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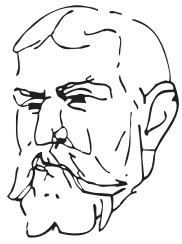

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CONTENTS

ORIGINAL ARTICLES

REVIEW ARTICLES

CASE STUDIES

ORIGINAL ARTICLE

HYPERPLASIA OF THE FEMALE REPRODUCTIVE ORGANS IN UKRAINE

DOI: 10.36740/WLek202303101

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ABSTRACT

The aim: To determine the role of infectious diseases as the cause of the Cervical, Ovarian and Breast hyperplasia in Ukraine.

Materials and methods: We conducted a retrospective multicenter cohort study from January 1st, 2020 to December 31st, 2022. This study included patients aged 20-59 years with a diagnosis of hyperproliferative pathology of the women reproductive organs without atypia, who sought medical care for hyperplastic processes admitted to the 12 hospitals from 9 regions of Ukraine.

Results: We had examined 4,713 women; out of which 81.1% met the clinical definition of female reproductive organs hyperplasia. Of all hyperplasia cases, most frequently recorded types were breast hyperplasia (41,7%), followed by cervical hyperplasia (31,1%) and ovarian hyperplasia (27,2%). History of Cervicitis ($p<0.001$), Vaginal cuff infection ($p<0.001$), Oophoritis ($p<0.001$), and Mastitis ($p<0.001$) were identified as independent risk factors of Cervical, Ovarian and Breast hyperplasia.

Conclusions: This study showed that surgical site infections after obstetric and gynecological operations are is the cause of Cervical, Ovarian and Breast hyperplasia. Therefore, early detection and treatment SSIs can reduce the risk of hyperplasia these organs.

KEY WORDS: cervical hyperplasia, ovarian hyperplasia, breast hyperplasia, surgical site infection, risk factors, Ukraine

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INTRODUCTION

Hyperplasia of women reproductive organs remain important public health problems. They are not cancer, but may become cancer. Before cancer cells form in tissues of the body, the cells go through abnormal changes called hyperplasia and dysplasia. Gynecological malignancies continue to be an important cause of cancer-related mortality [1]. With an estimated annual incidence of more than 3.6 million and mortality exceeding 1.3 million, these cancers account for nearly 40% of all cancer incidence and for more than 30% of all cancer mortality in women worldwide [2]. Breast cancer are the top three malignancies involving the female reproductive system worldwide. According to literature, in 2020, Breast cancer surpassed lung cancer as the most common type of cancer diagnosed in women, with an estimated 2.3 million new cases in 2020 accounted for 6.9% of all cancer-related deaths, making it the leading cause of cancer death in women as well. Cervical cancer is currently the second most common gynecological cancer, with 0.6 million new cases in 2020, and it is the fourth leading cause of cancer death in women, with approximately 342,000 deaths worldwide. Ovarian cancer is the fourth most common gynecological malignancy, with 313,959 new cases and 207,252 deaths in 2020, making it the most lethal gynecological cancer [2-4].

Researchers in many countries around the world are paying attention search for modern diagnostic criteria, risk factors of hyperplasia of women reproductive organs and optimal treatment concepts. Hyperplasia is thought to be part of the complex transition of cells that may evolve into reproductive organs cancer. The process begins when normal cell development and growth become disrupted, causing an overproduction of normal-looking cells (hyperplasia). However, it's not clear what causes hyperplasia.

Hyperproliferative pathology of the women reproductive organs (hyperplasia) occupies a special place among the risk factors for cervical, ovarian and breast cancer. Despite numerous studies, neither the etiology nor the pathogenesis of hyperplastic processes has been elucidated to date, so treatment options are not fully substantiated. According to literature, the leading role in the pathogenesis of hyperplasia in patients of reproductive age is attributed to the increased estrogen concentrations arising from the absence or insufficient antestrogenic effect of progesterone. However, the results of researches of the last years testify in favor of infectious-inf lammatory concept of developing the hyperplastic processes of genitals [2, 4-7].

In the context of economic turmoil, high mortality rates and given the low birth rate in Ukraine, the problem of maintaining reproductive health is extremely relevant and acquires high medical and social significance, in turn, is a qualitative criterion for the reproduction of the population at the population level [8, 9]. However, the data on the prevalence of Cervical, Ovarian and Breast hyperplasia in various population in our country is not known. There is an urgent need for initiation of community screening and educational programs for the control and prevention of female reproductive organs cancer in Ukraine.

THE AIM

The aim of this study was to determine the role of infectious diseases as the cause of the Cervical, Ovarian and Breast hyperplasia in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTINGS AND PARTICIPANTS

We conducted a retrospective cohort study from January 1st, 2020 to December 31st, 2022. This study included patients of the gynecological departments of the various hospitals with a diagnosis of hyperproliferative pathology of the women reproductive organs without atypia, who sought medical care for hyperplastic processes in reproductive age. We compiled list of the 14 women hospitals. Of these, only 12 hospitals from 9 regions (Lviv, Vinnytsia, Zhytomyr, Kyiv, Sumy, Dnipro, Kharkiv, Zaporizhzhia, and Odesa) of Ukraine agreed to take part in our study. The age of women ranged from 18 to 59 years (average 34.52 ± 2.51). The inclusion criteria in this study for participants were as follows: the presence of benign hyperplasia of the female genital organs; local residents. The exclusion criteria: pregnant women, menstruating women, women with invasive carcinoma at the time of clinical evaluation, and women previously treated for cervical neoplasm were excluded from the study.

DEFINITION

Diagnosis of hyperplasia of reproductive organs should be based upon histological assessment of a tissue sample obtained by biopsy, curettage, or hysterectomy and ultrasound method. In this study hyperplasia is classified by whether certain cell changes are present or absent. If abnormal changes are present, it is called atypical.

DATA COLLECTION

We examined 185 patients of the gynecological departments various hospitals. Histological examination of cervical, ovarian and breast tissue was performed according to the generally accepted method. The surgical material and cervical, ovarian and breast tissue obtained by hysteroscopy and aspiration biopsy were subjected to morphological examination. Biopsy material was fixed in 10% neutral formalin. Further processing was performed according to the standard generally accepted unified method. All procedures were carried out in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. All patients were divided into three groups, up to group I women with cervical hyperplasia; group II – patients diagnosed with ovarian hyperplasia; group III included patients with breast hyperplasia. This work includes interviews, questionnaires, and examinations medical records for the all patients. In our study a standard data collection form was created to extract demographic and clinical data, and outcome information from routine patient records. In this study patients' folders and the hospitals' database were used to obtain all the other information needed concerning the study participants clinical and gynecological history. Women who did not give informed consent for this study were excluded.

ETHICS

Ethical clearance for this study was obtained from the ethics committee of the Shupyk National Healthcare University of Ukraine. This study was performed in line with the principles of the Declaration of Helsinki.

STATISTICAL ANALYSIS

All clinical and other information needed concerning the study participants and gynecological history

were entered in an Excel (Microsoft Corp., Redmond, WA, USA) database for statistical analysis. Results are expressed as median (range), mean ± standard deviation for continuous variables, and number and corresponding percentage for qualitative variables. In this study chi-square test/Fischer's Exact test and the binary logistic regression analysis were employed to test for associations and the strength thereof between the dependent variable and independent variables. All statistical analyses were two-sided and significance was set at $P < 0.05$.

RESULTS

In our study, between January 2020 and December 2022, we had examined 4,713 women; out of which 3,822 (81.1%) met the clinical definition of female reproductive organs hyperplasia. The epithelial cell abnormalities constituted 3.2% of all cases and rest of 3,690 cases (96.8%) fell in the category of negative for intraepithelial lesion or malignancy. Of all hyperplasia cases, most frequently recorded types were breast hyperplasia (41,7%, [95% confidence interval (CI), 40.9-42.5]), followed by cervical hyperplasia (31,1%, [95% (CI), 30.3-31.8]) and ovarian hyperplasia (27,2%, [95% (CI), 26.5-27.9]).

This study showed that the situation with female reproductive organs hyperplasia in Ukraine varies greatly by region. In general, lower breast, cervical and ovarian hyperplasia percentages were reported by Ukrainian regions in the east while higher percentages were reported in the central region, north, south and west of Ukraine. In terms of regions, ten-fold fluctuations of the indicator values were observed – from the smallest in Kharkiv region to the largest in Dnipropetrovsk region and in Kyiv. The difference between the smallest and largest value of the indicator was threefold.

The ratio of risks of reproductive organs hyperplasia among patients for the period 2020-2022 in most regions was lower than the general figure for Ukraine. The lowest indicator of relative risk was in Lviv region (OR – 0.56 [95% CI 0.54-0.57], p<0.05), Vinnytsia (OR – 0.56 [95% CI 0.55-0,57], p<0.05), and Sumy (OR – 0.57 [95% CI 0.57–0.58], p<0.05). At the same time on the territory of other regions (Vinnytsia (OR – 1.05 [95% CI 1.04–1.07], p<0.05), Kharkiv (OR –1.12 [95% CI 1.11 –1.13], p<0.05), Dnipro (OR 1.49 [95% CI 1.48–1.50], p<0.05), Zhytomyr (OR 1.56 [95% CI 1.54–1.5], p<0.05) and Kyiv (OR – 1.26 [95%) CI 1.24–1.28], p<0.05).

Different risk factors associated with breast, cervical and ovarian hyperplasia detected in the present study were analyzed in detail. The findings are summarized below (Table I). In this study the greatest number of hyperplasia cases (45.7%) were in age group 30-49 years, followed by 34.7% in age group 20-29 years. The epithelial abnormalities including (atypical squamous and glandular cells of undetermined significance, atypical glandular cells of undetermined significance, low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, and squamous cell carcinoma constituted 3.2% of all cases. A progressive rise was seen in the frequency of cytopathological abnormalities with increasing age, and maximum frequency of low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, and breast, cervical and ovarian carcinoma was observed in age above 40 years.

Table II showed the odds ratio (OR) and 95% confidence interval (CI) for the risk factors associated with hyperplasia of female reproductive organs in logistic multivariate regression analyses. Unsurprisingly, cervical, ovarian and breast hyperplasia was associated with history of Cervicitis (p<0.001), Vaginal cuff infection (p<0.001), Oophoritis (p<0.001), and Mastitis (p<0.001) as shown in logistic regression analysis. Further, there were differences among risk factors associated with cervical, ovarian and breast hyperplasia.

DISCUSSION

To the best of our knowledge, this is the first study examining healthcare-associated infections associated with obstetric and gynecological surgeries as a cause of female reproductive organs hyperplasia in Ukraine. In this study we had examined 4,713 women; out of which 81.1% met the clinical definition of female reproductive organs hyperplasia. The epithelial cell abnormalities constituted 3.2% of all cases and rest of 96.8% fell in the category of negative for intraepithelial lesion or malignancy. Of all hyperplasia cases, most frequently recorded types were breast hyperplasia (41,7%), followed by cervical hyperplasia (31,1%) and ovarian hyperplasia (27,2%). Cervical, ovarian and breast hyperplasia was associated with history of Cervicitis, Vaginal cuff infection, Oophoritis, and Mastitis as shown in logistic regression analysis. Further, there were differences among risk factors associated with cervical, ovarian and breast hyperplasia.

In this study the main factors associated with cervical, ovarian and breast hyperplasia were history surgical site infections (SSIs) after obstetric and gynecological surgeries. The prevalence of SSIs after obstetric and gynecological surgeries varies greatly in different countries and regions, and change all the times. The SSI cases estimates use different definitions considering different periods, which make direct comparisons difficult between various studies. SSIs in Ukraine are among the most common healthcare-associated infections (HAIs) after, obstetric and gynecological surgeries [10].

Table I. Characteristics of women with breast, cervical and ovarian hyperplasia in Ukraine (2020-2022)

Variables	All hyperplasia cases (n=3,822)		p-value	95% CI
	n	%		
Age (years)				
20-29	296	7,7	<0.001	6.2 – 9.2
30-39	646	16,9		15.4 – 18.4
40-49	1243	32,5		31.2 – 33.8
≥50	1637	42,8		41.6 – 44.1
Education				
Primary	2529	66,2	0,517	65.3 – 67.1
High school or technical secondary school	321	8,4		6.9 – 9.9
Bachelor's degree and above	972	25,4		24.0 – 26.8
Smoking				
No	1399	36,6	0,681	35.3 – 37.9
No, secondhand smoke	784	20,5		19.1 – 21.9
Yes	1639	42,9		41.7 – 44.1
Drinking				
No	2184	57,1	0,638	56.1 – 58.2
Yes	1638	42,9		41.7 – 44.1
BMI (kg/m^2)				
Thin	1641	42,9	0,472	41.7 – 44.1
Normal	1796	47		45.8 – 48.2
Overweight	321	8,4		6.9 – 9.9
Obese	64	1,7		1.1 – 2.3
Bacterial vaginosis				
No	1984	51,9	0,512	50.8 – 53.1
Yes	1837	48,1		46.9 – 49.3
History of Pelvic abscess or cellulitis				
No	2678	70,1	<0.001	69.2 – 71.0
Yes	1144	29,9		28.6 – 31.2
History of Adnexa utery				
No	2891	75,6	<0.001	74.8 – 76.4
Yes	931	24,4		21.0 – 25.8
History of Cervicitis				
No	634	16,6	<0.001	15.2 – 18.0
Yes	3188	83,4		82.7 – 84.1
History of Oophoritis				
No	604	15,8	<0.001	14.3 – 17.3
Yes	3218	84,2		83.6 – 84.8
History of Endometritis				
No	2837	74,2	<0.001	73.4 – 75.1
Yes	985	25,8		24.5 – 27.1
History of Chorioamnionitis				
No	3610	94,5	<0.001	94.1 – 94.9
Yes	212	5,5		4.0 – 7.0

Table I. (continuation)

History of Vaginal cuff infection				
No	3109	81,3	<0.001	80.6 – 82.0
Yes	713	18,7		17.3 – 20.1
History of Episiotomy infection				
No	2810	73,5	<0.001	72.7 – 74.3
Yes	1012	26,5		25.2 – 27.8
History of Mastitis				
No	510	13,3	<0.001	11.8 14.8
Yes	3312	86,7		86.1 – 87.3
History of Chlamydial infections				
No	1789	46,8	0,378	45.6 – 48.0
Yes	2033	53,2		52.1 – 54.3
History of sexually transmitted infections				
No	2701	70,7	<0.001	69.8 – 71.6
Yes	1121	29,3		27.9 – 30.7

CI, confidence interval
BMI, Body Mass Index

Table II. Logistic multivariate regression analyses of risk factors for breast, cervical and ovarian hyperplasia among women in Ukraine (2020-2022)

Characteristics	p-value	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)
Age (years)				
	< 0.001		< 0.001	
20-29		Ref		Ref
30-39	0.003	9.379 (2.165–40.619)	0.011	6.862 (1.557–30.247)
40-49	0.012	6.618(1.549–28.274)	0.031	5.036 (1.163–21.83)
≥50	0.025	5.577 (1.244–25.011)	0.109	3.49 (0.758–16.071)
History of Cervicitis				
No		Ref		Ref
Yes	< 0.001	9.379 (2.165–40.619)	< 0.001	5.033 (1.162–21.81)
History of Oophoritis				
No		Ref		Ref
Yes	< 0.001	3.611 (2.234–5.831)	< 0.001	3.063 (1.819–5.158)
History of Vaginal cuff infection				
No		Ref		Ref
Yes	< 0.001	5.131 (2.662–9.878)	< 0.001	3.835 (1.908–7.712)
History of Mastitis				
No		Ref		Ref
Yes	< 0.009	3.623 (2.231–5.841)	0.001	3.081 (1.816–5.157)
Constant			0.003	0.109

CI, confidence interval
OR, Odd Ratio

According to literature, the prevalence of healthcare-associated deep pelvic tissue infection and other infections of the female reproductive tract after obstetric and gynecologic surgery in Ukraine was 26.3%. Incidence rate of HAI was: 13.3% Pelvic abscess or cellulitis, 14.6% Adnexa utery, 9.5% Salpingitis, 7.1% Oophoritis, 12.2% Parametritis, 4.6% Chorioamnionitis, and 38.8% Bacterial Vaginitis [11], and 11.6% breast abscess, and 88.4% postpartum mastitis [12]. The prevalence of HAIs varies from country to country and ranges from 1.8% to 48% [10]. Incidence of SSI after induced

abortion in Ukraine was 25.9%. Of these SSIs, 25.9 were Endometritis, 21.8% Bacterial Vaginitis, 14.3% Parametritis, 13.1% Cervicitis, 9.9% Adnexa utery, 7.8% Salpingitis, 6.3% Chorioamnionitis, and 0.9% other reproductive tract infections [8]. Despite the introduction into surgical practice of new diagnostic technologies and treatment, as well as broad-spectrum antibiotics, the number of SSI after obstetric and gynecological surgeries is not decreasing [13].

A number of different aspects should be considered in the treatment of the Cervical, Ovarian and Breast Hyperplasia. Depending on the histological features and the patient´s medical history, all established risk factors for progression to hyperplasia of reproductive organs or the concurrent presence of the infectious diseases should be determined.

Women who have a history of Cervical, Ovarian and Breast infections are at greater risk for progression to hyperplasia and of poor outcomes in pregnancies. Health providers in hospitals should be aware of this risk when treating patients with a history of poor pregnancy outcomes. In addition, a specialized gyneco-pathologist should be consulted given the diagnostic uncertainties of differentiating between Cervical, Ovarian and Breast Hyperplasia, atypical hyperplasia, and cancer of reproductive organs.

The WHO classification of hyperplasia women reproductive organs for the two—hyperplasia without atypia (benign hyperplasia) and atypical hyperplasia—should be applied in order to guarantee comparability of histopathological data both in clinical practice and in academic studies. The presence or absence of nuclear atypia is the most important factor for appropriate therapy planning and monitoring.

CONCLUSIONS

This study showed that surgical site infections after obstetric and gynecological operations are is the cause of Cervical, Ovarian and Breast hyperplasia. Therefore, early detection and treatment SSIs can reduce the risk of hyperplasia these organs. A number of different aspects should be considered in the treatment of the Cervical, Ovarian and Breast Hyperplasia. Depending on the histological features and the patient´s medical history, all established risk factors for progression to hyperplasia of reproductive organs or the concurrent presence of the disease should be determined. However, larger studies are needed to confirm these findings.

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The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CORRELATION OF SOME IMMUNOLOGICAL MARKERS WITH *HELICOBACTER PYLORI* IN PATIENTS IN THI-QAR PROVINCE

DOI: 10.36740/WLek202303102

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ABSTRACT

The aim: This study aims to investigate some of the immunological parameters related to *Helicobacter pylori* patients, including: interleukin (IL-17), cluster of differentiation 4 (CD4), macrophage inhibitory migration factor (MIF), nuclear factor kappa B (NF-kB).

Materials and methods: The immunological parameters were investigated by using ELISA technology, and compared with the healthy individuals (control).

Results: The level of IL-17A in the serum showed a significant increase ($p < 0.05$) in the HPP group compared to the control group. The CD4 serum concentration in infected with H. pylori patients was high level (4.23 ± 0.41 ng/ml) with significant increase ($p < 0.05$) than to healthy individuals (control) (1.93 ± 0.22 ng/ml). Also, there was significant elevation ($p < 0.05$) in in the level of serum MIF levels in *H. pylori* patients (75.23 ± 1.88 ng/ml) as compared to the control (65.11 ± 2.25 ng/ml). Serum NF-kB concentration in patients infected with H. pylori was at a high level (8.15 ± 0.58 ng/ml) with a significant elevated ($p < 0.05$) as compared to control (3.91 ± 0.47 ng/ml). On the other hand, the results proved that there is significant elevation ($p < 0.05$) in blood NF-kB level in smokers infected with *H. pylori* (9.43 ± 0.95ng/ml), compared with non-smokers infected with *Helicobacter pylori* (4.96 ± 1.46 ng/ml).

Conclusions: Both humoral and cellular immune response plays an important role in patients with Helicobacter pylori. The nuclear factor kappa B is considered a risk factor in smoking patients, infected with *Helicobacter Pylori* can be considered as an early diagnosis of stomach cancer.

KEY WORDS: immunological parameters, *Helicobacter pylori*, IL-17, MIF, CD4, NFkB

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INTRODUCTION

Helicobacter pylori are gram-negative microbacilli, which are spiral-shaped, bound bacteria that colonize the gastric mucosa in more than half of the world's population [1]. Infection with *Helicobacter pylori* is usually acquired during childhood, although the trigger strong innate and adaptive host immunological responses, *H. pylori* can live for decades in the mucous membrane of the human stomach [2]. *Helicobacter pylori* is a common causative agent of many gastrointestinal diseases, including active chronic gastritis, gastric ulcers, duodenal ulcers, mucosa-associated lymphoid tissue lymphoma and distal gastric carcinoma. Virtually all people colonized with *H. pylori* will develop gastritis. However, only 15% of these colonists develop the disease [3]. Infection of *H. pylori* causes a strong immune response, resulting in high levels of *H. pylori*-specific antibodies. However, this response is insufficient to eradicate the bacterium, and the infection will persist for life if not treated with antibiotics [4]. Helper T-cells (Th) are a type of T-cell that take part a critical role in the immune system, which are believed to differentiate into CD4+ cell. Types with different functions in response to different cytokines to stimulation, in particular Th1 and Th17 cells, are able to elicit an immune response in response to bacterial invasion [5]. Macrophage migration inhibitory factor (MIF) is a key innate immunity regulator [6]. CD74 is a MIF surface receptor [7]. Bacterial antigens excite white blood cells make the MIF to be released into the bloodstream. MIF in the bloodstream attaches to CD74 on different cells of the immune system, triggering a strong immunological responses. As a result, MIF are considered as inflammatory cytokines. In addition, glucocorticoids encourage white blood cells for secreting of MIF, which partially contradicts the suppressive influence of glucocorticoid on the immune system. Finally, the anterior pituitary is activated by shock, causing MIF to be release [4]. NF-κB transcription factors family is ubiquitously expressed and plays a role an essential role in regulating a wide range of biological processes, including cell differentiation, proliferation, survival, and most importantly, immune responses and inflammation [8]. The précis methods via which *H. pylori* infection cause an immunological response and contributes in stomach mucosal damage are still unknown, but several research have shown that cytokines and the immune

Table I. Distribution of patients infected with *Helicobacter pylori* (Hp) and healthy individuals.

Sample	Hp patients		Healthy individuals		Total	
	Male	Female	Male	Female	Male	Female
Number	34	26	18	12	52	38
%	56.67	43.33	60	40	57.78	42.22
Total	60		30		90	
%	100		100		100	

Table II. Age distribution of patients infected with *Helicobacter pylori* (Hp).

Age groups	Male	Female	Total number	%
20-30	4	6	10	16.67
31-40	11	5	16	26.67
41-50	15	8	23	38.33
51-60	4	7	11	18.33
Total	34	26	60	100

Table III. Distribution of male smokers and non-smokers infected with *Helicobacter pylori* (Hp).

Hp patients	Smoker	Non smoker
Number	18	16
%	52.94	47.05
Total	34	
%	100	

response aid to the control infection and maintenance of the progression of chronic inflammation [1]. Despite extensive research in this area, the mechanisms by which *H. pylori* escapes from the host in an immune response remains unclear [9].

THE AIM

Due to the absence of a specialized immunological study for this disease in Thi-Qar province, and the importance of this disease, which affects a large group of people, so the aim of this study is to investigate some of the immunological parameters related to Helicobacter pylori patients, and its role in the immune response in *Helicobacter pylori* infected patients.

MATERIALS AND METHODS

STUDY SUBJECT

Sixty patients attended to Imam Al-Hussein Teaching Hospital (34 male and 26 female), and they all had clinical manifestations of gastric and duodenal ulcers and/or gastritis, during the period between January 2021 and June 2021, aged 20-60 years, and 30 apparently healthy individuals(control) were enrolled in this study.

METHODS

Peripheral blood was collected from each of the study groups by vein puncture, which was divided into serological tests, which included: IgG Anti-*H. Pylori* Abs, and IL-17A, CD+4, MIF and NFkB assay using ELISA technology. The blood was collected in a sterile tube and left in room temperature until coagulated, then centrifuged at 3000 rpm for 5 minutes. The serum is aspirated from the tube and stored at -25°C until use. The *H. pylori* IgG Ab test kit is based on the principle of ELISA, according to *Helicobacter pylori* IgG ELISA Kit [Demeditic, Germany]. Serum IL-17A assay according to human interleukin 17A (IL-17A/IL-17) ELISA kit [Cusabio, China], enzyme immunoassay prepared according to manufacturer (Elabscience, China) for CD4, MIF and NF- kb.

STATISTICAL ANALYSIS

Statistical analysis was carried out on a computer using SPSS version 23. The data are presented as mean with standard error (SE). A comparative analysis of the patients and controls was conducted on the T-test. The results are statistically significant at the probability level of $P \leq 0.05$.

RESULTS

This study included 60 patients infected with Helicobacter pylori and 30 controls. In the group of patients with Hp (60 people), 34 (56.67%) men and 26 (43.33%) women (Table I). The age of patients were between 20 to 60 years, according to age groups, the results showed that there were 10 patients (16.67%) between 20 and 30 years of age (4 males and 6 females), 16 patients (26.67%) between 31 and 40 years of age (11 males and 5 females), 23 patients (38.33%) between 41 and 50 years of age (15 males and 8 females) and 11 patients (18.33%) between 51 and 60 years of age (4 males and 7 females) (Table II).

Our study showed that most infections were in 18 (52.94%) male smokers and 16 (45.05%) male non-smokers (Table III).

The mean serum IgG anti-*Hp* titer in H. pylori positive (HPP) it was higher than the control with a significant difference (Table IV).

Table IV. Distribution IgG anti-*Helicobacter pylori* (Hp) in patients and healthy individuals.

Groups	Mean ± SE		P value
	Patients	Healthy individuals	
IgG anti-Hp (U/ml)	54.38 ± 29.68	27.76 ± 22.19	p < 0.05

Table V. Concentration of IL-17 in infected patients with *Helicobacter pylori* (Hp) and healthy individuals.

Groups	Serum IL-17 level (pg/ml) Mean ± SE	P value
Hp patients	13.7 ± 5.61	p < 0.05
Healthy individuals	10.44 ± 2.84	

Table VI. Serum concentration of some immunological parameters in patients infected with *Helicobacter pylori* (Hp) and healthy individuals.

Groups	Mean ± SE					
	CD+4 (ng/ml)	P value	MIF (ng/ml)	P value	NF-KB (ng/ml)	P value
Hp patients	4.23 ± 0.41	p < 0.05	75.23 ± 1.88	p < 0.05	8.15 ± 0.58	p < 0.05
Healthy individuals	1.93 ± 0.22		65.11 ± 2.25		3.91 ± 0.47	
Male	2.57 ± 0.29	P> 0.05	71.14 ± 2.13	P> 0.05	8.41 ± 0.72	P> 0.05
Female	4.13 ± 0.86		71.72 ± 2.21		7.92 ± 0.87	
Smokers	2.81 ± 0.39	P> 0.05	73.13 ± 2.15	P> 0.05	9.43 ± 0.95	P> 0.05
Non smokers	2.53 ± 0.36		66.71 ± 4.62		4.96 ± 1.46	

Table VII. Correlation between immunological parameters in patients infected with *Helicobacter pylori* (Hp).

Parameters	r	P value ≤ 0.05	Result
MIF with NF-kB	-0.14	0.133	No significant negative correlation
CD+4 with NF-kB	0.035	0.042	Significant positive correlation
MIF with CD+4	0.0379	0.033	Significant positive correlation

The mean serum IL-17A titer was higher in the HP patients group (13.7 ± 5.61 pg/ml) than in the control group (10.44 ± 2.84 pg/ml), with a significant difference among the HPP and control (table V).

The results of the current study showed that there is a significant increase (p < 0.05) in CD4 serum concentration of *H. pylori* infected patients (4.23 ± 0.41ng/L) compared with healthy individuals (control) (1.93 ± 0.22ng/ml), while no significant differences (P> 0.05) among male (2.57 ± 0.29 ng/ml) and female (4.13 ± 0.86 ng/ml) infected with *H. pylori* and no significant differences (P> 0.05) among smoker (2.81 ± 0.39 ng/ml) and nonsmokers (2.53 ± 0.36 ng/ml) infected with *H. pylori*. Our results showed a significant elevation (p < 0.05) in the level of MIF in the blood of patients with Hp (75.23 ± 1.88 ng/mL) compared with controls (65.11 ± 2.25 ng/ml), while no significant differences (P> 0.05) among male (71.14 ± 2.13 ng/ml) and female (71.72 ± 2.21 ng/ml) and no significant differences (P> 0.05) between smoker (73.13 ± 2.15 ng/ml) and nonsmokers (66.71 ± 4.62 ng/ml) infected with *H. pylori*. In the current study, the serum concentration of patients with NF-kB H. pylori was at a high level (8.15 ± 0.58 ng/ml) with a significant elevated (p < 0.05) than in controls (3.91 ± 0.47 ng/ml). On the other hand, the results indicated that there was no significant differences (P> 0.05) in serum concentration of NF-kB among males (8.41 ± 0.72 ng/ml) and female (7.92 ± 0.87 ng/ml), and there was significant elevation (p < 0.05) in blood NF-kB level in smokers infected with H. pylori (9.43 ± 0.95ng/ml), compared with non-smokers infected with *Helicobacter pylori* (4.96 ± 1.46 ng/ml) (Table VI).

The current results illustrated no significant negative correlation relationship between MIF and NF-kB in Hp-infected patients with a correlation coefficient (r= – 0.14) (p=0.133) (Table VII), while there was significant positive correlation relationship between CD4 and NF-kB in Hp-infected patients with correlation coefficient (r=0.035) (p=0.042). The same positive correlation was detected in serum concentrations of MIF and CD4 in *Hp*-infected patients with a correlation coefficient (r=0.0379) (p=0.033) (Table VII).

DISCUSSION

In the current study provided that there were 34 (56.67%) males and 26 (43.33%) females (Table I). These findings are fully consistent with other studies [10, 11], which reported that the percentage of females was 44.7% and 55.3% were male [10], or 91.7% males and 8.3% female

[11]. This result is not similar to Hussen [12], who found that 57.7% are female and 42.3% are male. This may be attributed to the fact that *H. pylori* in males is asymptomatic, not pre-tested, and not detected at all. It seems that this difference between the gender can relies on the different environments in which patients live. Table III of the results showed that the proportion of smokers was 52.94%, non-smokers 47.05% of infection with *H. pylori*. According to our results, there was no difference in *H. pylori* prevalence between male smokers and non-smokers, that's agree with Akeel et al. [13], who found that there is no significant differences in *H. pylori* positive between male smokers and non-smokers, and other study showed that erosive gastritis in H. pylori-infected patients was more prevalent among smoking patients compared to non-smoking patients (46.7% vs. 15.6%, p = 0.00). In *H. pylori*-infected Egyptian patients, smoking may enhance the occurrence of intestinal metaplasia, erosive gastritis, reactive gastropathy, and glandular atrophy [11]. Some explanations regarding the negative relationship among smoking and *H. pylori* infection suggests that the increased secretion of acid and pepsin generated via smoking can protect the stomach mucosa against infection by *H. pylori* [13]. The mean serum anti-Hp IgG titer was significantly higher in the HPP group than the control groups with a big difference. In general, blood levels of IgG anti-Hp Ab increased in the presence of infection and could be used as a marker [14]. The mean serum IL-17A titer was higher in the HPP group compared to the control group with a big difference among HPP and control (Table V). These results agreement with other study [15] that showed increase IL-17 in HPP patients. Interleukin-17A plays a dual role in *Hp* infection as it exerts an anti-inflammatory effects on *Hp*-induced gastritis through suppression of Th1 differentiation in the animal model on the one hand [16]. On the other hand, it induces the release of IL-8, which attracts inflammatory-promoting neutrophils [17]. These finding imply results that IL-17A may take play an important role in causing of *Hp*-related gastritis and subsequent gastric ulcer development. Similar results have been reported recently [18]. Cluster of differentiation 4 (CD4) plays an important vital function in the body's immune system and is present in some cells of immune system like T cells, macrophages and monocytes [19]. Differentiation of cluster 4 T cells they were known as helper cells, possibly because of their ability to activate the body's response to infection [20]. Therefore, a lower CD4 count among *H. pylori* infected patients indicates a decrease in the T-cell-mediated immune system [21]. Infection with *Helicobacter pylori* produce serious localized stomach inflammatory disease. For example, an excess of CD4 T lymphocytes in stomach lamina propria (LP) of *H. pylori* patients could play a role in causing of the disease [19]. The frequency of CD4 T cells in the LP of the stomach with a memory the phenotype and polarization are increased to Th1/Th17 phenotypes during *H. pylori* infection, but these T cells do not react to this bacterium [1]. CD4 T cells account for more than fifty percent of the total LP population; T cells are essential for both intestinal homeostasis and antimicrobial protection [22]. CD4 T cells from the intestinal lamina propria take part a crucial vital function in maintenance of the intestinal homeostasis and immune reactions of the gut microbiota [23]. However, not much is known about whether the age associated to intestinal immune dysfunction contributes [22]. The concentrations obtained during this study were indicated a significant increase in *H. pylori*-infected individuals (Table VI) (4.23 ± 0.41 ng/ml) than in healthy individuals (control) (1.93 ± 0.22 ng/ml). There was no significant difference (P> 0.05) among males (2.57 ± 0.29 ng/ml) and female (4.13 ± 0.86 ng/ml) for people infected with H. pylori (Table 6). This is in agreement with Bagheri et al. [5] who state that *H. pylori* colonization causes an increase in CD4 T cells and this proves it there was a significant (P < 0.05) increase in blood level of CD4 in *H. pylori* patients. Increased number of CD4 T helper cells in response to pylori infection takes part a crucial role in the growth of peptic ulcer illness. Another proposed theory is that maintenance of *H. pylori* infection requires safety mucosal cell immunity, loss of CD4 T cell in the gastric mucosa will prevent persistent infection with H. pylori. Therefore, a similar drop in *H. pylori* proliferation with CD4 T cell counts is nevertheless consistent with this theory. There is no indication that T-cell immunity may lead to impairment in *H. pylori* infection loss. CD4 T cells it have been demonstrated increase gastritis caused by *H. pylori*, but, a low bacterial load has been linked to gastritis and *H. pylori* pro-inflammatory profiles are related to decreased seroprevalence of *H. pylori*. Although the polarized Th1 and Th17 T-cell populations are critical in H. pylori infection, infection is regulated by regulatory T cells able to overcoming this immunity caused by T cells [24]. In Table VI we can see that the mean MIF for people with H. pylori high concentrated compared to control (75.23 ± 1.88) and (65.11 ± 2.25) respectively, and there were also no statistically significant differences between genders (71.14 ± 2.13 ng/mL) in males and (71.72 ±2.21 ng/mL) in females for people, infected with *H. pylori*, and it is compatible with Yoon et al. [25], who mentioned that there is nothing to be mentioned variation in MIF level by age or gender. Migration Inhibitory Factor (MIF) is an inflammatory cytokine that causes carcinogenesis of many types of cancer [26]. It has been increasingly implicated in the development of cancer and progress by promoting the survival of cancer

cells and immunosuppression of vacuities [27]. Human tissue samples were used to examine the link among *H. pylori* and MIF clinically and in vitro. Overexpression of MIF has been reported by T cells, epithelial cells, and macrophages linked with *Helicobacter pylori* infection in stomach mucosa [28]. According to in vitro cell culture studies, H. pylori directly induced MIF released by cag pathogenic island (cag PAI) expression, which resulted in an infectious cell spread [29]. The effect was blocked by an anti-MIF antibody, which suggesting MIF acts as a mediator in H. pylori-induced tumor genesis. The progressive elevation of MIF levels in the epithelium and serum of *H. pylori* was linked by intestinal metaplasia, gastritis and stomach cancer, what suggested that MIF could be used as a biomarker for stomach cancer. *H. pylori* and MIF have a significant relationships which was confirmed by lower MIF rates thereafter germ stomach resection [1]. According other clinical trial serum level of MIF for patients It has outperformed carcinoembryonic antigen (CEA) in terms of diagnostic value, and when paired with CEA, it is linked to a 5-year survival rate [30]. We concluded that infection with *H. pylori* secrete MIF induced epidermal growth factor phosphorylation of receptors (EGFR). However, another report found that after infection with *H. pylori*, MIF secretion and expression did not increase in a direct manner, although the expression and secretion of IL-8 were controlled [25]. There was not big difference in the level of MIF present. According to it, the current search relies solely on the case of *H. pylori*. However, consideration of both pathogenesis and infection was found to be significant in the positive *H. pylori* group, and MIF levels in subgroup were markedly higher than the control. On the other hand, MIF levels did not differ significantly among abnormal growth, control, and infection in *H. pylori*-negative group. These results indicated that MIF controls a critical change in *H. pylori* gastric tissue from dysplasia to infection or possibly cancer [25]. Nuclear factor kappa B (NF-kB) is the short name for the activated B cell nuclear factor kappa light chain enhancer. It's not a singular protein, but, small families of inducible transcription factors that take part an important act in nearly every mammalian cell. It regulate cytokine production, cell survival, DNA transcription as well as other critical cell activities take part critical role in controlling the immunological response infection [31]. Nuclear factor kappa B also controls other critical cell activities, particularly cellular growth and apoptotic responses for inflammation. Nuclear factor kappa B the main role of the immune system is to control programmed cell death [32]. Whether transcription the agent leads to anti-apoptotic or pro-apoptotic the response depends on the cell type and stimuli. Although NF-κB inhibits apoptosis in B cells predominantly promote B cell activation, their effect on T cells is variable and depends on the type of stimuli [31]. In our study found that serum concentration of *H. pylori* infection was at a high level and this indicates a significant difference (8.15 ± 0.58 ng/mL) ($P < 0.05$) compared with healthy people. On the other hand, our results showed that there is no significance difference ($P > 0.05$) in serum NF-KB concentration among males (8.41 ± 0.72 ng/ml) and females (7.92 ± 0.87) (Table VI). These results were similar to Bagheri et al.[1], who stated that H. pylori is induced the activation of NF-kB that regulates transcription of oncogenes and mediates hyper proliferation in gastric epithelial cells. Our results prove that there is significant difference ($P < 0.05$) compared to healthy individuals and no significant difference among male and females. H. pylori infection of gastric epithelial cells leads to the secretion of pro-inflammatory substance cytokines such as IL8 (IL8), whose transcription is regulated by NF-*κB* [33]. In this study, it was found that the relationship between immune markers and smoking did not show significant differences ($P > 0.05$) in blood level of male smokers in terms of MIF with *H. pylori* (73.13 ± 2.15 ng/ml) compared to non-smokers male with H. pylori, similarly, the serum concentration of male smokers relative to CD4 with *H. pylori* (2.81 ± 0.39 ng/ml) compared to (2.53 ± 0.36 ng/ml) in non-smokers H. pylori infected males ($P > 0.05$), but, significantly ($p < 0.05$) the concentration of NF-kB in serum of male smokers infected with H. pylori (9.43 ± 0.95 ng/ml) compared to non-smokers H. pylori infected males (4.96 ± 1.41 ng/ml). This indicates a clear relationship between smoking and NF-kB (Table VI). Widespread activation of the nuclear factor kappa signaling pathway acceptable in smoking-related diseases and this pathway take part a crucial role in inflammation. The tumor necrosis signaling mechanism and the interleukin-1 signaling receptor are two signaling pathways that activate NF-kB [34]. Table VII showed the presence of a negative relationship between serum concentration of MIF and NF-kB in patients with *H. pylori* ($r = -0.14$). Macrophage migration inhibitory factor is a cytokine that describes a functional class of protein mediators regularly produced to influence the activation and differentiation of the immune response. Once these mediators are released, and they usually act in an autocrine or the paracrine manner and this leads to activation of the immune response of the innate (dendritic cells, monocytes/macrophages) or adaptive (T and B cell) types [35]. The nuclear factor kappa proteins forms eukaryotic transcription factors belonging to a structurally related family, participates in the regulation of a wide range of normal cellular and organ processes, including immunity and inflammatory responses, generated processes, cell proliferation and programmed cell death. This

group of transcription factors is also continuously active in some diseases, including cancer, arthritis, chronic infections, asthma, neurodegenerative diseases and heart disease [36]. The results of this study it was revealed that there is an inverse relationship between MIF and NF-kB, but this relationship remains unconfirmed by other research to date. There is also a positive association between serum CD4+ and NF-kB concentrations in patients infected with H. pylori (r =0.035) (Table VII). This study is consistent with Bourges et al. [37], where NF-kB signals in CD4 T cells resulted in a super enhancer composition at the level of the locus of the immune disease that leads to the expression of a major inhibitor of NF-κB, thus reducing inflammatory responses.

CONCLUSIONS

Both humoral and cellular immune response plays an important role in patients with *Helicobacter pylori*. The nuclear factor kappa B is considered a risk factor in smoking patients, infected with *Helicobacter Pylori* can be considered as an early diagnosis of stomach cancer.

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ORIGINAL ARTICLE

THE BASIS FOR PROVIDING QUALITY MEDICAL SERVICES AT THE STAGE OF REHABILITATION TREATMENT FOR PATIENTS WITH ASTHMA

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ABSTRACT

The aim: To analyze the quality of medical services provided to asthma patients as the stage of rehabilitation treatment and their legal support.

Materials and methods: A total 237 patients with asthma were examined on the basis of the SDC "Rehabilitation" of the Ministry of Health of Ukraine in Uzhhorod which has an accreditation. All patients were divided into three groups, depending on the type of rehabilitation treatment. The quality of the provision of medical services in rehabilitation in the treatment of asthma patients was evaluated by the percentage of positive clinical effect.

Results: The quality of medical services provided in 237 patients with asthma after the rehabilitation treatment was different in percentages of positive clinical effect in different treatment complexes. In the first complex it amounted to 56.2%, in the complex two – 55.5%. These two monotherapy complexes proved to be ineffective rehabilitation services. Highly specialized for each phenotype of asthma rehabilitation service was of high quality and established in the third treatment complex 88.9% and for each asthma phenotype ranged from 87.3% to 93,4%.

Conclusions: For the provision of quality rehabilitation services for asthma patients the existing regulatory acts are not enough, it is necessary to rely on international recommendations to specify the provision of differentiated treatment for different disease phenotypes.

KEY WORDS: standards of medical services, differentiated treatment, asthma phenotype, percentage of positive clinical effect

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INTRODUCTION

The history of health law stretches back more than 300 years, when medical practice fist became regulated and matters of medical expertise began to be used in court proceedings. As early as 1767, an English court ruled in favor of a patient who had undergone experimental therapy without the appropriate consent [1]. This precedent became the basis of the American law on malpractice. Cyril H. Wecht (2005) estimates that in Europe the development of the medical-legal system began in Germany in 1553 with the publication of the Caroline Code [2]. Health care legislation has since been developed and supplemented by new regulatory documents, but doctors' concerns about the court case are still emerging. More than 93% of surveyed doctors of various specialties reported on the practice of «defense medicine» and their fear of court [3]. However, the fear of litigation in some patients was disproportionate to malpractice litigation [4, 5].

In 1977, at the IV International Medico-Legal Conference in Prague, a proposal was made by scientists – physicians and lawyers to separate the legal rules governing medicine, health care into an independent area of law – medical law. The source of medical law is: 1) Constitution, laws of the country; 2) international regulatory acts; 3) by-laws; 4) legal custom;

5) decisions of the Constitutional Court and the European Court of Human Rights.

Thus, Article 3 of the Constitution of Ukraine states that the highest social value in a state is a person, his life and health. According to Article 49, everyone has the right to health, medical care and health insurance [6]. In the Constitution of Ukraine, the terms «medical care» and «medical care» are mentioned, but «medical services» are not mentioned.

Four approaches are justified in the scientific literature regarding the legal nature of health care relations and medical services. The first group of scientists see the provision of medical services as subject to civil law regulation. The second group relates to the provision of medical services in the field of administrative law. A third group of scholars views medical law as a subset of social security law. Whereas, the fourth approach is based on the recognition of the right to health care by a complex branch of law (legislation). Medical (medical law) or the right to health care is recognized as a system

of normative acts (norms) governing public relations in the field of medical activity [7].

The legal regulation of the provision of medical services was studied by domestic scientists Hertz A., Blyshchuk T., Abramovich N., but all of them give different definitions to the concept of "medical service" [8-10]. Therefore, the definition of the concept of medical service in the Law of Ukraine became necessary [11].

In the age of the Internet and social networks, disputes over the degree of responsibility of doctors for mistakes in their activity do not cease in society. There is still no clear definition of the term – a medical mistake. But the responsibility for its assumption lies with the doctors of all countries [3]. According to Antonova S.V. Errors in medical practice are quite common in the world. In the United Kingdom, errors in the work of health care staff cause about 70,000 deaths each year, with almost 100,000 deaths in Germany and the United States [12]. The situation in Ukraine is not better, although there are no statistics on this issue, which also needs reforming [13]. According to Mostovenko O. (2018), a medical (medical) error can occur for objective and subjective reasons. Objective reasons arise in circumstances beyond the control of the individual who treated the particular patient [14]. Maykut H.V. find that there is ambiguity in the treatment of erroneous actions by healthcare professionals, which impedes the provision of quality care and medical services, and diminishes the guarantees for the protection of the rights of both patients and healthcare professionals [15].

In most countries, consider Jancak Y. and Ryzhkova E., the main mechanisms that ensure the availability and proper quality of care are the regulatory framework of the industry that regulates the provision, management and control of care; industry standardization and expertise [16,17].

Concerning the provision of the rights of patients in Ukraine, then the standards and mechanism of ensuring the rights of patients were singled, out from a whole number of international legal acts. In addition, patients have the right to claim their rights in the European Court of Human Rights [18].

Apart from the national law, there is also an international law concerning physician. The World Health Organization and the World Association of medical Doctors brought the following declaration: Declaration on Promotion of Patients' Rights, the Revised Lisbon Declaration on Patients' Rights, the Revised Helsinki Declaration on Biomedical Research Involving Human Subjects and the Council of Europe's Convention on Human Rights and Biomedicine [19]. Most health care international acts are ratified by Ukraine and their provisions are implemented in the legislation [20]. Simultaneously, there is a row of the problems, which hinder the Ukrainian health care development and place obstacles in the way of European integration. All this needs modernization of state administration system in the health care sphere of Ukraine [20-22].

THE AIM

The aim of the work is to analyze the quality of medical services provided to asthma patients at the stage of rehabilitation treatment and their legal support.

MATERIALS AND METHODS

A total 237 patient with asthma were examined on the basis of the SDC "Rehabilitation" of the Ministry of Health of Ukraine in Uzhhorod which has an accreditation. All patients carefully collected allergic history, anamnesis of life, and disease. The study includes assessment of resting anthropometric data, physical activity habits, blood pressure, structure and quality of nutrition, family and socioeconomic data. All patients were divided into three groups, depending on the type of rehabilitation treatment. Complex Treatment (CT)-I intended 85 patients who were administered dosed aerosol inhaler (DAI) used for basic drug therapy 15 minutes before session halo aerosol therapy (HAT). CT-II – 74 patients are selected by inhalation of ventolin nebulizer for 30 minutes a session HAT. CT-III included 78 patients who were prescribed differential rehabilitation treatment depending on the asthma phenotype. Each complex consisted of six asthma groups according to the disease phenotype. The first (1)-group consisted 43 patients with atopic asthma (AA) – 18, 12, 13 patients in CT- I, II, III, respectively. The second (2)-groups included 35 patients with infection asthma (AI) – CT-I (13); CT-II (10); CT-III (17) patients. The third (3)-group consisted of 38 patients with late-onset asthma (ALO) – in CT-I it was 12 patients; in CT-II – 11 patients, and in CT-III – 15 patients. The fourth (4)-group included of 41 patients with asthma with concomitant obesity (AO) – 17 patients in CT-I; 13 patients in CT-II and 11 patients in CT-III. The fifth (5)-group – 43 patients with asthma-COPD-overlap (AXO) – in CT-I – 15; in CT-II – 13; in CT-III – 15 patients. The six (6)-groups consisted of 37 patients with severe asthma (AS) in CT-I; II; III – 10; 15; 12 patients, respectively. All patients were offered a questionnaire on criteria for quality of health services. The effectiveness of the provision of medical services in rehabilitation in the treatment of asthma patients was evaluated by the percentage of positive clinical effect (% PCE).

A survey of 237 asthma patients was conducted according to the Helsinki Declaration on Biometric Research Involving Human Subject.

RESULTS

Multiformity (heterogeneity) of asthma was revealed during a comprehensive examination of patients and analysis of the clinical course of the disease. There were 6 phenotypes of asthma identified by some similarity of laboratory-diagnostic parameters, the debut of the development of the disease, the presence of one or another comorbid pathology, controllability of clinical course and features of response to therapy.

1. The first (1)-group consisted 43 patients with atopic asthma (AA) – 18, 12, 13 patients in CT-I, II, III, respectively. Characteristic of this asthma phenotype was the presence of comorbid allergic rhinitis, the debut of the disease was observed in childhood, in the peripheral blood was a high level of eosinophils, histamine, total titer of immunoglobulin E (IgE). In half of the patients in this group the course of asthma was uncontrolled with frequent administration of high-speed drugs.
2. The second (2)-groups included 35 patients with infection asthma (AI) – CT-I (13); CT-II (10); CT-III (17) patients. The debut of this asthma phenotype developed in middle- aged patients after a cold, as a complication of pneumonia. Asthma exacerbation occurred at a frequency of 1.8 times a year, most often in the autumn and winter period against a cold. It is also characterized by generalized bronchial obstruction. The type of inflammation in the respiratory tract was dominated by the neutrophil type. Immunological examination of the blood indicated an increased titer to staphylococcal, streptococcal, pneumococcal, pulmonary, bronchial, adrenal antibodies and the level of circulating immunocomplexes. One third of patients in this group were characterized by uncontrolled asthma with frequent use of high- speed drugs.
3. The third (3)-group consisted of 38 patients with late-onset asthma (ALO) – in CT-I it was 12 patients; in CT-II – 11 patients, and in CT-III – 15 patients. By gender, this phenotype includes women with concomitant cardiovascular disease. Asthma debut develops in adulthood, especially in menopause or after gynecological surgery. The course of asthma in such patients is uncontrolled, severe in nature with glucocorticosteroid resistance.
4. The fourth (4)-group included of 41 patients with asthma with concomitant obesity (AO) – 17 patients in CT-I; 13 patients in CT-II and 11 patients in CT-III. These groups included patients with body mass index (BMI) ≥30kg/m^2. By cluster analysis asthma with obesity is characteristic of older women against the background of climacteric and gynecological diseases with hormonal dysfunction of the ovaries. The type inflammation in the respiratory tract was more often non-eosynophilic. Frequent concomitant disease in patients with asthma and obesity was arterial hypertension. Asthma in obesity has a pronounced respiratory symptomatology, although there is a slight obstruction and inflammation in the respiratory tract. This phenotype was characterized by impaired external respiration function of mixed type and the need for three or more medications for asthma control, one of which was inhalation glucocorticosteroids.
5. The fifth (5)-group – 43 patients with asthma-COPD-overlap (AXO) – in CT-I – 15; in CT-II – 13; in CT-III – 15 patients. This phenotype is characterized by a comorbid course of asthma and COPD. Most patients consider the cause of the disease to be runny, contact with chemicals and smoking. Exacerbations of asthma were more pronounced and frequent with the autumn-winter seasonality and meteotropic to wet, windy, cold weather. Inflammation in the bronchial tree was more often non-eosinophilic. In most patients in this group, asthma was complicated by pulmonary insufficiency and emphysema. In these patients were reduced all speed indicators of the function of external respiration. Of the drugs, this group of patients frequently used M-choline blockers.
6. The sixth (6)-groups consisted of 37 patients with severe asthma (AS) in CT-I; II; III-10; 15; 12 patients, respectively. This asthma phenotype is characterized by a severe uncontrolled course with frequent exacerbations (3-4 times a year). These patients receive high doses of inhaled glucocorticosteroids or basic systemic steroid therapy. External respiration rates are significantly reduced despite receiving high doses of glucocorticosteroids. All of these patients have complications of asthma – pulmonary insufficiency and emphysema.

Rehabilitation treatment for all patients was performed in accordance with the Law of Ukraine «On Health» [11], namely Article 33 on providing medical care, Articles 35-5 on medical rehabilitation and Articles 14-1 of the same Law on the system of standards. Treatment was carried out according to the standards of medical care: on the basis of clinical protocols, namely Order of the Ministry of Health of Ukraine №868 on treatment of bronchial asthma and №56 on sanatorium-spa treatment, according to the tables of logistical equipment and medical form – the list of registered in Ukraine medication. All patients according to clinical protocols were on basic medical therapy. The basis of rehabilita-

tion treatment at this medical facility is halo aerosol therapy (HAT) – an artificial analogue of speleotherapy. To increase the effectiveness of HAT, patients were assigned to the session either DAI or nebulizer inhalation with ventolin, depending on CT-I or CT-II. CT-III included differentiated rehabilitation treatment that took into account the peculiarities of different asthma phenotypes. In this complex, medications and additional means of rehabilitation therapy, such as: balneotherapy, diet therapy, therapeutic physical training, massage, apparatus physiotherapy (laser therapy), were required for each asthma phenotypeAs for the specificity of treatment of asthma of different phenotypes, we did not find it in Ukrainian clinical protocols. In these, asthma is considered as a mono-disease and treatment standards are the same for all phenotypes. Therefore, in our work we were guided by the recommendations of the International Expert Group on Diagnosis and Treatment of Asthma (GINA), which set out cluster characteristics of different asthma phenotypes their treatment characteristics [23].

At the end of the rehab course,% of PCE were calculated to determine the quality of health care services for the 7 major asthma symptoms for both CT as a whole and for each asthma phenotype in the middle of each CT. Thus, the total% of PCE in CT-I was 56.2% and in CT-II – 55.5%. Monotherapy CT-I and ST-II proved to be ineffective. It was most ineffective in the middle of CT-I for the ALO phenotype (46.6%); AO (46.5%); AS (40.5%). In mid-CT-II, rehabilitation treatment proved to be ineffective even when using the latest technologies (nebulizer inhalation) and especially for ALO phenotypes (49.8%); AXO (44.5%); AS (41.1%). Unexpectedly, there was a rise in the% PCE of the asthma phenotype with obesity from 46.5% in CT-I to 75.9% in CT-II. The overall% of PCE in CT-III was 88.9% and was almost the same for each phenotype, ranging from 87.3% to 93.4%.

Also, at the end of the rehabilitation course, all 237 patients completed the questionnaire with the main 9 criteria for quality of medical services. The following results were obtained:

1) the availability of medical services was 70.3% (67), which indicates problems with referral to a rehabilitation institution; 2) adequacy of medical services – 95.8% (207); 3) the continuity and continuity in the provision of rehabilitation services was only 59.9% (142), indicating a somewhat delayed provision of rehabilitation care after inpatient treatment; 4) the efficiency and effectiveness of medical services were 77.2% (183); 5) the focus of medical services on the patient was 94.5% (224); 6) safety of the treatment process – 91, 6% (217); 7) the timeliness of the provision of rehabilitation treatment was recognized by 60.3% (143); 8) the absence (minimization) of medical errors according to patients was at the level of 92.4% (219); 9) the scientific and technical level of medical care was 83.5% (198). Indicators did not differ significantly in CT, the lowest in the phenotypes AS, ALO, AO.

As we can see, the doctor and the patient evaluate the quality of the medical service somewhat differently. The patient evaluates from the point of view of his health after the treatment and the doctor. Doctors – as a result of treatment.

As we can see, the doctor and the patient evaluate the quality of the medical service somewhat differently. The patient evaluates from the point of view of his health after the treatment and the doctor. Doctors – as a result of treatment.

DISCUSSION

In a specific, highly specialized example, we sought to identify gaps in medical law. In the study of the legal mechanisms for ensuring the quality of the provision of rehabilitation services, we adhered to the whole complex of currently existing legal acts in the field of health care: standards of medical care, clinical protocols, tables of logistical documentation and medical form [16,17]. But they did not influence the quality of the provided rehabilitation services. The recommendations of the international expert group GINA allowed for differentiated rehabilitation treatment of asthma patients depending on the disease phenotype [23]. It is precisely this document and our understanding that asthma is a heterogeneous disease that has allowed us to raise the quality of rehabilitation services to a higher level. In addition, an unpleasant surprise was the Internet announcement that the protocols of sanatorium treatment Order of the Ministry of Health №56 was invalidated. It was through this Order that we were able to provide quality rehabilitation services. Because, in these protocols were given methods and methods of rehabilitation treatment, namely physical methods of influence on the body: apparatus physiotherapy, massage, therapeutic physical culture, balneotherapy. We believe that rehabilitation care, as an independent healthcare industry, should be guided by our own clinical protocols. To determine the criteria for quality of health services, we conducted a survey among all 237 patients [16]. The doctor used an indicator of a positive clinical effect. These two indicators differed due to the different approach to the problem of doctor and patient [7]. In our research, we found that the quality of health care delivery directly depends on the latest views on the pathogenesis, disease phenotype, and differentiated approach to its treatment, which is consistent with GINA data [23]. Medicine is the most complex form of human activity, requiring deep special

knowledge, practical skills, high mental qualities. The doctor is mistaken for dealing with the most complex object of nature – the human body.

And this may be a more ethical issue than a legal one. Objective causes of medical error – lack of scientific knowledge of disease science, outdated methods of exposure, subjective – lack of experience with a particular doctor. The reasons may also be related to the person of the doctor himself, who agrees with the position of Buletsa S. [7, p. 356]. In Ukraine, without a clear definition, «medical error» is governed solely by the norms of morality. Ethical principles originate in the oath of Hippocrates as defined in the oath of the Ukrainian physician. It is Hippocrates who says «treat not disease but sick», which is in line with the latest methods of treatment, which are adapted to the human genetic profile and the creation of «personalized medicine» [24]. Gary E. Marchant believes that the focus on the needs of the individual requires a fundamental transformation from a one-size-fits-all approach to the past to what may be called "personalized medicine".

We agree with the opinion of Chesnokova A.E (2016) that physicians should be confident and trusted in their ability to seek advice from the law and to better distinguish its intersection with ethics. Doctors must not only obey the law, but also rely on it for the benefit of their patients. The interaction of physicians with the law cannot be limited to health care reform in its entirety, but must be fundamental to the achievement of clinical goals and patient relationships [25].

CONCLUSIONS

For the provision of quality rehabilitation services for asthma patients the existing regulatory acts are not enough, it is necessary to rely on internasional recommendations to specify of differentiated treatment for different disease phenotypes.

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ORIGINAL ARTICLE

THE STRUCTURAL AND FUNCTIONAL STATE OF THE PANCREAS AND LIVER IN CHRONIC PANCREATITIS IN COMBINATION WITH CHRONIC VIRAL HEPATITIS C DEPENDING ON THE INDEX OF THE SURVEY ACCORDING TO THE INTERNATIONAL CAGE QUESTIONNAIRE

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ABSTRACT

The aim: To conduct a comparative analysis of parameters of the structural and functional state of the liver and pancreas in patients with chronic pancreatitis in comorbidity with treated etiologically chronic viral hepatitis C, depending on the results of testing according to the international CAGE questionnaire.

Materials and methods: 100 ambulatory patients with CP with concomitant HCV, treated etiotropically, were examined. All patients were examined according to generally accepted algorithms. To establish the role of alcohol on the formation of CP and the condition of patients with treated HCV, latent craving for alcohol was verified using the international CAGE questionnaire. The study of the density of the liver parenchyma and the liver of the patients was carried out not only according to the ultrasound data in the B-mode, but also with the simultaneous measurement of the shear wave elastography (SWE) method on the Ultima PA scanning ultrasound device with the further determination of the median of the parameters, which characterizes the stiffness in kilopascals (kPa). Determination of the presence and depth of pancreatic exocrine insufficiency (PEI) was carried out by the content of fecal elastase-1 (FE-1), which was determined by the enzyme immunoassay method.

Results: Screening-testing of patients with CP on the background of etiotropically treated HCV using the CAGE scale made it possible to state that 65.0% of such patients had a hidden craving for alcohol, and 21.0% of this cohort were women, which needs to be taken into account in the management of such patients. It has been proven that in the group of patients with CAGE≥2.0, the level of functional and structural changes in the liver and liver was significantly more severe (according to the deepening of the PEI, a decrease in fecal α-elastase by 13.01%, according to an increase in the total index of the coprogram by 15.11% and the total US-indicator of the pancreas structure by 28.06%, and the total US-indicator of the liver structure – by 40.68% ($p<0.05$) and corresponded to the average degree of severity of the process in panceas according to the criteria of the Marseille-Cambridge classification, and in the group with CAGE<2.0 – only a mild degree.

Conclusions: The negative effect of the factor of increased alcohol use according to CAGE was proven by increasing the density of the echostructure of the liver by 5.73% ($p<0.05$), and the liver by 5.16% ($p<0.05$). According to the results of the correlation analysis of the dependence of the structural state of the liver and PW of the studied patients on the value of the CAGE scale, which was $R=0.713$, $p<0.05$, and $R=0.686$, $p<0.05$, respectively, it was established that there is a strong direct dependence of the structural state of the liver and PW from the value of the CAGE questionnaire, which proved an independent, reliably significant role of alcohol consumption for patients with a comorbid course of CP and HCV.

KEY WORDS: chronic pancreatitis, chronic viral hepatitis C, latent craving for alcohol according to the CAGE questionnaire, shear wave elastometry, exocrine pancreatic insufficiency

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INTRODUCTION

Chronic pancreatitis (CP) is a polyetiological disease. According to Babinets L.S. et al., 2007, 2021, in the analysis of significant etiological factors for the formation of the disease among 218 patients with CP, established the following figures of influence of these factors: alcoholic – 8.26%, hepatobiliary – 44.50%, gastroduodenogenic – 51 .37%, infectious – 56.88%, ischemic – 20.18%, allergic – 8.33%, post-traumatic – 16.67%, after acute pancreatitis – 7.80% [1-5]. The majority of patients had a mixed genesis of CP, so the factors were often layered [6-9]. This state of affairs drew attention to the importance of infectious and hepatobiliary factors [10-14]. That is why the comorbidity of CP and chronic viral hepatitis C (HCV) after etiotropic treatment, which is very common in clinical practice, attracted attention and motivated the conduct of this study [15-17].

It has been established that in 35-56% of patients, diseases of the hepatobiliary system are considered to be a factor causing the formation or exacerbation of CP, with a decrease in the share of pancreatitis of alcoholic etiology, as it was previously believed [18, 19]. However, the role of the alcohol factor and its consideration in forming treatment tactics for CP and comorbidity with HCV also needs to be clarified, because it is known that excessive alcohol consumption and smoking increase the risk of developing pancreatitis by 8-17 times. Alcohol also affects the progression of CP and HCV, as well as complications of both nosologies [20, 21]. To identify the influence of the alcoholic factor on the formation of CP and the condition of patients with treated HCV, there is a simple, universally recognized tool – the determination of hidden craving for alcohol using the international CAGE questionnaire.

It is a proven fact that almost 40% of patients with CP develop exocrine organ failure, and 50% develop diabetes mellitus (DM), in particular, type 2 [22, 23]. Detection of exocrine pancreatic insufficiency (EPI) is necessary to determine the severity of CP according to the modern classification, and the determination of fecal elastase-1 (FE-1) is the best method in terms of simplicity and sensitivity for determining the exocrine function of the pancreas. In order to study the density of the liver parenchyma and pancreas, routine ultrasound in B-mode and measurements by shear wave elastography (SWE) were performed on patients [24-31]. All of the above research options were considered appropriate to be used to determine the effect of alcohol consumption on the structural and functional state of the pancreas in CP on the background of (treated) HCV.

THE AIM

The aim was to conduct a comparative analysis of parameters of the structural and functional state of the liver and pancreas in patients with chronic pancreatitis in comorbidity with treated etiologically chronic viral hepatitis C, depending on the results of testing according to the international CAGE questionnaire.

MATERIALS AND METHODS

100 ambulatory patients with CP with concomitant HCV, treated etiotropically, were examined. All patients were examined according to generally accepted algorithms. The control group consisted of 25 practically healthy people, comparable in age and gender.

The criteria for inclusion in the study group of patients with CP in combination with HCV were CP patients who were diagnosed with HCV in connection with an exacerbation or as an incidental finding. The period after diagnosed and treated HCV before the examination was on average (2.35±0.61) years.

Exclusion criteria: diabetes mellitus, hepatitis, except for HCV, and cirrhosis in the acute phase, including viral etiology, gallstone disease with existing calculus, acute and chronic diseases of vital organs and systems, oncological diseases, refusal of the patient to participate in the study.

The diagnosis of CP was verified according to the clinical and statistical classification proposed by the "Research Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine" in 2003, as well as according to the Order of the Ministry of Health of Ukraine dated September 10, 2014 No. 638. The diagnosis of HCV was established according to the criteria of the evidence-based Clinical Guideline "Virus hepatitis C", created by the working group under the order of the Ministry of Health of Ukraine dated 18.08.2020 No. 1908, based on WHO recommendations "Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection" (2018) and "EASL Recommendations on Treatment of Hepatitis C" (2020). To establish the role of alcohol on the formation of CP and the condition of patients with treated HCV, latent craving for alcohol was verified using the CAGE international questionnaire, which consists of four questions: a) Have you ever felt the need to reduce the consumption of alcoholic beverages?; b) does it annoy you when others criticize your abuse of alcoholic beverages?; c) do you feel guilty after drinking alcohol?; d) is it difficult for you to wake up the next day after drinking alcohol?

When analyzing the results of patient testing, each positive response was evaluated as one point. Obtaining two or more CAGE points was considered to be a significant hidden craving for alcohol, which affects the formation and clinical severity of CP and HCV.

Alcohol abuse was also detected in the presence of one of the signs described below (alcohol consumption despite the patient's knowledge that his constant or repeated social, domestic, physical, psychological, and professional problems are caused or aggravated by it; repeated use of alcohol in a situation where he can be life-threatening). It also influenced the ascertainment of the significance of the influence of the alcoholic factor and its consideration in the formation of a complex treatment program.

The assessment of the structural state of the liver and pancreas was carried out according to the ultrasound data of these organs, with the determination of the degree of severity of the process according to the parameters of the Marseille-Cambridge classification of CP, taking into account the following pathological signs as

one point: expansion of the Virsung duct more than 3 mm, intraductal echogenic formations (stones, calcifications); zones of reduced echogenicity with small (1-3 mm) inclusions (inflammatory tissue edema); hyperechoic inclusions (calcification of the gland); linear heavy inclusions (fibrosis); the uneven contour of the gland (fibrosis and atrophy of the gland); anechoic cavities (more than 5 mm in size) – the presence of pseudocysts.

During ultrasound of the liver, its size, contours (evenness, clarity), structure (homogeneity, echogenicity, presence of cysts, fibrosis, fatty hepatosis, the shape of the lower corner of the liver (sharp, rounded), the diameter of the portal vein were evaluated. The gallbladder was also examined, including its presence (absence), dimensions, wall thickness, presence of bends, concretions (their number and sizes), polyps, cholesterol; diameter of the common bile duct. The assessment was carried out by points, considering each pathological sign as one point.

The study of the density of the liver parenchyma and liver in patients was carried out not only according to the B-mode ultrasound data but also with the simultaneous measurement of fasting on the Ultima PA scanning ultrasound device ("Radmyr", Kharkiv, Ukraine) with a contact sensor of a convex format on frequencies of 2-5 MHz at a depth of 10-50 mm. The number of successful measurements had to be at least 10, with the further determination of the median, which characterizes the stiffness in kilopascals (kPa).

The determination of the presence and depth of EPI was carried out according to the "gold standard" of evaluation – by the content of fecal FE-1, a proteolytic enzyme of the pancreas, which was determined by the ELISA method using standard sets of the company BIOSERV ELASTASE 1-ELISA.

Incretory insufficiency of the pancreas was determined by the glucose content in fasting blood by the glucose oxidase method (normal – 4.44-5.55 mmol/l). The main criterion for the diagnosis and dynamics of diabetes was considered HbA1c (norm – 4-6% of the total amount of hemoglobin). The content of HbA1c was determined by ion exchange chromatography on a Humalyzer 2000 biochemical semiautomatic machine with running water using a kit for rapid determination of HbA1c; the data are compared with the results of determining the HbA1 standard. To establish insulin resistance, we used the HOMA-IR index (small model of homeostasis), proposed by D.R. Matthews and co-authors in 1985. The HOMA index is calculated by the formula:

HOMA= (fasting glucose (mmol/l)×fasting insulin (μIU/l))/22.5 (1)

The higher the HOMA-IR index, the lower the sensitivity to insulin and the higher the insulin resistance (the norm is an index greater than 2.7).

For the statistical processing of the research results, the variational statistical method of analysis was used, which was carried out on a personal computer Intel ® Celeron ® CPU 2.60 GHz using the Microsoft Excel 2007 spreadsheet application in Windows XP Professional (USA, 2010). The Fisher-Student variance statistics method was used to determine the arithmetic mean (M), root means square deviation (q), and error of the arithmetic mean (m). The analysis of the relationship between two features in the presence of a normal distribution of data was carried out according to the data of the Pearson correlation coefficient (r), in the case of a distribution different from the normal – the non-parametric Spearman rank correlation coefficient (R) was calculated. The correlation coefficient was evaluated according to the criteria generally accepted in statistics: $r<0.3$ – weak connection; 0.3-0.49 – moderate; 0.5-0.69 – significant; 0.7-0.89 – strong; >0.9 is very strong, close to a functional relationship [32].

RESULTS

In connection with comorbid liver damage, the analysis of the presence of an alcoholic factor in the anamnesis of the patients of the studied contingent was carefully considered. None of the patients was officially registered with a narcologist, but screening according to the CAGE scale showed that 65 patients (65.0 %) had a hidden craving for alcohol – in the group of comorbid CP with HCV, and there were 21 women in this cohort (21.0 %). The indicator on the CAGE scale was (3.09±0.18) points. The patients themselves did not consider this factor significant, but the international CAGE scale states the established indicators as indicating a significant urge to abuse alcohol.

It was considered expedient to analyze the functional and structural state of the liver and liver depending on the parameter of the CAGE scale, since the alcoholic factor is considered the most etiologically significant both for the formation of CP and for chronic hepatitis, regardless of other important factors.

Patients were divided into those with CAGE≤2.0 (n=35) and those with CAGE≥2.0 (n=65), with an average CAGE score of (3.09±0.18). In table I shows the data of a comparative analysis of the functional and structural state of the PW of patients with CP with concomitant HCV and the dependence on the CAGE parameter.

It was established that in the group of patients with a value of CAGE≥2.0, there was a deepening of the EPI due to a decrease in fecal α-elastase by 13.01%, an increase in the total index of coprogram by 15.11% and the total US index of the structure of the pancreas by 28.06%, and the total ultrasound index of the liver structure –

Table I. Comparative analysis of the functional and structural state of the pancreas of patients with CP with concomitant HCV and dependence on the CAGE questionnaire

Indicator of functional and structural state of the pancreas	Comparison group depending on the CAGE parameter		
	Control group (n=25)	Patients with CP and HCV (n=35) CAGE≤2,0	Patients with CP and HCV (n=65) CAGE≥2,0
α-elastase, μg/g	242.58±6.24	132.64±3.13*	115.39±1.98**
Blood glucose, mmol/l	4.70±0.10	5.83±0.29*	5.68±0.33*
HbA1c, %	4.55±0.11	5.88±0.19*	6.01±0.15*
HOMA index	1.47±0.08	2.44±0.10	2.59±0.09*
Total score of the coprogram, point	0.08±0.02	5.69±0.21*	6.55±0.13**
Total US-indicator of the pancreas structure	1.05±0.03	4.99±0.57*	6.39±0.35**
Total ultrasound index of the liver structure	0.07±0.01	2.63±0.11*	3.70 ± 0.23**

Note: 1. * - the probability of a difference in the indicators of patients with comorbidity of CP and HCV compared to those in the control group (p1-2<0.05);
2. ** - the probability of the difference in indicators of patients with comorbidity of CP and HCV with CAGE≥2.0 compared to those in the group with CAGE≤2.0 (p2-3<0.05).

Table II. Comparative analysis of the parameters of the liver and pancreas stiffness of patients with CP with concomitant HCV in groups according to the CAGE scale

Stiffness parameter, kPa	Comparison group depending on the CAGE parameter		
	Control group (n=25)	Patients with CP and HCV (n=35) CAGE≤2,0	Patients with CP and HCV (n=65) CAGE≥2,0
Liver stiffness index, kPa	4,85 ± 0,31	7,68 ± 0,18*	7,93 ± 0,11**
Pancreas stiffness index, kPa	4,71 ± 0,29	6,98 ± 0,16*	7,25 ± 0,09**

Note: 1. * - the probability of a difference in the indicators of patients with comorbidity of CP and HCV compared to those in the control group (p1-2<0.05);
2. ** - the probability of the difference in indicators of patients with comorbidity of CP and HCV with CAGE≥2.0 compared to those in the group with CAGE≤2.0 (p2-3<0.05).

by 40.68% (p<0.05). It was concluded that the group of patients with CAGE≥2.0 has the most profound structural changes of the liver and liver corresponding to the average degree of severity of the process, and in the group with CAGE<2.0 – a mild degree according to the criteria of the Marseille-Cambridge classification.

Thus, the assessment of latent craving for alcohol is extremely important, as it allows for identifying patients with a comorbid course of CP and HCV, who need a more significant effect to correct deeper damage to the structural and functional state of the liver and pancreas.

We also analyzed the parameters of liver stiffness and pancreas in groups of patients with CP in combination with HCV according to the CAGE scale (Table II).

A higher level of density of the echostructure of the liver of patients with CP in comorbidity with HCV was found in the group with CAGE<2.0 compared to such healthy people by 58.35%, and with CAGE≥2.0 – by 63.51%, which proved the negative influence of the amplification factor alcohol consumption according to CAGE increased liver density – by 5.16% (p<0.05). A similar pattern was established for the state of the echostructure of the pancreas: a higher level of density of the echostructure of the pancreas of patients with CP in comorbidity with HCV in the group with CAGE<2.0 compared to such healthy people was established by 48.20%, and with CAGE≥2.0 – by 53 .93%, which proved the negative effect of the factor of increased alcohol use according to CAGE on the increase in the density of the pancreas tissue – by 5.73% (p<0.05).

We also present the results of the correlation analysis of the dependence of the structural state of the liver and pancreas of the studied patients on the value of the CAGE scale, which were, respectively, R=0.713, p<0.05 (liver, Fig. 1) and R=0.686, p<0.05 (pancreas, Fig. 2). It was established that there is a strong direct dependence of the structural state of the liver and PW of the studied patients on the value of the CAGE scale, which motivates the formation of complex treatment of such patients to additionally include hepato- and pancreatotrophic drugs with a corrective effect on the alcohol factor to the generally accepted complex.

It was also established the presence of a strong direct correlation between the structural state of the liver and the PW of the studied patients with CP on the background of HCV (R=0.858; p<0.05) – fig. 3.

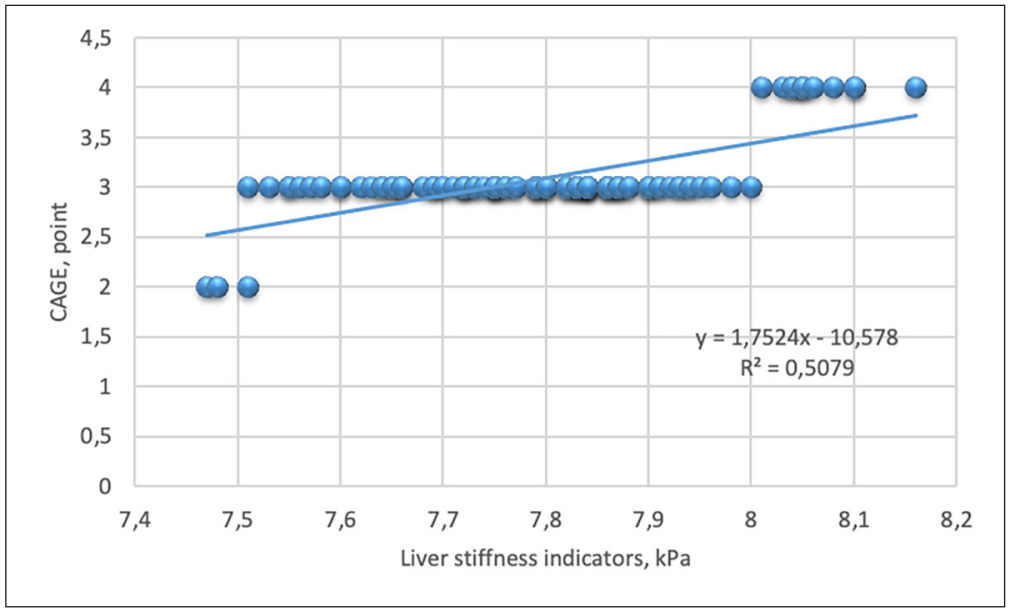

Fig. 1. Dependence of the structural state of the liver of patients with CP+HCV on the value of the CAGE questionnaire

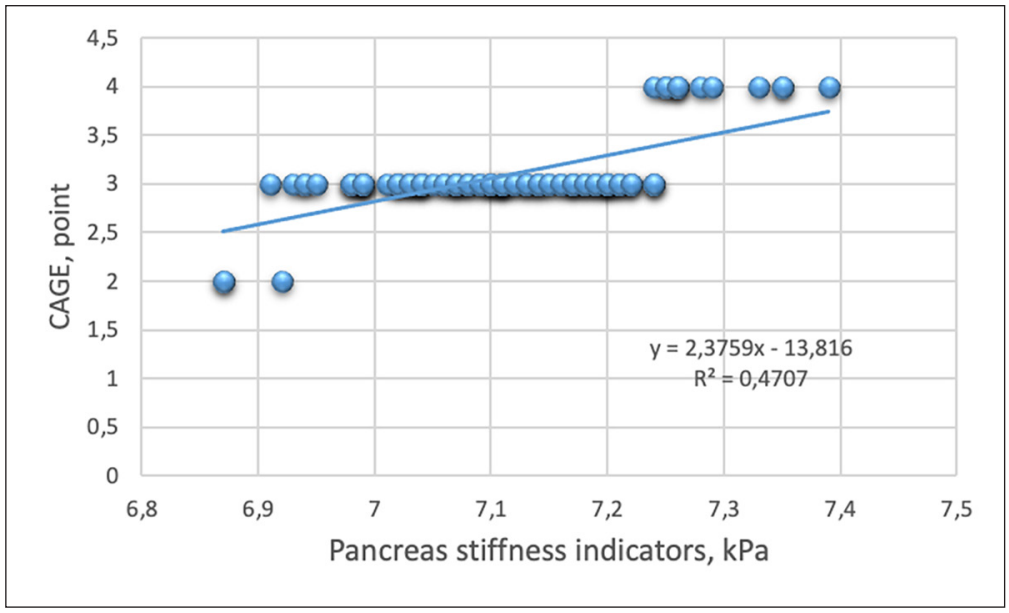

Fig. 2. Dependence of the structural state of the pancreas of patients with CP+HCV on the value of the CAGE questionnaire

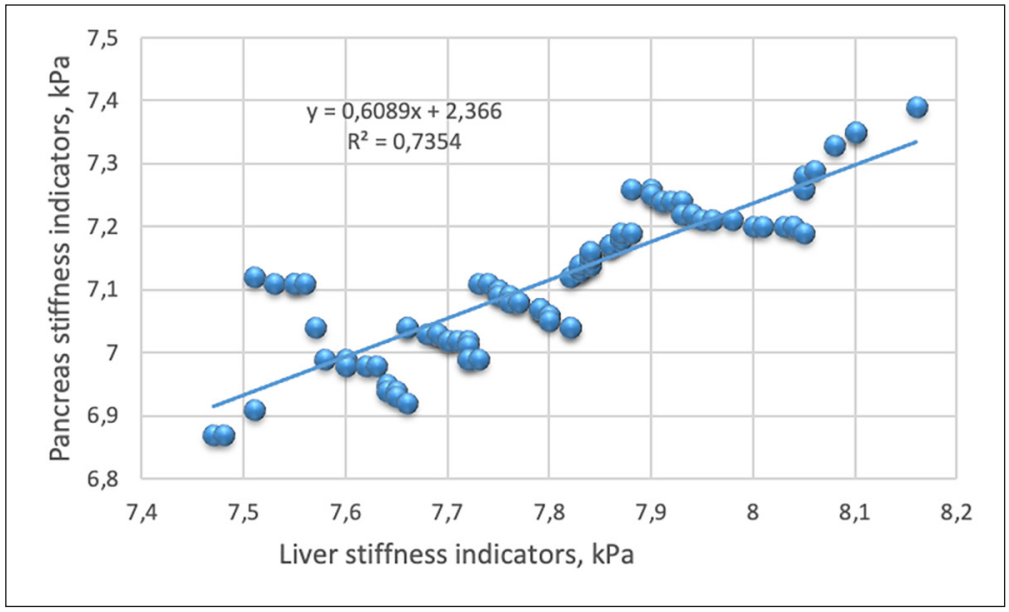

Fig. 3. – Interdependence of the structural state of the liver and the pancreas of patients with CP+HCV

This allows us to state the presence of interdependence of the state of the liver and pancreas in the comorbidity of CP and treated HCV and, of course, it motivated us to take into account the established fact in the future when forming a program of complex restorative treatment of patients with a combined course of CP and HCV.

DISCUSSION

Alcohol abuse is the leading etiological factor of CP, accounting for 60–70% of all CP (according to other data, 55–80%). Clinical signs of alcoholic pancreatitis usually appear at the age of 35–45 years. The disease is more often observed in men, although tolerance to alcohol is lower in women. The risk of developing CP increases logarithmically with increasing alcohol (ethanol) consumption, similarly, with an increase in the dose of ethanol, mortality from pancreatitis among patients who abuse alcohol also increases. 5–15% of patients who consume large doses of alcohol develop CP [33, 34]. Most patients consume more than 60–80 g/day, although it was not possible to establish a threshold dose, exceeding which would be accompanied by the development of CP, which indicates different individual sensitivity to alcohol and the possible role of other factors in the development of alcoholic CP. The interval between the beginning of systematic alcohol consumption and clinical manifestations is 12–18 years. A high-calorie, protein-rich diet with very high or very low-fat content, nicotine, and vitamin and micronutrient deficiency (copper, selenium) are discussed as possible cofactors that increase the toxic effect of ethanol [34, 35].

Add to this the patient's personal expenses and working days lost due to incapacity. That is, the social significance of CP is enormous, as it leads not only to significant financial losses, but also to a decrease in the number of working days and, accordingly, the products produced or services provided, leading to disability and a significant deterioration in the patient's quality of life. Therefore, timely diagnosis and treatment are the primary tasks of the doctor [36, 37].

Treatment of chronic pancreatitis should be aimed at reducing pain — analgesia, disease modification, and intervention in the development of complications. Regarding the second point of treatment strategies, there is currently no proven method of treatment that can change the progression of the disease [36, 37].

CONCLUSIONS

1. Screening testing of patients with CP on the background of etiotropically treated HCV using the CAGE scale allowed us to state that 65.0% of such patients had a hidden craving for alcohol, and 21.0% of this cohort were women, which needs to be taken into account in the management of such patients patients
2. It has been proven that in the group of patients with CAGE≥2.0, the level of functional and structural changes in the liver and liver was significantly more severe (according to the deepening of the EPI, a decrease in fecal α-elastase by 13.01%, an increase in the total index of the coprogram by 15, 11% and the total US-indicator of the pancreas structure by 28.06%, and the total US-indicator of the liver structure by 40.68% ($p<0.05$) and corresponded to the average degree of severity of the process in pancreas according to the criteria of the Marseille-Cambridge classification, and in the group with CAGE<2.0 – only to a mild degree.
3. The negative effect of the factor of increasing alcohol consumption according to CAGE was proven by increasing the density of the echostructure of the pancreas by 5.73% ($p<0.05$), and that of the liver by 5.16% ($p<0.05$).
4. According to the results of the correlation analysis of the dependence of the structural state of the liver and pancreas of the studied patients on the value of the CAGE scale, which was $R=0.713$, $p<0.05$ and $R=0.686$, $p<0.05$, respectively, it was established the presence of strong direct dependencies of the structural state of the liver and pancreas from the value of the CAGE questionnaire, which proved an independent, reliably significant role of alcohol consumption for patients with a comorbid course of CP and HCV.

In the perspective of further research, it is necessary to propose and substantiate the complex treatment of such patients with the additional inclusion of hepato- and pancreatotrophic drugs with a corrective effect on the alcohol factor to the generally accepted complex.

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ORIGINAL ARTICLE

COMPARATIVE EVALUATION OF THE TEMPOROMANDIBULAR JOINT STRUCTURES AFFECTED BY TMJ DYSFUNCTION

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ABSTRACT

The aim: To investigate the individual anatomical features of the temporomandibular joint structures affected by TMJ disorders and compare them with those of asymptomatic patients.

Materials and methods: The sample consisted of 41 patients. The study group included 29 patients. The retroposition of the right mandibular head was observed in 16 patients, the anterior position of the right mandibular head – in 13 patients, the retroposition of the left mandibular head – in 19 patients, and the anterior position of the left mandibular head – in 10 patients. The control group consisted of 12 patients with an anterior or central position of the right and left mandibular heads.

Results: In the study group, a comparative analysis of the ABC angle on the right and left sides found no statistically significant difference in Student's criterion (p=0.176). In the control group, a comparative analysis of the ABC angle on the right and left sides found no statistically significant difference in Student's criterion (p=0.131). To identify a possible difference in the inclination of the articular tubercle in the study and control groups (anterior position of the mandibular head), calculations were carried out and when comparing two related samples using Wilkinson's T-criteria, the difference is not statistically significant p=0.119. The mean values obtained using Student's criterion did not reveal any statistically significant difference between both groups, p*=0,811.

Conclusions: A comparative analysis of the ABC angle in patients with TMJ dysfunction and the control group did not reveal any statistically significant difference. At the same time, there was no statistically significant difference between patients with the anterior and posterior position of the mandibular head.

KEY WORDS: TMJ, height of the mandibular fossa, prominence of the articular tubercle, computed tomography

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INTRODUCTION

TMJ dysfunction is one of the most prevalent oral pathologies. TMJ disorders rank third among the diseases of periodontal tissue and hard dental tissues [1, 2]. The number of people affected by TMJ dysfunction is increasing every year.

Understanding this pathology is complicated by a variety of etiological factors [3]. Impaired functioning of one of the maxillofacial structures leads to pathological changes in the TMJ, which subsequently cause muscle and joint dysfunction [4]. It should be noted that articulatory-occlusive and neuromuscular disorders play a crucial role in the development of TMJ dysfunction [5,6]. Occlusal conditions frequently contribute to pathological changes in the temporomandibular joint [7]. In many cases, they start out with an asymptomatic course, which makes further treatment challenging. In this regard, a comprehensive examination of this group of patients is required. It includes an overall clinical examination and additional diagnostic procedures such as electromyography, joint hypermobility assessment using the Beighton score, which is a modification of the Carter and Wilkinson scoring system [8], computed tomography, etc. The analysis of individual TMJ components and a multidisciplinary approach allow for the proper selection of the most optimal treatment strategy [9].

THE AIM

The aim of the research was to investigate the individual anatomical features of the temporomandibular joint structures affected by TMJ disorders and compare them with those of asymptomatic patients.

MATERIALS AND METHODS

The sample consisted of 41 patients. The study group included 29 patients. The retroposition of the right mandibular head was observed in 16 patients, the anterior position of the right mandibular head – in 13 patients, the retroposition of the left mandibular head – in 19 patients, and the anterior position of the left mandibular head – in 10 patients. The control group consisted

Table I. The position of the mandibular heads in the studied sample

Position of the mandibular head	Retroposition of the right mandibular head	Retroposition of the left mandibular head	Anterior position of the right mandibular head	Anterior position of the left mandibular head
The study group	16	19	13	10
The control group	-	-	12	

Table II. Comparative analysis of the ABC angle of the right and left TMJ in the study group

Group	Number of patients	Mean value	Mean squared error	Mean squared error	Minimum	Maximum	Left side (CI 95%)	Right side (CI 95%)
The study group (right side)	29	36,24	6,383	1,185	16,39	47,05	33,81	38,66
The study group (left side)	29	38,53	6,374	1,184	23,7	53,67	36,1	40,95

Table III. Comparative analysis of the ABC angle of the right and left TMJ in the control group

Group	Number of patients	Mean value	Mean squared error	Mean squared error	Minimum	Maximum	Left side (CI 95%)	Right side (CI 95%)
The control group (right side)	12	41,28	5,882	1,698	31,38	52,69	37,54	45,02
The control group (left side)	12	38,83	6,374	1,705	27,71	46,59	35,08	42,59

Table IV. Comparative analysis of the ABC angle in patients with anterior position of the mandibular head

Group	Number of patients	Median	I quartile	III quartile	Minimum	Maximum	Median error	Left side (CI 95%)	Right side (CI 95%)
The study group	23	38,58	33,23	40,71	16,39	44,7	1,682	33,79	40,41
The control group	24	41,155	36,64	44,05	27,71	52,69	1,509	37,63	42,98

Note: * The distribution law does not differ from the normal one at the level of significance p>=0.02.
When comparing two related samples using Wilkinson's T-criteria, the difference is not statistically significant p=0.119.

Table V. Comparative analysis of the ABC angle in patients with the retroposition of the mandibular head in both groups

Group	Number of patients	Mean value	Mean squared error	Mean error	Minimum	Maximum	Left side (CI 95%)	Right side (CI 95%)
The study group*	35	37,68	6,498	1,098	23,7	53,67	35,45	39,91
The control group**	24	40,06	5,898	1,204	27,71	52,69	37,57	42,55

Note: * The distribution law does not differ from the normal one at the level of significance p*=0,811; p**=0,1.
The mean values obtained using Student's criterion did not reveal any statistically significant difference between both groups, p*=0,811.
When comparing Student's criterion, the average difference is not statistically significant, p=0.3.

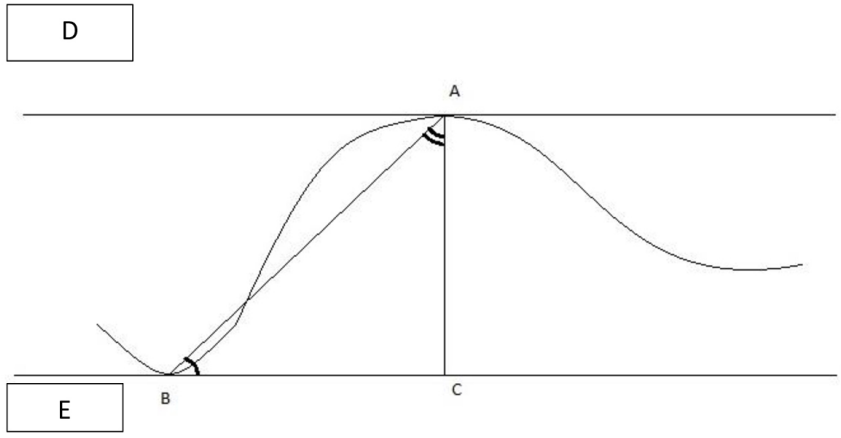
of 12 patients with an anterior or central position of the right and left mandibular heads. Computed tomography was used to assess and characterize the anatomical components of the TMJ (Table I).

The images of the TMJ were acquired, viewed, and processed with the help of the Planmeca Romexis Viewer. Statistical analysis was carried out using the IBM SPSS Statistics Base 22 program. The correlation between the height of the mandibular fossa (AC) and the projection of the prominence of the articular tubercle (the ABC angle) was investigated for further analysis of the TMJ anatomical structures (Fig. 1).

RESULTS

In the study group, a comparative analysis of the value of the angle of prominence of the articular tubercle (the ABC angle) relative to the depth of the mandibular fossa showed that in patients with the anterior position of the right and left mandibular heads, the distribution law did not differ from the normal one (p>=0.1) and Student's criterion was not statistically significant (p=0.176).

In the study group, a comparative analysis of the ABC angle on the right and left sides found no statistically significant difference in Student's criterion (p=0.176) (Table II).



Point A - the deepest point of the mandibular fossa

Point B - the most convex point of the articular tubercle

True horizontal D (a line that passes through the deepest point of the mandibular fossa (point A))

True horizontal E (a line that passes through the point of the top of the articular tubercle (point B))

AC - the depth of the mandibular fossa relative to the articular tubercle

BC - a projection of the mandibular head

AB - the prominence of the articular tubercle

The ABC angle - the prominence of the articular tubercle

Fig 1. Shematic representation of the TMJ structures

In the control group, a comparative analysis of the ABC angle on the right and left sides found no statistically significant difference in Student's criterion (p=0.131) (Table III).

To identify a possible difference in the inclination of the articular tubercle in the study and control groups (anterior position of the mandibular head), calculations were carried out and are presented in (Table IV).

In the study group, the ABC angle in patients with the retroposition of the right and left mandibular heads did not have any statistically significant difference. Therefore, we combined the values of the prominence of the articular tubercle on the right and left sides into one group.

To identify the possible influence and difference of the ABC angle in patients with the mandibular head retroposition, we statistically processed the data and presented them in (Table V).

DISCUSSION

Our literature review revealed a lack of scientific research or publications on the evaluation of the specific inclination of the articular tubercle of the temporal bone in patients with temporomandibular joint dysfunction. The only study to draw attention to a comparable issue is that conducted by Tonguç Sülün, DMD; its findings are summarized in his July 2001 article [10]. However, the depth of the mandibular fossa was the subject of particular focus, and the MRI investigation was used. Considering the fact that the mandibular head slides on another articular surface, namely the temporal bone, we assumed the possibility of a specific inclination of the tubercle in patients with temporomandibular joint dysfunction. For this, computed tomography, a modern method of

X-ray diagnostics, was used. We have developed and implemented our own calculation method for the biostatistical analysis of the research findings, ensuring the objectivity of the interpretation. To facilitate the understanding of the correlation, the author's method is presented and detailed in the article. Based on our study of the control and experimental groups, we found that the inclination of the temporal bone did not have a correlational dependence or any specific features when comparing the two groups with each other and the right-left TMJ. The investigation of other factors that can affect persistent dislocation of the mandibular heads is in progress.

CONCLUSIONS

A comparative analysis of the ABC angle in patients with TMJ dysfunction and the control group did not reveal any statistically significant difference. At the same time, there was no statistically significant difference between patients with the anterior and posterior position of the mandibular head.

Thus, it can be assumed that the skeletal development of the dentofacial system and, accordingly, the type of skeletal occlusion do not influence the prominence of the articular angle of the articular tubercle or the sagittal displacement of the mandibular heads. Therefore, the research needs further development and the study of other important etiological factors.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

EVALUATION OF ANTIOXIDANTS ENZYMES AND AUTOPHAGY GENES IN THE BLOOD OF IRAQI SMOKER VOLUNTEERS

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ABSTRACT

The aim: In this study, we investigated the expression level of LC3A, LC3B, Beclin1, and ATG5 in the blood of smokers as well as non-smokers volunteers. On the other hand, total antioxidant status (TAS), catalase (CAT), and superoxide dismutase (SOD) in the same individuals were measured.

Material and methods: About 5 ml of blood was collected from 55 smokers (workers in a coffee shop) and 24 non-smokers volunteers. The blood was divided into two parts: 2.5 ml collected in a K2-EDTA tube that was used for RNA extraction to estimate the autophagic genes including LC3A, LC3B, Beclin1, and ATG5 by using of qRT-PCR and for hematological studies. The other part – was centrifuged to obtain the serum samples to measure TAS, CAT, and SOD by spectrophotometrical method.

Results*:* The fold expression of autophagy genes was significantly increased in the blood of smokers as compared to non-smokers' individuals at ($p \leq 0.05$). On the other hand, TAS, CAT, and SOD were significantly increased in smokers as compared with non-smokers individuals at ($p \leq 0.05$). The hematological study revealed increased hemoglobin concentration and hematocrit in the smoker's blood as compared to nonsmokers' individuals. No significant variation was found in other hematological parameters in the smoker's individual as compared to non-smokers at ($p \leq 0.05$).

Conclusions: Our results indicate that smoke exposure may induce autophagy genes through increased antioxidant status and antioxidant enzymes, and the better way to be healthy is to quitting smoking.

KEY WORDS: Antioxidant, ROS, Autophagy, qRT-PCR, Cigarette Smoke, Iraqi volunteers

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INTRODUCTION

Several toxic substances are found in the air, which causes different pulmonary diseases. Exposure to cigarette smoke may increase the exacerbation of those diseases [1]. High exposure to cigarette smoke promotes the releasing of reactive oxygen plus nitrogen species as a result of continuous irritation caused by smoke. Consequently, the incidence of severe pulmonary diseases is elevated and is the major cause of mortality and morbidity, such as chronic obstructive disease [2]. Moreover, cigarette smoke consists of a thousand chemical compounds, many of these compounds are pro-oxidants and free radicals scavengers which play roles in induction of oxidative stress as well as autophagy. Several diseases occurs as a result of the linkage between oxidative stress and autophagy, for instance, Parkinson's disease, obstructive pulmonary disease, and aging, in addition to induction of cell death, inflammation, and extracellular degradation [1].

Autophagy is a catabolic process by which cellular proteins or dispensable components and damaged organelles follow lysosomal degradation under stress conditions. However, it found at low levels in nearly all normal cells to fulfill homeostatic functions [3]. Recently, studies provide evidence that autophagy is stimulated in cells as a response to cigarette smoke to provide pulmonary airway acclimation and classify as a crucial tissue damage modulator [4]. However, the mechanisms through which autophagy stimulates during cigarette smoke exposure are unknown. In diseases, it is documented that autophagy engages with multiple cellular processes and pathways. If we consider plenty of biological assignments of autophagy, it is believed that this function participates in the pathophysiological process resulting from cigarette smoke induction of pulmonary disorders [5].

There are different types of autophagy pathways: micro-, macro-, and chaperone-mediate autophagy [6, 7]. Among these types, all studies are concerned with macroautophagy (hereafter referred to as autophagy) since it is mediated by a specific organelle called an autophagosome. In mammals, light chain 3 (LC3) participates in autophagosome formation and serves as a marker of the manifestation of autophagy [8]. Removing of oxidizing proteins and damage mitochondria occur in most conditions of autophagy. In this context, dam-

aged mitochondria are specifically targeted by autophagy in a process called mitophagy [9]. Mitophagy plays a key role in cell differentiation, apoptosis, and increased the immune response [10]. Dysregulation of mitophagy was involved in neurodegenerative disorders, cardiac disorders, and arrest in addition to cancer [11, 12].

Reactive oxygen and nitrogen species induce autophagy and lead to reduce the damage resulted by oxidative stress. This mechanism protects the cells from these substances by eliminating ROS and eventually leads to preserving mitochondrial integrity, block programmed cell death, and raise antigen presentation. On the other hand, high induction of autophagy by high ROS products can lead to apoptosis under particular situations [13]. Taken together, selective autophagy participates in body disease wherever it can play either a preservative or harmful effects [14].

THE AIM

Current study aimed to investigate expression level of autophagy genes in the blood of cigarette smoker individuals in addition to non-smoker's voluntaries.

MATERIALS AND METHODS

Current study was conducted on individuals who in different coffee shops in Baghdad that smokes and exposed to cigarette smoke for a long time daily. Fifty-five individuals smoke and espoused to cigarette smoke were enrolled in this study with a mean of age 26.4 years and a range of 22-43 years. The study was achieved during the period from February 2019 to June 2019. All smoker individuals enrolled in this study are not receiving any medication that may affect the results of the study. The other group that participated in this study acted as a control group. This group consists of twenty-four healthy volunteers, with a mean of age (24), and range (20-34) years. None of the volunteers were clinical or laboratory have disease that may affect the parameters to be measured.

About 5 ml blood from venous was drawn using disposable needles and syringes from the smoker's individual and controls. A portion of blood was transferred into clean dry plain plastic tube without anticoagulants and left to clot, then the serum was obtained by centrifugation at 3000g for 10 minutes. The clear serum then was separated and used for estimation of enzymes, that include superoxide dismutase, catalase and total antioxidant status. Another portion of blood transferred into a tube contains K_2 EDTA and was used for RNA extraction then autophagy gene estimation and hematological studies.

RNA ISOLATION

For quantitative real time PCR, total RNA was extracted from the blood of smokers and non-smokers individuals using a standardized AccuZol™ total RNA Extraction protocol (Bioneer, South Korea). Expression of auto-

Table I. The sequences of specific primers used for determination of ATG5, LC3A, LC3B, Beclin1, and β-actin mRNA level by real-time PCR.

Gene name	Sequence 5′-3′	Tm
ATG5	Forward 5′- GCAGATGGACAGTTGCACACCA Reverse 5′- TTTCCCCATCTTCAGGATCAA	60°C 60°C
LC3A	Forward 5′- TCCCGGACCATGTCAACAT Reverse 5′- ACCATGCTGTGCTGGTTCAC	61°C 61°C
LC3B	Forward 5′-ACCATGCCGTCGGAGAAGATTTT Reverse 5′- ATCGTTCTATTATCACCGGG	62°C 62°C
Beclin1	Forward 5′-CTGGACACGAGTTTCAAGATCCT Reverse 5′-TGTGGTAAGTAATGGAGCTGTGAGTT	60°C 60°C
β-actin	Forward 5′- CCGCAAATGCTTCTAGGCG Reverse 5′- TGTTTTCTGCGCAAGTTAGGT	64°C 64°C

Table II. Autophagy genes expression levels in smokers and non-smokers individuals.

Groups	Non-Smoker (n=24) Mean± SD	Smoker (n=55) Mean ± SD	P-Value
ATG5	0.69 ± 0.12	3.00 ± 0.52	P≤0.05
LC3A	0.87 ± 0.17	3.43 ± 0.50	P≤0.05
LC3B	1.67 ± 0.18	4.64 ± 0.38	P≤0.05
Beclin1	1.95 ± 0.17	12.27 ± 1.57	P≤0.05

Table III. A comparison of the hematological parameters between 55 smokers samples and 24 non-smokers individuals.

Parameters	Group	No. of Samples	Mean	S.D	S.E	P-Value
Age	Smokers	55	31.95	8.35	1.74	P≤0.24
	Control	17	29.41	3.55	0.86	
Hb	Smokers	55	16.83	1.10	0.23	P≤0.05
	Control	17	13.46	0.47	0.11	
PCV	Smokers	55	52.49	3.04	0.63	P≤0.05
	Control	17	40.59	1.72	0.41	
WBC	Smokers	55	8300	2564.57	534.57	P≤0.3
	Control	17	7400	1380.86	335.63	
Platelets	Smokers	55	239.94	3571	744.57	P≤0.19
	Control	17	225.13	2649	642.01	

Hb: Hemoglobin; PCV: Packed Cell Volume; WBC: White Blood Cells

phagy genes: ATG5, LC3A, LC3B, and BCL1 were tested using the Stratagene mx3000p PCR Detection System.

QUANTITATIVE REAL-TIME PCR

To avoid nucleic acid contamination (DNA contamination), all primers for the qPCR were designed with NCBI/primer-BLAST online [15]. Real-time PCR was performed by using stratagen Agilent mx 3005p, using specific primer for autophagy genes as presented in (Table I). On the other hand, the house keeping gene β-actin [16], was used as control for cDNA quantity and quality. Reaction mixtures was contained: 10 µL of one step SYBR (SYBR fast, KAPA biosystem, USA), 2 µL of each primer (10 µM), 2 µl of RNA template, and 4 µl of sterile distilled water were incubated for 10 min at 42°C, followed by 40 cycles of 95°C for 5 min for deactivation of reverse transcriptase, followed a step for denature the double stranded formation at 95°C for10 s, and for primer annealing: 60°C (ATG5 and Beclin-1) for 30 s, 61°C for LC3A, 62°C for LC3B, and 64°C for βactin. After the amplification phase, a melting curve program (65°C to 95°C with a heating rate of 0.5°C per second and a continuous fluorescence measurement) was routinely performed to confirm the presence of a single PCR product.

ESTIMATION OF TOTAL ANTIOXIDANT STATUS (TAO)

For total antioxidant status, total antioxidant status kit (Elabscience Biotechnology, E-BC-K136- China) was used. The concentration of TAO in the cells was determined according to manufacturing kit. Briefly: about $1x10^6$ cells were collected by scraping cells and 400 µl of cold PBS (0.01M, pH 7.4) was then added. The mixture were treated with a mechanical homogenizer to destroy all cells in ice. Centrifugation was carried out cold temperature at 3000g for 15 minutes to collect the supernatant, the measurement of the TAO concentration was done using spectrophotometrically at 520 nm.

ESTIMATION OF SUPEROXIDE DISMUTASE ENZYME (SOD)

Total-superoxide dismutase was determined using (Elabscience biotechnology, E-BC-K019 China) kit. Briefly: t¬he_adherent cells were detached or scripted and then collected sedimentary by centrifugation (Suspension cells can be collected sediment by centrifugation directly). Centrifuge for 10 minutes at 4000g, then the supernatant was discarded. Attached cells were suspended in 1 ml of cold PBS, centrifuged for 10 minutes at 3000g, and then the supernatant was discarded. Cells are suspended in PBS solution (0.1 M, pH 7-7.4 pH). The cells were broken down by sonication. Cells thawed with gentle mixing. The concentration of SOD was measured by a spectrophotometer at 520 nm.

ESTIMATION OF CATALASE ENZYME (CAT)

The Catalase activity assay (Elabscience biotechnology, E-BC-K031-S China) kit was used. Briefly: during reaction that Catalase enzyme decomposes H_2O_2 can be quickly stopped by ammonium molybdate. The residual H_2O_2 reacts with ammonium molybdate to generate a yellow color complex. CAT activity can be calculated at 405 nm.

STATISTICAL ANALYSIS

Determination of fold gene expression using the equation of Livak $2^{-\Delta\Delta Ct}$ method [17]. An independent t-test was performed by using of SAS (Statistical Analysis System – version 9.1) to assess significant differences between means. $P \leq 0.05$ was considered statistically significant [18].

RESULTS

AUTOPHAGY GENE EXPRESSION LEVELS

The results of the expression level of autophagy genes showed that Beclin1 was highly expressed in smoker

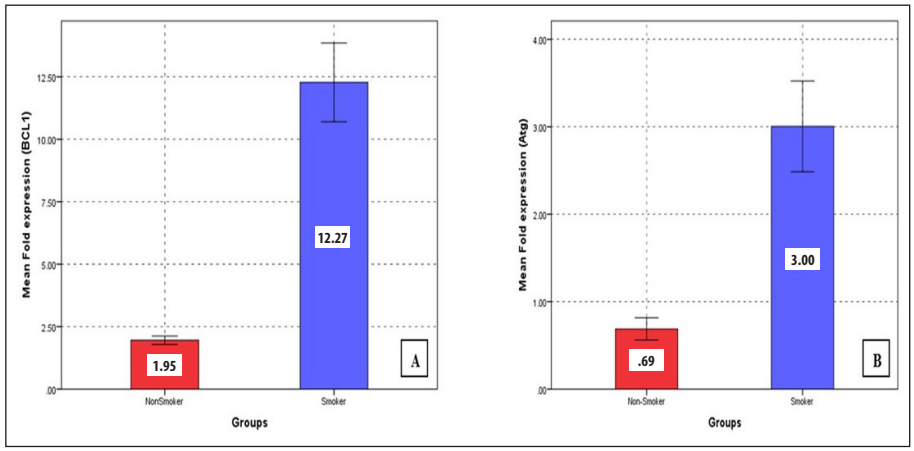

Fig. 1. The bar expressed the fold expression of autophagy genes in smokers and non-smokers individuals. (A): represents the fold expression levels of BCL1. The results showed a significant increase in fold expression in smoking individuals as compared with non-smokers. (B): expression levels of ATG gene. The results showed a significant increase in fold expression in smokers individuals compared with the non-smoker's group.

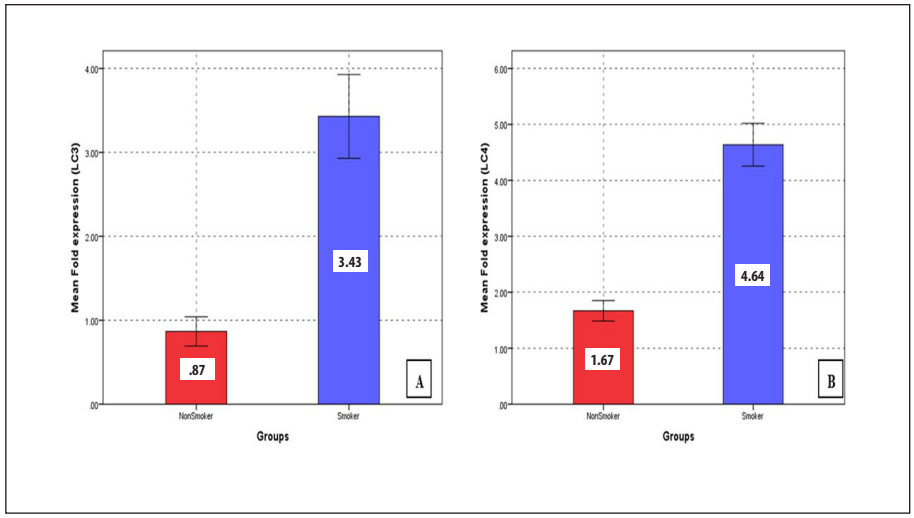

Fig. 2. The bar expressed the fold expression of autophagy genes in smokers and non-smokers individuals. (A): represents the fold expression levels of LC3A. The results showed significantly increased LC3A fold expression in smoking individuals as compared with non-smokers. (B): The results illustrated significant elevation in LC3B expression levels. The results showed a significant increase in fold expression of LC3B in smokers individuals compared with the non-smoker's group.

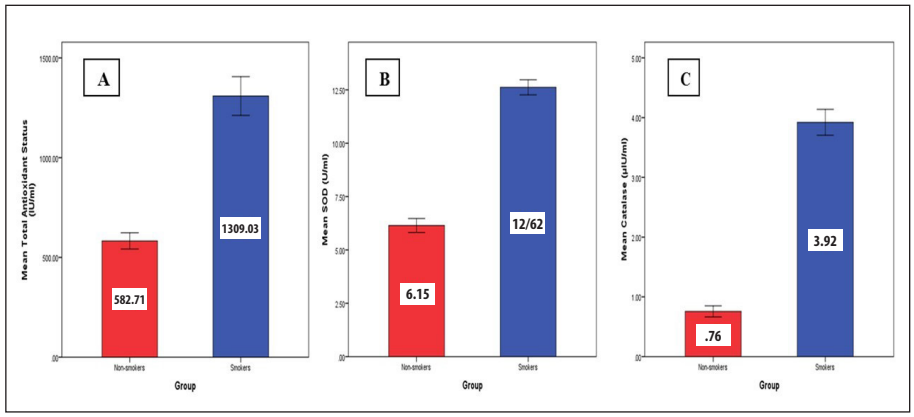

Fig. 3. Expression levels of TAS, SOD, and CAT in smokers and non-smokers individual in 55 samples of smokers and 24 non-smokers individuals. The results showed significant elevation in TAS in smokers as compared with non-smokers individuals at $p < 0.05$ (A). On the other hand, results revealed significant variation in SOD enzyme concentration in smokers as compared with the non-smoker's group (B). And (C): The bar showed the concentration of CAT in different groups. The results showed the CAT enzyme significantly increased in the smoker's group as compared with the non-smoker's group.

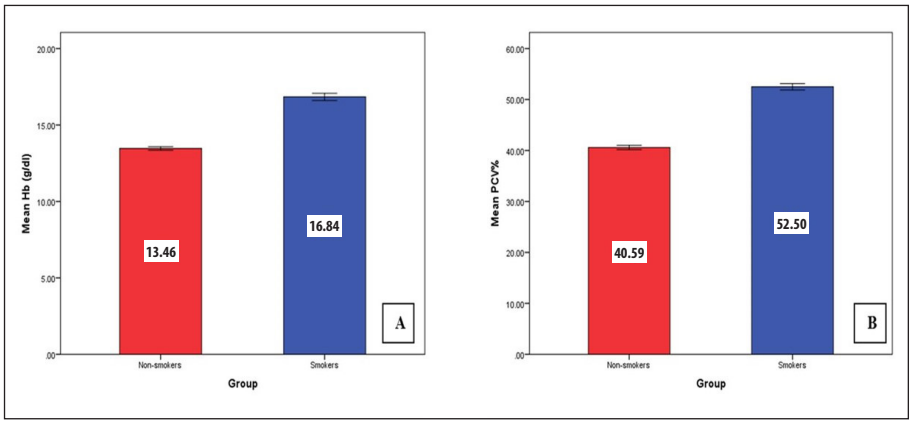

Fig. 4. The analysis of the smoking effect on hemoglobin and hematocrit in 55 smokers and 24 non-smokers individuals. (A): Bars represent the variation between the smoker's group and the non-smoker's one. The results showed significant variation in hemoglobin concentration between the two groups. (B): The results showed significant elevation in the smoker's group as compared with the non-smoker's group at $p < 0.05$.

individuals as compared to non-smokers. The results showed that Beclin1 was increased 12 times (12.27) as compared to approximately 2 times (1.95) in non-smokers individuals ($p \leq 0.05$) (Table II, Figure 1A). On the other hand, the results showed that the fold expression of the ATG5 gene was increased three times in smokers (3.00 times) as compared to less than one time (0.65) time in non-smokers individuals ($p \leq 0.05$) (Table II, Figure 1B). Meanwhile, the results showed significant variation in LC3A expression level. The results showed that the LC3A expression was increased more than 3 times (3.45 times) in smoker individuals as compared with less than one time (0.87 times) in non-smokers individuals ($p \leq 0.05$) (Table II, Figure 2A). The results of this study also revealed significant variation in LC3B expression levels. The results showed that the fold expression of LC3B increased almost 5 times in smoking individuals (4.64 times) as compared with 1.64 times in non-smokers individuals ($p \leq 0.05$) (Table II, Figure 2B).

DETERMINATION OF TOTAL ANTIOXIDANT STATUS (TAS), SUPEROXIDE DISMUTASE (SOD), AND CATALASE (CAT)

The results of our study showed significantly elevated TAS concentration in smokers as compared to non-smokers individuals. The concentration of TAS was 1309.03 U/ml in smokers as compared to 582.71 U/ml in non-smokers individuals ($p \leq 0.05$) (Figure 3A). On the other hand, the results illustrated high significant variation in SOD enzyme concentration in smokers as compared to non-smokers individuals. The results showed that the concentration of SOD enzyme were 12.62 U/ml in smokers compared with 6.15 U/ml in the non-smoker's group ($p \leq 0.05$) (Figure 3B). Meanwhile, the results showed significant variation in CAT enzyme concentration in smokers as compared to non-smokers individuals. The result illustrated that the concentration of CAT concentration was 3.92 U/ml as compared with 0.76 U/ml in non-smokers individuals ($p \leq 0.05$) (Figure 3C).

HEMATOLOGICAL PARAMETERS ANALYSIS

The effects of cigarette smokes on the age and hematological parameters of all participants in this study were illustrated in table III. The results showed a significant elevation in hemoglobin concentration of the smoker's group as compared to the non-smoker's group ($p \leq 0.05$) (Figure 4A). On the other hand, a significant variation was found in the hematocrit of the smoker's group as compared to non-smoker individuals (Table III, Figure 4B). No significant variation was found in other parameters such as white blood cells (WBCs) and platelets (Pl.) and participant's age.

DISCUSSION

This study reports marked upregulation of some autophagic genes in association with increased antioxidant activity and hemoglobin values in the blood samples of smoking men. The hazardous effects of smoking are well documented, including respiratory and cardiovascular diseases [19, 20] as well as the effect on the reproductive system [21, 22, 23] and many other harmful effects. More than 4,000 chemicals exist in cigarette smoke and more than 60 of these chemicals are carcinogens [24]. Smokers suffer from the harmful effect of smoking because of the cumulative exposure to these substances. Consequently, smoking is considered a cellular stress. The stressful conditions lead to stimulating autophagy machinery [25].

Autophagy is a pathway for the degradation of intracellular proteins and damaged organelles by forming a double-membrane vesicle that fuses later with lysosomes. In normal conditions, autophagy performs a homeostatic function and occurs at a low basal level in normal cells. It turnover the protein and organelles to generate building blocks and energy under stress conditions to conserve cell survival [26]. Several studies linked the reduction/induction of the autophagy process with smoking. In our results, we showed that the blood cells of smoker men have upregulated autophagy genes (Beclin-1, Atg5, LC3A, and LC3B) when compared to non-smokers (control group). Monick et al. [27] found a reduction in the autophagy process of alveolar macrophages of smokers, which led to the aggregation of dysfunctional mitochondria. This reduction is associated with a defect in the clearance of bacteria and a subsequent increase in the lung infection rate of cigarette smokers. In another clinical research, they found that cigarette smoke extract (CSE) induced autophagy and increased reactive oxygen species (ROS) in human bronchial epithelial cells [28]. CSE demonstrated the ability to upregulate the autophagic genes Beclin-1 and Atg5 in bronchial epithelia [29]. Many types of research explored the effect of smoking or CSE on different cells of human and experimental animals. However, our study considers us as the first study to investigate the autophagic genes in the blood of smokers.

Many cellular stresses are responsible for autophagy stimulation through the AMPK pathway, including oxidative stress [30, 31, 32]. The balance of production/removal of free radicals can determine the impact of cellular oxidative stress. Reactive oxygen species (ROS) represent signal transducers in diverse pathways within

the cell and execute crucial roles in cellular survival, death, and immunity. For instance, researchers found that the increasing amount of ROS production in tumor cells upregulated autophagy for survival [33].

Starke and his co-workers found that cigarette smoke exposure is responsible for the generation of over-abundant ROS, which led to phenotypic alteration of vascular smooth muscle cells and cerebral aneurysm formation and rupture [34]. In our study, we found that antioxidants activity (SOD, Catalase, Total antioxidant) increased in the blood cells of smoker men. Increased production of antioxidants could be a good sign for the removal of free radicals from the cells. However, the question remains, is the elevated level of antioxidants can remove the excess amount of free radicals from the cells? This matter needs to clarify in further study.

The induction of autophagy, which could be a consequence of ROS production in the smoker, may help to overcome the damage caused by smoking. Kim et al. proposed a protective role for autophagy in human gingival fibroblasts exposed to cigarette smoke [35]. However, another study found that inhibition of autophagy triggered an improvement in endothelial cell viability [36]. The benefits of autophagy induction in smokers need more clarification and research and are still in doubt.

In this study, the results revealed increased hemoglobin values in smoker individuals when compared to the non-smoker group. While there was significant variation also found in the values of hematocrit between these two groups of subjects, these results were correlated with other previous studies [37, 38]. Elevated hemoglobin concentration were realized to be intermediate between exposure to carbon monoxide (CO) and some researchers proposed that elevated hemoglobin concentration in the blood of smoker individuals could be a compensative technique. Carbon monoxide can bind to the hemoglobin of red blood cells. This binding led to form carboxyhemoglobin. This compound represents the inefficient shape of hemoglobin with no ability of carry oxygen. This formation led to a shift in the oxygen dissociation curve to the left, which led to a reduction in hemoglobin capability to carry oxygen to the cells. As a result of the ability of hemoglobin to deliver oxygen to the tissues, bone marrow produced a large new red blood cell to compensate for the decrease in oxygen delivering capacity, smokers preserve elevated hemoglobin concentration when compared with non-smokers individuals [39].

CONCLUSIONS

In conclusion, smoking is the main cause of several diseases. The better way to be healthy is to quitting smoking, although there are studies that try to understand the cellular mechanism that associates with it and study the side effects and how to overcome them. We plan to future studies to better understand the interplay of autophagy and antioxidants in smokers.

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The present study was approved by the Research Ethics Committee of the Cancer Research Center and according to the ethical standards laid down by the Declaration of Helsinki. The ethical committee was obtained from the Health Research Unite and protocol Review Committee in the Ministry of Health / Baghdad / Iraq.

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ORIGINAL ARTICLE

PECULIARITIES OF EATING BEHAVIOR IN CHILDREN WITH AUTISTIC SPECTRUM DISORDERS

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ABSTRACT

The aim: To determine of the nutrition peculiarities in children with ASD.

Materials and methods: The study involved 37 children with ASD from 2 -12 years and thier mothers, in according to reveal its disorder effect on the clinical course of ASD in children.

Results: It was shown role of irrational nutrition of the mother during pregnancy, peculiarities of family food traditions, problems of breastfeeding and complementary feeding. Eating behavior of mothers during pregnancy were: monotonous nutrition and an inadequate diet. The family food preferences were: varied and included both traditional and specific food preferences (vegan, vegeterian, monotony diet).

Conclusions: The analysis of the eating behavior in the ASD children, taking into account the age peculiarities, was carried out. Intolerance to certain products was noted. Also effectiveness of the elimination diet was shown. Elimination from the diet of the white flour products within 6 months has a positive result which evaluated by digestive and cognitive signs.

KEY WORDS: diet, psycho-cognitive disorders, eating habits, food preferences, digestive system, product intolerance

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INTRODUCTION

It is difficult to overestimate the relevance of studying autistic spectrum disorders in children (ASD). Today, there is a great increase in ASD incidence in the child population around the world.

Among the mechanisms of ASD development, the structural, genetic, metabolic, energy, and cytochemical disorders in the organism, which occur already at the period of early ontogenesis, are singled out [1–5].

Besides of mental and neurological disorders, children with ASD have many peculiarities of the general health. Peculiarities of the functioning of the brain and autonomous regulation of vital activity of children with ASD are manifested not only in the form of psychological and cognitive changes (aggression and auto-aggression, phobias, the attention deficit and hyperactivity syndrome, sleep disturbance, etc.) but also affect many vital functions, such as nutrition, respiration, metabolism products release [6, 7].

Disorders of digestion and eating behavior are extremely common (up to 90%) occur in this group of children [6–9] and are directly associated with the ASD development pathogenesis, and also correlate with the severity of clinical symptoms [8–10].

Eating disorders include several types, such as anorexia, bulimia, overeating and avoidant/restrictive food intake disorder.

Avoidant/restrictive food intake disorder (ARFID) is a condition when a child ignores food for various reasons and qualities, and is singled out as a separate nosological unit in DCM-5 and ICD-11. In this case, the diet of children consists of a limited amount of food, which leads to microelement, vitamin and energy deficiency, stunting of body mass and organic diseases [10, 11]. There is a need for the use of nutritional supplements and enteral nutrition. That is why ARFID occurrence prediction and the further development of programs aimed at overcoming the selectivity of nutrition are necessary at habilitation of children with ASD [12–14].

THE AIM

To study the peculiarities of eating behavior and reveal its disorder effect on the clinical course of autistic spectrum damage in children.

Table I. The features of pregnancy course and eating behavior in mothers of children with ASD

Characteristic of pregnancy, food preferences and eating behavior	Absolute value	Relative value M ± m, %
Pregnancy:		
singleton	35	94,5 ±3,7
multiple	2	5,4 ±3,7
Way of getting pregnant:		
- natural	32	86,5 ±5,6
- full IVF protocol	5	13,5±5,6w
The term of complicated pregnancy occurrence:		
1st trimester	23	62,2±7,9
2nd trimester	3	8,1±4,5
3rd trimester	5	13,5±5,6
Method of delivery:		
childbirth natural	26	70,3±7,5
Caesarian section	11	29,7 ±7,5
Gastro-intestinal diseases before	8	21,6±6,8
/ during the pregnancy	11	29,7 ±7,5
Mother's food habits during pregnancy:		
-high carbohydrate food	26	70,3±7,5
-meat products	6	16,2±6,0
-fruit	4	27,0±7,3
-milk products	2	5,4±3,7
-fish	4	10,8±5,1
-non-food products (earth, chalk)	1	2,7±2,6
-exotic food	1	2,7±2,6
-salty and sour foods	1	2,7±2,6
-vegan	3	8,1±4,5
-vegetarian (ovo- / lacto- eating)	4	10,8±4,5
Food habits in the family:		
-bread and flour products (cereals, bread)	26	72,2±7,3
-milk products	5	13,5±5,6
-meat	10	27,0 ±7,3
-fish dishes	1	2,7±2,6
-healthy eating diet	12	33,3±7,6
-traditional cuisine of Ukraine	33	89,2±5,1

MATERIALS AND METHODS

The study involved 37 children aged 2 to 12 years (the mean age (3,7±2,4) years). The distribution by gender was uneven: (72,9±7,3) % were boys and (27,1±7,3) % were girls. The inclusion criteria to the study: a confirmed ASD diagnosis, the age 2–11 years old, the informational consent for participation in the experiment. The exclusion criteria: acute and chronic pathology of the central nervous system, acute encephalopathy, children's cerebral palsy, epilepsy, genetic diseases affecting the central nervous system), hereditary metabolic disorders (phenylketonuria, Wilson's disease, etc.), organic diseases of the gastrointestinal tract (peptic ulcer, hepatitis, cholecystitis, etc.).

In order to evaluate the food preferences in children with ASD, the ChEDE-Q questionnaire (Children Eating Disorder Examination Questionnaire) in the author's modification was used. To assess the psycho-cognitive functions dynamics in children with ASD, the ATEC test (autism treatment evaluation checklist) was used.

The obtained digital data were statistically processed using the Microsoft Excel package. Statistical processing of the data involved an assessment of the normality of the data distribution. Continuous and categorical variables were defined as mean (M), standard deviation (m), relative (%). The normally distributed numerical variables were compared with an independent sample t-test. Numerical variables that were not normally distributed were compared with the Mann–Whitney U-test. The statistical significance of the indicators was determined at the level of $p \leq 0,05$.

RESULTS

Among the examined children, the ratio of boys and girls was 3:1, which indicates gender inequality among children with ASD. When evaluating the clinical features of the ASD course in children, the anamnestic data as-

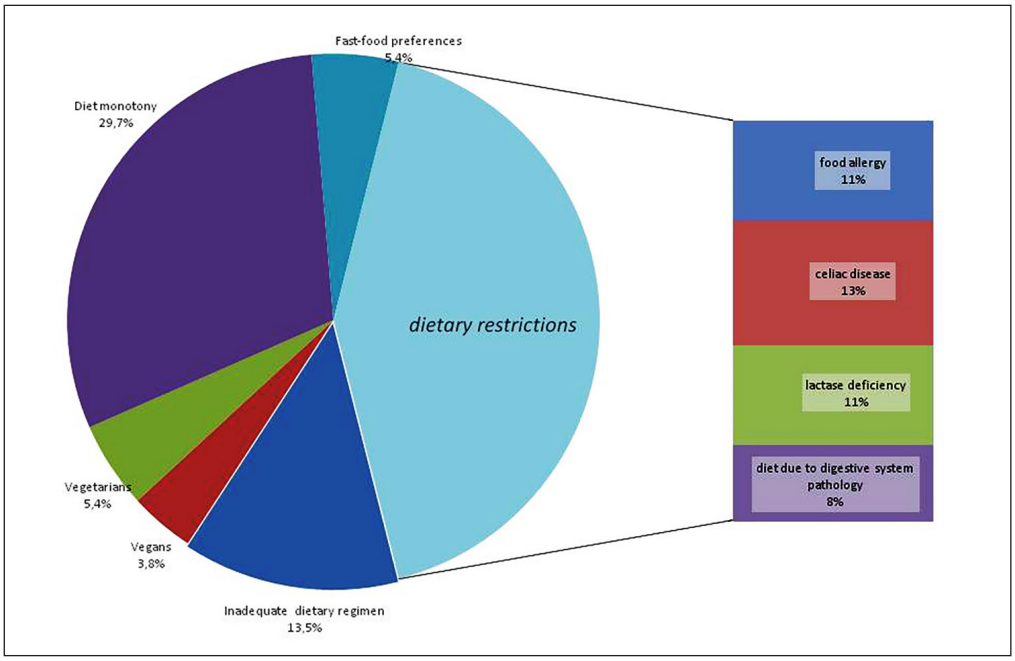

Fig. 1. Eating behavior peculiarities in ASD children's mothers.

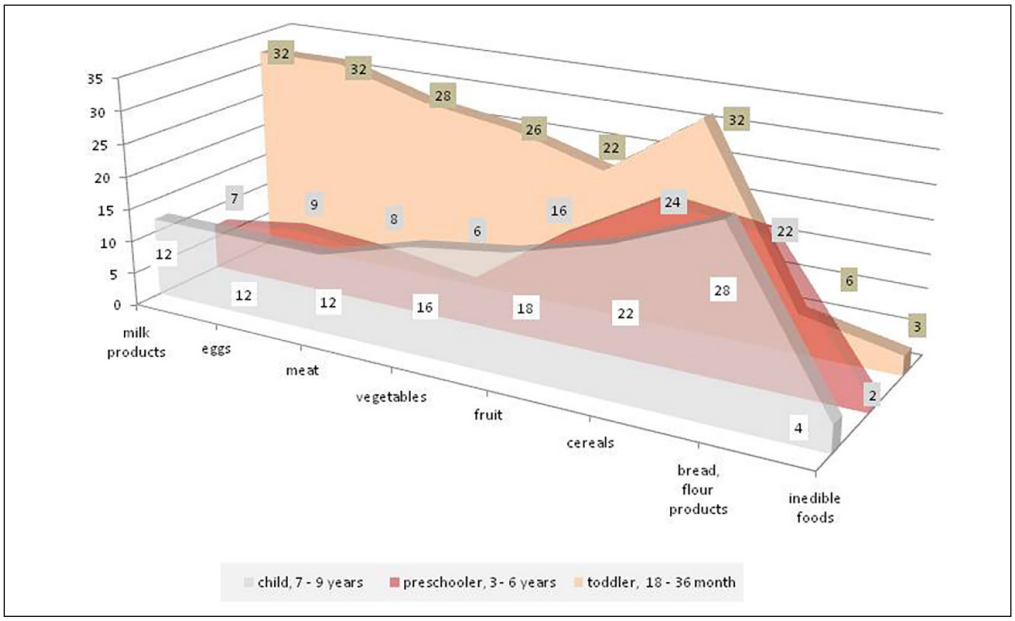

Fig. 2. Eating preferences in ASD children of different age groups

sociated with eating behavior of a child and his family were thoroughly analysed.

Taking into account the proved role of the pregnant woman's diet on the development of different pathologies in future in a child, a special attention was paid to studying the antenatal period characteristics, as well as food preferences of the pregnant women (Table I).

Among the data presented in the table, a high incidence (83,8±6,1%) of the complicated course of pregnancy draws the attention, and in some cases (13,5±5,6) % of problems were registered even at the pregravid period, as the result of which the spontaneous pregnancy did not occur and the parents had to fall back on modern reproductive technologies. In most cases, an induced pregnancy ended with operative delivery, which is associated with a number of features: a change in the formation of the intestinal microflora, which in turn affects the functioning of the digestive system, modification of immune and metabolic processes, an impact on the formation of the cerebrointestinal axis, and indirectly, on the subsequent child's eating behavior.

When studying the mother's eating behavior, a special attention was paid to forced dietary restrictions associated with various pathological conditions (Fig. 1). It is important to note that only in (21,6±6,8) % of cases such pathological conditions were documented and confirmed, most of them were chronic patholo-

gy of the digestive system (gastroesophageal reflux disease, chronic gastroduodentitis, gastric ulcer, pancreatitis, cholecystitis) and food allergy. In other cases, food restrictions were set independently on the basis of a subjective opinion and the sense of various diets effectiveness (low lactose, gluten-free), but without confirmation by laboratory tests.

The presented diagram shows that the features of the eating behavior of mothers during pregnancy were the monotonous nutrition (29,7±7,5%), as well as an inadequate diet (13,5±5,6%).

As a rule, the mother's gastronomical predilections to high-carbohydrate food was noted, which in most cases was associated with family food traditions. This made it possible to assume the influence of the food priorities of the mother and family on the formation of the child's eating behavior in the future.

After the birth, most of the children were breast-fed or mixed-fed (67,6±7,7)%; (10,8±5,1)% of children were breast-fed for more than 12 months. At the same time, the average period for the introduction of complementary food was 4–6 months (4,2±2,0) in (47,2±8,2) % of children. Most often complementary feeding started with vegetable puree (81,1±6,4) % and milk porridge (18,9±6,4)% with buckwheat and rice flour (72,9±7,3)%.

During the experiment course the analysis of the eating behavior in the examined children with taking into account the age peculiarities was carried out (Fig. 2).

At the younger age period (from the introduction of complementary food (4,9±2,2) months to (2,7±1,6) years, a priority intake of products of whole and preformed milk, cereals and groat, fruit and vegetable puree was noted. At the older age period (from (2,7±1,6) years to (8,3±2,8) years) food preference shifted towards excessive intake of bread and flour products, which can be associated with the emergence of an independent food search in a child with ASD and high availability and variety of shapes/kinds/flavours in the given food group. We can also note the frequent use of bread and flour products (crackers, cookies, biscuits) in the form of snacks and rewards (for example, when introducing the behavioural therapy), which does not have a favourable effect on the general somatic health of children with ASD.

Intolerance to certain products (vomiting and stool changes) was noted in (21,6±6,7)% of the respondents, and most often was associated with intake of dairy products and meat, which further necessitated the introduction of elimination diets. The gluten-free diet was followed by (27,0±7,3)% of children with a laboratory-confirmed increase in the concentration of IgG to gliadin, as well as a pronounced increase in the values of antibodies to tissue transglutaminase (tTg-IgA).

Taking into account the data obtained, effectiveness of the elimination diet was evaluated, which showed that elimination from the diet of the white flour products within 6 months gives a positive result in the form of the ATEC test score regression in 51,3% of ASD children — falling from 61 points to 50–60 points level (p>0,05). Improvement in behaviour was noted in (30,0±7,6)% of children, improvement of stool in (20,0±6,5)%, removal of digestive system problems — in (40,0±8,0)%. In spite of the fact that the positive influence of the used diets did not reach the reliable level, the obtained changes in children's behaviour, smoothing of complaints of digestive system problems, approval of parents gives an opportunity to consider the food correction as an important direction of the individual therapeutic programs with ASD.

Considering the role of the child's and family's eating habits, which at an early age underlie stable taste habits and form the attitude to the process of eating, during the examination the variants of eating behaviour patterns, such as bulimia nervosa, anorexia nervosa, compulsive overeating and selective eating disorder were assessed. Based on the data obtained, bulimia nervosa and anorexia nervosa were absent at the given group of ASD children. While compulsive overeating was noted in (8,1±4,5)% of children, and ARFID took place in (91,9±7,6)%.

It should be noted that all the children at the time of the study were at the age when the child should already have a formed eating interest and eating behavior. At the same time, (59,5±8,0)% of the examined children have to be forced and stimulated to eat because they have no hunger, and (32,4±7,7)% constantly have poor appetite, (45.9±8.1)% of children did not want to eat a certain product, and (29,7±7,5)% preferred a monotonous diet and homogenous food consistency in spite of absence of swallowing failure.

In (75,7±7,0)% of the examined children the ARFID development was connected with the use of the food as rewards, of them (62,2±7,9)% preferred quick meals.

In the formation of eating behavior in a child with ASD, it is necessary to note the attention of parents to the problem of the process of nutrition and eating. The family of a child with ASD is subject to close attention from society and is limited in the possibility of free movement and physical activity accessible to families with common children. When choosing a catering establishment to visit, in (83,8±6,1)% of cases, "fast food", "takeaway" food is preferred. Taking into account the psychological characteristics of children with ASD, preference in daily activities is given to calm games and developing static activities; (64,9±7,8)% of respondents have insufficient physical activity during

the day, which also contributes to the disruption of the formation of healthy eating habits and adversely affects the digestive system. The parents of children with ASD in (72,9±7,3)% are in permanent psychological stress, which is revealed in close attention of parents to the development, treatment, and, most importantly, to the nutrition of the child. The steady intention to vary the diet of a child with ASD with different products, a tendency to regular frequent meals, the demand to eat up a portion increases neurotic attitude in the family and negativity to food in a child with ASD. This group of children very needs balanced diet with essential nutrients in strict accordance with the age necessities of the growing organism.

DISCUSSION

Nutrition is a very important aspect of the successful life of any organism. Nutrition problem deserves a special attention in children with ASD. Concidering to numerous data, problems with the introduction of new foods, unsuccessful attempts to vary the ways of preparing and serving dishes, problems with the way of eating are typical for children with ASD [13–16], which was confirmed by this research.

The study conducted by Nugren G, Linnsand P, Hermansson J. was showed that 76% of children diagnosed with ASD have the problems with food, and 28% demonstrated a selective eating behavior, there were also nutritional problems in the form of refusal to eat, behavior problems during meals, rituals, which is correlated with the obtained data [14, 15].

The eating behavior of a child with ASD is a constant source of stress for the family, which only exacerbates the existing problem.

Malnutrition at the early childhood can lead to deficiency of body mass, height, or vice versa — to obesity in the future. In addition to metabolic changes, in children with ASD and ARFID, there are gastrointestinal tract disorders, the occurrence of allergic and deficient conditions (both macronutrient and micronutrient: mineral deficiencies, vitamin deficiencies) [17, 18]. Eating behavior disorders often underlie the development of functional disorders of the digestive system, which can transform into the organic chronic pathology [19], which was also observed in our patients in the study on the characteristics of the cerebrointestinal interaction, during which the markers of neuroinflammation in children with autism and concomitant functional pathology of the digestive system were identified [20, 21].

Selective nutrition in favour of the choice of wheat products, due to the convenience of intake and high availability for any family, is noted everywhere. There are views on the need to limit products of white wheat flour and products containing gluten, a so-called gluten-free diet [22-24]. Opinions on this issue vary, but surely, the refusal of gluten-containing products is not dangerous and cannot harm the health of the child [25–30]. The exceptions are cases in which a child with ASD may experience stress due to the abrupt withdrawal of the usual foods containing gluten.

In our study, cases of the negative effect of the elimination diet in the form of the emergence of protest behavior (aggression and auto-aggression) were also registered when white flour products were cancelled. It was found that in families of children with ASD, the level of stress in the family is significantly higher than in families raising normotypical children [30]. Based on the results of this study, recommendations were developed for the correction of ARFID in children with ASD based on applied behavior analysis. Separately it should be noted that, unfortunately, these recommendations did not take into account the presence of diseases of the digestive system and other concomitant somatic pathologies. That is why in our study, when making a plan for the correction of ARFID in children with ASD, anamnestic features were always taken into account and the concomitant somatic pathology diagnosis was carried out, which affects the child's eating behavior and which needs to be corrected in the first place.

To correct eating behavior in children with ASD, individual correcting programs were used and, if necessary, a transdisciplinary team of specialists was involved, consisting of a paediatrist, gastroenterologist and nutritionist, correctional teacher and psychologist.

The effectiveness of the correction of eating behavior was demonstrated in 83.8% of children with ASD. At the same time, the appetite improvement, the expansion of the diet, the normalization of stool was accompanied not only by improvement of psycho-cognitive indicators (improvement of social contact, a decrease in the frequency of unwanted behavior, normalization of night sleep), but also by a regression of clinical manifestations of functional disorders of the digestive system.

An integrated individual approach allows achieving the normalization of eating behavior, improving the state of somatic health in a child with ASD, and also contributes to the harmonization of intra-family relations.

CONCLUSIONS

Eating behavior is an essential component of autistic disorders in children. The most common pattern of eating behavior in ASD is selective eating behavior. The formation of eating behavior in a child with ASD is influenced by many factors, among which irrational

nutrition of the mother during pregnancy, peculiarities of family food traditions, problems of breastfeeding and complementary feeding, the presence of concomitant pathology and forced keeping to elimination diets. The presented factors, together with the problems of socialization, require careful further study.

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ORIGINAL ARTICLE

SURGICAL TREATMENT OPTIMISATION OF RECURRENT ABDOMINAL WALL HERNIAS ASSOCIATED WITH LIGATURE FISTULA

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ABSTRACT

The aim: To improve the efficiency of treatment of recurrent abdominal wall hernia associated with ligature fistula.

Materials and methods: We analysed the results of treatment of recurrent hernias with ligature fistula in 86 patients. 44 patients of group 1 were treated according to the developed algorithm (fistula and mesh explantation, wound debridement, mesh fixation and wound closure with antiseptic-containing polyurethane composite), 42 patient (group 2) were treated according to the traditional one.

Results: Decreased rate of seroma formation in group 1 if compared to group 2 was observed up to 6,7% against 23,8% (OR=0,23; 95%CI=0,06-0,92; p=0,038). Wound infection occurred in 1 (2,3%) case of group 1 against 7 (16,7%) of group 2 (OR= 0,12; 95% CI =0,01-0,99; p=0,027). 4 (9,5%) patients from group 2 developed recurrent ligature fistula (OR= 0,10; 95%CI= 0,01-1,90). Recurrence of hernia was observed in 1 (2,9%) patient of group 1 against 6 (17,7%) patients of group 2 (OR=0,14; 0,01-1,21; p=0,048).

Conclusions: Surgical treatment optimisation of recurrent abdominal wall hernia associated with ligature fistula improved the efficiency of treatment, which was proven by the obtained outcomes and relative risk of complications.

KEY WORDS: recurrent ventral hernia, recurrent inguinal hernia, ligature fistula, polyurethane composite, mesh repair

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INTRODUCTION

Mesh reinforcement is considered the standard for repair of the abdominal wall hernias because it is associated with decreased hernia recurrence rates [1-3]. But the risk of recurrence increased in patients who developed wound complication such as surgical site infection (SSI) including ligature fistula [1,4]. Authors reported that recurrent hernias occurred in more than 25% of patients who developed SSI after abdominal wall reconstruction [5]. This happens because healing process becomes slow in contaminated fields, which causes the lack of formation of vascularised granulation tissue required for proper mesh incorporation [3, 6]. As a result some parts of mesh don't incorporate leading to mesh migration and shrinkage, which makes the basis for recurrence [7]. Ligature fistula formation as a part of SSI is associated with bacterial contamination of ligatures which are used in mesh fixation [8, 9]. When mesh is situated at the bottom of the fistulous track, the recurrent hernia associated with ligature fistula occurs [10, 11].

Traditional single- or multistaged algorithm of recurrent ventral hernia with ligature fistula treatment includes re-operation, excision of ligature fistula, mesh explantation, wound debridement with antiseptics, antibiotic treatment and abdominal wall repair [3, 10, 12]. According to the scientific reports the outcomes haven't been successful because mesh explantations caused hernia recurrence in more than 40% of patients [13, 14]. on the other hand definitive repair with synthetic mesh, fixed with ligatures in contaminated surgical field is associated with high risk of infection [15].

In our opinion optimisation of traditional treatment algorithm of recurrent abdominal wall hernia with ligature fistula by the use of antiseptic-containing cross-linked polyurethane (PU) composite for mesh fixation without ligatures will improve postoperative outcomes.

THE AIM

To improve the efficiency of treatment of recurrent abdominal wall hernia associated with ligature fistula.

MATERIALS AND METHODS

A prospective-retrospective observational study of 5 years from November 2017 to January 2023 was undertaken at the Department of Surgery and Proctology,

of Shupyk National Healthcare University of Ukraine. Eighty six patients with recurrent abdominal wall hernia associated with ligature fistula, who required surgical treatment were randomly selected from elective surgeries. Out of the total 86 patients, 42 (48,8%) were male and 44 (51,2%) were female, with their mean age of 56,6 ± 1,4 years (from 40 to 75 years). The postoperative follow-up period was 24 months. 47 (54,6%) patients had concomitant diseases, among them cardiovascular comorbidities were the most common ones. Mean time of recurrence after mesh reinforcement was 4 ± 1,2 months. Recurrent ventral hernia with ligature fistula occurred after "sublay" technique in 24 (27,9%) patients, "onlay" – in 51 (59,3%) patients, Lichtenstein technique after recurrent inguinal repair in 11 (12,8%) cases.

Patients were divided into 2 groups depending on the treatment algorithm. Group 1 (main) included 44 (51,2%) patients, who were treated according to the developed algorithm. Group 2 (comparison) was retrospective and included 42 (48,8%) patients, who were treated according to the traditional algorithm.

There was no significant difference between groups 1 and 2 regarding hernia types, presence of ligature fistula, sex and age.

Recurrent hernia with ligature fistula treatment consisted of two stages in main and comparison groups. The first treatment stage of both groups included opening an external sinus of fistula, microbiological analysis of fistula fluid with antibiotic sensitivity testing, X-ray fistulography of fistula track, repeated debridement with antiseptic 0,02% decamethoxine solution during 5 days, excision ligatures, antibiotic therapy according to the results of microbiological examination. The analysis of X-ray fistulography showed that mesh was situated at the bottom of the fistulous track in all patients of both groups.

The second stage of treatment was different for groups 1 (main) and 2 (comparison). In group 1 the patients were treated according to the developed algorithm. After coloring, fistula track was removed with surrounding tissues and those parts of mesh, which didn't incorporate, were discharged from the edge of the abdominal wall defect and were situated at the bottom of fistula. Mean size of the removed mesh was 10x6 ± 1,2 cm in recurrent ventral hernias and 6x3 ±1,1cm in recurrent inguinal hernias. The wound was debrided with antiseptic 0,02% solution of decamethoxine. Polypropylene mesh was used for reinforcement of the abdominal wall whereas cross-linked polyurethane (PU) composite containing an antiseptic substance, decamethoxine, was used for mesh fixation. The mesh was completely covered with PU composite. The subcutaneous layer of wound wasn't closed with sutures but with decamethoxine-containing PU composite, which has high adhesive degree for adipose tissue. When the patients having undergone "sublay" hernia repair during previous surgery, "onlay" technique was performed, after "onlay" repair "sublay" technique was performed, after Lichtenstein repair transinguinal pre-peritoneal hernioplasty was performed. The size of mesh used in incisional hernia repair was 15x12 cm, in inguinal repair – 12x10 cm. All patients received antibiotic therapy during postoperative period.

All patients of group 2 (comparison) were treated according to the traditional argorithm, which included coloring fistula track, fistula excision with surrounding tissues and parts of mesh, which weren't incorporated, were discharged from the edge of the abdominal wall defect and were situated at the bottom of fistula. Mean size of the removed mesh was 10x6 ± 1,2 cm in recurrent ventral hernias and 6x3 ± 1,15 cm in recurrent inguinal hernias. The wound was debrided with antiseptic 0,02% solution of decamethoxine. Polypropylene mesh was used for abdominal wall reinforcement and was fixed with ligatures. The wound was traditionally closed with sutures. We performed the same techniques of placement the mesh during hernia repair in both groups 1 and 2. During postoperative period all patients also received antibiotic therapy.

The data of occurrence of postoperative complications (seroma formation, wound infection, recurrent ligature fistula and recurrence of hernia) was analysed to demonstrate the treatment efficiency.

All analyses were calculated using the STATA version 12.0 (Stata Corporation, College Station). We performed the Fisher exact test, Student's t test and determined the relative risk of complications.

RESULTS

Table I shows the frequency of postoperative complications in patients of both groups 1 (main) and 2 (comparison) (Table I).

In short-term outcomes 3 (6,7%) patients of group 1 developed seroma formation if compared to 10 (23,8%) patients of group 2. Seroma treatment was conservative and included antibiotic therapy, aspiration of seroma fluid with ultrasonography.

Wound infection was observed in 1 (2,3%) patient of the main group 1 (main) and in 7 (16,7%) patients of group 2 (comparison). The treatment of wound infection was traditional in both groups, which included conservative therapy, that is wound debridement with antiseptics and antibiotic therapy.

No evidence of ligature fistula was observed in any patient of group 1 (main), due to the use of cross-linked

Table I. Frequency of postoperative complications in patients with recurrent abdominal hernia associated with ligature fistula in group 1 (main) and group 2 (comparison).

Complication	I group (main) n = 44		II group (comparison) n = 42		P(I-II)	OR (CI)
	events	rates (%)	events	rates (%)		
Seroma formation	3	6,7	10	23,8	p=0,038*	0,23 (0,06-0,92)
Wound infection	1	2,3	7	16,7	p=0,027*	0,12 (0,01-0,99)
Recurrent ligature fistula	0	0	4	9,5	-	0,10 (0,01-1,90)
Recurrence of hernia	1/35	2,9	6/34	17,7	p=0,048*	0,14 (0,01-1,21)

(p < 0,05)* – significant difference between groups; Haldane-Anscombe correction for case the frequency of the studied group was equal to zero.

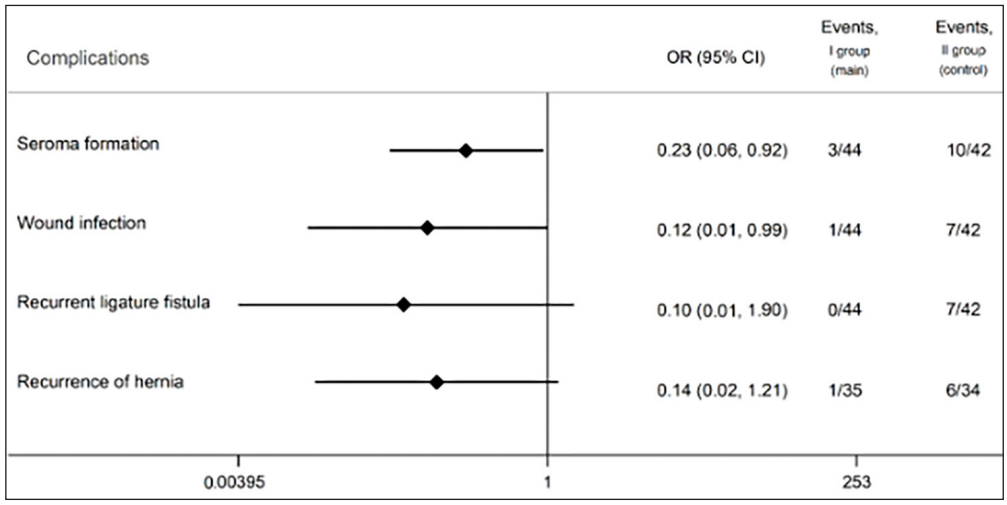

Fig. 1. Assessment of the risk of postoperative complications in groups 1 and 2.
OR – odds ratio, 95% confidence interval

PU composite for mesh fixation instead of ligatures. While in group 2 (comparison) ligature fistula occurred in 4 (9,5%) patients. (OR= 0,10; 95%CI= 0,01-1,90).

The wound healing time was shorter in group 1 compared with group 2 and lasted during 6±1,03 days against 14±2,05 days. (p=0,0001).

To obtain the long-term outcomes we examined 35 patients of group 1 (main) and 34 patients of group 2 (comparison) in the period of 6, 12 and 24 months after surgery intervention. Ultrasonography examination of abdominal wall was also performed. The recurrence of hernia occurred in 1 (2,9%) patient of group 1 (main) and in 6 (17.7%) patients of group 2 (comparison).

Figure 1 shows the assessment of the risk of postoperative complications in groups 1(main) and 2 (comparison).

DISCUSSION

Decreased rate of seroma formation in group 1 (main) if compared to group 2 (comparison) was observed up to 6,7% against 23,8% (OR=0,23; 95%CI=0,06-0,92; p=0,038), due to high adhesive degree of (PU) composite with decamethoxine which improves fixation of polypropylene mesh and musculo-aponeurotic tissues. Moreover, adhesion of adipose tissue with (PU) composite prevented occurrence of dead space and wound exudation by formation of a connective tissue. According to the report connective tissue capsule which surrounded polyurethane (PU) composite is represented by macrophages and fibroblasts which were actively producing collagen and other components of the extracellular matrix [16].

Lower rate of wound infection in group 1 (2,3% vs 16,7%, OR= 0,12; 95% CI =0,01-0,99; p=0,027) was reached due to the use of (PU) composite, which provided the formation of a connective tissue capsule which together with the presence of antiseptic inside the wound reduced the risk of infection.

In group 1 secondary hernia recurrence occurred 2 months after treatment in 1 (2,9%) patient with inguinal hernia, who developed wound infection and suffered from diabetes mellitus. No incidence of recurrence among other 35 (79,5%) examined patients from the main group was observed in the period of 24 months after treatment according to develop algorithm. Among 34 (80,9%) patients from group 2 (comparison) the recurrent hernia occurred in 6 (17,7%) patients (OR=0,14; 0,01-1.21; p=0,048), who also developed wound infection and ligature fistula formation. One patient underwent inguinal hernia repair surgery and 5 patients underwent incisional hernia repair. All recurrence events occurred during the first 6 months after traditional treatment algorithm

in case of SSI. This supports the fact that SSI increases the risk of recurrence [13].

The long-term outcomes of surgical treatment of recurrent abdominal wall hernias with ligature fistula proved that the efficiency of the developed treatment algorithm used in group 1 is higher, which was provided by the use of cross-linked PU composite containing antiseptic substance of decamethoxine. In addition, the absence of ligatures for mesh fixation and adipose tissue suturing as well as dead spaces formation, prevented by the use of antiseptic-containing PU composite, reduced the risk for seroma formation, wound infection and hernia recurrence.

CONCLUSIONS

Surgical treatment optimisation of recurrent abdominal wall hernia associated with ligature fistula including fistula debridement, mesh fixation and wound closure with antiseptic-containing cross-linked PU composite, in comparison with the traditional algorithm, improved the efficiency of treatment, which was proven by the obtained outcomes and relative risk of complications, such as the reduced rate of seroma in group 1 up to 6,7% against 23,5%, wound infection up to 2,3% against 16,7%, ligature fistula formation up to 0% against 9,5% and hernia recurrence up to 2,9% against 17,7%.

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ORIGINAL ARTICLE

EFFECT OF INTERMITTENT FASTING ON CARBOHYDRATE, LIPID AND ULTRASONOGRAPHIC PARAMETERS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND PREDIABETES

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ABSTRACT

The aim: To study intermittent fasting (IF) treatment in patients with non-alcoholic fatty liver disease (NAFLD) and prediabetes.

Materials and methods: Patients with NAFLD (n=95) were examined. The patients were divided into 2 groups: Group 1 – NAFLD with obesity, Group 2 – NAFLD and prediabetes. All patients in both groups had Body mass index (BMI) within the 2nd degree of obesity range (30.0 kg/m^2 to 34.5 kg/m^2).

Results: The effect of IF on anthropometric parameters, carbohydrate and lipid levels in patients with NAFLD with obesity and NAFLD with prediabetes, 6 and 12 months after treatment is shown.

Conclusions: Intermittent fasting has a statistically significant effect on anthropometric parameters in NAFLD with obesity and NAFLD with prediabetes. Metformin administration after intermittent fasting in 12 months showed a statistically significant improvement in lipid and carbohydrate profiles.

KEY WORDS: Ultrasonography, non-alcoholic fatty liver disease, daily blood pressure monitoring

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INTRODUCTION

Today, non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in European countries and the United States, occurring in one third of the adult population of some countries [1, 2]. According to the latest data, it is also one of the leading diseases in Ukraine, especially among patients with metabolic syndrome manifestations. Experts predict that NAFLD will become the most common cause of liver transplantation by 2030 [3-5].

The accumulation of fat in the liver disrupts the mechanisms that control metabolic reactions [6]. Lipidomic studies have revealed a potential link between lipotoxicity, inflammation, oxidative stress, and cellular function [6].

Many scientists have investigated the disorders of carbohydrate and lipid metabolism in the pathogenesis of NAFLD and proved it`s important role [7]. The pathogenesis of NAFLD is based on a decrease in tissue sensitivity to insulin, and disorders of carbohydrate metabolism are independent factors of cardiovascular risk [8]. A close relationship between proatherogenic dyslipidemia and the severity of arterial endothelial damage in hypertension has been proven [8]. Proatherogenic dyslipidemia, primarily hypertriglyceridemia, plays a significant role in the onset and progression of NAFLD. Treatment of NAFLD remains extremely difficult [9].

In recent years, the intermittent fasting (IF) method has been used to treat patients with NAFLD [10-12].

THE AIM

To study IF treatment in patients with NAFLD and prediabetes.

MATERIALS AND METHODS

Patients with NAFLD (n=95) were examined. The patients were divided into 2 groups: Group 1 – NAFLD with obesity (n=25), Group 2 – NAFLD and prediabetes (n=70). All patients in both groups had Body mass index (BMI) within the 2nd degree of obesity range (30.0 kg/m2 to 34.5 kg/m2). Group 2 after IF was divided into 2 subgroups: 2a – received metformin at a dose of 500 mg 1 p/d for 6 months, while 2b – did not receive metformin. In these groups, anthropometric parameters (AP), carbohydrate and lipid metabolism were assessed: before treatment, after 6 and 12 months. To compare some of the indicators, a control group of practically healthy individuals were included in group 3 (n=20).

Table I. Dynamics of anthropometric parameters of patients of group I under the influence of the prescribed treatment (M±m)

Comparison group		Anthropometric indicator				
		Body weight, kg	BMI, kg/m²	WC, м	WH, м	WC / WH, un
Group I (n = 25)	Before treatment	98,44 ±9,25	32,91 ±1,45	1,18 ±0,17	1,14 ±0,15	1,05 ±0,16
	After 6 months	86,92 ±8,36	29,07 ±1,22	1,02 ±0,57	1,08 ±0,49	0,95 ±0,53
	After 12 months	74,28 ±7,52	24,84 ±1,31	0,86 ±0,71	0,97 ±0,62	0,89 ±0,22
p0-6		<0,01*	<0,01*	0,14	0,51	0,31
p0-12		<0,01*	<0,01*	0,02*	0,14	0,02*
p6-12		<0,01*	<0,01*	0,33	0,44	0,69

Note: n - number of patients; p0-6 - significance of the difference in the indicators of patients I before treatment and after 6 months; p0-12 - significance of the difference in the indicators of patients I before treatment and after 12 months; p6-12 - significance of the difference in the indicators of patients I after 6 and 12 months of treatment; * - statistically significant difference when comparing indicators in dynamics.

Table II. Dynamics of anthropometric parameters of patients of group II under the influence of the prescribed treatment (M±m)

Comparison group		Anthropometric indicator				
		Body weight, kg	BMI, kg/m²	WC, м	Body weight, kg	BMI, kg/m²
Group II (n = 25)	Before treatment	99,48 ±10,25	33,22 ±1,11	1,17 ±0,19	1,14 ±0,15	1,05 ±0,19
	After 6 months	89,42 ±9,77	29,58 ±7,61	1,12 ±0,42	1,10 ±0,22	1,02 ±0,36
	After 12 months IIa	91,23 ±7,68	30,51 ±6,32	1,08 ±0,53	1,06 ±0,21	1,02 ±0,31
	After 12 months IIb	98,23 ±7,66	30,51 ±5,28	1,15 ±0,18	1,09 ±0,13	1,04 ±0,15
p0-6		0,06	0,24	0,55	0,41	0,68
p0-12		0,01*	0,05*	0,38	0,09	0,65
p6-12		0,16	0,55	0,74	0,47	1,00

Note: n - number of patients; p0-6 - significance of the difference in the indicators of patients I before treatment and after 6 months; p0-12 - significance of the difference in the indicators of patients I before treatment and after 12 months; p6-12 - significance of the difference in the indicators of patients I after 6 and 12 months of treatment; * - statistically significant difference when comparing indicators in dynamics.

Patients were recruited on an outpatient basis at the Department of Internal Medicine and Family Medicine. We studied the IF methodology in 50 patients, which was as follows: patients fasted for 5 days, followed by 10 days of recovery based on the DASH diet with a total caloric intake of 900 kcal/day (45% carbohydrates, 45% fat, 10% protein): breakfast of cereal or muesli, tea or coffee; lunch: chicken breast, rice, boiled egg (optionally, salmon baked with broccoli or baked chicken with vegetables), and dinner: 90 g of lean animal meat (veal, rabbit, etc.), 1 baked potato with olive oil, 1 slice of low-fat hard cheese, several slices of whole grain bread, 1 fruit, 200 ml of 1.5% milk.

All patients were monitored for 12 months, with two IF cycles for the first 3 months. For the next 6 months after IF, patients were on the DASH diet, which consisted of 50% to 65% of total energy intake from carbohydrates, 15% to 20% from protein, and 20% to 30% from fat, and ≥5 g of fiber per serving. From the 10th to the 12th month of the study, patients were treated once a month with IF. Some patients tolerated IF better during the period of religious fasting.

The diagnostic criteria for prediabetes were as follows: fasting FPG – 5.6-6.9-7 mmol/L; 2 hours after a meal FPG – 7.8-11 mmol/L; HbA1C – glycated hemoglobin – 5.7-6.4%.

RESULTS

It is noteworthy that after 6 months in patients of group 1, there were statistically significant changes in AP in all studied indicators. Patients in this group repeated the course of treatment and after 12 months, AP improvement was statistically significant. Thus, intermittent management of NAFLD is effective (Table I).

In patients with NAFLD with prediabetes, a decrease in body mass index and body weight was observed

Table III. Indicators of dyslipidemia in the examined patients (M±m)

Lipid profile parameter	Group of examined patients			Reliability indicator		
	Group I (n=25)	Group II (n=25)	Group III (n=20)	pI-II	pI-III	pII-III
Total cholesterol, mmol/l	5,18±1,06	5,75±0,83	4,03±0,66	<0,01*	<0,01*	<0,01*
HDLC mmol/l	1,23±0,35	1,04±0,34	2,27±1,76	<0,01*	<0,01*	0,01*
LDL, mmol/l	3,12±0,50	4,28±0,49	2,71±0,34	<0,01*	<0,01*	<0,01*
LDLC,mmol/l	1,04±0,32	1,34±0,55	0,83±0,13	0,01*	0,01*	<0,01*
Triglycerides, mmol/l	3,80±1,45	4,65±1,45	1,84±0,26	<0,01*	<0,01*	<0,01*
Atherogenicity coefficient	3,19±0,56	4,10±0,56	2,15±0,43	<0,01*	<0,01*	<0,01*

Note: n - number of patients; pI-II, pI-III, pII-III - reliability of the difference in the indicators of the respective groups; * - statistically significant difference when comparing the indicators between the respective groups ($p<0.05$).

Table IV. Dynamics of lipid profile parameters in patients of group I under the influence of the prescribed treatment (M±m)

Lipid profile parameter	Group of examined patients				Reliability indicator			
	Group I (n=25)			Group III (n=20)	p0-6	p0-12	p6-12	p12-III
	Before treatment	After 6 months	After 12 months					
Total cholesterol, mmol/l	5,19±1,06	4,39±2,08	3,22±1,72	4,03±0,66	0,08	<0,01*	0,03*	0,02*
HDLC mmol/l	1,28±0,36	1,47±0,46	1,82±0,42	2,27±1,76	0,09	<0,01*	0,01*	0,19
LDL, mmol/l	3,12±0,50	3,03±0,58	2,78±0,43	2,71±0,34	0,54	0,01*	0,07	0,49
LDLC,mmol/l	1,31±0,18	1,27±0,24	1,15±0,16	0,83±0,13	0,48	<0,01*	0,03*	<0,01*
Triglycerides, mmol/l	3,43±1,38	2,96±1,47	2,05±1,54	1,84±0,26	0,22	<0,01*	0,03*	0,47
Atherogenicity coefficient	3,63±0,29	3,14±0,58	2,44±0,74	2,15±0,43	<0,01*	<0,01*	<0,01*	0,07

Note: n - number of patients; p0-6 - significance of the difference in the indicators of patients of the corresponding group before treatment and after 6 months; p0-12 - significance of the difference in the indicators of patients of the corresponding group before treatment and after 12 months; p6-12 - significance of the difference in the indicators of patients of the corresponding group after 6 and 12 months of treatment; p12-III - significance of the difference in the indicators of patients of the corresponding group after 12 months of treatment and patients of group III; * - statistically significant difference when comparing indicators in dynamics.

Table V. Dynamics of lipid profile parameters in patients of group II under the influence of prescribed treatment (M±m)

Lipid profile parameter	Group of examined patients					Reliability indicator			
	Group II (n=25)				Group III (n=20)	p0-6	p0-12	p6-12	p12-III
	Before treatment	After 6 months	After 12 months, group IIa	After 12 months, IIb group					
Total cholesterol, mmol/l	5,17±1,07	4,28±0,15	4,26±0,54	5,09±0,75	4,03±0,66	0,46	<0,01*	<0,01*	0,16
HDLC mmol/l	1,17±0,34	1,27±0,76	1,23±0,39	1,15±0,37	2,27±1,76	0,72	0,55	0,87	0,01*
LDL, mmol/l	3,11±0,51	3,13±0,38	3,02±0,97	3,06±0,59	2,71±0,34	0,91	0,67	0,84	0,11
LDLC,mmol/l	0,77±0,14	1,39±0,27	0,81±0,72	0,87±0,15	0,83±0,13	0,94	0,78	0,87	0,88
Triglycerides, mmol/l	4,18±1,44	2,85±1,49	3,54±0,61	4,22±1,27	1,84±0,26	0,55	0,04*	0,11	<0,01*
Atherogenicity coefficient	2,72±0,34	3,12±0,70	2,39±0,37	2,6±0,33	2,15±0,43	0,30	<0,01*	0,08	0,03*

Note: n - number of patients; p0-6 - significance of the difference in the indicators of patients of the corresponding group before treatment and after 6 months; p0-12 - significance of the difference in the indicators of patients of the corresponding group before treatment and after 12 months; p6-12 - significance of the difference in the indicators of patients of the corresponding group after 6 and 12 months of treatment; p12-III - significance of the difference in the indicators of patients of the corresponding group after 12 months of treatment and patients of group III; * - statistically significant difference when comparing indicators in dynamics.

after 6 months, although these changes were not significant. It should be emphasized that patients with prediabetes in group 2a who took metformin after completion of intermittent fasting had much better AP compared with group 2b who did not take this drug (Table II).

Table VI. Indicators of carbohydrate metabolism in patients of groups I and II before treatment (M±m)

Indicator of carbohydrate metabolism	Indicator of carbohydrate metabolism			Reliability indicator		
	Group I (n=25)	Group II (n=25)	Group III (n=20)	pI-II	pI-III	pII-III
Blood glucose, mmol/l	5,35±0,58	6,8±0,54	4,08±0,59	<0,05*	<0,01*	<0,01*
HbA1c,%	5,22±0,28	6,38±0,60	5,13±0,44	<0,05*	>0,05	<0,01*
HOMA-IR	2,89±0,62	3,75±0,28	1,49±0,25	<0,05*	<0,01*	<0,01*

Note: n - number of patients; p - significance of the difference in the indicators of the respective groups; * - statistically significant difference when comparing the indicators between the respective groups.

Table VII. Indicators of carbohydrate metabolism in patients of groups I and II after treatment (M±m)

Indicator of carbohydrate metabolism	Indicator of carbohydrate metabolism					Reliability indicator		
	Group I (n=25)	Group II (n=25), after 6 months	Group II (n=25) after 12 months		Group III (n=20)			
			IIa group	IIb group		pI-II	pI-III	pII6-III
Blood glucose, mmol/l	4,7±0,33	4,6±0,51	4,1±0,48	6,41±0,21	4,08±0,59	>0,05	>0,05	<0,01*
HbA1c,%	5,0±0,18	5,06±0,37	5,0±0,5	6,85±0,51	5,13±0,44	>0,05	>0,05	<0,01*
HOMA-IR	1,9±0,59	3,25±0,29	2,92±0,21	3,13±0,38	1,49±0,25	<0,01*	>0,05	<0,01*

Note: n - number of patients; p - significance of the difference in the indicators of the respective groups; * - statistically significant difference when comparing the indicators between the respective groups.

The data obtained from the examination of patients with NAFLD confirm the link between the presence of NAFLD and lipid metabolism disorders. Thus, all patients with NAFLD included in the study were diagnosed with dyslipidemia. In addition, lipid metabolism parameters, except HDL, of patients with NAFLD were significantly higher than those of the control group (p≤0.01). The HDL-C level in patients with NAFLD was statistically significantly lower than in practically healthy individuals (p≤0.01).

Although the mean value of total cholesterol in group I (5.18±1.06 mmol/l) did not exceed the recommended level, dyslipidemia still occurred. Thus, the mean value of HDL cholesterol in patients of group I was 1.23±0.35 mmol/l, which indicated an average risk of atherosclerosis; the mean values of LDL and VLDL cholesterol in patients of group I were within the safe level and amounted to 3.12±0.50 mmol/l and 1.04±0.32 mmol/l, respectively. The mean value of triglyceride levels in patients of this group was within the limit level – 3.80±1.45 mmol/l. Despite the fact that the average value of LDL and VLDL in patients of group I did not exceed the norm, due to the reduced level of HDL, a moderate risk of atherosclerosis was observed in terms of the atherogenicity coefficient. The average value of the atherogenicity coefficient in patients of group I was 3.19±0.56, which was significantly (p<0.01) higher than in the control group – 2.15±0.43 (Table III).

Patients of group II had more pronounced lipid profile disorders compared to patients of group I and the control group (p≤0.01). The mean value of total cholesterol and HDL cholesterol in patients of group II was 5,75±0,83 mmol/l and 1,04±0,34 mmol/l compared to patients of group I was 5,18±1,06 mmol/l and 1,23±0,35 mmol/l.

During the study period, a clear trend towards improvement in lipid metabolism was observed among patients of group I who were on intermittent fasting: the mean value of total cholesterol significantly decreased by 37.96% after 12 months compared with baseline data (p<0.01) and by 26.65% compared with data after 6 months (p=0.03). In addition, the mean value of total cholesterol after 12 months in patients of group I was significantly lower than in practically healthy individuals (p=0.02). The mean value of HDL cholesterol in patients of group I after 12 months significantly increased by 42.19% compared with baseline (p<0.01) and by 23.81% compared with the mean value after 6 months of treatment (p=0.01). The mean value of LDL cholesterol significantly decreased after 12 months of treatment by 10.90% compared with the mean value before treatment (p<0.01). Moreover, there was no significant difference between the mean values of HDL and LDL levels of practically healthy individuals and the corresponding indicators of patients in group I after 12 months (p=0.19 and p=0.49, respectively). There was a significant decrease in the mean value of LDL-C level both after 12 months compared to baseline (by 12.21%, p<0.01) and after 12 months compared to the mean value after 6 months of treatment (by 9.45%, p=0.03). The

mean value of triglycerides significantly decreased after 12 months of treatment by 40.23% ($p<0.01$) compared with baseline data and by 30.74% compared with the data after 6 months ($p=0.03$) (Table IV).

Thus, due to the general tendency to improve lipid metabolism, patients in this group also showed an improvement in the atherogenicity coefficient, namely: at the beginning of the study, this indicator showed a moderate risk of atherosclerosis, after 6 months of treatment, the atherogenicity coefficient significantly decreased by 12.67% ($p<0.01$), thereby approaching normal ranges.

After 12 months of treatment, the aforementioned index decreased by 32.78% ($p<0.01$) and was within the normal range, as evidenced by the absence of significant changes between its average value after 12 months and the average value of this coefficient in practically healthy individuals (group III) ($p=0.07$).

Among patients of group II, statistically significant changes in the mean values of some lipid metabolism parameters were found. Thus, the mean value of total cholesterol significantly decreased after 6 months of treatment by 17.60% compared to baseline ($p<0.01$). It should be noted that after 12 months in patients of group 2a, all lipid profile parameters continued to remain normal, but they improved compared to those after intermittent fasting. It is noteworthy that the lipid profile in patients of group 2b after 12 months practically did not differ from that of patients with prediabetes before intermittent fasting (Table V).

From the above, it can be concluded that adherence to standard recommendations for nutrition and physical activity in patients with NAFLD with obesity and prediabetes was significantly effective, but did not provide a complete correction of lipid metabolism. The administration of metformin after intermittent fasting regulated lipid metabolism to the level of practically healthy individuals.

Indicators of carbohydrate metabolism are obviously most impaired in patients with diabetes mellitus, but they were statistically different in both obese patients and the control group. It is noteworthy that statistically significant differences between these subgroups were maintained in terms of glycated hemoglobin and insulin resistance index (Table VI).

After the treatment, carbohydrate metabolism parameters statistically significantly improved in obese patients with NAFLD and prediabetes after IF ($p<0.01$), both in terms of fasting glucose and glycated hemoglobin. It should be emphasized that metformin administration in the group with prediabetes after 12 months statistically significantly improved the HOMA-IR index (Table VII).

All patients had typical changes in the liver parenchyma in the form of diffuse echogenicity. There were 3 degrees of liver steatosis: Grade I – a slight increase in echogenicity of the liver parenchyma, normal visualization of the intrahepatic vessels and diaphragm; Grade II – a moderate diffuse increase in echogenicity of the liver parenchyma, a slight impairment of visualization of the intrahepatic vessels and diaphragm; Grade III – a marked increase in echogenicity of the liver parenchyma, visualization of the intrahepatic vessels, diaphragm and posterior part of the right lobe (RL) is significantly impaired or absent.

A comparative assessment of liver size was performed. An increase in liver size was found in the majority of patients – 83.9%. Indicators of the control group were determined within the normal range: the oblique vertical size of the RL was 14.67±0.42 cm, the thickness of the RL was 11.29±0.79 cm, the cranio-caudal size of the left lobe (LL) was 7.98±0.56 cm, the thickness of the LL was 6.52±0.27 cm, the thickness of the caudal lobe (TCL) was 1.75±0.28 cm. By all indicators, the difference between patients with NAFLD and the control group was significant ($p<0.001$).

At this stage of the study, the group of NAFLD with obesity and NAFLD with prediabetes were compared. Significantly larger sizes of the left and caudal lobes were found in patients with prediabetes. Thus, the index of TCL in them was 3.52±0.72 cm and was significantly higher than in patients with NAFLD and obesity ($p<0.05$).

The next step was a comparative characterization of portal hemodynamics of the portal vein (PV) and common hepatic artery (CHA). Statistically more significant changes were found in all parameters of the PV. Thus, the diameter of the PV was 10.01±1.56 mm in the group of NAFLD and prediabetes versus 9.57±1.01 mm in the group of NAFLD with obesity ($p<0.05$). Velocity indices also differed. Thus, Vmax PV, Vmin PV and Tmax PV were significantly lower in the group of NAFLD with prediabetes. The index of Tmax PV was 24.05±0.75 cm/s, in the comparison group of NAFLD with obesity – 22.24±0.70 cm/s ($p<0.01$).

The volume flow rate of the PV in patients with NAFLD with prediabetes exceeded the results of the control group and amounted to 1188.93±43.95 ml/min against 1069.21±57.19 ml/min in the group of NAFLD with obesity ($p<0.05$), which is probably due to an increase in the diameter of the vessel.

After the treatment, ultrasonographic parameters, including Doppler, did not change in all study groups. Statistically significant changes were characterized only by a decrease in steatosis.

DISCUSSION

NAFLD includes a wide range of liver diseases, ranging from simple steatosis to steatohepatitis, advanced fibro-

sis and cirrhosis, with histologic signs of damage [13]. Despite the high morbidity and mortality rate of NAFLD, no clear treatment method has been developed so far [14]. Lifestyle modification is one of the most valuable measures to improve the course of NAFLD. Many dietary regimens have been recommended with proven weight loss, reduced inflammation, and positive effects of IF on BP, laboratory parameters, cardiovascular and metabolic markers in patients with NAFLD [15].

Several dietary regimens have been proposed for patients with NAFLD: calorie restriction, low-carbohydrate, high-fat diets. With IF, patients are allowed to eat for a limited time and abstain from food and high-calorie liquids for the rest of the time in different regimens.

An argument in favor of IF may be that since there are different protocols for IF, it is more adaptable than other restrictive eating regimens such as the ketogenic diet, vegan diet, or daily calorie restriction.

It should be noted that IF without adequate protein replacement is a well-known cause of muscle wasting and should be avoided and not recommended for people with hormonal imbalances, pregnant and lactating women, young children, elderly adults, and immunocompromised individuals, including those with a history of serious illness, organ transplantation, and immunosuppressive medications.

Our proposed IF methodology has demonstrated positive results in reducing BMI and body weight, low-density lipoprotein cholesterol, total cholesterol, triglycerides, fasting plasma glucose, and liver ultrasound findings.

In addition, IF has a wide range of benefits for many diseases, including obesity, prediabetes, T2DM, and hypertension, and improves cardiovascular risk factors. Due to the lack of large randomized controlled trials on the effectiveness and side effects of IF in people with metabolic syndrome and NAFLD, prediabetes for a long time, it is difficult to determine the risk-benefit ratio of different IF regimens. To evaluate the effectiveness of lifestyle changes by incorporating IF, studies that evaluate long-term follow-up are needed.

CONCLUSIONS

According to epidemiologic studies, NAFLD is currently the most common chronic liver disease worldwide and occurs in approximately one-third of the adult population in most European countries. Recently, NAFLD has been considered as a multisystem disease, which is largely related to the components of the metabolic syndrome and associated with prediabetes. At the present stage, there are practically no recommendations for the treatment of NAFLD. The number of pharmacological agents with proven efficacy is limited. Therefore, in our work we studied the effect of IF on the course of NAFLD with obesity and prediabetes.

We have studied the features of the clinical course of NAFLD in patients with prediabetes and obesity, clarified ultrasound data on non-alcoholic steatosis and steatohepatitis in patients with prediabetes, and proposed an effective method of treatment for these patients.

In patients with NAFLD in combination with prediabetes, it was found that they are characterized by dyslipidemic changes, weight gain to the level of obesity, and impaired glucose metabolism.

The use of complex treatment, which included the appointment of IF, diet therapy, contributed to the regression of steatosis, improvement of AP, and indicators of lipid and carbohydrate metabolism ($p<0.05$).

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ORIGINAL ARTICLE

DETERMINANTS OF VACCINE HESITANCY AMONG PARENTS IN KYIV

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ABSTRACT

The aim: Assess of the determinants of vaccine hesitancy among parents regarding their children in Kyiv, Ukraine.

Materials and methods: Direct interview with survey on parents' attitudes and behaviors regarding their children's immunization. Vaccination hesitancy was determined with the median of responses and by self-reported question. The study was conducted among parents, whose children were patients at Children's hospitals, attend schools and kindergarten in Kyiv, Ukraine.

Results: The median of vaccine hesitancy was 14,2% of 797 parents in Kyiv. The results show that 81.5% of parents with university degree agree that vaccination of their child is important for the health of others in the community, whereas only 67% ($p \leq 0.05$) of people who graduated from high school supported this view. The only reason to vaccinate their child is so they can enter daycare or school was marked by only 4.5% of parents with university education background and 15.3% of people who graduated from high school ($p \leq 0,05$).

Conclusions: Vast majority of interviewed parents think that vaccines are important for their children; meanwhile only half of the parents fully trust the current National Immunization Schedule and fully agree that question of child vaccination is their responsibility. Consulting pediatricians and GPs are associated with more parental confidence than other medical workers. Main source of negative information about vaccines is the Internet, but some part of parents who received negative information indicates health care workers as a source of this information. Majority of parents thinks that their religion is compatible with vaccines.

KEY WORDS: vaccination, vaccine hesitancy, vaccine-preventable diseases, parental attitude

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INTRODUCTION

Vaccination is considered as one of the greatest medical achievements in the history of humanity [1]. Despite this fact Europe faced one of the biggest outbreaks of vaccine-preventable diseases – measles – in the last 20 years. The highest number of cases were reported in Ukraine: since the start of outbreak from summer of 2017 to the end of 2019, the Public Health Center of the Ministry of Health of Ukraine reported more than 115,000 cases and 40 deaths [2]. In addition, due to low vaccination coverage across Ukraine against other diseases like poliomyelitis (71.9%) diphtheria, pertussis and tetanus (72%), hepatitis B (68.7%) and Haemophilus influenza type b (62%) [3] (the information given with the lack of data from temporarily occupied territories in the east part of Ukraine and Crimea) there is a risk of increased incidence of these diseases. Among the reasons of the situation that exists in Ukraine today, vaccine hesitancy took one of the leading places. World Health Organization (WHO) admitted vaccine hesitancy as one of the ten biggest threats to global health in 2019. This complex problem is very context specific, varying across time, place and vaccines [4]. Vaccine-hesitant individuals are a heterogeneous group of people who hold varying degrees of indecision about specific vaccines or about vaccinations in general [5]. One of the main and largest groups are parents with their fears. Delivering security, awareness, accessibility to parents and identifying sources of negative information that they receive may vary from place to place. That is why it is important to have information not only at the National level, but also more specifically in the regions.

THE AIM

This research seeks to assess the determinants of vaccine hesitancy among parents regarding their children in Kyiv.

MATERIALS AND METHODS

Currently, there is no one universal instrument to perform assessment of vaccine hesitancy in different

populations. Previously, several groups have developed tools to identify the perceptions on the importance of vaccination and vaccine refusal in a medical school [6] and among healthcare workers [7]. For this cross-sectional study among parents, we adopt and use a questionnaire developed by the European Academy

Table I. Social characteristics of study sample

Social characteristic	Number	Percentages, %
Relationship to child		
Mother	760	95
Father	37	5
Parent ages		
18-29	247	30
>29	550	70
Marital status		
Married/Living with a partner	740	92
Single	16	3
Divorced	39	4
Widowed	2	1
Number of children in the family		
1-2	752	94
3-4	44	5
>5	1	1
Education		
No degree	1	1
School	58	7
University	738	92

Table II. Questions that concern parental beliefs

Item		Parent response	N (%)
Safety & efficacy	Q5. If you had another child today, would you want him/her to get all recommended vaccines?	Yes	593 (74,4)
		Yes, but only some of them	109 (13,7)
		No	76 (9,5)
		Don't know	19 (2,4)
	Q7. It is better for my child to develop immunity by getting sick than by getting vaccinated.	Yes	90 (11,3)
		No	703 (88,2)
		Hesitate to answer	4 (0,5)
	Q8. It is better for children to get fewer vaccines at the same time.	Yes	302 (37,8)
		No	493 (61,8)
		Hesitate to answer	2 (0,4)
	Q10. Overall I think vaccines are effective	Yes	675 (84,6)
		No	119 (14,9)
		Hesitate to answer	3 (0,5)
	Q13. New vaccines carry more risks than older vaccines	Yes	145 (18,2)
		No	647 (81,2)
		Hesitate to answer	5 (0,6)
	Q17. Overall I think vaccines are safe	Yes	576 (72,3)
		No	217 (27,2)
		Hesitate to answer	4 (0,5)

Table II. (continuation)

General attitudes	Q3. How confident are you that following the recommended vaccine schedule is good for your child(ren)?	Totally trust	474 (59,5)
		Don't agree with everything	323 (40,5)
	Q4. It is my role as a parent to question vaccinations".	Totally agree	459 (57,6)
		I agree	228 (28,6)
		Difficult to answer	55 (6,9)
		Disagree	25 (3,1)
		Strongly disagree	30 (3,8)
	Q9. It's important that child had her immunization	Yes	683 (85,7)
		No	107 (13,4)
		Hesitate to answer	7 (0,9)
	Q11. Vaccination of my child is important to keep other people in my community healthy.	Yes	642 (80,6)
		No	151(18,9)
		Hesitate to answer	5 (0,5)
	Q12. All "pediatric" vaccines that offered by the National Immunization Schedule are important.	Yes	578 (72,5)
		No	214 (26,8)
		Hesitate to answer	5 (0,7)
	Q14. Information that I receive about the vaccines which used in the National Immunization Schedule is reliable and true.	Yes	487 (61,2)
		No	299 (37,5)
		Hesitate to answer	11 (1,3)
	Q15. Vaccinating is a good way to protect my child from diseases.	Yes	678 (85,1)
		No	109(13,6)
		Hesitate to answer	10(1,3)
	Q18. Vaccines are compatible with my religious beliefs	Yes	686 (86,2)
		No	108 (13,5)
		Hesitate to answer	3 (0,3)
	Q19. My child does not need vaccines for diseases that are not common anymore.	Yes	165 (20,7)
		No	630 (79,1)
		Hesitate to answer	2 (0,2)
	Q20. I wish children would receive vaccines when they are older	Yes	160 (20,1)
		No	630 (79,1)
		Hesitate to answer	7 (0,8)
Behavior	Q1. Have you ever delayed having one or all of your children vaccinated for reasons other than illness or allergy?	Yes	397 (49,8)
		No	393 (49,3)
		Do not remember	7 (0,9)
	Q2. Have you ever refused to have one or all of your children vaccinated for reasons other than illness or allergy?	Yes	278 (34,8)
		No	514 (64,5)
		Do not remember	5 (0,7)
	Q6. The only reason I have my child / children vaccinated is so they can enter daycare or school.	Yes	41 (5,2)
		No	756 (94,8)
	Q16. Generally, I do what my doctor or health care provider recommends about vaccines for my child	Yes	543 (68,1)
		No	247 (30,9)
		Hesitate to answer	7 (1)

of Paediatrics Research in Ambulatory Setting Network (EAPRASnet) [8].

The survey contains 31 items: 10 items were about socio-demographic information and 21 questions about attitude to vaccination which utilizes different response formats: variations of multiple choice questions (e.g. depending on the context – "Yes", "Yes, but for some of them", "No", "Hesitate to answer" or "Don't know") and

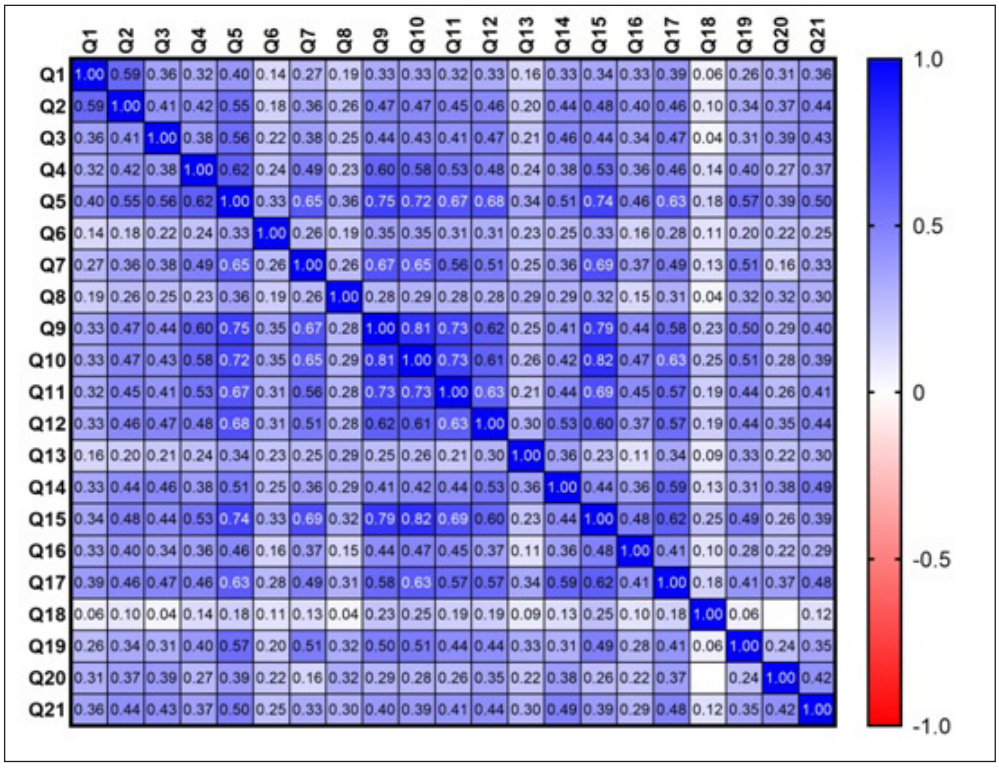

Fig. 1. Correlation analysis between defined questions

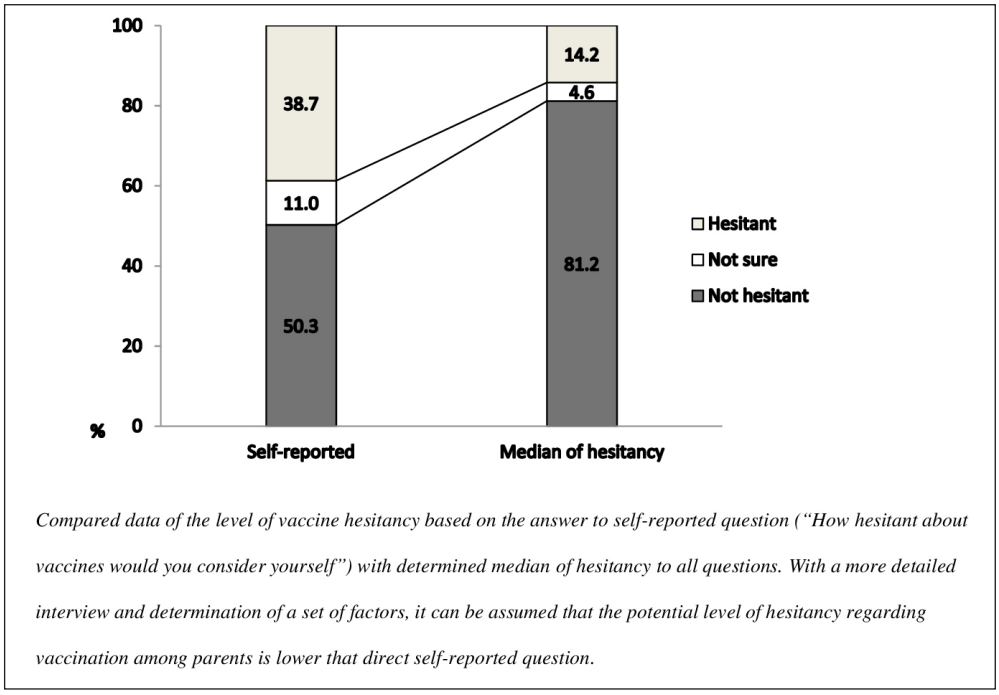

Fig. 2. Level of vaccine hesitancy among interviewed parents

5-point Likert scale ("Strongly agree", "Agree", "Not sure", "Disagree", "Strongly Disagree") . Responses related to vaccine hesitancy are assigned as 2 points, uncertain responses – 1 point and 0 point for non-hesitant answer. Median of hesitancy was determined for every responder based on response to 20 defined questions. The question: "How hesitant about vaccines would you consider yourself" was chosen to identify self-reported confidence.

Unlike a previous work [7], where Ukraine was a part of a large-scale study, parents were interviewed directly with the prior personal informed consent. The study was conducted among parents, whose children were inpatients at Children's clinical hospital №2, Children's Clinical Hospital №9, Children's Clinical Hospital №6, attended School №5 and Kindergarten № 581 in Kyiv, Ukraine.

The data collected from the questionnaire were statistically analyzed with Statistical Package for Social Science (SPSS version 12.0). A non-parametric Spearman rank correlation test was used for the correlation

analysis and performed using Graphprizm programm. The critical level of significance was estimated to be equal to or less than 0.05

RESULTS

The study took place in Kyiv and was conducted from 2019 to 2020. Total number of responses at the end of the study – 797. The numbers and socio-demographic characteristics of the sample are present in Table I.

For convenience the 20 items were divided into separate blocks. Distribution of parental responses are presented in Table II.

CORRELATION ANALYSIS

Correlation analysis between answers to 20 defined questions and one clarifying question of the questionnaire were performed (Figure I.).

According to the data of the correlation analysis, statistically significant connections were established between the majority of the answers to the questions. The strongest correlation was between following questions: (1) Q15 ("*Vaccinating is a good way to protect my child from diseases")* and Q10 *("Overall I think vaccines are effective");* (2) Q9 *("It's important that child had her immunization"*) and Q10; (3) Q15 and Q9.

LEVEL OF VACCINE HESITANCY IN KYIV

Vaccination hesitancy was assessed by calculating the median of 20 responses for each respondent. The group of those who did not hesitate included respondents with a median of 0 to 0.5 (83.1% responders), those who were not sure -1-1.5 (2.7%), and those who were completely hesitant had a median of 2 (14.2%). Evaluation of all respondents were compared with the answers to the question Q21 "*How hesitant about vaccines would you consider yourself*". Results are presented in Figure II.

Compared data of the level of vaccine hesitancy based on the answer to self-reported question ("How hesitant about vaccines would you consider yourself") with determined median of hesitancy to all questions. With a more detailed interview and determination of a set of factors, it can be assumed that the potential level of hesitancy regarding vaccination among parents is lower that direct self-reported question.

ASSOCIATIONS BETWEEN EDUCATION OF PARENTS AND THEIR HESITANCY

The part of study was supposed to determine the impact of parental education on taking decision about vaccination. We compared two groups: parents who only graduated from high school and those who have university degree. The results show that 81.5% of parents with university degree agree that vaccination of their child is important for the health of others in the community, whereas only 67% ($p \leq 0.05$) of people who graduated from high school supported this view. The only reason to vaccinate their child is so they can enter daycare or school was marked by only 4.5% of parents with university education background and 15.3% of people who graduated from high school ($p \leq 0, 05$). Half of the parents in both groups fully trust the current National Immunization Schedule and fully agree that question of child vaccination it is related to their role as parents.

INFLUENCE OF CONSULTATIONS OF HEALTH-CARE WORKERS OF DIFFERENT SPECIALTIES ON PARENTS' DECISION REGARDING VACCINATION

The reported health care professionals who parents usually consult with were a pediatrician (79.9%), a general practitioner (GP – 18.2%), a homeopathist (1.5%) and a nurse (0.4%). During analysis we found that 89% of parents that consulted with a pediatrician and 88.1% of parents consulted with a GP versus 60.7% of parents consulted by other healthcare workers did not agree with the statement "It is better for my child to develop immunity by getting sick than by getting vaccinated" ($p < 0.01$). The statement "*Overall I think vaccines are effective"* was supported by 86.1% and 83.2% of parents receiving advice from a pediatrician or a GP, against 60.7% ($p < 0.01$) of parents who consulted with people from other professions. Only 12.8% and 14% of parents who visit pediatricians and GPs, and almost half of parents who consult with other specialists, disagreed with the statement "*Having my child vaccinated is a good way to protect my child from disease*".

SOURCES OF NEGATIVE INFORMATION

From our study sample 785 respondents said that they received the negative information about immunization. Sources of information are presented in Figure III.

DISCUSSION

In this study, we used the calculated median of responses to the original study with Parent Attitudes about Childhood Vaccines scale (PACV) [9] and the previous study with a survey of parents in Ukraine [8]. We would like to note, that our correlation analysis showed statistically significant connections between the majority of the answers to the questions, and we assume that the

matter may be in the composition of the questionnaire questions.

Starting with the definition of vaccine hesitancy concept as one regarding a heterogeneous group of people, at the end of our study we realized that this is true not only for a country but also even within one city. In our sample of parents in Kyiv city, 49,8% want to delayed vaccination of their children, 34% have refused vaccinations; and 38,7% defined themselves as hesitant and 11% responded "not sure" to self-reported question on hesitancy. These numbers roughly reflect the same picture obtained in the framework of large scale study which took place in Ukraine before [8]. A comprehensive analysis of responses to all questions showed that the level of hesitation may actually be lower when asking additional or questions: only 14% of parents hesitant, and 4.2% were not sure. This can emphasize the complexity of the issue of vaccine hesitancy and how a number of factors can influence decision-making.

Vast majority of interviewed parents of our sample agree (85,7%) that vaccines are important for their children, and that overall vaccines are effective (84,6%). Virtually all parents indicated that they received negative information about vaccination. And the Internet was indicated most often as a source of negative data (30% of responders).

Taking a closer look at the data that were obtained in the neighboring to Ukraine country [10], we can try to extrapolate this and understand the impact that the Internet has on our population today – it has become a major source of information related to health. The lack of strategic and systematic work with the mass media only aggravates the situation.

In addition, according to our study, about 11% of parents identify health-care workers as source of negative information. Vaccine hesitancy among healthcare workers in Europe has been reported in many studies and it is important to realize that the roots of this belief grow back from medical school [11]. But in the course of analyzing the amount of hours spent on studying immunization to overall credits in combination with the senior colleagues' attitudes – we realized, these numbers are not surprising.

Importance of systemic strategy on dealing with vaccine hesitancy for achieving good results is currently demonstrated in the study from Switzerland [12]: thanks to the national research program and sequential exploratory mixed-methods design they can analyze Swiss context more deeply and make a decision based on this data.

Another interesting finding is that at a relatively low median of vaccine hesitancy, only half of all parents in the study fully trust the current National Immunization Schedule. Maybe closer work with pediatricians and GPs – health-care workers which parents trust more – can change the current situation.

The demonstration of heterogeneity of the issue is also interesting in terms of religion: according to our study in Kyiv the main questions of the questionnaire, in contrast to the re is no such problem in other European regions [13].

CONCLUSIONS

- Identification of vaccine hesitancy should include an integrated approach instead of self-reported and according to our study the prevalence of vaccine hesitant parents in Kyiv was 17,5%.
- Consulting pediatricians and GPs are associated with more parental confidence than other medical workers.
- Only half of the parents fully trust the current National Immunization Schedule and fully agree that question of child vaccination it is related to their role as parents.
- Main source of negative information about vaccines is the Internet.
- Majority of parents thinks that their religion is compatible with vaccines.

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ORIGINAL ARTICLE

BILATERAL CRYPTORCHIDISM IN PEDIATRIC SURGEON'S PRACTICE: CURRENT TACTICS OF PATIENT MANAGEMENT

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ABSTRACT

The aim: To provide best practices of disease management to improve treatment outcomes for this group of patients.

Materials and methods: The paper is based on first-hand experience in observing and treating 117 children aged from 6 months to 13 years with bilateral congenital cryptorchidism during a ten-year follow-up period, who were referred for surgical treatment, and 3 newborn boys with undescended testicles and testicular torsion. A complex of clinical and laboratory, instrumental, endocrinological, and genetic research methods was used for the survey of all patients.

Results: Recognizing the action of a common causative factor for bilateral cryptorchidism, which is a consequence of primary endocrine disorders, makes it possible to predict bilateral identity of the location of testicles in this pathology, which we observed in 81 patients: bilateral inguinal cryptorchidism was registered in 49 (41.88%) children, bilateral abdominal cryptorchidism – in 32 (27.35%) children, a combination of inguinal and abdominal cryptorchidism – in 24 (20.51%) children. The following types of treatment were used in the studied group of children: 1 – primary surgical intervention – 4 children, representing 3.42%. 2 – observation and non-surgical treatment by an endocrinologist – 113 (96.58%) children. 3 – comprehensive treatment (surgical correction after hormone treatment) – 67 (59.29%) children.

According to the research, hormone therapy had a positive effect on descent of the testicles in 89 (78.76%) patients: the testicles descended into the scrotum – in 22 (24.72%) children; the testicles descended in the inguinal canal – in 32 (35.95%) children; the testicles descended to the level of the opening to the inguinal canal – in 35 (39.33%) children.

Conclusions: 1. All doctors, starting from the maternity hospital, polyclinic, children's unit, should identify children with bilateral cryptorchidism. All children diagnosed with bilateral cryptorchidism are referred to a surgeon or endocrinologist. The parents of a child with bilateral cryptorchidism should immediately consult a doctor. The study of the reasons for late admission of children to the surgical hospital revealed that 76.92% of patients sought medical advice late, after 1 year of life. 2. At the stage of diagnosis and determination of treatment tactics, an examination by an endocrinologist and a geneticist is necessary; ignoring them is considered an error in diagnostic and therapeutic tactics, since the process of descent of the testicles into the scrotum is hormone-dependent. 3. The indications for primary surgical treatment of a child with bilateral cryptorchidism involve a combination of cryptorchidism with inguinal hernia and pain syndrome, which might be caused by testicular torsion. 4. Hormone therapy provides better results of surgical intervention in bilateral cryptorchidism. The ineffectiveness of two courses of hormone therapy necessitates surgical treatment. 5. Comprehensive treatment of children with bilateral cryptorchidism (non-surgical hormone therapy and surgical correction) has led to good postoperative results in 71.64% of patients, satisfactory results – in 22.39% of children, recurrences – in 5.97% of patients. 7. A long-term follow-up observation should be carried out by a surgeon and endocrinologist until patients reach their reproductive years.

KEY WORDS: bilateral cryptorchidism, children, diagnostics, inverted testis

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INTRODUCTION

Bilateral cryptorchidism (BC) is an urgent medical and social problem for the world and Ukraine. Periodic scientific discussions on the issue of cryptorchidism in children almost do not focus on bilateral cryptorchidism. However, the number of tactical diagnostic and treatment errors in this pathology remains high, despite the fact that patients with BC represent a large proportion of planned surgical corrections in childhood. Therefore, the issue of cryptorchidism in children remains relevant and outstanding today, despite a large number of publications on this topic, as there are still errors in diagnostic and treatment strategies of this pathology [1-3].

BC is a pathological condition defined as the failure of the testis to descend from the abdominal cavity into the scrotum in the antenatal period. It is one of the fairly common disorders of sexual development associated with the risk of infertility due to disorders of spermatogenic (reproductive) function. BC is a systemic disease, one of the symptoms of which is undescended testicles. Etiological factors of this pathology can involve de-

Table I. Number of pediatric patients with BC depending on the age and final diagnosis

Diagnosis/age	6 mths. - 1 yr.	1 yr. 1 mth. - 5 yrs.	5 yrs. 1 mth. - 10 yrs.	Over 10 yrs.	Total
Bilateral inguinal cryptorchidism	11	28	7	3	49 (41.88%)
Bilateral abdominal cryptorchidism	7	21	4	0	32 (27.35%)
Inguinal + abdominal	9	10	3	2	24 (20.51%)
Vanishing testes syndrome	0	9	3	0	12 (10.26%)
Total:	27(23.08%)	68 (58.12%)	17 (14.53%)	5 (4.27%)	117(100%)

creased production and impaired action of androgens, disorders of testicular organogenesis, 5α-reductase deficiency, androgen insensitivity syndrome, lack of gonadotropins, anti-Mullerian hormone, insulin-like factor 3, anatomical complications of testicular descent (inguinal canal obliteration, intra-abdominal adhesions, abnormal testicular fixation, inguinal hernia), dysplasia of connective tissue, which are found in more than 74% of patients with BC. The process of descent of the testicles into the scrotum is hormone-dependent. At present, most researchers consider hormonal disorders associated with dysregulation of the hypothalamic-pituitary-gonadal axis to be the main cause of BC.

The frequency of cryptorchidism among full-term children is 0.6-3.6%, among premature children – 30% or more. Clinical observations indicate that right sided cryptorchidism occurs in more than 50% of children, left sided – in 35-40% of cases, and bilateral – in 10-15% [4-7]. BC can be a component of many severe anomalies, such as congenital anomaly of the kidneys, hypospadias, prune belly syndrome, bladder exstrophy, gastroschisis and omphalocele, anogenital cleft, etc. Children with BC quite often have umbilical and inguinal hernia, congenital ophthalmocele, spinal curvature, broad nasal bridge, auricular dysplasia, abnormal occlusion, narrow palate, etc. Abnormal development of the central nervous system is registered in 83.3% of patients. Adiposis is significantly more common than in healthy boys. BC can be one of the manifestations of chromosomal pathology (Klinefelter's syndrome, gonosomic mosaicism, etc) [8-10].

The descent of the testicle depends on the interaction of hormonal and genetic factors that ensure the complex regulation of embryonic migration: insulin-like factor 3, differentiation of androgen producing Leydig cells and androgen receptor sensitivity, secretion of luteinizing hormone, the synthesis of which is carried out by the pituitary gland at 15-24 weeks of the fetal period. Testicles in boys are actively functioning, synthesizing anti-Mullerian hormone, which leads to regression of the Mullerian ducts, and testosterone. Testosterone and its active metabolite dihydrotestosterone are responsible for the formation of external and internal male genitalia. Low testosterone in boys at the 14th week of the fetal period will lead to violation of the process of fetal sex differentiation of varying degrees of severity (hypospadia, female structure of the external genitalia). Testosterone deficiency after the 14th week of intrauterine development will lead to underdevelopment of the external genitalia, often in combination with cryptorchidism [11, 12].

Nonpalpable testicles, according to Galvin D. et al. (2002), represent a unique problem both in terms of diagnosis and treatment. Until recently, the issues regarding management of children with BC have remained controversial [13]. Recommendations on this issue differ significantly depending on the position of the doctor and are not always sufficiently substantiated, and non-surgical, surgical and comprehensive treatment is used for correction without clearly defined indications. When the testicular tissue is damaged in cryptorchidism, the reproductive and hormonal function of the testicles suffers. Late diagnosis and treatment lead to infertility in 70% of patients, especially in BC [14, 15, 16].

The paper summarizes the data on first-hand experience in clinical observation of pediatric patients with BC.

THE AIM

Based on first-hand experience in observing and treating children with BC, to provide best practices of disease management to improve treatment outcomes for this group of patients.

MATERIALS AND METHODS

The paper is based on first-hand experience in observing and treating 117 children aged from 6 months to 13 years with bilateral congenital cryptorchidism during a ten-year follow-up period (Table I), who were referred for surgical treatment. The study was carried out on clinical sites of the Department of Pediatric Surgery of Shupyk National Healthcare University of Ukraine.

The largest number of children with BC in the study were aged 1-5 years (58.12%) and had bilateral inguinal cryptorchidism (41.88%). There were 27 boys under the age of 1 year, representing 23.08%.

In addition, 3 newborn boys with bilateral undescended testicles and testicular torsion were under observation. These children were premature; they were examined at the neonatal unit of the maternity hospital due to a sudden worsening of the condition (restlessness, food refusal, vomiting), which arose against the background of painful scrotal swelling and the presence of a bulge in the area of the inguinal canal. The children were examined by a pediatric surgeon within the first 3-4 hours from the onset of the disease. On the basis of clinical data, bilateral undescended testicles and testicular torsion were diagnosed, which was confirmed by Doppler ultrasonography.

Studying the reasons for the delay in seeking medical help (a total of 90 children older than 1 year, representing 76.92%) showed that 30% of parents considered their children to be healthy and did not consult a doctor (27 cases), 23 (25.55%) parents followed their pediatrician's advice to passively monitor their children until they reach an older age, 24 (26.67%) patients got advice from their surgeons to undergo surgical treatment at a later stage with an expectation of testicular descent with age, 16 (17.78%) patients followed their surgeon's advice to have surgical correction at an older age, considering it safer in terms of technical capabilities and general anesthesia, since the operation in young children is more complicated.

A complex of clinical and laboratory, instrumental, endocrinological, and genetic research methods was used for the survey of all patients.

Palpation of the inguinal region should be performed in the horizontal and vertical position of the child. If possible, the child is asked to strain or cough and the doctor tries to move the testicle into the inguinal canal, pressing on the lower abdomen from the top down.

The main diagnostic studies for BC are the following:

- visualization of the testicles by using ultrasound of the scrotum and inguinal canal to determine the location, size and structure of the testicle (CT without/with three-dimensional imaging and diagnostic laparoscopy are recommended as additional research methods) [17-20].

Doppler sonography is widely used to determine the state of vascularization. Laparoscopy, which is used in case of suspicion of an abdominal form of BC or vanishing testes syndrome, makes it possible to find the testicle, assess its condition, the condition of the internal inguinal ring, vessels and vas deferens.

- hormone testing (determining the level of luteinizing and follicle-stimulating hormones, prolactin, testosterone, estradiol, anti-Mullerian hormone, inhibin, etc);
- genetic testing (determination of sex chromatin, karyotyping, cytogenetic analysis of sex chromosomes in some cases).

Testing for human chorionic gonadotropin was performed when required. A positive test indicated the presence of testicles.

The compilation of best practices of pediatric surgeons, endocrinologists, and geneticists made it possible to develop recommendations for practical health care regarding management of patients with BC.

Statistical processing of research results was performed using standard methods with calculation of the relative value (absolute number of observations, percentage ratio).

RESULTS

Fifty-nine (50.43%) children in the study were overweight. Gynecomastia was registered in 7 (5.98%) boys, which was a consequence of endocrine disorders. Almost all children had hypoplastic (undeveloped) scrotum. Among the studied group of children, 28 (23.93%) had concomitant inguinal and/or umbilical hernias, 17 (14.53%) – hypospadia, 8 (6.84%) – abnormal occlusion, and 8 (6.84%) – neurological disorders.

Recognizing the action of a common causative factor for BC, which is a consequence of primary endocrine disorders, makes it possible to predict bilateral identity of the location of testicles in this pathology, which we observed in 81 patients, including 24 patients with a combination of different forms of cryptorchidism. Thus, among the studied group of 117 patients, bilateral inguinal cryptorchidism was registered in 49 (41.88%) children, bilateral abdominal cryptorchidism – in 32 (27.35%) children, vanishing testes syndrome – in 12 (10.26%) children, a combination of inguinal and abdominal cryptorchidism – in 24 (20.51%) children.

The following types of treatment were used in the studied group of children:

- primary surgical intervention – 4 children, representing 3.42%;
- observation and non-surgical treatment by an endocrinologist – 113 (96.58%) children;
- comprehensive treatment (surgical correction after hormone treatment) – 67 (59.29%) children.

Among 4 patients with BC who had indications for primary surgical treatment, 3 children had a combination of cryptorchidism with bilateral inguinal hernia and levels of gonadotropins within the age norm. One child with BC aged 13 years had complaints of pain in the undescended testicle, which arose after riding a bicycle and became an indication for surgical treatment. This child had a testicular torsion on the right side. Thus,

the indications for primary planned surgical intervention involved testicular retention in combination with inguinal hernias and BC, which was complicated by a testicular torsion. Newborns with a testicular torsion also underwent urgent surgery, namely detorsion and orchiopexy.

A low level of gonadotropins was registered in 98 (83.76%) children.

DISCUSSION

Until recently the issues regarding management of children with BC have remained controversial. The ratio between unilateral and bilateral cryptorchidism is 5:1, which was established by Odiorne W.B. and Simmons C.C. back in 1904 and is still relevant today [21]. In most children with BC, the level of luteinizing hormone was also low. It is luteinizing hormone deficiency that determines the effectiveness of hormone therapy for BC. Indeed, hormone therapy was effective in patients with low hormone levels. Therefore, children with a low level of gonadotropins first of all should consult an endocrinologist, who makes the decision on the need of hormone therapy. In the absence of effect, non-surgical hormone therapy is considered as preparation for surgical treatment. The ineffectiveness of two courses of hormone therapy necessitates surgical treatment.

Chorionic gonadotropin, pituitary gonadotropins, namely Prephyson, were used as a hormone therapy. There are reports of successful intranasal use of gonadotropin releasing hormone Kryptocur [14]. The hormone is usually prescribed twice a week for 4-5 weeks. Hormone therapy was ineffective in 24 (21.24%) children of the studied group.

In approximately 70% of cases BC is associated with reduced fertility [22].

According to the research, hormone therapy had a positive effect on descent of the testicles in 89 (78.76%) patients:

- the testicles descended into the scrotum – in 22 (24.72%) children;
- the testicles descended in the inguinal canal – in 32 (35.95%) children;
- the testicles descended to the level of the opening to the inguinal canal – in 35 (39.33%) children.

An increase in the size and testicular mobility in cryptorchidism occurred in most patients against the background of non-surgical hormone therapy.

Hormonal action provides certain guarantees of preserving fertility, improves the results of surgical treatment (reduction of postoperative recurrences); intraoperatively the testicles are easily separated from the surrounding tissues and descend into the scrotum without traction.

Comprehensive treatment of bilateral cryptorchidism was performed in 67 (59.29%) patients, namely surgical correction of the defect after two courses of hormone therapy. Among this group of patients, 32 boys had descent of the testicles in the inguinal canal, and 35 boys had descent of the testicles to a position near the internal inguinal ring against the background of non-surgical treatment.

Surgical treatment of BC involves sequential intervention first on one side. It is advisable to start the descent of the testicle from the side where the organ is relatively preserved. Our tactics of surgical treatment of children with BC involved moving and fixing undescended testicles sequentially. The surgery starts from the side where the testicle is located lower, is more mobile and more developed. If during surgery the testicle is absent in the inguinal canal and retroperitoneum, it is necessary to identify vas deferens, that will help find the testicle located high. Congenital testicular aplasia is diagnosed when vas deferens is identified as a blind ending. Thus, during the surgery for BC, it is necessary to find the testicle or any element of the spermatic cord. Operative exploration of these formations prevents diagnostic errors.

The following principal approaches should be followed when performing surgical intervention:

- mobilization of the elements of the spermatic cord not only in the inguinal canal, but also in the retroperitoneal space;
- with a high location of the testicle, the use of the technique of transposition of the vascular-nervous bundle and vas deferens by dissection of the deep inguinal ring, posterior wall of the inguinal canal and the intersection of the inferior epigastric vessels;
- preserving the distal portion of the processus vaginalis, which contributes to maintaining the optimal temperature regime, and also minimizes traumatization of the organ;
- less interruption of the inguinal canal structures to avoid additional plastics;
- testicular fixation without tension on the vascular bundle to preserve blood supply.

The results of surgical treatment of children with BC were evaluated as good, satisfactory and unsatisfactory. The results were considered as good when the testicles corresponded to the age norm in terms of size and consistency, or were larger than 50% of the age norm, were mobile, and were located in the scrotum. With satisfactory results, the testicles were smaller than 50% of the age norm, and were located in the upper third of the scrotum. The results were considered as unsatisfactory when the testicles were significantly reduced in size, traction to the root of the scrotum was observed.

Comprehensive treatment of children with BC has led to good postoperative results of surgical treatment in 48

(71.64%) patients, satisfactory results – in 15 (22.39%) children; 4 patients had recurrence of cryptorchidism, representing 5.97%.

CONCLUSIONS

1. All doctors, starting from the maternity hospital, polyclinic, children's unit, should identify children with BC. All children diagnosed with BC are referred to a surgeon or endocrinologist. The parents of a child with BC should immediately consult a doctor. The study of the reasons for late admission of children to the surgical hospital revealed that 76.92% of patients sought medical advice late, after 1 year of life.
2. At the stage of diagnosis of BC and determination of treatment tactics, an examination by an endocrinologist and a geneticist is necessary; ignoring them is considered an error in diagnostic and therapeutic tactics, since the process of descent of the testicles into the scrotum is hormone-dependent.
3. The indications for primary surgical treatment of a child with BC involve a combination of cryptorchidism with inguinal hernia and pain syndrome, which might be caused by testicular torsion.
4. Hormone therapy provides better results of surgical intervention in BC. The ineffectiveness of two courses of hormone therapy necessitates surgical treatment.
5. Comprehensive treatment of children with BC (non-surgical hormone therapy and surgical correction) has led to good postoperative results in 71.64% of patients, satisfactory results – in 22.39% of children. Four children had recurrences, representing 5.97% of the total.
6. A long-term follow-up observation should be carried out by a surgeon and endocrinologist until patients reach their reproductive years.

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ORIGINAL ARTICLE

INFLAMMATORY RESPONSE AND METABOLIC ADAPTATION IN CHILDREN WITH ACUTE RESPIRATORY PATHOLOGY

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ABSTRACT

The aim: To investigate the parameters change of the general immune responds and endocrine metabolism in the children with Acute Respiratory Pathology and their correlational relationship.

Materials and methods: The study group included: school-age children (10-14 years old) with a diagnosis of acute respiratory disease (ARI) as a general group of respiratory tract inflammatory diseases, of viral and bacterial origin (n=40), which included local inflammatory lesions of the respiratory tract and presented with acute pharyngitis (60.0%), acute bronchitis (20%), acute tonsillitis (22%) and a control group (n=25), identical in age and sex. The research was conducted at the clinical base of the CNE «UCChH» of the Uzhhorod City Council. General clinical, immunological studies, inflammatory response of the child's body were conducted. Statistical analysis of the results of the examination of patients was carried out using the Statistics for Windows v.10.0 computer program (StatSoft Inc, USA). The evaluation of the obtained results was carried out using parametric and non-parametric methods

Results: The inflammatory response parameters of the child's organism present indicative increases in the levels of cytokines with a significant predominance in comparison with the data of the children control group: the level of IL-1 increased in 2 times, IL-4 – in10 times, IL-6 – in 1.5 times, γ-IFN – in 3 times, TNF-α – in 25 times, Neopterin – in 9 times. The data of the general immune response indicate a 2-times increasing in the level of IgM (3.85 ± 1.89 g/l, $p<0.01$) and IgG level increased in 10 times (147, 35 ± 56.12 g/l, $p< 0.01$). The, according to the obtained data but, in comparison with the data of the control group. There are significant differences in the levels of Leptin ($p< 0.01$), C-peptide ($p< 0.01$), Thyroid stimulating hormone ($p<0.01$), Free thyroxine ($p=0.002$). The Leptin level, which is at the upper limit of the reference, the level of Thyroid stimulating hormone at the lower limit of the reference, and the slight predominance of the C-peptide level are noteworthy. Predominance of reliable correlations of pro-inflammatory cytokines IL 1, 4, 6 of varying degrees (r=0.34-0.45) are observed. Only IgG with Free triiodothyronine (r=0.45,p=0.004), IgE with Thyroid peroxidase antibody (r=-0.45,p=0.004) were identified as statistically significant correlations with high reliability.

Conclusions: The obtained date presents the increasing of the levels Cytocines (Il -1,4,6) in 2-10 times. The IgG level increased in 10 times and IgM – in 2 times. The indicators of endocrine metabolism are within the reference values. Reliable correlations of pro-inflammatory cytokines IL 1, 4, 6 of varying degrees (r=0.34-0.45) are observed. IgG with Free triiodothyronine (r=0.45,p=0.004) have significant reasonableness.

KEY WORDS: respiratory tract, cytokines, immunoglobulins, metabolic adaptation, children

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INTRODUCTION

Acute respiratory diseases (ARIs) are the most common pathology in the children's infectious diseases structure and are one of the main reasons for hospitalization [1]. ARI, mainly of the upper respiratory tract, is especially common in preschool children [2]. Morbidity in children is quite difficult to estimate, since acute respiratory syndrome is primarily treated in outpatient settings, and epidemiological data are recorded only in severe cases. Numerous clinically mild or asymptomatic forms of ARI remain unaccounted for [3]. Given that common childhood respiratory viruses and SARS-CoV-2 share similar routes of transmission, the combination of measures taken to combat COVID-19 more than halved the number of ARIs in children during the pandemic [4].

Acute throat infections are the sixth leading cause of primary care physician visits. Viruses cause 85 to 95% of throat infections in adults and children under 5 years of age; about 70% are among children aged 5 to 15 years, and the remaining 30% are caused by bacterial pathogens, mainly group A β-hemolytic streptococcus (GAS). According to epidemiological statistics, the incidence of pharyngitis in children reaches 20–50% [4,5]. In healthy children, acute inflammation of the mucous membrane and lymphoid structures of the oropharynx is usually a self-limiting disease, except for episodes caused by GAS. Due to an insufficiently developed immune system, children primarily suffer from SARS and are prone to the development of complications, including bronchitis, pneumonia, sinusitis, otitis. Each

Table I. Inflammatory activity indicators

Parameters	Main group (n = 40) M ± m	Control group (n = 25) M ± m	Statistical significance (p)
IL-1 (0-11, pg/ml)	27,63 ± 11,08	2,08 ± 0,49	< 0,01
IL-2 (0-10, pg/ml)	9,61 ± 6,73	0,41 ± 0,05	< 0,01
IL-4 (< 0,5 ng/ml)	5,95 ± 3,16	0,37 ± 0,14	< 0,01
IL-6 (0-10, pg/ml)	16,51 ± 7,22	3,29 ± 0,66	< 0,01
IL-10 (0-20, pg/ml)	14,88 ± 11,91	2,13 ± 0,31	< 0,01
γ-IFN (< 15, pg/ml)	52,92 ± 74,45	5,65 ± 0,85	< 0,01
TNF-α (< 6, pg/ml)	157,21 ± 21,05	3,43 ± 0,47	< 0,01
Neopterin (< 10 nmol/l)	90,43 ± 54,27	6,34 ± 1,14	< 0,01

Table II. Indicators of the general immune response

Parameters	Main group (n = 40) M ± m	Control group (n = 25) M ± m	Statistical significance (p)
Ig M (0,31-1,79, g/l)	3,85 ± 1,89	1,05 ± 0,09	< 0,01
Ig G (6,98-15,49, g/l)	147, 35 ± 56,12	10,39 ± 0,79	< 0,01
Ig E (до 120 IU/ml)	140,51 ± 64,15	41,71 ± 3,18	< 0,01

year, up to 12 cases of ARI can occur in one child, and the frequency of complications reaches 30% and leads to cases where the use of antibiotics is considered [3,6].

THE AIM

To investigate the parameters change of the general immune responds and endocrine metabolism in the children with Acute Respiratory Pathology and their correlational relationship.

MATERIALS AND METHODS

The study group included: school-age children (10-14 years old) with a diagnosis of acute respiratory disease (ARI) as a general group of respiratory tract inflammatory diseases, of viral and bacterial origin (n=40), which included local inflammatory lesions of the respiratory tract and presented with acute pharyngitis (60.0%), acute bronchitis (20%), acute tonsillitis (22%) and a control group (n=25), identical in age and sex. The research was conducted at the clinical base of the CNE «UCChH» of the Uzhhorod City Council. General clinical, immunological studies, inflammatory response of the child's body were conducted. Statistical analysis of the results of the examination of patients was carried out using the Statistics for Windows v.10.0 computer program (StatSoft Inc, USA). The evaluation of the obtained results was carried out using parametric and non-parametric methods

RESULTS

Inflammatory diseases of the respiratory tract are characterized by changes in the cytokine chain of homeostasis. During the development of the pathology, the synergism of the action of cytokines is observed, and the cascading nature of the formation of cytokines is also identified. Newly formed cytokines induce the synthesis of other cytokines, stimulate their synthesis, which supports the amplification of the process and the involvement of producer cells in it [7]. The state of the cytokine profile in our study group are represented in table I.

Table III. Parameters of endocrine metabolism

Parameters	Main group (n = 40) M ± m	Control group (n = 25) M ± m	Statistical significance (p)
Ferritin (7-140, ng/ml)	62,67 ± 29,92	71,59 ± 10,19	0,16
Adiponectin (5-37, ug/ml)	29,75 ± 8,36	26,28 ± 5,31	0,07
Leptin (2,05-11,09, ng/ml)	10,47 ± 2,93	7,54 ± 0,43	< 0,01
C-peptide (0,81-3,85, ng/ml)	4,56 ± 1,58	1,28 ± 0,12	< 0,01
Free triiodothyronine (1,2 - 2,8, nmol/l)	1,37 ± 0,56	1,32 ± 0,12	0,71
Free thyroxine (12,5 - 21,0, pmol/l)	15,05 ± 1,97	13,72 ± 0,51	0,002
Thyroid stimulating hormone (0,4 - 4,0, mIU/ml)	0,39 ± 0,07	1,98 ± 0,30	< 0,01
Thyroid peroxidase antibody (< 0,9, IU/ml)	0,67 ± 0,49	0,55 ± 0,02	0,20

Table IV. Correlation relationships of inflammatory markers

Parameters	Correlation coefficient (r)	Statistical significance (p)
IL-1про		
Leptin	-0,54	< 0,01
Thyroid peroxidase antibody	0,35	0,03
IL-4		
γ-IFN	0,34	0,03
IL-10 проти	0,45	0,004
IL-6 про		
γ-IFN	0,34	0,03
γ-IFN		
IL-4	0,34	0,03
IL-6	0,34	0,03
TNF-α	-0,42	0,007
Leptin	-0,32	0,04

Table V. Correlation relationships of general immune responds parameters

Parameters	Correlation coefficient (r)	Statistical significance (p)
Ig M		
Ferritin	0,33	0,04
Free triiodothyronine	0,33	0,04
Ig G		
Free triiodothyronine	0,45	0,004
Ig E		
Thyroid peroxidase antibody	-0,45	0,004

According to the data in Table I, there are significant increases in the level of the following cytokines with a significant predominance in comparison with the data of the children control group: IL-1 (27,63 ± 11,08 pg/ml,p< 0,01), IL-4 (5,95 ± 3,16 ng/ml, p< 0,01), IL-6(16,51 ± 7,22, p< 0,01), γ-IFN (52,92 ± 14,45 pg/ml, p< 0,01), TNF-α (157,21 ± 21,05 pg/ml, p< 0,01), Neopterin (90,43 ± 54,27 nmol/l, p< 0,01). The level of IL-1 increased in

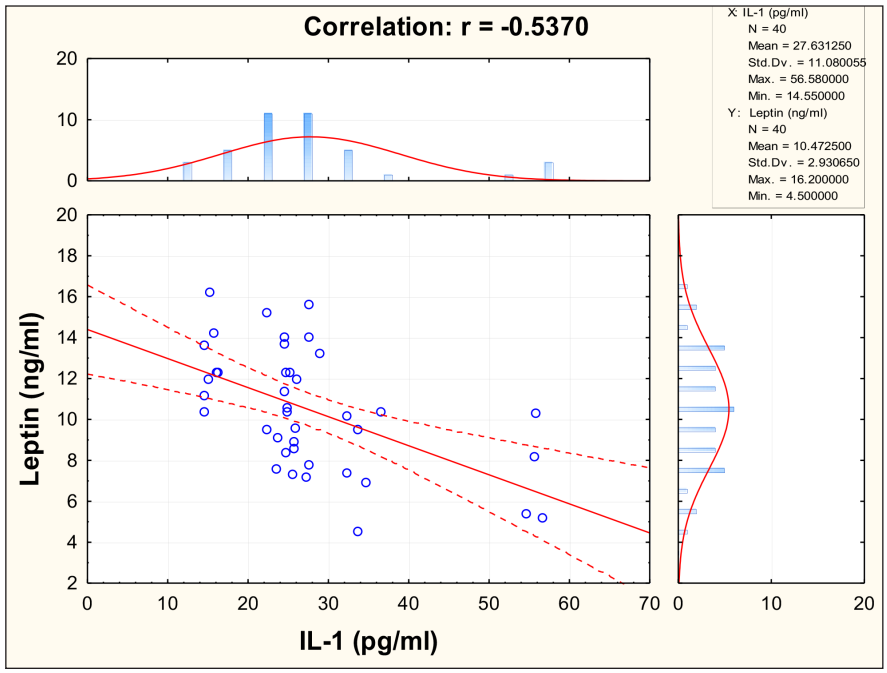

Fig. 1. Correlation relationship between the levels of Leptin and IL-1

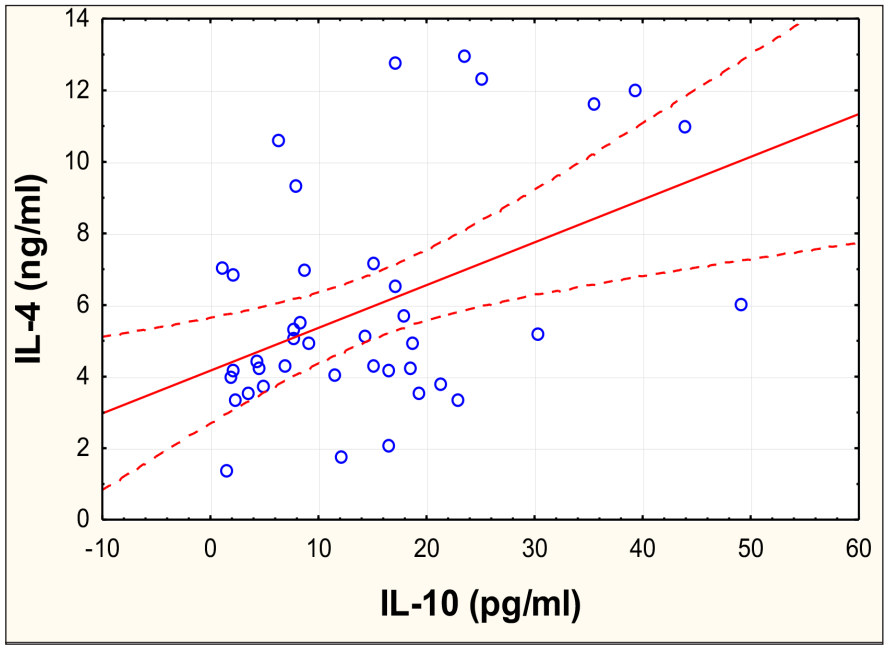

Fig. 2. Correlation relationship between IL-4 and IL-10

2 times, IL-4 – in 10 times, IL-6 – in 1.5 times, γ-IFN – in 3 times, TNF-α – in 25 times, Neopterin – in 9 times. The formation and biological activity of cytokines are interconnected and mutually regulated in response to a irritant. They form the so-called «cytokine cascade», which corresponds to the inflammatory response of the child's organism and, as a result, the clinical presentation is formed. Regulators of natural resistance – interferons, intelekins 1, 6 and 12, TNF-α, chemokines (IL 8, MCP-1, RANTES, etc.) are the main activators and regulators of nonspecific reactions of the organism to protect it from colonization by carriers of foreign genetic information [8].

The parameters of the general immune response indicators are represented in table II.

As we can see in table II, there is a 2-times increasing in the level of IgM (3.85 ± 1.89 g/l, $p<0.01$), which is natural for the growth of their production after the pathogen enters the body. The bactericidal activity of human blood serum largely depends on the level of IgM content. The next, higher stage of humoral immunological reactivity is the IgG molecules formation. Their level is increased in10 times (147, 35 ± 56.12 g/l, $p< 0.01$), according to our data. The IgG affinity increases thousands and tens of thousands of times. The presence of immune memory in relation to antibodies of this class

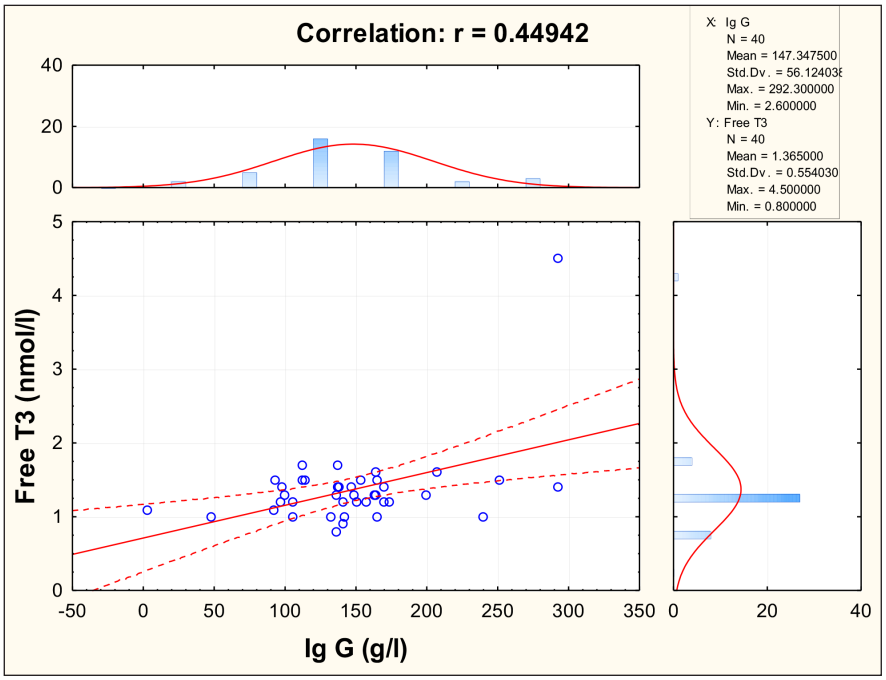

Fig. 3. Correlation relationship between Free T3 and Ig G

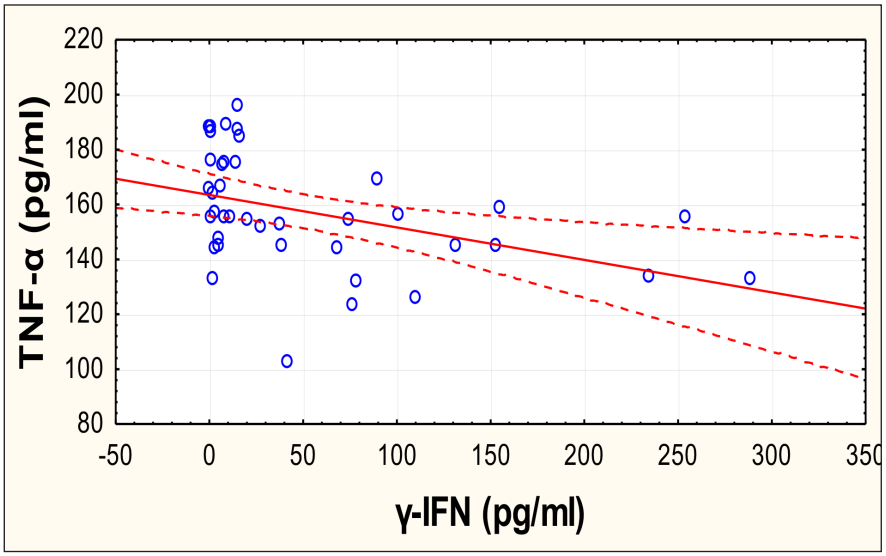

Fig. 4. Correlation relationship between TNF-α and γ-IFN

enables the body to dramatically increase its production, if necessary. The synthesis of IgM is switched to IgG in the process of the immune response. Switching from IgM to IgG is also necessary to regulate the level of production of specific antibodies. Since IgM, unlike IgG, does not have an inhibitory effect on the synthesis of class M immunoglobulins [8]. The level of IgE is slightly higher than the reference values, but it is 3.5 times higher than the level of childs in the control group (140.51 ± 64.15 IU/ml vs. 41.71 ± 3.18 IU/ml, $p<0.01$). It is believed that the main role of IgE is the protection of mucous membranes due to the induction of a local inflammatory reaction, according to the literature. This causes an inflammatory reaction.

The obtained results of Parameters of endocrine metabolism are given in table III.

According to the obtained data, the parameters of endocrine metabolism are within the reference values, but, in comparison with the control group data, there are significant differences in the levels of Leptin ($p< 0.01$), C-peptide ($p< 0.01$), Thyroid stimulating hormone ($p<0.01$), Free thyroxine ($p=0.002$). The Leptin level, which is at the upper limit of the reference, the level of Thyroid stimulating hormone at the lower limit of the reference, and the slight predominance of the C-peptide level are noteworthy.

Adiponectin and Leptin are the main adipokines secreted by adipose tissue. Their role has been established not only in obesity, but also in the production of inflammatory cytokines [10], which identified by our study. The C-peptide level increasing is also presented in the the articles of the researchers. C-peptide, originally

thought to be inert, can modulate the inflammatory response in conditions of endotoxemia and ischemia reperfusion. However, the spectrum of its biological action is unclear. Scientists suggest that exogenous administration of C-peptide can modulate pro- and anti-inflammatory signaling pathways and thus reduce lung inflammation [11].

The obtained results of correlation analysis are given in table IV.

There is a predominance of correlations of pro-inflammatory cytokines Il (1,4,6) of varying degrees (r=0.34-0.45), according to the data in table IV. Also, the cascading of induction of cytokine synthesis by producer cells is clearly expressed. Consideration of correlations is no less important parameters of the general immune response (table V).

Only IgG with Free triiodothyronine (r=0.45,p=0.004), IgE with Thyroid peroxidase antibody(r=-0.45,p=0.004) were identified with high reliability as statistically significant correlations. We proceed to the consideration of correlograms. The correlation relationship between the levels of Leptin and IL-1 is presented in the correlogram (Fig. 1).

IL-1 is one of the main mediators of the non-specific protective factors activation, especially during inflammation. IL-1 activates the endothelium of vessels, which helps to increase the ability of endothelial cells to bind of blood leukocytes and thereby promote their migration to the center of inflammation, increases the neutrophils mobility, the phagocytes and NK activity, the generation of bactericidal substances, activates a number of cells in the area of inflammation, which leads to increased production of many cytokines, prostaglandins, collagen, fibronectin. It induces the formation of some proteins of acute inflammation – C-reactive, mannose-binding, etc. IL-1 plays an important role in the implementation of intersystem interaction, especially with the neuro-endocrine system [8] The biological effect of Leptin is to directly or indirectly affect hematopoiesis, immunity. It is a proven fact that leptin level increasing stimulates the production of somatotropic and sex hormones, as well as thyroid hormones. Glucocorticoids, Insulin, Estrogens, Tumor Necrosis factor α, Interleukin-1 to stimulate the synthesis and secretion of Leptin by adipocytes [12]. That is, by our study, a negative reliable correlation can be traced, which corresponds to the scientific studies of many scientists, and signified about metabolic adaptation disorder in children with acute respiratory pathology.

The correlogram of the interleukins between IL-4 and IL-10 are given in Fig. 2. IL-4 has anti-inflammatory activity, which is due to its ability to suppress the secretion of pro-inflammatory cytokines by macrophages – IL-1, IL-6, TNF. Its presence stimulates the activity of macrophages and monocytes. IL 4 is involved in the formation of the focus of inflammation. Interleukin 10 (IL-10) has been known since 1989, it was called «the factor that inhibits the synthesis of cytokines». The positive correlation of the data in our study indicates the synergism of the action of interleukins 4,10. The following correlogram is informative for consideration too, which presents the relationship between free T3 and IgG (Fig. 3).

In the development of a pathological condition, in particular, acute respiratory pathology, both the immune and thyroid systems are involved. There is evidence of the involvement of cells of the immune system in the regulation of the activity of the thyroid gland [13]. Our data show about the reliable positive relationships of these links of homeostasis. Presentation of the correlogram of the relationship between γ-IFN and TNF-α are illustrated in Fig. 4.

TNF-α appears in blood serum during infectious diseases, cancer and some non-infectious pathologies,. The spectrum of biological action of TNF is very wide. The main ones are the lysis of tumor, transformed and virus-infected cells and the regulation of many organism functions. It was shown that the activity of macrophages is closely related to the presence of TNF-α in the cell membrane, the amount of which increases sharply after IFN treatment. γ-IFN has antiviral activity – it inhibits the reproduction of some viruses. This action may be due to the induction of γ-IFN. In many cases, the action of tumor necrosis factor is more pronounced when interacting with γ-IFN and IL-1[8,9]. The obtained data of our study are coherent with the available scientific developments and trends and are confirmed by the negative correlation data: TNF-α and γ-IFN r=-0.42, P =0.007.

DISCUSSION

Acute respiratory infections are the cause of high morbidity in children. Innate and adaptive immune responses to microorganisms are critical for maintaining a healthy respiratory system and preventing respiratory disease. High morbidity and mortality are the result of inadequate, incorrect or excessive immunity. The formation and biological activity of cytokines indicate interconnected and mutually regulated actions in response to a irritant. They form the so-called «cytokine cascade», which corresponds to the inflammatory response of the child's organism and, as a result, the clinical presentation is formed. Regulators of natural resistance – interferons, intelekins 1, 6 and 12, TNF-α, chemokines (IL 8, MCP-1, RANTES, etc.) are the main activators and regulators of nonspecific reactions of the body to protect it from colonization by carriers of

foreign genetic information [8]. Indicators of endocrine metabolism also pay attention. Their role has been established not only in obesity, but also in the production of inflammatory cytokines [10], which can be seen in our study. The C-peptide level increasing is also coherent with other scientific researchers. C-peptide, originally thought to be inert, can modulate the inflammatory response in conditions of endotoxemia and ischemia reperfusion. The understanding of pathochemical and pathophysiological changes in acute respiratory diseases is in a constant dynamic process. The obtained data of our research indicate disorders of immunological and metabolic adaptation of the child's organism systems during the infectious process, which require adequate methods of diagnosis, treatment and effective ways of prevention.

CONCLUSIONS

1. The inflammatory response parameters of the child's organism present indicative increases in the levels of cytokines with a significant predominance in comparison with the data of the children control group: the level of IL-1 increased in 2 times, IL-4 – in10 times, IL-6 – in 1.5 times, γ-IFN – in 3 times, TNF-α – in 25 times, Neopterin – in 9 times.
2. The data of the general immune response indicate a 2-times increasing in the level of IgM (3.85 ± 1.89, $p<0.01$), which is natural for the growth of their production after the pathogen enters the body. The IgG affinity increases thousands and tens of thousands of times. The IgG level increased in 10 times (147, 35 ± 56.12 g/l, $p< 0.01$), according to our data.
3. The indicators of endocrine metabolism are within the reference values, according to the obtained data but, in comparison with the data of the control group. There are significant differences in the levels of Leptin ($p< 0.01$), C-peptide ($p< 0.01$), Thyroid stimulating hormone ($p<0.01$), Free thyroxine ($p=0.002$). The Leptin level, which is at the upper limit of the reference, the level of Thyroid stimulating hormone at the lower limit of the reference, and the slight predominance of the C-peptide level are noteworthy.
4. Predominance of reliable correlations of pro-inflammatory cytokines IL 1, 4, 6 of varying degrees ($r=0.34-0.45$) are observed. The cascading of induction of cytokine synthesis by producer cells is also pronounced. Only IgG with Free triiodothyronine ($r=0.45, p=0.004$), IgE with Thyroid peroxidase antibody ($r=-0.45, p=0.004$) were identified as statistically significant correlations with high reliability.

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ORIGINAL ARTICLE

CHANGES IN SERUM SOMATOSTATIN AND GASTRIN LEVELS IN PATIENTS AFTER CHOLECYSTECTOMY AND GASTROESOPHAGEAL REFLUX DISEASE

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ABSTRACT

The aim: To study of changes in the level of serum gastrin (GN) and somatostatin (SST) in patients with GERD after ChECT and determined their characteristics from clinical forms of GERD.

Materials and methods: 64 patients with different clinical forms of GERD were examined. The patients with GERD were divide into 2 clinical groups. Group 1 included 34 patients with GERD after ChECT, among them there were 14 males (41.2 %) and 20 females (58.8 %), with the average age of 40.2 ± 3.2 years. Group 2 consisted of 30 patients with GERD without ChECT. Among them there were 18 males (60.0 %) and 12 females (40.0%), with the average age of 38.9 ± 4.7 years. All patients were tested for serum SST and GN level by enzyme-linked immunosorbent assay (ELISA).

Results: In all patients with GERD of both group there was a significant increase in the level of serum SST. At the same time, a more higher indicators have been established in 2 Group of patients (increase up to 0.702 ± 0.029 pg / ml – $p < 0.01$). Noteworthy is the change in the level of SST in the serum in both groups of the examined patients depending on the clinical form of GERD, with the maximum increase in patients with atypical manifestation of GERD. The analysis of the level of GN in blood serum indicates its decrease in the examined patients. In this case, the most pronounced changes were found in patients with extraesophageal clinical signs of GERD.

Conclusions: 1. In patients after ChECT gastroesophageal reflux disease often has atypical symptoms (mostly cardiac and bronchopulmonary forms in 45.0% and 25.0 % of examend patients). 2. There was detected an increase in the level of blood SST of patients with GERD while there was observed a decrease in the GN indicator in the serum, especially in its atypical forms. 3. Duodenogastric reflux is often diagnosed during endoscopic examination of patients with GERD after cholecystectomy. At the same time, its severity correlates with the level of SST in blood serum ($r=0.76$; $p<0.01$ in the typical form and $r= 0.72$; $p<0.05$ in the atypical clinical form of GERD).

KEY WORDS: gastroesophageal reflux disease; esophageal, extraesophageal manifestations of gastroesophageal reflux disease; cholecystectomy; somatostatin; gastrin

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INTRODUCTION

Diseases of the gallbladder are common and costly. The best epidemiological screening method to accurately determine point prevalence of gallstone disease is ultrasonography. Many risk factors for cholesterol gallstone formation are not modifiable such as ethnic background, increasing age, female gender and family history or genetics [1].

Gallstones are common and lead to significant morbidity, mortality, and health care utilization in the United States and worldwide. More than 20 million people in the United States have ultrasound-detected gallbladder disease. There were an estimated 1.8 million ambulatory care visits with an all-listed gallstone diagnosis in 2004 and rates were relatively stable over time. There were 622,000 overnight hospitalizations with an all-listed gallstone diagnosis in 2004. Hospitalization rates declined by 40% from 1991 due to the shift to outpatient laparoscopic cholecystectomy. There were 2,155 deaths with gallstones as underlying or other cause in 2004 and mortality rates fell between 1979 and 2004 by 70%. Based on data from the National Survey of Ambulatory Surgery conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention, gallstone disease resulted in 503,000 laparoscopic cholecystectomies in 2006 [2, 3].

In this case, cholecystectomy (ChCET) does not solve the problem if we talk about patients with gallstone disease, because the removal of the gallbladder does not rid patients of those processes that led to the formation

of a calculus in the biliary tract. After performing ChCET, new clinical symptoms remain or, on the contrary, appear, which is part of the concept of post-olecystectomy syndrome. Postcholecystectomy syndrome is manifested through various symptoms, inter alia, damage to the upper parts of the gastrointestinal tract. Notably, the symptoms are more pronounced if ChCET surgery has been performed on the functioning gallbladder.

Gastroesophageal reflux disease (GERD) is a common digestive disease based on pathological gastroesophageal (GE) reflux, which occurs due to esophageal cardia insufficiency and impaired barrier function of the lower esophageal sphincter. The prevalence of GERD in Western populations over the past 30 years has a clear tendency to increase and varies from 10.0 % to 30.0%. The relevance of GERD is also due to the presence of both typical and atypical (bronchopulmonary, cardiac, dental, otolaryngological) clinical manifestations that complicate the diagnosis of GERD [4, 5].

The study of various biologically active substances that can play a role in the formation of gastroesophageal reflux disease (GERD) in patients with combined pathology, including damage to the biliary system, is important, extremely problem of modern clinical medicine.

THE AIM

The aim of the study was to study of changes in the level of serum gastrin (GN) and somatostatin (SST) in patients with GERD after ChECT and determined their characteristics from clinical forms of GERD.

MATERIALS AND METHODS

64 patients with different clinical forms of GERD were examined. The examined patients were hospitalized in Gastroenterology and Surgery Departments of Municipal Non Profit Enterprise "Transcarpathian Regional Clinical Hospital named After Andrii Novak" of Transcarpathian Regional Council, and patients who were on outpatient observation by family doctors at the place of residence in the period of 2020-2023. The patients with GERD were divide into 2 clinical groups. The 1 Group included 34 patients with GERD after ChECT, among them there were 14 males (41.2 %) and 20 females (58.8 %), with the average age of 40.2 ± 3.2 years. Group 2 consisted of 30 patients with GERD without ChECT. Among them there were 18 males (60.0 %) and 12 females (40.0%), with the average age of 38.9 ± 4.7 years.

The control group included 30 healthy individuals: 14 males (46.7 %) and 16 females (53.3 %) without lesions of the musculoskeletal system and upper gastrointestinal tract. The average age was 40.3 ± 4.1 years.

All studies were performe with the consent of patients, and their methodology was in line with the Helsinki Declaration of Human Rights of 1975 and its revision in 1983, the Council of Europe Convention on Human Rights and Biomedicine, and the legislation of Ukraine.

All the examined patients were subject to general clinical, anthropometric, instrumental, and laboratory tests. Ultrasound examination of the abdominal cavity was performe on all patients according to generally accepted method. Standard and biochemical blood serum tests have been performed to determine the functional state of the liver, lipid metabolism indexes and carbohydrate metabolism indexes.

The diagnosis of GERD at observed patientes was established according to the criteria of the unified clinical protocol (order of the Ministry of Health of Ukraine dated 31.10.2013 № 943) taking into account complaints, endoscopic examination data, etc. To confirm the diagnosis, the examined patients underwent fibroesophagogastroduodenoscopy (FEGDS) using endoscopy equipment Pentax ERM-3300 video processor and flexible fiber endoscopes Pentax E-2430, GIF-K20. The Los Angeles (LA) classification (1998) was used for endoscopic assessment of the degree of damage to the esophagus [6].

All patients were tested for serum somatostatin (SST) level (using Human Somatostatin EIA-1 Kit test system No. 1.03930004301 from Ray Biotech) and serum gastrin (GN) level (using Gastrin-EIA test kit Cat. No CS001 30) by enzyme-linked immunosorbent assay (ELISA).

The criteria for inclusion in the study were: clinical symptoms of GERD (typical and atypical), changes in the mucose of the esophagus, characteristic of GERD, during FEGDS, cholecystectome in anamneses.

The exclusion criteria were as follows: non-erosive form of GERD, Barrett's esophagus functional or organic changes of the upper parts of the gastrointestinal tract, Helicobacter pylori positive patients.

The analysis and processing of the results of the examinations was performed by the computer program Statistics for Windowsv.10.0 (StatSoft Inc, USA) using parametric and non-parametric methods for evaluating the results.

RESULTS

Complaints of digestive organs characteristic of GERD (typical esophageal manifestations) were more often found in patients of 2 Group – 56.7 % of the examined patients ($p<0.05$), while patients of 1 Group were more often diagnosed with atypical manifestation of GERD – 58.8 % of the examined patients ($p<0.05$). The leading clinical manifestation of the upper digestive tract lesions in patients of 2 Groups was acid regurgitation, heartburn, dysphagia and sore throat.

Table I. Clinical manifestations of GERD in the examined patients

Symptoms	1 Group of patients (n=34), %	2 Group of patients (n=30), %
Typical manifestation of GERD	(n=14), 41.2 %	(n=17), 56.7 %*
Atypical manifestation of GERD	(n=20), 58.8 %*	(n=13), 43.3 %
Cardiac	45.0 %*	30.8 %
Bronchopulmonary	25.0 %	46.2 %**
Otlaryngological	20.0 %	15.3 %
Dental	20.0 %**	7.7 %

Note: the difference between the indicators in patients of 1 and 2 Groups within the clinical form of the disease is significant: * - p <0.05; ** - p <0.01.

Table II. The nature of endoscopic changes in the examined patients

Endoscopic manifestations	Examined patients			
	1 Group (n=34)		2 Group (n=30)	
	Typical manifestation of GERD (n=14)	Atypical manifestation of GERD (n=20)	Typical manifestation of GERD (n=17)	Atypical manifestation of GERD (n=13)
Reflux esophagitis (severity according to LA classification):				
LA–A	14.3 %	15.0 %	29.4 % **,++	15.4 %
LA–B	50.0 % **	30.0 %	47.1 % *	30.8 %
LA–C	28.6 %	35.0 % *	23.5 %	46.1 % *,^
LA–D	7.1 % +	20.0 % **,^	-	7.7 % *
DGR	71.4 % *,++	60.0 % ^^	23.5 %	30.8 % *
CE	28.6 % ++	25.0 % ^^	5.9 % *	-

Note: the difference between the indicators in patients of 1 and 2 Groups within the clinical form of the disease is significant: * - p <0.05; ** - p <0.01; the difference between the indicators in patients of 1 and 2 Groups with typical manifestation of GERD is significant: + - p <0.05; ++ - p <0.01; the difference between the indicators in patients of 1 and 2 Groups with atypical manifestation of GERD is significant: ^ - p <0.05; ^^ - p <0.01.

Atypical manifestation of GERD in patients of both groups were more often manifested by cardiac, bronchopulmonary masks. At the same time, there was a difference: patients of 1 Group (after ChECT) more often had cardiac of GERD (45.0 % of subjects – p <0.05), while patients without ChECT were more often diagnosed with bronchopulmonary form of GERD (46.2 % of examined patients – p <0.01). The dental "mask" of GERD was more diagnosted in 1 Group (20.0 % of subjects – p <0.01). The results are shown in Table I.

At endoscopic examination in all patients of both groups it was manifested by gastroesophageal reflux and reflux esophagitis (RE) of varying severity (Table II).

It was noted that in the group of patients after ChECT with typical manifestation of GERD, the severity of reflux-esophagitis (RE) more often corresponded to LA-B, while in patients with atypical manifestation – more often – LA-C (at 35.0 % patients – p <0.05). The same tendency was observed in patients of 2 Group. Attention was drawn to the high frequency of duodenogastric reflux (DGR) in patients of 1 Group (71.4% and 60.0% of patients with typical and atypical manifestations of GERD, respectively), against 23.5% – 30.8% in patients of 2 Group. Signs of candida esophagitis are also more often found in patients of 1 Group.

In all patients with GERD of both group there was a significant increase in the level of serum SST. At the same time, a more higher indicators have been established in 2 Group of patients (increase up to 0.702 ± 0.029 pg / ml – p <0.01) – table III. Noteworthy is the change in the level of SST in the serum in both groups of the examined patients depending on the clinical form of GERD, with the maximum increase in patients with atypical manifestation of GERD.

The analysis of the level of GN in blood serum indicates its decrease in the examined patients. In this case, the most pronounced changes were found in patients with extraesophageal clinical signs of GERD.

Correlation analysis established the relationship between serum SST and a decrease in serum gastrin – table IV. There was established dependence between the change in the SST level and the severity of endoscopic changes in reflux esophagitis (mainly LA–B and LA–C) in patients of both groups. A correlational dependence was identified between the somatostatin indicator and the severity of DGR only in patients of the first group.

Table III. Levels of somatostatin and indicators of calcium metabolism in the blood serum of the examined patients of the examined patients

Examined patients	Indicator	
	SST, pg/mL	GN, pg/mL
Control group (n=30)	0.423±0.015	75.30±2.16
1 Group: (n=34)	0.626±0.018 ¥	51.34±0.22 ¥
Typical manifestation of GERD (n=14)	0.584±0.033	56.13±0.25 ++
Atypical manifestation of GERD (n=20)	0.652±0.021	42.16±0.18
2 Group: (n=30)	0.702±0.029 ¥¥,*	40.15±0.26 ¥¥,*
Typical manifestation of GERD (n=17)	0.687±0.032 +	42.50±0.18
Atypical manifestation of GERD (n=13)	0.731±0.028 ^	38.10±0.24 ^

Note: the difference between the indicators in patients of 1 and 2 Groups and the control group is significant: ¥ - $p < 0.05$; ¥¥ - $p < 0.01$; the difference between the indicators in patients of 1 and 2 Groups within the clinical form of the disease is significant: * - $p < 0.05$; the difference between the indicators in patients of 1 and 2 Groups with typical manifestation of GERD is significant: + - $p < 0.05$; ++ - $p < 0.01$; the difference between the indicators in patients of 1 and 2 Groups with atypical manifestation of GERD is significant: ^ - $p < 0.05$.

Table IV. Comparison of the level of somatostatin with level of gastrin in the serum and endoscopic changes of the examined patients depending on the clinical form of GERD

Indicator	SST level			
	Examined patients			
	1 Group (n=34)		2 Group (n=30)	
	Typical manifestation of GERD	Atypical manifestation of GERD	Typical manifestation of GERD	Atypical manifestation of GERD
GN	r= 0.62; p<0.05	r= 0.78 p<0.01	r= 0.70; p<0.05	r= 0.92; p<0.01
LA–B	r= 0.80; p<0.01	-	r= 0.78; p<0.051	-
LA–C	r= 0.56; p<0.05	r= 0.88; p<0.01	r= 0.60; p<0.05	r= 0.90; p<0.01
DGR	r= 0.76; p<0.01	r= 0.72; p<0.05	_	-

Thus, in patients with after ChCET GERD is often manifested by atypical clinical symptoms. Examination of serum SST and GN level indicates its increase with the most pronounced deviation from the norm in atypical form of GERD. In this case, a correlation was found between the increase in serum SST level and the decrease in the level of ПGN in serum.

DISCUSSION

Scientific research of pathogenetic mechanisms of GERD formation at patients with comorbid states is carried out. Particular interest are studies aimed at determining the effect of biologically active substances on the tonus of the lower esophageal sphincter, which affect the formation of GERD.

Peptides of nervous origin (somatostatin, substance P, endorphins, enkephalins) were found in cells that produce hormones of the gastrointestinal tract, and cholecystokinin, gastrin were found in the central nervous system and nerve fibers; this confirms the close connection of the digestive and nervous systems. Spontaneous motor activity of the smooth muscles of the digestive tract is caused by their automaticity [7]. The effects of irritation of the autonomic nerves depend on the initial condition of the muscles, the frequency and strength of the irritation. Humoral substances regulate motility by directly affecting myocytes or neurons of the digestive tract [8, 9]. Thus, biologically active substances, neuropeptides play a leading role in maintaining the normal synchronous functioning of the organs of the digestive system, providing the balance within the acid formation system.

The obtained results indicate high levels of somatostatin in blood serum of the patients with GERD after undergoing cholecystectomy. At the same time, the level of somatostatin correlates with the level of gastrin in blood serum of, particularly, patients with atypical clinical signs of GERD. The revealed relationship between neuropeptides and the expression of DGR in patients with GERD after cholecystectomy also enables one to speak about their involvement in forming lesions of the upper parts of the gastrointestinal tract after performing cholecystectomy. The data obtained make it possible to recommend a more detailed clinical analysis connected to identifying atypical forms of GERD

in patients after they underwent cholecystectomy, as well as to take measures aimed at their prevention and treatment. Notably, further research in this area is needed for a more accurate understanding of pathogenetic mechanisms underlying the damage to other organs of the digestive system after cholecystectomy.

CONCLUSIONS

1. In patients after ChECT gastroesophageal reflux disease often has atypical symptoms (mostly cardiac and bronchopulmonary forms in 45.0 % and 25.0 % of examend patients).
2. There was detected an increase in the level of blood SST of patients with GERD while there was observed a decrease in the GN indicator in the serum, especially in its atypical forms.
3. Duodenogastric reflux is often diagnosed during endoscopic examination of patients with GERD after cholecystectomy. At the same time, its severity correlates with the level of SST in blood serum ($r=0.76$; $p<0.01$ in the typical form and $r=0.72$; $p<0.05$ in the atypical clinical form of GERD).

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ORIGINAL ARTICLE

ABDOMINAL PERFUSION PRESSURE IN PREDICTION OF THE TERMS OF ACUTE NECROTIZING PANCREATITIS INFECTION

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ABSTRACT

The aim: To determine the role of the abdominal perfusion pressure level at the beginning of the disease in predicting the timing of infection of acute necrotizing pancreatitis.

Materials and methods: A retrospective cross-sectional single-center study of 39 patients with acute severe pancreatitis (ASP) and pancreatic infection (PI) with measured and calculated minimal abdominal perfusion pressure (APP) in the first 48 hours of the disease. The existence of a correlation between the onset of PI and the level of intra-abdominal (IAP) and abdominal perfusion pressure was calculated and a single-factor mathematical model of linear regression was built.

Results: A negative strong correlation was found between IAP and the timing of PI onset, ρ=-0.818 ($p<0.001$), and a positive strong correlation was found between APP and the timing of PI onset, ρ=0.933 ($p<0.001$). The dependence of the outcome variable (PI term) on the APP value was revealed, adjusted coefficient of determination $R^2adj = 0.887$ was corrected, F value 288.5, $p<0.001$, root mean square errors RSE = 1.31 (with 37 degrees of freedom). The value of the coefficient X1 was 0.47±0.0, $p<0.001$.

Conclusions: An increase in IAP in the first 48 hours of the desease in patients with ASP was, on average, accompanied by a reduction in the start of PI. A decrease in APP in the first 48 hours of the desease in patients with ASP was, on average, accompanied by a reduction in the start of PI. In the study sample, it was possible to predict the time of PI initiation by measuring the APP level in the first 48 hours of the disease with a margin of error for 1.3 days. It was found that with a decrease in the APP level, the time of the PI occurrence was reduced ($p<0.001$), on average, by 0.47±0.02 days for each mm Hg of APP.

KEY WORDS: abdominal perfusion pressure, acute pancreatitis, infected pancreatitis, intraabdominal pressure

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INTRODUCTION

Infectious complications of acute necrotizing pancreatitis significantly worsen the disease prognosis: early infection of pancreatic necrosis is a risk factor for the development of fatal complications in this category of patients [1-3].

Given that pancreatic necrosis can be a substrate for infection [1-3], it is advisable to highlight the prerequisites for its occurrence, taking into account the pathophysiologically related factor of early perfusion disorders – the complex of symptoms of intra-abdominal hypertension, when not only the progression of the latter, but also the persistence of extra-threshold levels affects the patients' survival [2,4,5].

The studies of acute necrotizing pancreatitis over the past decade have focused on intra-abdominal hypertension (IAH) as a marker of existing and prediction of further complications of the disease that require longer intensive care, necessitate interventional treatment, and significantly worsen survival [6-9].

The control of abdominal perfusion pressure (APP) deserves special attention, which, supplementing the measured intra-abdominal pressure with indicators of the compromised function of the cardiovascular system in case of persistent multi-organ failure, can informatively reflect the probability of threatening complications.

THE AIM

To determine the role of the abdominal perfusion pressure level at the beginning of the disease in predicting the timing of infection of acute necrotizing pancreatitis.

MATERIALS AND METHODS

A retrospective cross-sectional single-center study of 39 patients with infected acute necrotizing pancreatitis treated at the Bogomolets department of general surgery No. 1 in the period from 2019 to 2021 was conducted. Among them 62% were men (24/39), 38% were women (15/39) with an average age 37.6±6.7 years. The study included patients with acute severe pancreatitis who were admitted no later than 12 hours

Table I. Presentation of data

Indicator, units of measurement	Average	Mean square deviation
Intra-abdominal pressure, mm Hg	14.9	2.2
Indicator	**Median**	**QI-QIII**
Abdominal perfusion pressure, mm Hg	60	55-70
Term of pancreatic infection, day of illness	10	7-15
Mean arterial pressure, mm Hg	74.5	71-83

Table II. Coefficients of the one-factor model for predicting the term of pancreatogenic infection in patients with acute necrotizing pancreatitis

Indicator	Value of model coefficient b±m(b)	The level of significance of the coefficient difference from 0, p
Const	-18.89 ±1.76	<0.001*
X1	0.47±0.02	<0.001*

*- the difference of the model parameter from 0 is statistically significant, $p<0.05$

after the onset of the disease and subsequently had infectious complications. In all patients, the level of APP was assessed in the first 48 hours of the disease, which was calculated by the difference in mean arterial pressure (MAP) and intra-abdominal pressure (IAP). The minimal APP value was selected for calculations out from the values measured during this period. Mean arterial pressure was calculated by dividing into three sums of systolic blood pressure and diastolic blood pressure multiplied by two (MAP = SAP + 2DAP * 2/3). Clinical and laboratory data from the medical records of patients, stratified according to the criteria of the Revision of the Atlanta Classification 2012, were evaluated, and systemic complications were analyzed by the Multiple Organ Dysfunction Score (MODS). All patients of the study sample had signs of organ failure in the first two days of the disease, the median (QI-QIII) MODS score corresponded to 4 (3-6) points. An indirect method was chosen to measure IAP [10]: 100 ml of sterile saline was slowly injected into the lumen of an empty bladder using a Foley catheter, with the use of a drip system. After that, the intravesical pressure was measured using a ruler in mm H2O, the level of the frontal symphysis was taken as zero. The results were converted to mm Hg: 1 mm Hg = 13.5951 mm H2O. The first positive bacteriological culture of the aspirate obtained during the puncture of acute fluid parapancreatic collections under sonographic navigation was considered the time of the infection onset. The first step was to analyze the relationship between the value of the intraabdominal pressure and the time of pancreatic infection occurrence (Infection Time). The Spearman's rank correlation coefficient ρ was calculated after checking the distribution of values for normality. The second step was to analyze the relationship between the value of APP (Abdominal perfusion pressure) and the duration of pancreatogenic infection (Infection Time). The Spearman's rank correlation index ρ was calculated after checking the distribution of values for normality. The third step was to build and analyze a single-factor linear regression model. The analysis was based on the linear dependence of the outcome variable Y (duration of pancreatic infection, Infection Time) on the factor variable X1 (APP value in the first 48 hours of the disease, Abdominal perfusion pressure). The collinearity of the factor of IAP and APP was previously assessed by calculating the variance inflation factor, VIF, with a threshold value of 5. The model coefficient, b±standard error m(b), adjusted coefficient of determination R^2adj, F value, and root mean square errors RSE were calculated. A value of $p<0.05$ was considered statistically significant. The EZR (R-statistics) package was used to calculate and analyze the data [11].

RESULTS

The median (QI – QIII) minimum APP was 60 (55-70) mm Hg; MAP – 74.5 (71 -83) mm Hg; mean IAP – 14.9 ± 2.2 mm Hg. The median (QI – QIII) of infection onset corresponded to day 10 (7 – 15) of the disease. Table I shows the data obtained. The distribution of IAP values did not differ from normal, $p=0.119$. The distribution of APP, MAP and the duration of pancreatic infection differed from the normal, $p<0.05$.

First, we found out whether there was a relationship between the level of IAP in the first 48 hours of the disease and the duration of pancreatic infection. For this purpose, the Spearman's rank correlation coefficient was calculated. The value of the correlation coefficient ρ = -0.818 (statistically significantly different from 0, $p<0.001$). Thus, the presence of a negative strong correlation between IAP and the timing of pancreatic

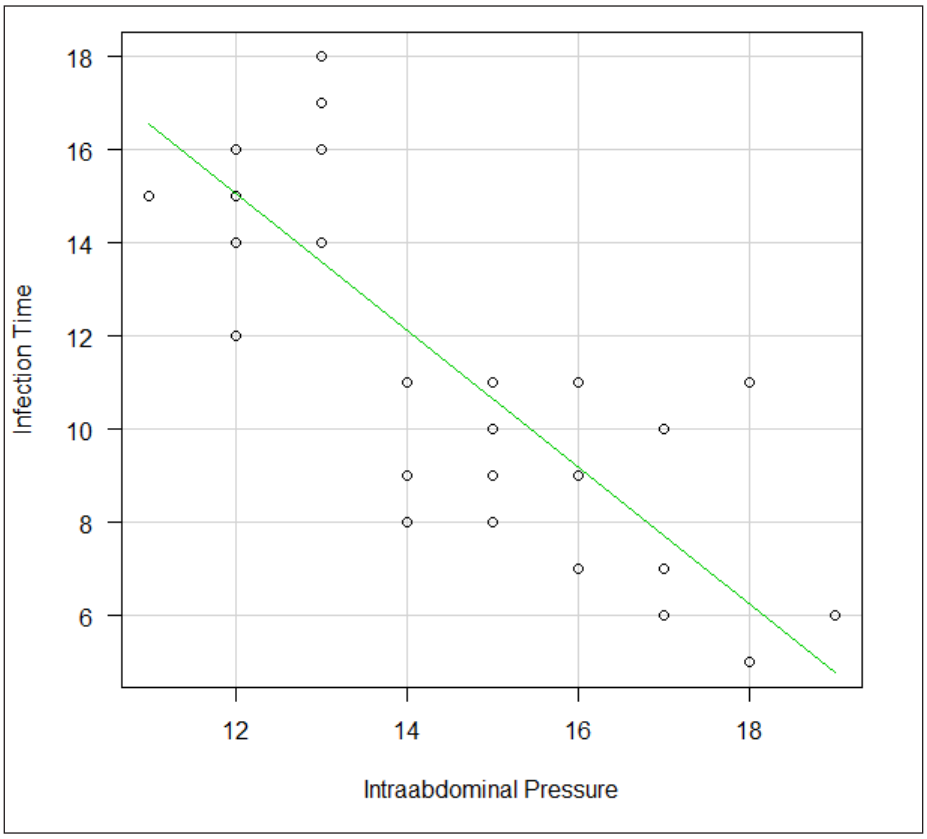

Fig. 1. Correlation field of IAP (Intraabdominal Pressure) values, mm Hg, and the timing of pancreatic infection, Infection Time, day of illness, $p<0.001$

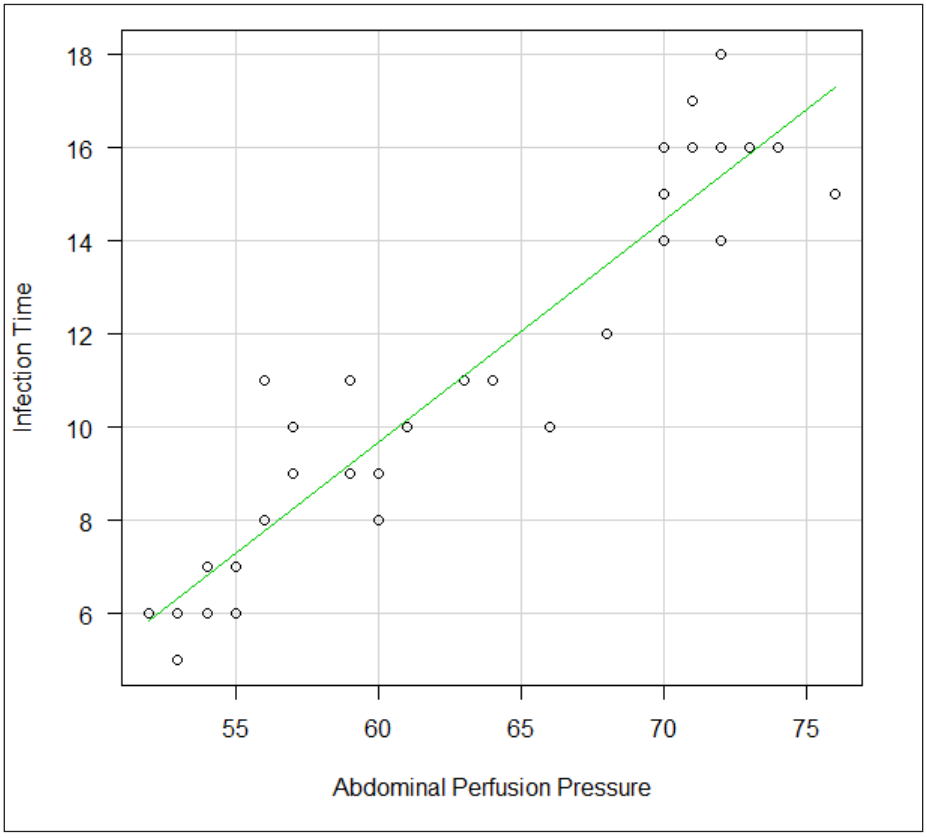

Fig. 2. Corellation field of APP (Abdominal Perfusion Pressure) values, mm Hg, and the term of pancreatic infection, Infection Time, day of illness, $p<0.001$

infection was revealed. An increase in IAP in the first 48 hours of ASP, on average, is accompanied by a reduction in the onset of pancreatic infection, Infection time (Fig. 1).

The second step was to find out whether there was a relationship between the APP value in the first 48 hours of the disease and the timing of pancreatic infection. For this purpose, the Spearman rank correlation

coefficient was calculated. The value of the correlation coefficient was $\rho = 0.933$ (statistically significantly different from 0, $p<0.001$). Thus, the presence of a positive strong correlation between APP and the timing of pancreatic infection was revealed. A decrease in APP in the first 48 hours of acute severe pancreatitis, on average, was accompanied by a reduction in the time of pancreatic infection occurence, Infection time (Fig. 2).

To analyze further the dependence of the pancreatic infection occurrence time due to the APP value on the first 48 hours of the disease, we used the method of constructing and analyzing a single-factor linear regression model. Previously, the value of IAP as a factor was rejected, given the linear relationship with the level of APP after calculating collinearity (VIF = 5.8). While building a one-factor model, the dependence of the outcome variability (the term of pancreatic infection) on the APP value was revealed. The adjusted coefficient of determination $R^2adj = 0.887$, F value 288.5, $p<0.001$, root mean square error RSE = 1.31 (with 37 degrees of freedom). Table II shows the results of estimating the model coefficients.

Thus, it was found that the timing of pancreatic infection in patients with ASP was associated ($p<0.001$) with the APP level in the first 48 hours of the disease. It was discovered that with a decrease in the level of APP, the onset of pancreatogenic infection time was reduced ($p<0.001$), on average by 0.47±0.02 days for each mm Hg of APP. The obtained mathematical model for predicting the duration of pancreatic infection can be expressed by the formula: $Y=(-18.89) + 0.47\times X1$. X1 – Abdominal perfusion pressure in the first 24 hours of the disease, Y – the time of onset of pancreatic infection.

DISCUSSION

Our study did not aim to reassess the conventional monitoring of IAP in patients with acute severe pancreatitis. Instead, we took into account the level of APP as an indicator that deserves attention in the management of the given patients. According to the updated guidelines of the World Society of the Abdominal Compartment Syndrome, the value of abdominal perfusion pressure in patients with diagnosed intra-abdominal hypertension or abdominal compartment syndrome should be maintained at 50-60 mm Hg [12,13]; in the patients included in our study with later diagnosed pancreatic infection, the APP level in the first 48 hours did not fall below the recommended values and was even higher than 60 mm Hg in almost half of the cases (49%). According to the previously mentioned APP formula, it is impossible to give preference to the value of IAP or only mean arterial pressure, as even a slight decrease in MAP can play a significant role in the presence of intra-abdominal hypertension [14].

The 2011 study [15] compared the effect of measured IAP and APP in the early period of acute pancreatitis in 50 patients on the development of complications, finding no effect of APP on infection compared to IAP. In our study, we paid attention to the early APP value in patients who were anyhow diagnosed with pancreatic infection, and developed a confirmed correlation by building a mathematical model of linear regression.

Returning to the issue of the significance of intra-abdominal hypertension in patients with acute pancreatitis, some of the revised guidelines for the management of acute pancreatitis over the past decade have not paid much attention to the dynamic measurement of intra-abdominal pressure or abdominal perfusion pressure [16, 17].

CONCLUSIONS

1. An increase in intra-abdominal pressure in the first 48 hours of the disease in patients with acute necrotizing pancreatitis, on average, was accompanied by a reduction in the onset of pancreatic infection time, $\rho = -0.818$ ($p<0.001$).
2. An increase in abdominal perfusion pressure in the first 48 hours of the disease in patients with acute necrotizing pancreatitis, on average, was accompanied by a prolongation of the onset of pancreatic infection. $\rho = 0.933$ ($p<0.001$)
3. In the study sample, it was possible to predict the onset of pancreatogenic infection by measuring the level of abdominal perfusion pressure in the first 48 hours of the disease with a margin error of 1.3 days. A decrease in the level of abdominal perfusion pressure by each mm Hg accelerated ($p<0.001$) the onset of necrotizing pancreatitis infection by an average of 0.47±0.02 days.
4. The value of abdominal perfusion pressure can be considered as one of the factors predicting the risk of early infection of acute necrotizing pancreatitis.

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ORIGINAL ARTICLE

CHANGES ANALYSIS OF THE HEPATOCYTE APOPTOSIS MARKERS LEVELS IN MALIGNANT OBSTRUCTIVE JAUNDICE COMPLICATED BY CHOLANGITIS

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ABSTRACT

The aim: To evaluate changes in the levels of hepatocyte apoptosis markers in malignant obstructive jaundice (MOJ) depending on the performance of preoperative biliary decompression (PBD) and the severity degree of primary ascending cholangitis (PAC).

Materials and methods: 136 patients with MOJ complicated by cholangitis were included in the study: group A (n=84) – patients who underwent PBD; group B (n=52) – patients without PBD. The level of CASP3 and Bcl-2 (Human Bcl-2(B-cell Leukemia/Lymphoma 2) in blood serum and bile was assessed according to the principle of Sandwich-ELISA. Material collection for research was performed at the PBD stage and intraoperatively.

Results: Comparative analysis of CASP3 levels in patients of the study groups revealed that the level of this indicator in the blood and bile of group A patients was statistically significantly higher compared to group B, p=0,004 and p<0,001, respectively. There was no statistically significant difference between the study groups in the intraoperative levels of blood serum Bcl-2 (p=0,786) and bile Bcl-2 (p=0,439). The presence of a correlation between apoptosis markers in group A patients with I and II degree of PAC at the time of PBD and the main surgical intervention was determined: blood serum CASP3 – r=0,733, p<0,001 and r=0,753, p<0,001; bile CASP3 – r=0,716, p<0,001 and r=0,792, p<0,001; blood serum Bcl-2 – r=0,609, p<0,001 and r=0,495, p=0,002; bile Bcl-2- r=0,744, p<0,001 and r=0,497, p=0,002, respectively. Binary logistic regression analysis showed that the development of grade I and II PAC did not relate with the levels of apoptosis markers (p>0.05). Linear regression analysis revealed a correlation between the levels of Bcl-2 in bile during PBD and intraoperatively in group A patients with moderate grade OJ (R^2=0,547, p<0,001) and between the levels of CASP3 in blood serum (R^2=0,614, p<0,001), CASP3 in bile (R^2=0,603, p<0,001), Bcl-2 in blood serum (R^2=0,484, p<0,001) and Bcl-2 in bile (R^2=0,485, p<0,001) in PBD and intraoperatively in patients with severe grade OJ.

A statistically significant difference in the levels of Bcl-2 in blood serum (p<0,001) and Bcl-2 in bile (p=0,016) was found when comparing apoptosis markers in patients with moderate grade OJ of the study groups. Binary logistic analysis showed that the performance of PBD had a significant (reducing) effect on CASP3 levels in blood serum and bile taken intraoperatively in study groups patients with moderate grade OJ (R^2= 0,292, p<0,001; R^2= 0,184, p<0,001).

Conclusions: Prolonged OJ leads to the pathological apoptosis process.

The performance of PBD statistically significantly reduces the level of CASP3 in blood serum and bile, which is confirmed by further determination intraoperatively in patients with OJ complicated by PAC, p<0,001.

Staged surgical intervention with the performance of PBD according to clear indications is a necessary treatment strategy in patients with MOJ complicated by cholangitis.

KEY WORDS: apoptosis, cholangitis, jaundice, biliary decompression

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INTRODUCTION

Apoptosis is a physiological process of cell death that includes morphological and biochemical changes. Prolonged obstructive jaundice (OJ) leads to severe apoptosis and secondary necrosis, which is due to the effect of cholestasis on tissues with the release of inflammatory mediators stimulating the inflammatory response and the cascade reaction of cytokines. This leads to a decrease in endotoxin clearance, immune function, which contributes to vascular dysfunction with the possible development of DIC syndrome, disruption of the intestinal mucosal barrier, damage to the hepatic sinusoidal endothelium, and ultimately causes hepatocyte ischemia and hypoxia. Hepatocytes apoptosis induces inflammatory mediators, which leads to the development of biliary infection [1]. Consequently, monitoring of apoptosis markers can be a sign of early damage to liver tissues and be useful in choosing a

Table I. Characteristics of patients in the study groups

Characteristic	Group A PBD (n=84)	Group B no PBD (n=52)	p-value
Age*	62 (56-69)	61 (55-67)	0,6
Males, n	50	26	0,06
Females, n	24	36	
Comorbidities, n	45	24	0,08
ASA, class			
II	3	2	0,7
III	21	22	0,06
IV	60	28	0,06

Note. * Median (QI-QIII); PBD – preoperative biliary decompression; ASA (American Society of Anesthesiologists) - Physical Status Classification System

Table II. Dynamics of changes in hepatocyte apoptosis markers levels in group A patients (n=84).

Marker	PBD	Intraoperatively	p-value
CASP3 blood serum	13,64 (12,02-20,74)	4,29 (2,25-9,13)	<0,001
Bcl-2 blood serum	4,1 (1,25-6,18)	10,78 (7,34-13,23)	
CASP3 in bile	13,09 (10,97-19,10)	5,29 (3,11-8,22)	
Bcl-2 in bile	3,6 (2,19-6,01)	10,01 (7,48-11,91)	

Note. * Median (QI-QIII); Comparisons were made using the non-parametric Wilcoxon test for paired samples.

Table III. Comparison of hepatocytes apoptosis markers levels in the study groups at the intraoperative stage

Marker	Group A (n=84)	Group B (n=52)	p-value
CASP3 blood serum	4,29 (2,25-9,13)	3,12 (2,54-4,28)	0,004
Bcl-2 blood serum	10,78 (7,34-13,23)	10,33 (9,15-11,41)	0,786
CASP3 in bile	5,29 (3,11-8,22)	3,26 (2,88-3,92)	<0,001
Bcl-2 in bile	10,01 (7,48-11,91)	10,03 (8,8-10,92)	0,439

Note. * Median (QI-QIII); Comparisons were made using the nonparametric Mann-Whitney test for independent samples.

treatment strategy and determining the effectiveness of therapy in patients with MOJ complicated by cholangitis.

THE AIM

The aim of our study was to evaluate changes in the levels of markers of hepatocyte apoptosis in MOJ, depending on the PBD application and the degree of PAC severity.

MATERIALS AND METHODS

The study design is a prospective single-center cohort study. The study was conducted on the clinical basis of the Department of General Surgery №1 National Bogomolets Medical University in 2016-2021. It included 136 patients with MOJ complicated by cholangitis: group A (n=84) – patients with PBD; group B (n=52) – patients without PBD. In group A 56 (66.7%) patients underwent endobiliary stenting (EBS) and 28 (33.3%) patients – percutaneous transhepatic biliary drainage (PTBD).

Inclusion criteria – tumor origin of OJ, primary tumor morphological verification, resectability of the primary tumor of the pancreatobiliary region, age of patients over 18 years, patient's consent to participate in the study and further outpatient follow up.

Non-inclusion criteria – any invasive interventions on the biliary tract due to the primary disease performed before admission, cholecystectomy in anamnesis up to 6 months before the diagnosis of the primary disease, risk of surgical interventions V-VI class according to ASA, IV clinical group of oncological patients, presence of acute surgical pathology unrelated to the main disease, decompensated comorbid pathology, diagnosed viral hepatitis and viral hepatitis in past medical history, chronic liver failure (Class B-D by Child-Pugh).

Exclusion criteria – the patient's refusal of diagnostic and treatment at any stage of the study, the patient's death not related to the main disease.

Table IV. Comparison of average apoptosis markers rates (M (QI-QIII) in group A patients with PAC depending on the stage of material collection

Stage	Marker	PAC severity grade		p-value
		I grade	II grade	
PBD	CASP3 blood serum	12,76 (10,67-14,78)	19,51 (13,60-21,94)	<0,001
	CASP in bile	11,73 (10,21-14,19)	17,87 (12,64-19,80)	0,001
	Bcl-2 blood serum	5,45 (3,18-7,11)	1,32 (1,01-4,19)	<0,001
	Bcl-2 in bile	5,0 (2,99-6,19)	2,29 (1,82-4,10)	<0,001
Intraoperatively	CASP3 blood serum	3,96 (2,19-6,35)	6,34 (3,30-10,60)	0,027
	CASP3 in bile	4,05 (3,02-6,10)	6,11 (4,22-10,09)	0,008
	Bcl-2 blood serum	12,11 (9,17-13,72)	8,41 (6,90-11,53)	0,002
	Bcl-2 in bile	10,22 (9,03-12,35)	8,12 (6,23-10,30)	0,002

Note. * Median (QI-QIII); Comparisons were made using the nonparametric Mann-Whitney test for independent samples; PAC - primary ascending cholangitis; PBD – preoperative bile decompression

Table V. Comparison of average apoptosis markers rates (M (QI-QIII) at the time of surgery in group B patients with and without PAC

Marker	PAC		p-value
	I grade	No PAC	
CASP3 blood serum	3,52 (2,07-4,98)	3,12 (2,56-4,14)	0,682
CASP3 in bile	3,14 (2,66-4,20)	3,31 (2,89-3,92)	0,773
Bcl-2 blood serum	9,99 (8,33-11,83)	10,38 (9,40-11,29)	0,520
Bcl-2 in bile	9,36 (8,02-11,06)	10,03 (9,24-10,69)	0,236

Note. * Median (QI-QIII); Comparisons were made using the nonparametric Mann-Whitney test for independent samples; PAC - primary ascending cholangitis

Table VI. Average apoptosis markers rates (M (QI-QIII) at the time of the main surgical intervention in patients of the study groups with I PAC degree

Marker	Group A (n=48)	Group B (n=21)	p-value
CASP3 blood serum	3,96 (2,19-6,35)	3,52 (2,07-4,98)	0,297
CASP3 in bile	4,05 (3,02-6,10)	3,14 (2,66-4,20)	0,068
Bcl-2 blood serum	12,11 (9,17-13,72)	9,99 (8,33-11,83)	0,065
Bcl-2 in bile	10,22 (9,03-12,35)	9,36 (8,02-11,06)	0,157

Note. * Median (QI-QIII); Comparisons were made using the nonparametric Mann-Whitney test for independent samples.

Table VII. Comparison of the average values (M (QI-QII) of apoptosis markers in patients with moderate and severe OJ in group A

Grade	Marker	Stage		p-value
		PBD	Intraoperatively	
Moderate	CASP3 blood serum	12,22 (10,93-13,95)	3,88 (2,18-5,12) ↓	<0,001
	CASP3 in bile	11,0 (9,18-12,69)	3,24 (3,05-5,09) ↓	
	Bcl-2 blood serum	6,14 (4,73-7,85)	12,22 (10,93-13,95)↑	
	Bcl-2 in bile	6,09 (3,81-7,36)	11,13 (9,71-13,92) ↑	
Severe	CASP3 blood serum	15,53 (12,34-21,16)	5,29 (3,15-9,88) ↓	<0,001
	CASP3 in bile	14,60 (11,84-19,63)	5,17 (2,44-10,61)↓	
	Bcl-2 blood serum	2,78 (1,20-5,78)	9,26 (7,26-12,59) ↑	
	Bcl-2 in bile	3,16 (2,13-5,17)	9,15 (7,09-10,88) ↑	

Note. * Median (QI-QIII); Comparisons were made using the non-parametric Wilcoxon test for paired samples.

Table VIII. Average values (M (QI-QIII) of apoptosis markers at the time of the main surgical intervention in the patients of the study groups with moderate-grade OJ

Markers	Group A (n=20)	Group B (n=52)	p-value
CASP3 blood serum	3,88 (2,18-5,12)	3,12 (2,54-4,28)	0,642
CASP3 in bile	3,24 (3,05-5,09)	3,26 (2,88-3,92)	0,30
Bcl-2 blood serum	12,22 (10,93-13,95)	10,33 (9,15-11,41) ↓	<0,001
Bcl-2 in bile	11,13 (9,71-13,92)	10,03 (8,80-10,92) ↓	0,016

Note. * Median (QI-QIII); Comparisons were made using the nonparametric Mann-Whitney test for independent samples.

The study groups did not differ statistically in age, gender, frequency of comorbidities, and physical status according to ASA – p >0.05 (Table I).

The patients` examinations were performed following the international and local standards of diagnosis and treatment of oncological patients accepted at the time of the study [2,3].

The diagnosis of primary ascending cholangitis (PAC) was verified according to Tokyo Guidelines, 2018, the severity of cholangitis was determined using the TG18 calculator [4].

The severe degree of obstructive jaundice was determined by the level of hyperbilirubinemia >250 μmol/l [5-8].

Decisions regarding PBD application and its type were made based on the examination data and the multidisciplinary council conclusion.

Endpoints of the study:

- to compare the levels of apoptosis markers (CASP3 and Bcl-2) in patients with OJ with and without PBD;
- to determine the dynamics of changes in the level of apoptosis markers (CASP3 and Bcl-2) at the time of PBD and the main surgical intervention at different degrees of cholangitis severity;
- to evaluate the dynamics of changes in the levels of hepatocyte apoptosis markers in patients with different degrees of OJ severity.

CASP3 and Bcl-2 levels in blood serum and bile were tested during PBD and primary surgery.

The level of CASP3 and Bcl-2 (Human Bcl-2(B-cell Leukemia/Lymphoma 2) in blood serum and bile was assessed according to the Sandwich-ELISA principle. Reagents set from Elabsience (USA) was used to determine the levels of the given markers: article E-EL-H0017 – ELISA kit for quantitative testing of CASP3 concentration, article E-EL-H0114 – ELISA kit – for Bcl-2.

Statistical analysis was performed using the statistical program SPSS 22.0 for Windows. The following methods of statistical analysis were utilized: descriptive statistics, comparison of mean values of independent samples applying the Mann-Whitney U-test. Pairwise comparisons of related samples were performed using the Wilcoxon test. The non-parametric Spearman test was run for correlation analysis. The reliability of the differences was determined using regression analysis methods: binary logistic regression and linear regression. The null hypothesis (about the absence of differences between variables) was rejected at $p < 0.05$.

This study was performed within the framework of the scientific research «Development and improvement of methods of diagnosis and treatment of inflammatory and non-inflammatory diseases of the pancreas», 2017-2019 (state registration number 0117U002262).

All study procedures were carried out following the current legislation of Ukraine on ethics, the principles of Good Clinical Practice (ICH 6CP), and the recommendations of the Helsinki Declaration of 2013.

RESULTS

The dynamics of changes in the levels of hepatocyte apoptosis markers in group A patients was characterized by a statistically significant decrease in the levels of CASP3 and an increase in Bcl-2 in blood serum and bile at the time of the main surgical intervention vs. PBD, p<0,001 (Table II).

Correlation analysis was performed using the non-parametric Spearman test. A strong correlation was established between the levels of CASP3 in blood serum (r=0,776, p<0,001), Bcl-2 in blood serum (r=0,691, p<0,001), CASP3 in bile (r=0,774, p<0,001) and Bcl-2 in bile (r=0,726, p<0,001) at the time of decompression and the main surgical intervention. Further linear regression analysis revealed a significant correlation between the levels of blood serum and bile apoptosis markers in PBD and intraoperatively: blood serum CASP3 (R^2= 0,616, p <0,001), bile CASP3 (R^2=0,613, p <0,001), blood serum Bcl-2 (R^2=0,489, p <0,001) and bile Bcl-2 (R^2=0,559, p <0,001).

Comparison of CASP3 levels in patients of the study groups found that the level of this indicator in the blood and bile of patients of group A was statistically significantly higher vs. group B, p=0,004 and p<0,001, respectively. There was no statistically significant difference between the study groups in the intraoper-

ative levels of Bcl-2 in blood serum (p=0,786) and bile (p=0,439) (Table III).

Primary ascending cholangitis was diagnosed in all patients of group A: 48 patients (57,1%) – I severity degree, 36 patients (42,9%) – II severity degree. In group B, I severity degree ascending cholangitis of the first degree was diagnosed in 21 (40,4%) patients.

Comparison of apoptosis markers rates at the time of PBD in patients with PAC of I and II severity degree found a statistically significant difference between the indicators (p<0,001). Also, it was revealed that at the intraoperative stage, the levels of CASP3 in blood and bile in patients with I PAC degree were statistically significantly lower vs II PAC degree (p=0,027 and p=0,008, respectively), wheras the levels of Bcl-2 in blood and bile were higher (p=0,002 and p=0,002, respectively) (Table IV).

A further comparative analysis (Wilcoxon test for related samples) detected a statistically significant difference in the indicators of apoptosis markers in patients with I PAC dgree at the time of PBD and the main surgical intervention. A statistically significant decrease in the levels of CASP3 in blood serum, CASP3 in bile and an increase in Bcl-2 in blood serum and Bcl-2 in bile was determined (p<0,001). Moreover, a statistically significant difference in the indicators of apoptosis markers was found in patients with II PAC degree at the time of PBD and the main surgical intervention. A statistically significant decrease in the levels of CASP3 in blood serum, CASP3 in bile and an increase in Bcl-2 in blood serum and Bcl-2 in bile were detected (p<0,001). Correlation analysis showed the presence of a relationship between apoptosis markers rates in patients with I and II PAC degree at the time of PBD and the main surgical intervention: blood serum CASP3 – r=0,733, p<0,001 and r=0,753, p<0,001; bile CASP3 – r=0,716, p<0,001 and r=0,792, p<0,001; blood serum Bcl-2 – r=0,609, p<0,001 and r=0,495, p=0,002; bile Bcl-2 – r=0,744, p<0,001 and r=0,497, p=0,002, respectively. Binary logistic regression analysis revealed that the development of I and II PAC degree did not depend on the apoptosis markers level (p>0,05). In the comparative analysis of the levels of apoptosis markers in group B patients with I PAC degree and without PAC, no statistically significant difference was found (p>0,05) (Table V).

There was no statistically significant difference between the levels of apoptosis markers in study groups with I PAC degree, p> 0,05 (Table VI).

Binary logistic regression analysis indicated that the presence of I PAC degree in group B patients did not relate with the levels of apoptosis markers (p>0,05).

Also, it was established that the presence of PBD had a significant effect on the reduction of CASP3 levels in blood serum and bile obtained intraoperatively in patients of the study groups (R^2=0,195, p<0,001; R^2=0,235, p<0,001).

In group A, 33,3% (n=28) of patients had moderate OJ and 66,7% (n=56) had severe grade. In group A the medians of CASP3 in blood serum and bile decreased statistically significant in moderate OJ grade at the intraoperative stage vs. PBD (p<0,001). A statistically significant increasing of median Bcl-2 in blood serum and bile obtained intraoperatively vs. PBD was also noted, p<0,001. A comparative analysis of the average values of apoptosis markers in patients of group A showed a statistically significant decrease in the levels of CASP3 in blood serum and bile and an increase in the levels of Bcl-2 in blood serum and bile intraoperatively compared to PBD, p<0,001 (Table VII).

In patients with moderate OJ, the correlation analysis did not reveal a statistically significant correlation between the levels of blood serum CASP3 (r=0,161, p=0,498), CASP3 in bile (r=0,439, p=0,053), Bcl-2 in blood serum (r=0,402, p=0,079) with PBD and surgery, respectively. However, a statistically significant correlation was found between Bcl-2 levels in bile obtained during PBD and intraoperatively (r=0,677, p=0,001) in patients with moderate OJ grade and between blood serum Bcl-2 levels (r=0,699, p<0,001), bile Bcl-2 (r=0,649, p<0,001), blood serum CASP3 (r=0,823, p<0,001), bile CASP3 (r=0,803, p<0,001) in group A patients with severe OJ grade in PBD and operations respectively. Further linear regression analysis revealed a correlation between the levels of Bcl-2 in bile in PBD and intraoperatively in group A patients with moderate OJ grade (R^2 =0,547, p<0,001) and between the levels of CASP3 blood serum (R^2=0,614, p<0,001), CASP3 in bile (R^2=0,603, p<0,001), Bcl-2 blood serum (R^2= 0,484, p<0,001) and Bcl-2 in bile (R^2=0,485, p<0,001) in PBD and intraoperatively in group A patients with severe OJ grade.

All patients in group B had moderate OJ.

While comparing the apoptosis markers in moderate OJ in the study groups (Mann-Whitney test), a statistically significant difference was found in the levels of Bcl-2 in blood serum (p<0,001) and Bcl-2 in bile (p=0,016) (Table VIII).

Binary logistic analysis showed that the PBD performance had a significant effect (reduce) on CASP3 levels in blood serum and bile taken intraoperatively in patients of the study groups with moderate severity of MOJ (R^2=0,292, p<0,001; R^2=0,184, p<0,001) .

DISCUSSION

Apoptosis is a gene-dependent programmed and controlled process caused by various physiological

and pathological conditions characterized by DNA damage, which was first described in 1885 by W. Flemming (calling it chromatolysis). Later in 1972, Kerr et al. presented the concept of two types of cell death (necrosis and apoptosis), in which they presented evidence that apoptosis is a genetically programmed type of physiological cell death, observed and activated in pathological conditions. And in 2002 the Nobel Prize was awarded to Brenner, R. Horvitz, and D. Salton for their work on the study of genetic regulation of organogenesis and «programmed death» of cells [9]. In case of critical damage apoptosis is a gene-controlled method of rapid self-destruction of the damaged cell by cascading activation of caspases and endonucleases with disintegration of its remnants by macrophages. Various pathophysiological processes can lead to an increase in the process of cell apoptosis and its transformation into a necrotic inflammatory process. In addition, there are mechanisms that regulate the level of apoptosis, namely the BCL-2 family of integral membrane proteins, which disrupt the CASP3-dependent proteolytic cascade [10].

CASP3 plays an important role in the development and regulation of apoptosis, as well as inflammatory processes. Expression of CASP3, as a pro-apoptotic signaling protein, can serve as an early marker of liver damage [11]. Assessment of its activity is considered one of the main methods of determining the apoptosis level. CASP3- "cell death" protease that induces apoptosis in cells, is expressed in almost all tissues, but is most pronounced in the structural components of liver: hepatocytes, sinusoids cells, the composition of the portal zones and intralobular focal necrosis, the epithelium of the bile ducts, which illustrates a tight relationship of all tissue elements of liver in the development of pathological processes. Apoptotic signaling is regulated by: the balance between pro- and anti-apoptotic factors. The severity of liver damage may be the result of an imbalance between these factors. With cholestasis process bile acids accumulate causing oxidative damage to cell membranes. Moreover, hyperbilirubinemia correlates with high levels of lipid peroxidation and low levels of antioxidants. Lipid peroxidation and oxidative stress cause increased apoptosis and necrosis and lead to liver damage [12]. Bcl-2 is one of the most important antiapoptotic proteins located on the membrane of the endoplasmic reticulum and the mitochondrial membrane, which prevents apoptosis caused by various stimuli [13]. An experimental study by Shao et al., 2018 with the determination of the Bcl-2 gene expression level in 146 mice with OJ (duration of 1,3,5,10 days), which were ligated the common bile duct with 1 ml of bile isolates, demonstrated that after 24 hours there were no statistically significant changes detected. A significant increase in the level of Bcl-2 was observed already at 72-hour survival, 2,6 times higher ($p=0,04$). After 5 days from the beginning of the OJ modeling, the activation of Bcl-2 gene expression increased by an average of 5,8 times ($p=0,002$). After 10 days of the experiment, the relative level of Bcl-2 gene expression began to gradually decrease, but still remained elevated 3,2 times ($p= 0,036$). Thus, it was concluded that 10-day OJ leads to the development of biliary endogenous intoxication, which is accompanied by a decrease in the level of expression of anti-apoptotic gene BcL-2, contributing to the "excessive" process of apoptosis – "necrapoptosis", the severity degree of which depends on the duration of cholestasis [14]. In 2014 in an experimental study Kosar et al. confirmed that OJ leads to hepatocyte damage with activation of the p53 gene, which triggers the apoptosis pathway to reduce DNA damage and cellular damage [15]. Wang et al., 2003 in an animal study found that biliary decompression significantly reduces the hepatocyte apoptosis index by 74,2% due to a decrease in the level of bile acid as an inducer of apoptosis, and also improves portal circulation, which improves hepatocyte proliferation [16]. Lalisang et al., 2010, studying morphological liver changes, confirmed this statement with their own results, stating that bile acid inhibition by decompression of the biliary tract leads to a decrease hepatocytes apoptosis level in patients with severe OJ [17].

According to the results of our own study, it was confirmed that the performance of PBD had a significant effect on the levels of CASP3 in blood serum and bile taken intraoperatively in patients with OJ ($p<0,001$). However, the development of grade I and II PAC did not relate with the levels of apoptosis markers ($p>0,05$). Most of the literature references reviewed presented the data over the last 20 years. Modern diagnostic methods reveal new possibilities for determining the pathophysiological changes that determine the severity of the course of the disease. Hence, in our opinion, an urgent need for further evaluation of the level of apoptosis markers with the possibility of their inclusion in the diagnostic and treatment algorithm in patients with OJ.

CONCLUSIONS

Prolonged OJ leads to the pathological apoptosis process.

The performance of PBD statistically significantly reduces the level of CASP3 in blood serum and bile, which is confirmed by further determination intraoperatively in patients with OJ complicated by PAC, $p<0,001$.

Staged surgical intervention with the performance of PBD according to clear indications is a necessary treatment strategy in patients with MOJ complicated by cholangitis.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

PHYSICAL HEALTH OF FEMALES FROM THE LOWLAND DISTRICTS OF ZAKARPATTIA ACCORDING TO THE METABOLIC LEVEL OF AEROBIC AND ANAEROBIC ENERGY SUPPLY DEPENDING ON THE COMPONENT BODY COMPOSITION

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ABSTRACT

The aim: To determine the aerobic and anaerobic productivity of females from the lowland districts of Zakarpattia region, depending on the component composition of body weight.

Materials and methods: A comparative analysis of physical health status of females in the post-pubertal period of ontogenesis, was carried out. Physical health status was assessed by indicators of aerobic and anaerobic productivity depending on the component composition of the body, which was determined by impedance measurement.

Results: Physical health of females from the lowland districts depends on the component composition of the body, namely: an excellent level of aerobic productivity is observed in females who have a normal body weight with a high relative fat content and a normal relative content of skeletal muscles, $VO_{2\,max\,rel.} > 38$ ml·min^{-1}·kg^{-1}; as a result, their physical health exceeds the "critical level" according to H.L. Apanasenko and corresponds to "excellent" according to Ya.P. Pyarnat's criteria. Females from lowland districts who are underweight with a normal relative fat content and a high relative skeletal muscle content have an average level of aerobic productivity, $VO_{2\,max\,rel.} < 34$ ml·min^{-1}·kg^{-1}; as a result, their physical health is below the "critical level" according to H.L. Apanasenko.

Conclusions: The presence of fat in females from lowland districts provides energy for muscle work, which contributes to better development of the muscular system. A high level of energy supply due to a high relative fat content determines the excellent physical health status of females from the lowland districts of Zakarpattia.

KEY WORDS: body mass, fat, skeletal muscles, post-pubertal age

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INTRODUCTION

The formation of physical health occurs under the influence of endogenous and exogenous factors [1, 2]. Moreover, prolonged exposure to exogenous factors can cause genetic changes in the body. Therefore, national and population differences in morphofunctional indicators stimulate scientists to search for relative standards for residents of certain regions [3-5]. In particular, there are territories in Ukraine with ecological features that determine the hormonal status, somatometric parameters, individual components of the somatotype, component composition of body weight, and functional state of the residents of these regions [6-8]. Zakarpattia is one of such regions.

According to the existing concepts of physical health, the aerobic productivity of the body is an integral health indicator [9, 10]. Therefore, the somatic health of a specific individual should be evaluated by physiological indicators that reflect the maximum possible metabolic rate of aerobic energy supply processes. To evaluate the aerobic energy supply processes of the organism, it is recommended to use such indicators as the maximum oxygen consumption or the anaerobic threshold (AnT) [11, 12].

A significant role in the formation of physical health is played not only by aerobic, but also by anaerobic energy supply processes. The results of the research indicate the existence of a close correlation between the aerobic and anaerobic productivity of the organism, where the anaerobic (lactic) productivity is a factor indicator [13, 14].

Therefore, in order to carry out an objective analysis of physical health status of people of different ages and

Table I. Distribution of females from the lowland districts of Zakarpattia by component composition of body weight, n=118

Relative fat content (%)							
< 21,0 (-) low		21,0 – 32,9 (0) normal		33,0 – 38,9 (+) high		>39,0 (++) very high	
number of persons	%	number of persons	%	number of persons	%	number of persons	%
8	6,8	65	55,1	45	38,1	-	-
Relative content of skeletal muscles (%)							
< 24,3 (-) low		24,3 – 30,3 (0) normal		30,4 – 35,3 (+) high		> 35,3 (++) very high	
number of persons	%	number of persons	%	number of persons	%	number of persons	%
-	-	76	64,4	42	35,6	-	-

genders, it is necessary to clearly determine the values and limits of physiological fluctuations of indicators of aerobic and anaerobic productivity of the body, depending on the component composition of body weight, in the healthy population of the Zakarpattia region.

THE AIM

The aim is to determine the aerobic and anaerobic productivity of females from the lowland districts of Zakarpattia region, depending on the component composition of body weight.

MATERIALS AND METHODS

A comparative analysis of physical health status of 118 post-puberty females aged 16 to 20, residents of the lowland districts of Zakarpattia region, was carried out. Physical health status was assessed by indicators of the aerobic productivity of the body, namely, the maximum oxygen consumption was measured ($VO_{2\,max}$) using the bicycle ergometry method. To evaluate the level of aerobic productivity, the Ya.P. Pyarnat's rating scale was used [15]. Indicators of anaerobic productivity of the body were studied by: measuring the power of anaerobic alactic energy supply processes by the Peak Power Output in 10 s ($WAnT_{10}$); the power of anaerobic lactic energy supply processes by the Peak Power Output in 30 s ($WAnT_{30}$), using the Wingate anaerobic test described by Yu.M. Furman et al. The anaerobic lactic productivity of the organism was measured by the Peak Power Output (PPO) in 1 min using A. Shogy and G. Cherebetin's method. The component body mass composition was determined using the impedance method with the application of Omron BF511 Body Composition Monitor to estimate the percentage of fat mass (subcutaneous and visceral fat) and the percentage of skeletal muscle [16]. The statistical processing of the material was carried out in Excel 7.0 and SPSS version 10.0 using Student's t-test to find out the reliability of the difference between the average values.

RESULTS

As a result of determining the component composition of body weight, the females studied were divided into three groups depending on the relative content of fat and into two groups depending on the relative content of skeletal muscles. The number of females with a normal relative fat content (21.0-32.9%) was the largest – 65 individuals (51.1%), while the number of females with a low relative fat content (33.0 -38.9%) was the smallest – 8 (6.8%). There were no individuals with a very high relative fat content (> 39.0%) among those studied. There were 76 individuals (64.4%) with a normal and 42 individuals (35.6%) with a high content of skeletal muscles. There were no females with low (< 24.3%) and very high relative content of skeletal muscles (> 35.3%) among those studied (Table I).

The value of the absolute $Vo_{2\,max}$ index in females with a low relative fat content is 2265.3±65.6 ml·min^{-1} and is significantly lower than the value of females with a normal relative fat content of 2474.5±71.2 ml·min^{-1} ($p<0.05$). The average value of $VO_{2\,max\,rel.}$ of individuals with a high relative fat content is 1.15 times lower than the average value of individuals with a normal relative fat content ($p<0.05$); however, it reaches "safe health level", which is estimated by the relative indicator of $VO_{2\,max\,rel.}$ and is 35.02±1.58 ml·min^{-1}·kg^{-1}. For females, "safe health level" is at the limit of 35.0 ml·min^{-1}·kg^{-1}. The average value of $VO_{2\,max\,rel.}$ relative index of maximum oxygen consumption in females from lowland districts with low and normal relative fat content exceeds "safe health level" and is 37.4±1.65 ml·min^{-1}·kg^{-1} and 40, 3±1.71 ml·min^{-1}·kg^{-1}, respectively. Study of the power of anaerobic lactic energy supply processes of the

Table II. Average values of indicators of aerobic and anaerobic productivity of the body (M±m) of females from the lowland districts of Zakarpattia, depending on the relative fat content, n=118

Indicators	Aerobic productivity		Anaerobic productivity					
	Maximum oxygen consumption		power of alactic energy supply processes		power of lactic energy supply processes		capacity of lactic energy supply processes	
Relative fat content (%)	VO_{2max} ml·min^{-1}	$VO_{2maxrel.}$ ml·min^{-1}·kg^{-1}	$WAnT_{10,}$ kgm·min^{-1}	$WAnT_{10rel.,}$ kgm·min^{-1}·kg^{-1}	$WAnT_{30.}$ kgm·min^{-1}	$WAnT_{30\ rel.,}$ kgm·min^{-1} ·kg^{-1}	PPO, kgm·min^{-1}	$PPO_{rel.,}$ kgm·min^{-1}·kg^{-1}
< 21,0 (-) low (n=8)	2265,3± 65,6 •	37,4± 1,65	2184,4± 68,4 •	40,1± 1,01 •	2102,5± 67,1 •	38,1± 0,82	1218,6± 36,2	21,8± 0,72
21,0 – 32,9 (0) normal (n= 65)	2474,5± 71,2	40,3 ± 1,71	2401,4± 77,3	43,9± 1,04	2297,4± 69,2	40,3± 1,06	1304,8± 39,3	22,7± 0,69
33,0 – 38,9 (+) high (n=45)	2388,7± 68,4	35,02± 1,58 * •	2384,6± 72,1	37,1± 0,92 • *	2196,8± 71,6	37,4± 0,54 •	1198,2± 30,1 •	18,4± 0,62 • *

Note: the probability of a difference in mean values ($p<0.05$):
* - relatively low fat content;
• - relatively normal fat content;
• - relatively high fat content.

Table III. Average values of indicators of aerobic and anaerobic body productivity (M±m) of girls from the lowland regions of Zakarpattia depending on the relative content of skeletal muscles, n=118

Indicators	Aerobic productivity		Anaerobic productivity					
	Maximum oxygen consumption		power of alactic energy supply processes		power of lactic energy supply processes		capacity of lactic energy supply processes	
Relative skeletal muscle content (%)	VO_{2max} ml·min^{-1}	$VO_{2maxrel.}$ ml·min^{-1}·kg^{-1}	$WAnT_{10,}$ kgm·min^{-1}	$WAnT_{10\ rel.}$ kgm·min^{-1}·kg^{-1}	$WAnT_{30.}$ kgm·min^{-1}	$WAnT_{30\ rel.,}$ kgm·min^{-1} ·kg^{-1}	PPO, kgm·min^{-1}	$PPO_{rel.,}$ kgm·min^{-1}·kg^{-1}
24,3 – 30,3 (0) normal (n=76)	2372,9±102,6	40,19±1,17	2436,0±51,8	41,4±1,73	2418,6±58,46	41,42±2,03	1482,1±27,4	25,2±0,9
30,4 – 35,3 (+) high (n=42)	2707,1±83, 4	39,8±1,73	2619,7±41,6	40,2±1,46	2689,7±73,4	41,2±1,44	1513,6±44,2	23,1±0,8
P	< 0,05	> 0,05	< 0,01	> 0,05	< 0,01	> 0,05	> 0,05	> 0,05

Note: P is the probability of the difference in indicators;

body based on the relative value of $WAnT_{30\ rel.}$ among females from lowland districts revealed a significant prevalence of this indicator in females with a normal relative fat content of 43.9±1.04 kgm·min^{-1}·kg^{-1} compared to individuals with a high relative fat content of 37.1±0 .92 kgm·min^{-1}·kg^{-1} ($p<0.05$). Peculiarities of the manifestation of anaerobic productivity in individuals from lowland districts with different component composition of body weight were also revealed when determining the relative power of anaerobic lactic energy supply processes of the body. It is worth noting that the lowest average values of $WAnT_{30\ rel.}$ 37.4±0.54 kgm·min^{-1}·kg^{-1} and 38.1±0.82 kgm·min^{-1}·kg^{-1} are observed in individuals from lowland districts with high and low relative fat content, respectively. At the same time, in females with a normal relative fat content, the average value of the absolute indicator of the capacity of anaerobic lactic processes of energy supply of the body of the PPO is the highest 1304.8±39.3 kgm·min^{-1} compared to the individuals of lowland districts with low 1218.6±36.2 kgm·min^{-1} and high relative fat content 1198.2±30.1 kgm·min^{-1} ($p<0.05$), respectively. In females from lowland districts with a high relative fat content, there is a significantly low relative index of the power of anaerobic lactic processes of energy supply. 18.4±0.62 kgm·min^{-1}·kg^{-1} compared to the indicator in females with low 21.8±0.72 kgm·min^{-1}·kg^{-1} ($p<0.05$) and normal relative fat content 22.7±0.69kgm·min^{-1}·kg^{-1} ($p<0.05$) (Table II.)

The value of the absolute $VO_{2\ max}$ indicator in females with a normal relative content of skeletal muscles is 2372.9±102.6 ml·min^{-1} and is significantly lower than

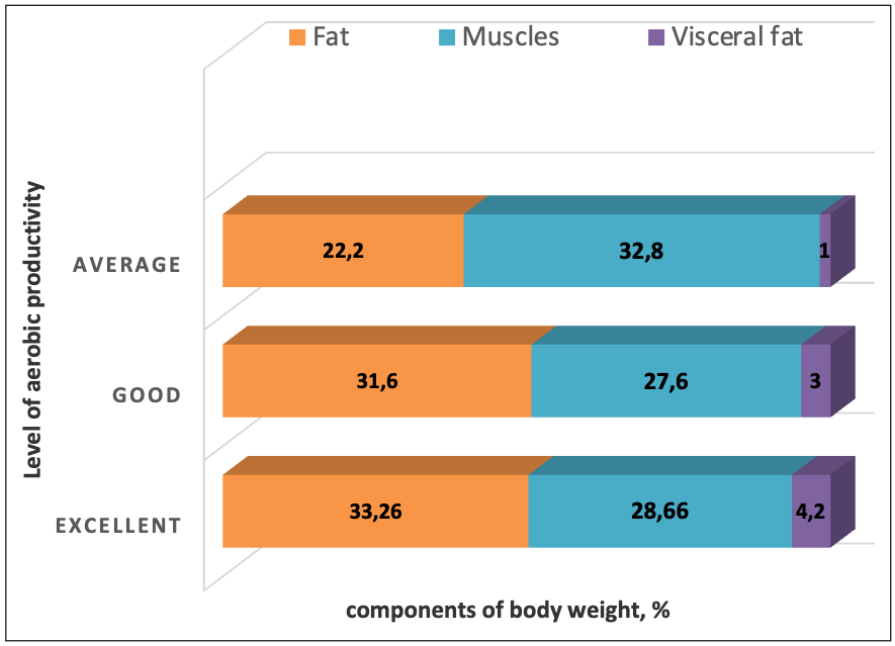

Fig. 1. Graphic representation of the dependence of the level of aerobic productivity of females from the lowland districts of Zakarpattia on the ratio of the component composition of body weight (n=118)

the value in individuals with a very high relative content of skeletal muscles 2707.1±83 .4 ml·min^{-1} ($p<0.05$). The average value of $VO_{2max\ rel.}$ in females from lowland districts with normal and high relative content of skeletal muscles is significantly higher than "safe health status", which corresponds to an excellent level of aerobic productivity and is 40.19±1.17 ml·min^{-1}·kg^{-1} and 39.8±1.73 ml·min^{-1}·kg^{-1}, respectively ($p<0.05$), although the indicators are not significantly different from each other ($p>0,05$). The results of studies of the power of anaerobic lactic processes of energy supply of the body by the absolute value of $WAnT_{10}$ in females from lowland districts revealed a significant prevalence of this indicator in females with a high relative content of skeletal muscles 2619.7±41.6 kgm·min^{-1} compared to individuals with a normal relative the content of skeletal muscles, which is 2436.0±51.8 kgm·min^{-1}. Peculiarities of the manifestation of anaerobic productivity in individuals from lowland districts with different component composition of body weight were also revealed when determining the absolute value of the power of anaerobic lactic energy supply processes of the body. It is worth noting that the lowest average values of $WAnT_{30}$ are reliably observed in females from lowland districts with a normal relative content of skeletal muscles of 2418.6±58.46 kgm·min^{-1}. At the same time, relative indicators of the power of anaerobic lactic energy supply processes of the body of females with normal and high relative content of skeletal muscles probably do not differ from each other. Also, females from lowland districts do not differ in terms of absolute and relative capacity of anaerobic lactic processes of energy supply (PPO) with different relative content of skeletal muscles ($p>0.05$) (Table III).

Thus, according to the results of the research of aerobic and anaerobic processes of energy supply in females from lowland districts, we came to the conclusion that females with a high relative fat content (33.0-38.9%) and a normal relative content of skeletal muscles (24, 3 – 30.3%) with normal body weight (18.5 ≤ BMI < 25 kg/m^2) have an excellent level of aerobic productivity, i.e. $VO_{2\ max\ rel.}$ > 38 ml·min^{-1}·kg^{-1}. Females with a normal relative fat content (21.0 – 32.9%) and a normal relative skeletal muscle content (24.3 – 30.3%) with normal body weight have a good level of aerobic productivity, i.e. $VO_{2\ max\ rel.}$ > 34 to 38 ml·min^{-1}·kg^{-1} (Fig. 1).

Females with a normal relative fat content and a high relative skeletal muscle content (30.4 – 35.3%), but insufficient body weight (BMI<18.5 kg/m2), have an intermediate level of aerobic productivity, i.e. $VO_{2\ max\ rel.}$ 28 – 33 ml·min^{-1}·kg^{-1}. At the same time, all the individuals studied have a normal level of visceral fat, in the range from 1 to 9%.

DISCUSSION

Current scientific research in clinical medicine is impossible without clinical anthropology and its methodology. Anthropometry, which is the basis of anatomical constitution and indicators of physical development, is successfully applied to identify the relationship with certain somatic diseases. A.V. Bobryk identified certain constitutional features in mature men with pathology of the respiratory, cardiovascular and digestive systems. Thus, mesomorphs with increase in longitudinal dimensions of the body and a decrease in body weight are prone to pathology of the respiratory system; mesomorphs with obesity of the first degree are prone to

heart disease, and ectomorphs with a Quetelet's index <18.5 kg/m^2 are prone to diseases of the gastrointestinal tract [17].

Specific types of constitution are characterized by various features of immunity and susceptibility to infectious diseases. Body structure or morphological phenotype, being one of the phenotypic characteristics of an organism, determines its characteristic reactivity, which determines the correlation between constitution and disease. Thus, E.G. Kornetova researched that individuals with schizophrenia have predominantly the asthenic type of constitution [18]. E.K. Grebennikova et al., studying the constitutional features of females with hyperplastic diseases of the uterus during perimenopause, found that 84.75% of females with gynecological pathology had the highest indicators of body length and weight, a higher relative content of the fat component and a low relative content of the muscle component, compared to females of other constitutions [19]. According to O.V. Yakovlev et al. pregnant women with the same type of constitution, are prone to the threat of premature birth in the 28-34th week of pregnancy due to the high probability of detecting isthmic-cervical insufficiency, premature ripening of the placenta, disruption of the uteroplacental blood flow and changes in the blood coagulation system [20].

The anatomical manifestation of the constitution is the somatotype. The somatometric or anthropometric factor is a significant indicator at the basis of a person's physical condition. It is also important to study the somatotypological and functional features of the body of people living in certain territories. Thus, O.V. Kalmin et al. conducted a comparative study of the level of physical development of individuals in post-pubertal period of the Krasnodar Krai, describing that young men of Krasnodar have average height, long limbs, a low relative content of muscle and a high content of fat component, which indicates a sedentary lifestyle. Krasnodar females, compared to individuals from other regions, have a tall height and a relatively high body weight, a narrow chest, a narrow pelvis, a mesomorphic somatotype with a high content of the fat component and a low relative content of skeletal muscles [21]. Also, T.V. Kazakova et al. conducted a comparative analysis of indicators of the autonomic nervous system activity in young males and females of different somatotypes and came to the conclusion that regardless of gender, adolescents with a high relative content of the muscle component have the highest reaction to orthostasis. At the same time, the greatest inertia of changes in indicators of the activity of the autonomic nervous system during orthostasis was recorded in adolescents who have a high relative content of the fat component [22]. Therefore, the anthropometric approach with the determination of the parameters of physical development and the component composition of the body is perfect for monitoring health and physical status.

CONCLUSIONS

Research results indicate that the physical health of females from the lowland districts of Zakarpattia depends on the component composition of body weight, namely: an excellent level of aerobic productivity is observed in females who have a normal body weight with a high relative fat content and a normal relative skeletal muscle content, with a normal level of visceral fat. As a result, their physical health status exceeds the "critical level" according to H.L. Apanasenko [23] and corresponds to "excellent" according to Ya.P. Pyarnat's criteria. An average level of aerobic productivity is observed in underweight females from lowland districts with a normal relative fat content and a high relative skeletal muscle content, with a normal level of visceral fat. As a result, their physical health status is below the "critical level" according to H.L. Apanasenko, i.e. $VO_{2max.} < 34$ ml·min^{-1}·kg^{-1}. The presence of fat in females from lowland districts provides energy for muscle work, which contributes to better development of the muscular system. A high level of energy supply due to a high relative fat content determines excellent physical health status of females from the lowland districts of Zakarpattia.

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ORIGINAL ARTICLE

THE DETERMINATION OF THE NEED TO PROVIDE ORTHODONTIC ASSISTANCE TO TEENAGERS IN CONDITIONS OF LIMITED RESOURCES

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ABSTRACT

The aim: To substantiate the need for a combination of interdisciplinary approaches to diagnosis, treatment and correction of dento-maxillofacial anomalies of teenagers based on the analysis of the need for orthodontic treatment using the DAI, IOTN, ICON aesthetic indices.

Materials and methods: Empirical, epidemiological, clinical, analytical-synthetic, sociological, psychological research methods, questionnaires, dental indexeshave been used in various combinations.

Results: As a result of a clinical examination of 2,260 teenagers (1,096 boys and 1,124 girls), 1,474 individuals have been bselected for orthodontic treatment with the following degree of complexity: mild – in 25 examined (35.71±4.95%), moderate – in 31 individuals (44.28± 5.48%), heavy – 14 (20.00±3.11%). After an in-depth dental examination and determination of the psychological profile, 70 teenagers have been selected for treatment.

Conclusions: The effectiveness of the use of dental indices as a screening tool to eliminate the discrepancy between objective medical indicators of the level of need for correction of dento-maxillofacial anomalies and the level of expected results in adolescents has been proven.

KEY WORDS: dentistry, orthodontic treatment, index of need for orthodontic treatment, DAI, IOTN, ICON

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INTRODUCTION

Global trends to reduce spending on the health care system encourage optimization of the processes of correction and treatment of dento-maxillofacial pathologies. In the conditions of limited material, labor and financial resources, the search for effective methods of orthodontics is becoming more urgent, because the treatment and correction of dento-maxillofacial anomalies is one of the resource-intensive types of dental work.

The result of orthodontic care depends on the quality of diagnosis and the clinic. Since not every malocclusion requires treatment, a comprehensive approach to predicting the course of the treatment process requires finding new ways of patient-doctor interaction. The use of dental indexes in combination with psychosociological methods will allow to identify patients who have a priority need for treatment, will contribute to the effectiveness of orthodontic treatment.

The peculiarities of mental development of teenagers [1] demand to single out this category of patients as the most vulnerable due to their tendency to psychological accentuations caused by sensitivity to their own appearance, social image attributes [2].

THE AIM

The aim of the research is to substantiate the need for a combination of interdisciplinary approaches to diagnosis, treatment and correction of dento-maxillofacial anomalies of teenagers based on the analysis of the need for orthodontic treatment using the DAI, IOTN, ICON aesthetic indices.

MATERIALS AND METHODS

Dental examinations of 2,260 teenagers in the age group 14-17 years old with a fully formed permanent bite have been carried out on the basis of the examination dental office of the polyclinic department of Uzhgorod City Children's Hospital by a multidisciplinary team of specialists (orthodontist, pediatrician, psychologist, teacher) from among students of general secondary education institutions of Uzhhorod. The level of need for orthodontic treatment of teenagers has been determined. In the selected group of 570 respondents (230 parents and 340 children), relationships between dental competence, conditions of socio-hygienic functioning, and level of dental health have been revealed. A group of 70 (-2) people has been selected for treatment.

Table I. Division of patients of the studied group according to the indicator of the complexity of orthodontic treatment of the ICON index

Level of complexity of orthodontic treatment		Abs.	%
Very light	<29 scores	-	-
Light	29 till 50 scores	25	35,71±4,95
Moderate	51 till 63 scores	31	44,28±5,48
Difficult	64 till 77 scores	14	20,00±3,11
Very heavy	>77 scores	-	-

Table II. Evaluation of the results of treatment by the level of improvement of the ICON index of the ICON index

Level of improvement (assessment before treatment - 4 x assessment after treatment)	Scores
A substantial improvement	>-1
A significant improvement	-25 till-1
Moderate improvement	-53 till -26

Table III. Division of patients according to the level of discrepancy between the levels of self-esteem and harassment in groups with different level of complexity of orthodontic treatment according to the ICON index

Level of complexity of orthodontic treatment	The level of difference between the levels of self-esteem and harassment					
	Light < 8 scores		Moderate 9-25 scores		Heavy > 26 scores	
	Abs.	%	Abs.	%	Abs.	%
Light N=25	3	12,0±1,26	18	72,00±4,26	4	16,00±3,11
Moderate N=31	5	16,12±1,85	20	64,51±4,09	6	19,35±3,68
Heavy N=14	-	-	11	78,57±5,11	3	21,42±4,09

Clinical research methods have been used to assess the state of the dento-maxillofacial system and the results of orthodontic treatment; epidemiological methods, x-ray, photometry, dental indices – for diagnosing the condition of the dento-maxillofacial system, evaluating the results of treatment; psychological – to assess the psycho-emotional state and level of quality of life of patients with dento- dento-maxillofacial anomalies; sociological – establishment of relationships between conditions of social and hygienic functioning and motivation for orthodontic treatment; statistical – to establish the levels of correlation, data dispersion, levels of consistency of the obtained results and verify the reliability of established dependencies and associations.

RESULTS

The analysis of the need for orthodontic treatment on a sample of 2,260 teenagers, students of educational institutions aged 14 to 17 years, according to the DAI indices, the dental health components of the IOTN and ICON indices, shows the need for treatment in 54.51±4.90%, 52.16±1.52% and 51.94±3.18% of the examined, respectively. Partial secondary adentia is the indication for orthodontic treatment in 18.58±1.21% of the examined persons. It is caused by the removal of permanent teeth as a result of complicated caries, which is a specific risk factor in the occurrence and progression of dentition deformations.

The analysis of the aesthetic component of the IOTN and ICON indices shows that 31.74% of the examined consider themselves to be in need of orthodontic treatment. When analyzing the structure of the subjective need for orthodontic treatment according to the aesthetic component of the IOTN, a high degree of need for treatment has been found in 4.22±0.58% of the examined. Although according to the dental component of the same index, this indicator is 8.93±0.71%, and according to the DAI index – 9.33±1.47%, which indicates a lack of awareness of the presence in patients of a particularly complex clinical form of dento-maxillofacial anomalies and accordingly, low motivation to receive medical care.

The analysis of the medical and social component of the need for orthodontic treatment based on a questionnaire of teenagers and their parents or guardians proved the urgent feasibility of increasing the importance of orthodontic treatment of teenagers in the Transcarpathian region, by objectifying the problem and increasing the motivation to carry out this treatment (36.20% of parents do not understand the essence of orthodontic treatment; 3.44% associate the successful future of their children with a beautiful smile; 6.89% are

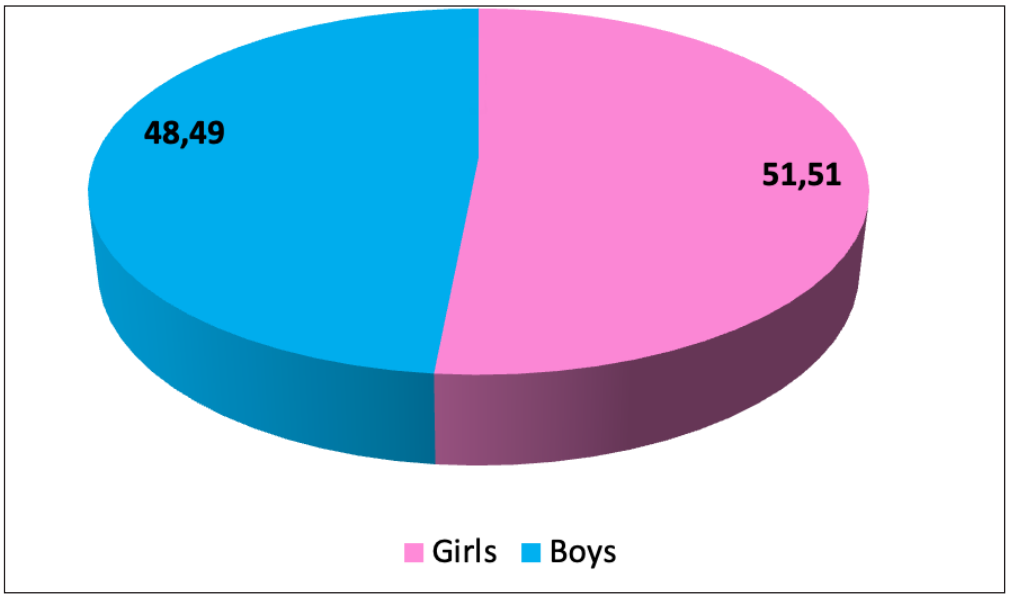

Fig.1. Division of the researched persons by gender at the first stage of the study

aware of the impact of orthodontic pathology on the child's psychological comfort).

As a result of an in-depth dental examination and determination of the psychological profile, 70 teenagers have been selected for orthodontic treatment with the use of non-removable equipment (bracket-system examination, average positive correlations have been determined between the indicator of the degree of complexity of orthodontic treatment according to the ISON index, the level of self-esteem and harassment according to the Dembo-Rubinstein scale, reactive anxiety ($r=0,45$; $p<0,05$) according to the Spielberger scale, the OHIP-14-RU scales "disruption of masticatory function" ($r=0,48$; $p<0,05$), "physical pain" ($r=0,57$; $p<0,05$), "psychological discomfort" ($r=0,45$; $p<0,05$), "social disability" ($r=0,62$; $p<0,05$).

Thus, orthodontic treatment eliminated the morphological basis of physical discomfort and had a positive effect on the psycho-emotional condition of patients. Patients with low self-esteem and a low level of harassment, patients with overestimated self-esteem against the background of an inappropriate level of harassment, teenagers with a high level of personal and reactive anxiety, demonstrate indicators for predictably complex and long-term orthodontic treatment with the need for a high level of responsibility and cooperation with the doctor, they need psychological training with the involvement of specialists.

Dento-maxillofacial anomalies in teenagers cause deterioration of dental health in general, requiring significant medical and economic resources. According to studies [3, 4], the prevalence of dento-maxillofacial anomalies in the structure of dental morbidity ranks second after dental caries and is from 30.0% to 82.0% in the world population with a tendency to increase in adverse environmental conditions [5]. In different regions of Ukraine, studies [6, 7] testify the prevalence of dento-maxillofacial anomalies and deformities in 75-90%. children and teenagers. In the Transcarpathian region, dental pathologies increase as a result of biogeochemical deficiency of trace elements, especially fluorine, iodine, calcium, magnesium in the environment [8-10].

In the conditions of limited resources against the background of the high prevalence of orthodontic pathologies, it is significant to take into account a wide range of tools that have a positive effect on the effectiveness of treatment, in particular, dental indices and psychosociological diagnostic methods as a screening tool for determining priority areas of treatment.

The dental indices recommended by the WHO, such as the Index of Orthodontic Treatment Need (IOTN), The Dental Aesthetic Index (DAI) to determine the need or priority of orthodontic treatment, ranking the need for corrective measures from "no need" or "little need" to "necessary treatment" have been considered as diagnostic tools [10].

DAI (The Dental Aesthetic Index) is one of the most widely used indices, which is calculated exclusively on the basis of clinical signs of pathology in the oral cavity, without taking into account its external manifestations and the self-esteem of a person. Data from the IOTN (Index of Orthodontic Treatment Need) esthetics and orthodontic treatment needs index can also be used. At the same time, DAI is used to determine the normative need for treatment, and AC-IOTN is used to determine the perceived need (Spalj S. et al., 2014). The use of the ICON index is convenient for comprehensive assessment of the need, complexity and result of orthodontic treatment.

The following research stages has defined:

The first stage (2016-2017) – diagnosis of the need for orthodontic treatment based on the principle of multi-stage selection using continuous and selective research with various combinations of clinical and psychosociological methods;

II stage (2018-2020) – orthodontic treatment and removal of fixed orthodontic appliances using clinical and paraclinical methods;

Stage III (2021) – a comprehensive evaluation of the results of correction of anomalies of the orthodontic system, which included clinical and radiological examination, photometry and psychodiagnostics, the ICON for the aesthetic assessment of orthodontic treatment, statistical processing of the obtained data.

At the 1st stage of the study, a multidisciplinary team of specialists (orthodontist, pediatrician, psychologist, teacher) examined teenager patients with a fully formed permanent bite on the basis of the examination dental office of the polyclinic department of the Uzhhorod City Children's Hospital under artificial lighting using a standard set of tools: a mirror, a probe, tweezers. The examination of the patient began with the clarification of complaints and desired changes in the dento-maxillofacial system.

During the external examination, the relative proportionality and symmetry of the face, the expressiveness of the nasolabial and chin folds, the anatomy of the smile have been examined. When studying the dentition, the number of teeth, their shape, size, state of hard tissues, position in the dentition have been taken into account. The shape and size of the dental arches, their relation to the alveolar processes and the apical bases of the jaws have been determined. The ratio of tooth rows in the sagittal, transverse and vertical planes has been studied. Dento-maxillofacial anomalies have been diagnosed according to the International Classification of Diseases X revision as well as Engel's classification of dento-maxillofacial anomalies.

The need for orthodontic treatment has been determined by calculating the DAI, IOTN and ICON indices.

2,260 people have been examined, among them 1,096 boys and 1,124 girls.

Evaluating the psychosociological type of the patient's personality, the stereotype of family upbringing and the level of complexity of the future treatment, it is possible to predict the degree of cooperation of the patient with the doctor. Patients with low self-esteem and a low level of harassment, patients with overestimated self-esteem against the background of an inappropriate level of harassment, adolescents with a high level of personal and reactive anxiety, especially those who demonstrate indicators for predictably complex and long-term orthodontic treatment with the need for a high level of responsibility and cooperation with the doctor need psychological training with the involvement of specialized specialists. In some cases, it is even recommended to postpone the start of orthodontic treatment during a course of psychological consultations until the patient realizes the need for treatment, overcomes the difficulties associated with it, and completes the treatment. In these cases, longer psychological preparation of the patient and his parents is required.

At the II stage of the study, orthodontic treatment has been carried out. 70 teenagers underwent an in-depth orthodontic examination, X-ray examinations (orthopantomogram and teleradiography), photometry before fixation of non-removable orthodontic structures (bracket systems).

During the first week, 2 patients refused treatment, 68 patients with a brace system have been also asked to fill out questionnaires about their pain sensations, which also allowed to assess the level of adaptation to orthodontic treatment.

In order to identify correlations between the level of complexity of orthodontic treatment, psychological profile and quality of life, patients have been divided into groups according to the degree of complexity of the predicted orthodontic treatment according to the ICON index (Table I).

At the II stage of the study, after the end of orthodontic treatment (the duration of treatment was from 1.5 to 2.0 years) and the dismantling of fixed orthodontic equipment for the patients of this group, a comprehensive assessment of the results of the correction of anomalies of the lower jaw has been carried out. It included clinical, radiological examination, photometry and psychodiagnostic research methods, as well as determination of the ICON index, namely the component of the aesthetic assessment of the result of orthodontic treatment by the degree of improvement: significant, significant or moderate (Table II).

Sociopsychological diagnosis was carried out before the beginning and after the end of orthodontic treatment independently and as a component in determining the integrative indicator of the patient's degree of adaptation to fixed orthodontic equipment and risk factors for maladaptation at the stages of orthodontic treatment, such as pain and emotional stress.

The diagnostic value for assessing the quality of cooperation with the patient is the ratio of the level of self-esteem to the level of harassment, which forms a complex of central personality phenomena, determines its development and acts as a regulator of human activity. Disharmony arising due to unresolved contradictions between these components, inadequacy or instability of at least one of them, leads to internal and external conflicts, is a prerequisite for frustration and neurotic personality development (Table III).

DISCUSSION

Orthodontic treatment, improving the aesthetics of the smile and face, has a positive effect on the psycho-emotional state, which is expressed in reducing reactive anxiety, normalizing self-esteem, thereby normalizing the psycho-emotional background and adaptive capabilities of patients. The improvement of aesthetic characteristics, as well as the elimination of the morphological basis of physical discomfort after the end of

orthodontic treatment, contributes to the achievement of psychological comfort and helps to direct the focus of patients' attention to the establishment and maintenance of social contacts, which coincides with the results of scientific research in psychology [1; 2].

The doctor's knowledge of the essence and mastery of the basics of psychodiagnostics, such as a comprehensive measurement of the level of self-esteem and harassment, assessment of personal and reactive anxiety, will allow to bring work with the patient to a qualitatively new level, understand and predict possible ways of interaction with the patient, determine management tactics, and, if necessary, involve in joint treatment of additional specialists of a psychotherapeutic profile. When planning treatment, it is necessary to take into account a complex of factors affecting the course of orthodontic intervention. Evaluating the patient's personality type, the stereotype of family upbringing and the level of complexity of the future treatment, it is possible to predict the degree of cooperation of the patient with the doctor.

Patients with low self-esteem and a low level of harassment, patients with overestimated self-esteem against the background of an inappropriate level of harassment, adolescents with a high level of personal and reactive anxiety, especially those who demonstrate indicators for predictably complex and long-term orthodontic treatment with the need for a high level of responsibility and cooperation with the doctor need psychological training with the involvement of specialized specialists. In some cases, it is even recommended to postpone the start of orthodontic treatment during a course of psychological consultations until the patient realizes the need for treatment, overcomes the difficulties associated with it, and completes the treatment. In these cases, longer psychological preparation of the patient and his parents is required.

CONCLUSIONS

On the basis of provided research, it has been concluded that in the conditions of limited medical and economic resources, it is advisable to combine interdisciplinary approaches for diagnosis, treatment and correction of dento-maxillofacial pathologies. The need to take into account the influence of a complex of medical, psychological, and social factors on the quality of orthodontic treatment of teenagers has been revealed. Data on the psychological state of a patient with a dento-maxillofacial anomaly, taking into account the influence of regional socio-cultural features, will allow to individualize specialized care and avoid possible complications at all stages of orthodontic treatment.

The effectiveness of using dental indices as a screening tool to eliminate the discrepancy between objective medical indicators of the level of need for correction of dento-maxillofacial anomalies and the level of expected results due to the age-related sensitivity of adolescents to their own appearance has been proven. The results of diagnostics using dental indices DAI, IOTN, ICON convince of the need to introduce aesthetic indices into the everyday practice of an orthodontist to determine the need for orthodontic treatment, the feasibility of correcting anomalies, and objectifying treatment results. The novelty of increasing the effectiveness of orthodontic treatment by means of an index assessment of indicators of the need and results of correction of dento-maxillofacial anomalies using methods of determining the psychosocial profile of an adolescent patient.

The proposed system of planning and organizing orthodontic care does not require significant additional resources, but it contributes to an individualized approach to working with the patient and improving the quality of its provision, which will allow the creation of a common database at the state level in the future. Such a database will provide an opportunity to share experience, develop new methods of orthodontic care, and evaluate treatment results.

The prospects for further work in the context of the conducted research can be seen in the development of protocols for standardizing diagnosis and providing orthodontic care to adolescent patients using sociopsychological methods.

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ORIGINAL ARTICLE

EFFICACY OF COMPREHENSIVE TREATMENT OF NONALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH PREDIABETES

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ABSTRACT

The aim: To evaluate the effectiveness of the proposed treatment recommendations, which included lifestyle changes, as well as the treatment with ursodeoxycholic acid, rosuvastatin, and omega-3 PUFA, on the severity of cytolytic and cholestatic syndromes in patients with NAFLD and prediabetes.

Materials and methods: Fifty-five patients with confirmed prediabetes and concomitant NAFLD underwent a comprehensive clinical examination and were treated with rosuvastatin 10 mg/d, omega-3 PUFA at a dose of 1000 mg/d and ursodeoxycholic acid at a dose of 10 mg/kg/d.

Results: The data obtained after 12 months of proposed treatment revealed a statistically significant improvement of indicators of cytolytic syndrome in patients with prediabetes and NAFLD. There was no significant difference between mean values of ALT and AST of treated patients and the corresponding indicators of apparently healthy persons, which confirms the effectiveness of the recommended treatment.

Conclusions: Proposed therapy which included recommendations for lifestyle changes and treatment with ursodeoxycholic acid, rosuvastatin and omega-3 PUFA significantly improved hepatic steatosis and cytolytic syndrome in patients with prediabetes and NAFLD.

KEY WORDS: non-alcoholic fatty liver disease, prediabetes, ALT, AST, rosuvastatin, omega-3 PUFA and ursodeoxycholic acid

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a multifactorial disease which is rapidly becoming the most common disease worldwide [1]. In the general population, the prevalence of NAFLD is about 25% [2], however, higher prevalence rates were found in high-risk groups, which include people with type 2 diabetes, obesity, and metabolic syndrome [3].

Epidemiological research data [3-5] confirm the tendency to increase the incidence of NAFLD in case of insulin resistance arising from obesity, type 2 diabetes and the presence of metabolic syndrome. NAFLD occurs in ~50% of obese individuals, in >95% of morbidly obese patients undergoing bariatric treatment, in 60-70% of patients with type 2 diabetes, in ~69% of patients with hyperlipidemia, in ~39% patients with arterial hypertension and in ~ 42% of patients with metabolic syndrome, but also in ~ 7% of patients with normal body weight. Nowadays NAFLD is considered to be recognized as the most common cause of elevated liver enzymes [6]. NAFLD affects an estimated 1 billion people worldwide and is the leading cause of liver cirrhosis, hepatocellular carcinoma, and death from liver disease [7].

The American Association of Diabetology (ADA) recommend to use the term "prediabetes" for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal. Patients with prediabetes are defined by the presence of impaired fasting glucose and/or impaired glucose tolerance and/or A1C 5.7–6.4% [8]. Patients with prediabetes, as well as the patients with NAFLD, are at high risk of diabetes and cardiovascular disease [9].

It is interesting that the expansion of NAFLD among people with prediabetes compared to patients with type 2 diabetes, remain insufficiently studied. The question of the choice of treatment tactics in the case of NAFLD and prediabetes is debatable.

THE AIM

To evaluate the effectiveness of the proposed treatment recomendations, which included lifestyle changes, as well as the treatment with ursodeoxycholic acid, rosuvastatin, and omega-3 PUFA, on the severity of cytolytic and cholestatic syndromes in patients with NAFLD and prediabetes.

Table I. Biochemical blood analysis indicators of patients of the group Ia 6 and 12 months after treatment (M±m)

Indicators	Group of comparisons				Reliability indicator
	Group Ia (n=28)			Control group (n=30) Before treatment	After 6 months
	Before treatment	After 6 months	After 12 months		
ALT, U/L	37,65 ±12,12	34,72 ±10,24	31,24 ±9,07	27,99 ±6,39	p0-6=0,33 p0-12=0,03* p6-12=0,18 p12-III=0,12
AST, U/L	34,51 ±12,37	30,48 ±9,68	27,71 ±8,60	29,17 ±5,66	p0-6=0,18 p0-12=0,02* p6-12=0,27 p12-III=0,45
GGT, U/L	48,52 ±10,90	46,53 ±11,12	47,22 ±9,42	43,58 ±9,30	p0-6=0,50 p0-12=0,64 p6-12=0,80 p12-III=0,15

Note: ww n- number of patients; p0-6 - the significance of the difference of the indicators before and after 6 months of the treatment; p0-12 - the significance of the difference of the indicators before and after 12 months of the treatment; p6-12 - the significance of the difference of the indicators after 6 and 12 months of the treatment; p12-III - the significance of the difference of the indicators of the patients after 12 months of treatment and indicators of group of apparently healthy person; * – the difference between the indicators is statistically significant as compared before and after the treatment and as compared to group of apparently healthy person.

Table II. Biochemical blood analysis indicators of patients of the group Ib 6 and 12 months after treatment (M±m)

Indicators	Group of comparisons				Reliability indicator
	Group Ib (n=27)			Control group (n=30)	p
	Before treatment	After 6 months	After 12 months		
1	2	3	4	5	6
ALT, U/L	37,56 ±13,27	41,79 ±12,63	44,21 ±9,77	27,99 ±6,39	p0-6=0,24 p0-12=0,04* p6-12=0,44 p12-III<0,01*
AST, U/L	37,06 ±15,04	39,42 ±13,41	38,71 ±14,12	29,17 ±5,66	p0-6=0,55 p0-12=0,68 p6-12=0,85 p12-III=0,001*
GGT, U/L	46,64 ±12,25	44,32 ±11,96	45,74 ±12,80	43,58 ±9,30	p0-6=0,49 p0-12=0,79 p6-12=0,68 p12-III=0,47

Note: n - number of patients; p0-6 - the significance of the difference of the indicators before and after 6 months of the treatment; p0-12 - the significance of the difference of the indicators before and after 12 months of the treatment; p6-12 - the significance of the difference of the indicators after 6 and 12 months of the treatment; p12-III - the significance of the difference of the indicators of the patients after 12 months of treatment and indicators of group of apparently healthy person; * – the difference between the indicators is statistically significant as compared before and after the treatment and as compared to group of apparently healthy person.

MATERIALS AND METHODS

Seventy-eight patients with impaired glucose tolerance underwent comprehensive clinical examination. Fifty-five patients with confirmed prediabetes and concomitant NAFLD were included to the study. Exclusion criteria were: age older than 74 years; coronary heart disease; connective tissue diseases; oncological diseases; type I and II diabetes mellitus; cirrhosis; previously transferred viral hepatitis; toxic (alcohol – consumption of more than 40 g of ethanol/d), medicinal (use of hepatotoxic drugs), severe metabolic liver diseases; Wilson's disease; autoimmune hepatitis; recent significant weight loss, parenteral nutrition for 2 weeks or more; chronic diseases of the gastrointestinal tract, accompanied by impaired absorption (malabsorption syndrome); refusal of the patient to participate in the study.

There were two groups of the patients, which were comparable in terms of age, sex, and NAFLD stage. Division of patients into groups was carried out in an arbitrary order, by means of random numbers.

As the initial examination of patients with prediabetes and NAFLD revealed very high cardiovascular risk, all patients were prescribed with rosuvastatin at a dose of 10 mg/d. Patients of group Ia (n=28) were treated with rosuvastatin 10 mg/d, omega-3 PUFA at a dose of 1000 mg/d and ursodeoxycholic acid at a dose of 10 mg/kg/d to improve hepatic steatosis.

Patients of the Ib group (n=27) made up the comparison group and, apart from rosuvastatin, did not take any medicines.

Patients of both groups followed dietary recommendations and in order to increase their physical activity performed 30-minute walks per day. A control group of apparently healthy individuals (n = 30) was used for comparison. Evaluation of the effectiveness of treatment was carried out 6 and 12 months after the initiation of the therapy.

All patients underwent a comprehensive clinical examination, which included the collection of anthropometric data, an objective examination, and the collection of venous blood for laboratory analysis.

For the diagnosis of NAFLD, the method of ultrasound diagnosis of the liver was used, taking into account the fact that ultrasound can reveal an increase in the echogenicity of the liver and confirm the diagnosis of NAFLD under conditions of fatty infiltration of the liver of more than 33%. The criteria for the presence of steatosis were a diffuse homogeneous increase in echogenicity of the liver ("white liver") with greater echogenicity than the right kidney (hepatorenal index) and dorsal attenuation of the ultrasound signal.

Statistical processing of the obtained results was performed on a personal computer using the Microsoft Office Excel 2003 and Statsoft Statistica 8.0 software packages. The discrepancy was considered probable if the probability value was equal to or greater than 95% ($p<0.05$).

RESULTS

During the period of observation and treatment among patients of the Ia group, there was a tendency to decrease cytolysis indicators, namely: the average value of the ALT level after 12 months of treatment statistically significantly decreased by 17.03% from the initial value ($p=0.03$), and the average value of the AST level – by 19.71% ($p=0.02$) (Table I).

The average value of the GGT level in patients of group Ia did not statistically significantly change during the study, and it also significantly did not differ from the average value of the GGT level of apparently healthy individuals (Control group) ($p=0.15$).

It turned out to be interesting that after 12 months of treatment, the average values of ALT and AST levels of patients of group Ia approached the corresponding indicators of individuals of control group and did not statistically differ from them ($p=0.12$ and $p=0.45$, respectively). This indicates the effectiveness of the selected therapeutic scheme.

The change in individual indicators of the biochemical blood analysis of patients in the Ib group was not statistically significant, except for the average value of the ALT level (Table II). Moreover, the change in the average value after 12 months was statistically significant: an increase of this indicator by 17.71% was observed compared to the indicator before treatment ($p=0.04$). When comparing the average values of ALT and AST levels after 12 months with the corresponding indicators of practically healthy individuals, a statistically significant difference was found: the average values of ALT and AST levels in patients of control group were statistically significantly lower ($p<0.01$ and $p=0.001$, respectively).

DISCUSSION

Currently, approved treatment for NAFLD is rather controversial and mainly is aimed at correcting risk factors. Screening and early intervention for obesity, prediabetes and type 2 diabetes, dyslipidemia and hypertension are cost-effective and safe [10]. Insulin resistance, increased serum insulin levels and oxidative stress are risk factors for NAFLD, diabetes and hypertension [11]. In animal models, ursodeoxycholic decreased fasting glucose, insulin, and hepatic insulin resistance, showing that this medication is effective in treating NAFLD in patients with diabetes [12]. Kim et al. in their study showed reduction of ALT, AST, and GGT levels in patients with liver dysfunction [13]. Moreover, there are studies, which demonstrate effectiveness of co-administration of ursodeoxycholic acid with rosuvastatin/ezetimibe in a non-alcoholic fatty liver disease model [14]. Tzanaki I. et al. in their review demonstrated the importance of effective lipid lowering therapy in patients with NAFLD [15].

However, there is no information in terms of treatment NAFLD in patients with prediabetes. The current study aims to evaluate the effectiveness of co-administration of ursodeoxycholic acid with rosuvastatin and omega-3 PUFA in special category of patients. These are patients with NAFLD and prediabetes – individuals who do not meet criteria for diabetes, nevertheless are at one-step to cardiovascular diseases.

CONCLUSIONS

Lifestyle changes alone in patients with prediabetes and NAFLD were not effective in terms of cytolytic and cholestatic syndromes. Treating NAFLD in prediabetic patients with ursodeoxycholic acid, rosuvastatin, omega-3 PUFA, dietary and physical activity recommendations showed reduction of AST and ALT, which ensures the effectiveness of the proposed program of complex treatment.

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ORIGINAL ARTICLE

THE INFLUENCE OF SPELEOTHERAPY ON BRONCHI PASSAGE IN CHILDREN WITH BRONCHIAL ASTHMA USING A PHARMACO-FUNCTIONAL TEST WITH SALBUTAMOL

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ABSTRACT

The aim: To investigate the reaction of the bronchi to inhalation of salbutamol in children with different severity of bronchial asthma under the conditions of speleotherapy.

Materials and methods: 40 children aged 6-15 years were examined, 20 of them had an intermittent course of the disease, 20 had a mild course, and the children were in the inter-relapse period. Determining the function of external respiration (FER) with a pharmaco-functional test (PFT) with salbutamol was carried out in the dynamics of observation before and after treatment and compared with the indicators of 40 healthy children. Speleotherapy was performed based on the children's department of the Ukrainian Allergological Hospital of the village Solotvino.

Results: A decrease in increased bronchial tone and restoration of bronchial patency at all levels of the bronchi in all patients with an intermittent course of the disease and a partial decrease in bronchial hyperreactivity with the improvement of bronchial patency in children with a mild course of bronchial asthma under the influence of speleotherapy was established.

Conclusions: Thus, speleotherapy contributes to a positive reaction of the bronchi to inhalation of salbutamol, which is reflected in the normalization of disturbed bronchial tone and the restoration of bronchial patency at all levels of the bronchi, in all patients with an intermittent course and partially with a mild course of the disease.

KEY WORDS: children, bronchial asthma, bronchial tone, speleotherapy, salbutamol

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INTRODUCTION

The study of bronchial patency using a pharmaco-functional test with the use of a beta2-agonist allows not only to assess of the degree of loss of external breathing function and to determine the reversibility of these disorders but also to investigate the effect of speleotherapy on bronchospasm as one of the pathogenetic mechanisms of bronchial obstruction in children with bronchial asthma. Bronchospasm characterizes the increased reactivity of the bronchi, which can be considered a leading symptom of BA and an important mechanism of disease development, which correlates with the severity of the disease. Bronchial hyperreactivity is manifested by bronchial obstruction – an increased secretion of mucus, swelling of the mucous membrane of the bronchi, and spasm of smooth muscles of the bronchial tree. At the same time, obstruction of the bronchi can be considered a sign of bronchial hyperreactivity and improvement of central bronchial patency – FVC, $FEV_{1.0}$, FEF_{25} [1-3] and patency of small bronchi FEF_{50}, FEF_{75} [4] after inhalation of bronchodilator beta-2 agonist salbutamol [5] confirms this. Speleotherapy is one of the non-medicinal means of influencing a patient with bronchial asthma. The essence of the speleotherapy effect is that as a result of isolation from the external environment, stable microclimate conditions, the absence of usual pollutants and allergens in the air, a low concentration of microorganisms, irritation of the mucous membrane of the respiratory tract is reduced and the activity of chronic allergic inflammation is inhibited [6]. Appropriate diagnosis and correction of bronchial reactivity under the influence of speleotherapy can help reduce the frequency of exacerbations of bronchial asthma and improve disease control. In the studied literature, there are isolated works devoted to the study of the positive impact of speleotherapy [7-9] and its artificial analogs [10] on the course of the disease in children, as for the formation of bronchial reactivity in the conditions of speleotherapy and its analogs in children, these works are single [11], which made it possible to formulate the appropriate goal work.

THE AIM

To investigate the reaction of the bronchi to the inhalation of salbutamol in children with different severity of the course of bronchial asthma under the conditions of speleotherapy.

MATERIALS AND METHODS

40 children aged 6-15 years with bronchial asthma were examined, 20 of them had an intermittent course of the disease, 20 had a mild course, and the children were in the inter-relapse period of the disease. The duration of the disease was 4.9 ± 1.9 years, there were 29 boys and 11 girls. The control group consisted of 40 healthy children who were determined to have bronchial patency and underwent a pharmaco-functional test with salbutamol. Informed consent for the examination was obtained from all parents the studied children. The criterion for including children in the examined group of patients was the absence of use of control therapy and acute respiratory infections for 2 months. The criterion for including children in the control group was the absence of acute respiratory infections during the last month before the examination.

The study of the function of external respiration (FER) was carried out in children in the morning hours on the computer spirograph "Masterscreen" of the company "Jaeger" (Germany). All children complied with the requirements: physical exertion and contact with strong odors (perfumes, household chemicals, etc.) were excluded 2 hours before the test. The examination was performed on an empty stomach or after a light breakfast and 15-20 minutes of rest before spirography. The study was conducted with the patient in a sitting position, the height of the oral tube and the height of the seat were adjusted so that the subject did not have to tilt his head or torso. Before each study, the child was instructed in detail, and the procedure for performing breathing maneuvers was also demonstrated. The obtained absolute values of the indicators were evaluated as a percentage of the appropriate values. For each patient, the value of the individual norm was calculated taking into account age, sex, height, and conditions of the study: temperature, humidity, and atmospheric pressure. The data by Shiryaeva I.S. with coauthors were used to determine the degree of violation of bronchial patency. The following indicators of FER were evaluated: forced vital capacity of the lungs (FVC), forced expiratory volume in 1 second ($FEV_{1.0}$), maximum volumetric velocities at the level of 25, 50 and 70% (FEF_{25}, FEF_{50}, FEF_{75}) FVC. Next, a bronchodilation test was performed. To perform the test, a short-acting beta 2 agonist (salbutamol) was used in a dose of 200 mcg in children under 12 years of age and 400 mcg in children over 12 years of age. Bronchospasm, characterized by increased bronchial tone, was defined as an increase in the flow-volume curve 20 minutes after inhalation. The test was considered positive if the sum of the increase in speed indicators at the level of central (FEF_{25}), medium (FEF_{50}), and small bronchi (FEF_{75}) exceeded the level of reproducibility of the result, which is 37% for these indicators. Determination of FER with PFT was carried out in the dynamics of observation before and after treatment and compared with indicators of 40 healthy children. Speleotherapy in the form of staying in an underground department was carried out based on the children's department of the Ukrainian allergological hospital of the village Solotvino. The microclimate of the underground compartment is characterized by the following parameters: air temperature is 22.5–23.5°C, relative humidity is 30–50%, absolute humidity is 5–10 g/m^3, air velocity is 0.15–0.2 m/sec, atmospheric pressure 760-770 mmHg, aerosol content 2.5-4.0mg/m^3, number of aerosol particles up to 3 μn – 71-81%. Sodium chloride in the aerosol is 99%. The bacterial contamination of the air is 70-100 microorganisms in 1 m^3, which equates to sterile conditions with a complete absence of pathogenic flora and mold. The children got 14 descents into the salt mine.

The results of the research were processed using the package of statistical programs "Exel" with the calculation of the average values of indicators (M), and standard error (m). The probability of differences in mean values (p) was determined using the Student's test. A *p-value* ≤ 0.05 was considered significant.

RESULTS

Before treatment, hidden bronchospasm, which characterizes increased bronchial tone, was observed in 14 (35%) children. Reduced bronchial patency after inhalation of salbutamol remained at the level of central bronchi in 10 (25%) children, and at the level of medium and small bronchi in 16 (40%) and 18 (45%) patients compared to the indicator of the control group of practically healthy children. The obtained data indicate the presence of increased tone mainly in the small bronchi, where it occurs 1.8 times more often ($p < 0.05$) than at the level of the central bronchi.

The study of impaired bronchial tone in children, depending on the severity of BA, revealed that it was observed in 4 (20%) patients with an intermittent course of the disease who were admitted to the speleological clinic for treatment. In children with a mild course of the disease, violation of bronchial tone was observed in every second patient and occurred 2.5 times more often

Table I. Bronchial patency indicators during the salbutamol test with different severity of BA in children

Indicators	Healthy children N = 40	Intermittent BA N = 20	Mild BA N = 20	P
FVC	108,8 ± 1,33	104,6 ± 1,48	96,5 ± 1,31	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 < 0,05$
FEV1.0	107,1 ± 1,22	102,2 ± 1,59	82,2 ± 1,73	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 > 0,05$
FEF25	96,2 ± 1,26	92,8 ± 1,42	72,6 ± 1,56	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 > 0,05$
FEF50	93,8 ± 2,10	87,8 ± 1,60	60,1 ± 1,69	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 < 0,05$
FEF75	92,1 ± 2,15	81,8 ± 1,76	53,9 ± 2,74	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 < 0,05$

P_1 - Healthy - patients with intermittent BA
P_2 - Healthy - patients with a mild course of BA
P_3 - Patients with an intermittent course of BA - patients with a mild course of BA

Table II. Indicators of bronchial patency during a test with salbutamol with different severity of asthma in the dynamics of treatment

Indicators	Healthy children N = 40	Intermittent BA N = 20	Mild BA N = 20	P
FVC	108,8 ± 1,33	114,5 ± 1,79	106,9 ± 1,85	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 < 0,05$
FEV1.0	107,1 ± 1,22	109,8 ± 1,58	104,2 ± 1,65	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 > 0,05$
FEF25	96,2 ± 1,26	97,4 ± 1,79	94,9 ± 1,85	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 > 0,05$
FEF50	93,8 ± 2,10	98,8 ± 1,66	84,3 ± 2,12	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 < 0,05$
FEF75	92,1 ± 2,15	94,5 ± 2,15	86,8 ± 3,29	$P_1 > 0,05$ $P_2 > 0,05$ $P_3 < 0,05$

P_1 - Healthy - patients with intermittent BA
P_2 - Healthy - patients with a mild course of BA
P_3 - patients with an intermittent course of BA - patients with a mild course of BA

compared to the intermittent course of the disease. The most pronounced decrease was the velocity indicators of medium bronchi (FEF_{50}) by 1.6 times ($p<0.01$) and at the level of small bronchi (FEF_{75}) by 1.7 times ($p < 0.001$) (Table I).

After the speleotherapy treatment in children with an intermittent course of the disease, the increased tone of the bronchi disappeared in all patients. Treatment contributed to a significant increase in bronchial patency at all levels of the bronchi by 10-13% ($p < 0.05$) and was accompanied by a tendency to exceed the bronchial patency of healthy children (Tabl II).

In children with a mild course of BA, after a course of treatment, increased bronchial tone decreased in 90% of patients and remained only in 2 (10%) cases. Among patients with a mild course of BA, the normalization of the patency of the large bronchi was observed in all cases, which was accompanied by an increase in the $FEV_{1.0}$ indicator by 22% ($p < 0.05$), and the bronchial patency indicators did not differ from the indicators of sighted children. The study

showed that bronchial patency normalized in children at the level of medium and small bronchi – in 72 and 69%, respectively. Indicators of bronchial patency at the level of the middle bronchi FEF_{50} increased by 1.4 times ($p < 0.01$). The FEF_{75} indicator, which characterizes bronchial patency at the level of small bronchi, increased most significantly by 1.6 ($p < 0.01$) and did not differ from the indicator of the control group of healthy children.

DISCUSSION

The achievements of modern fundamental clinical medicine testify to the growth of the role of universal non-specific mechanisms in the pathogenesis of most diseases, with the violation of the functioning of various organs and systems, which determines the expediency of the use of natural therapeutic factors with a multi-component mechanism of influence. Therefore, the use of natural healing factors is considered an effective and affordable method of achieving control over the course of the disease and forms the basis of restorative treatment technologies. The development of restorative medicine technologies significantly complements the principles of drug treatment, timely correcting and restoring the body's functional reserves. Among the natural healing factors, speleotherapy is one of the «young» methods of treatment, which began to develop thoroughly in the middle of the 20th century. The effectiveness of speleotherapy is quite high, but the mechanisms of its therapeutic effect are still not fully revealed since underground therapeutic objects are very different in terms of their microclimatic characteristics [8].

The general protective mechanisms of speleotherapy include isolation from the external environment, stable and in some cases comfortable microclimatic conditions, and absence of usual pollutants and allergens in the air – these factors reduce irritation of the mucous membrane of the bronchi and inhibit the inflammatory process. In addition, they have a pronounced bactericidal effect, which, together with the improvement of bronchial drainage, leads to a decrease in the inflammatory process in the bronchi and contributes to the restoration of the sensitivity of the receptor apparatus of the bronchi to bronchodilators [12]. The reduction of the inflammatory process in the bronchial tree also leads to the inhibition of bronchial remodeling processes [9], which, together with the improvement of the drainage function and the restoration of sensitivity to bronchodilators, causes a decrease in the phenomena of bronchial obstruction. Therefore, the complex of all the above-mentioned factors in combination with the general mechanisms of influence of speleotherapy and adequate broncholytic and anti-inflammatory drug therapy allows to achieve the maximum possible control over the course of the disease, in particular BA.

CONCLUSIONS

In this way, speleotherapy promotes a positive reaction of the bronchi to the inhalation of salbutamol, which is reflected in the normalization of the disturbed tone and the restoration of bronchi passage at all levels of the bronchi, in all patients with intermittent course and partially with a mild course of the disease

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ORIGINAL ARTICLE

VESTIBULAR DYSFUNCTIONS IN CHRONIC BRAIN ISCHEMIA IN THE POST COVID PERIOD

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ABSTRACT

The aim: The aim of the study is the clinical-pathogenetic reasoning of vestibular dysfunctions (VD) development against the background of chronic brain ischemia in the presence of degenerative changes in the cervical spine (CS) in the post COVID period.

Materials and methods: 82 patients, in the conditions of the clinical base of the Odessa National Medical University in 2019-2021 were examined. Group I with VD against the background of chronic brain ischemia (CBI) at the compensated phase; Group II with VD against the background of CBI at the subcompensated phase (33 men; 49 women), aged from 18 to 55 years. The control group (CG) consisted of 20 patients of the corresponding gender and age. The condition of the state of the autonomic nervous system, vestibular functions, cervical spine, cerebral arteries and emotional condition were examined.

Results: Vestibulo-ataxic disorders were higher compared to CG and increased along with the degree of brain damage. An important aspect of the development of VD is autonomic dysfunction against the background of pathological autonomic characteristics with predominant parasympathetic orientation of autonomic tone, especially in the case of insufficiency of autonomic recativity (AR) and pathological autonomic support of activity. Such changes significantly increased in the presence of subcompensation of CBI. The correlation between psychoemotional disorders and changes in autonomic characteristics with VD against the background of CBI with initial regularities depending on the degree of brain damage was defined. The progression of CBI is facilitated by coronavirus infection and manifested in autonomic and psychoemotional dysfunctions. A characteristic hemodynamic feature in groups with compensated and subcompensated CBI is the presence of reduced perfusion in basilar (BA) and vertebral (VA) arteries. Changes in cerebral vascular reactivity with a decrease in cerebrovascular reactivity indicators were characteristic of the subcompensated phase of CBI. Hyperactivity to rotational functional loads in both clinical groups has a high correlation with the presence of stair descent and, to a lesser extent, isolated instability in CS.

Conclusions: 1. The occurrence of VD is facilitated by the presence of autonomic dysfunction and degenerative-dystrophic changes in the CS, especially in case of subcompensation of CBI. 2. Psychoemotional changes were a characteristic feature of patients with VD against the background of CBI and had certain regularities depending on the phase of CBI. 3. Suffered coronavirus infection contributes to the progression of VD and further decompensation of CBI due to direct damage to the autonomic and vascular systems of the brain. 4. Changes in cerebral hemodynamics in the form of reduced perfusion in BA and VA, a decrease in cerebrovascular reactivity, and an increase in reactivity to rotational functional load were determined in patients with VD against the background of subcompensated CBI.

KEY WORDS: chronic brain ischemia, autonomic dysfunctions, degenerative-dystrophic damage, cervical spine, cerebrovascular reactivity

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INTRODUCTION

Chronic brain ischemia (CBI) in the structure of cerebrovascular pathology occurs much more often than acute conditions and leads to a long-term disability. It is the risk factor for the development of cerebral strokes. Prevention of the development of significant organic vascular changes in the brain is the most urgent problem of modern medicine and neurology [1-4]. The presence of vestibular dysfunctions (VD) in the clinical picture of vascular cerebral dyshemia correlates with the degree of brain damage [5,6]. VD is the most common syndrome in ischemic brain damage. The clinical variety of dizziness occurs against the background of a decrease in the compensatory capabilities of the central mechanisms of balance, the sensory system, especially in case of CBI with a predominant lesion of the vertebral-basilar basin against the background of the cervical spine (CS) pathology [7]. The important indicator of VD occurrence is the change in vegetative and vascular reactivity, which complicates the examination and differential diagnosis

of dizziness. The progression of ischemic brain damage is advanced by the development of the coronavirus infection, which negatively impacts the process of neurological rehabilitation [8-14]. The penetration of SARS-CoV-2 virus into the central nervous system (CNS) causes its damage and can activate some degenerative nervous system diseases [15]. Hypercoagulation due to systemic inflammation, cytokine storm, endotheliitis and other factors lead to infectious vascular lesions of the CNS [16,17]. Inflammatory damage of the vestibular apparatus reduces blood flow, causes vasospasm, leads to thrombosis as well as other vascular problems that may occur during the coronavirus infection.

THE AIM

The aim is the clinical-pathogenetic reasoning of VD development against the background of chronic brain ischemia in the presence of degenerative changes in the cervical spine (CS) in the post COVID period.

MATERIALS AND METHODS

82 patients were examined, Group I with VD against the background of CBI at the compensated phase (n =24); Group II with VD against the background of CBI at the subcompensated (n=38) phase (33 men; 49 women), aged from 18 to 55 years, the average age was 38.6 ± 1.6 years. All patients had a history of COVID 19. Control group (CG), n=20 – relatively healthy people who underwent professional screening. During the examination of the state of the autonomic nervous system (ANS) according to the questionnaire [8] all patients reported the dysfunction availability. In order to objectify statics and balance, an original electrical contact device was designed and used for ataxia assessment [18] with the calculation of the integrative index of ataxia (IIA). Emotional layers were examined using the hospital anxiety and depression scale [19], the cognitive sphere – according to the test of A.R. Luria [18]. All patients had an X-ray examination of the cervical spine with functional loads. X-rays of the cervical spine were performed using a digital radio-fluoroscopy system OPERA T90cex GMM (Italy). X-rays were executed in standard modes, in direct and lateral projections with functional load (flexion – extension).

Cerebral arteries were examined in triplex mode on an Ultima-PA ultrasound scanner (RADMYR, Ukraine). The parameters of time-averaged maximum blood flow velocity (TAMX) and resistance index (RI) in the anterior (ACA), middle (MCA), posterior (PCA) cerebral, vertebral (VA) and basilar (BA) arteries were studied. The state of cerebrovascular reactivity was assessed using the following functional loads: hypercapnic reactivity (reactivity coefficient to hypercapnic (CrCO2)), and hyperventilation reactivity (CrO2) test, functional nitroglycerin (CrFNT) tests, functional probes with rotation (RIRP), index of the vasomotor reactivity (IVMR). Statistics 8.0 was used for statistical processing with the assessment of the Wilcoxon test, as well as the Mann-Whitney U test. Differences at $p<0.05$ were considered statistically significant.

RESULTS

In the main groups, all patients complained of dizziness (predominantly non-systemic – 51.6%, systemic – 48.4%), caused by physical exertion (25.8%), head movements (38.7%), orthostatic changes (14.5 %), blood pressure increase (9.7%).

The main symptoms of the launch of accompanying pathological mechanisms of vestibulopathy have been revealed. Headache (75.8%) had vascular and/or autonomic components: vasomotor (24.2%), ischemic-hypoxic (48.4%), venous (27.4%) cephalalgia. Localization: diffuse (40.3%), in the occipital (33.9%), parietal (14.5%), frontal (11.3%) regions. The algic syndrome was manifested by pain in the neck (69.3%), including the ones with irradiation to the shoulder and corresponding hand (37.1%); back pain (56.4%); cardialgias (37.1%) and other pain phenomena. Muscle tension of shoulder girdle and neck had reflex-tonic or generalized character in 48.4% of cases. In addition, the most significant symptoms were: increased blood pressure (59.8%), noise in the head (38.7%), decreased hearing (30.6%), orthostatic hypotension (19.3%), asthenia (41.9%), emotional lability (58.1%), cognitive disorders (70.9%), dyssomnias (40.3%). In the objective, vestibulo-ataxic disorders of mild or moderate severity prevailed [9, 13]. The average values of IIA were increased in patients with CBI compared to healthy subjects (Group I – 2.7±0.09 relative units, Group II – 3.6±1.10 relative units, CG – 1 .8±0.08 relative units, $p<0.05$). High rates of IIA were accompanied by the presence of vagotonia (3.0±0.12 relative units versus 2.3±0.14 relative units in patients with eytonia, $p<0.05$). Manifestations of cervical osteochondrosis were diagnosed in all patients. Instability of the cervical spine was noted in half of the examined patients, more often in segments $C_4 – C_5$ (77.4%, $p<0.05$), less often – $C_3 – C_4$ and $C_5 – C_6$. Uncovertebral arthrosis was defined in 41.9% of studies. Pathological autonomic tone (AT) was manufested in 96.7% of patients, mostly shifted towards the vagal direction (53.2%); pathological autonomic reactivity (AR) – 83.9% of patients mainly had autonomic insufficiency (52.4%), which increased along with ischemic brain damage increase; changes in

Table I. Indexes TAMX (cm/s) in cerebral arteries in patients with CBI

	MCA	ACA	PCA	VA (V4)	BA
Group I	57,2±8,4	54,3±7,3	38,6±5,7	37,5±6,1	36,4±4,9
Group II	51,3±9,2	51,6±5,8	36,5±4,7	30,6±5,8	31,4±6,2
CG	62,6±10,1	52,3±6,7	36,5±5,7	34,7±9,1	38,9±8,4

Table II. Indicators of CVR in patients with CBI

	CrCO2	CrO2	IVMR	CrFNT
Group I	1,17±0,04*	0,34±0,04	62,9±7,5*	0,11±0,05
Group II	1,14±0,03*	0,26±0,03*	54,2±8,8*	0,05±0,03*
CG	1,28±0,06	0,36±0,03	81,5±6,9	0,16±0,04

* p <0,05 compared with CG

Table III. Indexes RIRP in patients with SDI, II and KA

	SDI	II	KA
Group I	1,27±0,03*	1,26±0,05*	1,20±0,04
Group II	1,32±0,05*	1,29±0,06*	1,19±0,03
CG	1,18±0,03	1,18±0,03	1,18±0,03

*p <0,05 compared with CG

autonomic support of activity (ASA) were characterized by excess (41.5%) or deficiency (47.1%). In the presence of subcompensated CBI, the latter increased up to 95.8% (p<0.01). A similar trend occurred in the presence of menopausal syndrome in women (59.4%, p <0.05), while ASA was always pathological. Clinically significant depression was registered in 58.1% of cases, and 80.5% of them were women (p < 0.05), and in the presence of menopausal syndrome it reached 94.4% (p < 0.05). With vagotonia, these indicators were 100.0% in men and 59.5% in women. Anxiety was defined in 30.6% without gender differences, more often at the compensated phase of CBI. In case of dyshormonal changes in women, anxiety occurred much more often (72.9%), with a predominance of sympathicotonic background (51.8%). The parameters of hemodynamics in patients of Group I did not differ significantly from the data of CG, only the values of blood flow in the MCA slightly lowered. In patients of Group II, a moderate decrease in blood flow indicators was observed in MCA, VA and BA. Analogous indicators in ACA and PCA did not significantly differ from normative ones. These changes can be explained by the appearance of local stenosing processes in the main arteries affecting cerebral hemodynamics in patients with subcompensated CBI (Table I).

Indicators of RI in VA exceeded the normative values in the direction of angiospasm, the average RI in Group II was more often interpreted as dystonic, and in Group I, persistent cerebral angiospasm was manufeste more frequently, especially against the background of sympathicotonia (up to 0.73±0.09 units, p <0.05), in cases of eytonia these indicators decreased (0.53±0.08 units), and in cases of vagotonia it reached the minimum values (0.46±0.08 units, p <0.05). In patients of Groups I and II, a significant decrease in CrCO2 indicators was observed (Group I – 1.17±0.04, CG – 1.28±0.06, p<0.05; Group II – 1.14±0.03, CG -1.28±0.06, p<0.05). CrO2 values in Group I did not change significantly, in Group II they significantly decreased (Group I – 0.34±0.04, CG – 0.36±0.03, Group II – 0.26±0.03, CG –1.28±0.06, p<0.05). The values of IVMR being an integral indicator of stability of cerebral autoregulation showed sharp decrease in Groups I and II (Group I – 62.9±7.5, CG – 81.5±6.9, p<0.05; Group II – 54.2 ±8.8, CG – 81.5±6.9, p<0.05). These changes were mostly characteristic of the patients of Group II. Also, hyporeactivity to FNT (0.05±0.03, CG – 0.16±0.04, p<0.05) was significantly manufested in Group II, which is the most sensitive indicator of the vasodilation function disorder at various phases of CVP (Table II).

According to X-ray examination, signs of stair descent instability (SDI) in CRS C2-C6 were defined in 19.3% of patients of Group I, in 22.1% of patients of Group II. Isolated instability (II) in CRS C2-C3 was observed in 5.1% of patients of Group I and in 6.3% of patients of Group II , in CRS C3-C4 – in 17.4% of patients of Group I and in 21.7% of patients of Group II , in CRS C4-C5 – in 4.5% of patients of Group I and in 4.3 patients of Group II, in CRS C5-C6 – in 3.2% of patients of Group I and in 5.6% of patients of Group II. Signs of Kimmerli's anomaly (KA) were observed in 8.7% of patients of Group I and 5.1% of patients of Group II. In the clinical group of patients with SDI, pronounced hyperreactivity to functional loads with rotation to the right and left

was defined (Group I – 1.27±0.03, CG – 1.18±0.03, p <0.05; Group II – 1.32±0.05, CG– 1.18±0.03, p<0.05). In patients with II indicators of reactivity index to rotation probes (RIRP) were also significantly increased (Group I – 1.26±0.05, CG -1.18±0.03, p<0.05; Group II – 1.29±0.06, CG – 1.18±0.03, p<0.05). In the group with KA, relative normal reactivity to the right and left rotation was observed (Group I – 1.20±0.04, CG – 1.18±0.03; Group II – 1.19±0.03, CG – 1.18 ±0.03) (Table III).

DISCUSSION

Ischemic damage to the brain due to degenerative-dystrophic changes in the cerebral spine is often accompanied by VD. The presence of the latter correlates with the degree of brain damage. Vestibulo-ataxic disorders were higher compared to CG and increased along with the degree of brain damage. An important aspect of the development of VD is autonomic dysfunction against the background of pathological autonomic characteristics with predominant parasympathetic orientation of AT, especially in the case of insufficiency of autonomic recativity (RA) and pathological ASA. Such changes significantly increased in the presence of subcompensation of CBI. The correlation between psychoemotional disorders and changes in autonomic characteristics with VD against the background of CBI with initial regularities depending on the degree of brain damage was defined. The progression of CBI is facilitated by coronavirus infection, which, in addition to neurotropic, leads to vascular damage, especially in the structures of the vestibular apparatus, which is sensitive to ischemia and manifested in autonomic, psychoemotional dysfunctions, and cognitive deficits. Our studies confirm the conclusions that coronavirus infection affects the vestibular analyzer both in the acute and post COVID periods of the infection [20,21], with changes in functional characteristics of the autonomic system [22], affects cerebral hemodynamics [23]. A characteristic hemodynamic feature in groups with compensated and subcompensated CBI is the presence of reduced perfusion in BA and VA. Changes in cerebral vascular reactivity with a decrease in CrO2 and CrFNT indicators were characteristic of the subcompensated phase of CBI. Hyperactivity to rotational functional loads in both clinical groups has a high correlation with the presence of stair descent and, to a lesser extent, isolated instability in CS.

CONCLUSIONS

1. The occurrence of VD is facilitated by the presence of autonomic dysfunction and degenerative-dystrophic changes in the CS, especially in case of subcompensation of CBI.
2. Psychoemotional changes were a characteristic feature of patients with VD against the background of CBI and had certain regularities depending on the phase of CBI.
3. Suffered coronavirus infection contributes to the progression of VD and further decompensation of CBI due to direct damage to the autonomic and vascular systems of the brain.
4. Changes in cerebral hemodynamics in the form of reduced perfusion in BA and VA, a decrease in cerebrovascular reactivity, and an increase in reactivity to rotational functional load were determined in patients with VD against the background of subcompensated CBI.

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ORIGINAL ARTICLE

THE DETERMINATION OF HIP CIRCUMFERENCE IN THE MIDDLE OF YOUNG BOYS AND YOUNG GIRLS OF HIGHER EDUCATION INSTITUTIONS OF BUKOVINA DEPENDING ON THE SPORT TYPE

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ABSTRACT

The aim: To find out the features of the hip circumference in the middle of both extremities by students of higher education institutions of Bukovina, depending on the sport type.

Materials and methods: The study of anthropometric parameters was conducted on 115 students of higher education institutions of Bukovina from 16 to 18 years where 78 (67.82%) – young boys and 37 (32.18%) – young girls. The main group of 75 (65.22%) students were represented by the first and the second year students of the Faculty of Physical Culture and Human Health of the Yuriy Fedkovich Chernivtsi National University, and control group consisted of 40 (34.78%) college students and students of the Stomatological Faculty of Bukovynian State Medical University. Among the students of the main group were – 57 (76.0%) young boys and 18 (24.0%) young girls who, in addition to physical activity, which was included in the program of their specialty, additionally engaged in the sports (football players, volleyball players, basketball players, handball players), the control group consisted of 21 (52.5%) young boys and 19 (47.5%) young girls who are busy with hours of physical education, according to the curriculum of their specialty and did not engage in additional sports. Anthropometric examination included the definition of total (height and body weight) parameters and partial (hip circumference in the middle third). Statistical analysis of the data was performed using a licensed program RStudio.

Results: Based on the Kraskel-Wallis test, it was found that there is a significant difference in the average length of the hip circumference (in the middle third) on the left depending on the sport. Based on the Conover-Iman test, it was found that there is a significant difference for the pairs «basketball» – «handball», «control» – «handball», «football» – «handball», «volleyball» – «control», «volleyball» – «football», «volleyball» – «handball».

Conclusions: The model for predicting the length of the hip circumference (in the middle third) on the right has the form $y = \beta1 + \beta2 + 0{,}328 * x_1 - 0{,}167 * x_2$, on the left it looks like $y = \beta1 + \beta2 + 0{,}451 * x_1 - 0{,}179 * x_2$, where *y* is the girth of the thigh in the middle third, is the weight, x_2 is the height. The coefficient $\beta1 = 58{,}181$ for young girls and $\beta2 = 53{,}302$ for young boys. Coefficient $\beta2 = 0$ for the group «basketball», $\beta2 = -3{,}358$ for the group «control», $\beta2 = -0{,}484$ for the group «football», $\beta2 = -1{,}991$ for the group «handball», $\beta2 = -0{,}824$ for the group «volleyball».

KEY WORDS: students, anthropometric parameters, hip circumference in the middle third

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INTRODUCTION

The study of age norms and variations of somatic features should be combined with the establishment of relative proportional indicators of body parts and somatipological features of its structure [1-3]. These studies allow us to determine the standards of physical development, taking into account the periods of puberty and aging processes [4-6].

One of the important problems of modern morphology is the study of changes that occur in the body under the influence of various factors his problem is especially important in connection with the development of sports [7]. Therefore, the study of changes that occur in individual organs, systems and the body as a whole, under the influence of physical activity of varying intensity and nature is relevant and important in practice [8-10].

The main problem in terms of training athletes is adequate selection and sports orientation [11]. Solving the problems of selection involves the creation of a model of the athlete of this specialization, ie a certain set of characteristics that determine athletic performance [12]. The set of features and the order of their enumeration differs for different sports [13-16]. In sports selection, such morphological features as total and partial body size, body proportions, body weight composition are taken into account [17-19].

However, so far the prognostic value and dominance

Table I. Distribution of participants by sport type

Sport type (amount/percent)							
Football 40 (53.34%)		Volleyball 18 (24.0%)		Handball 10 (13.34%)		Basketball 7 (9.32%)	
young boys	young girls	young boys	young girls	young boys	young girls	young boys	young girls
36 (48.0%)	4 (5.34%)	9 (12.0%)	9 (12.0%)	8 (10.67%)	2 (2.67%)	4 (5,32%)	3 (4.0%)

Table II. Body weight distribution of participants

Sport type (kg)							
Football (67.58 ± 3.02)		Volleyball (67.88 ± 3.02)		Handball (61.50 ± 3, 02 kg)		Basketball (67.57 ± 3.02)	
young boys	young girls	young boys	young girls	young boys	young girls	young boys	young girls
69.20 ±3.02	63.56 ±3.02	70.65 ±3.02	64.50 ±3.02	64.04 ±3.02	58.51 ±3.02	69.00 ±3.02	63.10 ±3.02

Table III. Height distribution of participants

Sport type(cm)							
Football (176.87 ± 2.03)		Volleyball (178.94 ± 2.03)		Handboll (175.30 ± 2.03)		Basketball (180.00 ± 2.03)	
young boys	young girls	young boys	young girls	young boys	young girls	young boys	young girls
176.52 ±2.03	171.51 ±2.03	179.32 ±2.03	177.22 ±2.03	174.82 ±2.03	174.15 ±2.03	182.85 ±2.03	178.1 ±2.03

of indicators of total and partial body size, morphometric and somatotypological characteristics in predicting the prospects for achieving high results in sports have not been established [20-22].

THE AIM

To find out the features of the hip circumference in the middle third of both extremities of students of higher education institutions in Bukovina, depending from the sport.

MATERIALS AND METHODS

The determination of anthropometric parameters was carried out on 115 students of Bukovynian higher educational institutions aged from 16 to 18 years, where 78 (67.82%) are young boys and 37 (32.18%) – young girls. The main group of 75 (65.22%) students were represented by the first and the second year students of the Faculty of Physical Culture and Human Health of the Yuriy Fedkovich Chernivtsi National University, and control group consisted of 40 (34.78%) college students and students of the Stomatological Faculty of Bukovynian State Medical University.

Among the students of the main group were – 57 (76.0%) young boys and 18 (24.0%) young girls who, in addition to physical activity, which was included in the program of their specialty, additionally engaged in the following sports (Table I), the control group consisted of 21 (52.5%) young boys and 19 (47.5%) young girls who are busy with hours of physical education, according to the curriculum of their specialty and did not engage in additional sports.

The body weight of the students of main group: young girls – 56.62 ± 3.02 kg, young boys – 69.70 ± 3.02 kg. Body weight distribution of participants of the main group (Table II), where the greatest body weight have volleyball players and football players, less the basketball players and the least body weight have handball players. The body weight of students in the control group: male – 77.04 ± 3.02 kg, female – 56.10 ± 3.02 kg).

The height of the students of main group: young girls – 173.92 ± 2.03 cm, young boys – 179.98 ± 2.03 cm, the greatest length of growth have basketball players and volleyball players less the football players and the least handball players (Table III). The average height of students in the control group – 172.25 ± 2.03 cm, in young boys – 176.47 ± 2.03 cm and in young girls – 164.26 ± 2.03 cm.

The girth of the right thigh in the middle third of the studied students of the main group shows that the largest girth of the right thigh in the middle third have volleyball players and basketball players, less the football players and the least handball players (Table IV). In the control group, the mean girth length in the middle third of the right thigh was – (43.25 ± 2.0 cm), of which 44.57 ± 2.0 cm in young boys and 41.78 ± 2.0 cm in young girls.

Table IV. Distribution of the length of girth in the middle of the right thigh

Sport type (cm)							
Football (41.80 ± 2.0)		Volleyball (44.61 ± 2.0)		Handball (40.00 ± 2.0)		Basketball (43.00 ± 2.0)	
young boys	young girls	young boys	young girls	young boys	young girls	young boys	young girls
41.6 ±2.0	41. 20 ±2.0	44.50 ±2.0	44.11 ±2.0	39.90 ±2.0	39.10 ±2.0	42.10 ±2.0	42.90 ±2.0

Table V. Distribution of the length of girth in the middle of the left thigh

Sport type (cm)							
Football (51.90 ± 2.0)		Volleybal (54.00 ± 2.0)		Handball (48.60 ± 2.0)		Basketball (54.14 ± 2.0)	
young boys	young girls	young boys	young girls	young boys	young girls	young boys	young girls
51.55 ±2.0	51.35 ±2.0	53.90 ±2.0	53.10 ±2.0	48.45 ±2.0	48.15 ±2.0	53.96 ±2.0	53.18 ±2.0

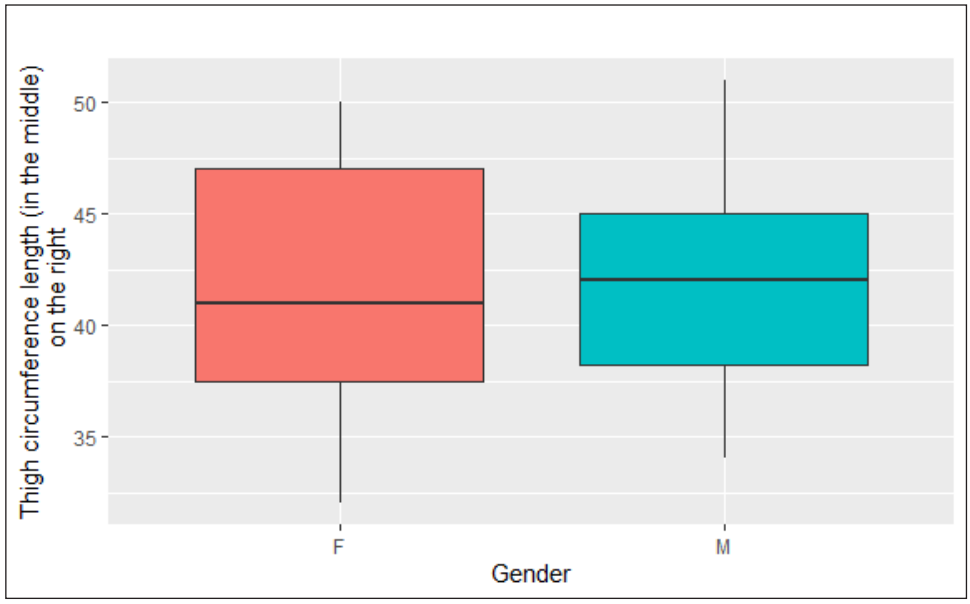

Fig. 1. Distribution of thigh length (in the middle third) on the right by respondents of the main group by gender

The girth of the left thigh in the middle third of the studied students of main group shows that the largest girth of the left thigh in the middle third have basketball players and volleyball players, less the football players and the least handball players ((Table V). In the control group, the mean girth length in the middle third of the left thigh was – (51.65 ± 2.0 cm), of which 52.80 ± 2.0 cm in young boys and 50.36 ± 2.0 cm in young girls

All students were subjected to anthropometric research, according to the method of VV Bunak in the modification of P.P. Shaparenko [23]. Anthropometric examination included the determination of total (height and body weight) parameters and partial (hip circumference in the middle third).

Determination of body weight was performed on floor scales (mechanical), a vertical height meter was used to measure height. The girth of the thigh in the middle third was determined by applying a centimeter tape in the largest part of the hip to medial direction and closed on the outer surface of the hip.

In studying the distribution of hip circumference in the main group by sport type used the Kraskel-Wallis test (nonparametric ANOVA), to identify a significant difference in the average rates of respondents depending on the sport (median distribution is considered as a central trend) [24]. To establish for which pairs of age groups there is a statistical difference in the medians, the Conover-Iman test was used [25]. Statistical analysis of the obtained data was performed using the licensed RStudio program.

RESULTS

The distribution of thigh length (in the middle third) on the right by respondents of the main group by gender shows that there is no significant difference in the

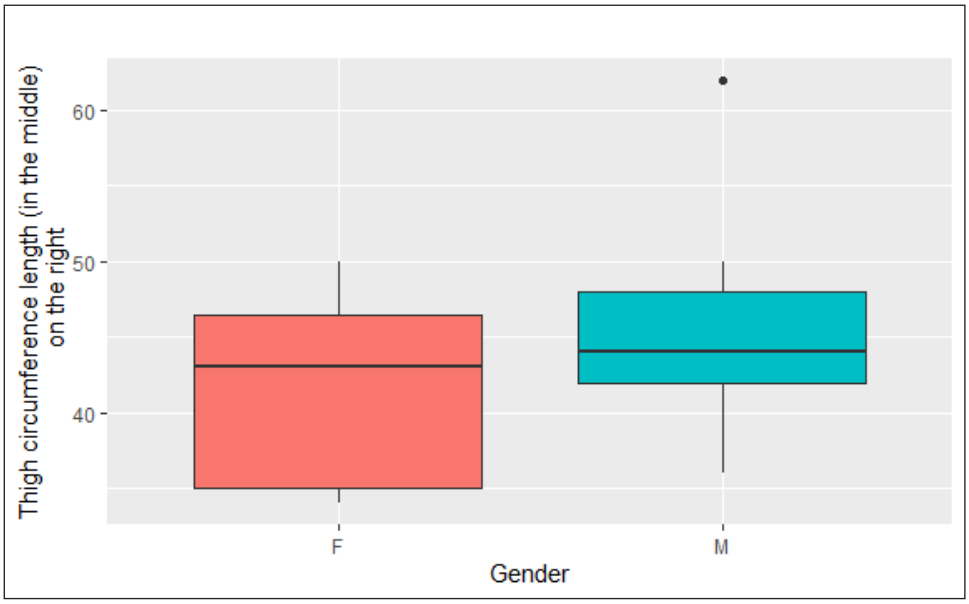

Fig. 2. Distribution of the length of the hip circumference (in the middle third) on the right of the respondents in the control group by gender.

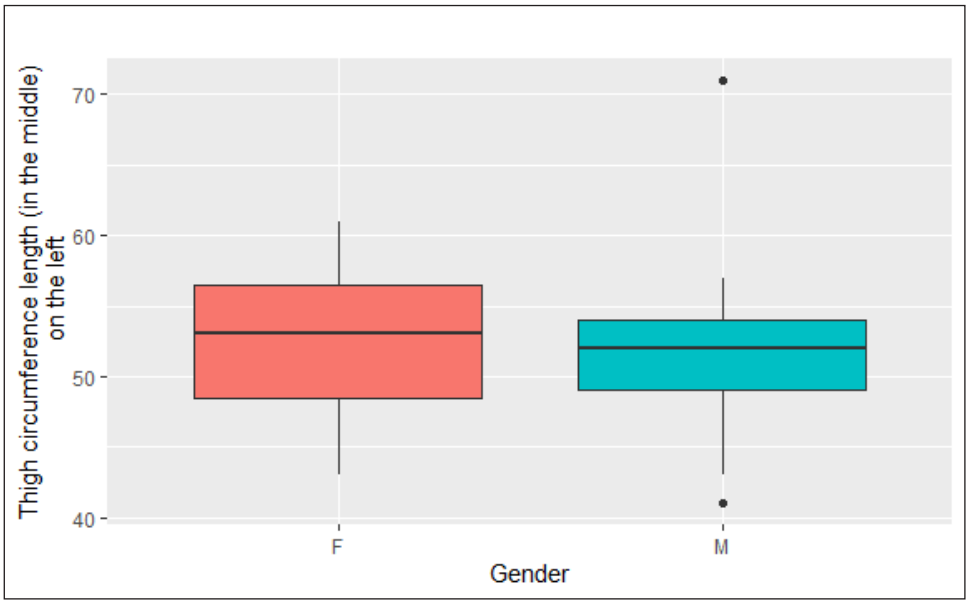

Fig. 3. Distribution of the length of the hip circumference (in the middle third) on the left of the respondents of the main group by gender

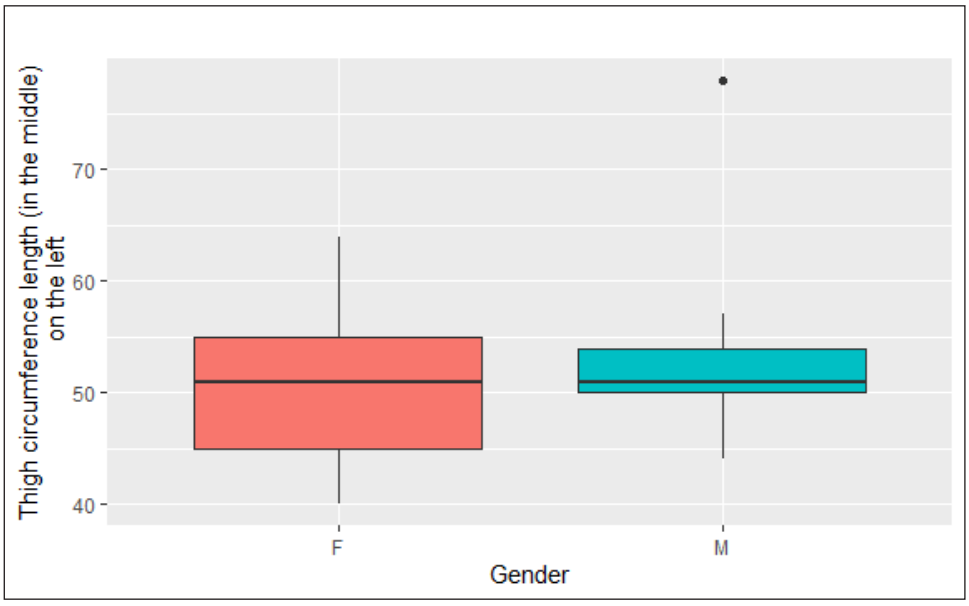

Fig. 4. Distribution of the length of the hip circumference (in the middle third) on the left of the respondents in the control group by gender

length of the hip circumference (in the middle third) in the case of young boys and young girls on average. This is also evidenced by the Welch t-test: t (41,252) = – 0,260, p = 0,797 (Fig. 1).

The distribution of the length of the hip circumference (in the middle third) on the right of the respondents in the control group by gender shows that there is no significant difference in the length of the hip circumference (in the middle third) in the case of young boys and young girls on average too. This is also evidenced by the Welch t-test: t (37,806) = – 1,466, p = 0,150 (Fig. 2)

The distribution of thigh circumference (in the middle third) is the case of respondents by sport shows that there is probably a significant difference in the average length of the thigh circumference (in the middle third) on the right depending on the sport, including the control group. Results of the Kraskel-Wallis test: (x^2 (6) = 10.419, p = 0.108) Since p = 0.108 ≥ 0.05, the difference between the medians of the groups is not statistically significant.

The distribution of the length of the hip circumference (in the middle third) on the left of the respondents of the main group by gender shows that there is no significant difference in the length of the hip circumference (in the middle third) on the left of young boys and young girls on average. This is also evidenced by the Welch t-test: t (43,627) = 0,698, p = 0,489 (Fig. 3).

The distribution of the length of the hip circumference (in the middle third) on the left of the respondents in the control group by gender shows that there is no significant difference in the length of the hip circumference (in the middle third) on the left of young boys and young girls on average. This is also evidenced by the Welch t-test: t (37,896) = – 1,189, p = 0,242 (Fig. 4).

The distribution of thigh length (in the middle third) on the left of respondents by sport shows that there is a significant difference in the average length of the girth of the thigh (in the middle third) on the left depending on the sport, including the control group. The results of the Kraskel-Wallis test (x^2 (6) = 17.009, p = 0.009). Since p = 0.009 ≤ 0.05, the difference between the medians of the groups is statistically significant.

So, let's establish for which age pairs there is a statistical difference of medians. To do this, we will conduct the Conover-Iman test. The results are as follows: there is a significant difference for the pairs "basketball" – "handball", "control" – "handball", "football" – "handball", "volleyball" – "control", "volleyball" – "football", "volleyball" "-"handball". No significant differences were found for other groups.

DISCUSSION

Competitive results of athletes mostly depend on physical development and anthropometric data of athletes. Thus, anthropometric indicators have reliable correlations of a high degree with the result of professional activity of athletes. There are almost no works devoted to the study of the comprehensive parameters of the thigh for sports. Namely, taking into account the scientific achievements of authors such as Sara Jane Cullen and others [1], who studied the anthropometric profiles of elite athletes, concluded that there are differences in anthropometric profiles between different athletes and different sports, emphasizing the need to have regulatory ranges for specific sports to ensure optimal monitoring of individual athletes, who are particularly different between sports, as well as age, training status. Kotko DM and others [26], studied changes in some anthropometric indicators in athletes – athletes at the stages of long-term training, including Kettle weight-growth index, the relative amount of muscle tissue, the absolute amount of bone component of the body.

In our opinion and other authors the determination of the length of the thigh girth (in the middle third) has the accuracy of measurement, because it is in the middle third of the thigh that the quadriceps and triceps are most pronounced.

So, the girth of the right thigh in the middle third of the studied students of the main group: the largest have the volleyball players – 44.61 ± 2.0 cm, of which 44.50 ± 2.0 cm in young boys and 44.11 ± 2.0 cm in young girls and basketball players – 43.00 ± 2.0 cm, of which 42.10 ± 2.0 cm in young boys and 42.90 ± 2.0 cm in young girls, less the football players – 41.80 ± 2.0 cm, of which 41.60 ± 2.0 cm in young boys and 41.20 ± 2.0 cm in young girls and the least have handball players – 40.00 ± 2.0 cm, of which 39.90 ± 2.0 cm in young boys and 39.10 ± 2.0 cm in young girls. In the control group, the mean girth length on the middle third of the right thigh was – (43.25 ± 2.0 cm), of which 44.57 ± 2.0 cm in young boys and 41.78 ± 2.0 cm in young girls.

The girth of the left thigh in the middle third of the studied students of the main group: the largest have basketball players – 54.14 ± 2.0 cm, of which 53.96 ± 2.0 cm in young boys and 53.18 ± 2.0 cm in young girls and volleyball players – 54.00 ± 2.0 cm, of which 53.90 ± 2.0 cm in young boys and 53.10 ± 2.0 cm in young girls, less the football players – 51.90 ± 2.0 cm, of which 51.55 ± 2.0 cm in young boys and 51.35 ± 2.0 cm in young girl and the least have handball players – 48.60 ± 2.0 cm, of which 48.45 ± 2.0 cm in young boys and 48.15 ± 2.0 cm in young girls. In the control group, the mean girth length on the middle third of the right thigh was – (43.25 ± 2.0 cm), of which 44.57 ± 2.0 cm in young boys and 41.78 ± 2.0 cm in young girls.). In the control group, the mean girth length in the middle third of the left thigh was – (51.65 ± 2.0 cm), of which 52.80 ± 2.0 cm in young boys and 50.36 ± 2.0 cm in young girls.

The model for predicting the girth of the thigh in the middle third on the right has the form $y = \beta1 + \beta2 + 0.328 * x_1 - 0.167 * x_2$, where y is the girth of the thigh in the middle third on the right, x_1 is the weight, x_2 is the height. The coefficient $\beta1 = 49{,}523$ for girls and $\beta2 = 47{,}281$ for boys. The coefficient of determination is 0.991.

Based on the Kraskel-Wallis test, it was found that there is a significant difference in the average value of the length of the thigh circumference (in the middle third) on the left depending on the sport, including the control group. Based on the Conover-Iman test, it was found that there is a significant difference between the pairs "basketball" – "handball", "control" – "handball", "football" – "handball", "volleyball" – "control", "volleyball" – "football", "volleyball" – "handball". No significant differences were found for other groups. Regression analysis shows that significant factors for hip girth in the middle third of the left are gender, sport type, body weight and height.

The model for predicting the circumference of the hip circumference in the middle third of the left has the form $y = \beta1 + \beta2 + 0.451 * -0.179 *$, where y is the hip circumference in the middle third of the left, is the body weight, is the height. The coefficient $\beta1 = 58{,}181$ for girls and $\beta2 = 53{,}302$ for boys. Coefficient $\beta2 = 0$ for the group "basketball", $\beta2 = -3{,}358$ for the group "control", $\beta2 = -0{,}484$ for the group "football", $\beta2 = -1{,}991$ for the group "handball", $\beta2 = -0{,}824$ for the group "volleyball". The coefficient of determination is 0.996.

It is also noted that there is a significant difference between the average length of the thigh circumference (in the middle third) on the left and right $t(255{,}99) = -14{,}714$, $p < 0{,}05$

CONCLUSIONS

Summing up, we can conclude that our research is relevant because it was found that there is a significant difference in the average length of the thigh circumference (in the middle third) on the right depending on the sport type, including the control group. Regression analysis shows that gender, body weight, and height are significant factors in mid-thigh girth.

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ORIGINAL ARTICLE

THROMBOLYSIS IN PULMONARY EMBOLISM TREATMENT

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ABSTRACT

The aim: To assess the effectiveness of thrombolytic therapy in treatment pulmonary embolism.

Materials and methods: The work analyzed the results of the survey and conservative treatment of 284 patients with pulmonary embolism treated in cardiological department in «Uzhgorod Central City Clinical Hospital» during 2019-2022. Patients were divided into two groups: group I – 250 (88%) patients received anticoagulant therapy; group II – 34 (12%) patients received thrombolytic therapy that was then switched to new oral anticoagulants.

Results: In I group, the first three days were carried out continuously intravenous infusion of heparin in a dose of 25-30 thousand units per day, on the fourth day switched to subcutaneous injection for 10-14 days with subsequent switching to rivaroxaban. 34 (12.0%) patients of the II group, was started with thrombolytic therapy. 32 (94.1%) patients were prescribed alteplase 100 mg/day, and 2 (5.9%) patients – streptokinase 1.5 million units/day. After thrombolysis, patients were prescribed rivaroxaban for prolonged period. Thrombolytic therapy made it possible to prevent fatal cases, and in monotherapy with anticoagulants – mortality was 4.8%. Minor hemorrhagic complications like hematuria, local hematomas at the injection site, bleeding gums were observed in 7.6% of patients during thrombolytic therapy. No cases of large hemorrhages were observed. Manifestations of chronic postembolic pulmonary hypertension in the distant period were found in 97.1% and 6.9% of patients of the I and II groups, respectively. Lethality in the remote period was 5.3% – all in the 1st group of patients due to PE recurrence and acute myocardial infarction.

Conclusions: Implementation of thrombolytic therapy in patients with thromboembolism of the pulmonary artery allows effectively prevent recurrence with a fatal outcome, restore the lumen of the pulmonary arteries and prevent the development of chronic postembolic pulmonary hypertension in the immediate and remote period of observation compared to isolated anticoagulant therapy.

KEY WORDS: deep vein thrombosis, thrombolytic therapy, anticoagulants, pulmonary thromboembolism arteries, chronic postembolic pulmonary hypertension

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INTRODUCTION

Venous thromboembolic complications occur in general population in 0.15 – 2.1% [1, 2], while the mortality rate 2.1 – 6.2% [3]. At the same time, some data allows to claim that in almost 25% of the world's population pulmonary artery thromboembolism (PE) occurs during lifetime [4]. Every year in the USA, 600,000 to 700,000 people develop a pulmonary embolism [5, 6], which in 200,000 to 300,000 cases leads to fatal consequences [7] and exceeds the total value of mortality rates from mammary gland cancer, HIV AIDS and traffic accidents [8].

In EU was diagnosed 317 000 deaths related to PE in the population of 454 million people of which in 34% of cases PE had been remained undiagnosed during life, 59% of cases had been diagnosed only after death and had been diagnosed correct in only 7% of patients [4, 9]. Diagnostic errors in PE reach up to 70% of observations [4]. European Association of Cardiology (2014) predicts a doubling of PE cases in patients older than 40 years each next decade [6].

In Ukraine, 50,000 episodes of PE are registered every year with mortality up to 25% of the general hospital rate [3].

Mortality from PE reaches 2.1 – 50% of cases of DVT [2, 9, 10], and if the patients have a condition that requires resuscitation measures, it increases to 65% [1]. More than a third of patients develop a fulminant PE [10, 11]. Within 10 years after the first episode of PE in 30% of patients recurrence is observed [7].

According to the Framingham study, mortality from PE is 15.6% of all hospital mortality (for surgical diseases – 18%, therapeutic – 82% of cases) [12], but only 39.5% of patients of surgical and 58.5% of patients with therapeutic profiles, with an increased risk of PE, receive adequate pharmacoprophylactic treatment [2].

At the same time, despite the progress in the treatment, mortality in the acute PE remains significantly

high, and with preservation of life the risk of chronic postembolic pulmonary hypertension increases rapidly as a result of repeated periodic thromboembolism of the pulmonary artery, which tremendously worsens the quality of life and often leads to disability of patients.

THE AIM

The aim of the study was to evaluate the effectiveness of thrombolytic therapy in treatment of pulmonary embolism.

MATERIALS AND METHODS

The work analyzed the results of the survey and conservative treatment of 284 patients with pulmonary embolism treated in the Cardiological department of the Uzhhorod city central clinical hospital during 2019-2022. 91 (32%) patients were men and 193 (68%) were women. Age of patients ranged from 29 to 83 years, the average age was 59±2.4 years.

All 284 (100%) patients were hospitalized urgently to Cardiological department, in particular 243 (85.6%) patients were delivered by an ambulance, 17 (6.0%) – referred by a family doctor and 24 (8.4%) applied independently.

269 (94.7%) were hospitalized on the 1st day of the disease, 9 (3.2%) within 2-3 days after clinical manifestation and 6 (2.1%) patients after more than 3 days.

Treated patients were divided into two groups:

- group I – 250 (88%) patients received anticoagulant therapy;
- group II – 34 (12%) patients who received thrombolytic therapy with subsequent switching to oral anticoagulants.

For the examination of patients, laboratory and nstrumental methods were used: echocardioscopy («Siemens Acuson SC-2000»), multispiral computed tomography with intravenous contrast («Siemens Somaton Emotion 16»), ultrasound dopplerography and ultrasound duplex scanning («Philips CX-50», Philips Ultrasound Inc., USA).

RESULTS

During admission the following clinical signs were observed:

- arterial hypotension – in 49 (17.3%);
- collapse – in 36 (12.7%);
- tachycardia – in 164 (57.7%);
- heart rhythm disorders – in 87 (30.6%);
- shortness of breath at rest – in 112 (39.4%);
- shortness of breath during physical exertion – in 57 (20.1%);
- tachypnea – in 169 (59.5%);
- chest pain – in 138 (48.6%);
- cough – in 41 (14.4%);
- hemoptysis – in 28 (9.9%);
- abdominal manifestations (abdominal pain, nausea, vomiting, flatulence) – in 16 (5.6%);
- cerebral manifestations (psychomotor agitation, meningeal and/or focal symptoms, convulsions) – in 9 (3.2%);
- fever (low fever) – in 4 (1.4%) cases.

In case of suspicion of PE, patients were noted during the collection of anamnesis the following:

- post-thrombophlebitic syndrome – in 45 (15.8%);
- deep vein thrombosis of the lower extremities – in 37 (13.0%);
- superficial thrombophlebitis – in 23 (8.1%);
- varicose disease of the lower extremities – in 67 (23.6%);
- history of pulmonary embolism in 31 (10.9%);
- thrombophilia – in 14 (4.9%);
- cardiac pathology – in 81 (28.5%);
- pulmonary pathology – in 62 (21.8%) observations.

At the first stage, when PE was suspected, electrocardiography and laboratory examination were performed. During electrocardiography, the following were observed:

- shift of the electrical axis of the heart to the right – 178 (62.7%) cases;
- signs of right ventricular hypertrophy – 134 (47.2%);
- low voltage on leads I, II and III – 102 (35.9%);
- negative T wave in leads III and aVF or V 1 – V 4 – 156 (54.9%);
- S wave in leads I and aVL more than 1.5 mm – 91 (32.0%);
- appearance of QS wave in leads III and aVF – 64 (22.5%);
- displacement of the ST segment above the isoline in leads III, aVF, aVR, V 1-3
- and/or its decrease in leads I, II, aVL, V 5-6 – 78 (27.5%);
- unstable Q wave in III and aVF leads – 112 (39.4%);
- sinus tachycardia, extrasystole – 235 (83.6%);
- paroxysmal or atrial fibrillation – 51 (18.0%);
- incomplete or complete blockage of the right brunch of the bundle of His – 86 (30.3%);
- P-pulmonale – 105 (36.8%);
- No changes – 56 (19.7%).

In the complete blood count, leukocytosis was observed – in 205 (72.2%), a shift of leukocyte formula to the left – in 83 (29.2%), increased sedimentation rate of erythrocytes – in 212 (74.6%), eosinophilia – 47 (16%), lymphopenia – 35 (12.3%), monocytosis – 32 (11.3%), thrombocytosis – in 195 (68.7%) patients.

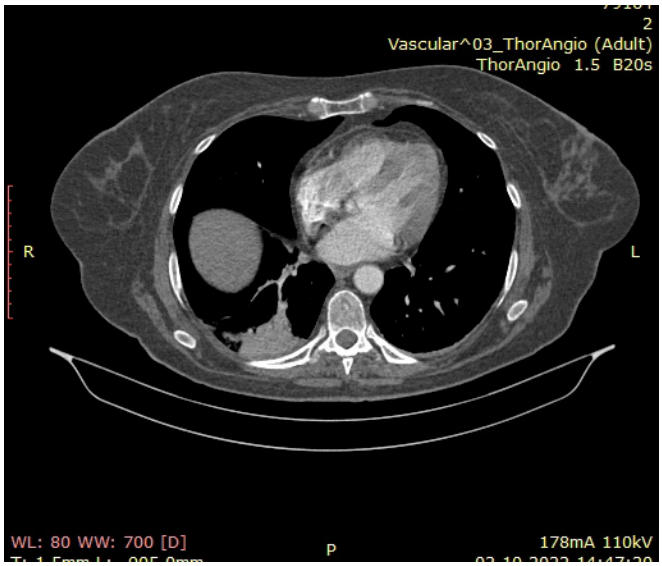

Fig. 1. MSCT-angiopulmonography: right-sided lower lobe infarction pneumonia.

The average level of D-dimer at the admission was 6321.7±1598.2 ng/ml.

During the coagulogram evaluation, an increase in coagulation factors was observed:

- increased D-dimer – in 284 (100%);
- increased hematocrit – in 205 (72.2%);
- an increase in the number of platelets – in 236 (83.1%);
- an increase in the average concentration of thrombocrit – in 236 (83.1%);
- shortening of activated thromboplastin time – in 258 (90.8%);
- shortening of activated recalcification time – in 244 (85.9%);
- increase in the prothrombin index – in 268 (94.4%);
- increase in prothrombin time – in 252 (88.7%);
- increased level of fibrinogen – in 278 (97.9%);
- a decrease of the international normalized ratio – to 271 (95.4%) of observations.

The next stage was conducting echocardioscopy to all patients. During which the following signs were found, which testified to overload of the right parts of the heart, hypertension in the small circle of blood circulation and, indirectly, about possible pulmonary embolism, in particular:

- direct visualization of thromboembolism – in 11 (3.9%);
- dilatation of the right ventricle – in 275 (96.8%);
- hypokinesia of the right ventricular wall – in 187 (65.8%);
- increase in the end-diastolic size of the right ventricle and decrease in contractility of the latter – in 263 (92.6%);
- prolapse of the interventricular membrane – in 97 (34.2%);
- tricuspidal regurgitation – in 279 (98.2%);
- pulmonary artery dilatation – in 127 (44.7%);
- a significant decrease in the degree of lowering of the Vena cava inferior – in 106 (37.3%).

The first stage of instrumental diagnostics necessarily included X-ray examination of chest. X-ray changes in PE first described by F.G. Fleichner (1965). To X-ray signs, in examined patients with PE included:

- decrease of the vascular pattern of the lungs (pathognomonic symptom,
- Westmark – described back in 1938) – in 12 (4.2%);
- deformation or enlargement of one of the lung roots – in 89 (31.3%);
- bulging of the pulmonary artery cone – in 49 (17.3%);
- expansion of the heart due to the right ventricle and atrium – in 95 (33.5%);
- expansion of the arc of the pulmonary trunk – in 51 (18.0%);
- a cone-shaped shadow directed by the apex to the root of the lung – at 65 (22.9%);
- high standing and limitation of mobility of the diaphragm on the side of lesions (Zweifel's symptom) – in 128 (45.1%);
- the presence of fluid in the pleural cavity – in 76 (26.8%);
- no X-ray changes characteristic of PE were detected in 69 (24.3%).

During next week of hospital stay in 179 (63.0%) patients with repeated X-ray or a tomographic examination revealed heart attack-pneumonia (Fig. 1). It should be noted that the absence of radiological symptoms which are common to venous thromboembolic complications does not necessarily exclude the diagnosis of PE, therefore, anamnestic and clinical data should be analyzed in a complex manner with laboratory and instrumental examinations.

In doubtful cases, 48 (16.9%) patients were performed multispiral computed tomography of the chest with intravenous contrast (angiopulmonography), which allowed to confirm the diagnosis of PE. Angiopulmonography in 39 (81.3%) of 48 patients made it possible to clearly visualize thrombotic masses in the lumen of the pulmonary arteries (Fig. 2).

CT-criteria of the PE included:

- filling defects (oligemia – decreased perfusion on the periphery of lungs) – in 32 (66.7%);
- vessel amputation – in 41 (85.4%);
- vessel stenoses of various lengths – in 15 (31.3%);
- sharp zigzag deformations of vessel contours – In 13 (27.1%);
- presence of thrombus, vessel obturation – In 39 (81.3%);
- increase in the diameter of the pulmonary artery – In 31 (64.6%);

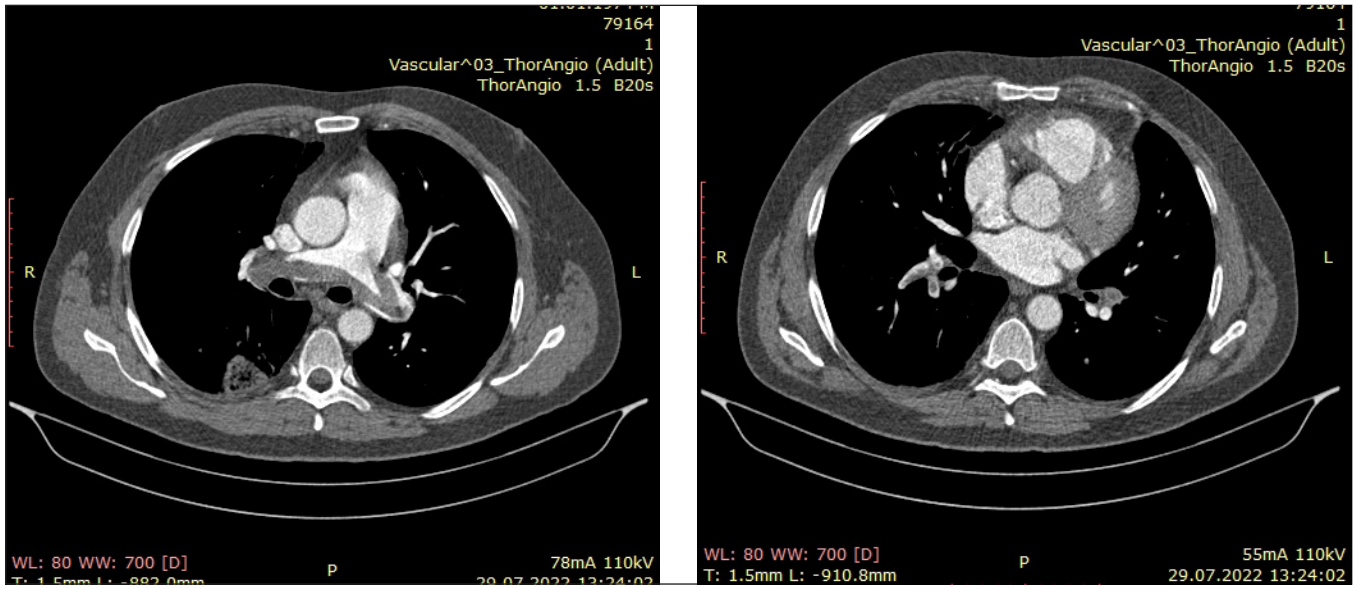

Fig. 2. MSCT-angiopulmonography: thrombotic masses in the lung trunk, pulmonary arteries (a) and segmental pulmonary arteries (b).

- lack of contrast of lung vessels on the affected side – In 33 (68.8%);
- "spilled" or "spotty" nature of vascular contrast – In 23 (47.9%).

After the diagnosis of PE, the patients were started intensive care measures that necessarily included anticoagulants or thrombolytic therapy. For anticoagulant therapy unfractionated heparin was used. The first three days were carried out non-stop intravenous infusion of heparin using an infusomat in a dose of 25 – 30 thousand units per day at the rate of 1000 – 1250 units/hour. With the following change on fourth day to subcutaneous administration at the rate of 450 units per kg, but not more than 30 thousand units. Treatment with unfractionated heparin was carried out for 10 – 14 days with subsequent transfer to oral anticoagulants. From the oral group of anticoagulants were prescribed rivaroxaban at a dose of 20 mg/day or dabigatran 150 mg – 2 times a day. Treatment of PE with unfractionated heparin was carried out in 250 (88.0%) of 284 patients. During the period of inpatient treatment in this group noted 12 (4.8%) fatal cases associated with PE recurrence.

In 34 (12.0%) of 284 patients, treatment was started with thrombolytic therapy. In 32 (94.1%) patients during the first day of hospitalization alteplase was prescribed in a dose of 100 mg/day, which was dissolved in a solvent to 100 ml. Initially, 10 ml (10 mg) of alteplase was administered intravenously for 2 minutes followed by an infusion of 90 ml (90 mg) over 2 hours. In 4 (12.5%) patients observed local hematomas at the injection site, bleeding from the gums. Large hemorrhages were not observed.

2 (5.9%) patients were prescribed thrombolytic therapy streptokinase at a dose of 1.5 million units/day. Intravenous infusion was started with introduction of 250,000 units within 30 minutes followed by 100,000 units/hour within 24 hours. When using streptokinase in both cases (100%) manifestations of hematuria, local hematomas at the injection site were observed. Thus, small hemorrhagic complications after thrombolysis were observed in 6 (17.6%) of 34 patients.

After thrombolysis, patients were prescribed rivaroxaban in a dose of 15 mg – 2 times a day for 3 weeks, followed by a dose reduction to 20 mg/day for a long time. Next to anticoagulant or anti-shock therapy, cardiac and phlebotropic agents.

Control of therapy at the inpatient stage: laboratory control of blood parameters and coagulogram was carried out on 2nd, 5th and 10th day or more often if necessary; in the vast majority of patients (n=256 (90.1%)). Echocardioscopy and X-ray control were performed on the 5th to 7th day at the time of the patient's admission to the hospital, in 28 (9.9%) patients – echocardioscopy and X-ray examination of chest , after started treatment carried out 2-3 times; in some cases, instrumental diagnosis was complemented by multispiral computed tomography of chest with intravenous contrast.

The average hospital stay of a patient with PE was 9.6±2.3 days. Fatal cases during hospital stay in the group of patients, who underwent thrombolytic therapy, were not observed.

Oral anticoagulants were prescribed for 8.9±1.4 months, under constant coagulogram monitoring,echocardioscopy and X-ray examination of chest, which, if necessary, supplemented with CT. The main

reason for the continuation therapy with oral anticoagulants for more than a year served pronounced cardiac pathology, the presence of postthrombophlebitic syndrome, chronic postembolic pulmonary hypertension. At the same time, rivaroxaban prescribed for a long time at a dose of 10 mg/day.

In the remote period, within 1-2 years, it was possible to track 209 (73.6%) patients, in particular in 180 (72%) patients after anticoagulant therapy and in 29 (85.3%) patients after thrombolysis. Manifestations of chronic postembolic pulmonary hypertension in the remote period was found in 68 (32.5%) of 209 patients, in particular, in 66 (97.1%) and 2 (6.9%) patients after anticoagulation and thrombolytic therapy, respectively. Throughout the remote period noted 11 (5.3%) deaths – all in the group of patients treated anticoagulant therapy. The cause of death was PE relapse (n=7) and acute myocardial infarction (n=4).

DISCUSSION

The recommendations of the latest European and American guidelines on the diagnosis and treatment of pulmonary embolism [13-15] indicate the prescription of new oral anticoagulants in the acute period of the disease with a high degree of evidence (class I) and in the period 3 to 6 months after an episode of venous thromboembolism as an alternative to low molecular weight heparins (class I). Although the frequency of pulmonary embolism and mortality from it is steadily increasing [13, 15], and the annual costs of treating this contingent of patients in the European Union is approximately near 8.5 billion euros [13]. At the same time, experts note that with the use of more effective methods of treatment, it is possible to improve the results of treatment of patients with venous thromboembolic complications [13]. Thus, thrombolytic therapy in the acute period of pulmonary embolism allows to restore the lumen of the pulmonary artery, disrupt pulmonary hypertension, and reduce dilatation of the right ventricle [13, 15, 16]. Systemic thrombolysis with isolated anticoagulant therapy with unfractionated heparin has a higher level of evidence (class I b) [13], but is dangerous due to hemorrhagic complications [14, 15]. At the same time, the American recommendations tell us about low level of evidence for the use of systemic thrombolysis in the acute period of PE, especially with severe arterial hypotension [14, 15], instead preferring catheter-guided regional thrombolysis [15]. However, there are no published studies that compare the effectiveness of anticoagulant therapy, catheter-based regional and systemic thrombolysis [15], and the choice of treatment method is based on the physician's experience. In addition to the route of thrombolytic administration, the choice of thrombolytic drug and the timing of initiation of thrombolytic therapy, depending on the age of PE, the assessment of long-term results of thrombolytic treatment remain debatable.

CONCLUSIONS

Thus, the introduction of thrombolytic therapy in patients with thromboembolism of the pulmonary artery allows you to effectively prevent relapse with with a fatal outcome, restore the lumen of the pulmonary arteries and warn the development of chronic postembolic pulmonary hypertension in the immediate and distant observation period compared to isolated anticoagulant therapy.

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ORIGINAL ARTICLE

OBSTETRIC AND PERINATAL ASPECTS OF METABOLIC DISORDERS IN PREGNANT WOMEN

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ABSTRACT

The aim: To determine the feasibility of using Tivortin in metabolic disorders during pregnancy and its effect on the course of pregnancy, childbirth, fetal and neonatal status.

Materials and methods: We examined 210 pregnant women with metabolic disorders using clinical and laboratory data, uterine artery Doppler, determination of lipid peroxidation and antioxidant system, leptin and placental growth factor content. The fetal condition was assessed by ultrasound examination with Doppler, determination of biophysical profile, and cardiotocography.

Results: Metabolic disorders in pregnant women increase the risk of obstetric and perinatal complications by activating lipid peroxidation and inhibiting the antioxidant system, reducing the content of placental growth factor and increasing the level of leptin in the blood plasma. After treatment, there was a significant decrease in leptin levels and an increase in placental growth factor levels, normalization of lipid peroxidation and antioxidant system, uterine artery pulsatility index and umbilical cord peak systolic velocity index, systolic-diastolic ratio, fetal biophysical profile and cardiotocography. The incidence of complications in childbirth decreased by 3 times, surgical interventions – by 2 times, postpartum infectious complications – by 1.7 times, and the birth of infants in a state of asphyxia – by 1.8 times.

Conclusions: Metabolic disorders in pregnant women are a significant factor in the development of obstetric and perinatal complications due to the intensity of lipid peroxidation and depression of the antioxidant system, and a decrease in the content of placental growth factor. The use of Tivortin in the treatment of pregnant women with metabolic disorders has proven its safety and efficacy.

KEY WORDS: pregnancy, metabolic disorders, Tivortin

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INTRODUCTION

The problem of metabolic disorders in obstetric practice is relevant both scientifically and practically, since these disorders are caused by genetic, hemodynamic, neurohumoral features and are manifested by a complex of pathogenetically interrelated disorders of tissue sensitivity to insulin, carbohydrate, lipid, purine metabolism, etc. According to WHO recommendations, the criteria for metabolic syndrome are obesity (body mass index >30 kg/m^2), blood pressure >160/90 mm Hg, and impaired glucose tolerance. According to the results of epidemiological studies over the past ten years, obesity in pregnant women occurs in 15-38% of cases and is associated with a high risk of complications during pregnancy, childbirth and the postpartum period due to an increased risk of gestosis, abnormal labor, bleeding, gestational diabetes, hypertension, as well as premature and delayed delivery [1-3]. Studies have shown that late gestosis occurs most often, and in 75% of cases it is complicated by the development of feto-placental insufficiency. Gestational diabetes develops in at least 3% of pregnant women and is caused by significant changes in carbohydrate metabolism, which are aimed at meeting the needs of the fetus and placenta, but also have a diabetogenic effect [4]. The incidence of metabolic disorders during pregnancy is 5-20%, which leads to numerous obstetric complications, high perinatal morbidity and mortality, and existing therapeutic and preventive measures are not always effective [5]. Pathological manifestations in these pathologies are multisystemic in nature, which is due to endothelial dysfunction, for the correction of which it is advisable to prescribe nitric oxide donors, namely L-arginine [6].

THE AIM

The aim was to determine the feasibility of using Tivortin in metabolic disorders during pregnancy and its effect on the course of pregnancy, childbirth, fetal and neonatal status.

MATERIALS AND METHODS

We examined 210 women aged 18 to 34 years with metabolic disorders at 16 to 36 weeks of pregnancy. The groups of pregnant women were homogeneous in terms of age, anamnesis, clinical and laboratory findings. 60 pregnant women with moderate preeclampsia were divided into 2 groups. Group I included 30 patients who were treated according to the clinical protocol with additional prescription of Tivortin, and Group II included 30 women who received treatment according to the clinical protocol. Similarly, 60 women with gestational diabetes were divided into groups III and IV. Among the 60 obese women, 30 pregnant women received tivortin along with diet and physiotherapy (group V), and 30 pregnant women received conventional treatment (group VI). The control group included 30 women with physiologically normal pregnancies.

The active ingredient of Tivortin (manufactured by Yuria-Pharm LLC, Ukraine) is L-arginine, which has antihypoxic, membrane-stabilizing, cytoprotective, antioxidant effects, acts as an active regulator of intermediate metabolism and energy supply processes, and plays a role in maintaining hormonal balance in the body. The drug is certified for use during pregnancy.

Tivortin was administered for 7 days once a day, 100 ml intravenously drop (slowly), then tivortin aspartate 1 g (5 ml) for 14 days orally 4 times a day in courses at 16 and 26 weeks of gestation. The effectiveness of the treatment was evaluated in dynamics in pregnant women of all groups based on clinical picture; laboratory data; uterine artery Doppler; determination of lipid peroxidation (LPO), in particular, malondialdehyde (MDA) and diene conjugates (DC) and antioxidant system (AOS), namely ceruloplasmin (CP) and catalase (C); leptin and placental growth factor (PGF) levels were determined at 26 weeks of gestation. The fetal condition was monitored in the dynamics by ultrasound with Doppler, determination of biophysical profile, cardiotocography using Dawes/Redman criteria and STV index, which reflects the degree of metabolic acidemia. For comparison, the parameters of the control group were used. The results were analyzed using the methods of variation statistics and considered significant at $p < 0.05$.

RESULTS

It was found that moderate preeclampsia was accompanied by a significant increase in the incidence of preterm labor, growth retardation syndrome, and fetal distress compared with the control group. In labor, the main complications were premature rupture of membranes, abnormal labor activity and fetal distress, $p < 0.05$. These complications were the main indications for cesarean section, the frequency of which was significantly higher compared to the control group. At the same time, there was an increase in the level of malondialdehyde in group I to 3.25±0.45 μmol/mL and in group II to 3.29±0.34 μmol/mL against 2.21±0.11 μmol/mL in the control group, $p<0.05$. The level of diene conjugates increased in group I to 24.3±0.3 μmol/l, and in group II to 26.8±0.2 μmol/l against 9.5±0.3 μmol/l in the control group, $p<0.05$. Against the background of intensification of peroxidation processes, significant changes in the antioxidant defense system were revealed. In particular, the activity of ceruloplasmin significantly changed (39.28±0.67 mg/dl in group I and 37.16±0.53 mg/dl in group II vs. 22.41±0,97 mg/dl in the control group), catalase (11.63±0.64 mg H_2O_2 /ml in group I and 12.36±0.35 mg H_2O_2 /ml in group II and against 14.56±0.52 mg H_2O_2 /ml in the control group). The results of the study indicate the presence of a significantly higher level of leptin (26.6±1.34 ng/ml in group I and 27.2±2.47 ng/ml in group II versus 10.7±0.57 ng/ml in the control group). In addition, a significantly lower level of placental growth factor was observed (638±11.8 pg/ml in group I and 754.3±7.4 pg/ml in group II versus 1102±15.8 pg/ml in the control group).

The course of pregnancy in patients with gestational diabetes was complicated by vomiting, spontaneous premature termination of pregnancy, late gestosis, polyhydramnios, inflammatory diseases of the urinary tract, progressive anemia, and macrosomia. The incidence of spontaneous abortion was 29.6%, in the control group – 7%, $p<0.05$. Late gestosis occurred more often before 34 weeks of pregnancy and was observed in 24% of cases, while in the control group – 2%, $p<0.05$. Polyhydramnios was observed in 15% of cases, in the control group – 1%, $p<0.01$. Urinary tract infection complicated the course of pregnancy in 19.4%, and in the control group in 7% of patients, $p<0.05$. In labor, premature rupture of the fetal bladder, clinically narrow pelvis, abnormal labor activity, fetal distress, surgical delivery, and newborn asphyxia were significantly more common compared to the control group, $p<0.05$. The content of malondialdehyde in group III was 3.11±0.25 μmol/mL, and in group IV – 3.19±0.19 μmol/mL against 2.21±0.11 μmol/mL in the control group, $p<0.05$. The level of diene conjugates increased in group III to 22.4±0.5 μmol/l, and in group IV to 25.5±0.2 μmol/l against 9.5±0.3 μmol/l in the control group, $p<0.05$. Ceruloplasmin activity changed significantly (43.32±0.24 mg/dl in group III and 39.35±0.35 mg/dl in group IV vs. 22.41±0,97 mg/dl in the control group), catalase (10.35±0.43 mg H_2O_2 /ml in group III and 11.93±0.32 mg H_2O_2 /ml in group IV against 14.56±0.52 mg H_2O_2 /ml in the control group). The level of placental growth factor

was 568±10.7 pg/ml in group III and 606.8±12.7 pg/ml in group IV against 1102±15.8 pg/ml in the control group, p<0.05. Leptin levels in groups III and IV did not differ significantly from those in the control group.

Obesity during pregnancy significantly increases the risk of gestational hypertension, preeclampsia, preterm or delayed delivery, abnormal labor, postpartum hemorrhage, fetal growth retardation syndrome, newborn asphyxia, macrosomia, gestational diabetes, fetal distress compared to the control group, p < 0.05. In addition, the results of the study indicate that obese women had significantly higher levels of leptin (39.6±1.23 ng/ml in group V and 37.2±2.27 ng/ml in group VI versus 10.7±0.57 ng/ml in the control group). The level of placental growth factor was 538±8.7 pg/ml in group V and 706.8±9.7 pg/ml in group VI versus 1102±15.8 pg/ml in the control group, p<0.05. The content of malondialdehyde in group V was 3.09±0.13 μmol/mL, and in group VI – 3.12±0.9 μmol/mL against 2.21±0.11 μmol/mL in the control group, p<0.05. The level of diene conjugates increased in group V to 19.4±0.7 μmol/l, and in group VI to 21.5±0.6 μmol/l against 9.5±0.3 μmol/l in the control group, p<0.05. Ceruloplasmin activity changed significantly (33.12±0.34 mg/dL in group V and 36.31±0.4 mg/dL in group VI vs. 22.41±0,97 mg/dl in the control group), catalase (9.87±0.59 mg H_2O_2/ml in group V and 10.25±0.42 mg H_2O_2 /ml in group VI against 14.56±0.52 mg H_2O_2 /ml in the control group).

In order to correct the identified disorders, along with treatment in accordance with the current clinical protocols of each nosology, we used the drug Tivortin. In patients of group I, proteinuria and edema decreased, blood pressure normalized, the percentage of preterm delivery and progressive anemia of pregnant women decreased, the pulsatile index of the uterine artery and the index of peak systolic velocity of the umbilical cord vessels in the second trimester of pregnancy normalized, a lower incidence of early preeclampsia and its transition to severe preeclampsia in the dynamics of observation and treatment was noted compared with pregnant women of group II, p<0,05 (Table I).

Along with this, the level of malondialdehyde in group I decreased to 2.25±0.54 μmol/mL versus 3.25±0.45 μmol/mL before treatment, p<0.05. In group II, the level of malondialdehyde decreased to 2.29±0.53 μmol/mL versus 3.29±0.34 μmol/mL before treatment, p<0.05. At the same time, the level of diene conjugates in group I decreased to 10.2±0.4 μmol/mL versus 24.3±0.3 μmol/mL before treatment, p<0.05. In group II, a decrease in the level of diene conjugates reached 11.6±0.6 μmol/mL versus 26.8±0.2 μmol/l before treatment, p<0.05. The increase in the activity of antioxidant defense was manifested by a significant change in ceruloplasmin activity to 26.34±0.45 mg/dL in group I against 39.28±0.67 mg/dL before treatment, p<0.05. In group II, ceruloplasmin activity was 28.12±0.35 mg/dL versus 37.16±0.53 mg/dL before treatment, p<0.05. The level of catalase in group I was 12.13±0.32 mg H_2O_2 /ml versus 11.63±0.64 mg H_2O_2 /ml before treatment, p<0.05. At the same time, in group II, it was 12.16±0.44 mg H_2O_2 /ml versus 12.36±0.35 mg H_2O_2 /ml before treatment, p>0.05. There was a significantly lower level of leptin 13.37±0.4 ng/ml in group I against 26.6±1.34 ng/ml before treatment, p<0.05 and 15.4±0.5±0.4 ng/ml in group II against 27.2±2.47 ng/ml before treatment, p<0.05. At 26 weeks of gestation, placental growth factor levels were: in group I 655±8.8 pg/ml versus 638±11.8 pg/ml before treatment (p>0.05), and in group II 783.4±5.4 pg/ml versus 754.3±7.4 pg/ml before treatment, p>0.05. The level of glycemia decreased in pregnant women of both groups III and IV, but in group III it was significantly lower than in group IV, p<0.01. Due to changes in carbohydrate metabolism during treatment, insulin therapy was adjusted in pregnant women. In group III, up to 22 weeks, the insulin dose decreased by 16%, in group IV – by 4%, p < 0.05. At 23-38 weeks of pregnancy, the insulin dose in group III decreased by 3.2%, and in group IV it increased by 11%, p<0.05 (Table II).

Along with this, the level of malondialdehyde in group III decreased to 2.05±0.51 μmol/mL versus 3.11±0.25 μmol/mL before treatment, p<0.05. In group IV, the level of malondialdehyde decreased to 2.09±0.23 μmol/mL versus 3.19±0.19 μmol/mL before treatment, p<0.05. At the same time, the level of diene conjugates in group III decreased to 12.3±0.4 μmol/mL versus 22.4±0.5 μmol/mL before treatment, p<0.05. In group IV, the decrease in the level of diene conjugates reached 13.4±0.3 μmol/mL versus 25.5±0.2 μmol/l before treatment, p<0.05. Ceruloplasmin activity significantly changed to 29.67±0.34 mg/dL in group III against 43.32±0.24 mg/dL before treatment, p<0.05, and in group IV it was 27.21±0.37 mg/dL against 39.35±0.35 mg/dL before treatment, p<0.05. The level of catalase in group III was 13.06±0.41 mg H_2O_2 /ml versus 10.35±0.43 mg H_2O_2 /ml before treatment, p<0.05. At the same time, in group IV, it was 12.08±0.23 mg H_2O_2 /ml versus 11.93±0.32 mg H_2O_2 /ml before treatment, p>0.05. The content of placental growth factor in group III was 752±5.8 pg/ml versus 568±10.7 pg/ml before treatment (p>0.05), and in group IV 791.4±6.3 pg/ml versus 606.8±12.7 pg/ml before treatment, p>0.05. The level of leptin in groups III and IV after treatment did not differ significantly from the control group. After the treatment, the percentage of gestational hypertension, preeclampsia, preterm labor, abnormal labor activity, postpartum hemorrhage, fetal growth retardation syndrome, macrosomia, ges-

Table I. Changes in the indexes of malondialdehyde (MDA), diene conjugates (DC), ceruloplasmin (CP), catalase (C), placental growth factor (PGF), leptin (L) in preeclampsia

Index	Control group	I group		II group	
		Before treatment	After treatment	Before treatment	After treatment
MDA μmol/mL	2,21±0,11	3,25±0,45*	2,25±0,54°	3,29±0,34*	2,29±0,53°
DC μmol/l	9,5±0,3	24,3±0,3*	10,2±0,4°	26,8±0,2*	11,6±0,6°
CP mg/dl	22,41±0,97	39,28±0,67*	26,34±0,45°	37,16±0,53*	28,12±0,35°
C mg H2 O2 /ml	14,56±0,52	11,63±0,64*	12,13±0,32*°	12,36±0,35*	12,16±0,44*
PGF pg/ml	1102±15,8	638±11,8*	655±8,8*	754,3±7,4*	783,4±5,4*
L ng/ml	10,7±0,57	26,6±1,34*	13,37±0,4°	27,2±2,47*	15,4±0,5°

Note: * - significant difference of indexes compared to control group, p<0,05;
° - significant difference of indexes before and after treatment, p<0,05

Table II. Changes in the indexes of malondialdehyde (MDA), diene conjugates (DC), ceruloplasmin (CP), catalase (C), placental growth factor (PGF), leptin (L) in gestational diabetes

Index	Control group	III group		IV group	
		Before treatment	After treatment	Before treatment	After treatment
MDA μmol/mL	2,21±0,11	3,11±0,25*	2,05±0,51°	3,19±0,19*	2,09±0,23°
DC μmol/l	9,5±0,3	22,4±0,5*	12,3±0,4°	25,5±0,2*	13,4±0,3°
CP mg/dl	22,41±0,97	43,32±0,24*	29,67±0,34°	39,35±0,35*	27,21±0,37°
C mg H2 O2 /ml	14,56±0,52	10,35±0,43*	13,06±0,41*°	11,93±0,32*	12,08±0,23*
PGF pg/ml	1102±15,8	568±10,7*	752±5,8*	606,8±12,7*	791,4±6,3*
L ng/ml	10,7±0,57	12,6±0,43	11,4±0,15	9,7±1,71	10,3±0,8

Note: * - significant difference of indexes compared to control group, p<0,05;
° - significant difference of indexes before and after treatment, p<0,05

Table III. Changes in the indexes of malondialdehyde (MDA), diene conjugates (DC), ceruloplasmin (CP), catalase (C), placental growth factor (PGF), leptin (L) in obesity

Index	Control group	V group		VI group	
		Before treatment	After treatment	Before treatment	After treatment
MDA μmol/mL	2,21±0,11	3,09±0,13*	2,09±0,12°	3,12±0,9*	2,17±0,31°
DC μmol/l	9,5±0,3	19,4±0,7*	11,4±0,6°	21,5±0,6*	12,7±0,4°
CP mg/dl	22,41±0,97	33,12±0,34*	26,37±0,34°	36,31±0,4*	25,14±0,35°
C mg H2 O2 /ml	14,56±0,52	9,87±0,59*	12,26±0,21*°	10,25±0,42*	11,13±0,24*
PGF pg/ml	1102±15,8	538±8,7*	552±2,8*	706,8±9,7*	725,4±4,3*
L ng/ml	10,7±0,57	39,6±1,23*	14,13±0,2°	37,2±2,27*	15,3±0,6°

Note: * - significant difference of indexes compared to control group, p<0,05;
° - significant difference of indexes before and after treatment, p<0,05

tational diabetes decreased in obese pregnant women (group V) compared to pregnant women of group VI, p < 0.05 (Table III).

In addition, the results showed that obese women had significantly lower levels of leptin – 14.13±0.2 ng/ml in group V versus 39.6±1.23 ng/ml before treatment, p<0.05 and 15.3±0.6 ng/ml in group VI versus 37.2±2.27 ng/ml before treatment, p<0.05. The concentration of placental growth factor was: in group V – 552±2.8 pg/ml vs. 538±8.7 pg/ml before treatment, p>0.05, and in group VI – 725.4±4.3 pg/ml vs. 706.8±9.7 pg/ml before treatment, p>0.05. At the same time, the level of malondialdehyde in group V decreased to 2.09±0.12 μmol/mL versus 3.09±0.13 μmol/mL before treatment, p<0.05. In group VI, the level of malondialdehyde decreased to 2.17±0.31 μmol/mL versus 3.12±0.9 μmol/mL before treatment, p<0.05. At the same time, the level of diene conjugates in group V decreased to 11.4±0.6 μmol/mL versus 19.4±0.7 μmol/mL before treatment, p<0.05. In group VI, the decrease in the level of diene conjugates reached 12.7±0.4 μmol/mL versus 21.5±0.6 μmol/l before treatment, p<0.05. In addition, ceruloplasmin activity significantly changed to 26.37±0.34 mg/dL in group V versus 33.12±0.34 mg/dL before

treatment, p<0.05. In group VI, ceruloplasmin activity was 25.14±0.35 mg/dL versus 36.31±0.4 mg/dL before treatment, p<0.05. The level of catalase in group V was 12.26±0.21 mg H_2O_2/ml versus 9.87±0.59 mg H_2O_2/ml before treatment, p<0.05. At the same time, in group VI it was 11.13±0.24 mg H_2O_2/ml versus 10.25±0.42 mg H_2O_2/ml before treatment, p>0.05.

Thus, standard therapy contributed to a significant suppression of excessive lipid peroxidation activity with a simultaneous increase in the activity of the antioxidant system, except for catalase, which indicates both profound changes in free radical oxidation in moderate preeclampsia, obesity and gestational diabetes, and the difficulty of their correction, which actually led to the expediency of using the drug Tivortin. Compared with groups II, IV, VI, pregnant women in groups I, III, V had a 3-fold decrease in the incidence of complications in childbirth, a 2-fold decrease in surgical interventions, a 1.7-fold decrease in postpartum infectious complications, a 1.8-fold decrease in the incidence of infants born in asphyxiation, and a corresponding decrease in hospital stay, p<0.05. Doppler ultrasound of the umbilical cord vessels showed normalization of the systolic-diastolic ratio after the course of Tivortin therapy (from 3.84±0.04 to 3.1±0.06, p<0.01). In groups II, I V and VI, this indicator did not change significantly (from 3.72±0.04 to 3.51±0.04, p>0.05). Determination of the fetal biophysical profile and cardiotocography using the Dawes/Redman criteria and STV index indicate a significant improvement in the fetal condition in pregnant women after treatment with Tivortin compared to groups II, IV and VI, which is confirmed by a satisfactory assessment of newborns on the Apgar scale. The use of Tivortin therapy in the complex treatment of pregnant women with metabolic disorders significantly reduced the percentage of surgical deliveries compared to groups II, IV and VI due to a decrease in the number of indications for cesarean section on the part of both the fetus and the mother.

DISCUSSION

The problem of reproductive health of the population of Ukraine is urgent [7]. The complexity of solving the issues that define this problem is due not only to the direct state of health of the population of our country, but also to a significant number of risk factors that influence the development of their disorders. Metabolic disorders during pregnancy are associated with a higher risk of complications during childbirth, surgical delivery, with a higher risk of developing a number of postpartum complications, such as bleeding, deep vein thrombosis, and the development of infectious complications. In addition, the metabolic syndrome during pregnancy is a risk factor for the birth of children both underweight and pathologically overweight, which, in turn increases the risk of developing metabolic disorders in this group of children further in life, i.e. contributes to the implementation of a growth program that leads to diabetes mellitus, obesity, arterial hypertension, etc.

At the same time, it should be borne in mind that the results of each analysis should be optimally interpreted taking into account all relevant anamnestic, clinical, other laboratory and instrumental data, which allows to identify to detect pathology with greater reliability than each method alone. Moreover it is possible to use the data obtained for risk assessment, early diagnosis, severity of the pathological process diagnosis, severity of the pathological process and effectiveness of its treatment. Therefore, the main task of treating metabolic syndrome is to identify and correct entire spectrum of existing metabolic disorders and prevention of the development of obstetric and perinatal complications. Accordingly, the research topic is relevant and has a certain scientific novelty. The goal was fully achieved and the relevant conclusions were drawn. The results are reliable and original. The incidence of metabolic disorders in pregnant women is increasing every year, so it is important to study the pathogenetic mechanisms of this pathology in all possible manifestations, which will allow the development and implementation of a set of effective therapeutic and preventive measures to reduce obstetric and perinatal complications in a certain category of patients.

CONCLUSIONS

The presence of metabolic syndrome in women is a significant risk factor for the development of obstetric and perinatal complications due to the significant intensity of lipid peroxidation, severe depression of the antioxidant system, decreased placental growth factor content and increased plasma leptin levels. Determination of these indicators in the dynamics of observation and treatment can serve as an additional diagnostic and prognostic criterion for a satisfactory clinical course of pregnancy and the effectiveness of therapeutic measures aimed at correcting disorders. The results of the studies proved the safety and efficacy of Tivortin in the complex treatment of pregnant women with metabolic disorders, which improves the course of pregnancy, childbirth, fetal and neonatal condition.

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ORIGINAL ARTICLE

EARLY DIAGNOSIS OF ASYMPTOMIC CHRONIC ISCHEMIA OF THE LOWER EXTREMITIES

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ABSTRACT

The aim: To assess the possibility of using a questionnaire and determining the Ankle Brachial Index(ABI) for early diagnosis of asymptomatic ischemia of the lower extremities in patients with various somatic diseases.

Materials and methods: The study involved 294 patients who were receiving inpatient treatment at Communal Non-Profit Enterprise «Uzhgorod Central City Clinical Hospital»,Communal Non-Profit Enterprise «Transcarpathian Regional Clinical Hospital» and Communal Non-Profit Enterprise «Uzhgorod District Clinical Hospital». The study was conducted in 36 patients of pulmonological, 52 – neurological, 22 – endocrinological, 28 – rheumatological, 67 – general therapeutic and 89 – surgical patients. In order to detect hidden ischemia, the patients were surveyed according to the Edinburg questionnaire, regional systolic pressure was measured on the tibial arteries of the lower extremities and calculation of the Bone-humerus index (ABI)at rest and after physical exertion (walking), also non-contact skin temperature was measured on the lower leg and thigh.

Results: During the study, (ABI) less than 0.9 was found in 108 (36.7%) patients, while in 47 (43.5%) cases, (ABI) decreased only after exercise.In the majority of cases, 98 (90.7%) a decrease in (ABI) was observed on one lower limb. A decrease in the skin temperature of the lower extremities was observed in 141 (48%) patients, 134 (95.1%) of which were diagnosed with diabetes.Symptoms of hidden ischemia, according to the questionnaire, were found in 99 (33.7%) patients.Smoking was observed in 61 (56.5%) patients with symptoms of hidden ischemia.

Conclusions: As a result of our study, it was found that the specificity of the Edinburg questionnaire in detecting the preclinical stage of ischemia of the lower extremities reaches 88.2%, and the sensitivity – 91.6%. The obtained results indicate the expediency of using the questionnaire in the complex of diagnostics of vascular pathology in patients of various profiles. False-negative results of(ABI)in people with diabetes are associated with mediacalcinosis. In such cases, it is necessary to assess the state of blood flow by measuring the pressure on the back of the foot after physical exertion.

KEY WORDS: chronic ischemia, Ankle Brachial Index, Edinburg questionnaire, diabetes mellitus, atherosclerosis

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INTRODUCTION

Asymptomatic diseases of the arteries of the lower extremities (ASD) is a preclinical stage of chronic arterial damage that does not cause distinct clinical symptoms of chronic arterial insufficiency. In a large number of patients, the symptoms of the lower extremities are not typical – they belong to the asymptomatic group of patients [1-3]. This cohort currently includes patients with no classic signs of intermittent lameness(IL).It should also be understood that in a certain part of patients, the absence of (ABI)symptoms may be due to not so much to the absence of arterial damage as to low physical activity [2,3]. Despite the selection of asymptomatic patients with (ASD), many of them have discomfort in the limbs and other manifestations that can be obtained with the help of special questionnaires. In most cases, the main cause of the development of such conditions is obliterating atherosclerosis [4-6], which can be both a manifestation of the metabolic pentad and an independent disease [5-8]. Among other factors, it is worth noting obliterating thromboangiitis, nonspecific aortoarteritis, diabetic angiopathy [6-9].

With the progression of the asymptomatic form of vascular pathology, changes in the arteries become irreversible, clinical symptoms become sharply expressed, such complications as critical ischemiaand acute thrombosis occur, which require reconstructive surgical interventions, which often, in the absence of sufficiently developed collaterals, become "doomed" to further limb amputation, invalidation of patients , long-term immobilization and desocialization, severe psychological upheaval and the need for expensive rehabilitation [8,9,11].

That is why the question arises about the relevance of detecting vascular pathology of the lower extremities at the preclinical stage. In addition to the possibility of predicting the risk of various cardiovascular events in a complex with other diagnostic procedures, with early

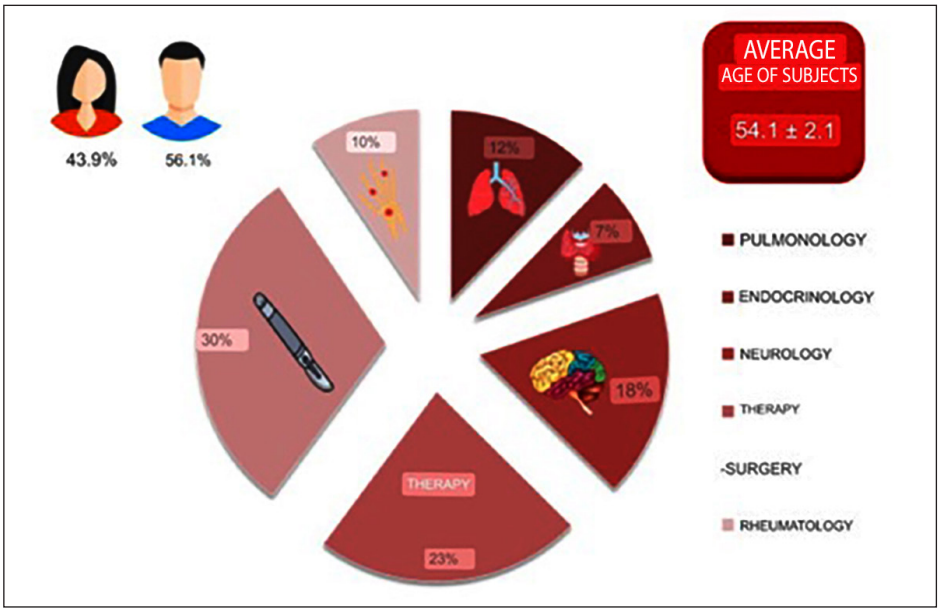


Fig.1. Research design

detection of (ASD), we can prevent the progression of the disease, the development of complications and the loss of an active, able-bodied representative to society, reduce the costs of expensive rehabilitation and resocialization of disabled patients [10-12].

THE AIM

To assess the possibility of using a questionnaire and determining the humeral index (ABI)for early diagnosis of asymptomatic ischemia of the lower extremities in patients with various somatic diseases.

MATERIALS AND METHODS

In the work, an analysis of the questionnaire and the results of the clinical examination of 294 patients with surgical and different therapeutic profiles was carried out. The subjects of the study were patients of the pulmonological (36), neurological (52), therapeutic (67), surgical (89), endocrinological (22) and rheumatological (28) departments who were being treated at the Transcarpathian Regional Clinical Hospital named after A. Novak, Uzhgorod City Central Clinical Hospital and Uzhgorod District Clinical Hospital, who were on inpatient treatment during 2019. The age of the patients ranged from 33 to 84 years. The average age was 54.1±2.1. (Fig. 1).

Among them, there were 165 (56.1%) men and 129 (43.9%) women.

The Edinburg questionnaire was used to examine patients. (Fig. 2).

In addition, several important questions were included that the researcher had to clarify:

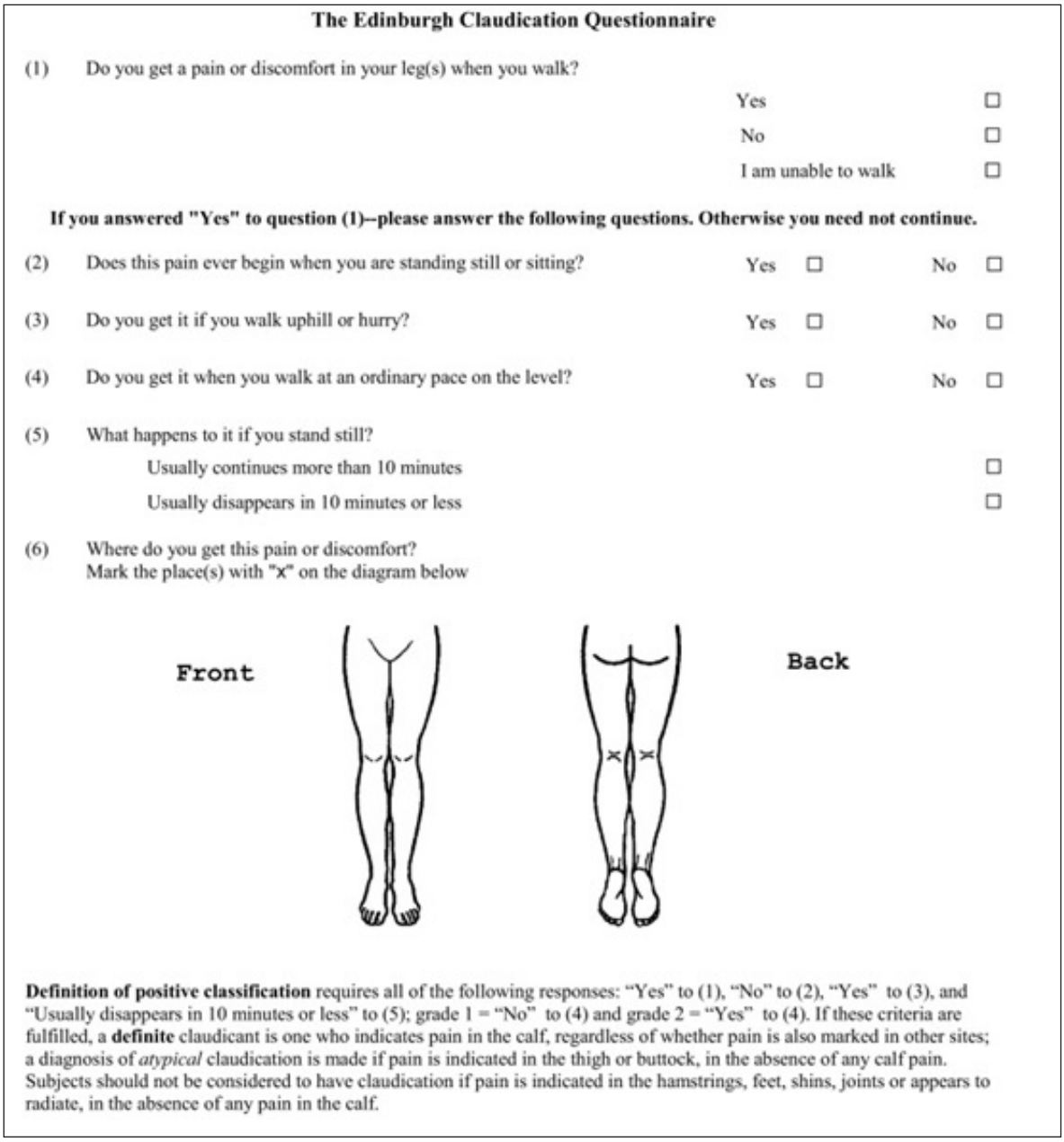
• Systolic blood pressure over the posterior tibial artery;
• Systolic blood pressure over the posterior tibial artery after exertion;
•Blood pressure;
• Bone-humeral index;
• Body mass index;
• T°C of the surface of the limbs was measured;

and also took into account the presence of comorbid pathologies: diabetes mellitus (DM), coronary heart disease, previous myocardial infarction, chronic kidney disease (CKD).

Pressure was also measured at the level of the shoulder (using a conventional tonometer) and lower leg (using a vascular Doppler sensorSonoTraxVascular 4Mhz). (Fig. 3). The Bone-humeral index was calculated at rest and after exercise.

As a physical effort, we offered the patients to walk along corridors of different lengths in order to reach the required mark of 100m. In patients with diabetes, in connection with possible mediacalcinosis and a decrease in the informativeness of (ABI) results obtained by the classical method, the pressure was measured at the level of the back of the foot.The Bone-humeral indexwas calculated. With the help of a Medica+ TERMOCONTROL non-contact infrared thermometer, the temperature was measured at different levels of the lower extremities (the measurement was carried out in three areas: the back of the foot, the leg, the thigh).

In the statistical processing of the research results and description of the sample, the average value (M), standard deviation of the average (SD) was used, and parametric criteria were used to compare two independent groups. differences at $p<0.05$ were considered statistically significant. The reliability of the difference of indicators represented by relative numbers was determined using Pearson's $\chi 2$ test.



The Edinburgh Claudication Questionnaire

(1) Do you get a pain or discomfort in your leg(s) when you walk?

Yes ☐
No ☐
I am unable to walk ☐

If you answered "Yes" to question (1)--please answer the following questions. Otherwise you need not continue.

(2) Does this pain ever begin when you are standing still or sitting? Yes ☐ No ☐

(3) Do you get it if you walk uphill or hurry? Yes ☐ No ☐

(4) Do you get it when you walk at an ordinary pace on the level? Yes ☐ No ☐

(5) What happens to it if you stand still?

Usually continues more than 10 minutes ☐
Usually disappears in 10 minutes or less ☐

(6) Where do you get this pain or discomfort?
Mark the place(s) with "x" on the diagram below

Definition of positive classification requires all of the following responses: "Yes" to (1), "No" to (2), "Yes" to (3), and "Usually disappears in 10 minutes or less" to (5); grade 1 = "No" to (4) and grade 2 = "Yes" to (4). If these criteria are fulfilled, a **definite** claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of *atypical* claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain. Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints or appears to radiate, in the absence of any pain in the calf.

Fig. 2. Questionnaire used during the research

RESULTS

125 (42.5%) patients were found to have chronic ischemia of the vessels of the lower extremities according to the Edinburg questionnaire. After calculating the (ABI) (with or without physical exertion) in 94 patients, the result was below the norm, which confirmed the pathology of the vascular bed (Figs. 4, 5).

In connection withthe fact that in patients withdiabetes mellitus(DM) due to mediacalcification, the results of (ABI) may be within the normal range, the level of glycosylated hemoglobin was taken into account. In 7 patients, the level of glycosylated hemoglobin was higher than 7%. Among patients with a normal (ABI), but with positive questionnaire data, diabetes mellitus was detected in 4 (80%) patients.In all these cases, the pressure at the level of the back of the foot after exercise was below thenorm, which confirmed the presence of asymptomatic compensated ischemic pathology. In 26 patients, in whom the survey was positive, the (ABI) at rest and during physical exertion was within the normal range. This made it possible to discard these patients and finally form the studied group.

Since the (ABI) was measured in all subjects of the examination, this indicator was below the norm in 9 patients, although the questionnaire data rejected vascular pathology. In this group of patients, there are signs of functional insufficiency of the vascular bed, which confirms the decrease in (ABI) after walking. The

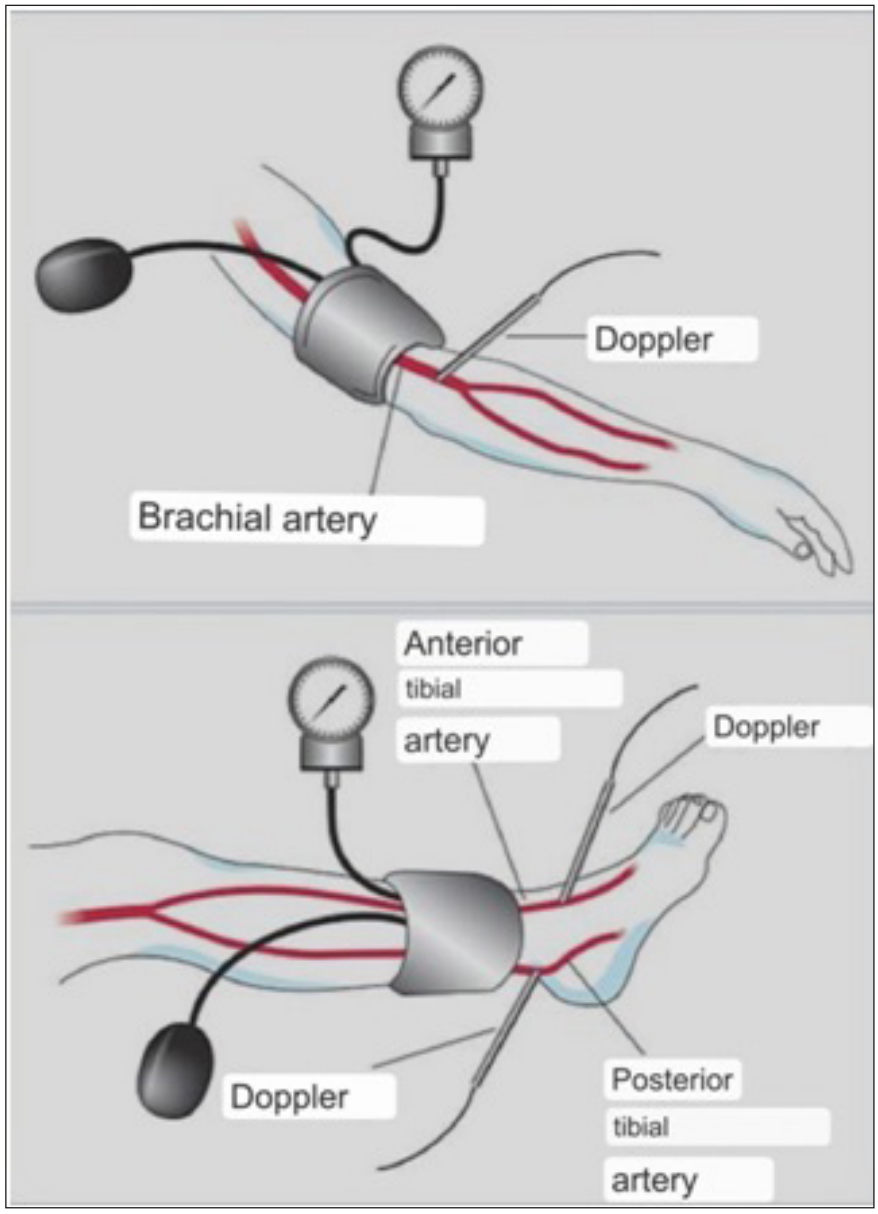


Fig. 3. Measurement of pressure on the arteries of the shoulder and lower leg

survey results themselves did not change after physical exertion in these patients.

Thus, the total number of examinees, in whom the data of the objective method of examination (ankle brachial index) showed hidden functional vascular insufficiency, is 108 patients, which is 36.7% of all surveyed patients (294). We can talk about the severity of ischemic manifestations thanks to the results of KPI measurement before and after physical exertion (dosed walking). In 15.7% of cases, a decrease in (ABI) was observed at rest (at the same time, the indicator did not fall below 0.8), in 84.3% of cases, the (ABI) was reduced only after physical exertion (at the same time, the indicator fluctuated between 0.9-0, 7 in different patients), which indicates a full compensation of the pathology, 68 patients (62.9%) with proven asymptomatic chronic ischemia were male, and 40 (37.1%) were female. In 91%, the decrease in (ABI) was isolated (on one leg).

In the comprehensive assessment of the studied group, 92.8% of the examined were found to have diabetes, signs and consequences of systemic atherosclerosis, BMI>30, or a combination of these pathologies. These results indicate a close and natural correlation between various metabolic disorders. 66.6% of the studied patients were smokers. More often it concerned male.Decreased temperature of the lower extremities was clinically insignificant. In another 33 patients, it was reduced with normal (ABI). Therefore, on the basis of this information, we can say that the sensitivity and specificity of non-contact temperature measurement on the limb for the diagnosis of vascular pathologies is very low.

As a result of our study, it was found that in 108 (36.7%) patients, was hidden ischemia of the lower extremities, without intermittent lameness. According to the survey, chronic ischemia was noted in 125 patients.

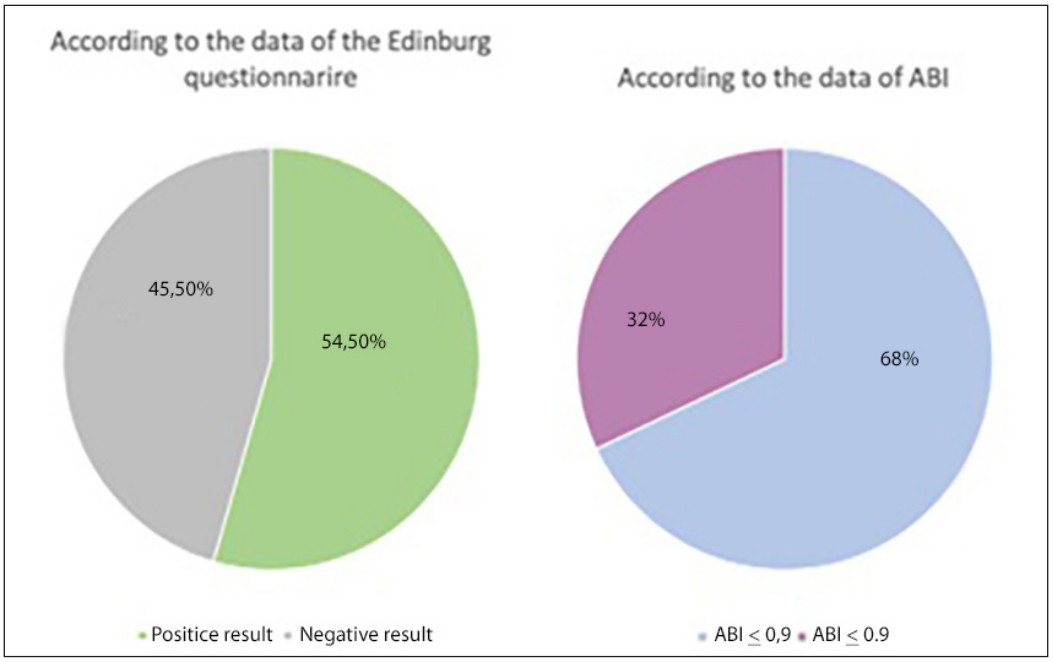


Fig. 4. Research results.

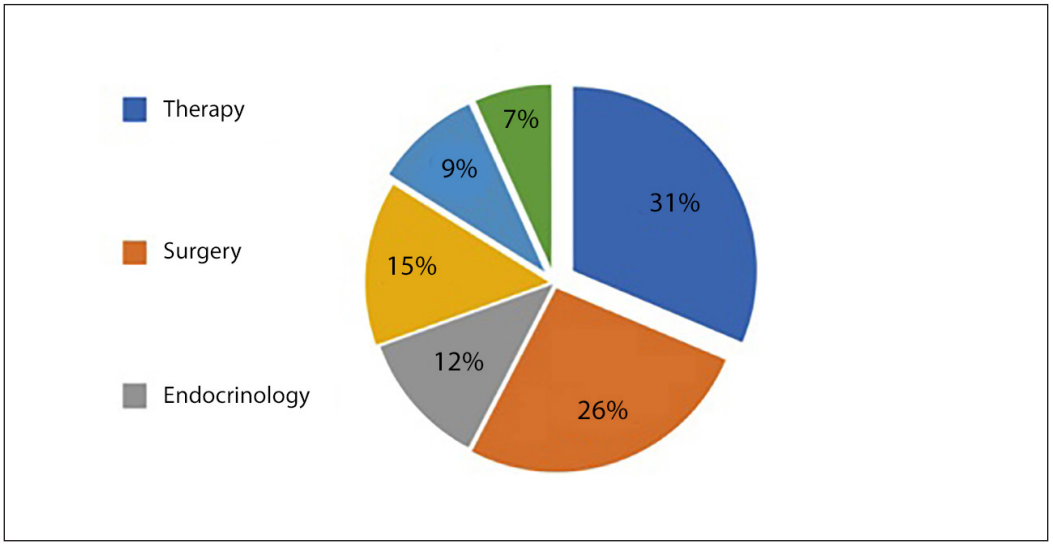


Fig. 5. Division of patients with chronic hidden ischemia of the vessels of the lower extremities by profile.

In another 9 patients, the diagnosis was confirmed by measuring the (ABI), as the questionnaire turned out to be false negative. The peculiarity of the questionnaire reaches 88.2%, and the sensitivity – 91.6%. The Edinburg questionnaire has confirmed its effectiveness in terms of primary non-instrumental detection of patients at risk groups.

Malepredominate among the studied group. In most of the research subjects, diabetes mellitus, obesity, signs and consequences of systemic atherosclerosis on the part of kidneys, eyes, arterial blood pressure or their combination were detected at the same time during the comprehensive examination. False-negative KPI results in people with diabetes are associated with mediacalcinosis. In such cases, it is necessary to assess the state of blood flow by measuring the pressure on the back of the foot.

A decrease in the indicator of the ankle brachial index in most cases was diagnosed after dosed physical activity. However, there was also a decrease in the KPI at rest, the value of which did not fall below 0.8.The majority of these patients had symptoms (or consequences) of systemic atherosclerosis. The tendency to the disease mainly in men is confirmed, which is connected with the hormonal background, habits (smoking) and working conditions. The measurement of temperature on the extremities of asymptomatic patients has not shown its reliability.

These results make it possible to talk about the possibility of introducing this questionnaire into the routine complex of pre-hospital assessment of vascular pathology in patients of various profiles. The progression of complications of vascular diseases leads to invalidation and socialization of patients, requiring the expenditure

of significant funds for treatment and rehabilitation. Therefore, the proposed method of evaluating all patients can reduce costs and reduce the incidence of vascular pathology in the population. These theses require further research to be confirmed or refuted.

DISCUSSION

The pre-clinical stage of chronic arterial damage is characterized by damage (most often atherosclerotic) of arteries without hemodynamically significant stenoses or with minor changes in regional hemodynamics, which is not manifested by a pronounced clinical picture of chronic ischemia of the lower extremities. [3,8,11]. A rather high frequency of combined affection of two or more arterial basins and the presence of other concomitant cardiovascular pathology, which can contribute to the deterioration of locomotor function and the appearance of symptoms on the part of the limb, are of important pathogenetic importance. [10,11]. The severity of symptoms may depend on the patient's level of physical activity. In addition, most of them have a low level of knowledge about peripheral artery disease and, as a result, may not tell you about their symptoms. A special group consists of patients with diabetes, who are in a very high risk group. All this requires the need to implement and use non-invasive methods of diagnosing the disease at the outpatient stage or during inpatient treatment of patients for other diseases, to actively identify patients with pathology of the arteries of the lower extremities in the early stages of the disease. [7-9,11].

Early diagnosis of asymptomatic ischemia of the lower limbs in patients with various somatic diseases, coverage of a wider cohort of examined patients makes it possible to detect a threat to the lower limbs in time and to offer the patient surgical treatment, revascularization of the lower limbs, which allows to stop ischemia of the limb, prevent necrotic processes and promotes the most effective healing of tissue defects. Assessment of vascular pathology at the pre-clinical stage significantly reduces costs for the treatment of patients and makes it possible to prevent the progression and complications of the disease [8,13,14].

CONCLUSIONS

1) As a result of our study, it was found that the peculiarity of the Edenburg questionnaire in detecting the preclinical stage of ischemia of the lower extremities reaches 88.2%, and the sensitivity – 91.6%.
2) The obtained results indicate the expediency of using the questionnaire in the complex of diagnostics of vascular pathology in patients of various profiles.
3) False-negative results of (ABI) in people with diabetes are associated with mediacalcinosis. In such cases, it is necessary to assess the state of blood flow by measuring the pressure on the back of the foot after physical exertion.

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ORIGINAL ARTICLE

DIFFERENTIATED CHOICE OF POSTERIOR METHODS OF DISCONNECTION OF ANATOMICAL COMPONENTS OF THE ABDOMINAL WALL IN COMBINATION WITH ALLOPLASTY IN POSTOPERATIVE VENTRAL HERNIAS OF GIANT SIZE

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ABSTRACT

The aim: The aim of the article is to increase the effectiveness of the treatment of postoperative ventral hernias of giant size by a differentiated approach to the selection of the posterior technique of dissection of the anatomical components of the anterior abdominal wall in combination with alloplasty.

Materials and methods: An analysis of the surgical treatment of 312 patients with giant postoperative ventral hernias (PVH). The main group consisted of 232 patients who underwent a differentiated approach to the selection of component separation in combination with alloplasty, taking into account intra-abdominal pressure (IAP) when simulating hernioplasty during surgery. In the second control group (80 patients), surgical treatment of PVH of giant sizes was performed using only the posterior Carbonell technique.

Results: In 78 patients of the 1st subgroup, IAP was 9.1±1.2 mm Hg. the posterior technique of separating anatomical components according to Carbonell was performed in combination with sublay alloplasty. In 80 patients of the II subgroup with IAP from 11.1 to 14.1±1.2 mm Hg – the TAR technique was performed with sublay alloplasty. In 74 patients of III subgroups with IAP from 16 to 20.1±1.2 mm Hg, performed the TAR technique, we improved in combination with IPOM alloplasty.

Conclusions: An increase in the effectiveness of surgical treatment was achieved in patients of subgroup I, reducing the probability of intra-abdominal hypertension to 5.1% versus 11.2%, in patients of subgroup II to 5% versus 11.2%, and in patients of subgroup III to 1.4% versus 11.2% of the control group.

KEY WORD: ventral hernia, CST, intra-abdominal pressure

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INTRODUCTION

Surgical treatment of postoperative ventral hernias of giant sizes is associated with the occurrence of intra-abdominal hypertension in the postoperative period. This is due to the displacement of the contents of the hernial sac, in particular the parts of the intestine and the large cap into the abdominal cavity and the closure of a large defect in the abdominal wall, which creates the prerequisites for intra-abdominal hypertension [1,2]. The occurrence of intra-abdominal hypertension of III and IV degrees, in particular with intra-abdominal pressure more than 20 mm Hg in the postoperative period can lead to abdominal compartment syndrome (ACS) [3-6]. In such cases, this complication can threaten the patient's life due to multiple organ failure, which requires urgent decompressive relaparotomy [7]. The introduction into the surgical treatment of postoperative ventral hernias of giant size of the posterior component separation techniques (CST) in combination with alloplasty contributes to an increase in the volume of the abdominal cavity and reduces the risk of an increase in IAP, but does not exclude the occurrence of intra-abdominal hypertension [8]. In our opinion, a differentiated approach to the selection of the posterior method of separation of anatomical components of the abdominal wall in combination with alloplasty based on monitoring of intra-abdominal pressure will contribute to reducing the probability of intra-abdominal hypertension and increasing the effectiveness of surgical treatment of postoperative ventral hernias of giant size.

THE AIM

To increase the effectiveness of the treatment of postoperative ventral hernias of giant size by a differentiated approach to the selection of the posterior technique of dissection of the anatomical components of the anterior abdominal wall in combination with alloplasty.

MATERIALS AND METHODS

An analysis of the surgical treatment of 312 patients with post-operative abdominal hernias of giant size, who underwent various options for dissection of the anatomical components of the abdominal wall in combination with alloplasty for the period from 2012 to 2021, was performed. The age of the patients was from 33 to 77 years (average age 56.4±1,3). There were 196 (62.9%) women, 116 (37.1%) men.

According to the classification of the European Hernia Society (EHS) [9], postoperative giant abdominal hernias were distributed as follows: $M_{1-4}W_3R_0$ – in 104 (36.2%), $M_{1-4}W_3R_1$ – y 39 (8.2%), $M_{1-5}W_3R_0$ – y 125 (45.3%), $M_{1-5}W_3R_1$ – y 44 (10.3%).

Most patients were diagnosed with concomitant chronic diseases in the stage of compensation, in particular: coronary heart disease in 184 (58.9%), hypertension in 195 (62.5%), varicose disease of the lower extremities in 42 (13.1%), type 2 diabetes in 21 (6.7%) and obesity I-II-III in 174 (55.7%).

The main group consisted of 232 patients with postoperative ventral hernias of giant size in which various variants of posterior methods of disconnection of anatomical components were performed in combination with alloplasty. Depending on the variant of the posterior CST the patients of the main group were divided into three subgroups. In subgroup I there were 78 patients who underwent the Carbonell technique in combination with sublay alloplasty [11,12]. In subgroup II there were 80 patients who underwent the TAR technique in combination with sublay alloplasty [13-15]. In the III subgroup, there were 74 patients who underwent improved TAR in combination with intraperitoneal onlay mesh (IPOM) alloplast [16].

The control group (retrospective) consisted of 80 patients with postoperative ventral hernias of giant size who underwent only the posterior method of dividing the anatomical components of the abdominal wall according to Carbonell in combination with sublay alloplasty [10,17].

In the patients of the main group, the choice of the option of the posterior method of separation of the anatomical components of the abdominal wall in combination with alloplasty was performed taking into account the IAP indicators during the operation during the contraction of the rectus abdominis muscles (hernioplasty simulation), with the implementation of exactly the method of operation that would create the optimal volume of the abdominal cavity and did not increase IAP. This approach to the selection of the option of the posterior CST was determined retrospectively on the basis of ICP monitoring during hernioplasty simulation during surgery, 6-24 hours and 48 hours after surgery.

To measure IAP intraoperatively and postoperatively, a Foley catheter and the UnoMeter Abdo-Pressure system were used [18]. A pubic fusion was considered a zero mark.

With IAP up to 10 mm Hg performed the posterior CST according to Carbonell with sublay alloplasty [10,17]. With ICP from 11 to 15 mm Hg – posterior t CST TAR with sublay alloplasty. [12-15]. At IAP 16 mm Hg and more performed the TAR technique improved by us in combination with IPOM intra-abdominal alloplasty, in which a mesh implant with an anti-adhesive coating was fixed along the perimeter to the mobilized edges of the transverse muscles and to the edges of the rectus muscles with their dosed reduction, creating an optimal volume of the abdominal cavity. The use of an intra-abdominal mesh implant made it possible to regulate the closure of the abdominal cavity without increasing IAP [16].

The criterion for evaluating the choice of the posterior method of dissection of anatomical components in combination with alloplasty was the monitoring of ICP during the erection of the rectus muscles during the operation, immediately after the operation, after 6-24 hours, and 48 hours after the operation. In addition to assessing the level of intra-abdominal hypertension, the frequency of local postoperative complications from the postoperative wound in the early postoperative period was assessed. The frequency of recurrences of PVH was assessed in the period from 6 to 36 months after the operation by means of repeated examinations of the ultrasound examination of the abdominal wall and questionnaires. The above-mentioned results were compared with the retrospectively obtained results of the control group.

RESULTS

The results of IAP monitoring and selection of the method of posterior CST technique in patients of the main group, in particular subgroups I, II and III with giant PVHs are shown in Table I.

The obtained results of IAP monitoring in the main group of patients with giant size PVH showed that the initial level of IAP before surgery was within 3.1±0.2, which corresponded to the norm. IAP indicators during the operation when simulating hernioplasty by contact contraction of the rectus muscles varied from 9.1±1.2 to 20.1±1.2 mm Hg. According to ICP indicators during surgery, when simulating hernioplasty by contracting the rectus muscles, subgroups of patients were created who underwent various variants of posterior techniques for dissociating anatomical components of the abdominal wall in combination with alloplasty. Thus, in 78 patients of the I subgroup

with an IAP of 9.1±1.2 mm Hg the posterior method of dissociation of anatomical components according to Carbonell was performed in combination with sublay alloplasty [10,17]. In 80 patients of the II subgroup with IAP from 11.1 to 14.1±1.2 mm Hg – the TAR technique was performed in combination with alloplasty sublay [12,13,14,15]. In 74 patients of the III subgroup with IAP values from 16 to 20.1±1.2 mm Hg performed the TAR technique we improved in combination with IPOM alloplasty. The essence of the improved technique was that, after cutting the transverse muscles, a mesh with an anti-adhesive coating (Paritex composite) of appropriate sizes was placed intra-abdominally along the edge of the internal oblique muscles. The musculo-aponeurotic edges of the defect above the mesh were dosed and sutured to the mesh so that IAP did not exceed 5 mm Hg [16].

After surgery, a slight increase in IAP was noted in patients of subgroups I, II and III. After 6-24 hours, among patients of the 1st subgroup, in particular, in 74 (94.9%) IAP was 9.1±1.3 mm Hg, and in 4 (5.1%) the average values of IAP were 15.1±1.3 mm Hg. In patients of the II subgroup, after 6-24 hours in 76 (95%) IAP was 8.2±1.3 mm Hg. Among these patients, 4 (5%) had grade II intra-abdominal hypertension of 16.2±1.3 mm Hg.

Intra-abdominal hypertension of I and II degrees of severity among patients of subgroup I (after the Carbonell technique) and subgroup II (after the TAR technique) was caused not only by a slight decrease in the volume of the abdominal cavity, but also by pronounced intestinal paresis. This fact is confirmed by literature data [6]. After epidural anesthesia, drug and mechanical stimulation of the intestines, the passage was restored, which led to a decrease in IAP. Within 48 hours after the surgical intervention in the I and II subgroups of patients, IAP indicators approached the norm and were comparable among themselves.

Among the patients of the III subgroup (improved TAR with IPOM alloplasty), 6-24 hours after the operation in 73 (98.6%) IAP was 7.1±1.3 mm Hg. Only 1 (1.4%) had an increase in IAP to 14.1±1.3 mm Hg which was caused by intestinal paresis. After conservative treatment and elimination of paresis after 48 hours, IAP was 5.7 mmHg.

In 80 patients of the comparison group, in which only the Carbonell technique was performed, with a retrospective assessment of postoperative results, it was shown that 9 (11.2%) patients were diagnosed with intra-abdominal hypertension of varying degrees of severity, in particular, 2 patients had III-degree intra-abdominal hypertension. Among them, 8 (10%) patients had intra-abdominal hypertension eliminated by conservative measures. In 1 (1.2%) patient with an ICP of 25.1±1.2 mm Hg decompressive relaparotomy was performed [7].

The statistical assessment of the intra-abdominal hypertension difference between the control group in comparison with the III subgroup is statistically significant – Pп-III=0.013, in subgroups I and II there is a tendency towards better results Pп-I=0.636, Pп-II=0.148 relative to the comparison group.

As for complications from the postoperative wound, among the patients of subgroup I, seroma of the postoperative wound was observed in 8 (10.2%) patients, suppuration of the postoperative wound in 2 (2.5%) and necrotic changes of the skin edges of the wound in 2 (2.5%).

In the II subgroup of patients: seroma – in 10 (12.5%), infection of the postoperative wound – in 2 (2.5%), necrosis of the skin edges of the wound – in 2 (2.5%).

In the III subgroup of patients: seroma – in 6 (11.8%), infection of the postoperative wound – in 1 (1.9%), necrosis of the skin edges of the wound – in 1 (2.0%). Among the patients of the comparison group, seroma of the postoperative wound was observed in 10 (12.5%) patients, suppuration of the postoperative wound in 3 (3.8%), necrotic changes in the skin edges of the wound in 3 (3.8%).

The difference between the subgroups in the frequency of complications is not statistically significant: seroma – p(I-II-III) =0.818; infection of the postoperative wound – p(I-II-III) =0.846; necrosis of the skin edges of the wound – p(I-II-III)=0.846.

Long-term results were studied in 52 (66.6%) patients of subgroup I, 50 (62.5%) of subgroup II and 51 (68.9%) patients of subgroup III and in 80 patients of the comparison group.

Recurrences of postoperative hernias were observed in 4 (5.1%) patients of subgroup I after the Carbonell technique, in 3 (3.8%) patients of subgroup II after the TAR technique, and in 1 (1.3%) relapse in patients of subgroup III after improved TAR, p(I-II- III) =0.407.

Among the comparison group, relapses were found in 10 (12.5%) patients, which is statistically significantly higher than the frequency of relapses in subgroup III (p=0.033) and in subgroup II (p=0.043).

The reason for recurrences of PVH in patients was infection of the postoperative wound and detachment and migration of the mesh implant.

A comparison of the treatment results of the study groups with the comparison group is shown in Figure 1.

The obtained results demonstrate a statistically significant ($p<0.05$) reduction in the relative risk of recurrence in the III subgroup by 90% (OR=0.10) and by 73% in the II subgroup (OR=0.27). According to other indicators of postoperative complications,

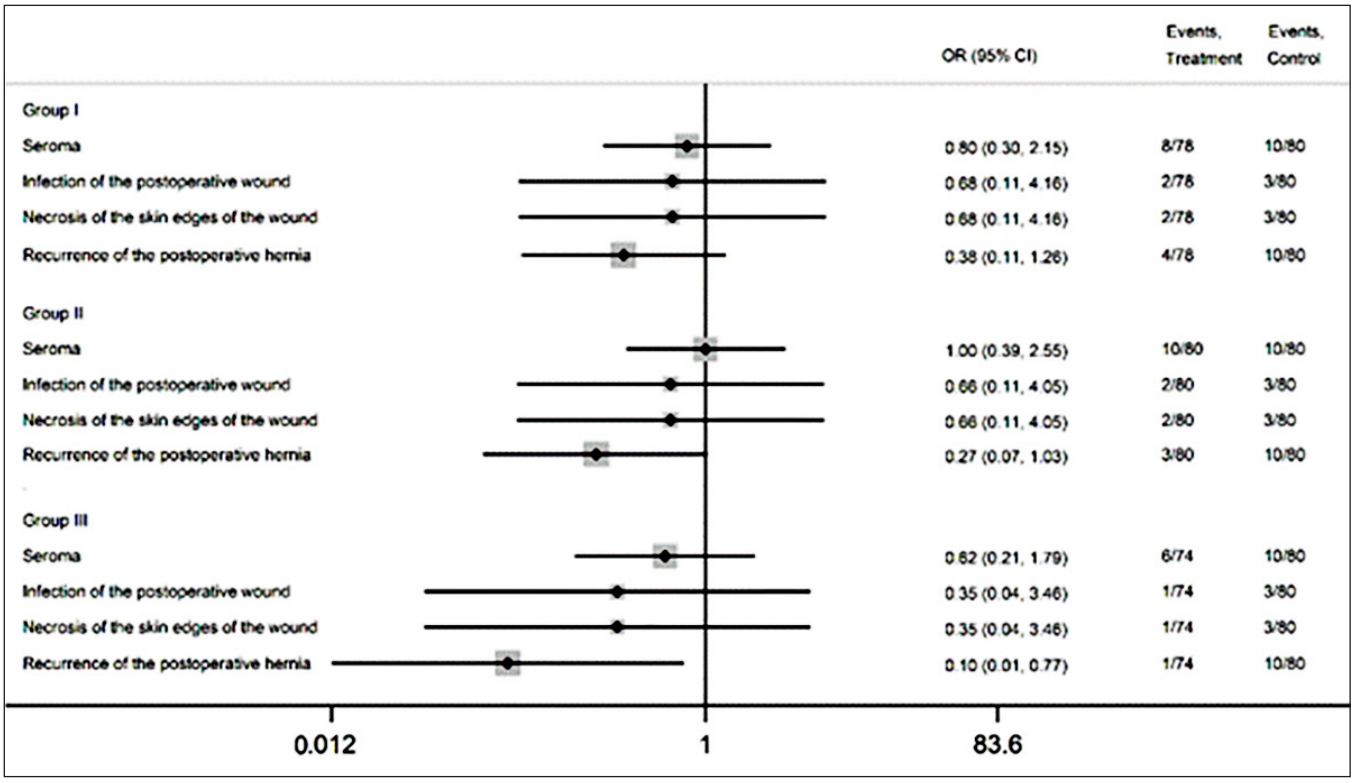

Fig. 1. Evaluation of the relative risk of postoperative complications in subgroups of the study in comparison with the comparison group – estimation of the odds ratio and 95% confidence interval, OR (95%CI).

the decrease in the relative risk of complications is not statistically significant, but it shows a tendency to decrease the probability of complications in the subgroups of the study from 20% to 32% (OR= 0.68-0.80) in subgroup I, from 0% to 34% (OR= 0.66-1.0) in subgroup II, and from 38% to 71% (OR=0.29-0.62) in subgroup III.

DISCUSSION

When comparing the results of the differentiated method selection in the patients of the main group with the control group, it was convincingly established that the differentiated approach to the selection of the posterior technique for the separation of the anatomical components of the anterior abdominal wall in combination with

Table I. IAP monitoring in patients of the main group who are divided into I, II and III subgroups with PVH of giant size (n=232).

Subgroups of patients and methods of operations	The initial IAP level before the operation was mm Hg	IAP during surgery in the simulation of hernioplasty during contact contraction of the rectus muscles, mm Hg	IAP immediately after surgery, mm Hg	IAP 6-24 hours after surgery, mm Hg		IAP 48 hours after surgery, mm Hg
I Carbonell method (n=78)	2,9±0,6	9,1±2,2	5,3±1,2	n=74(94.9%) 9,1±1,3	n=4(5.1%) 15,1±1,3	6,1±1,6
II TAR method (n=80)	3,0±0,7	12,6±2,4 (11,1- 14.1)	5,1±1,2	n=76(95%) 8,2±1,3	n=4(5%) 16,1±1,3	6,2±1,7
III Improved TAR method (n=74)	3,1±0,7	18,1±2.2 (16.1- 20.1)	5.1±1,2	n=73(98.6%) 7,1±1,3	n=1(1,4%) 14,1±1,3	5,7±1,3
P (I-III)	P(t)=0,060	P(t)=0,0001*	P(t)=0,290	P (x2)=0,192*		P(t)=0,061
P (II-III)	P(t)=0,374	P(t)=0,0006*	P(t)=0,990	P (x2)=0,202		P(t)=0,708
P (I-II)	P(t)=0,339	P(t)=0,0003*	P(t)=0,990	P (x2)=0,971		P(t)=0,706

Note. P(t) – score according to the t-criterion, P(x2) – score according to the Chi-squared criterion when control groups according to the frequency of detection of intra-abdominal hypertension (6-24 hours); * - the difference between the groups is statistically significant ($p<0.05$). Mean IAP values are presented as arithmetic mean and standard deviation (M±SD).

alloplasty in patients with PVH of giant size by measuring IAP during surgery during the erection of the rectus muscles have significant advantages over the performance of only the posterior method according to Carbonell without taking into account IAP indicators [10]. It is this approach to the selection of the posterior CST in the case of giant PVHs with IAP monitoring that significantly reduces the likelihood of intra-abdominal hypertension.

When comparing the results of IAP monitoring among patients of the I, II and III subgroups in the postoperative period, the most effective was the improved TAR technique, which allows more rational closing of the abdominal cavity in combination with alloplasty and minimizes the risk of intra-abdominal hypertension, which was confirmed by its occurrence only in 1(1.4 %) of the patient [11,12,17].

Taking into account the results of the study, it can be stated that the differentiated choice of the posterior technique helps to reduce the number of postoperative complications and reduces the frequency of relapses when compared with the comparison group.

This approach to the selection of the posterior method of disconnection of the anatomical components of the abdominal wall should be used by surgeons for the treatment of postoperative hernias of giant size.

CONCLUSIONS

1. A differentiated approach to the selection of the posterior method of component separation in combination with alloplasty in the case of giant-sized PVH, taking into account the IAP during surgery in the simulation of hernioplasty (adduction of the rectus muscles), increases the effectiveness of treatment in comparison with the traditional choice, namely in patients of the 1st subgroup reduces the probability of intra-abdominal hypertension to 5.1% versus 11.2%, in II subgroup patients to 5% versus 11.2%, and in III subgroup patients to 1.4% versus 11.2% of the comparison group.
2. The use of the advanced posterior component separation technique in combination with the IPOM technique ensures the optimal volume of the abdominal cavity, minimizes the likelihood of intra-abdominal hypertension and the need for decompressive relaparotomy.

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ORIGINAL ARTICLE

T-CRITERION AS A TOOL FOR DETERMINING THE RISK OF COMPLICATIONS OF THE GESTATIONAL PROCESS

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ABSTRACT

The aim: To conduct analyses of the course of the gestational process of women who contracted acute hepatitis A before pregnancy in order to predict and prevent obstetric complications and the possibilities of using the t-test for this.

Materials and methods: Clinical and statistical analysis of 500 gestational processes of women who suffered from acute hepatitis A before pregnancy, of which 100 cases were included in the main study by randomization.

Results: All pregnant women were divided into two groups – with obstetric complications during childbirth and without pathological obstetric changes during childbirth. Based on the analysis of 54 factors, the 8 most significant factors were selected in order to predict the occurrence of obstetric complications in childbirth for women who had hepatitis before pregnancy.

Conclusions: this method can be used as a marker of the success of treatment and prevention measures in any field of medical science.

KEY WORDS: hepatitis, prognosis, complications, pregnancy

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INTRODUCTION

Despite the achievements of medicine and the constant introduction of new medical technologies into practice in order to control infectious processes, viral hepatitis is a significant cause of increased morbidity and mortality [1-5]. Despite that hepatitis A /HA/ is an infection, which is vaccine-preventible, there are 1,4 million new cases globally occur annualy [6]. This amount of a cases of a newly diagnosed HA infection is lower in high-income countries. On the other hand poor hygienic conditions, lack of clean drinking water, malnutrition that are common for low-icome countries lead to rapid spread of the disease [7].

At the same time, the development and implementation of new methods of prevention and treatment is always accompanied by a number of issues related to both the integral assessment of the effect of pharmaceuticals (or other means) on the main pathological process and on accompanying complications. Indeed, when analyzing statistical data regarding the specific results of treatment approaches, one can always find significant positive shifts, but also minor or even negative outcomes. Even more difficult questions arise when comparing the effects of different drugs (methods), especially if there is no quantitative assessment of the severity of the patients' condition. In other words, there is an urgent need to create a relatively simple method for comparing therapeutic and preventive means and assessing the risks of complications during the gestational period.

We suggest using the t-test for such problems. The logical basis for its use is that the quantitative value of this criterion is proportional to the distance between the compared indicators. On the other hand, taking into account the statistical error makes it possible to avoid random changes in the selected indexes. Accordingly, the use of the additive function can provide a comprehensive description of the clinical situation.

THE AIM

Monitor the impact of hepatitis A, which has been overcome in the past, on the course of pregnancy, childbirth, and the postpartum period and the early neonatal period of their newborns in order to predict and prevent obstetric complications and the possibilities of using the t-test for this.

MATERIALS AND METHODS

A comprehensive examination of 500 convalescent women with hepatitis A (HA) was conducted, of which

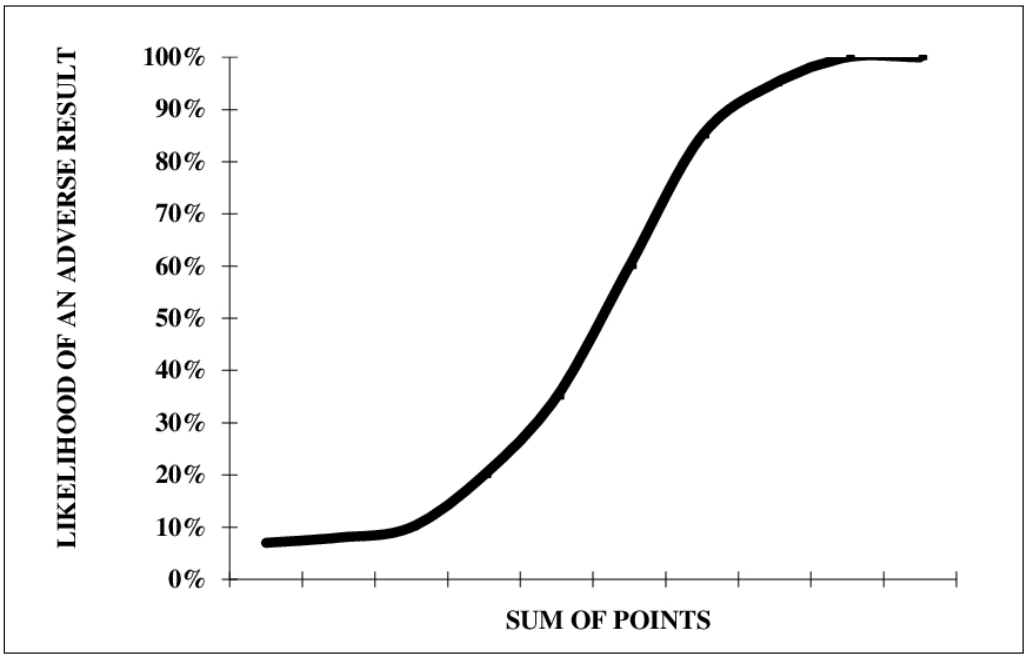

Fig. 1. General view of the dependence of the probability of an adverse outcome on the sum of risk points

100 cases were included in the main study by randomization along with an analysis of the condition of their babies in the early neonatal period and 100 somatically healthy women and their newborns.

Groups of women are homogeneous in age, social status (women are married), to a certain extent in specialty (housewives, or work in a profession not related to physical exertion and contact with teratogenic substances), live within the same time zone and conditions temperate continental climate.

Statistical processing of the observation results was carried out using the Statistika and Excel software packages. To calculate the prognostic significance of signs, the Student's criterion in the modification of N.M. Amosov and co-authors (1975) was used. This relatively simple approach assumes statistical independence of signs (symptoms and syndromes) that are used to describe the nature of the disease.

The essence of the methodology is to compare the frequency of an unfavorable result in patients with the investigated symptom (P1) with the average frequency of an unfavorable result in all patients examined for this indicator (P0). The corresponding mathematical value has the following form:

$$t = \frac{P_1 - P_0}{\sqrt{m_1^2 + m_0^2}}$$

where t is the "weight" of the feature (in points); m1 and m0 are average errors of P1 and P0 values.

In accordance with the formula, the parameter t was calculated for each symptom, and only positive characteristics of prognostic importance of the symptom were taken into account (that is, only risk factors). For further use, those clinical signs were taken for which the values of the t criterion were greater than one. In the case of a small number of observations, insufficient for a statistically reliable conclusion, expert assessments were again used.

At the next stage, the relationship (correlation) of the selected parameters was checked. With a correlation coefficient of $r \geq 0.7$, two parameters were replaced by a generalized one or one of them was chosen in order to avoid overestimating the prognostic importance of a set of features. If $0.3 < r < 0.7$, then to reduce the error, attention was paid only to the extreme values of each of the indicators, compared with the possible value of the other. If $r < 0.3$, the parameters were considered uncorrelated.

The most significant indicators were combined into a risk map.

Experimental verification of the risk map was carried out on the basis of three samples:

1) On the so-called "training" sample (observations with verified conclusions), which was used to assess the prognostic significance of clinical indicators;
2) The control sample, which also combined observations with verified conclusions, but which were not included in the training sample;
3) "Examination" selection of medical histories (the truth of the conclusions was checked by observations).

At the last stages, the dependence between the sum of points characterizing the condition of the patients and the probability of an adverse outcome was determined, as well as the degrees of risk were substantiated. The relationship between the sum of points, which characterizes the condition of patients, and the probability of

Table I. Prognostic significance of factors that determine obstetric complications during childbirth in women who contracted GA before pregnancy

№	Factor	Number of observations	Result			Average frequency of adverse results, %	Meaning, points
			Good	Bad			
			persons	persons	%		
1	Suffering from HA less than 1 year before pregnancy	18	6	12	66,7	32,0	2,25
2	The threat of late spontaneous abortion	19	8	11	57,9	32,0	1,55
3	Obesity	2	0	2	100,0	32,0	1,44
4	Suffering from HA more than 10 years before pregnancy	2	0	2	100,0	32,0	1,44
5	Age from 26 to 30 years	28	13	15	53,6	32,0	1,29
6	Anemia during pregnancy	15	7	8	53,3	32,0	1,16
7	Spontaneous miscarriage in the anamnesis	10	4	6	60,0	47,5	1,16
8	Threat of spontaneous abortion	11	5	6	54,6	32,0	1,02

Table II. Dependence of the probability of obstetric complications in pregnant women who are convalescents of hepatitis A from degree of risk

Degree of risk	Total points	Number of obser-vations	Result			Average theoretical frequency of adverse results, %
			Good	Bad		
				persons	%	
I	< 2,0	63	55	8	12,7	< 15,9
II	2,0-4,0	30	13	17	56,7	56,7
III	4,1-6,0	6	0	6	100,0	100,0
IV	> 6,0	1	0	1	100	100,0
Overall		100	68	32	32,0	

an adverse outcome, as a rule, was non-linear and most often had an S-shaped character.

For an integral assessment of complications, complications of the gestational process, which are the most significant in the opinion of the obstetrician, were identified and systematized:

- during pregnancy – threat of spontaneous miscarriage, threat of late spontaneous miscarriage, threat of premature birth, early toxicosis, gestational edema, preeclampsia, pyelonephritis, placental insufficiency, anemia, acute respiratory viral infections, drug addiction;
- during childbirth and the postpartum period – premature birth, delayed pregnancy, rapid childbirth, weakness of labor forces, inefficiency of labor induction, labor induction, labor augmentation, prenatal and early fusion of amniotic fluid, defect of the placenta and/or membranes, manual or instrumental revision of the uterine cavity, hypotonia , hyperthermia, anemia, postpartum endometritis, lochiometra, oligohydramnios and polyhydramnios, green or meconium amniotic fluid;
- regarding the condition of the fetus – antenatal death, asphyxia, cephalohematomas, clavicle fracture, acute ischemic damage of the central nervous system, hyporeflexia, respiratory disorders syndrome, cyanosis, intrauterine hypotrophy, prematurity, immaturity, hemolytic or conjugation jaundice, withdrawal syndrome and Erb's paresis.

RESULTS

All pregnant women were divided into two groups:

- with obstetric complications during childbirth;
- without pathological obstetric changes during childbirth.

Based on the analysis of 54 factors, the 8 most significant factors were selected in order to predict the occurrence of obstetric complications in childbirth for women who had hepatitis A before pregnancy. As in the previous groups, the factors that are easy to observe and accessible to a doctor even in the conditions of a women's consultation were selected (Table I).

In the table is shown only factors with positive values, i.e., those that increase the likelihood of obstetric complications during childbirth in women who had hepatitis A before pregnancy. A number of signs listed in the table rarely occurred. However, their clinical importance is not in doubt; the value in points was determined using heuristic evaluation.

In the future, in the process of dispensation or for short-term forecasting, indicators of prognostically important signs (points) were added. Given the danger of incorrectly increasing the sum of points due to the use of closely related factors, correlations between selected clinical indicators were checked. It turned out that there is no significant relationship between them (in no case did the correlation coefficient exceed 0.3).

As can be seen from the obtained results, the main number of risk factors is consistent with the data of other

scientists, which mainly characterize the period from hepatitis disease to the onset of pregnancy (less than one year) and the presence of extragenital pathology (obesity, anemia). It is unexpected to get into the factors that determine the occurrence of obstetric complications, the suffering of hepatitis A 10 or more years before pregnancy. Threats of termination, in particular, the threat of spontaneous abortion and late spontaneous abortion, play an important role in predicting the pathology of childbirth.

For practical convenience, in the process of predicting the course of childbirth in pregnant women who are convalescing, hepatitis A identified four degrees of probability of an adverse outcome:

- I degree – the sum of points is less than 2.0;
- II degree – 2.0-4.0 points;
- III degree – 4.1-6.0 points;
- IV degree – > 6.0 points.

By adding the indicators of the signs of each pregnant woman, the total number of points was determined. The division of women depending on the sum of points is shown in the table II.

A statistically significant increase in the probability of adverse outcomes was noted as the degree of risk increases (Fig. 1).

DISCUSSION

The results of the study are consistent with the data of other scientists that the combination of hepatitis with the gestational process leads to an increase in the frequency of complications [8-11].

Along with it, the course of the gestational process in convalescents was not studied, since it is believed that the long-term impact of hepatitis A on the course of pregnancy, childbirth, the postpartum period and the early neonatal period of newborns from mothers who contracted this type of acute viral hepatitis before the onset of pregnancy is unlikely.

The analysis of the gestational process in women who contracted acute viral hepatitis A before pregnancy showed that for them there is a statistically significant increase in the frequency of acute respiratory viral infections, rapid childbirth, pyelonephritis during pregnancy and early confluence of amniotic fluid during childbirth itself.

The probability of occurrence of obstetric complications is statistically likely ($p<0.05$) to increase as the degree of risk increases. At the I-st degree of risk, the probability of obstetric complications does not exceed 15.9%, while at the II-nd degree it reaches 56.7% ($p<0.05$). Such a sharp increase in the probability of complications during childbirth in women who had hepatitis A before pregnancy indicates the need to find additional risk factors to ensure a smoother increase in the integral risk of complications. On the other hand, it can be argued that the definition of II, and even more so III or IV degree of risk requires the mandatory use of preventive measures in the system of providing medical care to women suffering from HA.

CONCLUSIONS

In our opinion, this method can be used as a marker of the success of treatment and prevention measures in any field of medical science.

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ORIGINAL ARTICLE

BLOOD COAGULATION DISORDERS IN PATIENTS WITH LIVER CIRRHOSIS INFECTED COVID-19

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ABSTRACT

The aim: To investigate the features of coagulation homeostasis in patients with liver cirrhosis (LC) in COVID-19 infection.

Materials and methods: At the clinical base of the Department of Propaedeutics of Internal Medicine, 32 patients with LC infected with COVID-19 were examined – 1 Group of patients. The study also included 30 patients with LC who were not infected with COVID-19 (2 Group of patients).

Results: The analysis of the obtained data indicates disorders of the hemostasis system in patients with LC without the COVID-19 infection (Group 2), as well as in patients with LC at the time of being infected with COVID-19. The violation of the protein synthesis function of the liver is manifested through a decrease in the level of fibrinogen in blood serum (up to 2.0±0.5 gr/l in patients of Group 1 at the time of admission for inpatient care) and up to 21.9±0.5 gr/l in patients of group II – $p<0.05$. This was accompanied by an acceleration of prothrombin time, thrombin time and activated partial thromboplastic time in patients with LC, as well as an increase in the level of antithrombin III. The level of D-dimer was reduced both in patients of group II and in patients of group I at the time of being infected with COVID-19

Conclusions: Changes in coagulation homeostasis characteristic of hypocoagulation syndrome have been established in patients with LC. COVID-19 infection in patients with LC leads to hypercoagulation, especially in patients with complicated stage of LC (ascites, encephalopathy, hepatorenal syndrome).

KEY WORDS: liver cirrhosis, COVID-19 infection, coagulation homeostasis

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INTRODUCTION

Chronic liver disease (CLD) is marked by the gradual destruction of liver parenchyma over time. Various factors cause it; the most common are alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), chronic viral hepatitis, and genetic and autoimmune causes. Understanding the conditions that lead to severe disease and death among COVID-19–infected people is critical with the evolving pandemic [1].

The global COVID-19 pandemic, which has lasted for more than a year, has led to significant advances in the diagnosis, prevention and treatment of infected patients, promoting the increase in survival rates and the decrease in disabling complications. At the same time, patients having suffered from the coronavirus infection demonstrate the exacerbation and chronic progression of diseases, the emergence of new cases of cardiovascular and metabolic pathology [2, 3].

COVID-19 infection highlights the pre-existing weaknesses of the individual organ systems, making it logical to postulate that people with CLD may be susceptible to more severe respiratory infections or be at increased risk of death. In addition, it has been proposed that metabolic-associated fatty liver disease (MAFLD) or NAFLD is associated with significant or advanced fibrosis that might exacerbate the "cytokine storm" induced by the COVID-19 infection. The mechanism behind this is probably through the release of various proinflammatory hepatokines, which might contribute mechanistically to developing a severe form of COVID-19 infection. Several studies have found that hospitalized COVID-19 patients with CLD had an acute rise in liver enzymes, which results in a severe condition requiring mechanical ventilation and even leading to death. Existing evidence on COVID-19 outcomes among CLD patients has reported mixed results, making it difficult to determine a prognosis for these patients [4].

Thus, the study of the specifics of changes in the organs and systems of COVID-19 infected patients with chronic diffuse liver damage including cirrhosis of the liver is a particularly urgent task of contemporary medicine in the conditions of the pandemic caused by this virus. Debatable remain questions regarding the tactics of conducting medical actions with patients who feature changes in the blood coagulation system occurring when a patient suffers from liver cirrhosis and yet is infected with the COVID-19 virus. Therefore, the study of the specifics of coagulation homeostasis can

provide an answer regarding the tactics of treatment of these patients to prevent the formation/progression of liver cirrhosis (LC) complications.

THE AIM

The aim of the research is to investigate the features of coagulation homeostasis in patients with LC in COVID-19 infection.

MATERIALS AND METHODS

Comprehensive examination and treatment of patients was conducted in the setting of the Department of Propaedeutics of Internal Diseases of the Medical Faculty of Uzhhorod National University. The study is based on the sample of 32 patients with liver cirrhosis who were treated in the Municipal Non Profit Enterprise "Regional Clinical Infectious Hospital" of Transcarpathian Regional Council and COVID-center of Municipal Non Profit Enterprise "Transcarpathian Regional Clinical Hospital named After Andrii Novak" of Transcarpathian Regional Council within the period from May 2020 to January 2023 and were diagnosed with COVID-19 pneumonia (positive polymerase chain reaction (PCR test) to SARS-CoV-2 RNA (RdRP gene SARS-CoV-2 , gene E SARS-CoV-2), as well as lung lesions in the form of "frosted glass" on a computed tomography with a maximum percentage of lung tissue damage (up to 65.0 %) and did not require to be connected to the artificial lung ventilation machine. The decision was made to provide inpatient treatment for these patients due to the high risk of possible complications and more severe viral infection on the background of liver pathology. They made up 1 Group of examinees patients. Patients were diagnosted (determination of the level of procalcitonin (Pro-CT), interleukin-6 (Il-6), C-reactive protein (CRP), ferritin (FT), D-dimer in the blood serum) and were treated according to the standards of medical care for patients with COVID-19 infection, which included the appointment of antiviral therapy, glucocorticoids, anticoagulants, vitamin D3, zinc, and antibiotic therapy. Among them there were 20 men (62.5 %), 12 women (37.5 %); the average age was 46.3 ± 4.8 years.

The study also included 30 patients with LC who were not infected with COVID-19 – 2 Group of examines patients. There were 20 men (66.7 %) among them, 10 women (33.3 %; the average age was 44.1 ± 3.9 years);

The control group included 30 healthy individuals (there were 19 men (63.3 %), 11 women (36.7 %) with the average age 45.5 ± 6.3 years).

The criteria for inclusion to the study include mediate severe and severe condition of patients infected with COVID-19, the presence of alcohol, viral (hepatitis B, C, D viruses) liver damage, namely liver cirrhosis. The criteria for exclusion from the study include extremely severe condition of patients infected with COVID-19, type 1 diabetes, autoimmune liver damage.

All studies were performed with the patients' consent (written consent for appropriate diagnostic and treatment measures was obtained), and the employed research methodology was consistent with the 1975 Helsinki Declaration of Human Rights and its revision (1983), the Council of Europe Convention on Human Rights and Biomedicine and the legislation of Ukraine.

All patients were subjected to examination using general clinical, anthropometric, instrumental, and laboratory methods. To verify the diagnosis, attention was paid to the present complaints, medical history.
All patients underwent ultrasound examination of the abdominal cavity according to conventional methods. At the beginning of the inpatient phase of treatment, as well as on the eve of discharge from the hospital, standard general and biochemical studies were performed in the blood serum to determine the functional status of the liver (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB) and its fractions), kidneys (creatinine (CT), urea), lipid metabolism, carbohydrate metabolism. The level of fibrinogen (FG), antithrombin III (AT-III), von Willebrand factor (WwF), prothrombin time (PT), thrombin time (TT), activated partial thromboplastic time (APTT) in the blood serum was determined for the study of coagulation homeostasis in examined patients with LC.

The degree of liver damage was assessed using surrogate markers of fibrosis with the help of online calculators Fibrosis 4 calculator (FIB-4), as well as fibrotest, and the results of liver elastometry [5]. The severity of liver cirrhosis was assessed according to the Child-Turcotte classification in Pugh's modification (1973), taking into consideration the level of bilirubin, albumin, prothrombin time and the presence or absence of ascites and hepatic encephalopathy.

The analysis and processing of the results of the examined patients were performed with the help of the computer program STATISTICA 10.0 (StatSoft Inc, USA) using parametric and non-parametric methods of evaluation of the results.

RESULTS

Laboratory-instrumental examination of patients with LC infected with COVID-19 was carried out in dynamics at the stage of undergoing inpatient treatment, with the determination of the above examination methods. An assessment of The degree of severity of patients

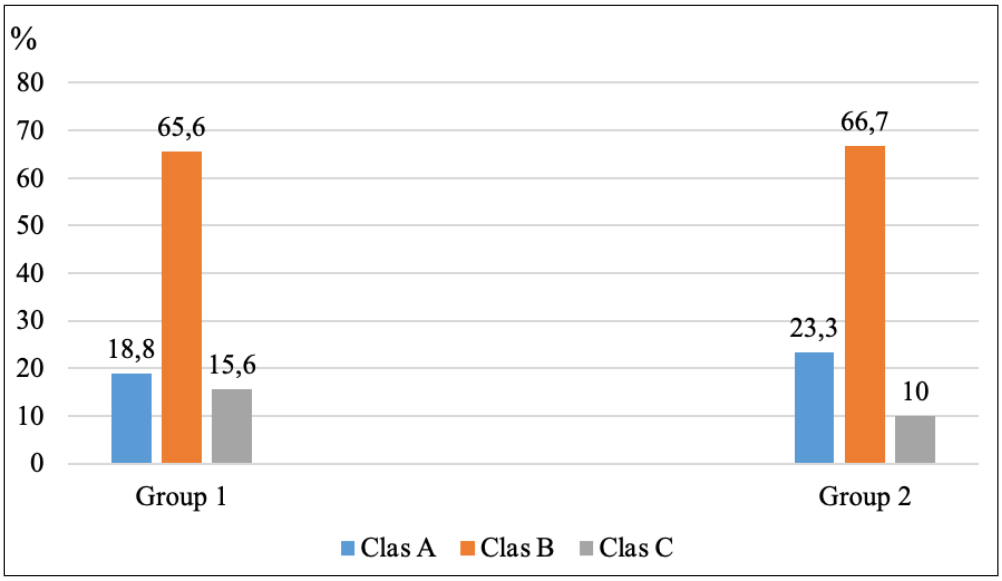

Fig. 1. Distribution of examined patients with LC according to the Child-Pugh Score for severity

with LC of both groups was also assessed according to the Child-Turcotte-Pugh classification at the stage of admitting the patients to inpatient care – Fig.1.

As can be seen from the above results, in both studied groups of patients, those in the stage of subcompensation of the cirrhotic process predominated – class B according to the Child-Pugh score, namely, 65.6% of patients of group I (at the time of admitting to hospital) and 66.7% of the examined patients of group II.

While analyzing acute-phase markers of inflammation, high levels of ferritin and procalcitonin were identified in the group I examined patients suffering from liver cirrhosis and infected with the COVID-19 virus. There was also found an increase in the level of interleukin-6 in blood serum of both studied groups of patients with liver cirrhosis, which was progressively rising in patients of the first group within the period from the 1st to the 14th day of inpatient treatment due to the COVID-19 infection. The maximum increase in the level of the C-reactive protein in blood serum of the first group patients was diagnosed on the 7th day of inpatient care due to the COVID-19 infection, with its gradual decrease during the treatment until the 14th day of inpatient care. There was also detected an increase in the level of the C-reactive protein in blood serum of the second group patients with LC, which indicates a chronic active inflammatory process in the bodies of these patients – Table I.

There was initially established an increase in AST and ALT indicators of the examined patients with LC in both groups. It has to be admitted that at the stage of inpatient care, a progressive increase of transaminases was identified in blood serum of the first group patients. The respective changes were observed in ALP and TB indicators in blood serum of patients with LC infected with COVID-19. Indicators of nitrogen metabolism, namely the level of CT and urea, were also higher than the norm in patients with liver cirrhosis, while a progressive increase in these indicators was found when being infected with the COVID-19 virus at the stage of inpatient treatment. Therefore, the COVID-19 infection, as well as medical measures aimed at eliminating the virus from the body of patients with LC, lead to the progression of liver damage.

The analysis of the obtained data indicates disorders of the hemostasis system in patients with LC without the COVID-19 infection (Group 2), as well as in patients with LC at the time of being infected with COVID-19. The violation of the protein synthesis function of the liver is manifested through a decrease in the level of fibrinogen in blood serum (up to 2.0±0.5 gr/l in patients of Group 1 at the time of admission for inpatient care) and up to 21.9±0.5 gr/l in patients of group II – $p<0.05$. This was accompanied by an acceleration of prothrombin time, thrombin time and activated partial thromboplastic time in patients with LC, as well as an increase in the level of antithrombin III. The level of D-dimer was reduced both in patients of group II and in patients of group I at the time of being infected with COVID-19 – Table II.

Significant changes in coagulation homeostasis occurred in group I patients with liver cirrhosis when infected with the COVID-19 virus. Against the background of a slight increase in the level of hemoglobin and platelets in the blood serum, a sharp increase in the fibrinogen index was found on the 7th day of inpatient treatment (3.7±0.6 gr/l – $p<0.01$), although the level of fibrinogen and platelets at the time of hospital admission in patients of group I was statistically significantly lower than the norm, as well as in patients of group II.

Table I. Change in indicators of homeostasis in the first group of the examined patients during hospital treatment

Indication	Control group (n=30)	Examined patient			
		Group 1 (n=32)			Group 2 (n=30)
		1 day of HT	7 day of HT	14 day of HT	
Hb, %	128.1±0.7	139.7±1.8	144.9±2.8*	152.2±2.0*	141.6±1.8*
PLT, 10^9/l	234.2±1.4	203.6±3.7*+	256.9±4.1^^	298.9±3.2**#	180.3±4.4**
ALT, IU/L	22.4±1.2	45.7±2.4	76.0±3.2**^	92.7±4.1**	54.9±3.3**
AST, IU/L	20.7±1.1	42.9±2.1*	84.3±3.3**^	101.3±4.2***##	68.9±3.0**+
TB, mmol/l	12.3±0.8	28.9±1.7*	34.8±1.6**	43.3±1.5**	41.9±1.7**+^
ALP, mmol/l	74.7±2.6	128.9±3.3*	132.8±2.7**	140.7±5.2**	138.9±5.0**
CT, mkmol/l	77.4±3.1	92.3±2,4	95.3±2,5*	100.8±1,4*	99.3±1.2*
Urea, mmol/л	5.2±0.7	5.9±0.6	6.0±0.4	6.8±0.8	6.9±0.4
CRP, mg/l	6.51±0,7	38.9±1.8**++	50.7±1.0***^^	35.7±0.7**##	18.9±0.6**
FT, ng/ml	135.5±2.7	528.9±4.4***	635.9±3.9***	588.9±4.7***	-
Pro-CT, ng/ml	0.06±0.002	3.05±0,04***	3.67±0.18***	2.77±0.05***	-
IL-6, pg/ml	4.2±0.4	6.8±0.7*+	7.3±0.5**^	9.4±0.8**##	5.9±0.4*

Note: between the indicators of the control group and the examined patients of groups I and II the difference is statistically reliable: * – p<0,05; ** – p<0,01; *** – p<0,001; between the indicators in the first and second groups of patients on the 1st day of examination the difference is statistically reliable: + – p<0,05; ++ – p<0,01; between the indicators in the first and second groups of patients on the 7th day of examination the difference is statistically reliable: ^ – p<0,05; ^^ – p<0,01; between the indicators in the first and second groups of patients on the 14th day of examination is statistically reliable: # – p<0,05; ## – p<0,01.

Table II. Indicators of coagulation pomeostasis in the examined patients' blood serum

Indication	Control group (n=30)	Examined patient			
		Group 1 (n=32)			Group 2 (n=30)
		1 day of HT	7 day of HT	14 day of HT	
PT, sek.	10.7±0.4	16.0±1.4*	10.4±0.7+	7.2±0.5*¥	15.1±0.8*^##
TT, sek.	16.2±0.5	24.9±0.7**	12.8±0,8*++	11.9±0.7*	25.2 ±0.6**^^##
APTT, sek.	27.9±0.4	32.6±0.7*	26.5±1.0+	11.0±0.3**¥¥	33.2±0.7*^##
FG, gr/l	3.3±0.4	2.0±0.5*	3.7±0.6++	2.9±0.8¥	1.9±0.5*^^#
WwF, %	79.3±3.5	89.9±2.2	154.8±5.6**++	168.0±4.4**	92.7±1.8^^##
AT-III, %	88.7±2.9	139.5±5.1*	103.5±4.6*+	79.8±2.6¥	142.8±2.7**^##
D-dimer, ng/ml	112.4±2.9	78.9±4.0*	223.7±4.1**++	187.0±5.2**¥	81.0±3.8*^^##

Note: between the indicators of the control group and the examined patients of the first and second groups the difference is statistically reliable: * – p<0,05; ** – p<0,01; between the indicators in the patients of the first and second groups on the 7th day of examination the difference is statistically reliable: ^ – p<0,05; ^^ – p<0,01; between the indicators in patients of the first and second groups on the 14th day of examination the difference is statistically reliable: # – p<0,05; ## – p<0,01; between the indicators in patients of the first group on the 1st and 7th day of examination the difference is statistically reliable: + – p<0,05; ++ – p<0,01; between the indicators in patients of the first group on the 7th and 14th day of examination the difference is statistically reliable: ¥ – p<0,05; ¥¥ – p<0,01.

Accordingly, this was accompanied by a decrease in prothrombin time, thrombin time, activated partial thromboplastic time on the 7th day of hospital admission in patients of group I. A sharp increase in the level of D-dimer (up to 223.7±4.1 ng/ml in patients of group I on the 7th day of treatment – p<0.01) also indicates a tendency to thrombosis. Thus, in patients with LC, being infected with the COVID-19 virus leads to a violation of the blood coagulation system, namely hypercoagulation, which requires a corresponding correction of treatment in these patients.

DISCUSSION

The mechanisms of hepatic injury at patientes infected COVID-19 include immune-mediated infammation, hypoxic injury due to severe pneumonia and drug related. It is also postulated that expression of ACE2 receptor on cholangiocytes may predispose to cholestatic injury. Data on post-mortem liver biopsies is limited and demonstrates moderate microvascular steatosis and mild lobular and portal activity. The acute insult in COVID-19 is systemic and it may progress to involve

other systems. Comorbidities like diabetes, hypertension, obesity, coronary artery disease and chronic liver disease (CLD) co-exist in general population, more so in middle aged and elderly. While the true burden of liver disease is not known; these accounted for 4.6% of all deaths. In fact, liver diseases contribute global disease burden in the form of metabolism associated liver disease (MAFLD), alcohol-associated liver disease and viral hepatitis. Hence, during COVID-19 pandemic, it is very likely that CLD patients would be exposed to SARS-CoV-2 infection. Moreover, many cirrhotic patients are required to attend hospitals regularly and thus become susceptible to SARS-CoV-2 infection. Importantly, the SARS-CoV-2 infection produces lymphocytopenia with or without leukopenia, thrombocytopenia and raised fbrinogen degradation products, which pre-exist in CLD patients due to bone marrow suppression and cirrhosis associated immune dysfunction syndrome [6-8].

Data in the literature highlight how the virus triggers an exaggerated immune response, which added to the cytopathic effect of the virus can induce endothelial damage and a prothrombotic dysregulation of hemostasis [7].

As is known, the COVID-19 infection leads to systemic changes in the human body. Admittedly, the «load» on all organs and systems of the body is observed. Patients with chronic diseases, including cerebral palsy, are a high-risk group not only in view of being infected with the virus, but also of the progression of liver damage with the formation of complications against the background of the COVID-19 infection.

It is likely that the activation of immunological processes in the body against the background of the COVID-19 infection, which is mainly observed on days 4-7 of inpatient treatment, is a «triggering» factor for the activation of the hypercoagulation syndrome in patients with liver cirrhosis, although in this category of patients, hypocoagulation changes in the blood coagulation system are pre-established. The obtained results indicate the need for dynamic monitoring of the state of the coagulogram in patients with LC when infected with COVID-19, especially in patients of classes B and C according to the Child-Pugh scoring with the progression of signs of ascites, hepatorenal syndrome, hepatic encephalopathy. Further research is needed in this area regarding the development of the treatment regimen for patients with liver cirrhosis when infected with the COVID-19 virus, as well as the elaboration of a system of measures at the stage of dispensary observation of these patients.

CONCLUSIONS

Changes in coagulation homeostasis characteristic of hypocoagulation syndrome have been established in patients with LC. COVID-19 infection in patients with LC leads to hypercoagulation, especially in patients with complicated stage of LC (ascites, encephalopathy, hepatorenal syndrome).

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ORIGINAL ARTICLE

IMPACT OF DISTANCE EDUCATION ON STUDENTS' HEALTH

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ABSTRACT

The aim: Studying the impact of distance learning on students' health

Materials and methods: Special research methods and medical-statistical method. Domestic and foreign students were subject of the study during the online form of education, in connection with Covid-19, poll was made using Google Forms.

Results: 333 students participated in the study (22.3% – domestic and 77.7% – foreign students). It was established that 88.3% of foreign and 40.5% of domestic students did not suffer from COVID-19 in the past. The overwhelming majority of respondents (86.5% domestic and 85.1% foreign) noted anxiety and concern for their health. 59.4% of domestic and 63.4% of foreign students noted the deterioration of their mental health and increased anxiety during distance learning. Depressive conditions were experienced by 49.3% of foreigners and 52.0% of domestic respondents. The respondents noticed the negative impact of distance learning on their daily routines, namely sleep, nutrition and active recreation, etc. The most frequent complaints were back pain, headaches, and visual impairment. Students noticed that during online classes their academic performance decreases.

Conclusions: The transition to online education had a negative impact on the physical and mental health of students, which was manifested in the presence and growth of anxiety and depression, a lack of live communication, sleep and eating disorders, reduced physical activity, the appearance of headaches and back pain, vision problems, attention disorders, and a decline in academic performance.

KEY WORDS: distance learning, medical students, foreign students, mental health

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INTRODUCTION

The COVID-19 pandemic has made adjustments to the organization of the educational process throughout Ukraine. According to the regulatory documents of the Ministry of Education and Science of Ukraine, all educational institutions, including universities, were forced to switch to online distance learning, which in turn led to the use of devices, changes in the daily regime and schedule in order to continue the educational process [1-4]. The lack of a national strategy for the development of medical education in the context of health care reform, the incoherence of relations between universities and medical institutions at the state and local levels led to the separation of medical university students from contact with patients, which was also facilitated by the high contagiousness of the COVID-19 virus. Since the basis of the future doctors training is continuous learning, distance learning was implemented in all specialized educational institutions. Undoubtedly, this form of education reduces the risk of teachers and students becoming infected with the virus during a pandemic. The educational community pays considerable attention to the implementation of innovative technologies into the educational process of higher education institutions [5-7]. Distance education is a forced measure in pandemic conditions to continue education process and has a negative impact on physical health and psycho-emotional state [1,7,8]. One of the main tasks of our society is to preserve the physical and mental health of the young generation. The authors of the study [9,10] emphasize that education, as a social tool, significantly affects the state of physical, social, and mental health of an individual. Since the beginning of the pandemic, in the conditions of distant and mixed forms of learning, we have lost one of the important components of future doctors education: the formation of the clinical thinking of a doctor, which includes the contact of a student and the patient, the ability to communicate, collect anamnesis, examine, empathize, and feel responsibility for the life of a specific person. Students participation in clinical rounds, daily meetings in the department, conferences, emergency care, have decreased significantly. The assimilation of practical skills and abilities is reduced, and that is indispensable for future doctors [5].

It has been established that the state of students' mental health depends on many factors, including an increase in the number of stressful situations, a

change in daily routine, nutrition, physical activity, etc. According to the results of medical-epidemiological, psychological-pedagogical, and sociological studies, the rapid spread of diseases and the growth of chronic pathology among student youth are accompanied by unsatisfactory functional adaptation to physical and educational loads, especially in the first years, are noted. More and more students are beginning to notice a deterioration in their well-being, namely: emotional burnout, an increase in the level of neuroticism, emotional excitability, apathy, fear, and the occurrence of depressive episodes [5,9,11,12]. The most common diseases among young people, according to the data of the State Statistics Service of Ukraine, are diseases of the respiratory organs, digestive system, eyes and appendages, diseases of the skin and subcutaneous tissue, musculoskeletal system, endocrine system, infectious and parasitic diseases, injuries and poisoning, diseases of the nervous system, genitourinary system [9,13]. In the article [5], the authors note the significant factors behind the decrease in the success of students in the period of distance learning, including the unpreparedness of teachers and students to work in the online mode, the impossibility in these conditions to master the necessary practical skills, and the large amount of material for learning a new form of education (online), which significantly hinders the mastery of the curriculum. Aggravation of chronic diseases also contributes to a decrease in success.

THE AIM

To study the impact of distance learning on students' health, including mental health.

MATERIALS AND METHODS

In this study, a special research method and a medical-statistical method were used. The basis was the survey method, which was conducted anonymously using a specially developed questionnaire that was created in the Google Forms service. The questionnaire contained 15 questions with several answer options. Domestic and foreign students of the State Higher Educational Institution «Uzhgorod National University» were the subjects of the study. The survey was conducted during the on-line (distance) form of education in connection with COVID-19 using the MS Office 2010 program.

RESULTS

As a result of the survey, it was established that 333 students took part in the study, of whom 74 were domestic students (22.3%) and 259 were foreign students (77.7%). The gender distribution was almost the same: 180 people (54.1%) were female and 153 were male, which was 45.9%. Students of all courses from 1st to 6th were represented in the study. The average age was 20-22 years.

In order to achieve the goal of the research, questionnaire included questions related to the state of personal health, including mental health, as well as the peculiarities of learning and changing the daily routine in the conditions of distance education.

When studying the question of the incidence of COVID-19 in the past, 227 foreign (88.3%) and 29 domestic students (40.5%) answered that they had not suffered from this disease. Among those who fell ill, the vast majority of students treated themselves (29.7% of domestic and 8.9% of foreign students), which was associated with a mild course of the disease, however, 28.4% of domestic and 2.5% of foreign students had to consult a doctor.

The vast majority of respondents, 86.5% of domestic and 85.1% of foreign students, noted a constant and periodic state of anxiety and concern for their health and the health of their relatives and friends.

This condition was aggravated by distance learning, which also had a negative impact on the health of the interviewees. Thus, 59.4% of domestic and 63.4% of foreign students noted the deterioration of mental health and increased anxiety during online education. Depressive conditions were experienced by 49.3% of foreigners and 52.0% of respondents.

It is known that communication plays an important role in a person's life and it is an important condition for the formation of a person's mental health. Insufficient level of communication can lead to emotional disorders, as well as mental health disorders. The coronavirus pandemic caused the implementation of strict quarantine restrictions, including the introduction of distance learning, which limited the possibilities of live communication. Thus, when answering the question «How much do you miss live communication with classmates and teachers during distance learning?» every third student (35.1% among domestic students and 32.8% among foreign students) answered that it was not enough to a large extent, every second student (54.1% and 60.1%, respectively) noted that it was moderately lacking, and only 7.0-10.0% of students were indifferent.

In addition, the respondents pointed to the negative impact of distance learning on the daily routine, namely sleep, nutrition, active recreation, etc. Thus, the vast majority of respondents (78.0% of domestic and 58.2% of foreign students) noted a decrease in physical activity

as a result of their constant stay at home; sleep disorders were found in 22.8% of domestic and 17.8% of foreign students, and eating disorders in 8.0%, 0.0%, and 10.0% of the respective respondents. Only about 9.0% of students believe that distance learning did not affect their daily lives and did not disrupt their usual daily routine.

The research established that as a result of distance learning, which is accompanied by a violation of the work regime, straining the musculoskeletal system, vision, attention, long and frequent use of a PC, etc., students have complaints related to their health. Domestic students most often complained of back pain (24.3%), headaches (21.6%), and visual impairment (21.8%). Among foreign students, the complaints were the same, only in other proportions: headache (23.0%), back pain (11.7%), and visual impairment (11.2%). Changes in the state of the central nervous system may be accompanied by impaired attention and rapid fatigue. Thus, three-fourths (25.3%) of foreign respondents and 19.2% of domestic students pointed to a violation of concentration periodically and constantly during online education.

Since the quality of education directly depends on the health of the student [14], we analyzed the data on changes in the educational load and success of students during distance learning. Domestic and foreign students were not of the same opinion regarding changes in the study load: about 35.0% of respondents believe that it has not changed, 33.6% believe that the load and the number of tasks have increased, and about 28.4% indicated a decrease in the study load; however, they share the same point of view that success rates decrease during online education.

DISCUSSION

The emergence of COVID-19-related restrictions has led to an increased demand for online learning. Over the past 20 years, many variations of distance learning have been developed and implemented at all levels of education [15,16]. This is especially relevant for students who require more flexible schedule in the learning process (e.g. working full-time and/or caring for children, living far from the place of education, etc.) [15,17,18].

Due to the situation that has developed since the end of 2019 and the beginning of 2020, a new form of education is inevitable in Ukraine and the world that would meet all the requirements of innovative education and ensure the effective implementation of educational programs. Distance learning is a fundamentally different way of communication and a different learning structure, which aims to combine the advantages of using modern distance technologies based on the use of traditional education, modern multimedia equipment and Internet technologies [19].

Students' views and satisfaction vary widely. Distance learning is an advantage because it allows you to study anytime and from anywhere. Staying at home is safer and less stressful for students during the pandemic. Distance education exacerbates physical and psychological health issues, including fear, anxiety, stress, and attention problems [20].

All educational institutions strive to provide high-quality educational services. The Internet is used to expand the system of distance education. The distance education system continues to evolve and requires further study and improvement, especially for medical professionals. Subsequent studies can be conducted with the participation of students, teachers, and system employees who are directly involved in the process in order to obtain a more detailed assessment.

CONCLUSIONS

The research established that the transition to distance education had a negative impact on both the physical and mental health of students, which was manifested in the presence and growth of anxiety and depression, a lack of live communication, sleep and nutrition disorders, a decrease in physical activity, the appearance of headaches and backaches, impaired vision, reduced concentration, and reduced student performance. All this requires the development of complex preventive measures and their implementation in the practice of family doctors, teachers, and students themselves. Communication between teachers and students remains an important aspect in terms of disseminating information regarding the prevention of violations caused by distance learning.

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REVIEW ARTICLE

CLINICAL EFFECTIVENESS OF EMPAGLIFLOZIN IN PATIENTS WITH HEART FAILURE

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ABSTRACT

The aim: To study the possibilities of increasing the effectiveness of treatment and improving the prognosis of patients with various phenotypes of heart failure when using empagliflozin.

Materials and methods: The analysis of the data regarding the results of existing studies evaluating the clinical benefit and safety of empagliflozin in patients with various phenotypes of heart failure has been conducted.

Conclusions: In the EMPA-REG OUTCOME study, empagliflozin has demonstrated the ability to improve cardiorenal outcomes and reduce the risk of hospitalization for heart failure in patients with diabetes. The results of the studies (EMPEROR-Preserved, EMPEROR-Reduced, EMPULSE) have shown the clinical advantages of empagliflozin over traditional heart failure therapy, manifested by a reduction in mortality and the number of hospitalizations for heart failure, as well as improvement in quality of life indicators. The clinical benefits of using empagliflozin were observed in patients with chronic heart failure with different left ventricular ejection fraction, as well as in patients with acute heart failure.

Empagliflozin is a sodium-glucose co-transporter 2 inhibitor with a convincing evidence base for the treatment of all categories of patients with chronic heart failure, regardless of diabetes status. The results of the conducted studies indicate the unconditional benefit of early initiation of empagliflozin therapy in patients with both chronic and acute heart failure after the stabilization of their condition.

KEY WORDS: heart failure, sodium-glucose co-transporter 2 inhibitors, empagliflozin

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INTRODUCTION

Chronic heart failure (HF) is one of the most frequent cardiovascular complications and the most important cause of patient death [1-3]. Heart failure is defined as a clinical syndrome consisting of subjective symptoms (e.g. breathlessness, ankle swelling, and fatigue) or objective signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral edema) that occur due to structural and/or functional abnormalities of the heart and lead to increased pressure in the chambers of the heart and/or inadequate cardiac output at rest and/or during exercise [4].

The prevalence of chronic HF is more than 60 million people worldwide and continues to increase steadily with the aging of the world population, which causes a significant global burden on the healthcare system. Heart failure significantly impairs the quality of life, leads to frequent re-hospitalizations, and is accompanied by loss of kidney function. More than 1 million people are hospitalized every year due to HF exacerbations in the USA and Europe. Decompensation of chronic HF often leads to death, which explains its substantial socio-economic significance. Slowing down the progression of chronic HF and preventing its decompensation is one of the main tasks of modern cardiology and medicine in general [5-8].

THE AIM

The aim is to study the possibilities of increasing the effectiveness of treatment and improving the prognosis of patients with various phenotypes of heart failure when using empagliflozin, a representative of sodium-dependent glucose co-transporter type 2 inhibitor.

MATERIALS AND METHODS

The analysis of the data regarding the results of existing studies evaluating the clinical benefit and safety of empagliflozin in patients with various phenotypes of heart failure has been conducted.

REVIEW

Standard therapy for chronic HF with reduced ejection fraction (HFrEF) was based for a long time on the use of

renin-angiotensin system (RAS) inhibitors, β-adrenoblockers (BAB), and mineralocorticoid receptor antagonists (MRA). Recently other pharmacological classes of drugs have been included in this group, namely: angiotensin II receptor-neprilysin inhibitors (sacubitril/valsartan) (ARNI) and sodium-glucose co-transporter 2 (SGLT2) inhibitors, which, according to clinical studies, can influence the course and prognosis of chronic HF when added to the above-mentioned traditional medicines [4, 9-13].

According to the results of the EMPA-REG OUTCOME study (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin has become the first SGLT2 inhibitor demonstrating a reduction in cardiovascular mortality and hospitalization for HF in patients with type 2 diabetes mellitus (DM) and established cardiovascular disease [12,14-16]. Patients (n = 7020) with type 2 diabetes and the established cardiovascular disease were enrolled in this randomized clinical trial. Further, they were allocated to empagliflozin (10 mg/25 mg) or a placebo. The average duration of treatment was 3.1 years. Patients treated with empagliflozin had a 14% (p = 0. 04) reduction in the incidence of the composite primary endpoint (cardiovascular death, nonfatal myocardial infarction – nonfatal major adverse cardiovascular events (MACE)) compared to the placebo group. This was primarily due to a 38% reduction in cardiovascular death (p < 0.001) [14]. The reduction of total death (mortality from all causes) is known to be the key indicator of all studies. It was reduced by 32% (p < 0.001) in the EMPA-REG OUTCOME study. This shows that one in three patients who could have died were saved by using empagliflozin. A 35% decrease in the frequency of hospitalizations due to the destabilization of chronic HF was also observed (p = 0.002). This result did not depend on the presence of HF in the patient's history or established HF at the beginning of the study [14,17].

The conducted subanalysis of the EMPA-REG OUTCOME has shown that empagliflozin was likely to reduce the endpoint of MACE in patients both with the history of myocardial infarction (MI) and without the history of MI in the anamnesis [18].

Since SGLT2 inhibitors have a renal mechanism of hypoglycemic action, consequently a question has arisen: is empagliflozin safe for kidneys? In the EMPA-REG OUTCOME study, patients with the estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m^2 on the background of empagliflozin therapy compared to placebo had a probable decrease of 39% (p < 0.001) of a renal endpoint as the onset or exacerbation of diabetic nephropathy [14]. Moreover, on the background of therapy, the relative risk of doubling the level of creatinine in the blood decreased by 44% in the group of patients who took empagliflozin (p < 0.001). There was also a decrease of 55% (p = 0.04) in the risk of renal replacement therapy [14]. The use of empagliflozin in patients with type 2 diabetes also led to a decrease in the progression of albuminuria by 16% (p = 0.0077) [15]. It should be noted that in the EMPA-REG OUTCOME study, two doses of empagliflozin (10 and 25 mg) were shown to be equally effective in reducing the probable risk of cardiovascular and total death, hospitalization for HF, or the frequency of renal events [14]. The results of the EMPA-REG OUTCOME study served as a starting point for changing the paradigm of treatment of patients with type 2 diabetes and indicated the advantages of early selection of therapy, which reduces the risk of developing cardiovascular complications [19]. The data obtained also contribute to the formation of the hypothesis that SGLT2 inhibitors can exert a cardioprotective effect and nephroprotective effect, regardless of the cause of heart or kidney damage, both in the presence and absence of diabetes. The results of this study have also formed the basis of a further study of the prospective use of SGLT2 inhibitors for the treatment of HF in people without diabetes.

In 2020, the results of the EMPEROR-Reduced study were presented at the European Congress of Cardiology [12]. Those data became the most important argument for the decision to include SGLT2 inhibitors in the treatment regimen of patients with chronic HF, regardless of the presence or absence of type 2 diabetes. The EMPEROR-Reduced study is a randomized, double-blind, placebo-controlled trial that included 3730 patients with chronic HF with reduced ejection fraction (HFrEF), 1863 of whom received empagliflozin, whereas 1867 patients received a placebo in addition to the standard therapy [12]. The average duration of therapy was 16 months.

It is important to note that the researchers planned to include patients with a left ventricular ejection fraction (LVEF) of less than 30%, and the exclusion criterion was eGFR below 20 ml/min/1.73 m^2. For the first time in history to study the effectiveness of SGLT2 inhibitors, patients with eGFR <30 ml/min/1.73 m^2 were included. The average age of the patients was 67 years, 24% of them were women, 75% had chronic HF with New York Heart Association (NYHA) class II symptoms, 24% had NYHA III, and 1% had NYHA IV. Half of the patients had a history of diabetes, 73% had an LVEF of 30% or less, 79% of patients had N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of at least 1000 pg/ml, 48% had an eGFR of less than 60 ml/min/1.73 m^2, and almost 20% of patients received sacubitril/valsartan [12].

The EMPEROR-Reduced study in patients with HFrEF met all of its planned endpoints with statistically significant results. A 25% reduction in the risk of the primary composite

endpoint of cardiovascular death or hospitalization for HF was shown ($p < 0.001$). A reduction in the frequency of the primary endpoint was observed in all patients regardless of initial therapy for chronic HF, including the use of sacubitril/valsartan, and regardless of the presence of diabetes [12,20]. A sustained statistically significant advantage of empagliflozin over placebo in the primary endpoint was achieved after 34 days of treatment. It highlighted the potential for early clinical benefit when the SGLT2 inhibitor is administered to patients with chronic HFrEF.

The analysis of such an endpoint as hospitalization due to HF is of both scientific interest and great practical benefit since hospitalization due to HF is a marker of the unstable course of chronic HF and an event that increases the risk of death in patients with chronic HF, which worsens the economic burden of this pathology at the population level [14,21]. In the studied EMPEROR-Reduced study, the frequency of primary and re-hospitalization was 13.2% in the empagliflozin group and 18.3% in the placebo group ($p < 0.001$). Empagliflozin reduced the risk of first hospitalization for HF by 31% compared with placebo [12]. In the subanalysis of the EMPEROR-Reduced study, it was shown that the advantage of empagliflozin in the prevention of readmissions first reached statistical significance compared with placebo as early as 12 days after randomization, and statistical significance was maintained throughout the study period. Moreover, the risk of re-hospitalization on empagliflozin therapy decreased regardless of the etiology of chronic HF, the level of glycosylated hemoglobin (HbA1c), and the status of diabetes [22,23].

It should be noted that in this study, patients received optimal medical therapy (about 90% of patients received RAS/ARNI inhibitors and 94.7% of patients received MRA), and despite this, empagliflozin showed a pronounced positive effect on the prognosis [22,23].

The results of the EMPEROR-Reduced study have also shown that empagliflozin can help improve the consequences of chronic HF, slowing the deterioration of kidney function. Empagliflozin therapy in patients with HFrEF reduced the risk of developing a combined renal endpoint by 50% (chronic dialysis or kidney transplantation, or the detection of a stable decrease in eGFR by 40% or more from the original). The difference in the reduction of eGFR in the empagliflozin group versus placebo was 1.73 ml/min per year ($p < 0.001$) in favor of the SGLT2 inhibitor. What is important is the fact that the treatment with empagliflozin was not associated with an increased risk of acute kidney injury and hyperkalemia compared with a placebo [12, 24].

Analyzing the data of the EMPEROR-Reduced study, it can be noted that the use of empagliflozin has certain advantages compared to traditional means of treating chronic HF (prescribing BAB, RAS/ARNI inhibitors, MRA). These advantages include a one-time administration of the drug in a single recommended dose, which eliminates the need for titration, the absence of a significant effect on hemodynamics, the presence of a proven nephroprotective effect, and a favorable safety profile. The frequency of adverse events when taking empagliflozin or placebo did not differ regardless of the presence of diabetes, except for uncomplicated genital infections (1.7% vs 0.6%) [20]. There were also no cases of ketoacidosis in the EMPEROR-Reduced study. A secondary analysis of the results of the EMPRER0R-Reduced study showed that empagliflozin not only reduced the risk of cardiovascular death or hospitalization for HF, but also significantly improved the health status and quality of life of patients, and this beneficial effect was sustained during their long-term follow-up [25].

In conclusion, it should be noted that empagliflozin was superior to a placebo in improving the treatment outcomes in patients with chronic HF regardless of whether they had type 2 diabetes [20]. Also, the results of the conducted study have indicated the unconditional benefit of early initiation of empagliflozin therapy in patients with HFrEF.

Heart failure with the preserved ejection fraction of the left ventricle (HFpEF) is one of the forms of the syndrome, the share of which in the structure of HF patients is more than 50%, while the total number of patients with this form of HF continues to grow steadily [26]. From a physiological point of view, HFpEF occurs when the process of properly filling the left ventricle of the heart in diastole is disturbed, which leads to a violation of adequate blood supply to the body. HFpEF is considered to be the most unsolved problem based on prevalence data, poor clinical outcomes, and lack of currently clinically proven treatments for this HF phenotype.

For many decades, the treatment of HFpEF has been nonspecific and has included the administration of diuretics and correction of comorbidities such as arterial hypertension and obesity, but the results of such therapy have been minimal and the prognosis has been questionable [4,27,28]. Meanwhile, in recent years, the situation has begun to improve due to the appearance of favorable results in several clinical studies. First of all, we should mention the data obtained during the analyzes in the subgroups of the TOPCAT and PARAGON-HF studies, which demonstrated a certain benefit from the inclusion of MRA (spironolactone) and ARNI (sacubitril/valsartan) in the treatment regimen of HFpEF [29,30]. However, the most promising results were obtained in studies of SGLT2 inhibitors. Anker et al. presented the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) study at the European Society of Cardiology meeting on August 27, 2021, the results of which convincingly confirmed the

beneficial effect of empagliflozin, SGLT2 inhibitor, on the course and prognosis of HFpEF [27].

Selection criteria for the randomized, double-blind, placebo-controlled EMPEROR-Preserved study, (n = 5988) met men and women aged ≥18 years with heart failure NYHA II–IV, LVEF >40% and a baseline level of the NT-proBNP >300 pg/ml (or >900 pg/ml for patients with atrial fibrillation) [27]. 80% of patients received RAS inhibitors, more than 80% – BAB, and about 30% – MRA. After a screening period of 4-28 days, patients were randomized 1:1 to receive a placebo or empagliflozin 10 mg/day in addition to standard therapy.

The results of the EMPEROR-Preserved study demonstrated the efficacy of empagliflozin in patients with HFpEF, which was manifested by a reduction in the relative risk of the combination of death from cardiovascular causes and hospitalization for HF by 21%, which was achieved mainly due to a reduction in the risk of decompensation of chronic HF by 29 %. The given effect with the use of empagliflozin in patients with HFpEF was manifested regardless of the presence of diabetes.

Taking into account the data from previous studies of various options for HFpEF therapy (candesartan, spironolactone, and the sacubitril/valsartan combination), which showed that the detected benefit from treatment can be observed mainly in patients with LVEF 40–49% [5, 9, 15, 31], the EMPEROR-Preserved authors divided participants into three subgroups based on LVEF <50%, ≥50% but <60%, and ≥60%. In contrast to earlier data, results in favor of empagliflozin on the primary endpoint were confirmed in each subgroup of patients, selected taking into account LVEF [27].

All the data obtained in the study indicate that empagliflozin can radically change the tactics of treatment of HFpEF. In general, the effects of empagliflozin observed in EMPEROR-Preserved were comparable to the effects registered in the study of patients with HFrEF (EMPEROR-Reduced) [12], which allows us to talk about the benefits of using empagliflozin in patients with all forms of HF (including HFrEF and HFpEF). European experts recognized empagliflozin as the drug of choice, as it is the only drug that affects the prognosis of patients with chronic HF regardless of the level of LVEF [32]. The safety profile generally corresponded to the known safety profile of empagliflozin.

For a long time, the question remained open whether SGLT2 inhibitors would be useful for patients hospitalized for acute HF, as well as whether it would be safe to start such therapy in the acute period of HF, and whether it is possible to prescribe it during hospitalization for the first episode of acute HF in patients who have not yet received background therapy for HF. The EMPULSE study was designed and conducted to study the effect of empagliflozin on survival, risk of HF destabilization, and severity of symptoms in patients hospitalized with acute HF [33].

The EMPULSE study included patients hospitalized for acute heart failure (de novo or decompensated chronic HF), regardless of LVEF or diabetes. Patients were randomized during hospitalization after stabilization (from 24 h to 5 days after admission to the hospital) to the groups receiving empagliflozin (10 mg 1 time/day) and placebo. The duration of observation was 90 days. In complex therapy, patients received RAS inhibitors (70% in total), MRA (57%), and loop diuretics (87%) [33].

DISCUSSION

The EMPULSE study has shown that early initiation of empagliflozin alongside standard therapy in patients hospitalized with acute HF provided a statistically and clinically significant benefit within 90 days of randomization, as demonstrated by a reduction in all-cause death and HF destabilizing episodes, as well as a reduced severity of symptoms (i.e., improved quality of life) in the empagliflozin group. The therapeutic effect of empagliflozin was stable in different patient subgroups, particularly among participants with reduced and preserved LVEF, de novo HF, or decompensated chronic HF, and among patients with or without diabetes. Empagliflozin was well tolerated by participants in the EMPULSE study with no apparent safety issues, including no increased risk of renal impairment, ketoacidosis, or hypovolemia. What is also important is that the effects of empagliflozin treatment recorded in the EMPULSE study were observed throughout the period, which began on average on the 3rd and ended on the 90th day after hospitalization for HF, that is, during the stage of the greatest vulnerability of patients with acute HF (the period of the most frequent registration of repeated hospitalizations due to decompensation of HF) [33].

Thus, the results of the conducted studies (EMPEROR-Preserved, EMPEROR-Reduced, EMPULSE) demonstrated the clinical advantages of empagliflozin over traditional HF therapy without the use SGLT2 inhibitors.

These clinical benefits are manifested by reduced mortality and improved survival, reduced HF readmissions, and quality of life measures. Clinical benefits were similar in patients with both preserved and reduced LVEF, as well as in patients with new-onset acute HF, or with acute decompensation of chronic HF, regardless of DM status. Prescribing empagliflozin in hospital significantly increases the likelihood of continuation of this therapy after discharge. empagliflozin's single dose and no need for titration, with a rapid improvement in prognosis, good tolerability, and safety profile provide additional opportunities to improve adherence and ensure continuity of treatment in patients with chronic HF.

CONCLUSIONS

1. Empagliflozin is a sodium-glucose co-transporter 2 inhibitor with a convincing evidence base for the treatment of all categories of patients with chronic heart failure, regardless of diabetes status.
2. The clinical benefits of empagliflozin demonstrated in the EMPULSE study open up new opportunities for improving treatment outcomes and prognosis of patients with acute heart failure.
3. The results of the conducted studies indicate the unconditional benefit of early initiation of empagliflozin therapy in patients with both chronic and acute heart failure after the stabilization of their condition.

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REVIEW ARTICLE

SOMATIC (PERSONAL) HUMAN RIGHTS: THE RATIO OF MEDICAL AND LEGAL CATEGORIES

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ABSTRACT

The aim: To find out the peculiarities of somatic (personal) human rights, while combining the basic principles of medicine and law.

Materials and methods: Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of somatic rights among other human rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main periods of the formation of somatic rights in the works of scientists. The application of the above-mentioned methods necessitates the inclusion of an activity method in the research methodology (this method, becoming a logical continuation of the integral structural-functional method, involves the study of somatic rights through the development of medicine).

Conclusions: We consider it expedient to use the term «somatic rights» and not «personal rights», firstly, due to the explanation of the danger of possible pluralism in social and humanitarian knowledge and the terminological similarity of the definition of «personal» rights with «personal» human rights and, secondly, due to the fact that when justifying the legal scientificity of the term «personal» rights, the main semantic load lies in the word «personality»; these are rights that have an individual, «purely personal character».

KEY WORDS: human rights and freedoms, fourth generation human rights, personal human rights, somatic human rights, medicine, law, ethical principles

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INTRODUCTION

The modern understanding of the categories of human rights is dynamically developing: the content of already existing rights is being clarified, new, previously unknown rights are emerging, and the mechanisms of their regulation and protection are being improved. Such a trend is connected both with the priority of human rights, as a basic value in a civilized society, and with the requirements of the time. Those rights based on the freedom of a person to dispose of his body have been updated by the requirements of the times. They are called somatic and/or personal. Today, the problem of somatic human rights appears as a new direction in legal science. This is due to the fact that modern achievements of biomedical science, due to their demand, are beginning to be applied without receiving proper legal regulation, thus becoming a source of unlimited interference in human nature, and, as a result, entail serious ethical and legal problems in this industry [1]. So, for example, the right to life and health, which can be ensured by transplanting the recipient of anatomical materials, borders on the ethical norms related to donation, especially in relation to a cadaver donor. The balance between medicine, law and ethical norms is quite sensitive [2]. Based on the analysis of the works of theorists of law and medicine, scientists directly involved in the study of somatic human rights, religious scholars [3], we can conclude that the historiography of somatic human rights in biomedical research in a broad sense is a field of scientific knowledge [4].

THE AIM

The aim is to find out the peculiarities of somatic (personal) human rights, while combining the basic principles of medicine and law.

MATERIALS AND METHODS

Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as

to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of somatic rights among other human rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main periods of the formation of somatic rights in the works of scientists. The application of the above-mentioned methods necessitates the inclusion of an activity method in the research methodology (this method, becoming a logical continuation of the integral structural-functional method, involves the study of somatic rights through the development of medicine).

REVIEW AND DISCUSSION

In the context of the topic of our research, we should dwell on the issue of the conceptual and categorical apparatus. It should be noted, writes N. Misko, that in modern scientific literature, the set of concepts of this or that branch of scientific knowledge is called «conceptual-categorical apparatus», «terminology», «term system» or, increasingly, «thesaurus». In addition, conducting such an analysis will avoid the polysemy of the terms used in our work [5]. As noted by V. Kraevskyi, «undemanding to terminological unambiguity is a significant shortcoming that affects the development of our science and forces us to question the belonging of some works claiming to be scientific to the field of scientific knowledge in general. The requirement of unambiguity is included among the scientific indicators of the research» [6]. E. Khrykov emphasizes the importance of clarifying the conceptual apparatus of the dissertation work: «Due to the fact that dissertation studies are an important component of modern science, their conceptual balance is an important condition for the development of scientific knowledge. That is, clarifying the concepts used by the researcher, their interpretation is a mandatory condition of pedagogical research» [7].

Thus, I would like to focus attention on the issue of the categories «somatic» and «personal» in the context of human rights. There is no consensus on the content and terminology of such rights. Moreover, the terminological aspect seems to us to be no less important, since semantic ambiguity in law is a necessity that allows us to avoid contradictions between the definition of a term and its legal essence, difficulties in the interpretation of laws. Violation of the requirement of uniformity in definitions leads to the emergence of «terminological polysemy» [8].

O. Lukasheva defines the personal rights of a person as a category that is not subject to the state: «... this category of rights is characterized by the fact that the state recognizes the freedom of the individual in a certain sphere of relations, which is left to the discretion of the individual and cannot be the object of state harassment. It provides the so-called negative freedom. These rights, being an attribute of every individual, are designed to legally protect the sphere of action of private interests, to guarantee the possibility of individual self-determination and self-realization of the individual». [9].

A. Kovler in his work on the anthropology of law devoted a separate chapter to personal rights [10], referring to the definition and definitions presented by V. Kruss. In particular, O. Nesterova points out, researchers defined the problem statement in the field of constitutional law and legal philosophy, but such provisions served as a foundation for building ideas about personal rights in legal theory [11].

O. Starovoytova in her dissertation work, devoted to the legal mechanism of realization of somatic rights, defines their essence through the right to the body, and refers, again, to the definition of V. Kruss. At the same time, it is interesting that O. Starovoytova considers the entire set of problems related to the legal regulation of somatic human rights in the framework of a new direction in legal science, «legal somatology». The scientist made an attempt to understand the problem of the human body from the standpoint of jurisprudence. In her writings about human somatic rights, which are part of natural rights. The author draws attention to the fact that a person's right to his body is his natural and inalienable right. At the same time, quite faithfully researching the legal mechanism of the somatic rights of a person, she, unfortunately, does not give the author's definition of the central category in the studied problem and presents only a historical and legal analysis of some rights [12].

O. Nesterova refers to V. Chkhikvadze, who points out that «the essence of a person is rooted in his body, the external physical forms of the human body, as a material carrier of the personal principle. To think differently means to absolutize the consciousness of a person as the only bearer of the personal principle» [13]. At the same time, O. Nesterova determines that it is more correct to use the term «personal rights», in the legal interpretation it acquires a legal meaning, defines the existence as a legal category, but does not deny the term «somatic rights», recognizing the possibility of their equal application and doctrinal recognition [11].

At the same time, the same scientist notes that despite a number of scientific approaches to the problem of the existence of personal rights, to the diversity of opinions and radically different understanding of the goals of recognizing these rights from the side of morality, ethics, religion, politics, studied in the aspect of law and philosophy, the conclusion follows – these rights,

which differ in close connection with basic rights and the physiological essence of a person, dependence on progress in the field of biomedicine, are the product of modern development of society, require an appropriate mechanism of legal protection and, undeniably, are a large group of human rights. Personal (somatic) rights require the definition of a worthy place in the system of human rights and the system of national and international law [11].

M. Lavryk, justifying the opposite point of view, explains the danger of possible pluralism in social and humanitarian knowledge, terminological similarity of the definition of «personal» rights with «personal» human rights [14]. Taking into account the etymological dynamism, as well as the fact that in jurisprudence the term «somatic» was not used, we conclude, – writes the scientist, – that it may well be suitable for the designation of «somatic human rights», as a rule, those that belong to the human body (or more precisely, a person's disposal of his body). In any case, it is necessary to specify the content of this concept and it should be taken into account that the term "somatic" acquires its meaning in the legal interpretation. When using this concept, a certain clarity of understanding is achieved, in addition, it is meaningfully suitable for this (indicates the appropriate scope of application of these rights, emphasizes the object for which this group of rights is allocated) [14].

It is interesting, in our opinion, the statement of A. Smirnov, who defines that human somatic rights should necessarily be considered personal (subjective) human rights (not the state, not society, not religion), since they are related to private, intimate life of a person, they have a natural origin, arise in a person from birth and are inalienable (from the standpoint of the concept of a modern legal state) [15]. That is why, rightly writes Yu. Turyanskyi, the researched newest group of rights is sometimes singled out as personal rights, which are a type of personal rights, that is, civil rights, as rights of the first generation (A. Kovler, in particular, is a supporter of this idea. However, such a terminological coincidence, the scientist considers it not very appropriate, since the similarity of sound can lead to the identification of the definition of «personal» rights with the «personal» rights of a person [16].

It should be noted, M. Lavryk points out, that at the end of the XIX century. under personal law – as opposed to property law – was understood as the object of which is a person, first of all, it is family and binding legal relations [14]. However, already in the middle of the 20th century. the meaning of the term personal rights has fundamentally changed, and it has come to mean political, labor, housing and other property and non-property rights of citizens that are not subject to assessment and are inseparable from their owners [17]. Over time, personal rights in Soviet law came to mean human rights, which in international law are called civil rights and, together with political, economic, social and cultural rights, form the basic human rights and freedoms [18].

M. Lavryk also notes that the term «personal rights» is quite widely used by supporters of the concept of somatic rights, and their relationship with personal rights is often given in such a way that personal rights are a type of personal rights, which, however, is far from indisputable [14].

In general, writes Yu. Turyanskyi, we believe it is a valid opinion that the latest possibilities related to the physicality of a person can be grouped under a single name – «somatic». The scientist motivates his position with the following provisions:

a) since the beginning of the third millennium, the scientific school of somatic rights has been developing quite successfully in the post-Soviet space, scientists have generally identified signs, principles and prerequisites for the existence of such rights, some of these provisions are practically implemented in legislation;

b) other names do not clearly reflect the substantive component of this group of rights, which may lead to dual interpretation, tautology and legal uncertainty;

c) the choice of a term of Greek origin indicates the universality of the concept and will make it possible to avoid mistakes during translation [16].

Arguing the above, scientist Yu. Turyansky writes: «the legal nature of somatic rights is complex. On the one hand, it indicates the personal capabilities of a person related to his body, organs and private life, reflects the principle of personal freedom of a person. On the other hand, the protection of bodily and personal capabilities is an important element of human rights, therefore the state and public guarantee of the absence of unauthorized influence on the bodily sphere is a component of the legal status of a person. It is not only the presence of a right that is important, but the inviolability, protection and protection of this right by other subjects – individuals, state authorities, officials, the state in general, people and society. The basis of somatic rights is quite extraordinary, since a person can not only change the natural primary basis of his physicality (by the way, not only his own – this issue can be decided by parents in relation to a child or close relatives in the case of a person who is on the verge of death), but also puts forward demands / obligations ties to society regarding the perception of this corporeality, and to the state – regarding the protection of its choice, if it is legal. The subject of a legal claim in somatic rights also appears to

be unique – corporeality, which can cover not only the existing essence, but also hypothetical changes, refers to personal characteristics personality The subject of somatic rights is not only actual real objects, but also a hypothetical possible result, in particular certain moments of modernization, improvement, modification of one's physicality» [16].

Justifying the term «personal rights», V. Kruss defines them as rights «having a purely personal character» [19]. Let's try to define what is «purely personal character» or «purely personal manifestations of human personality». Fundamental here is the concept of personality. The word personality is quite ambiguous and is used in different senses in everyday life, philosophy, psychology and sociology [20]. Most often, a person is defined as a human individual in the aspect of his social qualities, which are formed in the process of historically specific types of activity and social relations [21]. Hence, a person's personal qualities are derived from his lifestyle [22].

So, we fully agree with M. Lavryk's statement [14], that due to the terminological similarity of the concepts «personal rights» and «personal rights», as well as the huge pluralism in social and humanitarian knowledge regarding the category «personality», and the fundamental impossibility of an unambiguous definition at the moment of whether corporeality is a purely personal characteristic of a person, for the sake of clarity of legal terminology (to the extent possible), we also suggest abandoning the use of the term «personal rights». In addition, T. Matveeva points out, the possibility of different interpretations of this concept is so great that they are not even related to the jurisprudence of the interpretation [23].

CONCLUSIONS

Thus, we consider it expedient to use the term «somatic rights» and not «personal rights», firstly, due to the explanation of the danger of possible pluralism in social and humanitarian knowledge and the terminological similarity of the definition of «personal» rights with «personal» human rights and, secondly, due to the fact that when justifying the legal scientificity of the term «personal» rights, the main semantic load lies in the word «personality»; these are rights that have an individual, «purely personal character».

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REVIEW ARTICLE

ETHICAL EXPERTISE OF BIOMEDICAL RESEARCH AS A WAY OF HUMAN RIGHTS PROTECTION

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ABSTRACT

The aim: To find out the peculiarities of ethical expertise of biomedical research as a way of human rights protection.

Materials and methods: The dialectical method of cognition, based on the epistemological possibilities of the laws and categories of dialectics, provided a study of the formation and activity of bodies and institutions responsible for the ethical examination of biomedical research. Formal and logical methods of analysis and synthesis made it possible to reveal the meaning of the concepts that make up the subject of the study, to carry out their classification, as well as to formulate intermediate and general conclusions. The systematic method made it possible to investigate the role and significance of biomedical human rights among other human and citizen rights and freedoms. Using the historical method, the main stages of the formation of biomedical research with human participation were determined. The structural-functional method made it possible to clarify the internal structure of the mechanism of constitutional and legal protection of the rights and freedoms of a person and citizen in the process of conducting biomedical research, as well as to determine the functional purpose of each of the elements of this mechanism. The content of legal regulations governing social relations, within which the organization and functioning of the human rights protection mechanism in the process of conducting biomedical research is carried out, was revealed with the help of a special legal method of cognition. The comparativist method made it possible to identify similar features and differences in the constitutional and legal regulation of the mechanism for the protection of human rights in the process of conducting biomedical research.

Conclusions: Despite such a large number and variety of bioethics committees, it is worth noting that today it is not possible to state with certainty the existence of a full-fledged system of interconnected ethical committees, since the existing normative documents on their activities are of a temporary nature, and do not always clearly define the assigned their functions and tasks. In addition, there is an opinion that attempts to bureaucratize the existing situation (establish clear departmental subordination, define vertical and horizontal connections between ethics committees) are highly undesirable. Of course, on the one hand, excessive complication and bureaucratization will not contribute to progressive development in the activities of committees, and the system that has chaotically developed today is also not satisfactory.

KEY WORDS: personal human rights, somatic human rights, medicine, ethical principles, biomedical research, human rights protection

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INTRODUCTION

The sphere of health care is a paradigm that connects all countries of the world, is established in international standards and is reflected in various legal systems and legislation [1]. Based on the analysis of the works of theorists of law and medicine, scientists directly involved in the study of somatic human rights, religious scholars [2]. The search for an effective legal mechanism for the consolidation and real provision of human rights in the field of health care is the primary task of a modern, developed democratic state. Its study in the countries of the former USSR was carried out mostly by doctors, philosophers, sociologists, political scientists, and less by lawyers, therefore, a systematic examination of the issue from a legal standpoint seems to be in great demand today. The statement that the legislation of our country does not provide full protection of human rights, including when conducting biomedical research, does not require additional argumentation.

THE AIM

The aim is to find out the peculiarities of ethical expertise of biomedical research as a way of human rights protection.

MATERIALS AND METHODS

The dialectical method of cognition, based on the epistemological possibilities of the laws and categories of dialectics, provided a study of the formation and activity of bodies and institutions responsible for the ethical examination of biomedical research. Formal and logical methods of analysis and synthesis made

it possible to reveal the meaning of the concepts that make up the subject of the study, to carry out their classification, as well as to formulate intermediate and general conclusions. The systematic method made it possible to investigate the role and significance of biomedical human rights among other human and citizen rights and freedoms. Using the historical method, the main stages of the formation of biomedical research with human participation were determined. The structural-functional method made it possible to clarify the internal structure of the mechanism of constitutional and legal protection of the rights and freedoms of a person and citizen in the process of conducting biomedical research, as well as to determine the functional purpose of each of the elements of this mechanism. The content of legal regulations governing social relations, within which the organization and functioning of the human rights protection mechanism in the process of conducting biomedical research is carried out, was revealed with the help of a special legal method of cognition. The comparativist method made it possible to identify similar features and differences in the constitutional and legal regulation of the mechanism for the protection of human rights in the process of conducting biomedical research.

REVIEW AND DISCUSSION

The Association Agreement between Ukraine and the EU provides for the unification of the conditions for legitimizing the results of scientific research in the field of biology and medicine. The provisions of Chapter 22 «Public Health» of Chapter V of the Association Agreement require adaptation of the provisions of national legislation to EU legislation in the field of biomedical research. The active entry of domestic science into the European scientific space should take place rapidly and on the basis of European scientific deontology.

It should be noted that certain domestic fields of biology and medicine are quite competitive and are able to represent not only Ukrainian science, but also the market for relevant services. The mechanisms of ethical control over biomedical research are being improved in accordance with modern ideas about the admissibility and scope of human research. A strict requirement to comply with ethical standards in the conduct of biomedical research is put forward regardless of the degree of intervention in the human essence. As noted at the 5th National Congress on Bioethics in 2013, Ukrainian scientists faced the problems of publishing their scientific results in internationally recognized scientific publications that are included in the relevant scientific databases. The obstacle was not the lack of scientific novelty, but, in fact, the lack of internationally recognized proper ethical examination of biomedical research. Therefore, the urgency of not only reforming, but also the creation of appropriate national legislation is obvious [3].

Recently, scientists have become more and more often raising the question of feasibility, for example, gender, public or social expertise. According to E. Trukhanova, the position of M. Utyashev and I. Larinbaeva that today it is necessary to talk about the examination of legislation on the observance of human rights is considered justified. The bioethical examination of legislation in the field of health care proposed by scientists must become a part of such an examination and one of the most important areas of activity of ethical committees [4].

Let us turn to terminological aspects, in particular, to the differentiation of ethical and bioethical expertise and, accordingly, ethical and bioethical committees.

Ethics is the science of human attitude to morality itself: about what sense, what internal necessity a person sees in accepting certain moral norms, what he bases his choice on, where does his need for moral self-restraint arise in general. Without turning to this sphere of theoretical and practical universals (the largest generalizations that describe a certain state of the world and human relations to the world in general), we will not be able not only to find out the actual moral quality of this or that biomedical research, but even to determine its fundamental relationship to field of morality in general. However, these universals are the subject of reflections and searches of philosophy as a special branch of human knowledge. From this it follows that ethics, at least in its essential basis, can only be a philosophical science (which, of course, does not exclude the existence of partial branches of ethical knowledge distant from the philosophical subject — say, these or other applied professional ethics, empirical moral science, etc.) [5].

Bioethics is a set of ethical norms and principles that integrates into a single conceptual whole the aspects of classical ethics and the latest trends initiated by the rapid development of scientific and technical progress and the impact of negative changes in the environmental situation on human health. Bioethics as a system of views, ideas, norms and assessments, which regulates the behavior of people from the standpoint of preserving life on Earth, plays an increasingly important role in society. The problems of bioethics acquire a pronounced interdisciplinary character and therefore should cover all the main areas of human activity, starting with the development of measures aimed at preserving the environment, and ending with the

adoption of political decisions. Bioethics should create a set of moral principles, norms and rules binding on all mankind, determine the limit of human intervention in nature, the crossing of which is inadmissible [6].

Bioethics, or the ethics of life, is a branch of applied ethics – a philosophical discipline that studies moral problems, first of all, in relation to humans and all living things, determines which actions towards living things are morally permissible and which are unacceptable. Thus, we fully agree with the opinion that the terms «bioethical expertise» and, accordingly, by analogy, «bioethical committee» are the most appropriate, as they carry more specifics; at the same time, the use of the phrases «ethical examination» and «ethical committee» is also permissible, and in some cases these concepts can be synonymous [4].

The modern world has developed single general principles for the creation and functioning of ethics committees. There are: national (central) ethics committees, which are usually established at ministries of health or other relevant institutions, whose competence includes clinical research of medicinal products, regional and local (local) committees, which are established at medical institutions or universities , where clinical trials are conducted and directly ensure compliance with the ethical principles of the trial.

According to the rules of Good Clinical Practice (GCP), no research can be started without prior review and approval of the ethics committee, the provisions of GCP are implemented into national legislation [7].

The famous foreign scientist T. McCormick once identified eight reasons for the creation of ethics committees:

1) complexity of problems. Researchers and medical professionals want to make ethically acceptable decisions, while bioethical problems can be inherently difficult to understand, ambiguous, and the arguments proposed as a result of solving the situation can cause serious disagreements. On the basis of special knowledge, members of ethics committees can deeply study the problematic issues facing them and formulate possible solutions;

2) range of opinions. This range is often much wider than the range of opinions expressed by a single researcher or medical professional. Committees are able to express the widest range of opinions and offer the most constructive approach to solving problematic issues;

3) protection of research and medical institutions. In modern society, it is often possible to observe the preoccupation of medical institutions with their reputation, public opinion regarding the effectiveness of their activities. In most cases, this concern boils down to the desire to minimize the risk of litigation. This fact determines the desire of scientists and medical workers to enlist the support of their colleagues in order to avoid individual decision-making and to share joint responsibility with them;

4) the nature of judgments on the basis of which decisions are made. Researchers and medical professionals do not always have the necessary specialized knowledge (except knowledge of conducting research and the ability to provide qualified medical care) that would allow them to make informed bioethical decisions that take into account all the multifaceted aspects of this or that problem. Being interdisciplinary, ethics committees provide an excellent opportunity to make the most acceptable decision, even if they cannot recommend an ideal way out of the situation;

5) the special significance of the problem of the patient making an independent decision. The emergence of contradictions between the basic values of subjects and researchers often require the intervention of a third party (mediator), the role of which is to be fulfilled by ethics committees, which stand guard over the dignity of each patient and respect his right to make an independent decision;

6) the presence of an economic component. Taking into account the current state of affairs in terms of the limited resources allocated for research and medical measures, as well as the ever-increasing requirements for them, it is necessary to make decisions on a permanent basis about the fair and equitable distribution of not only the allocations allocated for conducting research, maintenance of hospitals and pharmacies, as well as the ever-increasing expenditure of time and effort of scientists and medical workers, whose personal interest today is increasingly and more often connected with the economic interests of employers;

7) religious beliefs of certain social groups. Research and medical institutions need a platform to discuss their bioethical and religious principles as they relate to scientific and medical practice. In such institutes, theological disagreements on a number of bioethical problems are often observed. Currently, religious policy, which can be formulated at the administrative level of the institution, goes far beyond the limits of scientific and medical special knowledge;

8) individual decisions that depend on the pluralism of public opinion. Researchers and medical workers must accept the opinions of the most diverse sections of society. When conflicting bioethical problems arise, their solution cannot be achieved by simple reference to scientific and medical conclusions. In this case, it will be necessary to make such policy decisions that go far beyond the decision of a single researcher or doctor [8].

The above causal series, defined by McCormick, quite objectively reflects a complex of interconnected conditions and reasons that demonstrate the need for the creation of ethical committees and the formation of an adequate legal basis for their functioning. At the same time, such a need is realized not only by practicing doctors, researchers, and lawyers, but is also quite clearly visible among the population.

Currently, world practice has formed a two-level system of ethics committees and two models (types) of the functioning of ethics committees: the American and European models. The «American model» is characterized by the attribution of prohibitive powers to veto research to the competence of ethics committees. Instead, the «European model» is characterized by «advisory-advisory» powers [9]. Speaking about the American model, V. Ignatiev emphasizes that the system of ethics committees in the USA is characterized by state control over the conduct of research, implemented in the clear regulation of their creation and activity at the legislative level, as well as the presence of prohibitory powers in the committees. In contrast to this, a distinctive feature of the European model is the consolidation of the processes of creation and activity of ethical committees not through legislative regulation, but through the adoption of decisions by certain professional associations; in addition, in the European model, ethics committees do not have the opportunity to impose a ban on conducting research that violates, in their opinion, ethical norms and principles [10].

Returning to the «European model» of biotic committees, we note that in Europe, bioethical committees began to be created in the 80s of the 20th century. Thus, in 1983, the National Advisory Ethics Committee in the field of life and health sciences began its activities in France, later in Italy (the National Advisory Committee for the Protection of Life and Health, the biotic movement in this country is actively supported by the Catholic Church, in particular, the Center for Bioethics at the Catholic University of the Sacred Heart in Rome).

In 1985, the Committee of Ministers and the Council of Europe created the Expert Committee on Bioethics, which in 1992 changed its name to the Steering Committee on Bioethics in the Council of Europe. It performs expert functions and is responsible for the preparation of bioethics documents at the European level, such as international bioethics conventions and guidelines. It consists of 60 experts proposed by the member states of the Council of Europe together with other representatives of the Parliamentary Assembly and the European Commission, observers from countries that are not part of the Council of Europe, as well as representatives of international organizations. The most important document developed by this institution and approved by the Committee of Ministers is the "Convention on the Protection of Human Rights and Dignity in Connection with the Application of the Achievements of Biology and Medicine: Convention on Biomedicine" (adopted in 1996, Oviedo, Spain) [11].

Analysis of the practice of creating bioethics committees in the countries of the world allows us to draw a conclusion about the existence of such committees at three main levels: national, regional and local. At the same time, national bioethical committees, as a rule, are created at the level of an individual state and, depending on what creates the body, can be classified into: 1) created by a state authority (for example, the Government, the relevant ministry, etc.). In most cases, such committees have full power, as their creation is conditioned by an administrative-authority decree; 2) created by a non-governmental body, such as a professional organization (for example, the Academy of Sciences) or a non-commercial human rights organization, as well as a result of joint actions of several organizations; 3) created under the national commission for UNESCO affairs.

Ethics committees at the regional level are characteristic of states with a federal state territorial system. Regional ethics committees may be known by different names: «non-departmental», «external», «independent», «contractual», «professional» and others. Their main goal is to consider bioethical problems arising in the regions and the availability of solutions to ethical problems for the general population [4].

Local ethics committees are created locally – in health care institutions or research institutes with the aim of improving the quality of medical care for patients. Now all services related to practical medicine have begun to show increased interest in ethics committees, in the activity of which they see a way of harmonious development of relations between medical workers and patients [9].

Ethical committees conducting ethical examination of biomedical research perform the following functions: 1) conducting independent ethical examination of research projects. Making amendments to the project in order to improve it; 2) monitoring of scientific research that has already begun. Monitoring compliance with the research protocol and the procedure for informing patients (volunteers) on the ground; 3) ensuring the training of researchers in ethics and bioethics through training, participation in relevant conferences, symposia, seminars, schools, etc.; 4) control over the researcher's humane treatment of experimental animals in biomedical research; 5) ensuring coordination

with other institutions (public organizations, local and regional bioethics associations, associations for the protection of patients' rights, etc.) on the basis of the introduction of bioethics principles into biomedical practice; 6) promoting the education of the population on issues of ethics and bioethics with the help of mass media and the publication of relevant printed materials; 7) development and submission to local and regional bodies of proposals for improving the existing practice of ethical examination of scientific research and clinical trials [12].

The effectiveness of the work of bioethical committees mostly depends on the methodological principles, their uniformity and the level of ethical expertise. However, as S. Pustovit points out, the space of ethical regulation and control of medical scientific projects is always characterized by a number of methodological problems: the first is the intro- and interdisciplinary nature of the research subject itself, the second is the scientization and medicalization of the life of a modern person [13].

The interdisciplinary character should be understood as the process of proliferation of ethical aspects in the middle of separate, clearly defined, historically formed scientific fields, for example, in medicine, biology, veterinary medicine. The interdisciplinary nature of bioethics involves connecting to the solution of moral dilemmas both natural and humanitarian sciences (and in the future – there are still «non-traditional» fields of knowledge). However, this is not the process of bringing philosophical ideas to the natural sciences, or, on the contrary, most likely, it is their convergent development on the basis of a fundamentally new general scientific picture of the world and a general worldview paradigm. The scientific picture of the world, as a global research program, is the basis for the translation of methods and principles from one science to another, and the further development of philosophical foundations is a necessary prerequisite for the expansion of the methodology of natural sciences into new subject areas [14].

The second methodological problem of the ethical regulation of biomedical research is the further scientization and medicalization of the life of a modern person as a prerequisite for the formation of certain prejudices of the members of the biotic committees of the research subjects, researchers and representatives of other parties involved in the conduct of medical research and their ethical regulation. The term «scientization» in this context means the dominance of the attitudes of a natural-scientific approach to research with human participation. The term «medicalization» means increasing the role of medicine in society, its expansion into those areas of social and individual life that did not belong to it before, for example, fertilization, gene therapy, neurolinguistic programming, therapeutic hypnosis, etc. [15].

CONCLUSIONS

Despite such a large number and variety of bioethics committees, it is worth noting that today it is not possible to state with certainty the existence of a full-fledged system of interconnected ethical committees, since the existing normative documents on their activities are of a temporary nature, and do not always clearly define the assigned their functions and tasks. In addition, there is an opinion that attempts to bureaucratize the existing situation (establish clear departmental subordination, define vertical and horizontal connections between ethics committees) are highly undesirable. Of course, on the one hand, excessive complication and bureaucratization will not contribute to progressive development in the activities of committees, and the system that has chaotically developed today is also not satisfactory.

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REVIEW ARTICLE

MOTIVATION THEORIES AS THE KEY TO MANAGEMENT OF MEDICAL STAFF

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ABSTRACT

The aim: To identify positions that are relevant for practical use in improving the process of human resource management in healthcare.
Materials and methods: Comparative analysis of motivation theories.
Conclusions: Human resources are a key intangible resource of a society or any organization. In today's post-industrial society, the development of a knowledge-based economy with the introduction of innovative technologies, principles of teamwork; improving the educational, cultural and qualification level of employees, democratization of socio-economic life in the country against the background of increasing population mobility and competition in the context of globalization, sets requirements for human resource management in such an important area as health care, in particular, in terms of activities to increase their motivation. Understanding the essence of motivation theories proves that people have different needs, so knowledge of different motivation theories can be used to manage medical staff.

KEY WORDS: motivation, theories of motivation, medical staff, management

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INTRODUCTION

Medical staff is the basis of health care system (HCS) in the world. It is the health care workers who play a key role in the provision of medical services. At the same time, the effectiveness of the health care system and the quality of health care services directly depend on the efficiency of medical staff, their knowledge and skills, and motivation [1].

The problem of motivation for work (of course, first its practical aspects, and later theoretical ones) was important, probably, since the emergence of the very phenomenon of work. While the elements of purposeful transformation of reality by living organisms – highly organized colonies of insects (ants, bees, termites, etc.), birds (nest-builders) or animals (e.g., beavers) – are determined by instincts, in humans the motive for labor becomes conscious. Even in ancient times, it was clear that meaningful activity is more effective, and the work of a motivated person is more productive. At the same time, the motives for work can be different – from simple preservation of life and creation of conditions for survival to obtaining reward or recognition, to a more complex sense of satisfaction with oneself and one's place in society. The different sides of motivation are illustrated by the well-known parable of the three masons who were working hard under the scorching sun. When asked "what are you doing?" the first one answered that he was doing hard, dirty work; the second one said that he was earning money to feed his family; and the third one proudly said: I'm building a temple!" [2].

Motivation through understanding the process of work and one's own place in it significantly affects the behavior of an individual (or team) and its effectiveness. This is especially important in such a specific area as health care, which requires a complex set of knowledge, practical skills and communication skills for professional activity.

THE AIM

To carry out a comparative analysis of a number of motivation theories and to identify, on their basis, positions relevant for practical use in improving the process of human resource management in health care.

MATERIALS AND METHODS

The main method that was used in this work is a comparative analysis of motivation theories. The materials for the analysis were various theories of motivation.

REVIEW AND DISCUSSION

In the twentieth century, the problem of motivation to work, the search for increasing the efficiency of each employee and labor collective was the subject of research by many scholars. The theory of motivation enhancement by B. Skinner (1938) made a certain contribution to the study of the mechanism of human motivation to work by studying the dependence of motivation on the person's previous work practice. The author argued that people take into account their work experience and try to choose those tasks that have been successful in the past and, conversely, avoid those tasks that have had negative results.

D. McClelland's theory of motivation, developed by an American psychologist in the 1940s, identifies three groups of needs: the need for involvement (participation, social interaction with others), power, and success. To select a way to influence behavior, this theory identifies two types of motivation: to succeed and to avoid failure. The first type is developed through receiving benefits and incentives, a more creative attitude to work and, as a result, a fuller realization of the individual's potential. Instead, the second type of motivation, failure avoidance, is developed under the influence of fear of reprimand, penalty, fine or other punishment or unwillingness to feel guilty for failure. It is characterized by limiting creative manifestations and initiative, excessive caution under the slogan "initiative will be punished!" [3].

F. Herzberg's theory of motivation and job content enrichment [4] is based on human needs. The development of the theory was preceded by a survey of 200 specialists of a large company (engineers and accountants) on the characteristics of certain situations when work was most satisfying or, conversely, particularly unpleasant. Herzberg distinguished two categories of factors for assessing the degree of job satisfaction: those factors that keep you at work, or external factors, and those that motivate you to work, or internal factors. There is a certain correspondence with A. Maslow's pyramid of needs: external factors are at the lower level, and internal factors are at the higher levels of the hierarchy. F. Herzberg called the ten factors external to work, by analogy with the concept of "hygienic" used in medical terminology (i.e., those factors that contribute to health, but do not necessarily improve it).

The list of hygienic (supporting) factors includes:

- Company policy (organization, institution) and management style.
- Technical management.
- Interpersonal relations with the immediate superior.
- Interpersonal relations with colleagues.
- Interpersonal relations with subordinates.
- Salary.
- Security of employment.
- Confidentiality.
- Conditions of employment.
- Status.

It was believed that a decrease in at least one of the ten factors to a level unacceptable to a particular employee would cause job dissatisfaction and inevitably have a negative impact on their work performance. It should be realized that compliance with all hygienic factors provides only temporary satisfaction from professional activity and is not a guarantee of motivation and long-term behavioral guidance, because the presence of their complex alone is not able to motivate a person to take actions to improve performance.

According to F. Herzberg, hygienic factors are related to the work environment, while motivating factors mainly relate to the inner world of the employee. Among the true motivators or factors of self-actualization capable of forming a sense of dedication to work, F. Herzberg classified six such factors as:

- personal success,
- recognition,
- promotion,
- independent work and decision-making,
- the possibility of career growth,
- responsibility.

It may seem paradoxical that Herzberg does not include salary in the group of motivators. But practice shows that if it does act as a motivating factor, it does so up to a certain point.

If external factors cannot provide maximum return, internal factors stimulate the individual to apply maximum effort, skills and abilities in the course of labor activity. Restricting the search for satisfaction solely to external factors creates an unpleasant feeling of dependence, which results in a desire to get rid of it in various forms (from passive, through reduced productivity, to active (looking for another job, sabotage, strike). However, a lack of motivators can also lead to job dissatisfaction, and well-combined hygiene factors (primarily, the remuneration received), on the contrary, can determine a long-term sense of employee satisfaction.

It was the realization of the destructive consequences of the excessive division of labor, the spread of conveyor methods of mass production to various fields of activity in the second half of the twentieth century that determined the practical continuation of F. Herzberg's theory in the form of the so-called concept of enrichment of labor, increasing its diversity both by expanding the content of the work itself and

improving the satisfaction of both parties: producers (service providers) and consumers.

However, the results of more recent studies have shown that Herzberg's assumption of increased labor productivity is not always supported by the mere fact of having satisfaction from work.

The Equity theory by J. S. Adams [5] (1963) is based on the realization that employees seek to maintain a balance between their own contributions to the common cause and the results obtained (tangible and intangible) and the perception of the same contributions and rewards of other employees. The main idea of this theory is that all employees want to establish fair relations with other employees, and the feeling of injustice leads to activity to eliminate (minimize) it, and such actions do not contribute to effective work. A study by an American scientist based on the well-known large company General Electric allowed to express the opinion that if there is a feeling that the remuneration is less than the effort spent on the work, it becomes a powerful impetus for demotivation to work in general and the employer in particular. Accordingly, a person's internal state is reflected in a decrease in labor productivity, increased dissatisfaction, and sometimes can even result in deliberate sabotage at the workplace (or revenge against more successful employees, in the opinion of offended team members). A practical recommendation arising from this theory is to introduce an atmosphere of openness and transparency regarding the remuneration received, to inform the staff in advance of the possibility of different assessments of their performance and practices of calculating remuneration and distributing bonuses and other incentives, and to ensure that authorized managers are able to explain the differences in a balanced, clear and reasonable manner. The conclusion "from the opposite" was the practice of remuneration adopted in some organizations, the amount and composition of which is known only to a narrow circle of people, in addition to the recipient.

From the provisions of Equity theory, it can also be traced that any person can have his or her own assessment of the fairness of the reward received for achieving certain results Satisfaction here is the result of internal and external rewards, taking into account the awareness of their fairness, and is also an indicator of the value of the reward received for the individual. And it is this assessment that will influence a person's perception of certain situations in the future.

In his classic work "Work and Motivation" [6] (1964), Canadian psychologist V. Vroom presented the Expectancy theory. It argues that the level of employee motivation depends on their perceptions of their own abilities and ability to perform specific tasks and receive rewards for this work. A person is motivated by the expectation that a certain behavior they choose will lead to the desired result.

Although both theories (V. Vroom and J.S. Adams) are based on the ratio of effort expended and reward expected for them, the theory of justice simultaneously takes into account not only a person's internal perception, but also the influence on him of the situation of a similar balance among people from the work environment with similar responsibilities (positions), which provided the basis for subjective comparison, comparisons, and conclusions about the fairness of the situation.

Studies in different countries and different fields of activity have shown that despite the declared position of remuneration based on the final result, in practice, most often the compensation of efforts expended is based on the time spent in the workplace and seniority (as well as compliance with the current minimum wage legislation), rather than a real assessment of the achieved performance.

In 1968, L. Porter and E. Lawler [3] developed a comprehensive procedural theory of motivation that includes elements of both expectancy and equity theories. The Porter-Lawler model of motivation theory includes five main variables, which include a person's effort, perception, results, reward, and satisfaction. This model establishes a reward-results relationship, i.e., an employee satisfies his or her own needs by receiving rewards for the results of labor activity.

Lawler, in particular, considered it appropriate to split the salary into three components. The first part is for the performance of job duties, the same for all those who perform similar functions in the organization. The second component is determined by length of service and cost-of-living factors in the country (cost of living, minimum wage, etc.). This part is received by everyone, it changes and is automatically adjusted at certain intervals. The third part is the most variable and is formed separately for each employee, the measure being the period achieved in the previous payment. The value of the third part can reach the sum of the other two components for an effective employee, but not forever. It may change based on the results of the next year. However, the first two parts can also grow with changes in the employee's level of responsibility and range of duties, length of service, and rising cost of living. The point of the system is to link remuneration to the results in the previous period, to determine the increase in pay by productivity. It emphasizes the difference between the value of a certain type of activity and the value of a person in

that position (despite the obvious interconnection between these concepts).

The following statements became important practical provisions of the theory:

- Effort depends on the reward for the work, the value (that is, the attitude of the employee to the promised salary) and the probability of receiving it
- Only the presence of personal motivation is not enough to achieve the goal when the employee lacks the necessary abilities (talent) and skills
- Obtaining the desired result is impossible if the employee is not aware of his role and does not have the necessary tools
- The staff's own opinion about the work performed is of great importance. Receiving less than the expected reward leads to a decrease in satisfaction and, therefore, to a decrease in motivation
- There is a relationship between the worker's morale and his efforts. For stimulation according to Porter-Lawler, tasks should be clearly set, performance should be monitored and decent and adequate payment for work should be made.
- Awareness that increasing activity and efficiency does not lead to changes in pay leads to loss of motivation.

According to the theory, there is a direct connection between the effort expended at work, reward, and satisfaction. The employee exerts the effort corresponding to the expected salary. Material satisfaction from the work performed is followed by moral satisfaction: a person is happy not only with money, but also with the goals achieved. Indeed, employees usually feel satisfied with their work results. But it's important to note that this is only the case if the pay meets the expectations (or at least is not less than that)!

In the twenty-first century, research into the theoretical aspects of motivation continues. Typically, the study of reward dependence has focused on the relationship between the level of remuneration, individual or group incentives, and employee performance. Recently, scholars in various fields have increasingly focused on the interaction between pay and individual characteristics (such as psychological individual differences, demographic (gender, age, marital status, etc.), qualifications and productivity, or the position of an individual in a group of employees). Recently, an interesting study was published on the differences in the strength of individuals' reactions to compensation. The authors develop a theory of compensation activation that considers compensation characteristics as "situations" in the workplace that provide signals that activate the relevant fundamental social motives of individuals that have become visible through stable or temporary individual characteristics [7].

It is quite natural that since the 1970s, in the most advanced management science in the USA at that time, the usual concept of "personnel management" was replaced by "human resources management", which characterized the recognition of employees as a valuable strategic resource and the economic feasibility of investing in them (and, of course, realizing the economic benefit from it).

According to the generally accepted definition, "human resources" means a separate type of resources, namely: a set of independent individuals capable of self-realization and personal development. From this follows the need to create conditions for the fullest possible coverage of the capabilities and abilities of specific people and to take into account their individual differences.

As noted in WHO resolution WHA64.10 (2011) "Strengthening national health emergency and disaster management capacities and health system resilience" and in document A68/27 "Global Health Emergency Human Resources", "the internal health workforce of countries, particularly in countries with weak health systems, is the first responder to threats in all countries and plays a key role in building resilient health systems" [8].

The main obstacle to achieving universal health coverage under target 3.8 of the Sustainable Development Goals is the mismatch between the population's need for medical staff and their availability at the present and in the future. Given the global shortage of healthcare workforce, a sufficient number of healthcare workers is the main criterion for achieving the goals of the Goals [9]. As noted by researchers in the field of medical management [10], the actual presence of an unmotivated workforce that will work without internal and external motives will not change the current situation of the medical staffing crisis.

The definition of the very concept of motivation and its role for employees of different specialties is interpreted by scientists and experts in different ways. What the entire scientific community agrees on is the importance of the role of motivation as a mechanism for influencing the work of employees in all areas of activity. Motivated employees work better, are more productive and engaged in the process. However, it should be remembered that every person has certain needs or desires that make them do certain things as an employee (determine their behavior, including professional behavior), which meet their needs (determine the level of satisfaction). Therefore, a change in motives can change which needs and desires are primary for a person in the process of work.

Thus, motivation is recognized as the main function of management, including medical staff. In today's conditions, which are determined by the new requirements of medical science and technology, the increasing role of the doctor's personality in the healthcare system, the need for medical business and management to find new approaches to implement practical models of motivation of medical staff that are appropriate to the current stage of development of the healthcare system, knowledge of motivation theories is essential.

CONCLUSIONS

1. Human resources are a key intangible resource of a society or any organization. In today's post-industrial society, the development of a knowledge-based economy with the introduction of innovative technologies, principles of teamwork; improving the educational, cultural and qualification level of employees, democratization of socio-economic life in the country against the background of increasing population mobility and competition in the context of globalization, sets requirements for human resource management in such an important area as health care, in particular, in terms of activities to increase their motivation.
2. Lack of knowledge about motivation theories can lead healthcare managers to the misconception that monetary incentives are the only way to motivate healthcare staff, but understanding the essence of motivation theories proves that people have different needs. In view of this, it is on the basis of various theories of motivation that it is possible to identify and formulate positions that will be relevant for practical use in improving the process of human resource management in healthcare in modern conditions, both in a single healthcare institution and in the medical industry as a whole.

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REVIEW ARTICLE

TREATMENT OF FRACTURES OF THE PROXIMAL TIBIAL METAEPIPHYSIS

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ABSTRACT

The aim: Analyze the literature data on the treatment of fractures of the proximal metaphysis of the tibia.

Materials and methods: The article used data from domestic and foreign scientific literature. Research methods such as bibliosemantic and informational-analytical were applied.

Conclusions: Tibial condyle fractures are serious injuries that lead to a decrease in quality of life. The congruence of the joint surface and axis must be restored as accurately as possible during the treatment of tibial condyle fractures, which requires constant improvement of fracture treatment methods

KEY WORDS: plateau fracture, tibia, fracture treatment, literature review

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INTRODUCTION

In Ukraine, approximately 2 million adults and over 300,000 children are injured annually. In particular, injuries rank third among the causes of mortality and primary disability in the country [1,2].

One type of injury is fractures of the proximal part of the tibia, which are relatively rare and belong to severe damage of the lower extremities. Epiphyseal fractures of the tibial plateau usually occur as a result of indirect trauma and are intra-articular. They occur more often when falling on straight legs or when deviating the tibia outward or inward, accounting for 2 to 11% of all tibial fractures and 2 to 5% of all skeletal fractures [3,4]. A range of different damages can occur as a result of a fracture of the tibial plateau, from minor avulsion fractures to complete fragmentation of the epiphysis, depending on the physiological, varus or valgus position of the limb at the time of trauma [3,5].

Fractures of the tibial plateau are increasingly recognized as an important prognostic factor for functional outcome [6-9]. Tibial plateau fractures with dislocation often result in functional limitations and subjective complaints from patients. Quality of life criteria are becoming increasingly important, along with functional and radiological outcomes [10].

THE AIM

Analyze the literature data on the treatment of fractures of the proximal metaphysis of the tibia.

MATERIALS AND METHODS

The article used data from domestic and foreign scientific literature. Research methods such as bibliosemantic and informational-analytical were applied.

REVIEW AND DISCUSSION

Fractures of the tibial plateau are a serious injury and can progress permanently. These fractures can occur in both elderly patients with a number of accompanying illnesses, such as osteoporosis, arthritis, osteoarthritis, and other chronic conditions that affect the bones and joints, as well as in young people who engage in active sports or use two-wheeled vehicles [11,12].

Following AO recommendations, the goal of treating tibial plateau fractures is to achieve anatomical reduction of the articular surface, reduce the risk of post-traumatic osteoarthritis, achieve proper alignment of the lower extremity, and provide stable fixation [12-16]. The wide range of morphological manifestations of tibial plateau fractures was the basis for classifications [6,17-19]. These fractures are usually accompanied by soft tissue injuries, which affect their treatment. It should be noted that complications from soft tissues are possible with any type of tibial plateau fracture [12]. Therefore, treatment of this type of fracture is important, as untreated fractures and subsequent sagittal displacement can lead to worse treatment outcomes, which negatively affect patients' quality of life [6,20]. The gold standard for treating this type of fracture is

open reduction and internal fixation (ORIF). Ring external fixators, as well as minimally invasive osteosynthesis or ORIF, can be used to treat complex joint fractures [12]. Currently, the search for new surgical strategies with the development of implants is relevant [6,21-24].

There are many variations, among which varus/valgus deformity and posterior plateau angulation of the tibial plateau only make up a small percentage. Due to the significant variability in anatomy [the right and left tibias are not always perfectly symmetrical, including at the level of the tibial plateau], an individualized approach to the patient can improve the treatment process, including implant fitting, biomechanical stability, anatomical reduction, and complications that may be associated with the equipment [6].

In the study [25,26], scientists aimed to evaluate surgical techniques for the placement of a titanium cage with augmentation of bovine demineralized bone matrix xenograft for the treatment of subchondral bone defects associated with fractures of the tibial plateau. It was found that fixation with augmentation using a titanium cage with xenograft augmentation is an effective and safe treatment for tibial plateau fractures with depression.

The authors of the research [27] have established that the new concept of fiction in the treatment of complex fractures of the tibial plateau is the tri-column fixation, which is particularly useful for multi-fragment fractures involving the posterior column. The combination of posterior and anterolateral approaches is an effective and safe method of direct reduction and satisfactory fixation of this type of fracture. The updated concept of the three columns, which can evaluate the morphology of the fracture and the mechanism of injury, can be used for surgical treatment of fractures of the tibial plateau. The results of the study show the successful use of fixation constructs that are biologically safe, while avoiding fixation failures and complications in both simple and complex fractures of the tibial plateau [28, 29].

It has been established that a new universal anatomical fixation plate can provide strong fixation, satisfactory postoperative reduction of the fracture, and good restoration of knee function for fractures associated with the posterolateral column of the tibial plateau [29].

The use of anatomical compression fixation plates largely prevents settling of reduced joint surface fragments, allowing for improved patient outcomes compared to conventional plates and screws [30].

For fractures of the lateral plateau of the tibial bone, including compression and split fractures (Schatzker type 2), the authors of the study [11] have proposed a new minimally invasive technique that involves the use of a balloon and two percutaneously placed fixation screws, which are connected with the filling of polymethylmethacrylate cement. Visualization of associated injuries, cement leakage, and fracture reduction can be achieved using arthroscopy. Before obtaining clinical validation, this therapeutic approach was developed and refined through cadaver testing. This minimally invasive technique of tuberoplasty for treating fractures of the tibial plateau is a good alternative to the traditional bone tamp method. This method provides anatomical reduction of the fracture in a gentle and progressive way, mechanical stability, and minimally aggressive osteosynthesis, which ensures early rehabilitation and quick weight bearing. This method, developed on cadavers, demonstrates the relevance of tuberoplasty. The researchers plan to perform biomechanical studies to quantitatively determine acceptable mechanical loads for quick weight bearing [11,31-34].

CONCLUSIONS

Tibial condyle fractures are serious injuries that lead to a decrease in quality of life. The congruence of the joint surface and axis must be restored as accurately as possible during the treatment of tibial condyle fractures, which requires constant improvement of fracture treatment methods.

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CASE STUDY

SARS-COVID-19 TRIGGERED WERNICKE'S ENCEPHALOPATHY (CLINICAL CASE)

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ABSTRACT
Patient P., born in 1956, was found by relatives in a state of confused consciousness, an act of involuntary urination and defecation, numbness and weakening of the strength of both lower limbs were recorded. He was taken by ambulance to the reception room of the Regional Clinical Center of Neurosurgery and Neurology. The following concomitant diseases are known from the life anamnesis: Atrial fibrillation, gout, hypertension and type II non-insulin-dependent diabetes mellitus. Objective status: general condition of medium severity, tophuses of small joints of hands and feet, knee and elbow joints. Pronounced deformity of hands and feet due to gouty lesions. Heart tones are weakened. Breath sounds are weakened. The abdomen is soft, not painful on palpation. Glasgow coma scale 14-15 points. Consciousness is confused, disoriented in time, space and own person. To clarify the diagnosis, clinical and laboratory and instrumental diagnostic methods were used.
Neurological complications, in particular, acute encephalopathy, on the background of coronavirus infection, may develop in patients with the presence of such risk factors as advanced age, cardiovascular diseases, hypertension, diabetes, gout. Most of the neurological complications in COVID-19 are probably not related to the direct penetration of the virus into the CNS, but are a trigger for the development of the pathology. Neuroimaging in such cases does not reveal pathological changes or reflects non-specific disorders.

KEY WORDS: acute encephalopathy, coronavirus infection, patient

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INTRODUCTION

COVID-19 continues to remain an important medical and social problem [1, 2]. The number of reports of severe neurological damage, encephalitis/meningoencephalitis, encephalopathies, epileptic status, ischemic/hemorrhagic strokes, severe neuropathies, against the background of COVID-19 is increasing, which makes this problem particularly relevant.

There are reports of documented persistent damage to many organs and systems (lungs, heart, brain, kidneys and vascular system, etc.) in patients who have suffered from COVID-19 [3]. Among the main risk factors for the development of a severe course of COVID-19, the most important are advanced age, arterial hypertension, diabetes mellitus (DM), chronic obstructive pulmonary diseases, cardiovascular and cerebrovascular diseases [4,5].

The National Institute for Health and Care Improvement of Great Britain (NICE) offers the following terminology for COVID-19 [6]:

- acute COVID 19: signs and symptoms persisting for up to 4 weeks;
- prolonged symptomatic COVID 19: signs and symptoms persist from 4 to 12 weeks;
- post-COVID 19 syndrome: signs and symptoms that persist during and after the infectious disease (>12 weeks) and do not have an alternative diagnosis.

The Infectious Diseases Society of America (IDSA) distinguishes between «prolonged COVID», «post-COVID syndrome» and «post-acute COVID-19 syndrome».

Among the reasons that lead to the development of post-covid syndrome, the following are distinguished: persistent viremia due to a weak or absent antibody response, relapses or re-infection; inflammatory or other immune reactions; mental factors (post-traumatic stress); the presence of concomitant diseases.

The neurovirulence capacity of coronaviruses, including SARS-CoV-2, may contribute to the relatively high prevalence of neurological complications in patients with COVID-19, especially among hospitalized patients with severe or critical illness [7]. Early reports estimated the incidence of neurological complications to be approximately 37% [8,9].

Neurological manifestations arising from coronavirus infection can be divided into two categories: central and

peripheral [10]. Central manifestations include headache, dizziness, confusion, encephalopathy, delirium, syncope, seizures, difficulty walking, cerebrovascular events, encephalitis, and the development of postinfectious autoimmune disorders. Peripheral disorders include isolated cranial nerve dysfunction (impaired sense of smell and taste), Guillain-Barré syndrome, and myositis-like muscle damage. Although most neurological symptoms develop during the course of the disease, others, such as acute stroke, may be initial manifestations.

Encephalopathy with COVID-19 is quite common, especially in severe cases of the course of the disease. Encephalopathy is a collective concept of similar lesions of the brain with a violation of its function, which can be both a syndrome accompanying other diseases (secondary) and an independent nosological unit (primary). [11]. Symptoms and clinical course of this condition can be very heterogeneous.

Pathological mechanisms of encephalopathies caused by SARS-CoV-2 are: hypoxia, sepsis, severe systemic inflammation, renal failure, cytokine storm. The absence of an inflammatory reaction in the cerebrospinal fluid and affected brain tissue indicates that the disease is not inflammatory [12].

Hospitalized patients positive for SARS-CoV-2 show a characteristic form of encephalopathy associated with systemic hyperinflammation, mainly triggered by an abnormally excessive innate immune response. This kind of encephalopathy is characterized by generalized brain dysfunction with confused consciousness, often combined with hyperactive delirium and excitement or, conversely, depression and a catatonic state [13]. Manifestations are often more intense, neuropsychiatric signs are more pronounced (delusions, agitation, mood changes, and irritability) and, as a rule, are less amenable to correction with traditional antipsychotic drugs compared to the usual spectrum of encephalopathies in critical illness.

It is recommended to perform a cerebrospinal fluid analysis to rule out meningoencephalitis or detect destructive markers after hypoxia. It should be noted that the analysis of the cerebrospinal fluid in such cases is either within the reference values or indicates a moderate increase in the level of protein without pleocytosis. This suggests that most of the neurological complications associated with SARS-CoV-2 are probably not related to direct entry of the virus into the CNS.

With the help of computed tomography (CT) or magnetic resonance imaging (MRI), it is possible to detect structural lesions, brain edema, as well as hemorrhagic and necrotic changes. It is recommended to conduct an analysis of cerebrospinal fluid to rule out meningoencephalitis or detect destructive markers after hypoxia.

The combination of general and neurological examinations with appropriate diagnostic studies (serological, CMR, EEG and neuroimaging) allows to establish a diagnosis of this type of inflammatory encephalopathy caused by an enhanced innate immune response. Encephalopathy has been frequently reported in patients with acute respiratory distress syndrome (ARDS) associated with COVID-19, and its etiology remains unclear. These patients have a hypercatabolic state, weight loss, which are risk factors for thiamine deficiency. The diagnosis of Wernicke's encephalopathy (WE) is complex and is based on risk factors for thiamine depletion. There is information that thiamine deficiency may represent a relevant etiology of encephalopathy associated with COVID-19[14].

General recommendations for the examination and basic principles of care for patients with post-covid syndrome are described in the Stanford Hall Consensus (Stanford Hall Consensus, 2020) [15].

CASE REPORT

For prepearing this article was used literature review and analysis of clinical, anamnestic, dynamic laboratory and instrumental methods of research of patient P. Analysis of disease course and treatment.

The article presents literature data and clinical observation of a patient with SARS-COVID-19 triggered Wernicke's encephalopathy. Hospitalized patients positive for SARS-COVID-19 show a characteristic form of encephalopathy associated with systemic hyperinflammation, mainly triggered by an abnormally excessive innate immune response. This kind of encephalopathy is characterized by generalized brain dysfunction with confused consciousness.

Patient P., 67 years old, was found by relatives in the morning of October 28th, 2022, in the condition of confused consciousness. Involuntary urination and defecation, numbness and weakening of the strength of both lower limbs were recorded. According to relatives, the patient was last seen healthy at 2.00 AM the same day. At 15:30 he was taken to the reception room of the Regional Clinical Center of Neurosurgery and Neurology by an ambulance. Multispiral computed tomography (MSCT) of the brain was urgently performed. No signs of hemorrhage were found. He was hospitalized outside the therapeutic window of systemic thrombolytic therapy (STLT).

Relatives reported the presence of the coronavirus infection in the family for the last 2 weeks, but the patient was not tested, did not seek medical help. They also noted the patient's refusal to eat for the last 2 weeks, the appearance of general weakness, general clinical tests had been performed.

The following concomitant diseases are known from the anamnesis of life: Atrial fibrillation, (cardioversion in 2017), gout, hypertension and non-insulin-dependent type II diabetes. Medications, taken on a regular basis are: nebivalol 5 mg/d, adenuric, metformin 500 mg/d;

Objective status: general condition moderately severe, the patient is well-fed. Blood pressure 170/100 mmHg, body temperature 36.7°C. The skin of the legs and hands is dry, with pronounced trophic changes. Tophus of small joints of hands and feet, knee and elbow joints are noted. Pronounced deformity of hands and feet due to gouty lesions. Cardiac activity is arrhythmic. Heart rate – within 80-100 bpm. Heart tones are weakened. Breathing is weakened. The abdomen is soft, not painful on palpation.

Neurological status: Glasgow Coma Scale is 14-15 points. Consciousness is confused, the patient is disorientated in time, space and his own person, he answers questions selectively, monosyllabically. Performs simple commands. Cranial nerves: isocoria, normal reaction of the pupils to light. Ophthalmodynamics in full. Nystagmus when looking to both sides. Surface sensitivity on the face cannot be assessed objectively. The face is symmetrical. Swallowing is not impaired. Tongue behind the midline. Tendon reflexes from arms and legs: reduced, distal-torpid. Pathological foot signs are negative. Muscle strength in all limbs up to 5 points, it is impossible to assess objectively due to the patient's uncooperativeness. Superficial and deep types of sensitivity cannot be assessed due to confusion of consciousness.

To clarify the diagnosis, the following laboratory and instrumental diagnostic methods were performed:

Multispiral computed tomography (MSCT) of the brain from 10.28.22: cerebral atherosclerosis with angiopathy phenomena.

Multispiral computed tomography of the chest from 10.28.22: according to the CT scan, bilateral polysegmental pneumonia is detected. Dilated cardiomyopathy. Coronarosclerosis

Magnetic resonance imaging of the brain from 10.28.22: magnetic resonance signs of focal parenchymal damage of both cerebral hemispheres of vascular character – cerebral microangiopathy, Fazekas 1. Mediated MR-signs of fluid dynamics disorders of moderate severity. Atrophic changes in the cortex of both cerebral hemispheres (CGA 3)-ddx with neurodegenerative diseases.

C-reactive protein: more than 100 ng/ml.

As of 10.29.22, the patient's condition has slightly improved regarding consciousness, however, the patient's body temperature has risen to 37.8 degrees. The maximum values are 38.6 degrees.

On October 29, 2022, detection of RNA for COVID-19 by the PCR method was performed – the result was positive.

Study of the hemostasis system: 856,0 ng/ml.

Blood electrolytes: sodium – 133 mmol/l, potassium – 3 mmol/l, chlorine – 94 mmol/l.

Uric acid: 422 μmol/l.

Based on the results of examination, the following diagnosis was established: G93.4 Acute encephalopathy against the background of coronavirus infection.

In connection with the positive results of the PCR – testing for Coronavirus infection, the patient was transferred to the «Pulmonary Disease Center» of Transcarpathian Regional Council, where the following laboratory results were obtained:

31.10.22 Complete blood count: ESR 70 mm/h, hemoglobin 95 g/l, erythrocytes 2.9 T/l, leukocytes 8.9 T/l (lymphocytes 12.6%, monocytes 2.2%, granulocytes 85.2%), platelets 231 T/l

31.10.22 Biochemical blood analysis ALT 15U/l, AST 16.3U/l, amylase 26.3U/l, albumin 33.1g/l, total protein 49.6g/l, urea 5.87mmol/l, creatinine 61.5mmol/l, total bilirubin 13.53 μmol/l, calcium 1.77 mmol/l, potassium 2.5 mmol/l, blood sugar 7.6 mmol/l, LDH 172.0 U/l. Blood sugar 12.00-14.00 -9.3-9.0 mmol/l.

01.11.22 Biochemical blood analysis: ALT-15.0 U/l, AST 17.5 U/l, amylase 23.9 U/l, albumin 53.1 g/l, total protein 53.7 g/l, urea 7.06 mmol/l, creatinine 63.9 mmol/l l, total bilirubin 12.00 μmol/l, calcium 1.91 mmol/l, potassium 3.3 mmol/l, blood sugar 8.5 mmol/l, LDH 224.5 U/l.

31.10.22 Coagulogram: prothrombin index 113% / 11.8sec, AChT- 27.6sec, thromb.time 12.6' INR-0.90, hematocrit 0.33 g/l, fibrinogen 5.52.

01.11.22 Coagulogram: prothrombin index 102% / 13.1sec, AChT-28.6 sec, thrombus time 14.0'INR- 0.98, hematocrit 0.32 g/l, fibrinogen 5.70. Blood group B(III)Rh(+).

Ultrasound examination of the heart (31.10.22): Mitral vlave – reg 1-2+, Aortal valve – reg+. Moderate left ventricular hypertrophy. Dilatation of the left ventricles. Contractile ability is slightly reduced due to diffuse hypokinesis. DR type 1. Slight pulmonary hypertension.

Ultrasound examination of the chest organs on 31.10.2022: During sonography of the front and lateral parts of both lungs – A-profile (normal). In the back parts of both lungs S6, S9, S10, the pleural line is unevenly thickened with shallow subpleural consolidations against the background of multiple diffuse B- lines – moderate interpleural interstitial syndrome with minimal amount of fluid. Conclusion: Signs of polysegmental bilateral pneumonia complicated by minimal bilateral pleurisy.

01.11.22 Retesting for SARS-CoV-2 (PCR) – «negative», in connection with which on 02.11.22 the patient was

transferred to the Regional Clinical Center of Neurosurgery and Neurology, to the Department of Cerebrovascular Pathology.

Ultrasound of extracranial vessels from 02.11.2022: Echo signs of atherosclerotic lesions of extracranial vessels of the neck, without hemodynamically significant stenoses. Hypoplasia of the right vertebral artery.

03.11.22 MRI of the brain 1.5 TL: in view of the obtained set of radiological data, there are more signs in proof of dysmetabolic damage of the supra- and infratentorial parenchima by type of Wernicke's encephalopathy. MR-signs of cerebral microangiopathy (Fazekas II), with changes in the brain parenchyma according to the ischemic-gliotic type, moderate liquefaction disorders in the form of replacement expansion of the external and internal CSF spaces. Phenomena of cerebral atrophy.

In order to further examine the patient, a lumbar puncture was performed (04.11.): cerebrospinal fluid samples were sent for general analysis, TORCH infection.

General analysis of liquor from 04.11.22: colorless, transparent, protein 1.61 g/l, glucose 4.5 mmol/l, erythrocytes 0-1 in the field of vision unchanged, cytosis – 0.

Cyanocobalamin level from 02.11.22: 343.0 (reference range 311.0-911.0 pg/ml), folic acid 20 ng/ml (3.0-17.0 pg/ml), estimated against the background of taking medications.

Diagnosis of TORCH infections in the cerebrospinal fluid by PCR (02.11.22): DNA of Toxoplasma gondii, DNA of cytomegalovirus, DNA of herpes simplex viruses types 1 and 2, DNA of Epstein-Barr virus – not detected.

Vitamin B1 in whole blood from 02.11.22: 11.5 μg/l (reference range 28-85 μg/l). Taking into account the previously detected anemia, additional blood tests were performed on 12.11.22: transferrin saturation 14.98% (reference range 8.00-45.00%), iron 7.10 μmol/l (11, 60-31.30 μmol/l), iron-binding capacity of serum 47.4 μmol/l (44.8-80.6 μmol/l).

Complete blood count from 11.11.22: ESR – 130 mm/h, hemoglobin 95 g/l, hematocrit 29.0%, erythrocytes 3.17×1012/l, leukocytes 14.0×109/l, platelets 436 ×109/l, thrombocrit 0.430%, average volume of erythrocytes 91.7 fL, average hemoglobin content in one erythrocyte 30.0 pg, average concentration of hemoglobin in erythrocytes 327 g/ l, red cell distribution width 17.2%, average volume of platelets is 9.8 fL; neutrophils 88.2%, lymphocytes 6.6%, monocytes 4%, eosinophils 0.2%, basophils 0.1%, large undifferentiated cells 0.8%, blasts – not detected, reactive lymphocytes – not detected, immature granulocytes – not detected, shift of the leukocyte formula to the left +, segmentation index 1.90, microcytes +, macrocytes – not detected, anisocytosis +, hypochromic erythrocytes +, hyperchromic erythrocytes – not detected, fragments of erythrocytes – not detected, shadows erythrocytes were not detected, large platelets were not detected.

Echocardioscopy from 12.11.2022: left ventricular hypertrophy, left and right ventricular dilatation. Slight expansion of the ascending aorta. Degenerative changes of the aortal and mitral valves. Moderate aortal and mitral insufficiency. 1-2nd stage pulmonary hypertension. Small amount of fluid in the pericardium with fibrin striations without signs of collapse of the right heart. Moderate hypokinesis of the interventricular septum, anterior-septal wall of the left ventricle. Moderate diffuse hypokinesis of other walls. Contractile ability is somewhat reduced. In dynamics – decrease in the amount of fluid in the pericardium.

On 12.11.22 the patient was consulted by a cardiologist with EchoCS, ECG data revision. A concomitant diagnosis of I30.8 Acute pericarditis was established.

Recommendations included: ibuprofen 600 mg every 8 hours for 1-2 weeks, with subsequent gradual dose reductions, colchicine 0.5 mg x 2/day with subsequent gradual dose reductions; complete blood count, C-reactive protein and EchoCS in dynamics, antibiotic therapy.

Echocardiogram control from 24.11.2022 found a decrease in the amount of fluid in the pericardium. Complete blood count control from 25.11.2022: reduction of ESR level (95 mm/h), treatment of anemia in outpatient settings was recommended.

The patient received the following treatment: infusion therapy with 0.9% NaCl 800 ml/d, KCL 7.5 20 ml/d, spironolactone 25 mg/d; amlodipine 5 mg/d, quetiapine 12.5 mg/d; Vitamin B1 10 ml/d; Vit B12 2.0 ml/d; Dexamethasone 4 mg/d; Enoxiparin 0.8 ml/d; Metformin 500 mg/d; Omeprazole 40 mg/d; Hepacef 2.0 ml/d; Rosuvastatin 20 mg/d; folic acid 3r/d; sorbifer 1 tab/d; adenuric 120 mg/d; nebivalol 5 mg/d; Lorista 25 mg/d; torasemide 10 mg/d; lactulose 45 ml/d; glycerin candles symptomatically.

At the time of discharge consciousness is confused, compared to previous days – improved communication with surrounding. Follows instructions. Nystagmus when looking to both sides. Tendon reflexes from arms and legs are reduced, distal reflexes – torpid. Muscle strength in all limbs – 5 scores. Pathological reflexes are negative. Meningeal signs are negative. Final diagnosis: SARS-COVID-19 triggered Wernicke's encephalopathy. Essential hypertension 2nd stage, cardiac insufficiency IIa with reduced left ventricular systolic function (EF 48%). Atrial fibrillation, permanent form, normosystole. Gout, rheumatoid-like form. Polyarthritic attack. Multiple tofuses. Diabetes type II, non-insulin dependent. Mild anemia. Dysphagia. Oculomotor disorders. Profound cognitive deficit.

We considered a clinical case of SARS-COVID-19 triggared Wernicke's Encephalopathy. Wernicke's Encephalopathy (WE) was described by Karl Wernicke in 1881 and is characterized by a clinical triad: encephalopathy,

ophthalmoparesis and ataxia, secondary to thiamine deficiency according to the literature, Thiamine deficiency is also observed in critical conditions, in particular, in patients with sepsis. Critically sick patients with COVID-19 have the same reasons for the development of toxic-metabolic encephalopathy. Examinations in patients with a severe course of COVID-19 demonstrate a hyper-inflammatory status (cytokine storm), a high catabolic state, intensive nutritional disorder with significant weight loss, frequent use of diuretics and dialysis therapy. An important component is the hyperactivity of the immune system, a high level of cytotoxicity, which contributes to adaptive and metabolic disorders. The occurrence of WE in three critically sick patients with COVID-19 and their positive response to thiamine therapy was first reported [14]. The clinical case described by us presents scientific information coherent with the general medical content

CONCLUSIONS

Neurological complications, in particular, acute encephalopathy, on the background of coronavirus infection, may develop in patients with the presence of such risk factors as advanced age, cardiovascular diseases, hypertension, diabetes, gout. Most of the neurological complications in COVID-19 are probably not related to the direct penetration of the virus into the CNS, but are a trigger for the development of the pathology. Neuroimaging in such cases does not reveal pathological changes or reflects non-specific disorders.

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CASE STUDY

CLINICAL CASE OF FALLOPIAN TUBE CANCER IN PATIENT OF POSTMENOPAUSAL AGE

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ABSTRACT

Fallopian tube cancer (FTC) is an extremely rare case in oncogynecological practice with an incidence of 0,14-1,8 % among all malignant diseases of the female genital organs. The lack of specific symptoms, imitation of other malignant gynecological diseases, significant similarity with endometrial and ovarian cancer make FTC a disease that is difficult to diagnose. At the preoperative stage, FTC can be detected in 0 to 21% of cases. We present a clinical case of FTC at an early stage in a 64-year-old woman. The patient was referred to the gynecological department of the hospital because of abnormal uterine bleeding (AUB) and pain in the lower abdomen, which had been bothering her for the last 2 months. During the gynecological examination, a tumor-like mass up to 5 cm in diameter was palpated on the left side, with a dense consistency, sensitive to palpation, and limited mobility. Transvaginal ultrasound, CT, oncological markers were made. 7 days later, after performing hysteroresectoscopy with polypectomy, the patient underwent Pfannenstil laparotomy, total hysterectomy with bilateral salpingo-oophorectomy and omentectomy, drainage of the abdominal cavity. Morphological result: in the wall of the left fallopian tube, the growth of adenocarcinoma, pT1a, G2 with foci of necrosis and invasion into the muscular layer of the wall of the fallopian tube is determined. Perineural and lymphovascular invasion in the studied material is not determined. This case of FTC in a postmenopausal woman confirms that it is difficult to detect malignant tumors of tubal localization at the preoperative stage.

KEY WORDS: fallopian tube cancer, diagnostic, case report

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INTRODUCTION

Fallopian tube cancer (FTC) is an extremely rare phenomenon in the practice of gynecological oncologists. The incidence of its occurrence is 0.14-1.8% among all malignant diseases of the female genital organs [1]. Most cases of fallopian tube cancer among women in the age category occur between 40-65 years, the average age is 55 [2]. However, this rare type of oncopathology is characterized by a rather aggressive course, the 5-year survival rate ranges from 35-56% [3]. The main obstacle to timely treatment of FTC is the difficulty of diagnosis. It is the non-specific symptoms of FTC that often lead to a false diagnosis of ovarian cancer or endometrial cancer due to the significant similarity of these oncopathologies. Another important factor that prevents early suspicion of FTC is its ability to imitate other gynecological diseases, namely: tuboovarian abscess, ectopic pregnancy, ovarian tumors, hydrosalpinx, hematosalpinx [4].

Pain, which can be pin-shaped or dull, remains the most common studied symptom of FTC at present. In one third of patients with fallopian tube carcinomas, the appearance of bloody discharge from the vagina is common. In 10% of cases with FTC, the phenomenon of watery tubular discharge is present, the peculiarity of which is that the colicky pain is relieved after the release of vaginal watery fluid. The erased clinical course, which is characteristic of malignant tumors of the fallopian tubes in the early stages, is a frequent reason for putiing the diagnosis during surgery or after obtaining a postoperative morphological result. At the preoperative stage, the possibility of detecting tube cancer varies from 0 to 21% of cases [5].

The aim was to report an incidental finding of left fallopian tube cancer at an early stage, which was confirmed by morphological post-operative findings.

CASE REPORT

A 64-year-old woman was referred by a gynecologist to the gynecological department due to complaints of pain. Anamnesis morbi – the pain had been bothering her for 2 months and the presence of moderate vaginal bleeding for the past few days. She hasn't been consulted by gynecologist beforehand. Menopause for 9 years. 2 pregnancies, 2 deliveries. Menarche at 14. Medical

history: appendectomy, cervical large loop excision due to cervical inrtaepithelial neoplasia. She denies inherited diseases in herself and relatives.

Objective datas: mammary glands were the same in size, symmetrical, palpation did not reveal any pathological changes, there were no discharges from the nipples. The external genitalia were properly developed, the entrance to the vagina was free, the cervix was macroscopically unchanged, the uterus was of normal size, mobile, not painful, a tumor-like mass up to 5 cm in diameter was palpable on the left side, dense consistency, sensitive to palpation, with limited mobility. Vaults were deep, paramertium was free. During transvaginal ultrasound, a mass of 30x25 mm in size, with reduced echogenicity, with clear, even contours, uniform structure, and signs of an endometrial polyp were visualized in the area of the left ovary. General analysis of blood and urine, biochemical analysis, coagulogram were normal. In connection with the presence of abundant bloody vaginal discharge, the patient underwent hysteroresectoscopy with polypectomy. Morphological examination revealed: a glandular polyp of hypoplastic endometrium. After the removal of the endometrial polyp, the woman continued to experience lower abdominal pain. Therefore, as part of the follow-up examination in the following days, after hysteroresectoscopy with polypectomy, a CT scan of the pelvic organs and a blood test for ovarian tumor markers were prescribed. CT of pelvic region revealed that the right ovary was thickened, measuring 15x10 mm, the left ovary was unevenly thickened, measuring 34.5x19 mm, containing a solid-cystic area, measuring 27x11 mm. According to the CT scan, a formation of the left ovary (thecoma/Cr ?). The results of blood analysis for oncological markers were as follows: ROMA index (HE4/CA-125)– 42.53%, ovarian tumor marker (HE4)– 54.66 pmol/l, ovarian tumor marker (CA-125) 142 IU/ml. The patient was sent for consultation to an oncologist, as there was a suspicion of a high risk of ovarian cancer. Taking into account the complaints, medical history, objective examination data, ultrasound, CT of pelvic region, analysis of ovarian tumor markers, a preliminary diagnosis was made: proliferative tumor of left ovary. 7 days later, after performing hysteroresectoscopy with polypectomy, the patient underwent Pfannenstil laparotomy, total hysterectomy with bilateral salpingo-oophorectomy and omentectomy, drainage of the abdominal cavity. During the operation, it was found: the uterus was hypotrophic, the right appendages were not enlarged. The left ovary contained a cystic formation 1.5 cm in diameter, the left fallopian tube in the ampullary part was dilated to 4x5 cm, with liquid content. During the post-operative morphological examination of the uterus with appendages, it was found that the fallopian tube, 3 cm in length, with a tumor of 2 cm in diameter. The tumor is whitish in color and soft in consistency. Macroscopically, the tumor infiltrates the muscular layer of the fallopian tube, without sprouting into the serous membrane. Microscopic: the growth of adenocarcinoma, pT1a, G2 with foci of necrosis and invasion into the muscle layer of the wall of the uterine tube is determined in the wall of the left fallopian tube. Perineural and lymphovascular invasion in the studied material is not determined. The right fallopian tube had a normal histological structure. Atrophic endometrium. Cervix without pathological changes. Fibrous bodies and moderate fibrosis of the stroma are determined in the ovaries. Omentum without tumorous elements. The patient was discharged in satisfactory condition. He is under the supervision of an oncologist.

Today, the causes of FTC are not fully understood, but it is believed to be a polyetiological disease [1]. An important place in the etiology of FTC is chronic inflammatory processes of the pelvic organs, infertility, endometriosis of fallopian tubes [2]. It should be noted that BRCA1 and BRCA2 carriers have a significant risk of FTC [4]. Cases have been described in which patients with abnormal vaginal bleeding were suspected of having endometrial carcinoma, but in fact it was FTC [6]. There is a case of FTC, which manifested itself in the form of vaginal adenocarcinoma with the only clinical symptom – vaginal bleeding [7].

As for the localization of the malignant process, usually the ampullary part of the fallopian tubes is more often involved in the pathological process. Only in 8% of cases, the primary tumor is localized in the area of the fimbriae. As a rule, FTC is characterized by a unilateral lesion, bilateral tumors are observed in only 3-12.5% [5]. Among the histological variants of primary fallopian tube cancer, serous adenocarcinoma occurs in 85-90% of cases [4].

The following types of metastatic spread are characteristic of FTC: lymphogenic, hematogenous, transluminal migration. As a result of transcoelomic exfoliation of tumor cells, there is a great threat of peritoneal carcinomatosis. Involvement in the malignant process of pelvic and para-aortic lymph nodes is noted only in 42-59% of patients. A case of FTC was described, in which only an isolated enlargement of the left supraclavicular lymph node was observed and there were complaints of pain in the pelvis and back [2]. Axillary lymphadenopathy also occurs as the first clinical manifestation of serous fallopian tube carcinoma [8].

As for diagnosis, malignant tumors of the fallopian tubes are difficult to diagnose with the help of imaging methods such as ultrasound, CT, and MRI. Regarding ultrasound, there

are unfortunately no specific signs for FTC, so this method is of limited value. In some cases, sonographically visualized tubular shaped formations or even a tumor with the appearance of a tubular circle. At MRI, it is also sometimes possible to see the presence of specific changes that can warn about the presence of FTC: a tubular-like mass with a characteristic homogeneous signal, in T1- images – low signal intensity, in T2-images – high signal intensity, hydrosalpinx, intrauterine fluid . MRI is a reliable method for differential diagnosis of FTC and ovarian cancer [9]. But it is worth, once again, to understand that each case of FTC is characterized by different results both with ultrasound and with CT and MRI.

The determination of tumor markers is an important task, although they are reported to play no role in the diagnosis of FTC. On the other hand, results of lots of investigations inddicate that CA-125 is the most common tumor marker used for diagnosis and monitoring of FTC. An elevated level of CA-125 is observed in 80% of patients with FTC [2]. CA-125 can be used as a marker of disease recurrence in FTC, because its increase in blood serum precedes clinical symptoms and imaging changes by about 3 months. β-subunits of hCG are also of great importance in the diagnosis of FTC, since it is believed that the secretion of the β-subunit reflects the aggressive course of FTC. It is possible to establish increased levels of the β-subunit of hCG in the blood serum of patients with FTC in 37% of cases [10].

Cytological examination of smears from the cervix is not of great importance in the detection of FTC. Abnormal cytology was detected in smears in only 10-36% of patients with FTC [1,11]. Some scientific works claim that only in 0-23% of cases, Pap smears were positive for FTC. If the Papanicolaou smear is abnormal, and the results of colposcopy, endometrial curettage and cervical biopsy are normal, then the presence of malignant tubal tumors should not be excluded. Treatment of patients with fallopian tube cancer is the same as in the case of ovarian cancer [11]. For FTC, the method of choice is total abdominal hysterectomy with bilateral salpingo-oophorectomy and infracolic omentectomy, appendectomy, as well as abdominal lavage and peritoneal biopsy. The performance of pelvic and para-aortic lymphadenectomy in FTC remains a controversial issue [12].

CONCLUSIONS

This clinical case confirms that FTC is an insidious pathology that is difficult to detect at the preoperative stage of diagnosis due to the lack of specific symptoms. Both doctors and patients should be extremely aware of the fact that the appearance of abnormal uterine bleeding, pain in the lower abdomen, watery vaginal discharge, increased levels of β-subunits of hCG, CA-125, the appearance of enlarged lymph nodes can serve in favor of malignancy of fallopia tubes. Therefore, it is always necessary to include FTC in differential diagnosis with respect to other malignant and inflammatory diseases.

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CASE STUDY

PATIENT MANAGEMENT TACTICS AT DIFFERENT STAGES OF GASTROINTESTINAL STROMAL TUMORS (GIST)

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ABSTRACT

The aim: To analyze the results of treatment even in limited groups of patients.

Materials and methods: Clinical cases of GIST based on the materials of the surgical clinic of the Central Municipal Hospital in Uzhgorod (Transcarpathian region) were discussed. Clinical, ultrasound and CT monitoring was provided. CT dynamics were assessed according to RECIST 1.1.

Conclusions: Only surgery resection is enough in case of the "small" tumor originated from the stomach. Otherwise, in case of locally-widespread GIST it is expedient to refrain from radical surgical intervention. High-grade GIST was verified by the IHC examination with mutation of the KIT gene in exon 11. Imatinib mesylate 400 mg PO daily was prescribed. More than 1-year follow-up result: firstly more than 50% reduction of the tumor size with subsequent stabilization of the disease.

Minimally invasive processes allow surgical interventions and do not require aggressive adjuvant therapy. The presence of a giant GIST is a serious diagnostic and treatment challenge. Only management of the patient by a multidisciplinary team allows to resolve diagnostic and treatment contradictions, to create the prospect of achieving complete or partial remission and long-term survival.

KEY WORDS: Gastrointestinal stromal tumors (GIST), surgical care, immunohistochemical (IHC) study, targeted therapy, imatinib mesylate

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) are a heterogeneous group of c-KIT positive mesenchymal tumors that have specific morphological, immunohistochemical and molecular characteristics. In routine morphological diagnosis, GIST is often mistakenly described as "mesenchymal tumor", "neuroendocrine tumor", "carcinoid". An IHC study allows to verify GIST by CD 117 and DOG1 markers [1, 2]. Proliferative potential is determined by mitotic activity (counting the number of mitoses in 50 fields of view of the micropreparation), as well as by Ki 67 marker, which predicts the aggressiveness of the disease course. It is also advisable to conduct a molecular study on the presence and nature of mutations in KIT (wild type or mutation in exons 9, 11, 12), which allows predicting the response to target therapy. The topography of GIST in the gastrointestinal tract is as follows: the majority (up to 70%) affects the stomach, 30% – other parts of the gastrointestinal tract, mainly the small intestine.

The majority of patients are 50+. The incidence rate of GIST does not exceed 0.8 – 1.5 cases per 100,000 population, prevalence rate – up to 13 patients per 100,000 population [3]. Intensive prevalence rates (less than 50 patients per 100,000 population) allow GIST to be classified as an "orphan" disease with ORPHACode 44890 [4, 5]. Given the low incidence and prevalence rate, it is reasonable to analyze the results of treatment even in limited groups of patients.

In routine clinical practice, GISTs are often diagnosed at locally disseminated and metastatic stages. Operative treatment is indicated for local processes originating from the organs of the upper gastrointestinal tract (stomach, small intestine). Preliminary information about the morphology of the tumor allows to reduce the standard volumes of intervention (for the stomach – subtotal and wedge-shaped resections instead of gastrectomy and D2 lymphodissection). The requirements for radicalism of handing (R0) remain unchanged. Locally disseminated tumors, the resectability of which is often doubtful, also require surgical revision. According to the literature data, cytoreductive interventions in such cases are not the optimal solution [6]. GISTs are resistant to "standard" polychemotherapy regimens. The introduction into clinical practice in 2000 of targeted drugs, in particular, tyrosine kinase inhibitors (imatinib mesylate, sunitinib, regorafenib), significantly improved the prognosis of patients with GIST [7].

THE AIM

To evaluate the results of a multimodal approach to the treatment of GIST.

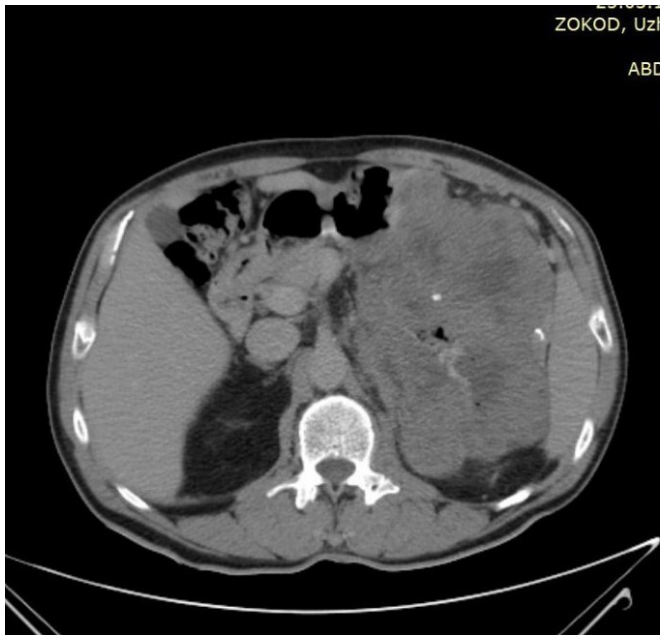

Fig. 1. CT data 24.09.2021, tumor 213x141x118 mm.

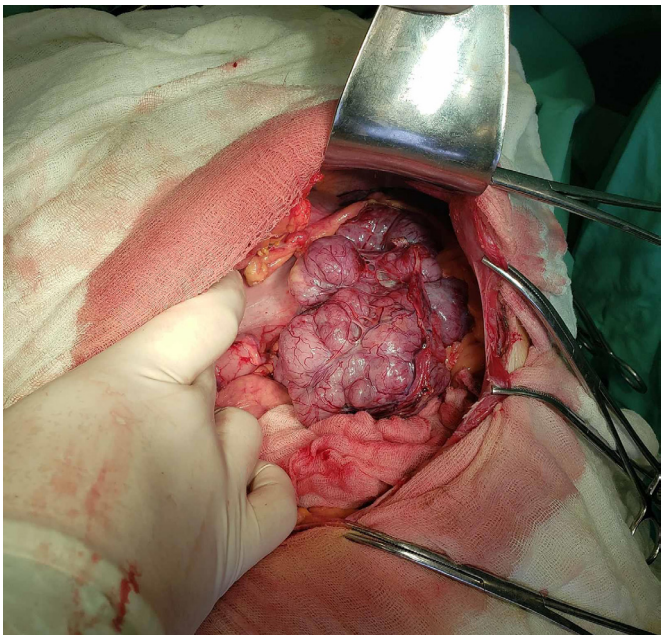

Fig. 2. Laparotomy 27.10.2021, surgical revision of the abdominal cavity

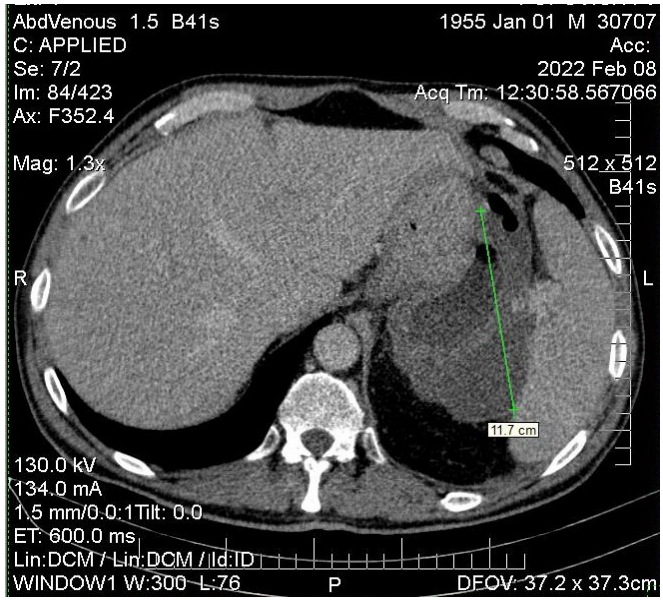

Fig. 3. CT data 08.02.2022, tumor 112x93x90 mm

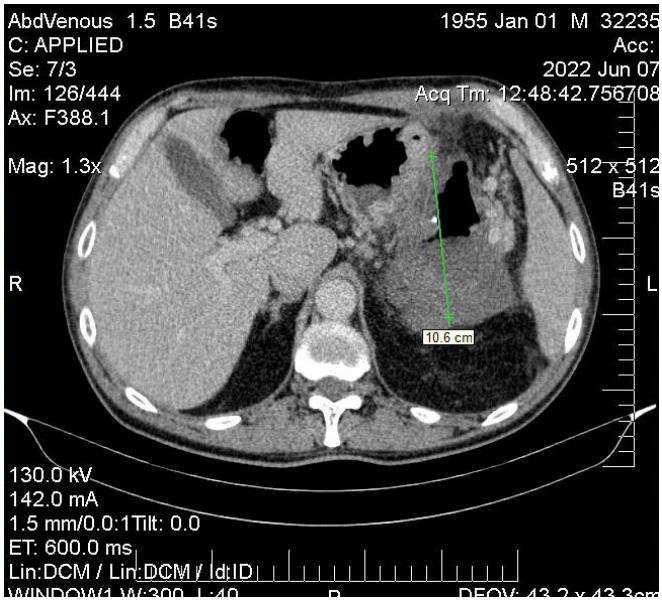

Fig. 4. CT data 07.06.2022, tumor 104x93x84 mm

MATERIALS AND METHODS

We considered clinical cases of GIST based on the materials of the surgical clinic of the Central Municipal Hospital in Uzhgorod (Transcarpathian region). Given the low incidence rate, we have only 3 GIST cases for analysis in the last 3 years (2021 – 2023).

CASE STUDY

Patient N., 68 years old, was operated on in the scope of a wedge-shaped resection of the stomach (R0), since the morphology of the process was previously verified on the material of the gastrobiopsy. She categorically refused adjuvant targeted therapy. As of January 2023, ECOG = 0, there are no data for prolongation of the process, the patient is working.

Patient K., 64 years old, was urgently operated in November 2022 at the height of bleeding in the amount of subtotal resection of the stomach with anastomosis according to B-II. General morphology – carcinoid, IHC (CSD morphological laboratory, Kyiv) – GIST (G1). A low proliferative index for Ki-67 allowed the observed tactics to be applied.

Locally disseminated and metastatic processes require alternative tactics. Patient P., 65 years old, was hospitalized with intense pain in the epigastrium,

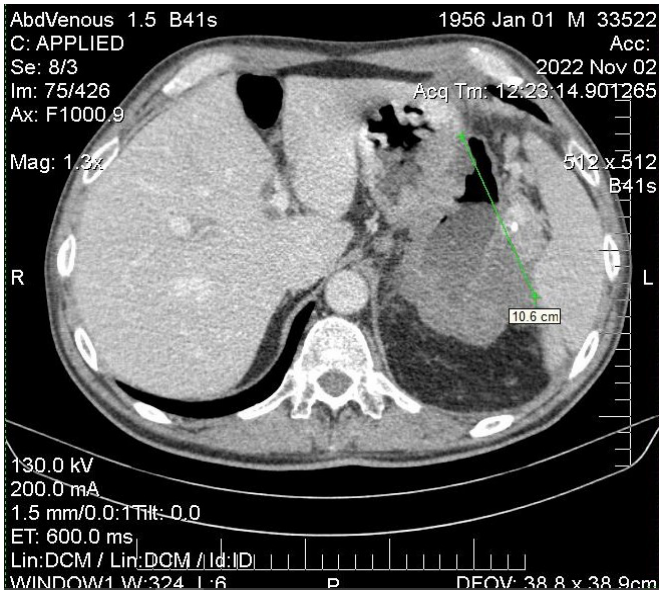

Fig. 5. CT data 02.11.2022, tumor 106x95x86 mm

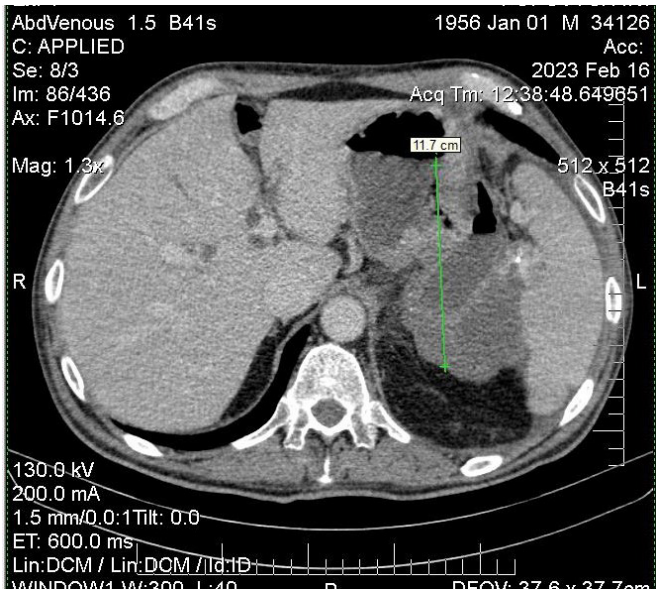

Fig. 6. CT data 16.02.23, tumor 115x86x72 mm

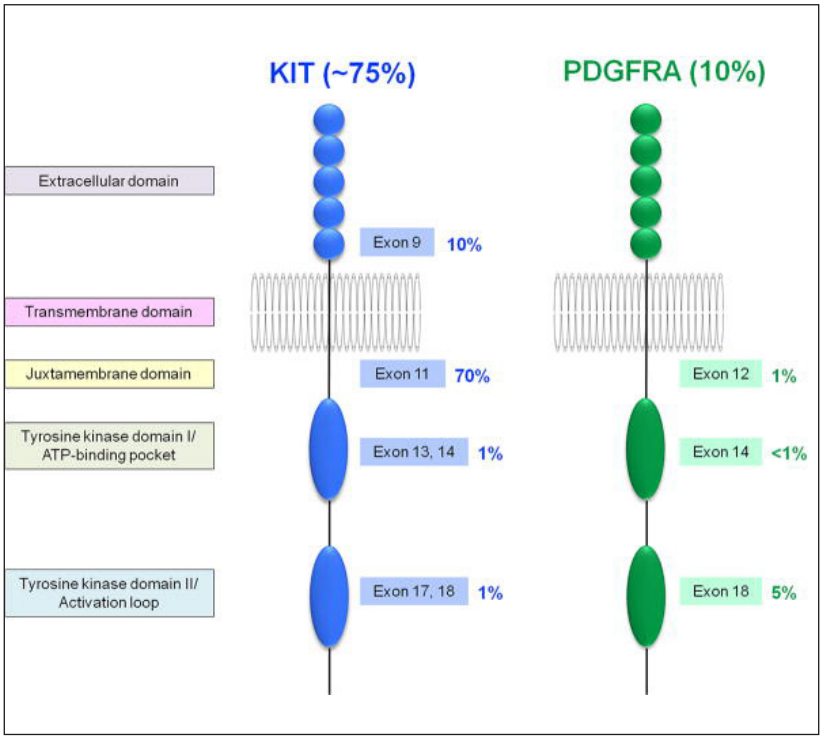

Fig. 7. Tyrosine kinase mutations in GIST: distribution of KIT and PDGFRA
(by I-M. Schaefer, A. Mariño-Enríquez, J. A. Fletcher, 2017)

pronounced general weakness, severe anemia, and hypoproteinemia. He has been experiencing these complaints for more than 5 months, and has lost more than 20 kg of body weight. During the examination, the skin and mucous membranes were pale, in the abdominal cavity, a tumor is contoured through the anterior abdominal wall and palpable, occupying the epi- and mesogastric area, mostly to the left of the midline. CT scan on September 24, 2021 – signs of a tumor measuring 213x141x118 mm (Fig. 1).

CT dynamics were assessed according to RECIST 1.1. The commission decided to start with an attempt at operative treatment. Intensive preoperative preparation (hemo-plasma transfusion) was carried out. Intraoperative findings: the tumor originated from the stomach with the formation of an ulcer defect in the cardiac part, intimately surrounds the aorta with spread to the posterior mediastinum, grows into the spleen, pancreas, the upper pole of the left kidney and the retroperitoneal space on the left (Fig. 2).

Intraoperatively, the case was consulted by an oncologist and a vascular surgeon. Taking into account the results of the revision, it was decided to refrain from radical surgical intervention An excisional biopsy of the tumor

was performed. The postoperative period was not complicated. Pathohistological conclusion – neuroendocrine tumor. GIST was verified by the CD 117 and DOG-1 markers [8], and a high-grade tumor (G2) by the number of mitotic figures was verified by the IHC examination in the certified laboratory CSD (Kyiv). Molecular research revealed a mutation of the KIT gene in exon 11 – a variant that is present in 67% of GIST cases [9]. Start of treatment – after 1 month after the laparotomy. Imatinib mesylate 400 mg PO daily was prescribed. Clinical and ultrasound evaluation was performed every month. CT control after 3 months from the start of treatment. February 8, 2022 – reduction of tumor size to 112 x 93 x 90 mm, June 7, 2022 – 104 x 93 x 84 mm (according to RECIST 1.1 criteria – regression by 47.4% and 51.2% respectively, partial response). (Fig. 3, 4).

CT 02.11.2022 – no dynamics, stabilization of the process (Fig. 5).

The general condition of the patient is satisfactory, as of January 2023, ECOG = 1, weight gain of 11 kg, no hematological changes, disturbances in the indicators of liver and kidney function. Side effects of treatment are moderate and do not significantly affect the quality of life. Objectively: on the CT scan from February 16, 2023, there is a slight increase in the mass to 115 x 86 x 72 mm, which can be considered as stabilization of the process (+9.6%), since according to RECIST 1.1 it does not exceed 20% of the previous data (Fig. 6).

DISCUSSION

Our results on surgical treatment of low-grade local GISTs at the height of gastric bleeding correlate with publications on successful surgical treatment in similar cases of gastrointestinal bleeding. [9]. In this case, the low-grade tumor did not require adjuvant targeted therapy. Tactics for the treatment of GIST with a high level of aggressiveness "high grade" require either surgical eradication (R0) followed by adjuvant target therapy, or conservative tactics with the use of tyrosine kinase inhibitors in inoperable cases. The overall mutation frequency of GIST reaches 85-90%, mainly in KIT and PDGFRA. Most of them demonstrated a high sensitivity to imatinib mesylate with KIT mutation in exon 11 (67.5%) [10]. The mutation frequency of KIT reaches 75-80% [11], (Fig.7).

On the other hand, the latest data on the molecular profile of GIST require a more precise stratification. For example, patients with rare KIT exon 11 homozygous mutations and KIT intron 10/exon 11 junction deletions demonstrated the highest recurrence rate and are associated with poor prognosis of patients with gastrointestinal stromal tumors [12].

Development of secondary tumor resistance to imatinib is possible in the future. According to the ESMO clinical recommendations, further tactics include switching to the 2nd line of targeted therapy (sorafenib) [14]. And other possible choice – the next, 3rd line of target therapy– regorafenib. [13]. Mutational profile of our patient tumor (mutation of the KIT gene in exon 11) does not predict a response to an increase in the daily dose of imatinib to 800 mg in our case [14].

CONCLUSIONS

The analysis of literature data and the above clinical cases show the following. Minimally invasive processes allow surgical interventions in smaller volumes than in other gastrointestinal tumors (adenocarcinomas) under the condition of radicalism (R0) and do not require aggressive neoadjuvant or adjuvant therapy. The presence of a giant GIST in a patient is a serious diagnostic and treatment challenge. Only a comprehensive examination of the patient, the use of modern intrascopic technologies followed by an adequate intraoperative assessment of resectability and a justified refusal of "over-radicalism" protect such patients from unjustified intra- and postoperative risks. Morphological, IHC and molecular verification of GIST, management of the patient by a multidisciplinary team allows to resolve diagnostic and treatment contradictions, to create the prospect of achieving complete or partial remission and long-term survival with a satisfactory quality of life.

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