms of resources in the context of the transition to distance learning formats was the active use of ready-made open online courses in the educational

process. Some universities have been quick to adapt and optimize the costs of moving to distance learning by taking advantage of available massive online courses, including from leading universities. Many elite universities have themselves actively developed online courses and systems. For example, Tsinghua University in China decided to continue working entirely online and quickly developed 4,000 courses [12], which then became widely available throughout China.

Many other universities have also made their online courses available to the public by publishing them on specially created electronic resources or posting them in sections of their official websites. In addition, such platforms as Coursera and Udemy have opened access to their online courses. With the start of the military invasion, Ukrainian medical educators and scientists were given free access to their electronic platforms ClinicalKey, Complete Anatomy, Osmosis (Elsevier Company), as well as the Research4Life project.

Online learning has necessitated the transformation of physical libraries of universities into digital libraries for online provision of information services. University libraries have provided access to full-text materials and diverse educational resources that have already been created during the pandemic [13].

With all the variety of formats, online learning, in terms of didactic characteristics, has two technologically different processes for obtaining knowledge, namely synchronous and asynchronous. This division is due to the communication approaches they use. Synchronous form is a learning format when all participants interact in real time in a text or video environment. The synchronous format often has a limited time frame and leaves the audience little time for activities. But it can be useful for discussing topics that are prepared in advance, getting quick feedback and enhancing the social presence of students. Asynchronous form is a format in which the contact between the student and the teacher is delayed in time. Participants do not intersect in the physical space and do not "see" each other in the virtual one. At the same time, the course fulfills its functions: students receive knowledge, feedback and move along a certain educational trajectory.

Obviously, the synchronous approach practically blurs the line between real and virtual learning and thus provides the maximum approximation to the conditions of traditional education. The advantages of asynchronous approach include flexible timeframe, the possibility of learning, taking into account the different pace of assimilation of educational material. But it requires the student to be dedicated, independent and self-organized, and the role of the teacher is rather reduced to the role of a facilitator or moderator of communication.

In mass transition to distance learning, universities used both synchronous and asynchronous learning formats in their educational activities, depending on the educational tasks being solved.

Olha Bratanych et al. believe that the only possible form of mass education in Ukraine in war conditions is synchronous distance learning. Compared to offline learning, synchronous distance learning significantly increases the share of emerging feedback, which contributes not only to the activation of the learning process, but also to the socialization of students [14].

Online learning can be seen as an alternative method of teaching in the classroom to learn theoretical material. However, concrete experience is an important part of any learning process. In medical education, clinical experience is a central part of the development of medical competence. The teaching of clinical disciplines has always been based on the formation of skills that require personal presence of students and their direct contact with patients and teachers.

Faced with new conditions, most medical universities were forced to make appropriate adjustments to the organization of the educational process. The COVID-19 pandemic forced us to change not only the methods of teaching students clinical disciplines, but also their content in an emergency mode.

Medical educators developed clinical and procedural skills through e-learning using open access didactic materials, podcasts, reflective sessions, remote simulations, and even clinical rotations [15].

Due to the limitation of the educational process at clinical sites, new possibilities for using simulation teaching methods have become apparent. Simulation training in the last decade has been an integral part of the professional development of future specialists. Their importance has increased significantly in the conditions of martial law in Ukraine.

The World Academic Council for Emergency Medicine has published a paper describing the best practices of simulation centers, from when COVID-19 first hit countries around the world to the current state of their functioning in the "new normal" [16].

The spectrum of simulation training has expanded from simple partial task simulators, low to high fidelity simulations, hybrid simulations, the use of standardized patients, laparoscopic surgical simulators, simulated operating rooms and rehabilitation suites, and even applications that include virtual, augmented and mixed reality techniques.

For example, VR simulations have been successfully used in training in resuscitation, communication, and bronchoscopy. In contrast, AR has shown utility in

teaching anatomical correlates using diagnostic imaging such as ultrasound. Alternative reality is used as a tool for developing clinical thinking skills, longitudinal management of a panel of patients [17].

The hardware provides the user with an immersive experience through stereoscopic 3D displays, motion tracking, haptic feedback, and natural user interfaces. Simulation-based learning using virtual reality or game environment enriches online educational programs with synthetic clinical scenarios.

For example, one of the papers [18] describes the implementation of a neonatal phantom that can simulate physiological vital parameters such as pulse rate and thermoregulation. It also mimics the look of premature babies using a 3D printed base structure coated with multiple layers of skin-colored modified silicone. Thus, the proposed neonatal phantom can be used to simulate various life parameters of premature babies and allows implementing image processing algorithms for health analysis.

Another study describes the experience of using ultrasound puzzle phantoms to assist in teaching isolated transducer movements and sonographic concepts to medical students prior to human anatomy imaging [19]. This experience is confirmed by the results of a survey after an online ultrasound course using virtual simulators. 58% of students believe that they have achieved the goal of the ultrasound imaging course [20].

Classes on endovascular simulators significantly improve the attitude of students towards interventional radiology (IR), which is a rapidly developing field of medicine, but also stimulate interest in a particular subspecialty [21].

A growing group of researchers are conducting powerful retrospective reviews of patient-specific 3D models generated from large numbers of medical scans on hospital image servers to illustrate the power of 3D reconstructions combined with imaging to improve understanding of new surgical approaches and options in surgical anatomy [22 -23].

It can be argued that due to the development of technology and the use of augmented reality, virtual environments, students have the opportunity to study in conditions as close as possible to real ones, which can significantly increase the level of their professional training. When organizing the educational process, conditions are created for the formation and consolidation of various skills through visual contact and tactile interaction with equipment simulating real situations, which provides additional interactivity, immersion and safety. This, in turn, increases the involvement of students in the learning process and reduces the level of stress, increases adaptability to professional activities. In addition, they have the opportunity to repeatedly practice actions at various stations, honing their skills to maximum accuracy.

An integral part of teaching students within the framework of simulation training is debriefing, which allows discussing and, in the future, eliminating inaccuracies and mistakes. Debriefing provides an opportunity to assess the knowledge, skills and attitudes of participants in the simulation course, on the basis of which they make decisions during the task. This form of feedback is used to find the cause of inconsistencies between actions taken and expected. Watching audio and video recordings during debriefing can be a useful tool for evaluating the work done [24].

Healthcare is a team activity and it makes perfect sense that medical professionals need team training. Simulations to eliminate misunderstandings and other sources of error, especially in the context of team learning and systems practice, are also a key component in optimizing patient outcomes.

In the context of the pandemic and military aggression, the demand for telemodeling has significantly increased as one of the alternative methods of simulation training. Telesimulation is defined as the use of Internet communication technologies to provide simulation-based medical education when students and teachers are located remotely from each other [25].

Telesimulation can be performed with all students and facilitators participating in physically remote locations. Using a video teleconferencing platform such as Zoom, Google Meet, or Skype, facilitators can share audio clips, still images, or pre-recorded videos [26].

An example is the Simbox toolkit for simulating patient admissions, hosted in the public domain by the American College of Emergency Physicians (ACEP *https://www.emergencysimbox.com/*) [27]. It contains pre-recorded videos of medical examination results and patient monitors that can be controlled by facilitators using a video conferencing platform in accordance with the scenario and actions of participants during the simulation. Students interact with each other, built-in participants and a simulated patient and/or a display of vital signs on a computer screen. Facilitators observe students in real time and provide immediate feedback during a remote session. Telesimulation eliminates the need to co-locate instructors, students, and high-precision patient simulators (HPS), allowing simulation-based classes to be conducted in facilities remote from simulation centers or when other barriers limit face-to-face communication [28].

These electronic resources provide an opportunity to participate in live broadcasts of lectures by leading experts, professors, researchers; include training videos

of operations, methods for diagnosing diseases, their prevention and treatment; video lessons in important scientific areas; highlight the latest scientific discoveries and achievements of medical science.

The introduction of telemedicine technologies in the educational process helps prepare doctors for effective future work in hospitals and clinics and the provision of high-quality medical care to patients. Telemedicine in medical education is a very important area that requires the mandatory inclusion of this type of training in curricula. In addition, telemedicine facilitates remote collaboration and provides access to expensive remote tools that are not always available.

Nowadays, an increasing number of students recognize the importance of telemedicine and, more importantly, express a clear desire for telemedicine to be included in the curriculum from the first year of study [29].

Engaging medical students in telemedicine activities will help preserve and improve patient health, empower medical teams and systems, and increase medical student engagement, opportunities for hands-on learning, and professional identity building.

Under the conditions of the military invasion in Ukraine, final-year students of medical universities receive clinical skills, taking an active part in helping the sick and wounded, participating in volunteer organizations. Due to the increasing burden on the healthcare system, medical students are increasingly on duty in hospitals, go to calls with ambulance teams. Many universities are urgently introducing courses on emergency medical care, artificial lung ventilation, new methods of diagnosing and treating patients in high-risk conditions, requiring well-coordinated teamwork and knowledge of new action algorithms, into the curriculum. The formation of the universal competencies of a doctor to act in extreme situations is a fundamental need for Ukraine in the conditions of war, power outages and possible man-made/environmental disasters. It is undeniable that these acquired clinical skills greatly enhance the opportunities for students in their future career as a doctor. This unique practical experience has yet to be comprehended.

Back in the middle of the 20th century, C.S. Lewis proposed three rules that could help counter the educational crisis during the war, and they remain relevant to this day: self-control instead of excitement, faith instead of disappointment, and sobriety of thought instead of fear [30]. Favorable conditions for learning will never come, and a person must learn to seek knowledge in any conditions. Education is a door that opens up many possibilities. And when these opportunities happen is unknown, so it is important not to stop, but to go towards your goals, despite any obstacles.

CONCLUSIONS

Distance learning has become a challenge for all participants in the educational process. At the same time, distance learning helped to implement the progressive principles of modern educational strategies: mobility, accessibility, openness [31].

Successful cases of distance learning include implemented online platforms and learning management systems that provide effective interaction between teachers and students, round-the-clock access to educational material in synchronous and asynchronous modes, the use of simulation teaching methods and telemedicine technologies.

An analysis of studies on the prospects for the development of the healthcare sector leads to the conclusion that it is necessary to modernize the medical education system based on an innovative approach focused on the predictable digitalization of healthcare and the effective use of medical data, increasing the role of practical training.

Taking into account the cyclicity in the manifestation of social risks, it is fair to talk about the need to develop special action protocols in education in cases of emergency situations.

REFERENCES

1. Smalley A. Higher education responses to coronavirus (COVID-19). In: National Conference of State Legislatures [Accessed May 15, 2020]. Available from: https://www.ncsl.org/research/education/higher-education-responsesto-coronavirus-covid-19.aspx
2. Vérillaud F. How French Universities Responded to Covid-19. [Accessed May 25, 2020]. Available from: https://www.institutmontaigne.org/en/expressions/how-french-universities-responded-covid-19
3. Osypchuk A, Yakovlev M, Suslov A, Usachova V, Shulimov S. Universities during the war: from an educational institution to a social mission. Kyiv: NaUKMA; 2022 (in Ukrainian).
4. Dohaney J, de Roiste M, Salmon RA, Sutherland K. Benefits, barriers, and incentives for improved resilience to disruption in university teaching. Int J Disaster Risk Reduct. 2020; 50: 101691. doi: 10.1016/j.ijdrr.2020.101691
5. Holm-Hadulla RM, Klimov M, Juche T, Möltner A, Herpertz SC. Well-Being and Mental Health of Students during the COVID-19 Pandemic. Psychopathology. 2021; 54(6): 291-297. doi: 10.1159/000519366

6. Seetan K, Al-Zubi M, Rubbai Y, Athamneh M, Khamees A, Radaideh T. Impact of COVID-19 on medical students' mental wellbeing in Jordan. PLoS One. 2021; 16(6): e0253295. doi: 10.1371/journal.pone.0253295
7. Peters ZV, Norwood LN, Modi HP, Goodman H, et al. Addressing the mental health needs of learners and nonlearners in an academic medical center during COVID-19. Bull Menninger Clin. 2021; 85(3): 283-297. doi: 10.1521/bumc_2021_85_02.
8. Ahlers CG, Lawson V, Lee J, March C, et al. A Virtual Wellness and Learning Communities Program for Medical Students during the COVID-19 Pandemic. South Med J. 2021; 114(12): 807-811. doi: 10.14423/SMJ.0000000000001330
9. Salvati A. Medical Education in the Digital Era. Revista Argentinade Cardiologia. 2019; 87: 236.
10. Fengchun M, Ronghuai H, Dejian L, Rongxia Z. Ensuring effective distance learning during COVID-19 disruption: guidance for teachers. Paris: United Nations Educational, Scientific and Cultural Organization; 2020. doi: 10.54675/HKXT1562
11. Keegan D. A., Chan M., Chan T. M. Helping medical educators worldwide to pivot curricula online: pivotmeded.com. Medical education. 2020; 54(8): 766-767. https://doi.org/10.1111/medu.14220.
12. Coates H, Wen W, Shi J. Crisis is making online education economy go mainstream. University World News. 02.03.2020. Available at: https://www.universityworldnews.com/post.php?story=20200302091409436 (accessed on 17.06.2023).
13. Rafiq M, Batool SH, Ali AF, Ullah M. University libraries response to COVID-19 pandemic: A developing country perspective. The Journal of Academic Librarianship. 2021; 47(1): 102280. doi: 10.1016/j.acalib.2020.102280
14. Bratanych O, Myroshnychenko N. . (2023). Feedback practices in the context of synchronous esp distance learning in a non-language university under martial law in Ukraine. Studies in Comparative Education. 2023; 2. doi: 10.31499/2306-5532.2.2022.270966
15. Fitzgerald DA, Scott KM, Ryan MS. Blended and e-learning in pediatric education: harnessing lessons learned from the COVID-19 pandemic. Eur J Pediatr. 2022; 181(2): 447-452. doi: 10.1007/s00431-021-04149-1.
16. Lateef F, Suppiah M, Chandra S, Yi TX, et al. Simulation Centers and Simulation-Based Education during the Time of COVID 19: A Multi-Center Best Practice Position Paper by the World Academic Council of Emergency Medicine. J Emerg Trauma Shock. 2021; 14(1): 3-13. doi: 10.4103/JETS.JETS_185_20.
17. Kassutto SM, Baston C, Clancy C. Virtual, Augmented, and Alternate Reality in Medical Education: Socially Distanced but Fully Immersed. ATS Sch. 2021; 2(4): 651-664. doi: 10.34197/ats-scholar.2021-0002RE
18. Lyra S, Voss F, Coenen A, Blase D, Aguirregomezcorta IB, Uguz DU, Leonhardt S, Antink CH. A Neonatal Phantom for Vital Signs Simulation. IEEE Trans Biomed Circuits Syst. 2021; 15(5): 949-959. doi: 10.1109/TBCAS.2021.3108066
19. Maloney LM, Seidman PA, Zach KM, Tewari NK, Tito MF, Page CR. Use of gelatin puzzle phantoms to teach medical students isolated ultrasound transducer movements and fundamental concepts. BMC Med Educ. 2020; 20(1): 26. doi: 10.1186/s12909-020-1937-8
20. Meuwly JY, Mandralis K, Tenisch E, Gullo G, Frossard P, Morend L. Use of an Online Ultrasound Simulator to Teach Basic Psychomotor Skills to Medical Students During the Initial COVID-19 Lockdown: Quality Control Study. JMIR Med Educ. 2021; 7(4): e31132. doi: 10.2196/31132
21. Stoehr F, Schotten S, Pitton MB, Dueber C, Schmidt F, Hansen NL, Baeßler B, Kloeckner R, Dos Santos DP. Endovascular simulation training: a tool to increase enthusiasm for interventional radiology among medical students. Eur Radiol. 2020; 30(8): 4656-4663. doi: 10.1007/s00330-019-06646-2
22. Tai AX, Sack KD, Herur-Raman A, Jean WC. The Benefits of Limited Orbitotomy on the Supraorbital Approach: An Anatomic and Morphometric Study in Virtual Reality. Oper Neurosurg (Hagerstown). 2020; 18(5): 542-550. doi: 10.1093/ons/opz201
23. Donofrio CA, Capitanio JF, Riccio L, Herur-Raman A, Caputy AJ, Mortini P. Mini Fronto-Orbital Approach: "Window Opening" Towards the Superomedial Orbit - A Virtual Reality-Planned Anatomic Study. Oper Neurosurg (Hagerstown). 2020; 19(3): 330-340. doi: 10.1093/ons/opz420
24. Dreifuerst KT, Bradley CS, Johnson BK. Using Debriefing for Meaningful Learning With Screen-Based Simulation. Nurse Educ. 2021; 46(4): 239-244. doi: 10.1097/NNE.0000000000000930
25. Lioce L, Lopreiato J, Downing D, Chang TP, eds. Healthcare Simulation Dictionary - Second Edition. Rockville, MD: Agency for Healthcare Research and Quality; 2020. doi: 10.23970/simulationv2
26. Herbstreit S, Benson S, Raiser C, Szalai C, Fritz A, Rademacher F, Gradl-Dietsch G. Experience with an OSCE anamnesis station via Zoom: Feasibility, acceptance and challenges from the perspective of students, simulated patients and examiners during the COVID-19 pandemic. GMS J Med Educ. 2022; 39(4): Doc44. doi: 10.3205/zma001565
27. Sanseau E, Sooby RC, Kou M, Auerbach M, Tay KY. How to Use TeleSimBox "Off the Shelf" to Connect Remote Content Experts With In-Person Simulation Participants. Cureus. 2021; 13(7): e16317. doi: 10.7759/cureus.16317
28. Thomas A, Burns R, Sanseau E, Auerbach M. Tips for Conducting Telesimulation-Based Medical Education. Cureus. 2021; 13(1): e12479. doi: 10.7759/cureus
29. Pit SW, Velovski S, Cockrell K, Bailey J. A qualitative exploration of medical students' placement experiences with telehealth during COVID-19 and recommendations to prepare our future medical workforce. BMC Med Educ. 2021; 21(1): 431. doi: 10.1186/s12909-021-02719-3
30. Lewis C. S. On Living in an Atomic Age (first published 1948). In: Hooper W, eds. Present Concerns: Essays by C.S. Lewis. New York: Harcourt Brace Jovanovich; 1986, p. 73–80.
31. Tsekhmister Y. The problem of pedagogical innovations and trends in the development of the educational environment. Futurity Education. 2022; 1(2): 22-30. doi: 10.57125/FEL.2021.09.25.0410.57125/FED/2022.10.11.16

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ABSTRACT BOOK

SCIENTIFIC AND PRACTICAL CONFERENCE INVOLVING YOUNG SCIENTISTS «CURRENT STATUS OF PERSONALIZED MEDICINE: GLOBAL ISSUES AND PROSPECTS FOR FUTURE RESEARCH»

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DYNAMICS OF TUBERCULOSIS MORBIDITY AMONG ADOLESCENTS IN UKRAINE OVER 17 YEARS

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Introduction: The epidemiological situation of tuberculosis (TB) in Ukraine remains complex with a large number of patients remaining as a source of infection with Mycobacterium tuberculosis, which is particularly dangerous for the most vulnerable populations – children and adolescents.
The aim: To analyze the main epidemiological indicators of TB in adolescents in Ukraine from 2006 to 2022 years.
Materials and methods: Epidemiological, clinical, statistical. The work was carried out with funding from the state budget.
Results: The incidence of TB in adolescents decreased 3.5 – fold over 17 years, from 34.9 per 100,000 people of appropriate age to 10.0 in 2022. The percentage of relapses almost did not change from 2.8 % to 3.1 % in 2022. Adolescents were most frequently diagnosed with pulmonary TB (from 83.7 % in 2006 to 91.9 % in 2022) and much less frequently with extrapulmonary respiratory TB (from 13.5 % in 2006 to 5.6 % in 2022). Despite the decrease in the incidence of TB, the severity of the disease is increasing and the amount of "small" forms of TB without bacterial excretion or destruction is decreasing. In 2006, the quantity of adolescents with bacterial excretion was 25.1 % of all pulmonary forms of TB, rising to 53.8 % in 2022, and destruction was detected in 30.8 % in 2006 and 33.0 % in 2022. The incidence of adolescents in contact with MDR-TB patients significantly exceeded the incidence of adolescents in the population, so in 2006 this figure was 1040.5 per 100 thousand contact persons, in 2022 – 2119.6 per 100 thousand). The incidence of adolescents who came into contact with patients without bacterial excretion was lower – in 2006 it reached 78.9 per 100 thousand contact persons, in 2022 – 1521.7 per 100 thousand (in 2021 it was 11.4 times lower and equaled 134.0 per 100 thousand).
Conclusions: A precipitous drop in the incidence rate occurred after the abolition of mandatory screening examination for adolescents. In 2022, almost half of adolescents with newly diagnosed TB had bacterial excretion and a third had destruction, indicating significant shortcomings in early detection of TB infection and an increase in the number of common and neglected forms of TB. The incidence of adolescents who have been in contact with TB patients is ten times higher than in the general population, especially in 2022, which may be due to a full-scale war.

KEY WORDS: tuberculosis, incidence, adolescents, bacterial excretion, contacts.

PERIPHERAL CALCIUM SCORE AS A CRITERIA TO USE OF ROTATIONAL ATHERECTOMY IN THE CALCIFIED LESIONS BELOW THE KNEE ARTERIES

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Introduction: The progression of the process of atherosclerosis of arteries and arterioles leads to the formation of calcified atherosclerotic plaques of various locations, especially in coronary arteries and peripheral arteries. The most informative method of visualization and calculation of atherosclerosis and calcinosis is CT coronary angiography and CT peripheral angiography with the calculation of calcium score. Based on the obtained data, it is possible to stratify risks and choose optimal treatment tactics for patients with atherosclerosis of coronary arteries in combination with atherosclerosis of peripheral arteries, taking the calcium score data.

The aim: To establish and compare the peculiarities of evaluating the coronary calcium score (CCS) and the peripheral calcium score (PCS) in patients with chronic coronary heart disease and peripheral artery disease with calcification.

Materials and methods: Retrospectively analyzed the data of 42 patients aged 51 to 84 years over a period of 18 months. All patients had normal excretory renal function and combined symptoms of chronic coronary heart disease (classified by NYHA class from I to III) and peripheral artery disease (classified by Rutherford Classification stage from 2 to 5). All patients underwent CT coronary angiography and CT peripheral angiography of the lower extremities according to the standard method, and calculated the calcified areas of the coronary arteries and the calcified areas of the below the knee (BTK) arteries using the Agatson score method. Based on the obtained data, the optimal treatment tactics were chosen and endovascular surgical interventions were performed both on the coronary arteries and on the target BTK arteries.

Results: All 42 patients were divided into 2 groups. Endovascular intervention (angioplasty) on the target BTK arteries, according to the data of the calcium score less than 400 underwent 35 patients (group I). The percutaneous coronary intervention was performed in one patient in this group. Endovascular intervention with the use of rotational atherectomy was performed on the target BTK arteries, according to the data of the calcium score more than 400 underwent 7 patients (group II). Percutaneous coronary intervention with rotational atherectomy was performed in two patients in this group. In group I technical success of endovascular surgical treatment of the target BTK arteries was achieved in 34 patients (97.1%). In group II, technical success was achieved in 100% of patients.

Conclusions: Anatomical similarity in sizes of the coronary arteries and the BTK arteries and the similarity of the evaluation of the CCS and the PCS by the Agatson method gives the possibility to propose calcium score data as a criterion for selection of patients with calcified BTK lesions, for the use of rotational atherectomy, to improve the results of endovascular treatment. However, the scientific data available today require further investigations in the field of preoperative preparations in patients with combined atherosclerotic pathology to increase the effectiveness of therapy methods.

KEY WORDS: endovascular treatment, cardiovascular, calcium score, peripheral artery disease, rotational atherectomy

OPTIMIZATION AND PERSONALIZATION OF PRIMARY HEALTH CARE FOR ELDERLY PEOPLE

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Introduction: Optimization and personalization of health care for older people are important aspects that contribute to improving the quality of life of older people and provide more effective health care support in accordance with their unique needs. This topic is particularly relevant as the population ages and the number of older people in need of additional support and care increases. This process is gaining global proportions and is of concern to governments in many countries, which realize the enormous implications for healthcare systems, their human resources, and budgets.
The aim: To develop a patient registry in a primary care center as a tool for managing the long-term health monitoring of older people based on the principles of the ICOPE (Integrated Care for Older People) concept of comprehensive care for older people recommended by WHO.
Materials and methods: The basis for determining the accounting features in the registry was based on the components of the anamnestic questionnaire of patients, individual programs for the prevention of chronic diseases, episodes of medical care and their causes. The formation of the registry was carried out in stages, first of all, a group of patients with limited physical mobility was formed (587 people, out of 32756 assigned to medical care).
Results: In 2018, preventive medical examinations of the adult population based on individual programs for the prevention of chronic non-communicable diseases were introduced into the practice of the primary care of the State Institution of Science "Research and Practical Center of Preventive and Clinical Medicine" State Administrative Department, which were preceded by anamnestic questioning of patients from organized and unorganized groups. The individualized prevention program helped to identify non-communicable chronic diseases in the target groups at early stages. It was found that one patient from the observation group has three to ten chronic diseases. In order to optimize and personalize the provision of medical care, in particular to older people, recommendations were made to conduct a comprehensive assessment of the functional status of older people to identify risks and early signs of functional loss.
Conclusions: The integration of the ICOPE program will allow to create a system of medical care aimed at maintaining the activity, health, and independence of older people, providing them with a full and satisfactory life. A personalized approach that takes into account the individual characteristics of each older person will help ensure more effective and favorable medical care, as well as prevent possible problems and complications.

KEY WORDS: optimization of medical care, personalization, ICOPE.

COMPARISON OF THE DURATION OF PARTIAL MENISCUS RESECTION USING ARTHROSCOPIC PUNCHERS, RADIOFREQUENCY ABLATOR AND A RADIOFREQUENCY MENISCUS RESECTION TOOL «MENISCUS RESECTOR»

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Introduction: A study of comparison of partial meniscus resection using traditional instruments and instruments for radiofrequency resection «Meniscus Resector» was conducted.
The aim: To determine and compare the time of partial meniscus resection using arthroscopic punchers, radiofrequency ablator and the instrument for radiofrequency meniscus resection «Meniscus Resector».
Materials and methods: The study was conducted on 30 macropreparations of human knee meniscus obtained during total knee arthroplasty, which were divided into two groups: Group 1 - 15 macropreparations, partial resection of which was performed using arthroscopic punchers, and the contours of the meniscus surface after resection were treated with a radiofrequency ablator; Group 2 - 15 macropreparations, partial resection of which was performed using a tool for radiofrequency resection of the meniscus «Meniscus Resector». In both groups, the same volume of meniscus was resected - 500 mm^3. Visualization and time measurement were performed using an arthroscope.
Results: In group 1, the average duration (median, interquartile range) of partial resection of a 500 mm^3 fragment was 11,8 (10,2-12,9) sec, in group 2 the average duration of partial resection of a 500mm^3 fragment was 1,9 (1,4-2,3) sec ($p<0,001$). Thus, the use of «Meniscus Resector» (group 2) favored, on average, 6,2 times faster partial meniscus resection, as compared to arthroscopic punchers and radiofrequency ablator (group 1).
Conclusions: The study suggests that the use of the «Meniscus Resector» provides a faster method of radiofrequency meniscus resection compared to arthroscopic punchers and radiofrequency ablators. Further studies and trials are needed to confirm these results and evaluate safety in different clinical settings.

KEY WORDS: meniscus, partial resection, radiofrequency.

ANALYSIS OF TREATMENT EFFECTIVENESS AND RECURRENCE-FREE COURSE IN PATIENTS WITH COMBINED PATHOLOGY (UTERINE FIBROIDS AND ADENOMYOSIS)

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Introduction: The main indicator of the effectiveness of any conducted comprehensive treatment for various pathologies is considered to be the duration of the recurrence-free period of the disease.
The aim: Analysis of treatment efficacy and recurrence-free course in patients with combined pathology (uterine fibroids and adenomyosis).
Materials and methods: A total of 100 patients suffering from submucous uterine myoma (MM) with concomitant adenomyosis, accompanied by heavy menstrual cycles (MC) and dysfunctional uterine bleeding (DUB), were examined using clinical and laboratory methods. The statistical analysis of the recurrence-free duration of MM in the context of adenomyosis, both with and without various hormonal therapies (HT), was performed using the method of survival analysis. The recurrence-free period (RFP) was defined as the time interval from the beginning of primary treatment to the earliest documented date of disease recurrence (first episode of heavy MC or DUB).
Results: All patients underwent hysteroscopic myomectomy as a surgical procedure. Hormonal therapy (HT) during the postoperative period, for a duration of 6 months, included the following: combined oral contraceptive (COC) with monophasic progestogen and low estrogen content - in 30% of cases; progestogens only - in 30%; GnRH agonists (aGnRH) - in 20% of cases; and 20% of patients did not receive any treatment.
When analyzing the impact of different HT options and their duration on the recurrence-free course during the postoperative period, it was determined that among patients receiving HT, the duration of recurrence-free period was statistically significant (Pearson's Chi-square test=35.97; df=4; $p<0.001$). The comparative assessment of the recurrence-free period using the Kaplan-Meier method for the respective HT groups showed that the use of aGnRH resulted in a longer recurrence-free period compared to other treatment groups.
Conclusions: The obtained results indicate that the most effective hormonal therapy (HT) for the combination of uterine myoma and adenomyosis is the use of GnRH agonist (aGnRH) drugs, which show the longest remission duration when administered in courses of at least 6 months. The median duration of recurrence-free period in patients receiving this treatment option reaches 7 months. The minimum recurrence-free period is observed in patients who received combined oral contraceptive (COC) and progestogen therapy, and it amounts to 3 months.

KEY WORDS: Uterine myoma, reproductive function, endometriosis, infertility.

MORPHO-IMMUNOHISTOCHEMICAL CHARACTERIZATION OF THE ENDOMETRIUM IN WOMEN WHO UNDERWENT UNSUCCESSFUL EMBRYO TRANSFER OF A DONOR EMBRYO

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Introduction: The effectiveness of assisted reproductive technology (ART) is determined by both the quality of the obtained embryos and the functional activity of the endometrium.
The aim: To investigate the structural changes in the endometrium in programs of in vitro fertilization (IVF) where patients had unsuccessful donor embryo transfers, a retrospective study was conducted.
Materials and methods: The study included 88 healthy patients who underwent IVF with donor embryos: 55 patients with a previous unsuccessful donor embryo transfer (first group) and 33 patients who had a successful embryo transfer (second comparison group).
Results: The results of morpho-immunohistochemical -ultrastructural examination of the endometrial biopsy taken during the presumed «implantation window» demonstrated pathological changes in the first group were compared with results of the second group : in 51.1% of cases showed the increased collagen formation and fixed immune complexes on the subepithelial membranes of subendometrial vessels; increased numbers of specific resistance cells, such as lymphocytes and plasma cells, and decreased numbers of non-specific resistance cells, such as segmented neutrophils in the endometrium; 33.3% cases showed the absence or reduced number of microvilli on the apical surface of secretory cells; cilia of ciliated cells were shortened or partially fused together; fully developed mature pinopodia were observed in only 50% of patients.
Conclusions: Based on the analysis of our own data, it can be observed that the morphological changes, specifically the inconsistency in the structural organization of the implantation window, along with the discordant expression of hormone-producing cell receptors, and the overall discoordination of the immune cell network in the endometrium, directly contribute to the reduced effectiveness of embryo transfer in assisted reproductive technology programs for women with a history of unsuccessful donor embryo transfer.

KEY WORDS: donor embryo transfer, prevention, prediction, innocence of pregnancy.

THE ROLE OF PLASMATHERAPY IN THE MINIINVASIVE TREATMENT OF COMPLICATED VARICOSE DISEASE WITH VENOUS ULCERS

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Introduction: An increase in the number of cases of complicated forms of varicose veins in Ukraine leads to an increase in the number of surgical interventions in the presence of venous trophic skin changes, namely ulcers. One of the key points in the performance of minimally invasive operations is the postoperative healing of ulcerated skin defects of the lower limbs. At present, trophic skin damage against the background of varicose veins is often the cause of temporary incapacity of patients. This is a socially significant problem.
The aim: To determine the optimal method of minimally invasive treatment of a complicated form of varicose with the help of surgical correction and a combination of topical treatments.
Materials and methods: The results of the treatment of 20 patients with primary superficial varicose C6s according to the CEAP classification, operated on using various minimally invasive puncture techniques in the surgical department of the State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administrative Department were analyzed.
Results: The method of miniinvasive surgical treatment was selected according to ultrasound changes of the venous system and considering the area of the skin lesion. The main methods of eliminating venous reflux in this group of patients were endovenous laser ablation (16 cases) and the electrowelding method (4 cases). Electrowelding was used for varicose veins of a larger diameter (more than 18 mm). The sizes of ulcer defects ranged from 1.0*2.5 cm to 8.0*6.5 cm. After the surgical treatment, it was mandatory to prescribe a compression for the period until the ulcers are completely healed. This is on average from 1 month to 3 months. After surgery, local bandages with hyaluronic acid and collagenase and plasma therapy for ulcer defects were used in some patients (17 cases). Plasmotherapy was carried out once a week three times. Others had only bandages without plasma treatment. Examinations were once a week for the first month, then after a month. In patients where plasmotherapy was used, the ulcers actively granulated and healed completely already 1-1.5 months after the operation. The patients of the other group were fully healed 2-3 months after surgical treatment.
Conclusions: In patients with trophic skin damage, key points to treatment are a combination of a miniinvasive method, selected individually according to the ultrasound scan results, as well as topical injection treatment - namely plasmotherapy of the ulcer to speed up the skin healing process.

KEY WORDS: varicose, venous ulcer, plasmotherapy, topically treatment of ulcer, combine treatment of varicose.

RISK FACTORS FOR THE DEVELOPMENT OF POSTOPERATIVE HYPOCALCEMIA AFTER OPERATIONS ON THE THYROID GLAND

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Introduction: One of the most frequent complications during operations on the thyroid gland is the development of early hypocalcemia. Research conducted by various clinics tried to determine the main factors affecting the occurrence of postoperative hypocalcemia, but a clear and unanimous answer was not received. Therefore, this study is devoted to the search for risk factors for the development of hypocalcemia.
The aim: To determine the risk factors that may affect the development of postoperative hypocalcemia during operations on the thyroid gland.
Materials and methods: A retrospective study of the medical histories of 455 patients operated on by one surgeon for various thyroid pathologies was conducted. The presence of postoperative hypocalcemia was determined not only by the presence of clinical manifestations but also by the results of determining the level of ionized calcium in the blood the day after the operation. During the study, the following factors were also taken into account: sex, age, distribution by age groups, the hormonal status of the thyroid gland before surgery and preoperative diagnosis, preoperative and postoperative level of ionized calcium in the blood, and volume of surgical intervention.
Results: According to the results of the study, gender, volume of surgical intervention, and thyroid gland function before surgery showed a significant correlation with the development of postoperative hypocalcemia. In female patients, the complication occurred in 16% (73 of 455) compared with 1.7% (1 in 60) in men. A significant difference also arose depending on the volume of surgical intervention: after total thyroidectomy – 18.1% and with hemithyroidectomy – 1.1%. Thyroid status before surgery also influenced the development of complications: in the presence of thyrotoxicosis, hypocalcemia occurred in 35.2% of cases, and in 4.4% of surgical interventions for other thyroid pathology.
Conclusions: Analyzing the obtained results, it can be concluded that such criteria as the patient's gender, the scope of the surgical intervention and the presence of thyrotoxicosis before the operation are the main risk factors for the development of postoperative hypocalcemia. And the age of the patient and the nature of the pathological process in the thyroid gland are not factors in the development of postoperative hypocalcemia.

KEY WORDS: thyroid gland, postoperative hypocalcemia, thyroidectomy, thyrotoxicosis, thyroid cancer.

MECHANISMS OF STATE REGULATION OF DENTAL CARE IN UKRAINE IN NEW SOCIO-ECONOMIC CONDITIONS

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Introduction: Human health, as a socio-economic category, is an element of national wealth, which is declared by a lot of international acts, which orients the countries to specific actions in response to new challenges and threats to public health. Dental care is a medical and social problem. Dental treatment is one of the most common types of medical care in the world.
The analysis of the literature proved that fundamental scientific research on the issue of effective state regulation of dental care in the new socio-economic conditions is still far from being completed.
The aim: To substantiate the theoretical and practical aspects of the mechanisms of state regulation of the system of dental care for the population in the context of new socio-economic conditions in Ukraine (in particular, in the conditions of martial law).
Materials and methods: The methods of the historical-bibliographic and systematic approach were used.
Results: The problematic issues of dental care management in Ukraine are the high prevalence of diseases, curtailment of preventive measures, and reduction of state funding. The problem with the domestic dental service is the decrease in the provision of the population of Ukraine with dentists in health care institutions from 4.67 to 4.0 per 10 000 population in the period from 2018 to 2023. In recent years, with the simultaneous increase in the number of dentists in privately owned dental institutions, the availability of dental care for low-income segments of the population has decreased. The preservation of national personnel also remains an important issue, since in modern conditions there is a mass departure of doctors abroad. It is important to note that state administration and state regulation are two separate types of state authority activity. Thus, public administration provides for direct managerial influence on the objects of administration using administrative powers and methods marked by mandatory directives. State regulation, on the other hand, provides only for the establishment of certain restrictions, limits of activity of objects in which they can function freely. It is aimed not only at the object of management and also at its environment.
State regulation of dental care provides for the establishment of general rules and procedures for performing dental activities, in particular the provision of dental care, and responsibility for compliance with these rules. It also includes the influence of the state and its bodies on the activities of dental institutions. State regulation should be based on a legitimately defined social development strategy, and state medical programs. The defined mechanisms of state regulation of the system of dental care for the population are based on mutual relations and interactions with each other in the public sphere, form characteristic features of the complex mechanism of state regulation of the system of dental care, among which the following can be noted: systematicity and independence of unified mechanisms; performance of each mechanism of its specific function; the use of different methods of state regulation for the implementation of separate mechanisms; planning nature; publicity of the results of implementation of mechanisms.
Conclusions: The conducted analysis proved that based on the use of mechanisms of state regulation of the system of dental care for the population in Ukraine, a gradual change in the paradigm of the development of the system of dental care for the population is taking place. We dare to assert that all these changes imply the objective expediency of a more detailed understanding of the peculiarities of the formation and implementation of the mechanisms of state regulation of the system of dental care, which is the perspective of our further scientific research.

KEY WORDS: state regulation, mechanisms of state regulation, the system of dental care for the population, mechanisms of state regulation of the system of dental care for the population, socio-economic conditions.

CLINICAL PATHWAYS FOR PATIENTS WITH NODULAR THYROID GLAND FORMATIONS IN THE OUTPATIENT MEDICAL CARE STAGE

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Introduction: The prevalence of nodular formations in the thyroid gland, combined with the main risk factors for malignancy and the complexity of their diagnosis, highlights the importance of optimizing the diagnostic process at the outpatient stage of medical care for the adult population.
The aim: To determine the clinical pathways for patients with nodular formations in the thyroid gland who underwent ultrasound examination during the provision of outpatient medical care.
Materials and methods: The information source for determining patient pathways was the medical information system of the State Institution of Science «Research and Practical Centre of Preventive and Clinical Medicine» State Administrative Department (SIS «RPS PCM» SAD) for the period from 2015 to 2022, with a total of 30,708 registered outpatient medical episodes.
Results: Ultrasound examination, in accordance with international standards, is considered the fundamental diagnostic method for nodular thyroid gland formations. Annually, approximately 6000 ultrasound examinations are performed for this category of patients at the SIS «RPS PCM» SAD.
Based on the observation results, the following clinical pathways for patients requiring ultrasound examination of the thyroid gland were determined: 1. Patients with suspicion of nodular thyroid gland formations (referred by primary care physicians, endocrinologists, surgeons, gynecologists, etc.). 2. Patients with confirmed nodular goiter: 2.1. Requiring dynamic observation. 2.2. Requiring further diagnostic fine-needle aspiration biopsy (FNAB) with cytological verification. 2.3. Requiring preoperative evaluation. 3. Patients requiring dynamic observation after thyroid gland surgery.
Conclusions: The determined clinical pathways for patients with nodular thyroid gland formations at the outpatient stage of medical care will form the basis for clinical audits and will be further optimized in accordance with international standards requirements.

KEY WORDS: thyroid gland, outpatient medical care organization, ultrasound examination (ultrasonography).