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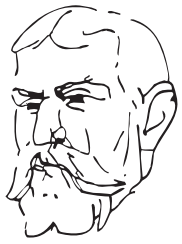

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Biegański

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ORIGINAL ARTICLE

COMPARATIVE EVALUATION OF CLINICAL APPLICATION OF MONOLITHIC AND FOLDING IMPLANTS IN REHABILITATION OF ELDERLY PATIENTS WITH VARIOUS DEGREES OF ATROPHY OF ALVEOLAR PROCESSES

DOI: 10.36740/WLek202204201

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ABSTRACT

The aim: Comparative evaluation of long-term results of clinical application of one- and two-stage surgical protocols of dental implantation with the use of monolithic and collapsible implants in the rehabilitation of elderly patients.

Materials and methods: Under clinical observation were 46 patients with various clinical diagnoses of dentition defects aged 60 to 70 years.The following methods were used in the study: one - stage surgical protocol of dental implantation operation with non - detachable implants of ART IMPLANT system with subsequent temporary splint fixed prosthesis and immediate occlusive functional load, mechanical oscillatory - resonance method, questionnaire and statistical analysis.

Results: The duration of surgical stages of treatment and complete rehabilitation showed statistically significant differences ($p < 0.05$) and was significantly less when using a single-stage protocol of dental implant surgery and non-detachable implants and averaged 3.9 ± 0.8, $p < 0.05$ months against 7.3 ± 1.2, $p < 0.05$ months in implants according to the two-stage protocol. Assessment of patient satisfaction with the treatment was directly correlated with his timing.

Conclusions: Thus, it should be noted that the clinical use of one-stage surgical protocol of implantation and non-detachable (monolithic) dental implants of the system «ART IMPLANT» in the rehabilitation of elderly patients with varying degrees of atrophy of the alveolar processes of the jaws is clinically justified.

KEY WORDS: monolithic implants, single-stage implantation, elderly patients, stability index, ART IMPLANT system

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INTRODUCTION

Studies by the World Health Organization (WHO) indicate that there is a huge unmet need for restorative dental care, especially among the elderly [1,2]. And one of the difficult problems of dentistry is still the problem of prosthetics for elderly and senile patients who have completely lost their teeth. Atrophic processes occurring in the jaws often lead to such unfavorable clinical conditions in the oral cavity, in which rehabilitation of this group of patients by traditional methods is not always possible. It should be noted that the share of elderly and senile people in our country is quite large and is in different regions up to 30% of the total population [1-17]. Due to the trend of steady aging of the population in the developed world and due to the accumulation of unmet needs for dental restoration, many researchers see the opportunity to develop these promising and sophisticated methods of dental care. According to research by leading analytical agencies in Europe and the United States, the demand for orthopedic structures on implants exceeds the demand for all other types of dental care. And the market for dental implants and bone and plastic materials is the fastest growing segment in the field of dental. Today, implantology is one of the most dynamically developing areas of modern dentistry, the use of modern technologies has allowed to approach the problem of treatment of complete and partial absence of teeth at a new level. The vast majority of modern dental implant designs are collapsible. The collapsible structure is always less durable than the monolithic one, and the joint area is a constantly infected area.A significant amount of modern research has been devoted to the problem of connecting the intraosseous and extraosseous parts of the implant and ways to increase its strength and sealing. At the same time, the classic two-stage method of dental implantation has a number of significant disadvantages, the negative consequences of which may not be detected immediately, but in the long term after treatment. To date, a well-established and increasingly widespread in world practice single-stage surgical protocol using new one-component designs of dental implants, which allows their use in cases of insufficient volume and quality of bone tissue. Installation of single-stage monolithic implants in the treatment of patients with atrophy of the alveolar processes of the jaws is recognized by various authors as the best, simplest and most gentle, with a high percentage of long-term

survival [13,14,18,19].The use of single-stage implants can reduce the duration of prosthetics from 1 to 30 days with immediate implantation and reduce atrophy of the alveolar process after tooth extraction. 97.8% of patients maintained a long-term good functional result of prosthetics, and the success of osseointegration of direct and delayed loading of implants depended on the primary stability during their installation [1,3-5,20]. In modern implantology, the requirements for the formation of stable secondary stability of dental implants (osteointegration) have been studied in detail, which allows to predict with a high level of confidence a satisfactory result of prosthetics. At the same time, the primary stability of the installed implants is one of the main (if not the main) conditions for the success of their osteointegration [6-8,21,22].In recent years, the most important indicators of the effectiveness of dental treatment are the criteria of quality of life based on the patient's emotional perception of the results of treatment. The use of these indicators in dentistry is becoming an urgent strategic task. Traditional dental examination does not allow to assess how the result of dental treatment affects the mental and emotional well-being of the patient [9,10,12].The use of questionnaires at the dental reception allows doctors to optimize the choice of treatment, monitor and evaluate the treatment process, which increases the effectiveness of rehabilitation. In accordance with the requirements of the International Association for the Assessment of Quality of Life (IQOLA), the choice of dental questionnaire should be mediated by a personalized clinical situation. Therefore, the rehabilitation of elderly patients with partial and complete defects of the dentition with varying degrees of atrophy of the alveolar processes using single-stage protocols and one-component dental implants is today an important and priority medical and social task.

THE AIM

Comparative evaluation of long-term results of clinical application of one- and two-stage surgical protocols of dental implantation using monolithic and collapsible implants in the rehabilitation of elderly patients with dentition defects and varying degrees of atrophy of alveolar processes.

MATERIALS AND METHODS

The clinical study was conducted on the basis of the Department of Postgraduate Dentistry, Uzhhorod National University and the Dental Clinic Art Dentistry (Zaporizhzhya, Ukraine). 46 patients with various clinical diagnoses of dentition defects were under clinical observation. At diagnosis the generally accepted classification MKH-10 was used. The first group (table I) of the study included: 15 patients (32.61%) with dentition defects with sufficient bone volume, who used a one-stage surgical protocol of dental implant surgery with non-detachable implants Solidum system "ART IMPLANT" followed by temporary splinting fixed prosthesis and immediate occlusive functional load [18,23,24].The Solidum implant is a monolithic self-tapping implant (d = 3.2-4.5 mm). Due to its design features, this implant is installed subcrystalline in a wide alveolar ridge. In the process of bone remodulation, it forms the effect of a "displaced wound canal", which prevents precervical resorption of the cortical bone and recession of the mucous membrane. The second group included patients with dentition defects with insufficient bone volume, who used a one-stage surgical protocol of dental implant surgery with non-detachable Simplex implants of the ART IMPLANT system, followed by a temporary splint fixed prosthesis and immediate occlusive function.Simplex implant is a monolithic self-tapping cone-shaped implant (d = 2.8 mm), allows to use this implant in conditions of insufficient bone volume in a narrow alveolar ridge by minimally invasive protocol and cylindrical narrow heat-treated neck. This group included 15 people (32.61%). The third (comparative) group included patients with dentition defects with insufficient bone volume, who used the traditional two-stage surgical protocol of dental implant surgery with a detachable implant Virtus (d = 3.5-5.0) system "ART IMPLANT") . This group also included 16 people (34.78%). The distribution of patients into groups was carried out randomly and was not fundamental.

Table I. Distribution of patients by age, gender and type of surgical protocol

INDEX		QUANTITY (abs.,%)
Total patients		**46**
Sex	Men	23 (50%)
	Women	23 (50%)
Age (years)		60 – 70
Study groups of patients		3
Main research groups:		
One-stage surgical protocol with occlusal functional load		2 groups
The first group (sufficient bone volume), "Solidum"		15 (32,61%)
Second group (insufficient bone volume), "Simplex"		15 (32,61%)
Two-stage surgical protocol		1 group
Third (insufficient bone volume), "Virtus"		16 (34,78%).

Table II. The results of the assessment of the mobility index of installed dental implants in the study groups at different control times

Research groups	Implant Mobility Index (IMI)							
	Post-operative	1 week	2 weeks	4 weeks	8 weeks	3 months	6 months	12 months
The first group (sufficient bone volume, one-stage surgical protocol "Solidum")	-6,4	+0,1*	+1,2*	-2,6*	-5,5	-6,4	-6,6	-6,8
The second group (insufficient bone volume, one-stage surgical protocol "Simplex")	-2,8	+1,6*	+2,2*	+1,8*	-0,7	-2,2	-2,6	-3,1
Third (insufficient bone volume, two-stage surgical protocol "Virtus")	+1,7	+5,9*	+8,7*	+4,1*	+3,8*	+1,1	-1,1	-1,5*

*Note. p≤0.05 statistically significant changes relative to the original data.

Table III. Duration of surgical treatment and complete rehabilitation depending on the types of dental implants and surgical protocols used

Average terms of treatment of patients (months)	One-stage implantation protocol		Two-stage implantation protocol
	Non-detachable implants "Solidum" (group 1)	Simplex non-demountable implants (group 2)	Collapsible implants "Virtus" (group 3)
Surgical stages of treatment	3,9±0,8**	4,4±0,9*/**	7,3±1,2
Duration of complete rehabilitation	4,5±0,9**	5,5±1,3*/**	9,8±1,4

Note. * p <0.05 statistically significant difference between non-detachable and collapsible implants. ** p <0.05 statistically significant differences between one- and two-stage implantation protocol..

Table IV. Assessment of patients' satisfaction with the treatment depending on the types of installed dental implants, the timing of complete treatment and the methods of dental implantation used

Surgical protocol	Type of implant system "ART IMPLANT"	Patient satisfaction with the treatment				Average rating
		Unsatisfactorily	Satisfactorily	Good	Excellent	
One-stage implantation protocol	Solidum	-	-	4 (8,7%)	11 (23,91%)	4,73±0,14, p<0,05
	Simplex	-	1 (2,7%)	5 (10,87%)	9 (19,56%)	4,53±0,12, p<0,05
Two-stage implantation protocol	Virtus	6 (13,05%)	3 (6,52%)	6 (13,05%)	1 (2,7%)	3,69±0,11, p<0,05
TOTAL:		6 (13,05%)	4 (8,69%)	15 (32,62%)	21 (45,64%)	4,32±0,12, p<0,05

The study was carried out taking into account the main provisions of the GCP ICH and the Helsinki Declaration on Biomedical Research, the Council of Europe Convention on Human Rights and Biomedicine (2007) and the recommendations of the Bioethics Committee of the Presidium of the NAMS of Ukraine (2002). . The age of patients ranged from 60 to 70 years, including men - 23 people (50%), women - 23 people (50%). At the same time, the timing of healing, the condition of dental implants, their stability and satisfaction of patients with the treatment and psycho-emotional well-being in relation to treatment using the method of dental implants were studied. In some clinical cases, patients underwent immediate implantation with passive occlusive loading [18,22,24] according to traditional one- (Fig. 1) and two-stage surgical protocols (Schwartz-Arad D. et al., 2007) under local anesthesia Sol. Articaini 4% with vasoconstrictor 1: 100000. Measurement of the degree of stability of the installed dental implants was performed using a mechanical oscillatory - resonance method using the device Periotest M (Gulden Medizintechnik, Germany).The scale of measurements of the mobility index (IP - PTV) ranges from -8 to +50 and the lower this value, the higher the stability of the implant. Interpretations of values of the mobility index: a) from -8 to 0 good osseointegration, complete immobility: implant and can be loaded; b) from +1 to +9 further clinical observation is required, usually loading is not desirable, but possible at the discretion of the physician in the associated multi-support structures; c) from +10 to +50 osteointegration is insufficient, the implant is mobile and cannot be loaded.

Fig. 1. Stages of one-step implantation (Art Implant, Ukraine)

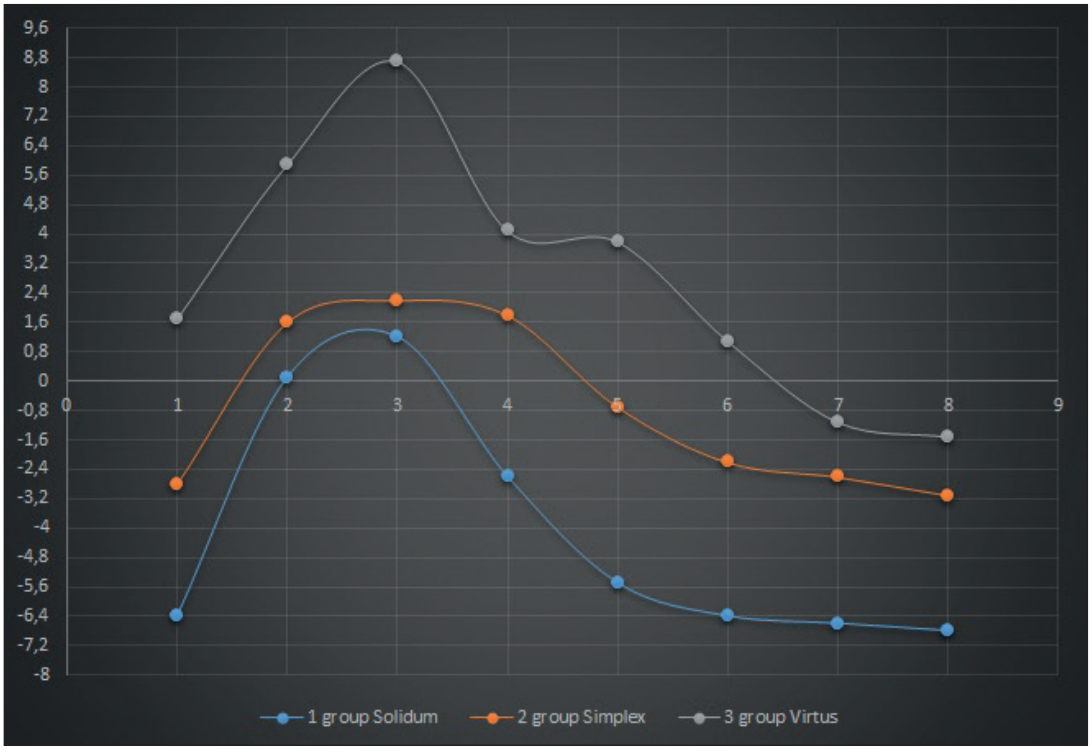

Fig. 2. Dynamics of the mobility index of installed dental implants in the studied groups.

A significant increase in the values of the mobility index, in the remote period after implantation, is evidence that the implant is unstable, one of its screws is untwisted or loosened, or there is destruction of peri-implant tissues (peri-implantitis). Therefore, it is recommended to record all the measurements that allow you to control the treatment process in the dynamics. The obtained results were included in the "Questionnaire for assessing the clinical capacity of dental implants" developed by us, compiled on the basis of the above-mentioned criteria, taking into account the features and priorities of the study. The main emphasis was on the stability of the clinical outcome, the timing of

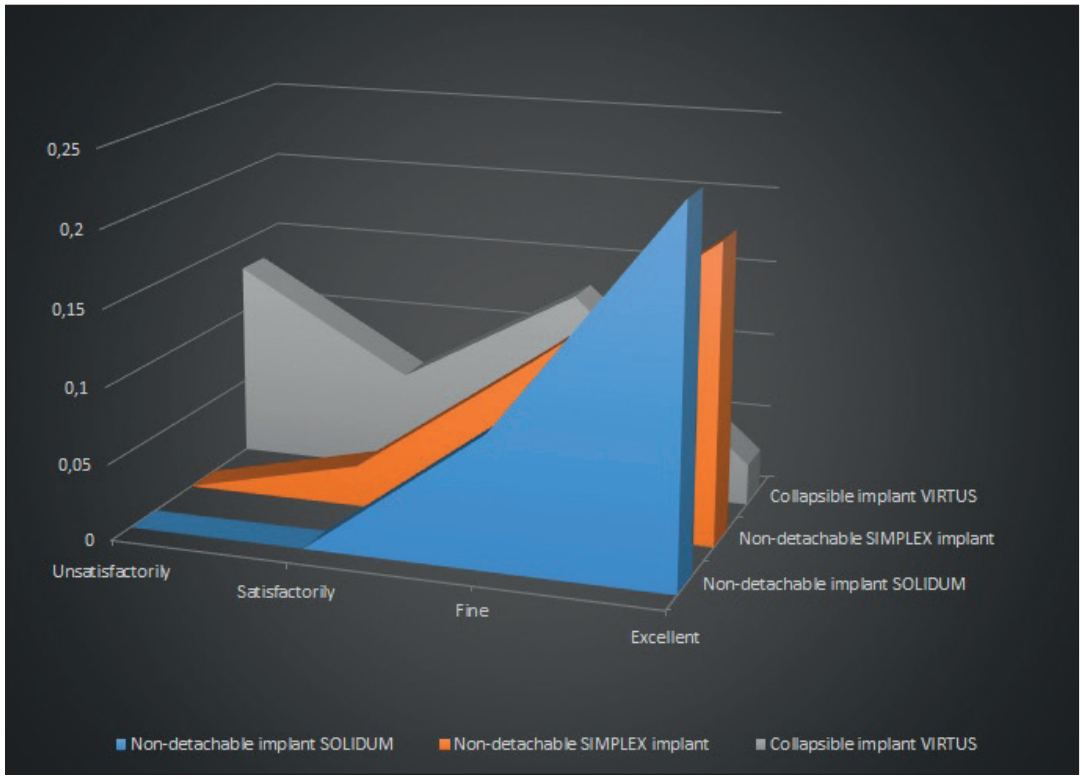

Fig. 3. Duration of surgical treatment and complete rehabilitation depending on the types of installed dental implants of the «ART IMPLANT» system

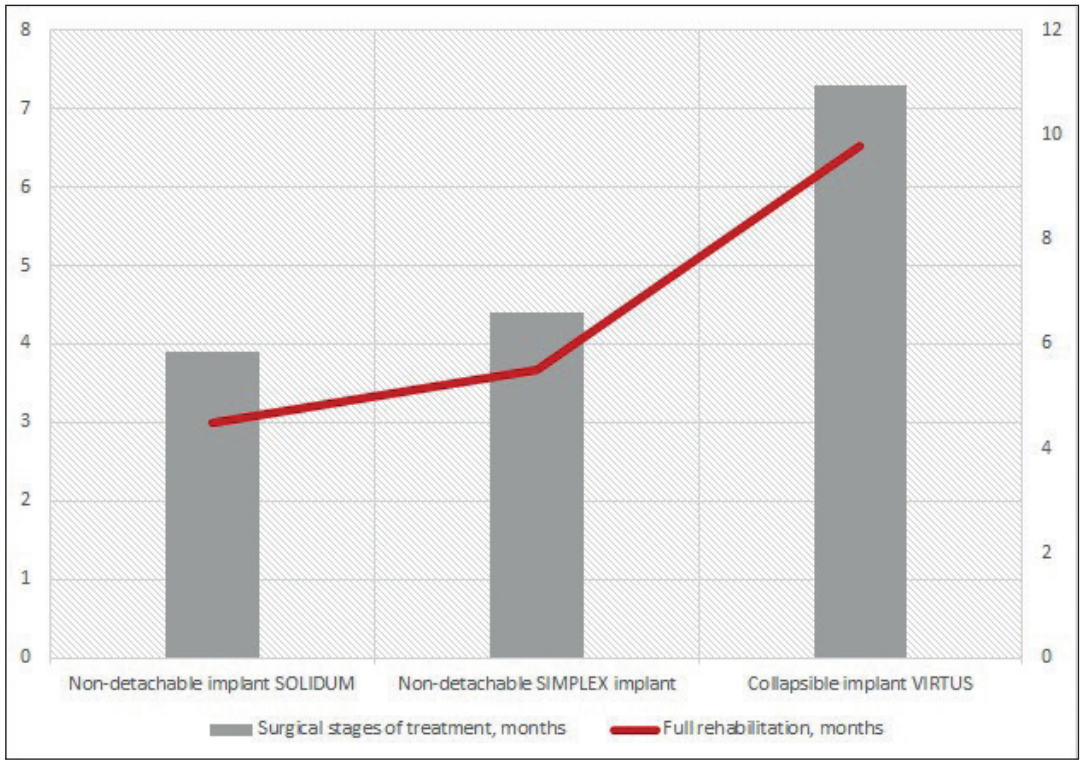

Fig. 4. Assessment of patients' satisfaction with the treatment depending on the types of ART IMPLANT dental implants

the surgical stage of treatment and the whole rehabilitation in general, the type of dental implants. To assess the satisfaction and psycho-emotional attitude of patients to the treatment, we used a special questionnaire developed by us with a 5-point scale. The results of laboratory and clinical studies were processed by methods of variation statistics to determine the average value, its errors, Student's t-test for multiple comparisons, using Excel (MS Office 2010, Microsoft, USA) and STATISTICA 6.0 (StatSoft, USA). Differences in indicators at the level of significance $p < 0.05$ were considered statistically significant.

RESULTS

In the study, one of the indicators of osseointegration and reliability of functional load in patients with atrophy of the

alveolar processes of the jaws was the degree of mobility (stability) of the installed dental implants before the final orthopedic stage. The results of these measurements after the surgical phase and the healing period showed that the index of mobility (IP) of installed dental implants in patients with alveolar atrophy of varying degrees corresponded to that in patients with sufficient bone volume and quality and uncomplicated clinical conditions (Table II).

The mobility index (mobility index) of the installed implants indicated its initial increase within 2 weeks and subsequent gradual decrease. Starting from 4 weeks, the mobility of the implants in all study groups gradually decreased and showed little further regression after 6 months, sometimes there was a slight decrease during 6-12 months (Fig. 2).

In patients of the first group with sufficient bone volume of the alveolar processes of the jaws and the use of a single-stage surgical protocol of implantation of the system «Solidum» all follow-up, starting from the end of the 2nd week. . The rate of mobility in this group after 4 weeks showed statistically significant changes compared to baseline and averaged -2.6 ± 0.08, p≤0.05 relative units, after 3 months this figure increased 2.5 times and amounted to -6.4 ± 0.06, p≤0.05. Subsequently, there was a slight progressive increase in the level of resistance of dental implants up to 1 year.In patients of the second group of the study with insufficient bone volume of the alveolar processes of the jaws and the use of a single-stage surgical protocol of implantation of the system «Simplex», also from 2 to 4 weeks we observe an increase in ± 1.02, p≤0.05 relative units, after 3 months this indicator increased 3 times and amounted to -2.2 ± 0.08, p≤0.05. Subsequently, there was a slight progressive increase in the level of resistance of dental implants up to 1 year. In patients of the third group of the study with insufficient bone volume of the alveolar processes of the jaws and the use of two-stage surgical protocol of implantation of the system «Virtus» only 3 months there is a positive dynamics of stability of dental implants, which after 6 months averages -1.1 ± 0.09, p≤0.05 and slightly increases up to 1 year -1.5 ± 0.08, p≤0.05.When assessing the duration of treatment of patients based on the analysis of implantation maps, there was a statistically significant difference between non-detachable and collapsible implant structures, as well as between one- and two-stage surgical implantation protocol in favor of non-detachable (monolithic) implants and one-stage surgical protocol.

In patients of study group 1 with sufficient bone volume and the use of non-detachable implants, the duration of surgical stages of treatment was 3.9 ± 0.8, p <0.05, which is 1.9 times shorter than the study group 3 with insufficient bone volume and using a collapsible implant, where the duration of the surgical stages of treatment was 7.3 ± 1.2, p <0,05. Regarding the duration of complete rehabilitation, it is 2.2 shorter in the first group of study 4.5 ± 0.9, p <0.05, than in the third - 9.8 ± 1.4, p <0.05.

Based on the study, there is a direct relationship between the timing of treatment and the degree of satisfaction of patients with the used protocol of dental implant surgery and the type of dental implants (table 4). A comparative assessment of patients' satisfaction with the treatment showed a statistically significant difference in the assessment of treatment as «excellent» in the group of patients who used a one-stage surgical protocol of dental implant surgery. The lowest number of higher assessments of patient satisfaction with the treatment was found in the group of patients who used a two-stage surgical protocol of dental implant surgery (Fig. 4).

DISCUSSION

Due to the widespread use of dental implantation in outpatient practice and the high frequency of atrophy of the alveolar processes of the jaws in elderly patients, much attention is paid to the problems of using this technique in complex anatomical conditions. Despite some successes in the use of various osteoplastic techniques and materials, one of the most difficult problems of such interventions remains complexity, trauma, unpredictability of results and duration. At the same time, the patient's satisfaction with the treatment is directly dependent on these factors and the degree of restoration of masticatory function and aesthetics. Currently, extensive clinical experience in the use of single-stage (monolithic) intraosseous dental implants.Numerous experimental studies of different types of surface and design of the intraosseous part of implants, biomechanical interactions of the implant with the surrounding bone tissue, large-scale randomized studies of long-term results and their condition. Since the patients were carefully selected, and the surgery was performed by the same operator under standard conditions, the higher MBL around implants installed through a two-stage approach can be attributed to the histological process of bone repair after trauma and the surgical procedure done for submerge fixtures [Sharon M Compton, Danielle Clark, Stephanie Chan, Iris Kuc, Berhanu A Wubie, Liran Levin]. The analysis of clinical and experimental studies allows us to conclude that the use of single-stage dental implants in the rehabilitation of patients with atrophy of the alveolar processes of the jaws of various degrees is a reasonable method and creates favorable conditions for functional prosthetics.However, the complex of factors influencing the duration of permanent prosthetics after single-stage dental implantation in this category of patients, in particular the condition of the surrounding bone and soft tissues, the degree of stability (mobility) of implants and its dynamics, the objective duration of treatment and its criteria, the degree of patient satisfaction with treatment [11]. One of the tasks of improving the effectiveness of rehabilitation of patients is to clarify the clinical indications for the use of single-stage dental implantation in the treatment of patients with dentition defects and varying degrees of atrophy of the alveolar processes of the jaws [Cavallaro JS Jr, Greenstein G.].In this regard, we studied the long-term results of treatment after surgery based on observation of patients. Improving the effectiveness of rehabilitation of patients using the

method of dental implantation is the formulation of the principles of postoperative management and rehabilitation of patients using the method of single-stage implantation. It was found that the main condition for a favorable prognosis of treatment is sufficient primary stability of the installed dental implant, the index of mobility, measured using a mechanical oscillatory-resonance method with the device Periotest M, and should not exceed +10. 97.8% of patients maintained a long-term good functional result of prosthetics, and the success of osseointegration of direct and delayed loading of implants depended on the primary stability during its installation (Yaremenko AI et al., 2013; Testori T., Bianchi F. et al. , 2003; Ersanli S., Karabuda C. et al., 2005; Fischer K., Stenberg T., 2006; Zhou W., Han C. et al., 2009).It was found that the reduction in the number of stages and duration of treatment is directly related to increasing patient satisfaction with treatment. As a result, we performed the task of developing and implementing in clinical practice an algorithm of treatment using the methods of single-stage dental implantation in the treatment of patients with varying degrees of atrophy of alveolar processes. The duration of surgical stages of treatment and complete rehabilitation showed statistically significant differences ($p < 0.05$) and was significantly less when using a single-stage protocol of dental implant surgery and non-detachable implants and averaged 3.9 ± 0.8, $p < 0.05$ months against 7.3 ± 1.2, $p < 0.05$ months in implants according to the two-stage protocol. Assessment of patient satisfaction with the treatment was directly correlated with his timing. Collapsible dental implants did not statistically show patient satisfaction with the treatment ($p > 0.05$) compared with the installed non-collapsible dental implants (mean score 3.69 ± 0.11, $p < 0.05$ vs. 4.63 ± 0.13, $p < 0.05$ on a five-point scale).

CONCLUSIONS

Thus, it should be noted that the clinical use of one-stage surgical protocol of implantation and non-demountable (monolithic) dental implants of the ART IMPLANT system in the rehabilitation of elderly patients with varying degrees of atrophy of the alveolar processes of the jaws demonstrates implants, reduces the waiting period for permanent prosthetics, as well as reduce the duration of the entire treatment, which ultimately leads to increased optimization of treatment effectiveness and patient satisfaction. The use of single-stage conception and single-stage implants is an alternative to the generally accepted two-stage protocol technique and allows in many clinical cases to successfully avoid bone grafting, which is quite traumatic, lengthy, expensive and unpredictable procedure. One-stage (monolithic) implants are free from the disadvantages of two-stage (collapsible), simpler in prosthetics, but at the same time, require a more accurate positioning from the doctor during the operation. They are not an expensive choice, especially in complex clinical cases that require simple solutions.

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ORIGINAL ARTICLE

EVALUATION OF COVID-19 VACCINES EFFICACY IN IRAQI PEOPLES

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ABSTRACT

The aim: The present study was carried out on patients recovered from COVID-19, including those patients who have taken vaccine and those who have not.
Materials and methods: The patients were recruited via an online panel and surveyed at different regions of Iraq from June 1, 2021, to August 30, 2021.
Results: Our results demonstrated that the highest percentage of people recommended Pfizer vaccine followed by Sinopharm, while AstraZeneca vaccine was least recommended.
Conclusions: The efficacy of different vaccines differed significantly; the highest effectiveness was observed with Pfizer vaccine followed by AstraZeneca and Sinopharm with effectiveness ranging from 94%, 89%, and 74%, respectively. Further, the highest percentage of re-infected patients was observed with Sinopharm vaccine followed by Astra Zeneca and Pfizer vaccine, respectively. Also, the highest percent of re-infection with masking used was seen in the case of Sinopharm vaccine followed by AstraZeneca and Pfizer vaccine. Although, we observed that post-vaccination symptoms were lowest than pre-vaccination symptoms, the percent of asymptomatic cases post-vaccination was highest than pre-vaccination cases for all vaccines.

KEY WORDS: COVID-19, Pfizer vaccine, Astra Zeneca vaccine, Sinopharm, post-vaccination symptoms

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INTRODUCTION

The past two years have been the most difficult years of the modern era because of the ongoing COVID-19 pandemic. COVID-19 is caused by novel strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. SARS-CoV-2 was first detected in December 2019 in Wuhan, China [2]. Coronaviruses are enveloped, positive-sense single-stranded RNA viruses with a helical nucleocapsid. They belong to the *Coronaviridae* family in the order *Nidovirales*, subfamily *Orthocoronaviridae* and are divided into four genera namely alpha, beta, delta, and gamma coronavirus [3]. Several vaccines have been developed during the past one and half year. The mRNA-based vaccine has been developed by *BioNTech /Pfizer* company under the name BNT162 [4]. The efficacy of this vaccine was investigated in a total of 45 healthy volunteers, which were divided into 4 groups, the first two groups received two doses of 10 and 30 μg intramuscularly, 20 days apart, and the third group received 100 μg dosage but did not receive a second dose and a fourth group of 9 participants received a placebo [5]. Seven days after the second dose, the first two groups showed increased IgG levels and it remained elevated even after 14 days. While in the third group, the IgG levels peaked at 21 days after the first dose and did not increase thereafter [5]. Non-replicating Viral Vector Vaccines has been developed by Astra Zeneca in collaboration with the University of Oxford, under the name ChAdOx1 and now designated as AZD1222 [6]. The efficacy of AZD1222has been checked in 1077 healthy participants recruited in the UK. The participants who received vaccine were divided into two groups; the AZD1222 vaccine group received a dose of vaccine particles (n = 543), 10 participants received a second booster dose of the vaccine after 28 days interval or a placebo group received meningococcal vaccine Men ACWY (n = 534) [7]. The AZD1222 vaccine group showed elevated antibodies and these levels remained until day 56. Additionally, the 10 participants who received a booster dose, a much higher specific antibody response was noted after day 56 and also, T cell response observed in all participants, peaked at day 14 and remained elevated through day 56 for both single or two doses [7]. Sinopharm has developed inactivated vaccine in collaboration with Wuhan Institute of Biological Products and Beijing Institute of Biological Products [8]. The efficacy of this vaccine has been tested in 224 participants divided into one of two dual-dose programs - days 0 and 14 or days 0 and 21days interval, the both schedules showed high antibodies response, however, 97.6% (41 out of 42) seroconversion noted for both. Additionally, for the specific antibody response, a much higher response was shown with the 0- and 21-day schedule 100% than the 0- and 14-day schedule 85.7% [9].

Table I. Total number and percentage of people taken or not taken vaccines, also the number and percent of the two genders

Vaccine type	N	%	Gender		Gender %	
			Male	Female	Male	Female
Pfizer	96	38.4	58	38	60	40
AstraZeneca	64	25.6	34	30	53	47
Sinopharm	68	27.2	43	25	63	37
Not take vaccine	22	8.8	8	14	36	64
Total	250	100.0	143 (57.2%)	107 (42.8%)		

Table II. The Total and percent of different age that participate in this study

Age	Frequency	Percent
20-30	144	57.6
31-40	75	30.0
41-50	23	9.2
51-60	5	2.0
>60	3	1.2
Total	250	100.0

Table III. The total and percent of participates in this study that previously infected or not, also the percent of people symptoms and need

	N	Percent	Symptoms	Percent
Yes	135	54	Mild	24.0
			Moderate	14.8
			Sever	1.6
			Asymptomatic	59.6
			Need	Percent
			Hospital admission	2.4
			O2	2.4
			NON	95.2
No	115	46.0		
Total	250	100.0		

THE AIM

The present study was carried out on patients recovered from COVID-19, including those patients who have taken vaccine and those who have not.

MATERIALS AND METHODS

This was a prospective study of patients recovered from COVID-19 including those who took vaccines or those who did not take vaccine. The respondents were recruited via an online panel and surveyed at different regions of Iraq from June 1, 2021, to August 30; 2021. Verbal informed consents were obtained from patients or their surrogates for the urgent need to collect data. Data was collected by direct individual interview through questionnaire. Medical records, demographic and clinical data were obtained including age, gender, clinical symptoms, admission to hospital, taken the vaccine or not, type of vaccine, re-infected and symptoms after vaccination were collected from the patients' medical records. All cases withCOVID-19 enrolled in this study were diagnosed on the basis of World Health Organization by RT–PCR (Real Time Polymerase Chain Reaction) and the diagnostic and vaccinated guideline for COVID-19 issued by the Ministry of Health (MOH) and update protocol supported by World Health organization (WHO) [10].

STATISTICAL ANALYSIS

The counts and percentage were used to calculate the descriptive and categorical variables. The association between gender groups, type of vaccines, clinical symptoms and severity of disease were analyzed by application of chi square (x^2) test, used as appropriate, at level of significance $\alpha = 0.05$. All statistical analyses were applied using SPSS 26.0 for Windows and graphs were draw by Graph Pad prism 8.02 v.

VACCINE TYPES

The results of this study revealed that the percentage of people taking vaccines was more than those who were not taking vaccines. However, the highest percentage of people gave preference to the Pfizer vaccine followed by Sinopharm and the last one was AstraZeneca vaccine (38.4%, 27.2%, and 25.6%, respectively).

There is a difference between the total numbers of people taking the vaccine. Moreover, there is a significant difference ($p<0.05$) between the Pfizer and other vaccines, while there is an insignificant difference ($p>0.05$) between Sinopharm and AstraZeneca vaccines. There is a significant difference ($p<0.05$) between the gender to take the vaccine depend on the percentages; however, the male gender has highest percent as compared with female gender, see table I, and figure (1).

AGE

According to age, we found that the total number and the percentage of people taking vaccines was highest for age 20-30 years, followed by 31-40 years, and the lowest percentage taking vaccine was for the age group 60 years and older (57.6%, 30.0%, and 1.2%, respectively), see table II and figure (2).

PREVIOUSLY INFECTED WITH COVID-19

We found that the total no. and the percentage of people previously infected with COVID-19. The highest percentages of infected people were asymptomatic and the lowest percent had severe symptoms. However, about 95% of infected cases did not need hospital admission, see table III and figure (3).

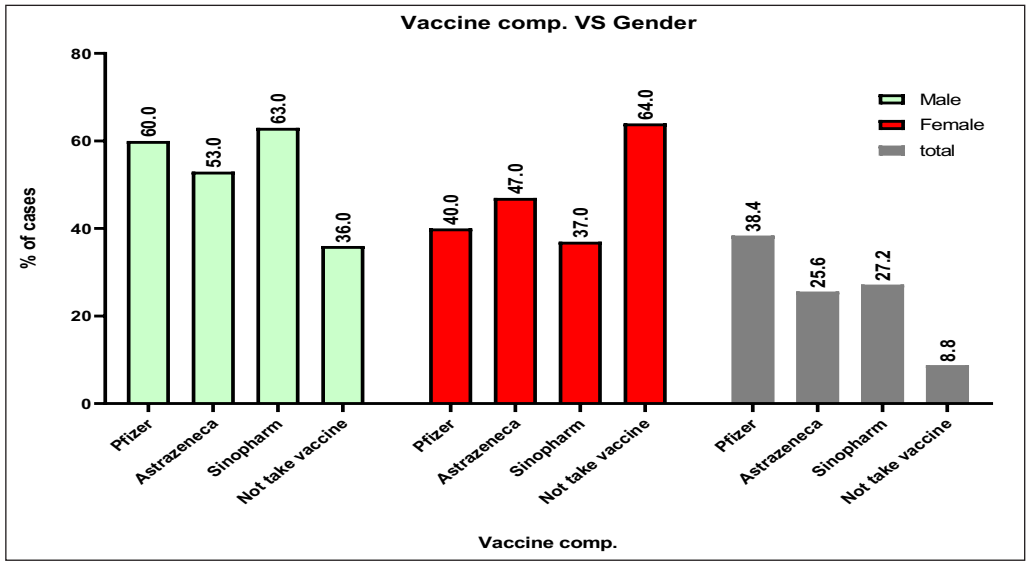

Fig. 1. Gender difference in terms of taking vaccines or not taking vaccine

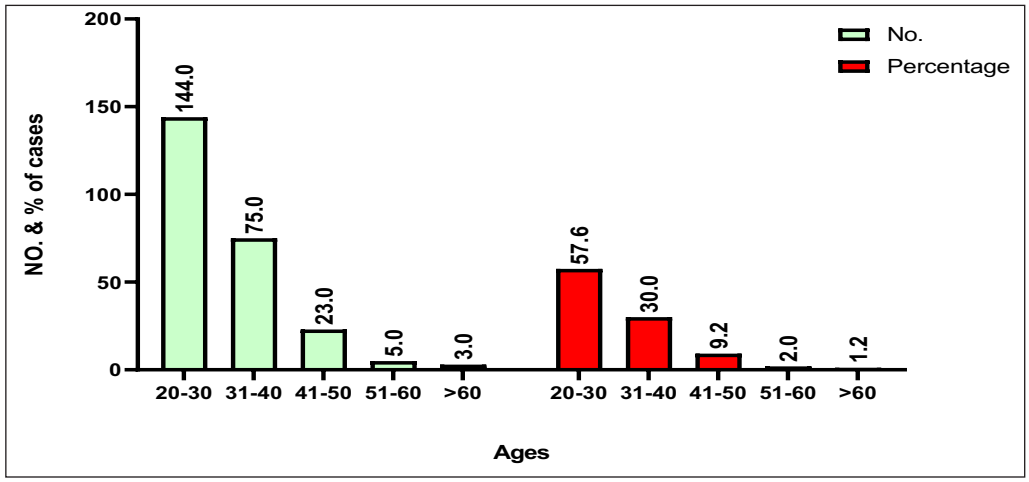

Fig. 2. The total and percent of different age that participate in this study according to age

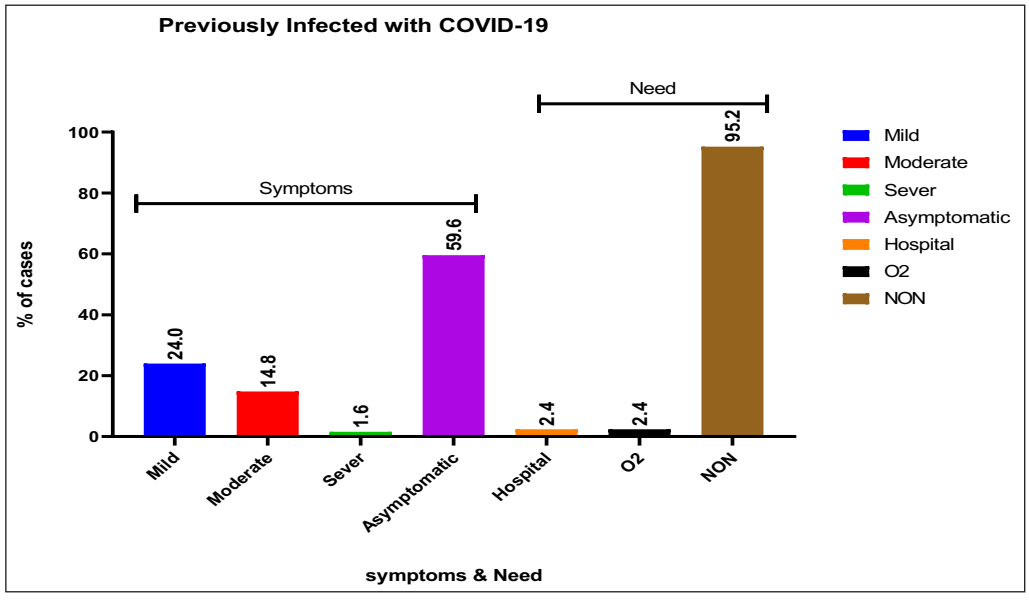

Fig. 3. The percent previously infected patients and the percent symptoms and need

INFECTION AFTER VACCINATION

We found that the percentage of patients infected after vaccination was less than that not vaccinated. However, the highest percentage of re-infected patients was notified in Sinopharm followed by AstraZeneca and lastly the Pfizer vaccine. We noticed that most of patients were re-infected after two doses. There is a difference between the re-infected patients and not infected. Moreover,

Table IV. The percent of re-infection and protection efficacy after vaccination and after the doses, also show that the difference between vaccines

Company	Re-infected %		
	Infected %	After one dose	After Two doses
Pfizer	6.25	16.6	83.4
AstraZeneca	11	43	57
Sinopharm	26.5	5.5	94.5
	Not infected %		
Pfizer	93.75		
AstraZeneca	89		
Sinopharm	73.5		

Table V. The percent of re-infection after vaccination at different duration for three companies $P < 0.05$

Duration	2-5 days		6-9 days		10-14 days		> 14		
Company/doses	One dose	Two doses	One dose	Two doses	One dose	Two doses	One dose	Two doses	P value
Pfizer	0	0	0	20	0	40	0	40	*
AstraZeneca	14	14	0	14	14	0	14	29	*
Sinopharm	0	33	0	6	0	0	6	56	*

Table VI. The relationship between masking used and re-infection for all companies

	Masking used	No Masking used	Re-infection	P value
Company/percent	61.6	29.6		
Pfizer	67	33	6.25	*
AstraZeneca	57	43	11	*
Sinopharm	78	22	26.5	*

Table VII. The difference in percent between the pre- and post-vaccination of totally and three companies

Comp./symptoms	Total %		Pfizer		AstraZeneca		Sinopharm	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mild	24	11.6	23	17	43	53	28	6
Moderate	14.8	5.2	50	17	29	0	28	88
Sever	1.6	0.8	17	17	0	0	6	6
Asymptomatic	59.6	82.4	10	49	28	47	38	0
Total	100	100	100	100	100	100	100	100

Fig VIII. The difference in percent between the pre- and post-vaccination of totally and three companies

	Percent	Pfizer	AstraZeneca	Sinopharm
Same	4.4	17	53	0
less	8.4	50	0	28
more sever	2.4	17	0	11
Asymptomatic	76.0	17	47	61
Not take vaccine	8.8			
Total	100.0			

the re-infected data showed that there is a significant difference ($p< 0.05$) between the Pfizer and Sinopharm, while there is an insignificant difference ($p>0.05$) between Pfizer and AstraZeneca vaccines, and also between Sinopharm and AstraZeneca vaccines, see table IV, and figures 4 and 5.

DURATION OF INFECTION TIME AFTER VACCINATION

When we compared the percent of the re-infection after one dose with those after two doses at different duration, we observed that the patients infected after two dose vaccination was highest than that after patients after one dose. However, the highest percentage of re-infected patients was notified

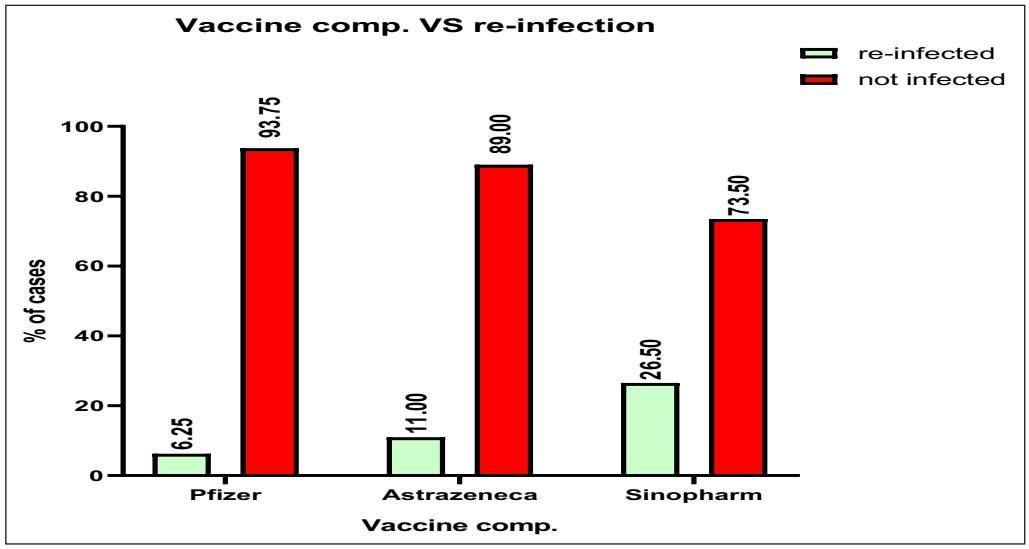

Fig. 4. The percent of re-infection and protection efficacy of different vaccines

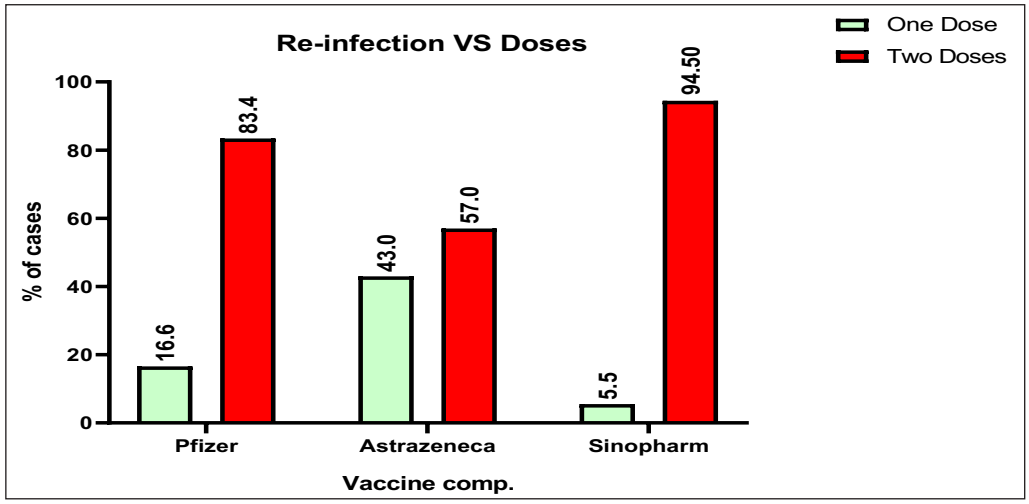

Fig. 5. The percent of re-infection after one and two doses of different vaccines

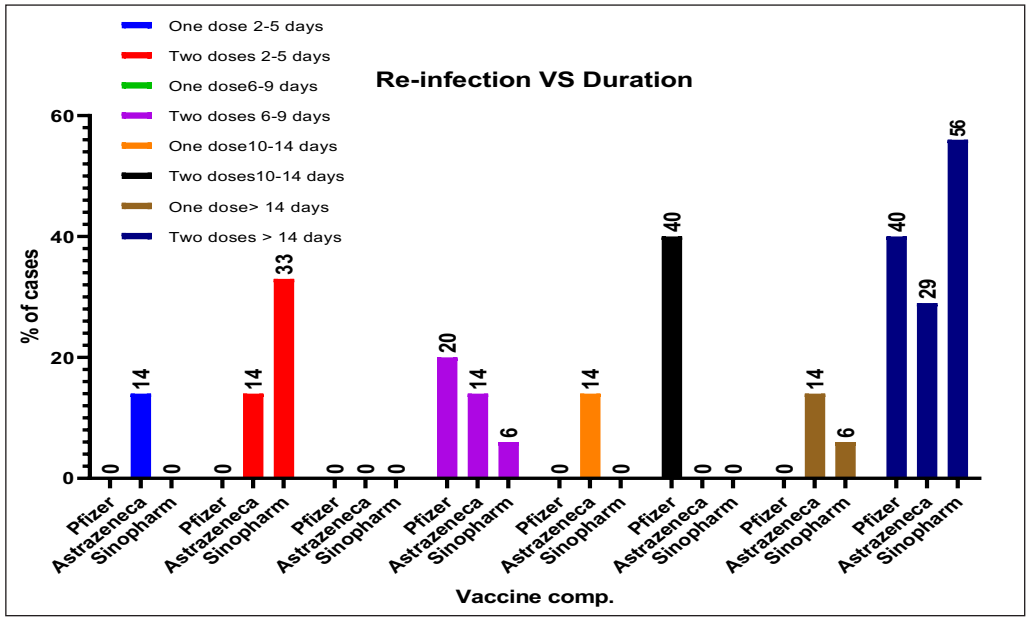

Fig. 6. The percent of re-infection after vaccination at different duration for three vaccines

at duration more than 14 days and after two doses for all vaccines. Our results showed that there is significant difference ($p>0.05$) among the companies; the highest percent of re-infection was seen in the Sinopharm followed by Pfizer and lastly AstraZeneca vaccine. Table 5 and figure 6

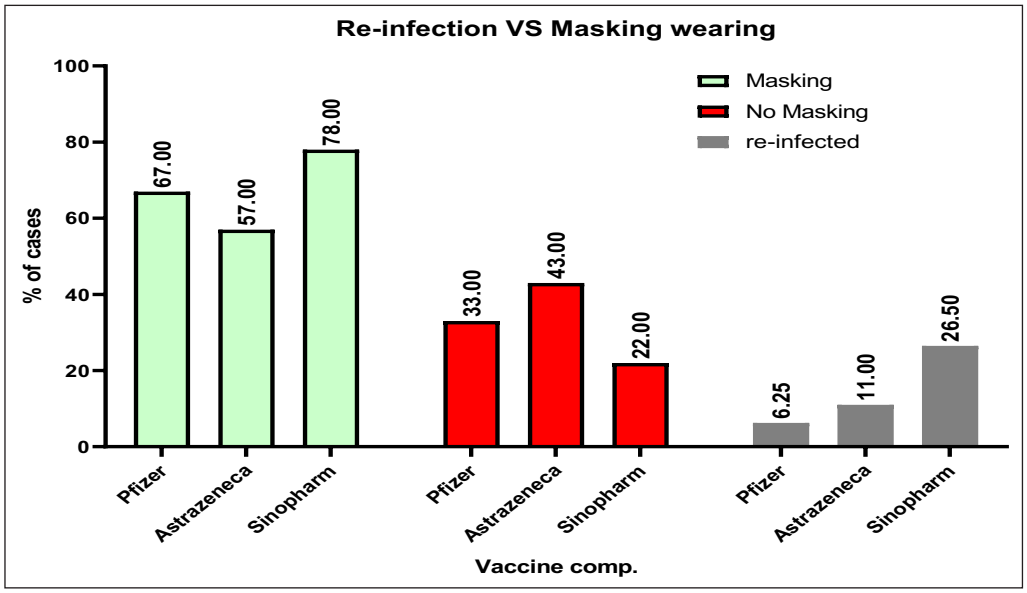

Fig. 7. The percentage of masking used and re-infection for all vaccines

Table IX. The difference in hospital admission of three vaccines as compared with pre-vaccination

vaccine	Pfizer		AstraZeneca		Sinopharm	
	pre	post	pre	post	pre	post
%	2	1	5	0	11	6

USE OF MASKING WEARING AFTER VACCINATION

We found that the percent of the patients used mask after vaccination was highest than those not used mask. Our results showed that there was a significant difference ($p<0.05$) between vaccines; the highest percentage of re-infected people with mask used was seen in the Sinopharm followed by Pfizer and the least percentage seen with AstraZeneca vaccine. Table VI and figure 7

SYMPTOMS OF INFECTION AFTER VACCINATION SYMPTOMS

The percent of the different symptoms pre- and post-vaccination are shown in table VII and figure 8. There was a significant difference ($p<0.05$) between total percent of mild, moderate, and sever symptoms. However, we noticed that these post-vaccination symptoms were lowest than pre-vaccination, while the percent of asymptomatic of post-vaccination was highest than pre-vaccination. Our results showed that there is significant difference ($p<0.05$) between pre- and post-vaccination of all companies, the Pfizer company reduced the post mild, moderate, and sever symptoms while the asymptomatic increased as compared with pre-vaccination. The AstraZeneca shows that there is insignificant difference ($P>0.05$) in mild symptom between pre- and post-vaccination, while there is significant difference ($P<0.05$) in moderate symptom and asymptomatic, moreover, the post mild and asymptomatic showed highest percent as compared with pre-vaccination as well as the moderate shows lowest than pre-vaccination. The Sinopharm shows lowest mild and asymptomatic pre-vaccination as compared with post-vaccination.

DIFFERENCE BETWEEN SYMPTOMS AFTER AND BEFORE VACCINATION

We found significant differences ($p<0.05$) in symptoms between vaccines. However, we noticed that those patients who took Pfizer vaccine, have less symptoms as compared with pre-vaccination while AstraZeneca showed that about 50% of patients had both same symptoms and asymptomatic as compared with pre-vaccination. The patient taken Sinopharm vaccine, most of them had asymptomatic (61%) and about 28% had fewer symptoms as compared with pre-vaccination, table VIII and figure (9).

ADMISSION TO HOSPITAL

According to our results, we found significant difference ($p<0.05$) between vaccines. However, we noticed that the patient taken the Pfizer and Sinopharm vaccines have had lower hospital admission to half percent as compared with pre-vaccination while AstraZeneca showed that about 100% of patients lowered as compared with pre-vaccination. Table IX and figure 10.

DISCUSSION

There are many strategies that have been recommended to improve vaccine effectiveness depending on disease awareness, clinical symptoms, hospital admission and increase vaccine accessibility [11]. The introduction of corona virus vaccines in a clinical practice demonstrated as a factor that influence the pathological and the progression course of diseases and can contribute favorably

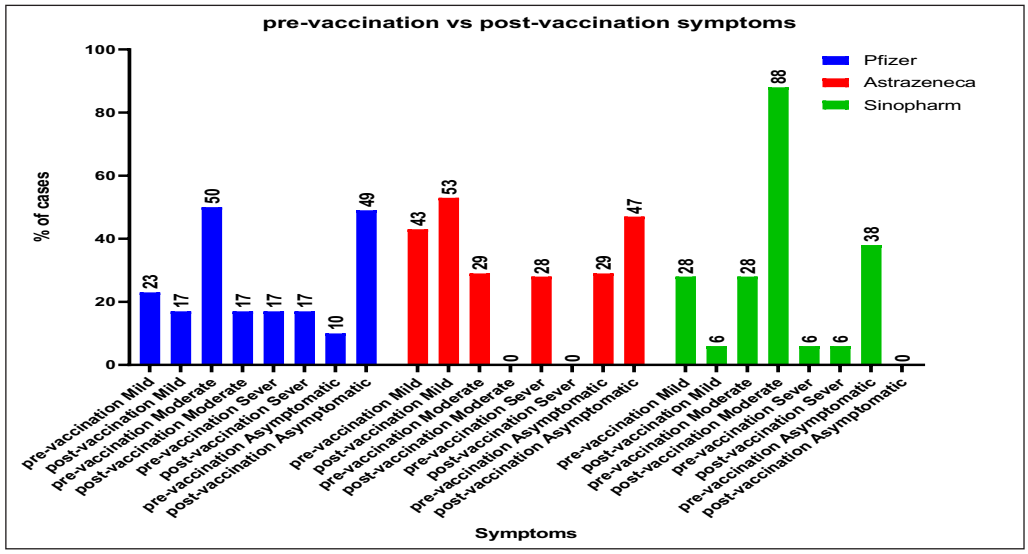

Fig. 8. The difference in percent between the pre- and post-vaccination of totally and three companies

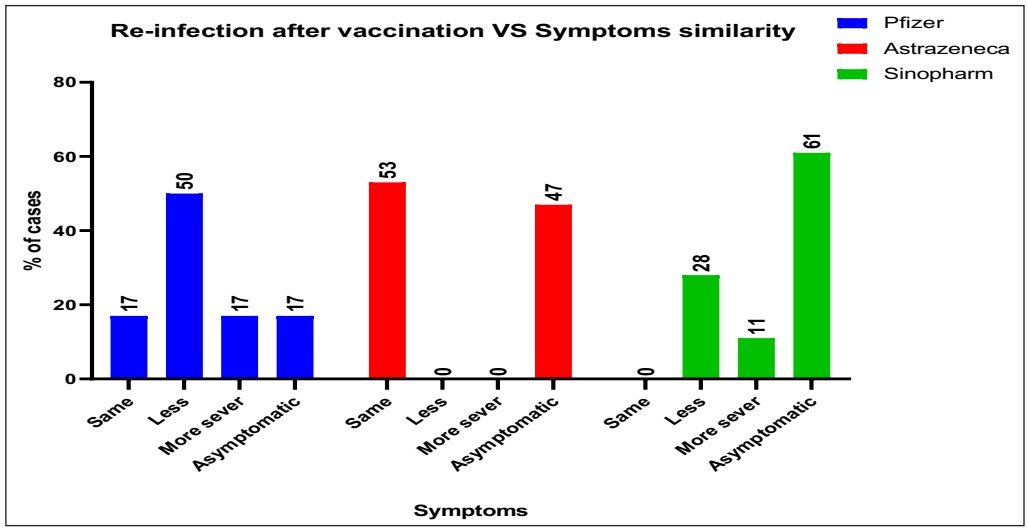

Fig. 9. The similarity in symptoms of three vaccines as compared with pre-vaccination

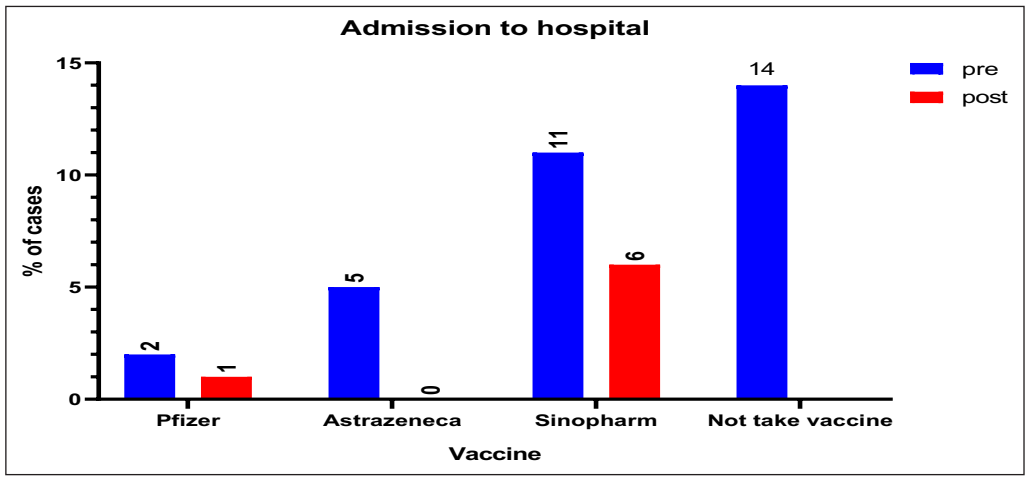

Fig. 10. The difference in hospital admission of three vaccines as compared with pre-vaccination

to the prevention, and treatment strategies, making health services more effective and efficient [12,13]. The present study demonstrated that vaccines evaluation is a crucial determinant in the management of COVID-19 to stratify the population and organize targeted approaches to monitoring vaccination compliance. Furthermore, the overall results of this study indicate that the type of vaccine, age and gender of recipients were potential modulators of the efficacy of COVID-19 vaccines. According to our results, the people taking vaccines had higher percent as compared with that not taken it which indicated that the effectiveness of vaccines or awareness from the complications of disease

itself. However, the Pfizer vaccine has more acceptance rates in Iraqi people followed by Sinopharm and the AstraZeneca vaccine. Also, as we note that the male gender had more acceptance than female one which may be due to the fear behaviors of the female. In addition to that the 20-30 years old has highest percent than other age groups and lower one was ages less than 60 years old, which may be due to Know agent of these groups than others groups. *N. Dagan* et al. were found that vaccine is effective for a wide range of Covid-19–related outcomes [14]. Shyh Poh Teo was observed that Pfizer-BioNTech and AstraZeneca demonstrated high efficacy and immunogenicity [15]. The percentage of patients that participates in our study and previously infected with COVID-19 was 54% that's indicated about half of participates suffer from the disease with different symptoms, however, about 60 % of them were asymptomatic, 24% mild, 15% moderate, and 1% sever symptoms while those who not need hospital admission and O_2 about 95%. We found that the percentage of patients infected after vaccination was less than that not vaccinated. However, the highest percentage of re-infected patients was notified in Sinopharm followed by AstraZeneca and lastly the Pfizer vaccine. We noticed that most of patients were re-infected after two doses after different duration; however, most re-infected time was after 14 days. The efficacy of vaccines was differed; the highest effectiveness was shown by Pfizer vaccine followed by AstraZeneca and the lowest one was Sinopharm vaccine (94%, 89%, and 74% respectively). Moreover, the percentage of patients who were vaccinated with Sinopharm vaccine and used mask higher than the patients vaccinated with other vaccines. We found that the symptoms after vaccination were low as compared with pre-vaccination in all vaccines. However, the Pfizer vaccine showed the mild and moderate symptoms, which were reduced after vaccination and also most patients become asymptomatic, moreover, 50% of cases showed less symptoms. Also, when we look to AstraZeneca vaccine data, it reduced moderate and sever symptoms and increased asymptomatic cases as compared with pre-vaccinated. Also about 50% of cases had either same symptoms or were asymptomatic that indicated the effectiveness of the vaccine.

CONCLUSIONS

The efficacy of different vaccines differed significantly; the highest effectiveness was observed with Pfizer vaccine followed by AstraZeneca and Sinopharm with effectiveness ranging from 94%, 89%, and 74%, respectively. Further, the highest percentage of re-infected patients was observed with Sinopharm vaccine followed by Astra Zeneca and Pfizer vaccine, respectively. Also, the highest percent of re-infection with masking used was seen in the case of Sinopharm vaccine followed by AstraZeneca and Pfizer vaccine. Although, we observed that post-vaccination symptoms were lowest than pre-vaccination symptoms, the percent of asymptomatic cases post-vaccination was highest than pre-vaccination cases for all vaccines.

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ORIGINAL ARTICLE

LATERAL MEDULLARY INFARCTION: A PROSPECTIVE HOSPITAL-BASED COHORT STUDY OF CLINICAL AND IMAGING FEATURES AND A CASE REPORT IN A WHITE ADULT

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ABSTRACT

The aim: The purpose of this study is to determine clinical and imaging features of lateral medullary infarction in a prospective hospital-based cohort study, illustrated with a clinical case presentation in a white adult.

Materials and methods: We prospectively recruited 120 acute posterior circulation stroke patients, admitted to the Neurological Center of the University Hospital (Oleksandrivska Clinical Hospital) in Kyiv, Ukraine, within 6 to 24 hours from the onset of the stroke symptoms. Comprehensive neurological, clinical, laboratory, ultrasound, and imaging examination was performed on all patients.

Results: Out of 120 adult patients (68 men, 52 women aged 28 to 89 years; average age 60.7 ± 12.1 years) with an acute ischemic MRI/CT-proven posterior circulation stroke, 22 (18.3%) patients have acute medulla oblongata infarctions.We provided a complex clinical, neurological, laboratory, and instrumental analysis of lateral medullary infarction illustrated with a clinical case presentation.

Conclusions: Specific clinical and imaging features of lateral medullary infarction were determined, analyzed, compared, and described.

KEY WORDS: stroke; posterior circulation stroke; lateral medullary infarction; lateral medullary syndrome; imaging; prospective study; case report

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INTRODUCTION

Posterior circulation stroke is a life-threatening condition that is less represented in thescientific literature, is more difficult to diagnose, has a more severe clinical course, and has higher mortality compared to anterior circulation stroke [1-5]. Consequently, posterior circulation stroke is misdiagnosed 30-60% of the time [6].

The lateral medullary infarction (LMI) is the most common form of posterior ischemic stroke that is often misdiagnosed or missed. Failure to rapidly diagnose LMI delays time-sensitive treatments, resulting in higher risks of disability and mortality [7]. That is why it is critical to promptly determine clinical and imaging features of LMI to prevent its severe consequences promptly.

THE AIM

We aimed to determine clinical and imaging features of lateral medullary infarction in a prospective hospital-based cohort study, illustrated with a clinical case presentation in a white adult.

MATERIALS AND METHODS

STUDY SETTING AND PATIENTS

We have conducted a prospective, hospital-based, cohort study of acute posterior circulation stroke patients. All study participants were admitted to the Neurological Center of the University Hospital (Oleksandrivska Clinical Hospital, Kyiv, Ukraine), within the first 6 to 24 h since the first stroke symptoms occurred.

Oleksandrivska Clinical Hospital represents the largest tertiary care center in the capital of Ukraine, Kyiv. Started its work on November 26, 1875, as the city hospital named after Royal Tsarevich Oleksandr, it become the highest scientific and pedagogical institution with a catchment population of approximately two million [8]. There are 27 specialized departments with over a thousand beds in the Hospital. Cardiological, cardiovascular, neurological, surgical, neurosurgical, urological, otolaryngological, ophthalmological, gynecological, infectious diseases, and hemodialysis departments work around a clock, admitting patients and providing urgent care. The Neurological Center of Oleksandrivska Clinical Hospital consists of an admission department, clinical department of neurology, department of cerebrovascular pathology with intensive care/stroke unit, and a research department of neurology. Healthcare is provided free of charge to all citizens and registered long-term residents.

Study subjects were recruited from the hospital's emergency departments and in-hospital wards between 2011 and 2020. All stroke patients were reviewed by at least two board-certified neurologists with training in cerebrovas-

cular diseases. Clinical history, 12-lead electrocardiogram, blood testing, carotid ultrasound (Toshiba, Japan), head CT and/or brain MRI (Siemens, USA, 1.5 T) were obtained for all study participants.

PATIENT INCLUSION AND EXCLUSION

The methods of the study, inclusion and exclusion criteria have been reported in detail previously [9-11]. In brief, only acute PCS patients aged 18 years or older were included.

STUDY ENDPOINTS AND RISK FACTORS DEFINITIONS

Study endpoints of interest were acute ischemic PCS. Stroke and TIA were defined according to the criteria of the World Health Organization, AHA/ASA guidelines for adult stroke, and was confirmed by imaging [12, 13]. The etiology of stroke was classified according to the TOAST criteria [14]. The National Institutes of Health Stroke Scale, the Modified Rankin Scale, the Barthel index, and the Charlson Comorbidity Index were determined for all participants. Secondary stroke prevention was prescribed according to the American Heart Association/American Stroke Association and the European Stroke Organization Guidelines, immediately after the stroke diagnosis was made [15, 16]. Stroke education programs were provided to all study participants [9, 17-21].

STATISTICAL ANALYSIS

Parametric and non-parametric statistic methods were applied. The log-rank test was used for univariate comparisons of event-free survival between groups. A two-sided $p<0.05$ was considered significant for all analyses. All statistical analyses were performed using IBM SPSS Statistics, Version 24.

ETHICS

Institutional ethics board approval was obtained and written informed consent was received from all participants or legally authorized representatives for this study.

RESULTS

BASIC CHARACTERISTICS OF THE STUDY POPULATION

In total, 120 adult patients (68 men, 52 women aged 28 to 89 years; average age 60.7 ± 12.1 years) with an acute ischemic MRI/CT-proven PCS were screened. The breakdown for study group by stroke type was as follows:

- 10.9% (n=13) of patients were diagnosed with acute midbrain infarctions;
- 18.3% (n=22) of patients diagnosed with acute medulla oblongata infarctions;
- 18.3% (n=22) of patients diagnosed with acute thalamic infarctions;
- 20.8% (n=25) of patients were diagnosed with acute cerebellar infarctions;
- 31.7% (n=38) of patients have a proven diagnosis of acute pons infarctions.

In this article, we are focused on 22 patients diagnosed with acute medullary infarction.

ANATOMICAL FEATURES OF MEDULLARY INFARCTION

According to our data, out of 22 patients with acute medulla oblongata infarctions, LMI was identified in 15 (68.2%) patients, medial medullary infarction - in five (22.7%) subjects, combined lesions of the medial and lateral parts of the medulla oblongata were diagnosed in two (9.1%) patients.Therefore, isolated medullary infarcts were identified in 14 (63.6%) examined patients, combined - in eight (36.4%). Out of these eight patients with combined lesions, additional ischemic focus in the cerebellar hemispheres was diagnosed in sixout of eight patients, in the thalamus - in one patient, andthe cerebral peduncles- in another one patient [9]. In eight (53%) patients with LMI, neurogenic oropharyngeal dysphagia was detected as a component of the bulbar syndrome, which negatively affected the oral and pharyngeal phases of the swallowing process.

CLINICAL FEATURES OF LATERAL MEDULLARY INFARCTION

In the study patients, LMI most often manifested by systemic dizziness, nausea, vomiting (80%), nystagmus (80%), cerebellar ataxia on the affected side (80%), Bernard-Horner syndrome (73%) on the side of the lesion (dysfunction of the descending sympathetic fibers), impaired sensitivity on the face (60%) by the segmental dissociated type in the areas of Zelder that is located on the stroke side (due to damage to the descending tract and the spinal nuclei of V pair of cranial nerves), and hypoesthesia of pain and temperature sensitivity by the Hemi type (60%) on the opposite to the stroke side (due to dysfunction of the spinal-thalamic pathway). These neurological symptoms are part of the alternating Wallenberg syndrome.

We found the *classic alternating Wallenberg syndrome* in 9 (60%) patients with LMI, ie this syndrome was pathognomonic for this clinical form of cerebral infarction. In another 6 (40%) patients, the neurological status corresponded to the *incomplete Wallenberg syndrome*, that the most often manifested with systemic dizziness, nystagmus, cerebellar ataxia, and bulbardisorders. Such neurologicalsymptoms occurred when the paramedian branches of the lower BA, medial or lateral branches of PICA were occluded with the following development of the small lesions (4–6 mm3) in the medulla oblongata.

IMAGING FEATURES OF LATERAL MEDULLARY INFARCTION

In study patients, MRI of the brain, performed after 12-24 hours from the beginning of the stroke, revealed isolated

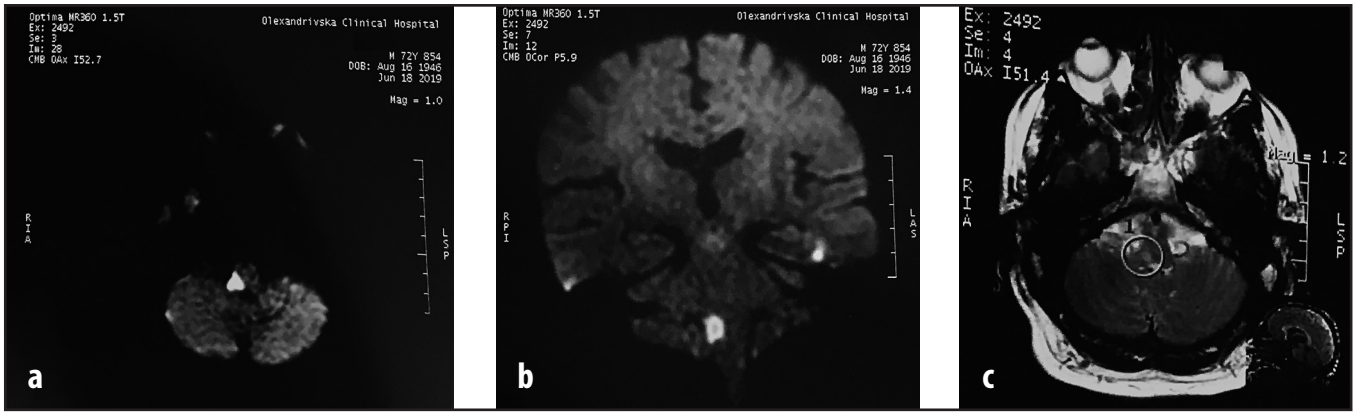

Fig. 1a,b,c. Magnetic resonance imaging of the brain of patient P., 72 years old, with acute lateral ischemic infarction of the medulla oblongata, in diffusion-weighted mode (axial projection). The MRI was done within 8 hours after the symptom's onset. The right posterolateral region of the medulla oblongata revealed hyper-intensive acute ischemia with a reduced diffusion coefficient.

lesions of the medulla oblongata in 3 patients, combined lesions of the medulla oblongata and cerebellum - in 6 patients. Most lateral medullary round infarcts were localized in the middle part of the medulla oblongata (75%), less often - in the upper and lower (25%). Their average size was 45.6 mm3. In 6 patients, the focus of ischemia was not visualized, although they had a typical neurological clinical picture of medullary lateral infarction. False-negative results, in this case, are explained by the presence of small infarct foci that are not visualized in the spatial image [22].

CLINICAL CASE PRESENTATION

To illustrate the features of a clinical course LMI, we present our clinical case observation. Patient P., 72 years old, was hospitalized in the neurology department of the University Hospital (Oleksandrivska Clinical Hospital, Kyiv, Ukraine) in June 2019, with complaints of severe systemic dizziness, nausea, repeated vomiting, impaired coordination of movements (inability to walk and stand with a tendency to fall to the right). All symptoms developed suddenly during the elevation of the blood pressure to 170/120 mm Hg. Since 2003, pt monitored for hypertension. However,antihypertensiveprescriptions have not been taken systematically.

Findings: pulse - 72 beats/min, rhythmic, blood pressure - 160-80 mm Hg. Bernard-Horner syndrome on the right, horizontal nystagmus, segmental anesthesia of pain and temperature sensitivity on the right part of the face, pronounced dysphagia, dysphonia, dysarthria, stuck out tongue not deviating, decreased pharyngeal reflex. Paresis of the extremities was not detected, tendon reflexes on the hands - symmetrical, knee reflexes are S>D, Achilles reflexes are D = S, a positive symptom of Strumpel bilateral. Decreased muscle tone in the right extremities. Left-sided hemihypesthesia of pain and temperature sensitivity by the conductive type, intentional tremor when performing finger, heel-knee tests. The volume of the neurological deficit on the NIHSS scale is 9 points. The average severity of impairment on the scale of B. Hoffenberth and co-authors is 22 points (severe impairment).

Ultrasound examination of the main vessels of the head and transcranial Doppler revealed intracranial stenosis of the lumen of the right VA up to 86%, stenosis of PICA - 72%. MRI of the brain is presented in Figure 1. The neurological deficit in this clinical observation is due to the lesions of laterally localized structures of the medulla oblongata.

Diagnosis: lateral cerebral infarction with alternating Wallenberg syndrome in a patient with subcortical hypertensive and arteriosclerotic encephalopathy of III stages.

DISCUSSION

LMI causes a range of symptoms due to ischemia in the lateral part of the medulla oblongata in the brainstem. The most prevalent etiological factor is an occlusion of the intracranial portion of the vertebral artery (VA) followed by the posterior inferior cerebellar artery (PICA) and its branches [23-25]. Cerebral embolism, hypoplastic vertebral artery, or vertebral artery dissection is the commonest cause of LMI in young patients.

ANATOMICAL FEATURES OF LATERAL MEDULLARY INFARCTION

According to the anatomical topography and features of its blood supply, the medulla oblongata is referred to the proximal intracranial area of the brain stem [9]. The blood supply of this area is carried out by arterial branches, which successively depart from the intracranial VA. These branches are anterior and posterior spinal arteries, as well as PICA, and its numerous branches. The small paramedian arterial branches of VA and PICA supply blood to the lateral part of the medulla oblongata. There are lateral, medial (paramedian), and dorsal branches of the posterior circulation arteries and the corresponding areas of the medulla oblongata, which correspond to the location of the infarct in the case of acute cerebrovascular accident [26]. Accordingly, there are lateral, medial infarctions of the medulla oblongata, as well as combinations of lateral and medial infarctions [27-29].

J. S. Kim and co-authors (1999) [30] in a clinical study reported that by the localization, 75% of medulla oblongata strokes are lateral and only 25% are medial. According to other authors [31], the frequency of lateral and medial infarctions is 78 and 19%, respectively, ie, their ratio is 4:1. Dorsal medulla oblongata stroke is quite rare [2, 9].

LMI occurs in the area of its lateral parts due to occlusive lesions of small paramedian arteries and lateral branches, which depart from VA, PICA, lower divisions of the basal artery, rarely anterior inferior cerebellar artery [9]. Therefore, such concepts as the "lateral medullar syndrome" and"dorsolateral cerebral infarction" are still used as synonyms for LMI.

CLINICAL FEATURES OF LATERAL MEDULLARY INFARCTION

The clinical manifestation of LMI was first described in 1895 by the famous German neurologist Adolf Wallenberg (1862-1949), who initially identified the development of cerebral infarction of the medulla oblongata with embolic occlusion PICA [32].

C. M. Fisher and co-authors (1961) [26], based on the analysis of the arterial system of sixteen patients with LMI and 26 observations of other authors, concluded that lateral cerebral infarction in approximately 75% of cases is caused by VA's occlusion. JS. Kim and co-authors (1995) [33] during the examination of 34 patients diagnosed occlusive lesions in the area of PICA (23.5%), VA (38.2%), and simultaneous lesions of VA and PICA (26.5%). However, occlusive lesions of the arteries were not detected in 11.8% of cases.

Therefore, LMI can occur in the case of lesions of the intracranial HA, PICA, rarely BA, and PICA. Therefore, the clinical course of LMI should not be identified with the previously described PICA syndrome and its variants.

The clinical presentation of LMI is closely related to the topography of the lesion of the medulla oblongata (upper, middle, lower). This topographycan be determined on sections of T2-weighted MRI, using the following criteria: the upper part of the medulla oblongata corresponds to dorsolateral protrusion at the level of the lower leg of the cerebellum; the middle part of the medulla oblongata corresponds to the ventrolateral protrusion of the lower nucleus of olive; the lower part is a rounded shape of the medulla oblongata.

W. Kameda and co-authors (2004) [31] analyzed the clinical and MRI parameters of 214 patients and showed that the most often LMIs were localized in the middle part of the medulla oblongata (35% of cases), in the upper part - in 29% of cases, and the least - in the lower part (15%).

Summarizing the data of the neurological clinical features of lateral medullary infarcts, given in publications, the representative symptoms that are characteristic for the alternating Wallenberg syndrome,known as lateral medullary syndrome and posterior inferior cerebellar artery syndrome, can be identified as follows:

- impaired sensitivity on the face (89%) by the segmental dissociated type in the areas of Zelder that is located on the stroke side.It developed due to damage to the descending tract and the spinal nuclei of V pair of cranial nerves;
- hypoesthesia of pain and temperature sensitivity by the Hemi type on the opposite to the stroke side. It occurs due to dysfunction of the spinal-thalamic pathway;
- dysarthria, dysphonia (75%) due to paresis of the muscles of the vocal cords and soft palate, caused by the damage to the motor double nucleus (Nucl. ambiguous);
- dizziness (73%) - dysfunction of the vestibular nuclei;
- Bernard-Horner syndrome (72%) on the side of the lesion (dysfunction of the descending sympathetic fibers);
- cerebellar ataxia on the side of ischemia due to lesions of the anterior and posterior spinocerebellar pathways;
- horizontal nystagmus (57%) due to damage to the vestibular nuclei and their connections;
- dysphagia (57%) as a result of damage to the nuclei of the IX and X pairs of nerves;
- headache (47%).

In the clinical situation, described above, the pathological process (thrombosis - in 60% of cases, embolism - in 35%) is localized in HA, and not PICA, as thought previously [34].

If the LMI extends to the lateral surface of the bridge, then its typical features are accompanied by signs of muscle paresis innervated by VI and VII cranial nerves.

IMAGING FEATURES OF LATERAL MEDULLARY INFARCTION

DWI MRI is the best diagnostic test to confirm LMI. The infarcted area has a high DWI signal. LMI was identified by the MRI of the brain, performed within 24-48 hours after the onset of the stroke. On MRI LMI foci has the shape of a triangle (7–10 mm long in the rostrocaudal direction), facing the apex to the bottom of the IV ventricle, and the base to the lateral surface of the medulla oblongata. Ventrally, the infarct area was limited by olive, medially - by the roots of the XII pair of cranial nerves, dorsally reaching the gray matter of the bottom of the fourth ventricle, rostrally - to the pons.

CONCLUSIONS

LMI results from a vascular event in VA or PICA and characteristically has varied neurologic manifestations. LMI often affects descending spinal tract, descending sympathetic tract fibers, inferior cerebellar peduncle and dorsolateral medulla, the nucleus of the trigeminal nerve, nuclei, and fibers of the vagus nerves and glossopharyngeal, spinothalamic tract, and vestibular nuclei. As a result, it presents as complete (classic) or incomplete lateral medullary syndrome, also called Wallenberg syndrome or posterior inferior cerebellar artery syndrome. The first case of LMI was reported and described by Jewish neurologist and neuroanatomist who practiced in Germany, Adolf Wallenberg (1862-1949). Knowledge of the features of the neurological clinical course and im-

aging features of LMI is important for the medical doctor, helping to diagnose this type of posterior circulation stroke promptly, timely, and choose adequate methods of therapy and assessment of long-term functional prognosis.

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ORIGINAL ARTICLE

ADAPTIVE CAPABILITIES OF MIDDLE SCHOOL-AGED GIRLS DEPENDING ON THE RATIO OF ADIPOSE AND MUSCLE TISSUE

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ABSTRACT

The aim: This study aimed to determine the dependence of adaptive capacities of middle school-aged girls with excessive body weight and increased volume of adipose tissue on the ratio of adipose and muscle tissue volume.

Materials and methods: 52 female subjects aged 10-12 years were examined and divided into 3 groups according to their BMI. Cardiorhythmogram was recorded in all subjects using the "CardioLab" hardware-software complex. The indices of heart rhythm variability (HRV) were determined at rest and after an active orthostatic test based on the recorded cardiothythmogram. Body weight and total fat tissue amount were determined using the Tanita BC-601 device.

Results: The analysis of HRV indices revealed features of autonomic rhythm regulation depending on morphological body features of the middle school-aged girls, namely, on the amount of fat and muscle tissue. Obese subjects had higher values of VLF %, LF % and LF/HF indices, which indicate a higher sympathetic influence on cardiovascular system activity and less significant parasympathetic division of the autonomic nervous system (ANS), as well as the PARS index. This trend of HRV indices points to an unsatisfactory level of adaptation, tension of the regulatory systems and the possibility of their failure. In contrast, subjects with normal and excessive body weight had higher values of HF ms^2, HF % and TR ms^2, and lower values of VLF %, LF/HF and PARS, which points to the dominance of the parasympathetic part of the ANS, lower level of tension in their regulatory systems, a satisfactory level of adaptation, satisfactory functional reserves of the cardiovascular system and high capabilities of the body.

Conclusions: Obese girls exhibited disturbances in the ANS functional state towards sympathicotony and increased functional activity of suprasegmental ANS divisions, which can be interpreted as an autonomic dysfunction.

KEY WORDS: heart rate variability, autonomic nervous system, children, excess body weight, obesity, adaptive capacity of the body

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INTRODUCTION

In recent years an increasing number of people are diagnosed with excessive body weight and obesity both among the adult population and among children and adolescents [1,2]. However, despite the rate of increase in prevalence, these conditions are probably still insufficiently understood as health care problems. Nevertheless, the published literature has thoroughly elucidated the clinical and social significance of obesity as a trigger factor and an aggravating cause of a large number of diseases that lead to reduced life quality and expectancy. [1,3]. The cause for concern in children with an increased amount of adipose tissue is the triggering of mechanisms that form a springboard for early manifestation of cardiovascular, endocrine, reproductive, neoplastic, cerebrovascular, musculoskeletal, and other diseases [1,3]. Childhood obesity also leads to short- and long-term adverse effects on physical and psychosocial health, which are important for general well-being [4,5].

Childhood obesity is also characterized by disorders of the autonomic nervous system (ANS) [3], which is crucial in ensuring the harmony of physiological processes and adaptation to various environmental factors. The occurrence of disorders of the ANS is in turn important in the pathogenesis of functional abnormalities of various organs and systems that can cause the development of chronic diseases and irreversible changes in adulthood. Therefore, investigating the level of functional reliability of the organism in children with an excessive amount of fat tissue is interesting, on the one hand, because of the insufficient maturity of autonomic support systems and mechanisms of their regulation, and on the other hand, because of the chronic inflammation of adipose tissue, which is accompanied by the production of proinflammatory agents, the synthesis of which grows proportionally to the level of obesity and distribution of adipose tissue in the body [6].

Currently, the standards for assessment of the functional state are the physiological indicators reflecting the mechanisms of cardiac activity regulation. Therefore, among many existing tests, the method of heart rhythm variability (HRV) measurement and the indicator of activity of regulatory systems (PARS) suggested by R. M. Bayevsky are the most widely used, because they allow to establish typological features of autonomic regulation of heart rhythm, demonstrate the level of functional and adaptive capacities of the organism, and allow to predict and to control dynamic processes of prophylactic measures and treatment procedures [7-9].

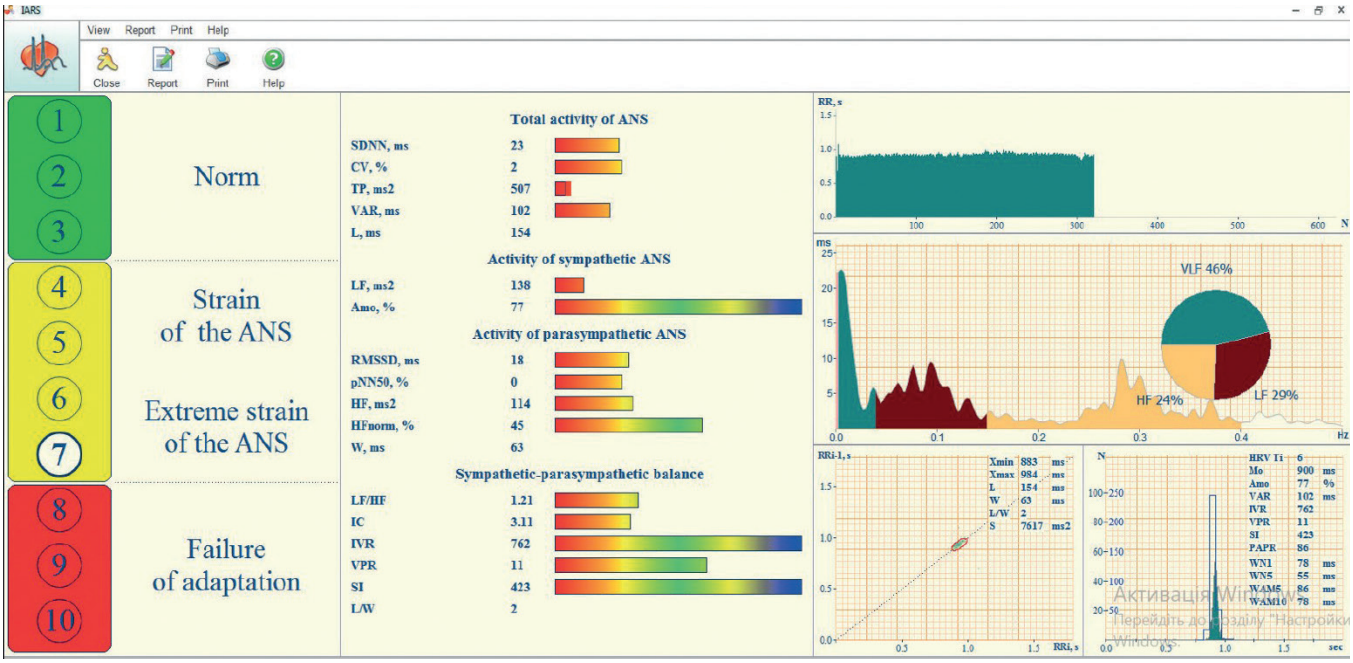

Fig. 1. Evaluation of PARS using the CardioLab device

THE AIM

The aim of this study was to determine the dependence of adaptive capacities of middle school-aged girls with excessive body weight and increased volume of adipose tissue on the ratio of adipose and muscle tissue volume.

MATERIALS AND METHODS

The study involved 52 girls aged 10-12 years without pathological changes according to the clinical examination and the principles of biomedical ethics. They were divided into 3 groups based on the body mass index (BMI). Normally, children's BMI is lower than that of adults, and its normal value is in the range from 15 to 18.5 kg/m^2, depending on the age. To characterize BMI deviations from normal values, the majority of clinicians use a 5-point scale (Table I) [10]. At the same time, the International Obesity Task Force (IOTF) recommends that children from 2 to 18 years old be considered overweight if their BMI is between 25 kg/m^2 and 30 kg/m^2, and considered obese if their BMI is >30 kg/m^2 [10,11].

In addition, current recommendations define obesity in children and adolescents if the body weight exceeds the reference values for the given age by 20% or more, and the amount of total body fat exceeds 25% for boys and 30% for girls [12]. The percentage amount of total fat (TF, %) in the bodies of examined subjects was determined using the Tanita BC-601 (Japan) scale/analyzer that functions by measuring the electrical impedance of tissues when a low-intensity constant electrical current is passed through them.

According to these considerations, Group 1 included children with BMI of 5 points, Group 2 included children with BMI of +4 and +3 points, and Group 3 included children with BMI of +2 points.

The functional state of the ANS was assessed by intervalocardiography using the hardware-software complex "CardioLab" (HAL "Medica", Ukraine), which allows obtaining spectral indices of heart rhythm variability (HRV) and characterizing the functional activity of different branches of the ANS. Specifically, the tone of the sympathetic, parasympathetic, and suprasegmental branches of the ANS was assessed by the power of the low-frequency (LF, ms^2), high-frequency (HF, ms^2), and very low-frequency (VLF, ms^2) spectral ranges respectively. The balance of the sympathetic and parasympathetic ANS branches was evaluated by the ratio of low- and high-frequency components of HRV: LF/H.

The adaptive capabilities of the subjects were assessed by the PARS value, which allows to quantitatively evaluate the functional state of the body in points, as well as by the response to the orthostatic test. The analysis of PARS values allows to diagnose the following functional health conditions: the green zone (1 to 3 points) – the normal state, satisfactory adaptation, and high functional capacities; the yellow zone (4 to 7 points) – the state of tension of the regulatory systems, decrease of the functional reserves, i.e. the premorbid state; the red zone (8 to 10 points) - the state of deterioration of the regulatory systems, failure of the adaptation processes – asenization.

Clinical assessment of the results of the orthostatic testing was done using the coefficient of response to orthostatic testing (Cr), which shows the degree of rhythm increase in percentage points during the transition process. The possible outcomes of the orthostatic test and the associated Cr values are as follows: normal, Cr below 30%; decreased, Cr below 30%; and paradoxical with rapid stabilization of rhythm; Cr above 30%.

The results were analyzed using Jamovi 0.8-1.0 software (Affero General Public License 3). The method of descriptive statistics with the estimation of arithmetic

Table I. Criteria for assessing the deviation of BMI from the ideal value according to the 5-point system.

Body weight assessment in girls							
Score Age	-2	-3	-4	5	+ 4	+ 3	+ 2
10	14.3	15.0	15.9	17.1	18.0	21.8	24.2
11	14.6	15.3	16.2	17.8	19.0	23.0	25.7
12	15.0	15.6	16.7	18.3	19.8	23.7	26.8

+4 - mild increase in body weight
+ 3 - moderate increase in body weight
+ 2 - pronounced increase in body weight
4 – mild decrease in body weight
3 - moderate decrease in body weight
2 - pronounced decrease in body weight
5 - exact correspondence of body weight to age

Table II. Mean values of HRV indicators in middle school-aged children with different BMI values (M±m)

HRV indicators	Group 1 (n=22) (BMI 5 points)	Group 2 (n=18) (BMI +4 and +3 points)	Group 3 (n=12) (BMI +2 points)
TP, ms2	3448±91	2657±163 **	1822±212 *
HF, ms2	751±81	515±148 *	181±97 **
LF, ms2	1593±10	948±125 **	713±135 **
VLF, ms2	1157±1	1024±159	957±145*
LF/HF	2,1±0,22	1,84±0,23	3,9± 0.26 **
HF, %	18,6±2.4	15,8±3,6	8,4±2.7 **
LF, %	46,0±2.7*	43,2±4. 7	38.2±2.5 *
VLF, %	35,4±3.1*	41,0±2.7*	53,4±3.9 **
PARS, units	2,164±1,617	2,579±1,625	5,478±1,581 **
Cr, %	26,5±3,9*	47,2±4,6*	66,0±5,8*

Note: Differences were statistically significant at * $p \leq 0.05$; ** $p \leq 0.01$

mean (M) and the error of the arithmetic mean (m) was used. The Mann-Whitney U-criterion was used to make a cross-group comparison of the quantitative indicators. The results were considered significant at $p<0.05$.

RESULTS

According to the BMI, the 1st group included 22 (42%) children, the 2nd group included 18 (35%) children, and the 3rd group included 12 (23%) children. The average BMI of girls in the 1st, 2nd, and 3rd group was 17.7±0.4 kg/m^2, 20.9±0.6 kg/m^2, and 25.6±0.9 kg/m^2 respectively. The percentage of total fat was 17.2±0.8%, 20.6±0.7%, and 25.3±1.2% in the 1st, 2nd, and 3rd group respectively. There was a statistically significant difference in the average values of BMI and TF% between groups 1 and 2, 1 and 3, and 2 and 3.

To evaluate the mechanisms of regulation of physiological functions of the body, the features of autonomic regulation, the relationship between sympathetic and parasympathetic branches of the ANS, and the tension of the regulatory systems and functional reserves, the analysis of HRV indices in girls with different morphological status was used. These indices are summarized in Table II.

The analysis of HRV indicators in groups of children with different BMI revealed that girls with normal and excessive body weight had similar indicators, while girls with obesity had significantly different indicators compared to the other two groups.

The TP indicator, which reflects the total level of activity of the regulatory systems, in children with normal body weight was 3448±113 ms^2, in overweight children - 2657±163 ms^2, and in children with obesity - 1822±212 ms^2. The power indicator in high-frequency range (HF) in group 1 was 751±78 ms^2, in group 2 - 515±148 ms^2, and in group 3 - 181±97 ms^2. The power in the low-frequency range (LF) in children with normal body weight was 1593±100 ms^2, in overweight children - 948±125 ms^2, and in children with obesity - 713±135 ms^2. The power in the range of very low frequencies (VLF) in the 1st group was 1157±114 ms^2, in the 2nd group - 1024±159 ms^2, and in the 3rd group - 957±154 ms^2. Low- to high- frequency ratio (LF/HF) was 2,1±0,22 in children with normal body weight, 1,84±0,23 in children with excessive body weight, and 3,9±0,26 in obese children. The value of the complex index of activity of the regulatory systems (PARS) was equal to 2,164±1,617 units in children in the 1st group, 2,579 ± 1,625 units in children in the 2nd group, and 5,478 ± 1,581 units in children in the 3rd group.

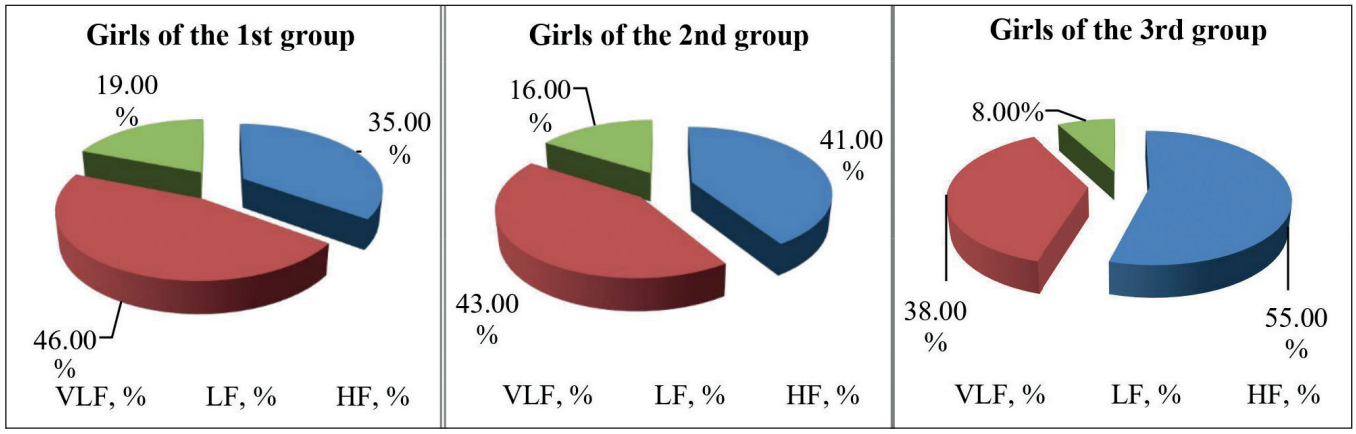

Fig. 2. The relationship between the ANS effect pathways on heart rhythm in groups of middle school-aged children with different values of BMI.

Although the highest absolute values of VLF ms^2, LF ms^2, and HF ms^2 were recorded in children with normal body weight as compared to children with excessive body weight and obesity, the relative values of these indicators differed. The highest value of the fractional contribution of the power in the very low frequency range (VLF) to the TP was found in children with obesity (53,4±3,9%), a slightly lower value was found in children with excessive body weight (41,0±2,7%), and the lowest value was recorded in children with normal body weight (35,4±3,1%). However, the fractional contribution of the power in the high frequency range (HF) to the TP was the lowest in obese children (8,4±2,7%), and practically equal in children with normal and excessive body weight (18,6±2,4% and 15,8±3,6% respectively). The fractional contribution of the low frequency range (LF) to the TP in children with different BMI values was as follows: group 1: 46,0±2,7%, group 2: 43,2±4,7%, and group 3: 38,2±2,5%.

The analysis of the contribution of the frequency components of the TP to the structure of the heart rhythm modulation within each group revealed that the wave structure of heart rhythm in children with normal and excessive body weight was LF> VLF> HF, while in obese children it was VLF> LF> HF.

During the transition from the clino- to the orthoposition, differences were also found in the value of the Cr indicator among girls of different constitution. Thus, representatives of groups 2 and 3 had an accelerated type of heart rate response to changes in body position compared with those of the first group. It also indicates on the autonomic dysfunction due to excessive activation of the sympathetic ANS in these individuals.

DISCUSSION

The comparison of HRV indices between the groups of children shows that obese girls have abnormalities in the functioning of some systems, in particular of the cardiovascular and regulatory systems, and in their adaptation abilities.

The analysis of the levels of tension of the regulatory systems showed that the sum of PARS points in girls of the 3rd group averaged 5,478± 1,581 units, which exceeds the normal value of this indicator and points to the presence of premorbid state in subjects of this group. This is manifested by the tension of the regulatory systems, decreased functional reserves and the beginning of the development of energy and metabolic imbalance [13].

The evaluation of the indicator of the total activity of the regulatory systems in girls of the same group revealed a decrease in the total power of the spectrum (TP) (1822±212 ms^2), the normal value of which is within 1906-5790 ms^2 [14]. Overall, the neurohumoral regulation in subjects in this group was characterized as VLF> LF> HF. Relative to the total power, VLF accounted for 55%, LF - for 38%, and HF – for only 8%. This proportion reflects an increased level of humoral and metabolic influences in modulation of heart rhythm and a decreased level of parasympathetic influence. Because VLF index is a sensitive indicator of the regulation of metabolic processes and reliably reflects energy-deficient states, the predominance of its influence in heart rhythm modulation points to the tension of regulation mechanisms and depletion of adaptation resources [13].

The analysis of spectral indices of the vagosympathetic balance (LF/HF) in obese girls also suggests the domination of sympathetic influences and a decrease of vagus activity in relation to the cardiovascular system, and a decrease of the central control loop activity. This can be regarded as a prognostically unfavorable risk factor [15]. The lowest absolute values of VLF ms^2, LF ms^2 and HF ms^2 in the 3rd group compared to the 1st and 2nd groups also indicate a significant preponderance of the role of the sympathetic branch of the ANS over its parasympathetic branch.

Therefore, our study revealed that obese girls have a decreased activity of the parasympathetic nervous system and an increased activity of the sympathetic nervous system, which can be considered as an increased tension of the adaptation mechanisms, a decrease of reserve capacities, and the development of functional autonomic disturbances with their further transformation. Our data is confirmed by the results of the research on this problem, namely, those showing that BMI in obese children is negatively associated with HF, and positively associated with LF and the HF/LF ratio [16].

CONCLUSIONS

Obese girls exhibited disturbances in the functional state of the ANS towards sympathicotony and increased functional activity of the suprasegmental ANS divisions, which can be interpreted as an autonomic dysfunction.

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ORIGINAL ARTICLE

CORRELATION OF RELAPSE-FREE SURVIVAL WITH NEOADJUVANT TREATMENT IN PATIENTS WITH STAGE IIIA NON-SMALL CELL LUNG CANCER

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ABSTRACT

The aim: The aim of this study was to investigate disease-free and overall survival in patients with stage IIII A NSCLC after neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, and neoadjuvant chemotherapy.

Materials and methods: For the study, 3 groups of 65 people were taken. All patients underwent radical surgery in the form of lobectomy, bilobectomy or pneumonectomy. All groups received 3 or 4 courses of neoadjuvant chemotherapy according to the scheme Docitaxel (Paclitaxel) and Cisplatin (Carboplatin), while groups II and III also received, respectively, neoadjuvant and adjuvant radiation therapy in the amount of 30 Gy to the chest and mediastinum. Survival was assessed using the Kaplan and Mayer scale.

Results: 1. At a survival period of 6 months, the results of relapse-free survival in the NCRT and NCT groups do not differ. 2. From 12 months to 5 years, the highest recurrence-free survival rates are observed in the NHL group. 3. The overall five-year survival rate in the main group was 28.1±5.9%, in the NCT group - 10.4±3.8% and - 5.8±2.0% in the NCT + RT group.

Conclusions: The best recurrence-free survival results are observed in the NHLT group. Also, the largest number of cases of molars morphological response, correlated with the highest survival rates, also occurs in the NHL group.

KEY WORDS: Non-small cell lung cancer, neoadjuvant therapy, chemoradiotherapy, chemotherapy, overall survival

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INTRODUCTION

Treatment of stage IIIA non-small cell lung cancer remains a difficult problem today. There was no unified strategy on this issue. In order to identify the optimal method for the treatment of this pathology, it is necessary to analyze the overall and relapse-free survival with existing treatment methods:

Lung cancer is a common type of disease in the world and the main cause of death in men.

Etiological causes of the disease:

1. Smoking - 85% of non-small cell lung cancer is associated with smoking;
2. Radon exposure;
3. Asbestos;
4. Dust pollution;
5. Ionizing radiation on the chest area in the anamnesis;
6. Inhalation of air contaminated with metals and polycyclic hydrocarbons;
7. Pulmonary fibrosis;
8. Human immunodeficiency virus;
9. Heredity [1,2].

Small cell lung cancer is treated with chemotherapy, targeted therapy and immunotherapy, and non-small cell lung cancer is treated with neoadjuvant chemotherapy or chemoradiotherapy and radical surgery, if necessary, adjuvant chemo or radiation therapy is performed [1].

Survival in stage IIIA of non-small cell lung cancer remains low even after a full course of treatment - 58% of patients do not live a year from the moment of diagnosis[1]. A clear strategy for the treatment of stage IIIA non-small cell lung cancer in some cases is dual or absent altogether. For example, the NCCN clinical protocol of 2020 shows the possibility of neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy and adjuvant radiation therapy without specifying the number of courses and radiation regimen, and in the clinical protocols of the CIS countries they are mandatory and at least 3 courses of neoadjuvant chemotherapy are carried out. Radiation therapy is not considered mandatory [2,3].

The literature data found on pub med indicates that over the past 20 years, a large number of studies have been conducted, both case-control and retrospective studies, as well as randomized clinical trials and meta-analyses [4-6]. The research results are contradictory. Some indicate an increase in survival with the use of neoadjuvant chemoradiotherapy, others indicate that there is no difference with both methods. There is evidence that the use of chemoradiotherapy increases the likelihood of a complete morphological response (a

Table I. Cumulative relapse-free survival with different methods of treatment of patients with stage III A of NSCLC

Survival time	Treatment methods		
	NHL	NHT	NHT + LT
6 months	79.52 ± 5.06	59. ± 6.4	82.9 ± 4.7
12 months	56.6 ± 6.3	27.5 ± 6.3	42.3 ± 6.4
36 months	24.6 ± 5.7	0	6.5 ± 3.5
5 years	19.5 ± 5.4	0	0

Cumulative relapse-free survival with different methods of treatment of patients with stage III A of NSCLC

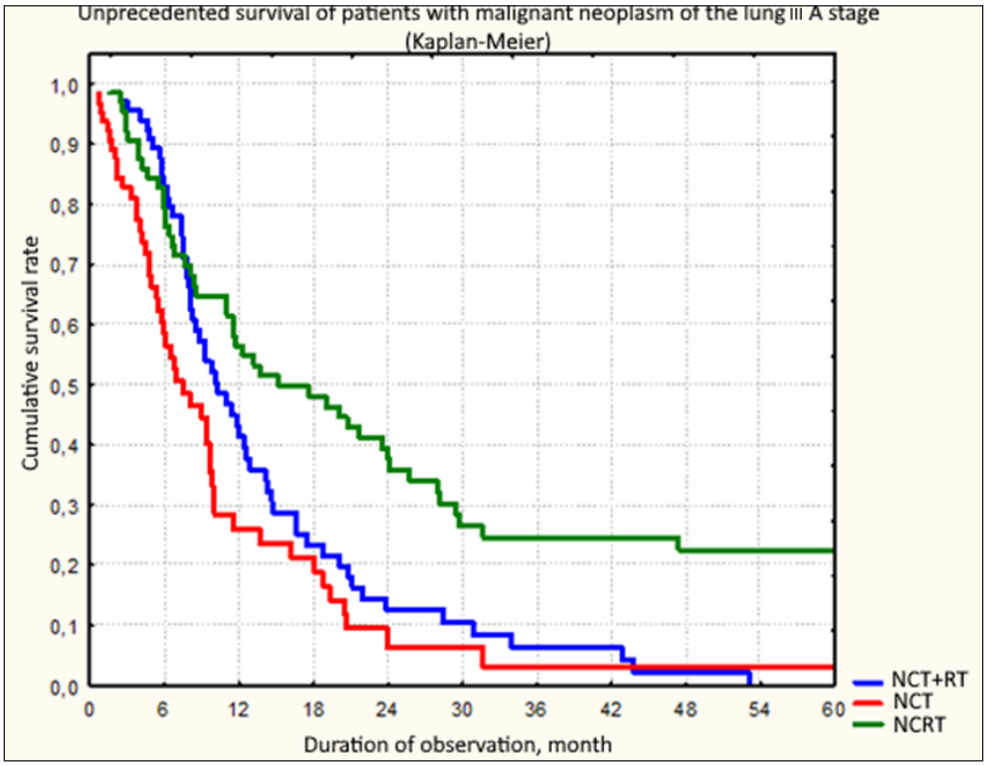

Fig. 1. Cumulative unprecedented patient survival with malignant neoplasm of the lung III A stage

phenomenon when, after neoadjuvant treatment, areas of fibrosis are observed on the site of cytologically or histologically confirmed malignant cells), and a complete morphological response, in turn, is associated with an increase in survival. Perhaps such contradictory results are based on the lack of standardization of the number of courses of chemo and radiation therapy, the dosage of radiation therapy, types of linear accelerators and drugs for chemotherapy [2-8].

It should be noted that there is no convincing data in the literature on relapse-free survival in stage IIIA non-small cell lung cancer using different methods of neoadjuvant therapy [8-12].

It becomes obvious that it is necessary and promising to study the effectiveness of methods of neoadjuvant chemotherapy and chemoradiotherapy for stage IIIA non-small cell lung cancer under the conditions of standardized treatment and relapse-free survival for each of the methods.

THE AIM

The aim was to determine the relapse-free survival in patients with stage IIIA NSCLC after various types of neoadjuvant and adjuvant treatment.

MATERIALS AND METHODS

The work was carried out on the basis of the Department of Chest and mediastinal tumors of the National Cancer Institute, Ukraine. For the study, 3 groups of patients with stage IIIA NSCLC were taken, each of which consisted of 65 people. All patients underwent radical surgery in the volume of lobectomy, bilobectomy or pneumoneectomy. The first group of patients received neoadjuvant chemoradiotherapy, the second group received neoadjuvant chemotherapy, the third group received neoadjuvant chemotherapy and adjuvant radiation therapy. Neoadjuvant radiation therapy was carried out in the amount of 30 SOD GY with a single dose of 2 GY, chemotherapy was 3-4 courses with Carboplatin or Cisplatin and Docetaxel or Paclitaxel.

T he volume of examinations of patients in all 3 groups was standard:

A general blood test;
Biochemical blood analysis;
Coagulogram;
Blood type and Rh factor test;
Gastroscopy;

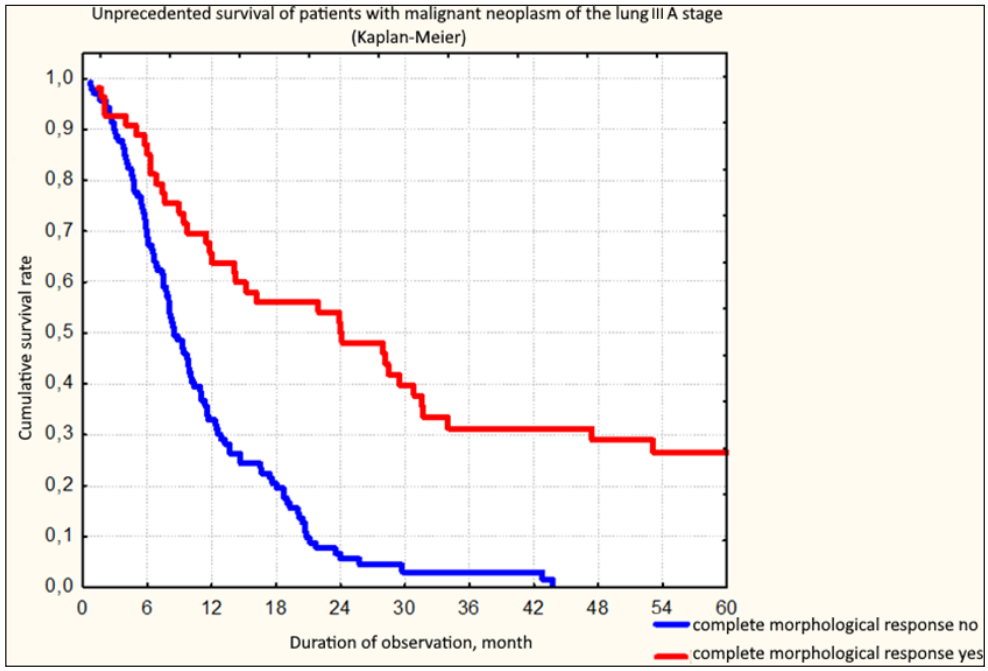

Fig. 2. Cumulative unprecedented survival of patients with malignant neoplasm of the lung III A stage NCT (Kaplan-Meier)

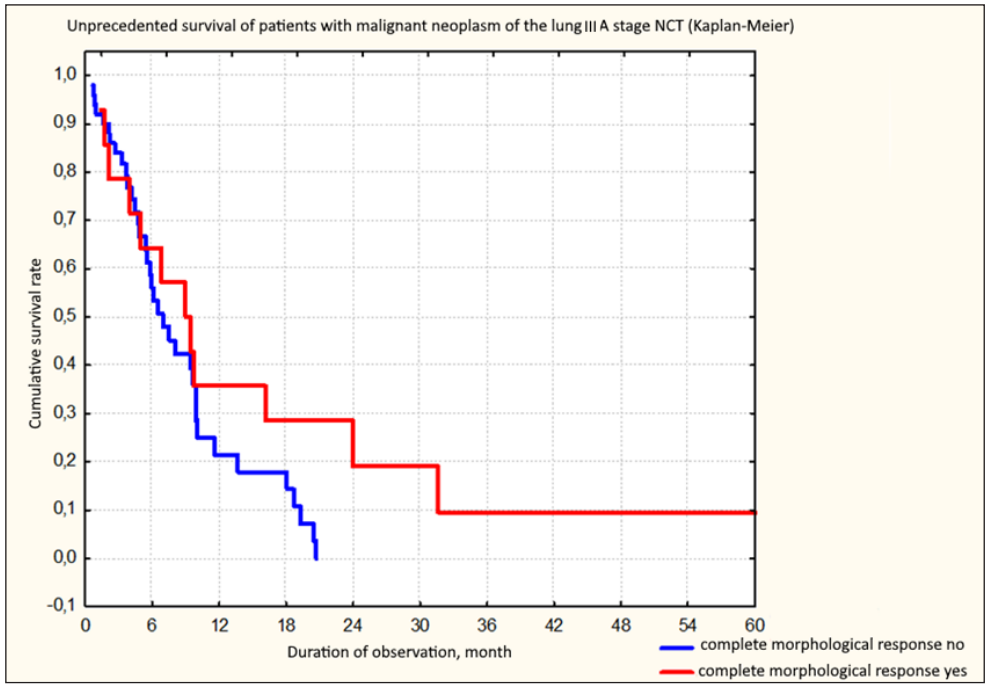

Fig. 3. Cumulative unprecedented survival of patients with malignant neoplasm of the lung III A stage NCT+RT (Kaplan-Meier)

CT of the chest, abdominal cavity and pelvis with intravenous contrast before treatment and before surgical treatment. After the treatment, the patients remained on the dispensary register.

Relapse-free survival was studied in all 3 groups. It was evaluated on the Kaplan and Major scale [13-17].

RESULTS

To analyze the effect of different treatment methods, calculations of cumulative relapse-free survival according to Kaplan and Mayer were used, and look like this:

Also installed:

1. At a survival period of 6 months, the results of relapse-free survival in the NCRT and NCT groups do not differ. There are distinct differences in the survival period of 12 months - in the NCRT group, better results are noted than in other groups. The lowest cumulative survival results were observed in the NCT group. At the 36-month survival period, the best results are observed in the NCRT group, the worst results in the NCT+RT group, and there are no cases of relapse-free survival at this time in the NCT group. At a survival period of 5 years, cases of relapse-free survival are noted only in the NCRT group.

2. NCRT shows advantages over other methods of neoadjuvant and adjuvant treatment in the long term.

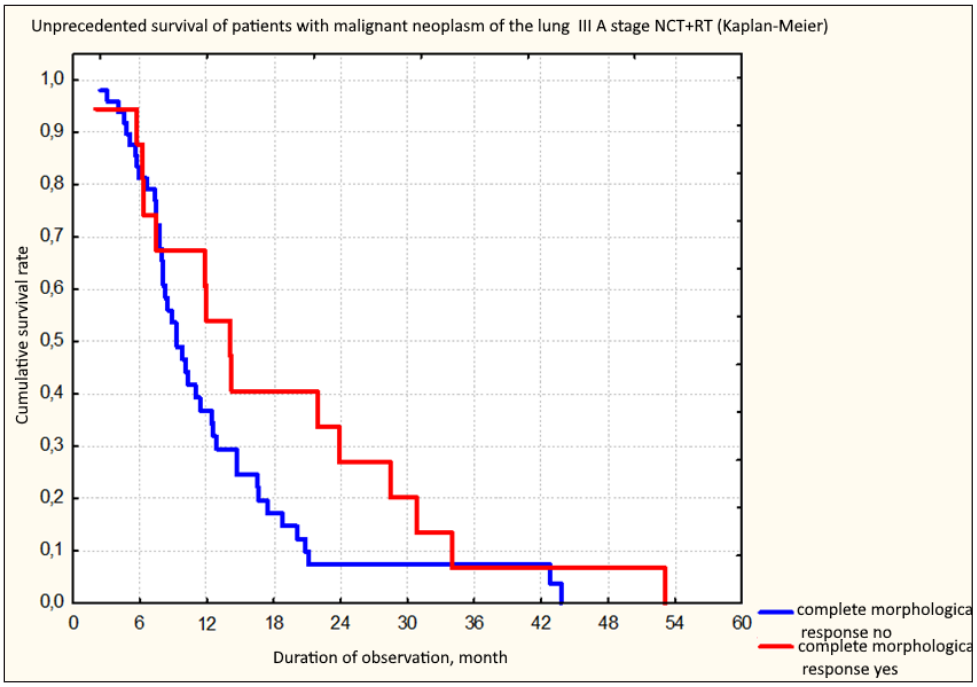

Fig. 4. Cumulative unprecedented survival of patients with malignant neoplasm of the lung III A stage NCRT (Kaplan-Meier)

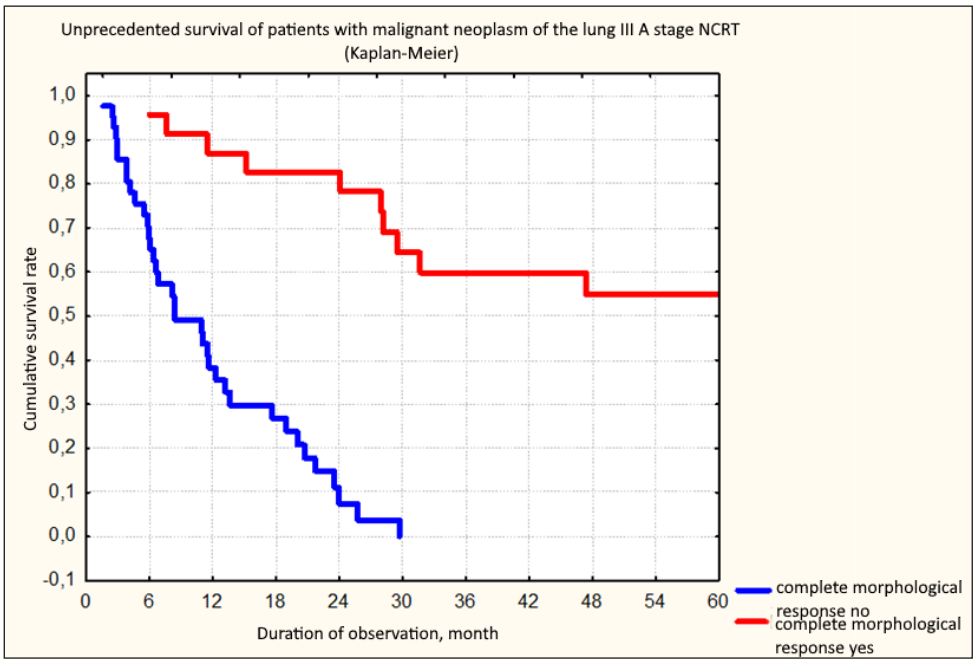

Fig. 5. Cumulative relapse-free survival with different methods of treatment of patients with stage IIIA of NSCLC

3.The overall five-year survival rate in the main group was 28.1±5.9%, in the NCT group - 10.4±3.8% and - 5.8±2.0% in the NCT + RT group.

DISCUSSION

To date, no single strategy has been identified for the treatment of stage IIIA NSCLC. NCCN assumes 3 main strategies - NCRT, NCT and NCT +RT, while drugs for chemotherapy are defined, but the dosage of radiation therapy is not indicated [18, 19].

There are many studies in this direction, but they do not give a complete picture of an unambiguous answer. There are case–control studies, non-randomized clinical trials, randomized clinical trials, meta-analyses that show contradictory results. None of the studies provided a sufficient number of materials with the same drugs for chemotherapy, the number of chemotherapy courses, and radiation therapy dosages. Therefore, some studies show the benefits of NCRT, some studies do not show the difference between NCRT and NCT, some studies show better results with NCT. There are no relevant data for NCT + RT, there are no data on the duration of relapse-free survival in the treatment of stage IIIA NSCLC [18-22].

Our study showed an advantage in relapse-free and overall survival of NCRT compared to other methods. The phenomenon of a complete morphological response was noted. Patients with a complete morphological response

had significantly greater relapse-free and overall survival than the rest of the patients in their group. The predominant number of such patients was registered in the NCRT group.

Also, these studies show a tendency to improve survival in NCRT and further studies are required to prove the benefits of this technique with the identification of the optimal dosage of radiation therapy for patient survival.

CONCLUSIONS

This study allowed us to draw the following conclusions:

1. The duration of relapse-free survival is directly correlated with the duration of overall survival.
2. At a survival period of up to 6 months, the cumulative relapse-free survival rate is highest in the NCT + RT group, the cumulative relapse-free survival rates for the NCRT and NCT groups do not differ.
3. Since the period of survival of 12 months to the end of the study, the best indicators of relapse-free survival observed in the group NCRT.
4. Patients with the phenomenon of complete morphological response and the phenomenon of a high degree of morphological response had a significantly longer period of relapse-free survival and overall survival than other patients in their group. The largest number of patients with a complete morphological response was found in the NCRT group.

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Conflict of interest:
The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

ESTABLISHMENT OF TYPES OF THE CONSTITUTIONS IN STUDENTS-ATHLETES AND IN STUDENTS-MEDICISTS WITH THEIR FURTHER ANALYSIS

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ABSTRACT

The aim: Establishing anthropometric parameters and determining the patterns of formation of types of constitution in students-athletes and medical students while studying in higher education.

Materials and methods: We conducted a study of anthropometric parameters on 129 first and second year students of higher educational institutions in Chernivtsi (aged 16 to 21). The vast majority of students - 121 (93.8%), were from 17 to 19 years, 16 years - 5 (3.9%), 21 years - 2 (1.5%), 21 years - 1 student (0.8 %). Of these, 83 (64.4%) were male and 46 (35.6%) were female. All respondents are divided into two groups: the main group - 89 (69%), control group - 40 (31%). Among the students of the main group there were 62 (69.7%) male and 27 (30.3%) female. The control group consists of 21 (52.5%) men and 19 (47.5%) women. Students of the main group, in addition to physical activity, which was included in the program of their specialty, additionally engaged in the following sports: football - 40 (44.9%) students, volleyball - 18 (20.3%), tennis - 10 (11.2 %), fitness - 9 (10.1%), basketball - 7 (7.9%), freestyle wrestling - 5 (5.6%).All students underwent anthropometric research, according to the method of VV Bunak in the modification by PP Shaparenko. Anthropometric survey included the definition of total (length and body weight) and partial dimensions - longitudinal, transverse, circumferential. Determination of the somatotype was performed by MV Chornorutsky based on the Pinier index L - (P + T), L - body length, P - weight, T - chest circumference. In hyposthenics (asthenics) this index is more than 10, in hypersthenics less than 10, in normosthenics in the range from 10 to 30 and according to V.M. Shevkunenko, where Ind: length of the lower limb / height x 100. Based on the index, dolichomorphic type of structure of the lower limb corresponds to a value greater than 55, from 50 to 55 indicates a mesomorphic (middle) type of structure of the lower limb. If the figure is less than 50 - brachymorphic type of structure.

Results: The probable difference of types of the constitution of students of the main group for MV Chornorutsky on the based the Pinier index and VM Shevkunenko, using the Shevkunenko index. So, between the asthenic type and the hypersthenic type of constitution, because in the main group, according to the Pinier index of asthenics - 26 (29.2%), while according to the Shevkunenko index - 3 (3.4%). Hypertensives according to the Pinier index are - 9 (10.1%), on the difference according to the Shevkunenko index - 25 (28%). The result of a study of students in the control group based on the Pinier index by MV Chornorutsky, and according to VM using the Shevkunenko index, Shevkunenko also showed a significant difference for all types of constitution: according to the Pinier index of normosthenics - 23 (57.5%), while according to the Shevkunenko index - 19 (47,%), according to the Pinier index - 7 (17.5%) - hypertensive, according to the Shevkunenko index - 25 (28%), according to MV Chornorutsky, asthenics - 10 (25%) at the same time as according to Shevkunenko dolichomorphic type of constitution in students of the control group, was not observed during the study.

Conclusions: There is a significant discrepancy in terms of determining the types of constitution, according to MV Chornorutsky, based on the Pinier index and VM Shevkunenko, using the Shevkunenko index. Based on this, it is necessary to further study this issue because the criteria and methods of evaluation, indices, analysis of index results and in order to find common approaches to the methodology of establishing the types of constitution remain unrelated.

KEY WORDS: students, anthropometry, type of the constitution

Wiad Lek. 2022;75(4 p2):955-958

INTRODUCTION

One of the means of studying the state of human health is anthropometric assessment of its physical development with the determination of dimensional and component indicators [1-4]. The study of age norms and variants of somatic features should be combined with the establishment of relative proportional indicators of body parts and somatipological features of its structure.

These data will determine the standards of physical development, taking into account the periods of puberty and aging. In addition, these standards need to be periodically updated due to the acceleration processes taking place in society [5-7].

Also, somatotyping is an extremely relevant scientific field in sports today, as evidenced by a sufficient amount of both domestic and foreign data on the relationship of individual somatotypological and anthropometric parameters, both normal and to assess the risk of various pathological conditions [6 -9].

In recent years, scientists have accumulated a significant amount of material that suggests that the constitution of the

athlete's body is formed largely at the genetic level, because it is a set of individual morphological, physiological and mental properties of the body due to heredity [10-14].

Therefore, the success of the athlete depends mainly on these factors, it is important to study the constitution of the body and somatotype, based on the results of which it is possible to predict high results of future athletes [15-19].

THE AIM

Establishing anthropometric parameters and determining the patterns of formation of types of constitution in students-athletes and medical students while studying in higher education.

MATERIALS AND METHODS

We conducted a study of anthropometric parameters on 129 first and second year students of higher educational institutions in Chernivtsi (aged 16 to 21). The vast majority of students - 121 (93.8%), were from 17 to 19 years, 16 years - 5 (3.9%), 21 years - 2 (1.5%), 21 years - 1 student (0.8 %). Of these, 83 (64.4%) were male and 46 (35.6%) were female.

All respondents are divided into two groups: the main group - 89 (69%), are first-year students of the Faculty of Physical Culture and Human Health of Chernivtsi National University named after Yuriy Fedkovych, control group - 40 (31%) - college students and students Faculty of Dentistry, Bukovynian State Medical University, Chernivtsi.

Among the students of the main group there were 62 (69.7%) male and 27 (30.3%) female. The control group consists of 21 (52.5%) men and 19 (47.5%) women. Students of the main group, in addition to physical activity, which was included in the program of their specialty, additionally engaged in the following sports: football - 40 (44.9%) students, volleyball - 18 (20.3%), tennis - 10 (11.2 %), fitness - 9 (10.1%), basketball - 7 (7.9%), freestyle wrestling - 5 (5.6%).

The subjects of the control group were loaded with hours of physical education, according to the curriculum of their specialty and did not additionally play sports.

All students underwent anthropometric research, according to the method of VV Bunak in the modification by PP Shaparenko [1, 3, 9], in accordance with the requirements of anthropometric research, which ensures the accuracy of measurements and allows to compare results. Anthropometric survey included the definition of total (length and body weight) and partial dimensions - longitudinal, transverse, circumferential.

All anthropometric measurements were performed in the morning, on an empty stomach, on the right and left parts of the body [1, 9].

Determination of the somatotype was performed by MV Chornorutsky based on the Pinier index L - (P + T), L - body length, P - weight, T - chest circumference. In hypostenics (asthenics) this index is more than 10, in hypersthenics less than 10, in normosthenics in the range from 10 to 30 and according to V.M. Shevkunenko, where Ind: length of the lower limb / height x 100. Based on the index, dolichomorphic type of structure of the lower limb corresponds to a value greater than 55, from 50 to 55 indicates a mesomorphic (middle) type of structure of the lower limb. If the figure is less than 50 - brachymorphic type of structure [2].

All obtained results were statistically processed.

RESULTS

Having determined the somatotypes among 129 first and second year students of higher educational institutions in Chernivtsi, according to MV Chornorutsky, on the basis of the Pinier index, the following data were obtained that the normosthenic type of constitution was in 77 (59.6%) students, asthenic (hypostenic) in 36 (28%), and hypersthenic type in 16 (12.4%) students.

So, according to the results obtained, the largest number of students are normosthenics, and the smallest are hypersthenic, among all students.

During the analysis in both groups separately, we obtained the following results:

the main group, where normosthenics are - 54 (60.7%), asthenics - 26 (29.2%), hypertensives - 9 (10.1%);

control group, in which 23 (57.5%) are normosthenics, 10 (25%) are asthenics and 7 (17.5%) are hypersthenics.

Based on the results, a comparison of the both study groups, it was determined that the normosthenic type of constitution predominates, fewer students with asthenic type and the smallest number in both groups - hypersthenic.

When determining the type of lower extremity constitution of the studied students of both groups, using the Shevkunenko index, the following data were obtained that the main group is dominated by mesomorphic type of lower extremity constitution - 61 (68.5%), brachymorphic type - 25 (28.0%), respectively dolichomorphic type was observed in 3 (3.4%) students.

In the study of students in the control group (40 students), according to the Shevkunenko index, brachymorphic type of constitution prevails - 21 (52.5%), mesomorphic in 19 (47,0%) students, dolichomorphic type of constitution, was not observed during the study.

Based on the results, a comparison of both study groups by V.M. Shevkunenko, using the Shevkunenko index, it was determined that in the main group the mesomorphic type prevails over the brachimorphic type, and in the control group, on the contrary, more students with the brachimorphic type of constitution than with the mesomorphic one. At the same time, as in the main group with dolichomorphic type of constitution the number of subjects was small, in the control group this type of constitution was not observed at all.

So, between the asthenic type and the hypersthenic type of constitution, because in the main group (89 students), according to the Pinier index of asthenics - 26 (29.2%), while according to the Shevkunenko index - 3 (3.4 %) students. Hypertensives according to the Pinier index are - 9

(10.1%), on the difference according to the Shevkunenko index - 25 (28%).

So, summarizing the data we can conclude that there are significant differences in determining the types of constitution, according to MV Chornorutsky, based on the Pinier index and VM Shevkunenko, using the Shevkunenko index.

DISCUSSION

The our opinion, the difference between the somatotypes of student-athletes and medical students is that athletes in the relevant sports have physical activity on the muscles of the lower extremities, and as a result increase not only comprehensive anthropometric parameters, but also longitudinal, which are used when determining the Shevkunenko index.

So, taking into account the results of the study of students of the main group, the difference between the types of constitution according to M.V. Chornorutsky, based on the Pinier index and V.M. Shevkunenko, using the Shevkunenko index [11].

Analyzing the research data of the students of the control group on the basis of the Piné index according to M.V. Chornorutsky, and according to V.M. Shevkunenko, using the Shevkunenko index, we can also note a significant difference for all types of constitution: according to the Pinier index of normosthenics - 23 (57.5%), while according to the Shevkunenko index - 19 (47,%), according to the Pinier index - 7 (17.5%) - hypertensive, according to the Shevkunenko index - 25 (28%) students, according to MV According to Chornorutsky, asthenics - 10 (25%), while according to the Shevkunenko index dolichomorphic type of constitution in students of the control group, was not observed during the study.

Considering the differences between the methods of determining the types of constitution according to M.V. Chornorutsky, based on the Pinier index and V.M. Shevkunenko, using the Shevkunenko index, it is not possible to use these techniques for the relevant sports for further sports selection.

Based on this, it becomes possible that further study of this issue is necessary because the criteria and methods of evaluation, indices, analysis of index results and in order to find common approaches to the methodology for establishing types of constitution remain unclear.

CONCLUSIONS

1. Significant differences in the types of constitution according to MV Chornorutsky, based on the Pinier index and VM Shevkunenko, using the Shevkunenko index. namely, between the asthenic type and the hypersthenic type of constitution, because in the main group, according to the Pinier index of asthenics - 26 (29.2%), while according to the Shevkunenko index - 3 (3.4%), hypertensives according to the Pinier index, they make up 9 (10.1%), and according to the Shevkunenko index, they make up 25 (28%).
2. Further study of the criteria and methods of determining the patterns of formation of types of constitution, because the criteria and methods of evaluation, indices and analysis of the results of index indicators are not clarified.

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ORIGINAL ARTICLE

THE RELATIONSHIPS OF IRS-1 POLYMORPHISM WITH HEMODYNAMIC DISORDERS IN HYPERTENSIVE PATIENTS DEPENDING ON BODY WEIGHT AND METABOLIC COMORBIDITY

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ABSTRACT

The aim: The aim was to study the relationships of IRS-1 gene polymorphism with indicators of the structural and functional state of the heart and blood vessels in patients with arterial hypertension under conditions of different metabolic comorbidity and body weight.

Materials and methods: We examined 340 patients with arterial hypertension with different body weight and different types of metabolic comorbidity and 30 healthy individuals aged 45-55. Anthropometric, Biochemical, Molecular genetic methods, Instrumental, Statistical methods were used.

Results: The presence of G/R + R/R genotypes in hypertensive patients with normal body weight was associated with an increase in intima-media thickness (CIMT), pulse wave velocity of carotid artery (cPWV) and lower endothelium-dependent vasodilatation (EDVD) compared with G/G genotype carriers. Hypertensive patients with obesity, carriers of G/R and R/R genotypes displayed more pronounced similar changes in vascular remodeling (higher CIMT, cPWV and lower EDVD) and as well as cardiac remodeling (larger sizes and left ventricular mass (LVM)) compared with G/G genotype carriers. Overweight carriers of the G/R + R/R genotypes were characterized by enlargement of LVM and its sizes, a higher CIMT indicator, but this effect was less than in the comorbidity of hypertension and obesity. In hypertensive patients with hypertension, obesity and type 2 diabetes mellitus, the presence of G/R + R/R genotypes was associated with an increase in left ventricular size, left ventricular mass index (LVMI) and CIMT.

Conclusions: The relationships of IRS-1 polymorphism with indicators of cardiovascular remodeling in hypertensive patients depending on body weight and the presence of various metabolic comorbidity have been established.

KEY WORDS: arterial hypertension, insulin receptor substrate-1 gene, metabolic comorbidity, genetic polymorphism

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INTRODUCTION

For many years hypertension concerned being a sort of an epidemic, having a leading position in terms of prevalence and overall mortality and is often associated with obesity (OB) and overweight [1, 2]. Genetic predisposition to hypertension is manifested under the influence of environmental factors - high-calorie diet, excessive fat intake and low physical activity [3, 4]. These environmental factors contribute to the development and progression of components of the metabolic syndrome in hypertension due to impaired expression of genes that control the signal of insulin, polymorphic lipid disorders, defects in enzymes of glucose metabolism [4, 5].

A number of studies have shown that gene polymorphism has a greater impact on the hypertension course and complications than on its development [6]. A significant number of studies are devoted to the study of genetic polymorphism of key components of RAAS [7, 8]. Some provisions regarding the expression and polymorphism of various AH genes and their relationship with blood pressure levels and the degree of hypertensively-associated organ lesions remain discussed and actively studied [6, 9].

According to most researchers, the most significant predictors of hypertension and obesity are hereditary risk factors. At the same time, despite significant advances in genetic research, there are conflicting views on the role of gene expression and genetic polymorphism in the development and course of disease in different patient populations, as well as their impact on the drug therapy effectiveness [4, 9, 10].

Hyperinsulinemia and IR largely determine the severity of cardiovascular complications in patients with hypertension and obesity. Recently published results of clinical and experimental studies indicate that IR causes a violation of the physiological mechanisms of vasodilation. The action of insulin on the endothelium is mediated by its own receptors and is realized through a multistage signaling system associated with increased synthesis of nitric oxide

Table I. Distribution of G / G and G / R + R / R genotypes of the IRS-1 gene in study groups

Genotype	Group 1	Group 2	Group 3	Group 4	Group 5
	AH + obesity	AH and normal body weight	AH and overweight	AH, obesity and type 2 diabetes	The test group
	n=200	n=50	n=50	n=40	n=30
G/G	110 (55%)[1-5]	32 (64%)[2-5]	22 (44%)[2-3, 3-5]	16 (40%)[2-4, 4-5]	25 (83,4%)
G/R+ R/R	90 (45%)[1-5]	18 (36%)	28 (56%)[3-5]	24(60%)[4-5]	5(16,6%)

Note. 1-5 – statistically significant differences between groups 1 and 5;2-3 – statistically significant differences between groups 2 and 3; 2-4 – statistically significant differences between groups 2 and 4; 2-5 – statistically significant differences between groups 2 and 5; 3-5 – statistically significant differences between groups 3 and 5;4-5 – statistically significant differences between groups 4 and 5.

(NO). In patients with hypertension in the conditions of IR significantly induced NO endothelium-dependent vasodilation (EDVD) [11].

Presence of two components: genetic (hereditary) and acquired is clearly traced in the IR development [12]. Despite the fact that IR has a clear genetic condition, the exact genetic disorders that underlie it have not yet been identified. That indicates its polygenic nature. One of the most recognized polymorphisms of the IRS-1 gene, which is associated with the development of IR in many populations, is G972R - polymorphism [13, 14].

The results of numerous studies of IRS-1 polymorphism have proved its association with the development of type 2 diabetes in different populations [13–17], but there are insufficient data on its influence on the formation of comorbidity of hypertension and obesity, in particular, at the stage of IR absence.

THE AIM

The aim was to study the relationships of IRS-1 gene polymorphism with indicators of the structural and functional state of the heart and blood vessels in patients with arterial hypertension under conditions of different metabolic comorbidity and body weight.

MATERIALS AND METHODS

Clinical - anamnestic with office measurement and home blood pressure monitoring in accordance with the 2018 ESC/ESH Guidelines for the management of AH [1] - to assess the clinical manifestations of AH and study the etiological factors of the disease. Anthropometric - to assess the degree of obesity and diagnose abdominal obesity height, body weight, body mass index, waist circumference, thigh volume, index «waist – thigh" were determined. The insulin concentration, fasting glycemia were determined for calculating the HOMA index. Molecular genetic methods using polymerase chain reaction - established the presence of genetic polymorphisms G972R gene IRS-1 (genotypes G/G, G/R and R/R). Instrumental - to assess the structural and functional state of the heart and blood vessels the ultrasound scanner "IMAGIC Agile" was used.

Left ventricular diastolic function was evaluated by pulmonary artery blood flow and transmitral diastolic blood flow in pulsed Doppler with the determination of the following parameters: maximum early LV filling rate in spectral mode (E), maximum late (atrial) filling speed (A), ratio of maximal rates of early and late filling of LV at spectral mode (E/A), time of isovolumic relaxation of LV (IVRT), time of deceleration early diastolic flow rate (DT), maximum early LV filling rate at tissue mode (e´), mean pulmonary artery pressure (AP) by Kitabatake, ratio of E and e´ (E/e´). For studying endothelial function, the degree of endothelium-dependent vasodilation (EDVD) in reactive hyperemia was determined in all patients according to the method of Celermajer D.S. in the modification of the method by Ivanova O.V. [18, 19]. We measured the intima media thickness (CIMT) of the carotid artery according to the generally accepted method. The pulse wave velocity (PWV) in the carotid artery (cPWV) was determined by the W-Track method; determination of the PWV in the abdominal aorta (aPWV) was performed using a phased sensor.

Difference between SBP and DBP evaluated as pulse BP.

Average BP was calculated by the formula:

Average BP = 0.42 × (SBP – DBP) + DBP

The volumes of left and right atria (LAV and RAV, respectively), end-systolic and end-diastolic diameters (LVESD and LVEDD, respectively) of the left ventricle (LV), diameters of LA and aorta (LAD and AD, respectively) were evaluated. The ejection fraction (EF) was calculated by the formula:

EF = (EDV – ESV) / EDV,

where ESV and EDV are the end-systolic and end-diastolic LV volumes, respectively.

The thickness of the posterior wall of the LV and the thickness of the interventricular septum in the systole (TPWs and TIVSs, respectively) and diastole (TPWd and TIVSd, respectively) were measured. The relative wall thickness of the LV (RWT) was calculated by the formula:

RWT = (TPWd + TIVSd) / LVEDD

The LV myocardial mass index (LVMI) was calculated as the ratio of the LV myocardial mass (LVM) to the surface area of the body (S):

LVMI = LVM / S

The statistical processing of the obtained data was carried out using the package of statistical software "SPSS 17" (IBM), Microsoft Office Exel-2003. The data are presented as mean values ± standard deviation. Significance was set at a p value of < 0.05 in all cases.

Table II. Comparative evaluation of hemodynamic parameters of obese hypertensive patients and obese hypertensive patients with type 2 diabetes depending on the genotypes G / G and G / R + R / R of the IRS-1 gene

Indicators	AH + obesity			AH + obesity + type 2 diabetes		
	G/G	G/R + R/R	p	G/G	G/R + R/R	p
	n = 110	n = 90		n = 16	n = 24	
Weight [kg]	97,15 ± 10,77	105,41 ± 9,08	0,000	103,25 ± 7,85	100,63±7,64	0,199
BMI [kg/m2]	33,36 ± 2,76	36,58 ± 1,49	0,000	34,49 ± 0,40	36,01 ± 1,05	0,003
Waist [cm]	106,70 ± 7,61	108,79 ± 7,30	0,051	107,56 ± 0,73	105,71 ±9,47	0,122
Hip [cm]	117,34 ± 8,84	114,14 ± 7,45	0,007	107,38 ± 6,62	110,58 ± 6,88	0,163
Waist-to-hip ratio	0,92 ± 0,11	0,96 ± 0,10	0,005	1,00 ± 0,11	0,96 ± 0,09	0,126
HOMA-IR	3,03 ± 1,15	3,87 ± 1,38	0,000	6,16 ± 0,97	9,04 ± 0,86	0,000
SBP [mm Hg]	172,74 ± 4,08	171,74 ± 4,75	0,102	166,38 ± 2,90	166,17 ± 2,79	0,772
DBP [mm Hg]	101,69 ± 3,16	101,17 ± 2,92	0,228	98,63 ± 1,86	99,33 ± 1,76	0,199
Heart rate [bpm]	71,65 ± 1,88	71,80 ± 1,95	0,571	72,56 ± 1,36	72,75 ± 1,45	0,825
Pulse BP [mm Hg]	71,05 ± 3,69	70,58 ± 4,32	0,110	67,75 ± 3,96	66,83 ± 3,61	0,334
Average BP [mm Hg]	131,53 ± 3,08	131,39 ± 3,14	0,511	127,08 ± 1,31	127,40 ± 1,38	0,709
CIMT [mm]	0,88 ± 0,08	0,95 ± 0,08	0,000	0,93 ± 0,09	0,98 ± 0,05	0,037
CIMT bifurcation [mm]	1,34 ± 0,16	1,38 ± 0,15	0,076	1,34 ± 0,13	1,37 ± 0,18	0,610
cPWV [m/s]	8,34 ± 1,01	8,85 ± 1,11	0,001	8,87 ± 0,94	9,03 ± 1,07	0,669
aPWV [m/s]	8,36 ± 0,97	8,63 ± 1,14	0,077	9,12 ± 1,23	8,94 ± 1,32	0,825
EDVD (%)	7,09 ± 1,24	6,69 ± 1,01	0,015	6,76 ± 0,60	6,51 ± 0,67	0,264
TIVSd [cm]	1,15 ± 0,12	1,20 ± 0,11	0,008	1,16 ± 0,06	1,20 ± 0,10	0,314
TIVSs [cm]	1,44 ± 0,16	1,50 ± 0,14	0,005	1,39 ± 0,09	1,48 ± 0,12	0,008
TPWd [cm]	1,17 ± 0,13	1,20 ± 0,15	0,176	1,16 ± 0,10	1,19 ± 0,15	0,508
TPWs [cm]	1,58 ± 0,32	1,64 ± 0,38	0,222	1,44 ± 0,18	1,57 ± 0,32	0,147
LVEDD[cm]	4,84 ± 0,33	4,95 ± 0,34	0,017	4,7 ± 0,16	4,96 ± 0,39	0,036
LVESD[cm]	3,17 ± 0,26	3,28 ± 0,27	0,006	3,09 ± 0,13	3,27 ± 0,34	0,126
EDV [mL]	110,34 ±18,31	116,54 ±19,54	0,022	103,20 ± 8,54	116,93 ±21,99	0,036
ESV [mL]	40,51 ± 8,53	43,81 ± 9,17	0,010	37,83 ± 3,85	43,99 ± 11,69	0,126
EF (%)	63,35 ± 3,64	62,55 ± 2,84	0,089	63,33 ± 2,34	62,76 ± 3,30	0,858
LVM [g]	254,43 ±64,97	276,17 ±68,38	0,023	240,34 ±29,25	274,81 ±67,58	0,090
LVMI [g/m^2]	122,22 ±30,37	128,79 ±32,23	0,140	113,68 ±13,71	130,27 ±31,53	0,038
RWT	0,48 ± 0,04	0,48 ± 0,05	0,716	0,49 ± 0,03	0,48 ± 0,04	0,517
LAD [mm]	38,44 ± 3,07	38,07 ± 3,40	0,419	38,01 ± 4,04	33,19 ± 1,44	0,270
AD [mm]	33,31 ± 1,83	32,92 ± 0,83	0,205	32,66 ± 0,81	17,18 ± 3,51	0,581
Mean pulmonary AP [mm Hg] by Kitabatake	16,12 ± 3,48	16,50 ± 2,87	0,400	17,30 ± 2,71	17,18 ± 3,51	0,923
RAV [mL]	40,13 ± 5,34	38,53 ± 3,86	0,018	37,44 ± 2,84	39,55 ± 5,02	0,362
LAV [mL]	52,51 ± 5,21	51,41 ± 4,57	0,121	50,56 ± 3,37	52,19 ± 3,60	0,544
e´[cm/s]	11,58 ± 2,34	11,38 ± 2,09	0,537	10,83 ± 2,68	10,96 ± 1,69	0,679
E [cm/s]	67,01 ± 12,30	66,95 ± 6,93	0,970	64,01 ± 7,33	68,49 ± 12,43	0,143
A [cm/s]	79,78 ± 11,84	77,32 ± 9,33	0,110	75,30 ± 8,95	72,42 ± 12,54	0,314
E/A	0,85 ± 0,18	0,87 ± 0,11	0,330	0,85 ± 0,08	0,97 ± 0,24	0,095
DT [s]	0,16 ± 0,11	0,15 ± 0,07	0,435	0,15 ± 0,04	0,15 ± 0,04	1,000
IVRT [s]	0,12 ± 0,02	0,12 ± 0,03	0,896	0,11 ± 0,02	0,10 ± 0,02	0,155
E/e´	5,91 ± 1,12	6,05 ± 1,13	0,374	6,26 ± 1,78	6,47 ± 1,78	0,517

BP - blood pressure; DBP - diastolic blood pressure; SBP - systolic blood pressure; A - maximum late (atrial) filling speed; AP - artery pressure; DT - time of deceleration early diastolic flow rate; E - filling rate in spectral mode; e - maximum early LV filling rate at tissue mode; E/A - ratio of maximal rates of early and late filling of LV at spectral mode; E/e - ratio of E and e; IVRT - time of isovolumic relaxation of LV; EDVD - endothelium-dependent vasodilatation; EF - ejection fraction; CA - carotid artery; IMT - intima-media thickness; LVM - left ventricular mass; LVMI - left ventricular mass index; PWV - pulse wave velocity (cPWV – carotid artery, aPWV - abdominal aorta); RAV - right atrial volume; LAV - left atrial volume; TIVSd - thickness of the interventricular septum (diastole); TIVSs - thickness of the interventricular septum (systole); TPWd - thickness of the posterior wall of the left ventricle in diastole; TPWs - the thickness of the posterior wall of the left ventricle in systole; LVEDD - end-diastolic diameters; LVESD - end-systolic diameters; EDV - end-diastolic volume; ESD - end-systolic volume; RWT - relative wall thickness; LAD - left atrial diameter; AD - aortic diameter.

Table III. Comparative evaluation of hemodynamic parameters of hypertensive patients with normal BMI and hypertensive overweight patients depending on the genotypes G / G and G / R + R / R of the IRS-1 gene

Indicators	AH + normal weight		p	AH + overweight		p
	G/G	G/R + R/R		G/G	G/R + R/R	
	n = 32	n = 18		n = 22	n = 28	
Weight [kg]	68,06 ± 5,20	70,39 ± 6,58	0,275	77,77 ± 7,31	85,39 ± 8,25	0,001
BMI [kg/m2]	23,76 ± 0,75	23,83 ± 0,78	0,824	27,02 ± 1,53	28,46 ± 1,59	0,002
Waist [cm]	79,22 ± 6,38	76,67 ± 4,79	0,192	80,18 ± 6,49	81,57 ± 6,81	0,564
Hip [cm]	95,44 ± 6,08	98,33 ± 5,51	0,075	98,00 ± 6,75	97,00 ± 5,20	0,755
Waist-to-hip ratio	0,83 ± 0,08	0,81 ± 0,06	0,061	0,82 ± 0,08	0,84 ± 0,06	0,385
HOMA-IR	1,98 ± 0,36	2,81 ± 0,22	0,000	2,09 ± 0,32	2,82 ± 0,42	0,000
SBP [mm Hg]	168,56 ± 5,24	170,56 ± 3,13	0,102	171,00 ± 4,78	172,61 ± 3,95	0,201
DBP [mm Hg]	101,41 ± 2,94	101,41 ± 2,17	0,132	100,77 ± 1,97	101,86 ± 2,89	0,287
Heart rate [bpm]	71,59 ± 2,14	71,59 ± 1,72	0,176	72,23 ± 1,85	71,64 ± 2,16	0,423
Pulse BP [mm Hg]	67,16 ± 4,29	69,16 ± 4,58	0,069	69,23 ± 5,00	70,75 ± 2,96	0,209
Average BP [mm Hg]	128,45 ± 3,47	127,65 ± 1,32	0,107	130,01 ± 2,40	131,57 ± 3,04	0,204
CIMT [mm]	0,81 ± 0,10	0,81 ± 0,12	0,002	0,82 ± 0,09	0,91 ± 0,08	0,000
CIMT bifurcation [mm]	1,12 ± 0,19	1,12 ± 0,23	0,002	1,23 ± 0,18	1,26 ± 0,13	0,605
cPWV [m/s]	7,40 ± 0,67	7,40 ± 1,48	0,013	7,75 ± 0,90	7,86 ± 0,72	0,682
aPWV [m/s]	8,04 ± 0,83	8,04 ± 1,23	0,176	8,39 ± 0,75	8,17 ± 0,61	0,319
EDVD (%)	9,03 ± 1,08	9,03 ± 1,70	0,004	8,46 ± 1,12	8,46 ± 0,92	0,815
TIVSd [cm]	1,10 ± 0,11	1,11 ± 0,10	0,856	1,10 ± 0,09	1,15 ± 0,07	0,033
TIVSs [cm]	1,50 ± 0,16	1,48 ± 0,16	0,754	1,47 ± 0,12	1,46 ± 0,12	0,907
TPWd [cm]	1,11 ± 0,09	1,15 ± 0,08	0,102	1,09 ± 0,11	1,15 ± 0,11	0,077
TPWs [cm]	1,65 ± 0,30	1,59 ± 0,23	0,592	1,51 ± 0,28	1,53 ± 0,22	0,653
LVEDD[cm]	4,78 ± 0,22	4,83 ± 0,24	0,379	4,78 ± 0,26	4,97 ± 0,26	0,007
LVESD[cm]	3,09 ± 0,16	3,14 ± 0,21	0,621	3,13 ± 0,19	3,22 ± 0,20	0,109
EDV [mL]	106,54 ±12,21	109,32 ±13,32	0,379	107,10 ±14,17	116,94 ±14,31	0,007
ESV [mL]	37,75 ± 4,82	39,31 ± 6,78	0,621	39,10 ± 5,75	41,83 ± 6,17	0,109
EF (%)	64,57 ± 2,19	64,16 ± 2,35	0,880	63,45 ± 3,20	64,26 ± 2,61	0,482
LVM [g]	227,64 ±33,55	239,65 ±29,96	0,157	227,93 ±35,61	259,80 ±40,32	0,007
LVMI [g/m^2]	128,11 ±19,57	131,42 ±15,89	0,518	120,69 ±16,83	130,21 ±17,85	0,068
RWT	0,47 ± 0,03	0,47 ± 0,04	0,671	0,46 ± 0,03	0,46 ± 0,03	0,274
LAD [mm]	34,02 ± 2,55	32,28 ± 7,62	0,092	37,99 ± 3,29	37,10 ± 1,95	0,637
AD [mm]	33,10 ± 0,92	32,91 ± 0,79	0,223	32,75 ± 1,96	13,97 ± 1,40	0,056
Mean pulmonary AP [mm Hg] by Kitabatake	13,18 ± 2,41	13,77 ± 3,42	0,701	14,50 ± 2,45	13,97 ± 1,40	0,274
RAV [mL]	39,16 ± 3,21	38,61 ± 2,82	0,223	37,36 ± 5,34	40,09 ± 5,07	0,097
LAV [mL]	46,29 ± 4,18	44,82 ± 3,94	0,115	46,06 ± 5,06	48,05 ± 2,88	0,237
e´[cm/s]	12,16 ± 2,34	12,40 ± 2,74	0,770	12,36 ± 2,60	12,88 ± 3,15	0,674
E [cm/s]	66,36 ± 8,10	66,37 ± 11,13	0,679	70,67 ± 11,97	65,78 ± 11,20	0,305
A [cm/s]	76,51 ± 11,73	83,11 ± 8,01	0,054	71,27 ± 9,10	80,62 ± 12,03	0,004
E/A	0,89 ± 0,18	0,80 ± 0,12	0,056	1,00 ± 0,16	0,82 ± 0,13	0,001
DT [s]	0,26 ± 0,36	0,19 ± 0,18	0,524	0,15 ± 0,03	0,14 ± 0,03	0,324
IVRT [s]	0,11 ± 0,02	0,11 ± 0,02	0,701	0,11 ± 0,01	0,10 ± 0,02	0,229
E/e´	5,64 ± 1,18	5,58 ± 1,44	0,808	5,72 ± 1,38	5,75 ± 1,76	0,422

BP - blood pressure; DBP - diastolic blood pressure; SBP - systolic blood pressure; A - maximum late (atrial) filling speed; AP - artery pressure; DT - time of deceleration early diastolic flow rate; E - filling rate in spectral mode; e - maximum early LV filling rate at tissue mode; E/A - ratio of maximal rates of early and late filling of LV at spectral mode; E/e - ratio of E and e; IVRT - time of isovolumic relaxation of LV; EDVD - endothelium-dependent vasodilatation; EF - ejection fraction; CA - carotid artery; IMT - intima-media thickness; LVM - left ventricular mass; LVMI - left ventricular mass index; PWV - pulse wave velocity (cPWV – carotid artery, aPWV - abdominal aorta); RAV - right atrial volume; LAV - left atrial volume; TIVSd - thickness of the interventricular septum (diastole); TIVSs - thickness of the interventricular septum (systole); TPWd - thickness of the posterior wall of the left ventricle in diastole; TPWs - the thickness of the posterior wall of the left ventricle in systole; LVEDD - end-diastolic diameters; LVESD - end-systolic diameters; EDV - end-diastolic volume; ESD - end-systolic volume; RWT - relative wall thickness; LAD - left atrial diameter; AD - aortic diameter.

The study protocol was approved by the Ethics Committee. All participants were informed about the aim of the study and signed a written consent form.

RESULTS

According to the objectives of the study, 340 patients aged 45-55 were surveyed. Group 1 included 200 patients with AH with class I - II obesity, group 2 - 50 patients with AH and normal body weight, group 3 - 50 patients with AH and overweight, group 4 - 40 patients with AH, obesity and type 2 diabetes. The test group consisted of 30 healthy individuals without AH and obesity, according to the clinical-instrumental study data. Groups were formed by age and gender.

The prevalence of genotypes G/R and R/R in the polymorphism G972R of the IRS-1 gene in obese hypertensive patients is 45 %, that is 2.7 times higher than in the healthy group, 1.3 times higher than in the group with normal body weight and, accordingly, less 1.2 times and 1.3 times than in the group with excess body weight and triple comorbidity (AH, obesity and type 2 diabetes). The prevalence of G/G genotype in the G972R polymorphism of the IRS-1 gene in patients with AH with obesity is, respectively, 1.2 times and 1.5 times less than in patients with normal body weight and a group of healthy people, but 1. 4 times more than with triple comorbidity. (Tab. I).

Hypertensive patients with obesity (Group 1), carriers of G/R and R/R genotypes displayed more severe vascular remodeling (higher CIMT (p = 0,000), cPWV (p = 0,001) and lower EDVD (p = 0,015)) and cardiac remodeling (larger sizes: TIVSd (p = 0,008), TIVSs (p = 0,005), LVEDD (p = 0,017), LVESD (p=0,006), EDV(p = 0,022), ESV (p = 0,010) and LVM (p = 0,023) compared with G/G genotype carriers. (Tab. II).

The presence of G/R + R/R genotypes in hypertensive patients with normal body weight (Group 2) was associated with an increase in CIMT (p = 0.002), cPWV (p = 0.002) and lower EDVD (p = 0.004) compared with G/G genotype carriers. (Tab. III).

Overweight (Group 3) carriers of the G/R + R/R genotypes were characterized by enlargement of LVM (p = 0.007) and its sizes (LVEDD, EDV (p = 0.007 for both indicators)), a higher CIMT indicator (p = 0.000), but this effect was less than in the comorbidity of hypertension and obesity. (Tab. III).

In hypertensive patients with triple comorbidity, the presence of G/R + R/R genotypes was associated with an increase in left ventricular sizes, LVMI (p = 0.038) and CIMT (p = 0.037). (Tab. II).

DISCUSSION

Arterial hypertension (AH) is referred to as "regulatory disease" in which the activity and interaction of neurohumoral factors of blood pressure are disrupted, leading to structural changes in the heart and blood vessels. A feature of hypertensive heart in patients with metabolic syndrome (MS) is left ventricular hypertrophy (LVH), inadequate blood pressure, as metabolic disorders themselves lead to structural and functional changes in the myocardium, myocardial microcirculation disorders and can provoke relaxation and myocardial infarction. This, in turn, contributes to the formation of left ventricular (LV) diastolic dysfunction and diastolic heart failure (HF) [20, 21].

Detection of marker gene polymorphisms associated with both CVD risk and overweight is due to the need to further study the contribution of the hereditary component to the pathogenesis of cardiovascular remodeling and the reasonable need to develop new methods for early diagnosis and treatment of non-resistant and resistant hypertension [22].

According to the results of the presented part of the scientific work in all studied groups, regardless of body weight and metabolic comorbidity, the IRS-1 polymorphism is more associated with the progression of the vascular remodeling than the cardiac one.

This proves the need for genetic screening of IRS-1 in patients with hypertension to detect G/R + R/R genotypes in order to strengthen control over the state of neurohumoral factors associated with the progression of cardiovascular remodeling in these groups of patients.

CONCLUSIONS

The relationships of IRS-1 polymorphism with indicators of cardiovascular remodeling in hypertensive patients depending on body weight and the presence of various metabolic comorbidity have been established.

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ORIGINAL ARTICLE

SURGICAL TECHNIQUE IN LEIOMYOSARCOMA OF THE INFERIOR VENA CAVA DEPENDING ON ITS LOCATION

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ABSTRACT

The aim: To improve the outcomes of IVC leiomyosarcoma, propose own classification of IVC segments, which correlates with surgical access, methodology, sequence and amount of surgery.

Materials and methods: In the period from 1991 to 2021 in the Transcarpathian Regional Clinical Hospital of A. Novak and in the Transcarpathian Antitumor Center 8 patients with IVC leiomyosarcoma were operated. The prevalence of leiomyosarcoma in IVC was determined according to the division of IVC into 7 segments. Defeat of one segment of IVC was in 50% of cases, two - in 37.5%, three - in 12.5%. In 5 (62.5%) cases circular resection and alloprosthesis of IVC were performed; in 2 (25%) - circular resection, alloprosthesis of IVC and implantation of the right and left renal veins in the prosthesis; in 1 (12.5%) - circular resection, alloprosthesis of IVC and implantation of the left renal vein in the prosthesis. All surgeries were performed with laparotomy access (87.5% by Chevron type).

Results: The average operation time was 215 (160-320) minutes, the average blood loss was 305 (250-500) ml. Postoperative complications were recorded in 2 (25%) cases. There were no cases of pulmonary embolism, venous thrombosis, prosthesis thrombosis, perioperative mortality. In 7 (87.5%) cases, surgery was radical. The overall 1-year, 2-year and 3-year survival rates were 87.5%, 71.4% and 57.7%.

Conclusions: The division of IVC into 7 segments characterizes the detailed definition of the cranial limit of leiomyosarcoma and segmental involvement of IVC in the tumor process, which allows to choose the right surgical tactics, perform radical resection of IVC and maintain laminar blood flow to IVC and its tributaries.

KEY WORDS: leiomyosarcoma, inferior vena cava, resection, prosthesis

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INTRODUCTION

The incidence of leiomyosarcoma in the structure of all malignant soft tissue sarcomas is about 10% [1]. However, vascular origin of leiomyosarcoma occurs in only 0.5% of cases and at the same time, the share of inferior vena cava (IVC) accounts for 60-90% of these tumors [2].

Leiomyosarcoma of IVC is one of the rare types of malignant soft tissue sarcoma of mesenchymal origin that develops from smooth muscle in the vein wall. Evidence of this is the nature of publications, which are based mainly on literature reviews and include own data presented on a case-by-case basis within up to 10 observations. Today, only two studies have been presented in the available literature, based on the results of the treatment of a large number of patients. Thus, in 1996 the results of the world experience of surgical treatment of 218 patients with leiomyosarcoma of IVC were published, and in 2015 the presented analysis included 377 cases [3,4]. The results of these studies have shown that radical surgical resection with a negative surgical margin is the most important factor in cancer-specific survival.

The radicalism of surgical treatment can be achieved through adequate exposure of the tumor and related organs and structures, which can be achieved through properly chosen surgical access. The most common access is median laparotomy, which is considered by most of surgeons and provides good visualization of any segment of the IVC [5]. Some authors prefer right-sided thoracoabdominal access [6], right-sided subcostal access [7] or double-side subcostal access [8]. When the suprahepatic segment of the IVC is affected or the tumor thrombus spreads towards the right atrium, it is necessary to use combined approach: median laparotomy and sternotomy [9].

The question of the choice of the amount of resection and reconstruction of the IVC and its visceral branches of the first order remains controversial [5,10,11].

The numerous of studies use a three-level classification of IVC segments according to C.J. Staley et al.[12]. The inconsistent approach to the division into IVC segments makes it difficult to interpret the data obtained to determine the spread of the tumor process.

Active introduction of IVC leiomyosarcoma surgery into clinical practice requires a revision of the approach to the classification of IVC segments, as this affects the personalized algorithm of surgical treatment of patients.

THE AIM

To improve the outcomes of IVC leiomyosarcoma, propose own classification of IVC segments, which correlates with surgical access, methodology, sequence and amount of surgery.

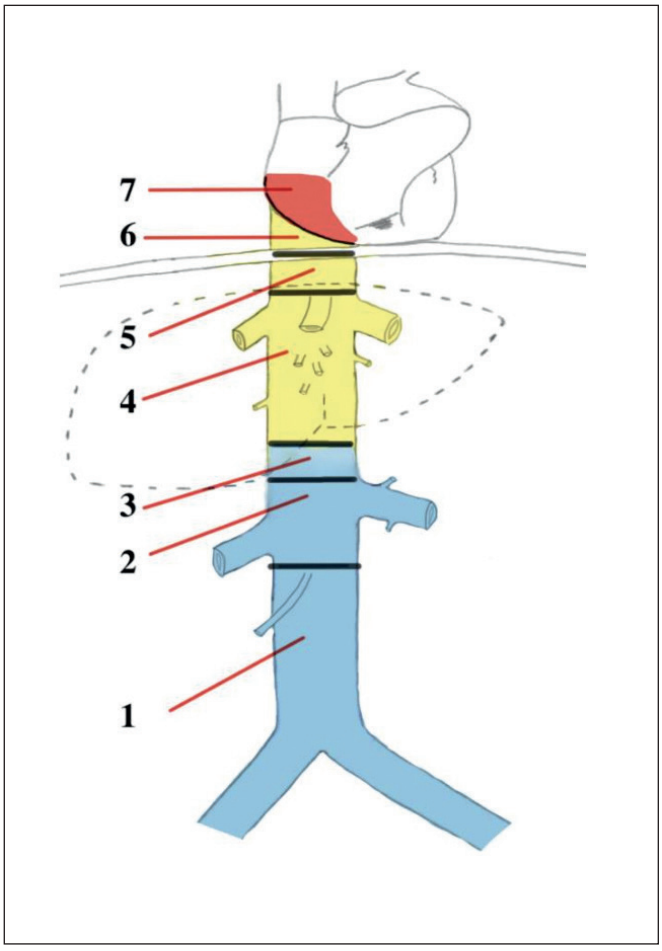

Fig. 1. Scheme of IVC segments: 1 – infrarenal; 2 – interrenal; 3 – suprarenal; 4 – retrohepatic; 5 – infradiaphragmatic; 6 – supradiaphragmatic; 7 – intracardiac

MATERIALS AND METHODS

In the period from 1991 to 2021 in the surgical department of the Transcarpathian Regional Clinical Hospital of A. Novak and the Transcarpathian Antitumor Center performed surgery on 8 patients with leiomyosarcoma IVC: 7 women and 1 man, aged 45 to 74 years (mean – 57).

Color Doppler ultrasound and intravenous contrast computed tomography were performed during the examination. X-ray contrast phlebography was performed in 2 patients.

Based on the analysis of literature data and own experience of surgical treatment of tumor and hemorrhagic thrombosis of IVC, taking into account cranial border of venous obstruction, we used our own classification of IVC segments, according to which we consider 7 segments of IVC (Figure 1): 1) infrarenal – from the confluence of common iliac veins to the orifice of lower limit of the right renal vein; 2) interrenal – from the lower limit of the orifice of the right renal vein to the upper limit of the orifice of the left renal vein; 3) suprarenal – from the upper limit of the orifice of the left renal vein to the short hepatic veins; 4) retrohepatic – from the short hepatic veins to the upper limit of the orifice of the main hepatic veins; 5) infradiaphragmatic – from the upper limit of the orifice of the main hepatic veins to the lower limit of the diaphragm; 6) supradiaphragmatic– from the upper limit of the diaphragm to the right atrium; 7) intracardiac – penetration into the right atrium.

Intraluminal localization of the tumor was observed in 3 (37.5%), extraluminal – in 1 (12.5%), combined – in 4 (50%) patients. In 4 (50%) patients, the tumor was localized in one segment (in the infrarenal segment of IVC), while in 4 patients the tumor spread to several segments of IVC: in 1 (12.5%) – in infrarenal and interrenal, in 1 (12.5%) – in infrarenal, interrenal and suprarenal, in 1 (12.5%) – in suprarenal and retrohepatic segments of IVC, in 1 (12.5%) – in the infrarenal and interrenal segments of IVC with the right kidney invasion. The size of intraluminal tumors varied from 5 to 7 cm, extraluminal – from 12 to 17 cm in the largest dimension.

Surgical access: in one (12.5%) case a median laparotomy was performed, in 7 (87.5%) – a double-side subcostal laparotomy of the chevron type. To penetrate the right retroperitoneal space, a Cattel-Braash technique was performed, which involved mobilization of the cecum, ascending and hepatic curvature of the colon along the right side channel of the abdominal cavity along the Told's line to the level of common iliac vessels. The retroperitoneal tissue was stratified in a blunt and sharp pathway and the hepatic curvature of the colon and the ascending colon were removed downwards and medially. Small vessels were coagulated and large vessels were ligated. The hepato-colon and hepato-renal ligaments were dissected and Kocher's duodenum was extensively mobilized with careful gentle isolation of IVC and aorta, providing capacious access to the right kidney, duodenum, IVC, renal veins and aorta.

IVC were mobilized by dissecting the peritoneum on both sides of it. Performed mobilization of renal veins. Lumbar veins were ligated and dissected. IVC were first isolated in the interrenal and infrarenal segments, after which they were transferred to the suprarenal segment. During the mobilization of IVC, we imposed turnstiles and all 4 areas of interest: infrarenal and suprarenal segments of IVC, right and left renal veins.

In the case of intraluminal localization of the tumor, IVC intersected at a distance of at least 5 mm from the caudal limit of invasion of the tumor into the vein wall, its distal end was raised, which contributed to adequate revision of the posterior surface of the IVC where branches of lumbar veins can left which were not detected in front access. If the tumor was localized only in the infrarenal segment, then above the tumor by 5 mm, but below the renal veins, IVC intersected again and removed the drug in one block. When the tumor spread to the suprarenal segment, the upper limit of the IVC section passed above the renal veins, and the renal veins themselves were cut off from the IVC at a distance of 5 mm from their orifice. After that, end-to-end alloprosthesis and end-to-side one or both renal veins implantation was performed in the prosthesis

In the case of extraluminal or combined tumor growth, the resection amount included the involved of IVC segment and

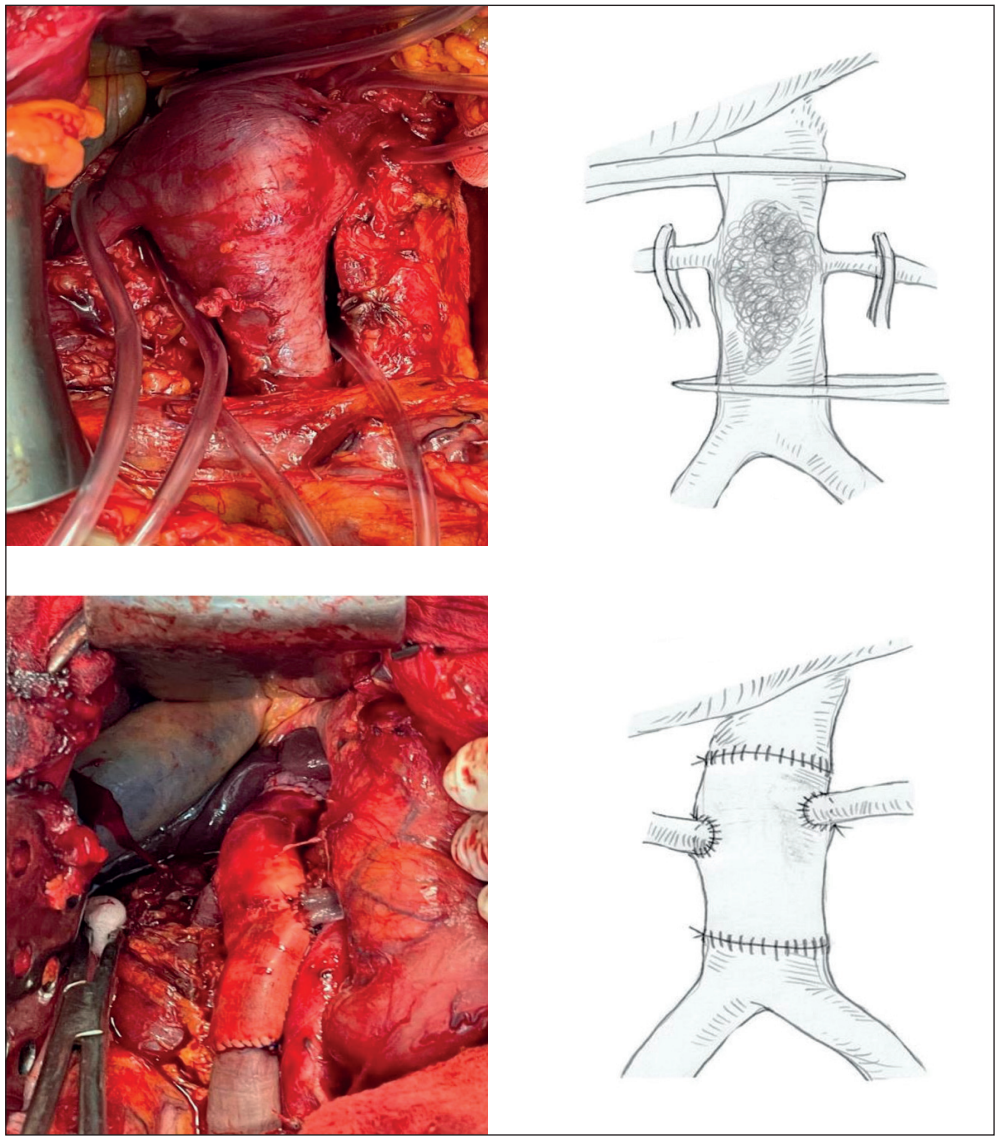

Fig. 2. Intraluminal tumor of infrarenal, interrenal and suprarenal segments of IVC, segmental resection and prosthesis of IVC with Gore-tex prosthesis with implantation of right and left renal veins: a-b) intraluminal tumor of infrarenal, interrenal and suprarenal segments of IVC (type of surgical wound and scheme); c-d) segmental resection and prosthesis of IVC with Gore-tex prosthesis with implantation of right and left renal veins (type of surgical wound and scheme).

adjacent organs and tissues. In one (12.5%) case, when the tumor spread to the right kidney, one unit performed segmental resection of the IVC, right nephrectomy, prosthesis IVC and implantation of the left renal vein in the prosthesis (Figure 3 a b c).

In the case of involvement of a retrohepatic segment of IVC, the liver was mobilized by dissecting the entire ligaments. Mobilization of the right lobe of the liver continued toward the IVC, dissecting the hepato-renal and hepato-colonic ligaments and any other additional fixation apparatus of the right lobe of the liver. Additional short hepatic veins, which could be on the posterior surface of the liver in the area of the right and caudal lobes intersected between the imposed ligatures. Gentle movements were performed to rotate the right lobe of the liver using the piggyback technique to the left subcostal area. The piggyback technique of liver mobilization and Pringle maneuver were used in 1 (12.5%) case. After squeezing the hepato-duodenal ligament, we paused for up to 5 minutes, which helped reduce the volume of the liver and made it easier to rotate the liver.

Alloprosthesis of IVC were performed with polytetrafluoroethylene (PTFE) (n = 6) or Gore-tex (n = 2) prosthesis with a diameter of 18-22 mm. In 5 (62.5%) cases circular resection and alloprosthesis of IVC were performed; in 2 (25%) – circular resection, alloprosthesis of IVC and implantation of the right and left renal veins in the prosthesis; in 1 (12.5%) – circular resection, alloprosthesis of IVC and implantation of the left renal vein in the prosthesis.

IVC prosthetics began with the imposition of the cranial part of the anastomosis, followed by implantation of one or both renal veins. At each stage of the formed anastomosis used early restoration of venous return from the organs by local application of vascular clamps. The caudal part of the anastomosis was formed under conditions of complete recovery of venous return from one or both kidneys. Means of thermal ischemia of the kidneys were not used. Initial systemic heparinization and periodic local heparinization were used all the time during prosthesis suturing. In the early postoperative period up to 14 days used systemic administration of low molecular weight heparin in a prophylactic dose and then patients were prescribed an oral form of low molecular weight heparin in a prophylactic dose for 6 months.

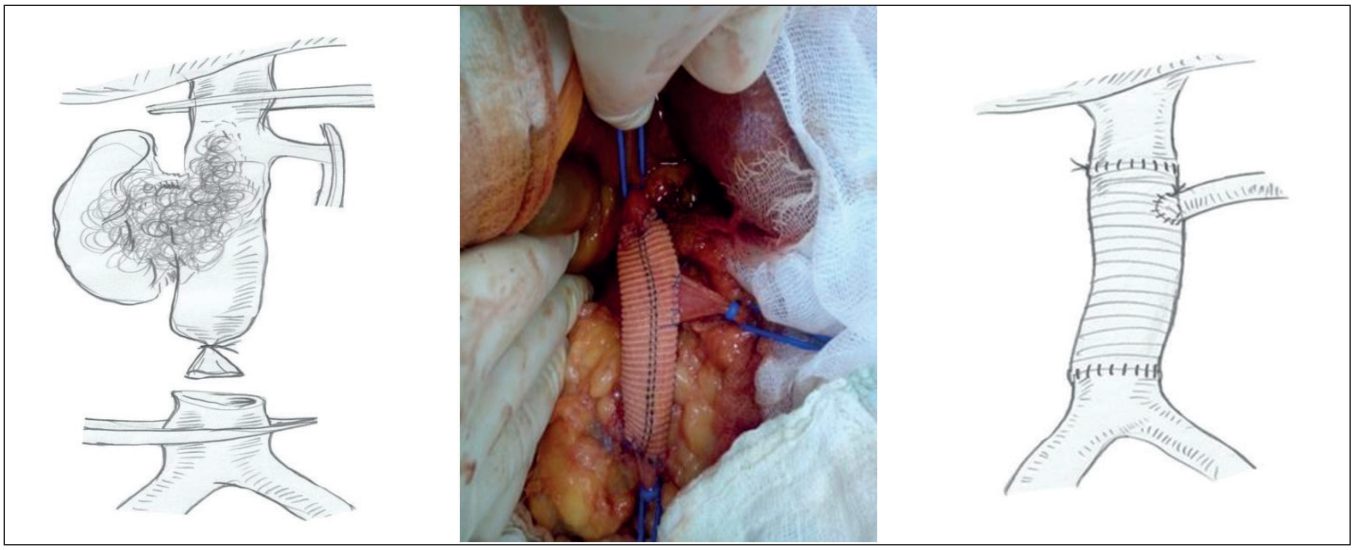

Fig. 3. Combined nature of tumor growth of infrarenal and interrenal segments of IVC with spread in the right kidney, segmental resection and prosthesis of IVC with PTFE prosthesis with left renal vein implantation: a) tumor of combined growth of infrarenal and interrenal segments of IVC with spread in the right kidney (scheme); b-c) segmental resection and prosthesis of IVC with PTFE prosthesis with implantation of the left renal vein (type of surgical wound and scheme).

Postoperative complications were assessed according to the Clavien-Dindo classification. Throughout the follow-up period, signs of venous thrombosis, pulmonary embolism, myocardial infarction and kidney damage were monitored at standard postoperative visits and the overall survival of patients was studied.

Given that the study group of patients is less than 10 people, we used simple methods of statistical analysis using which we calculated the average values of indicators.

RESULTS

The average surgery time was 215 (160-320) minutes, the average blood loss was 305 (250-500) ml.

Postoperative complications were recorded in 2 (25%) cases (I-II severity according to the Clavien-Dindo classification). There were no cases of pulmonary embolism, venous thrombosis, prosthesis thrombosis, perioperative mortality.

In 7 (87.5%) cases, surgery was radical. One (12.5%) patient with large volume of the IVC invasion to the retrohepatic segment and the right lumbar muscle on histological examination revealed a positive surgical margin of the lumbar muscle. After 7 months, this patient developed a local recurrence in the right lumbar muscle and showed signs of disease progression in the form of multiple metastases in the liver and both lungs. The patient died 3 months after disease progression.

The overall 1-year survival was 87.5%. One patient is under observation for one year, the observation continues. The overall 2-year and 3-year survival was 71.4% and 57.7% respectively (among 7 patients).

DISCUSSION

During the characterization of IVC different variants of division into segments are used, which leads to the diagnosis of a more general location of the IVC, covering its long sections. The greatest use in clinical practice was the classification of S.J. Staley et al. (1967), according to which it is accepted to divide IVC on the level of renal and hepatic veins into three segments: lower (from the level of confluence of common iliac veins to the level of renal veins), middle – (including the level of renal and hepatic veins) and upper – (above hepatic veins to the atrium) [12]. The segments of IVC where the cranial border of the tumor can be localized are left out, because they are automatically absorbed by this classification and are part of either the middle or upper segments. A clear definition of the cranial border of the affected segment of IVC is directly reflected in the understanding of the level of involvement of IVC in the process and tactics of surgical treatment.

Coverage of the location of the leiomyosarcomaaffected segment of the IVC remains ambiguous. Thus, some authors point to the predominant invasion of the middle segment (from renal to hepatic veins) of IVC, which consists of two separate segments – suprarenal and retrohepatic and therefore, it is not known for sure what is the cranial limit of IVC invasions [9,13], while others indicate a predominant invasion of the infrarenal segment [10,14].

In addition, some authors detail the IVC invasions and provide data on the invasions of one, two or three segments [9]. We also apply a detailed characterization of the segmental spread of leiomyosarcoma by IVC. Thus, in our study, lesions of one segment of the IVC were in 50% of cases, two – in 37.5%, three – in 12.5%.

Based on our own classification approach to the division of IVC into segments, we propose the following algorithm for surgical treatment of IVC leiomyosarcoma: 1) in infrarenal, interrenal and suprarenal spread is performed laparotomy, radical resection of IVC with implantation in the prosthesis of renal veins, if they were involved in the process; 2) in retrohepatic, infradiaphragmatic and supradiaphragmatic spread

is performed laparotomy, diaphragmotomy (if necessary), piggyback liver mobilization technique and Pringle maneuver, radical resection of IVC with implantation in a prosthesis of renal or hepatic veins, if they were involved; 3) at intracardiac distribution the combined access – a thoracolaparotomy in the conditions of artificial blood circulation is carried out.

The most complex segments of IVC at the stage of mobilization are retrohepatic and intracardiac, because access to them is provided by mobilization of the liver and its rotation and diaphragmotomy or thoracotomy. The rest of the IVC segments are available to a wide range of surgeons. If, in most cases, intracardiac and supradiaphragmatic thrombi of IVC can be transferred by finger displacement of the apex of the thrombus into the infradiaphragmatic and sometimes retrohepatic segment of IVC, and removed, the localization of leiomyosarcoma in these segments of IVC involves radical incision.

CONCLUSIONS

The division of IVC into 7 segments characterizes the detailed definition of the cranial limit of leiomyosarcoma spread and segmental involvement IVC in the tumor process, which allows you to choose the optimal surgical tactics, perform a radical resection of the IVC and maintain laminar blood flow through the IVC and its tributaries of the first order, which provides satisfactory immediate and long-term results.

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ORIGINAL ARTICLE

EFFECTIVENESS OF HEPATOPROTECTOR IN THE COMPLEX CORRECTION OF CLINICAL MANIFESTATIONS OF CHRONIC PANCREATITIS AND TYPE 2 DIABETES MELLITUS COMORBIDITY

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ABSTRACT

The aim: To investigate the effectiveness of complex protocol treatment with the additional inclusion of a course of the sublingual form of hepatoprotector on the clinical manifestations of patients with chronic pancreatitis in combination with type 2 diabetes mellitus.

Materials and methods: We studied 57 outpatients with chronic pancreatitis in the phase of stable or unstable remission in combination with diabetes mellitus in the phase of stable or unstable remission. Two groups were formed according to randomization principles to study the effectiveness of the proposed correction programs: 1st group (30 patients) took protocol treatment for one month, 2nd group (27 patients) – received protocol treatment with a course of hepatoprotector.

Results: It was found the results of the impact of two treatment programs on some clinical symptoms and syndromes in patients with chronic pancreatitis. Positive dynamics of clinical symptoms/syndromes were found in both groups of patients, but the therapeutic effect in the 2nd group was more significant. Analysis of the dynamics of the Quality of Life parameters on the scales of a specialized gastroenterological questionnaire under the influence of two treatment programs found statistically significant ($p<0.05$) changes in the group with the inclusion of hepatoprotector for treatment for all parameters in contrast to the group of protocol treatment, where statistically significant changes on three scales (abdominal pain, gastric reflux, and dyspepsia).

Conclusions: 1) itisprovedthattheproposedinclusionintheprotocoltreatmentof a combinationofchronic pancreatitisandtype 2 diabetes mellituscourseofsublingualademethionineledtoanincreaseinitseffectivenessinthecorrectionofabdominalpain – by 8.2%, dyspepsia – by 17.8%, constipation – by 7.4% , diarrhea – by 12.9%, astheno-neurotic – by 21.5%, allergic – by 15.9%, autonomic – by 20.1% ($p<0.05$); 2) foundhigherefficacyoftreatmentwiththeinclusionofademethionineinrelationtothatinthegroupof PL onthedynamicsoftheparametersofthescalesofthe GSRS questionnaireby a totalof 13.7%, $p<0.01$: abdominalpaindecreasedby 22.6% vs. 16.7%, gastricreflux – by 34.7% against 16.9% ($p<0.05$), diarrhea – by 23.9% against 8.2% ($p<0.001$), constipation – by 20.6% against 5.9% (0.01), dyspepsia – by 32.4% against 17.9% ($p<0.01$), respectively; 3) it proved the feasibility of using sublingual ademethionine in the complex rehabilitation treatment of patients with comorbidity of chronic pancreatitis and diabetes mellitus in order to correct clinical symptoms.

KEY WORDS: chronic pancreatitis, type 2 diabetes mellitus, hepatoprotector

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INTRODUCTION

Most clinicians and researchers believe that the current epidemiology of chronic pancreatitis (CP) is much worse than other diseases. In Ukraine, the incidence of pancreatitis has more than doubled in the last three decades, and the epidemiological rates of CP in our country are 3-4 times worse than in Europe, in Ukraine, there are 880 thousand patients with CP [1, 2]. In 15-20% of cases, patients with CP die from complications arising from exacerbations of pancreatitis, others – due to secondary digestive disorders, infectious complications, and incretory insufficiency of the pancreas in the form of type 2 diabetes mellitus (DM2), which makes CP social and a medically significant problem of medicine [3, 4].

Despite the sufficient number of studies by scientists, the issues of diagnosis, treatment, and rehabilitation of patients with CP with concomitantDM2, which is a global problem of mankind, remain unclear [5]. There is an increase in the number of patients with DM2, which exceeds the mark of two million people. In the world, diabetes is becoming a pandemic [6]. According to WHO experts, the world is projected to increase the number of patients with diabetes to 300 million people. The relationship between exocrine and endocrine function of the pancreas in patients with CP combined with diabetes mellitus has not been fully studied [7].

We found more significant clinical and pathogenetic pathological disorders of inflammatory, intoxication and trophological nature in the comorbid course of CP and diabetes mellitus in comparison with isolated CP motivated us to strengthen the standard treatment of patients with such nosologies by additional therapy, regulated by Orders of the Ministry of Health of Ukraine from 10.09.2014 "On approval and implementation of medical and technological documents on standardization of medical care for chronic pancreatitis" and № 1118 of 21.12.2012 "On approval and implementation of medical and technological documents on standardization of medical care for type 2 diabetes"[8-10].

Table I. Comparative analysis of the dynamics of clinical symptoms in the study groups of patients with CP with diabetes mellitus under the influence of PT and PT with the inclusion of ademetionine

Clinicalsymptom/syndrome	Comparisongroup (numberofpatients (abs./%))			
	1st group(PT) (n=30)		2nd group(PT+AM) (n=27)	
	beforetreatment	aftertreatment	beforetreatment	aftertreatment
Abdominalpainsyndromeanditseq uivalents	30 (100.0)	8 (26.7)*	27 (100.0)	6 (18.5)*
Dyspepticsyndrome	28 (93.3)	10 (33.3)	25 (92.6)	4 (14.8)
Diarrhea	12 (40.0)	7 (23.3)	12 (44.4)	4 (14.8)
Constipation	15 (50.0)	5 (16.7)	14 (51.9)	3 (11.1)
Astheno-neuroticsyndrome	25 (83.3)	7 (23.3)	26 (96.3)	4 (14.8)
Anemicsyndrome	15 (50.0)	5 (16.7)	14 (51.9)	2 (7.4)
Hypovitaminosis	27 (90.0)	10 (33.3)	25 (92.6)	5 (18.5)
Changesinappetite	16 (53.3)	9 (30.0)	14 (51.9)	5 (18.5)
Allergic syndrome	10 (33.3)	7 (23.3)	10 (37.0)	3 (11.1)
Polydipsia	16 (53.3)	5 (16.7)	14 (51.9)	1 (3.7)
Vegetativesigns	25 (83.3)	11 (36.7)	22 (81.5)	4 (14.8)

Note: * – clinicalmanifestationinpatientswith CP withdiabetesaftertreatmentwasconsideredtobepresentintheabsenceofsignificantpositivedynamics

Table II. Comparative analysis of the dynamics of the scales of the questionnaire quality of life GSRS patients with CP with diabetes mellitus under the influence of PT and PT with the inclusion of ademetionine

GSRS questionnaire scale. score	Comparison group				p
	1st group (PT) (n=30)		2nd group (PT+AM) (n=27)		
	before treatment	after treatment	before treatment	after treatment	
AP (abdominal pain)	10.29±0.21	8.82±0.19 $p_2<0.01$	10.50±0.29 $p_1>0.05$	7.90±0.14 $p_2<0.001$	$p_3<0.01$
RS (gastric reflux)	11.51±0.31	9.85±0.27 $p_2<0.01$	11.88±0.31 $p_1>0.05$	8.82±0.20 $p_2<0.001$	$p_3<0.05$
DS (diarrhea)	10.84±0.70	10.02±0.60 $p_2>0.05$	10.70±0.69 $p_1>0.05$	8.63±0.32 $p_2<0.001$	$p_3<0.001$
CS (constipation)	8.63±0.61	8.15±0.49 $p_2>0.05$	8.67±0.51 $p_1>0.05$	7.19±0.25 $p_2<0.001$	$p_3<0.01$
IS (indigestion)	14.38±0.43	12.20±0.39 $p_2<0.01$	14.39±0.42 $p_1>0.05$	10.87±0.29 $p_2<0.001$	$p_3<0.01$

Notes:
1) p1 – a significant difference in data differences in groups of patients before treatment;
2) p2 – a significant difference in the differences between these patients in their group before and after treatment;
3) p3 – a significant difference in data differences in groups of patients after treatment.

THE AIM

The aim of the study is to investigate the effectiveness of complex protocol treatment with the additional inclusion of a course of the sublingual form of ademetionine on the clinical manifestations of patients with chronic pancreatitis in combination with type 2 diabetes mellitus.

MATERIALS AND METHODS

We studied 57 outpatients with CP in the phase of stable or unstable remission in combination with diabetes mellitus in the phase of stable or unstable remission. Two groups were formed according to randomization principles to study the effectiveness of the proposed correction programs: 1 group (30 patients with CP and DM2) took protocol treatment (PT) for one month, which included normalization of lifestyle and dietary recommendations, enzyme preparation of pure pancreatin inadequate dose (25-40 IU of lipase) during meals, proton pump inhibitor (pantoprazole 40 mg), antispasmodic (mebeverine) and/or prokinetic (motilium) – on-demand, metformin 1000 mg twice daily. The basic components of the PT were the outpatient regime, the diet in accordance with the order of the Ministry of Health of Ukraine dated 29.10.2013. № 931; Group 2 (PT+AM – 27 patients) – received PT with

a course of ademetionine (sublingual tablets Agepta 400 mg) one tablet 2 times a day 30-60 minutes before meals, holding under the tongue for at least 15-20 minutes – until complete dissolution by a course lasting one month.

We analyzed the presence of significant clinical manifestations in% of the total number of patients in the group before treatment. After treatment, the clinical manifestation in patients with CP with diabetes was considered to be present in the absence of significant positive dynamics. The Quality of Life (LQ) was also assessed using the Gastrointestinal Symptom Rating Scale (GSRS) developed by the ASTRA Hassle (I. Wiklund, 1998), which is used to assess the LQ of patients with gastrointestinal disease. It consists of 15 items, grouped into 5 scales: a) abdominal pain (AP); b) indigestion syndrome (IS); c) diarrheal syndrome (DS); d) constipation syndrome (CS); e) gastric reflux syndrome (RS). Each question is evaluated from 1 to 7 points. Lower values correspond to weaker symptoms and higher LQ.

Statistical processing of indicators was performed by the method of variation statistics Fisher-Student with the determination of arithmetic mean (M), standard deviation (q), arithmetic mean error (m). The average values are presented as M± m. An unpaired Student›s t-test was used to compare the two independent samples, and a paired Student's t-test, included in the 2007 Microsoft Excel suite, was used to assess changes in dynamics and treatment effects.

RESULTS

Table I shows the results of the impact of two treatment programs on some clinical symptoms and syndromes in patients with CP. Positive dynamics of clinical symptoms/syndromes were found in both groups of patients, but the therapeutic effect in the 2nd group was more significant.

According to the dynamics of abdominal pain, the effectiveness of treatment with the inclusion of ademetionine was 81.5% against 73.3% in the protocol treatment group. The dynamics of the effectiveness of dyspeptic syndrome in group 2-1 was 77.8% vs. 60.0%, constipation – 48.2% vs. 40.8%, diarrhea – 29.6% vs. 16.7%, astheno-neurotic – 81.5% vs. 60.0%, allergic – 25.9% vs. 10.0%, for manifestations of autonomic dysfunction – 66.7% vs. 46.6% of that in the group of protocol therapy.

Thus, the analysis of the dynamics of treatment programs on the elimination of the most important clinical symptoms/syndromes in patients with comorbidity of CP and diabetes mellitus proved significantly higher efficiency of the complex with the additional inclusion of ademetionine in protocol therapy, which was also effective ($p<0.05$).

The next stage of the study of the proposed treatment complexes was to study their effectiveness on the state of LQ patients with a combined course of CP and DM 2 on the scales of the international questionnaire GSRS (Table II).

Analysis of the dynamics of LQ parameters on the scales of a specialized gastroenterological questionnaire under the influence of PT and PT+AM found statistically significant ($p<0.05$) changes in the group with the inclusion of ademetionine for treatment for all parameters in contrast to the group of PT, where statistically significant changes on three scales (abdominal pain, gastric reflux, and dyspepsia).

Thus, the method of inclusion in the protocol complex therapy of patients with CP and DM2 outside the exacerbation of the course of the aminoacid drug ademetion in the form of sublingual table tsin order to correct clinical manifestations due to metabolic, antioxidant, anti-inflammatory, and detoxifying restoration of the functional state of the pancreas and liver.

DISCUSSION

The evidence base for the use of ademetionine in liver disease is quite large – more than 8,000 publications and more than 200 clinical studies. In particular, a meta-analysis was conducted based on 12 randomized clinical trials involving 705 patients with chronic liver disease (cholestasis of pregnant women, toxic hepatitis, viral hepatitis with intrahepatic cholestasis, alcoholic liver disease, nonalcoholic fatty liver disease). liver disease), where the safety of ademetionine was studied (frequency of side effects, long-term prognosis, mortality rate, number of liver transplants, as well as the level of total bilirubin, ALT, AST, etc.)[11-14]. The results obtained after data analysis and independent comparisons show a significant reduction in total bilirubin and ACT levels with ademetionine treatment. A meta-analysis confirmed that a proven level of safety and effect on liver function is the basis for the use of ademetionine as a basic drug in the treatment of chronic liver disease. The level of side effects of the drug corresponded to the level of placebo[15, 16].

However, due to the tendency of the liver to retain approximately 60% of the dose of ademetionine, the likelihood of using SAMe to take it orally in the form of gastro-resistant tablets is complicated by its lack of bioavailability, which necessitates very high oral doses (1600 mg/day). or administered by intramuscular injection, which is not always convenient due to invasiveness, pain, and discomfort in an outpatient setting[17]. The possibility of taking SAMe in the form of tablets for absorption allows achieving significant levels of bioavailability also by oral administration. The use of SAMe by sublingual absorption ensures that the first passage through the liver is overcome. From the moment venous blood passes from the sublingual plexus, it flows directly into the superior vena cava. A study of 6 healthy volunteers compared the pharmacokinetic absorption parameters of SAMe taken orally in the form of gastro-resistant tablets (200 mg of the active substance SAMe) or in the form of lozenges (119.76 mg of the active substance)[18, 19]. The results showed that the levels of bioavailability obtained by taking the lozenges were approximately twice as high as those determined with the use of gastro-resistant tablets. Thus, the results showed that the use of tablets for resorption allowed when taking SAMe orally can provide the same levels of bioavailability as when administered intramuscularly[20, 21]. This has attracted our attention in terms of possible use for positive effects on the liver as an organ of metabolic detoxification and other pleiotropic effects, but requires scientific justification for use in patients with CP in comorbidity with diabetes, as we have not found similar studies.

CONCLUSIONS

1) it is proved that the proposed inclusion in the protocol treatment of a combination of CP and DM2 course of sublingual a demethion in eledtoan increase in its effectiveness in the correction of abdominal pain – by 8.2%, dyspepsia – by 17.8%, constipation – by 7.4% , diarrhea – by 12.9%, astheno-neurotic – by 21.5%, allergic – by 15.9%, autonomic – by 20.1% ($p<0.05$); 2) found higher efficacy of treatment with the in clusion of a demethion in relation to that in the group of PL on the dynamics of the parameters of the scales of the GSRS questionnaire by a total of 13.7%, $p <0.01$: abdominal pain decreased by 22.6% vs. 16.7%, gastricreflux – by 34.7% against 16.9% ($p <0.05$), diarrhea – by 23.9% against 8.2% ($p<0.001$), constipation – by 20.6% against 5.9% (0.01), dyspepsia – by 32.4% against 17.9% ($p <0.01$), respectively; 3) it proved the feasibility of using sublingual demethion in the complex rehabilitation treatment of patients with comorbidity of CP and diabetes mellitus in order to correct clinical symptoms.

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ORIGINAL ARTICLE

INFLAMMATORY RESPONSE STATUS IN INFANTS WITH INTRAUTERINE INFECTION FROM MOTHERS WITH IDENTIFIED TORCH INFECTION

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ABSTRACT

The aim: To investigate the status and possibilities of markers of the inflammatory response of organism in infants with identified IUI born to mothers diagnosed with TORCH infection.

Materials and methods: The study group included: infants diagnosed with IUI (n = 40), born to mothers (age 31.31 ± 2.08 years) with the diagnosis of TORCH infection and a control group (n = 25 infants). Childbirth in all newborns was physiological. The average weight of newborns was 1877.69 ± 981.78 g (min – 600 g; max – 4000 g). Gestational age: 32.25 ± 5.15 weeks. Observation and treatment of newborns lasted up to 7 days (included stay in the emergency department of the Uzhhorod maternity hospital in the Zakarpattia region). Cytokine profile, γ-IFN, TNF-α, Pg E2, serum neopterin and procalcitonin levels were studied.

Results: The values of the parameters of the cytokine profile (IL-1, IL-6, IL-8, IL-10) varied within the reference values, but with significant differences with the values of the control group, which was 1,2; 4; 10; 6 times, respectively. The levels of inflammatory mediators (γ-IFN Procalcitonin Neopterin TNF-α Pg E2) differed significantly from the data of the control group of infants and exceeded the upper limit of the reference values by 1,3; 3; 25; 4 times, respectively. According to the correlation analysis, there are positive correlations of medium level: IL 1 and procalcitonin (r = 0.33); IL 6 and IL10 (r = 0.44); IL 10 and prostaglandin E2 (r = 0.44); neopterin and prostaglandin E2 (r = 0.39), which indicates synergism in the performance of biologically active processes. Negative correlations of moderate degree were observed between the following parameters: IL 1 and gestational age of infants (r = -0.36); IL 6 and IL 8 (r = -0.34); γ-IFN and TNF-α (r = -0.43), which indicates the diversity of interactions between participants in the inflammatory response of the organism.

Conclusions: Various infectious agents can act as «primary affect» of sepsis as a complex pathological process involving the organism, and each of the infections has its own characteristics of the pathological process, therefore curent changes in infectious circumstances make new demands on research. It has been proven that intrauterine infection has a negative effect on the homeostatic parameters of infants, in particular, on the indicators of the inflammatory response of the child's organism. Symptomatic inflammatory biomarkers can be used to identify the pathological condition of the infant, in addition to routine laboratory tests, for early correction of VUI. This delay in identifying affected infants can lead to long and unnecessary therapy, the emergence of resistant strains of microorganisms, increased treatment costs and, in particular, a higher risk of complications such as cerebral palsy or intraventricular hemorrhage.

KEY WORDS: intrauterine infection, inflammatory response, cytokine profile, newborns

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INTRODUCTION

One of the biggest problems that doctors face is deciding when to diagnose an intrauterine infection and what correction to prescribe. Intrauterine infections (IUI) and neonatal sepsis are the most relevant and controversial issues of modern neonatology, given that infectious pathology determines a high level of morbidity and mortality in newborns [1, 2]. In recent years, the problem of IUI has become particularly relevant, as the achievements of modern resuscitation allow to ensure the survival of newborns who have suffered severe IUI [3, 4]. The results of studies conducted in obstetrics and gynecology and neonatal clinics have shown that a variety of opportunistic pathogens not only cause acute and chronic inflammatory processes of the pelvis of the pregnant woman, but also lead to severe of the IUI fetus and newborn, and can form pathology directly not associated with the development of the inflammatory process [5, 6]. IUI is an established fact of intrauterine penetration of microorganisms into the fetus, in which there are pathophysiological changes characteristic of infectious pathology, manifested prenatally or shortly after birth, while intrauterine infection of the fetus and newborn is the pathological condition formed under the influence of infectious pathology of the mother. associated infection of amniotic fluid, placenta, umbilical cord, fetus on the background of changes in the immunological reactivity of the newborn without signs of infectious disease [7, 6]. The frequency of IUI has not been definitively established, however, according to resources, the prevalence of IUI can reach 10-15% of all pregnancies, and intrauterine infection ranges from 6 to 55%, reaching 80% among premature infants. In the structure of IUI viral and / or virus-associated infections are the most dangerous

Table I. Parameters of the inflammatory response in infants

Laboratory indicators	M ± m (n=40)	min	max	Reference values	Control group (n=25)
IL-1, pg/ml	0,83 ± 0,73•	0,00	3.39	0-11pg/ml 1,6 pg/ml	0,65 ± 0,06
IL-6, pg/ml	10,79 ± 5,24•	1,23	19,30	0-10 pg/ml 2,0 pg/ml	0,77 ± 0,04
IL-8, pg/ml	4,56 ± 3,72•	1,00	25,20	0-10 pg/ml 2,0 pg/ml	0,48±0,056
IL-10, pg/ml	7,78 ± 6,65•	0,50	28,30	0-20 pg/ml 5,0 pg/ml	1,2 ± 0,25
γ-IFN, pg/ml	20,14 ± 25,56•	0,10	102,80	no more than 15,0 pg/ml	5,8±0,3
Procalcitonin, ng/ml	1,67 ± 1,09•	0,15	4,23	no more than 0,5 ng/ml	7,6 ± 1,5
Neopterin, nmol/l	32,32 ± 18,50•	0,50	77,40	no more than 10 nmol/l	0,12±0,022
TNF-α, pg/ml	157,21 ± 21,05•	102,30	196,30	till 6 pg/ml 0,5 pg/ml	8,4 ± 0,32
Pg E2, pg/ml	1671,38 ± 1555,16•	956,80	11190,20	200-400 pg/ml	390,21± 31,19

Significance of values: P <0,001 •

and difficult to predict. Viral infections during pregnancy lead to a number of consequences for the mother and fetus, ranging from asymptomatic disease to critical conditions that cause severe maternal morbidity, stillbirth, premature birth, birth defects and congenital anomalies that become apparent at birth or later [5, 8]. The highest risk of infection of the fetus is observed in the case of primary infection of the pregnant woman [9]. Thus, IUI, especially viral, remain almost uncontrollable causes of reproductive loss, childhood morbidity and disability. Pathological effects of microorganisms on the fetus during pregnancy lead to various disorders, including abortion, organ defects, the development of severe infectious inflammation or latent process with elements of persistence in the postnatal period. IUI infection is often accompanied by the development of life-threatening conditions in newborns, which determining the medical and social significance of the problem and requires further in-depth research.

THE AIM

To investigate the status and possibilities of markers of the inflammatory response of organism in infants with identified IUI born to mothers diagnosed with TORCH infection.

MATERIALS AND METHODS

The study group included: infants diagnosed with IUI (n = 40), born to mothers (age 31.31 ± 2.08 years) with the diagnosis of TORCH infection and a control group (n = 25 infants). Childbirth in all newborns was physiological. The average weight of newborns was 1877.69 ± 981.78 g (min – 600 g; max – 4000 g). Gestational age: 32.25 ± 5.15 weeks. Observation and treatment of newborns lasted up to 7 days (included stay in the emergency department of the Uzhhorod maternity hospital in the Zakarpattia region). Cytokine profile, γ-IFN, TNF-α, Pg E2, serum neopterin and procalcitonin levels were studied.

RESULTS

The examination revealed pathological changes in the levels of immunological parameters and inflammatory response factors of the organism, their interactions and relationships (table I.).

According to table I, there is a significant increase in the level of IL-1 (0.83 ± 0.73 pg / ml) compared to the control group (0.65 ± 0.06 pg / ml), but within the reference values; significant increase in IL-6 levels by 14-fold (10.79 ± 5.24 pg / ml) compared to controls group of infants (0.77 ± 0.04 pg / ml) and within the upper limit of reference. The level of IL-8 in the studied contingent (4.56 ± 3.72 pg / ml) also differs significantly from the data of the control group (0.48 ± 0.056 pg / ml), almost 10 times, but the variation occurs within the reference. There is also a significant, difference between the values of IL-10 (7.78 ± 6.65 pg / ml) from the values of the control group (1.2 ± 0.25 pg / ml).

Consequently, the values of the cytokine profile varied within the reference values, but with significant differences

Table II. Statistically significant correlations between the studied laboratory parameters

Laboratory indicators	Pearson's correlation coefficient, r	Statistical signifacance, p
IL-1 Procalcitonin	0,33	0,04
IL-1 Gestational age	0,36	0,02
IL-6 IL-8	0,34	0,03
IL-6 IL-10	0,44	0,005
γ-IFN TNF-α	-0,43	0,006
Pg E IL-10	0,44	0,006
Pg E2 Neopterin	0,39	0,02

with the values of the control group, which was 1,2;14;10; 6 times, respectively.

The level of γ-IFN (20.14 ± 25.56 pg / ml) also differed significantly (in 4 times) from the data of the control group (5.8 ± 0.3 pg / ml) and exceeded the reference values by 1.3 times. The value of procalcitonin (1.67 ± 1.09 ng / ml) differed significantly from the control group (7.6 ± 1.5 ng / ml) and exceeded the upper limit of reference by 3 times. The level of Neopterin (32.32 ± 18.50 nmol / l) differed significantly (267 times) from the data of the control group (0.12 ± 0.022 nmol / l) and was 3 times higher than the upper limit of the reference. The value of TNF-α (157.21 ± 21.05 pg / ml) in the study group differed significantly from the data of the control group (8.4 ± 0.32 pg / ml) and was 25 times higher than the upper limit of reference. The Pg E2 study also presented a significant difference in levels (1671.38 ± 1555.16 pg / ml compared to 390.21 ± 31.19 pg / ml), which was a significant difference in data and exceeded the upper limit of reference by 4 times.

Therefore, the values of γ-IFN Procalcitonin Neopterin TNF-α Pg E2 differed significantly from the data of the control group of infants and exceeded the upper limit of the reference values by 1,3; 3; 25; 4 times, respectively.

A correlation analysis of the relationships between the studied parameters was performed, and reliable correlation coefficients of different degrees were identified (Table II.).

According to table II, there is a correlation between the average level of IL-6-IL-10 (r = 0.44) and IL-6 -IL-8 (r = -0.34), which corresponds to the physiological patterns of interactions between interleukins. IL-1, 6 – make up the group of pro-inflammatory interleukins, while IL-10 belongs to the anti-inflammatory group. IL-10 suppresses the production of almost all proinflammatory cytokines and prevents the adhesion of leukocytes to the endothelium, inhibits the secretion of superoxide radicals and cytokines (IL6, IL8, TNFα) [8]. According to leading scientists, IL-10 has been shown to inhibit the effect of interferon-γ and neopterin synthesis by monocytes / macrophages.

A complete immune response is provided only by active interaction between cytokines. The biological effect of one cytokine is usually realized together with the action of others. The main correlograms of relationships between the participants in the inflammatory response are as follows.

Consider the correlogram of the relationship between the level of γ-IFN and TNF-α in the blood of examined newborns (Fig. 1.)

It is known that cytokines have a wide range of biological properties – interact with each other, form a universal network that triggers and regulates the cascade of inflammatory, immune, metabolic processes – both local and systemic, aimed at neutralizing and eliminating pathogens. In addition to cytokines, interferons also belong to inflammatory mediators involved in the development of the inflammatory response. The main proinflammatory mediators are TNF-α and IL-1. The role of TNF-α in the development of sepsis is associated with: increasing the procoagulant properties of the endothelium, activation of neutrophil adhesion, induction of other proinflammatory cytokines, stimulation of catabolism, fever, synthesis of acute phase proteins.

The importance of IFNγ in the immune system is ascribed to its ability to directly inhibit viral replication, as well as its ability to act as immunostimulator and immunomodulator. According to our data, the multidirectional correlation between the levels of γ-IFN and TNF-α in the blood of the examined newborns is r = -0.43, which is due to the characterological data of the considered indicators.

Consider the correlogram of the relationship between the levels of IL-6 and IL-10 in the blood of examined newborns (Fig. 2.)

Interleukins are cytokines responsible for the transfer of information between leukocytes. When used, one group of leukocytes may affect another. Interleukin 6 (IL 6) is multidirectional. It is produced by monocytes and macrophages. IL 6 directly and effectively stimulates inflammatory processes. However, high concentrations of this substance can limit the development of inflammation. This is because interleukin 6 blocks the synthesis of inflammatory cytokines through a feedback inhibition mechanism. IL-6 is a proinflammatory

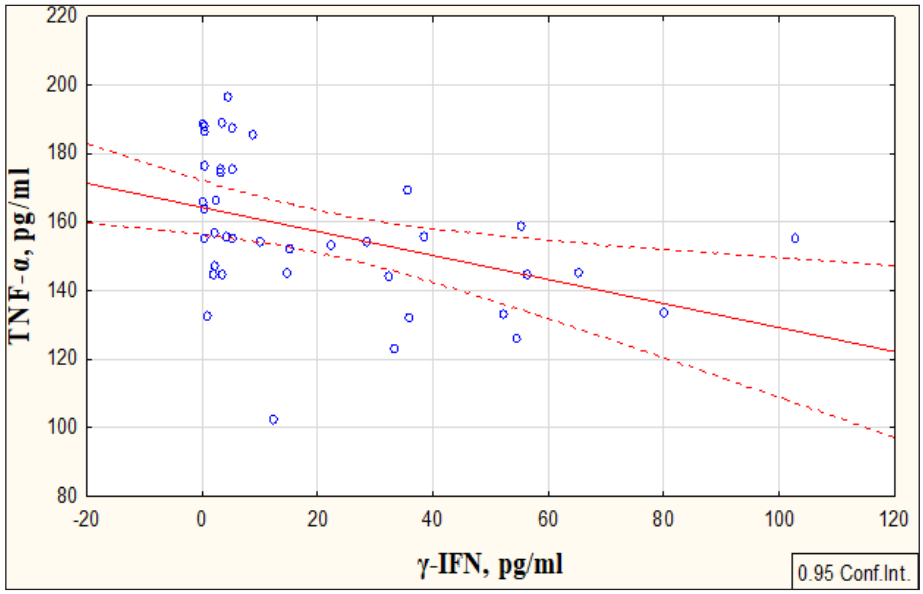

Fig. 1. Correlation between γ-IFN and TNF-α levels in the blood of examined newborns.

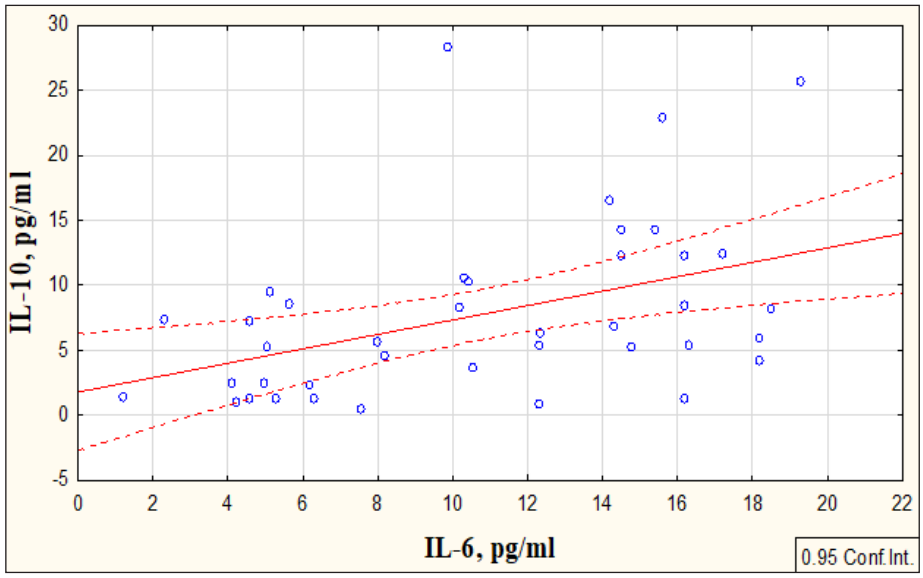

Fig. 2. Correlation between IL-6 and IL-10 levels in the blood of examined newborns

cytokine with two directions of action. On the one hand, it inhibits the production of proinflammatory cytokines by macrophages, on the other hand, it induces the production of acute phase proteins, promotes the activation of T lymphocytes by antigen-presenting cells, enhances B cell proliferation and induces the formation of immunoglobulins, stimulates hematopoiesis and platelet formation, is synthesized by activated macrophages and T cells [10,11]. Increase in the level of the anti-inflammatory cytokine IL10 can be explained by increase in secretion in response to the elevated content of pro-inflammatory cytokines in the serum. IL10 suppresses the production of almost all proinflammatory cytokines, inhibits leukocyte adhesion to the endothelium and inhibits the secretion of superoxide radicals and cytokines (IL6, IL8, TNFα). The positive correlation coefficient between interleukins 6 and 10 (r = 0.44) demonstrated compliance with the classical rules.

Consider the correlogram of the relationship between Procalcitonin and Interleukin 1 (Fig. 3.)

Interleukin 1 (IL 1) defines a whole group of cytokines that are crucial in the inflammatory process, are the main trigger mechanism for initiating the production of other proinflammatory cytokines. As a result, the biochemical and functional cascade of inflammatory pathobiochemical processes is developing. It is produced in response to a variety of antigens.

The Procalcitonin test also has a high diagnostic potential, which can be traced in our studies and allows to diagnose the disease, determine the severity, course and subsequent prognosis. Synergism of interactions and a positive correlation with the proinflammatory cytokine Interleukin-1 (r = 0.33) is observed.

An important milestone in research is the gestational age of infants, which has significant effects on the development of the disease and the nature of the inflammatory process. Here is a correlogram of relationships (Fig. 4.).

When analyzing the correlogram (Fig. 4) attention should be payed to the features of nonspecific resistance in

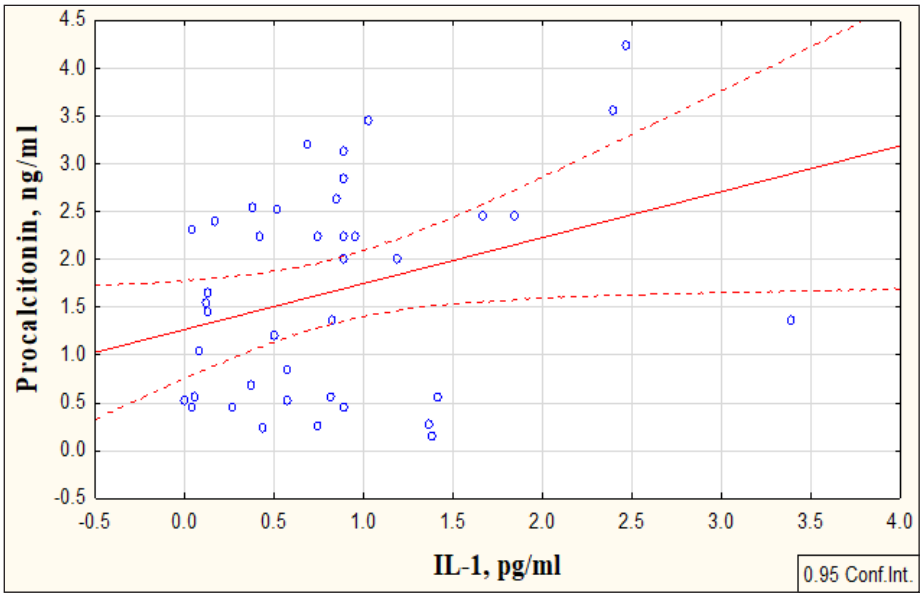

Fig.3. Correlation between Procalcitonin and IL-1 levels in the blood of examined newborns

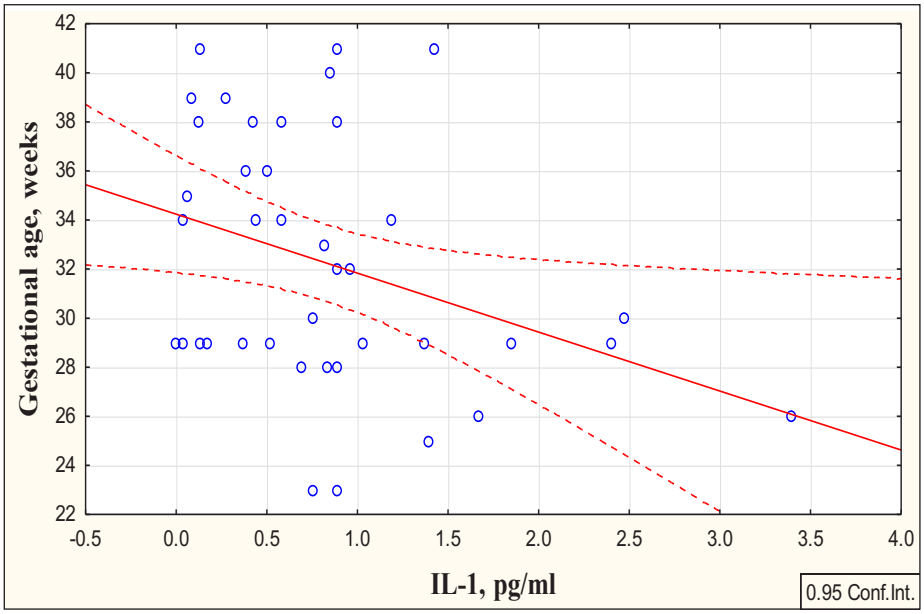

Fig. 4. Correlation between IL-1 level and Gestational age in the blood of examined newborns

the fetus and newborn. Intrauterine capacity of phagocytic cells is relatively insignificant. After birth, the phagocytic ability of leukocytes increases. At the same time, both neutrophils and monocytes in the first 6 months of life do not cope with the final phase of phagocytosis – the destruction of the ligand, which is especially evident in relation to pathogenic microorganisms. At this age, the child's phagocytes are unable to fight pneumococci, which explains the frequent occurrence of pneumonia and relatively high mortality in infants. In the newborn, along with the imperfection of phagocytosis, there is a low ability to synthesize interferons [1,8]. In this regard, the newborn has a tendency to generalized bacterial inflammation and sepsis. These patterns are observed in our studies. The IL-1 relationship and gestational age have a mid-inverse correlation (r = -0.36). This fact can be interpreted as follows: the smaller the gestational age, the greater the production of IL-1 due to physiological age characteristics.

Consider the correlogram of the relationship between the levels of IL-6 and IL-8 in the blood of examined newborns (Fig. 5.)

The action of IL-6 is realized after interaction with two components of a specific heterodimeric receptor (gp130 and IL-6R). IL-6 is a proinflammatory cytokine with two directions of action. On the one hand, it inhibits the production of pro-inflammatory cytokines by macrophages, on the other hand, it induces the production of acute phase proteins (which activate corticosteroid synthesis), promotes the activation of T-lymphocytes by antigen-presenting cells, enhances B-cell proliferation and induces the formation of immunoglobulins, stimulates hematopoiesis and platelet formation. IL-8 is one of the main proinflammatory chemokines formed by macrophages, epithelial and endothelial cells. Interleukin 8 (IL 8) is a cytokine that stimulates the migration of immune cells throughout the body. This means that it stimulates the movement and

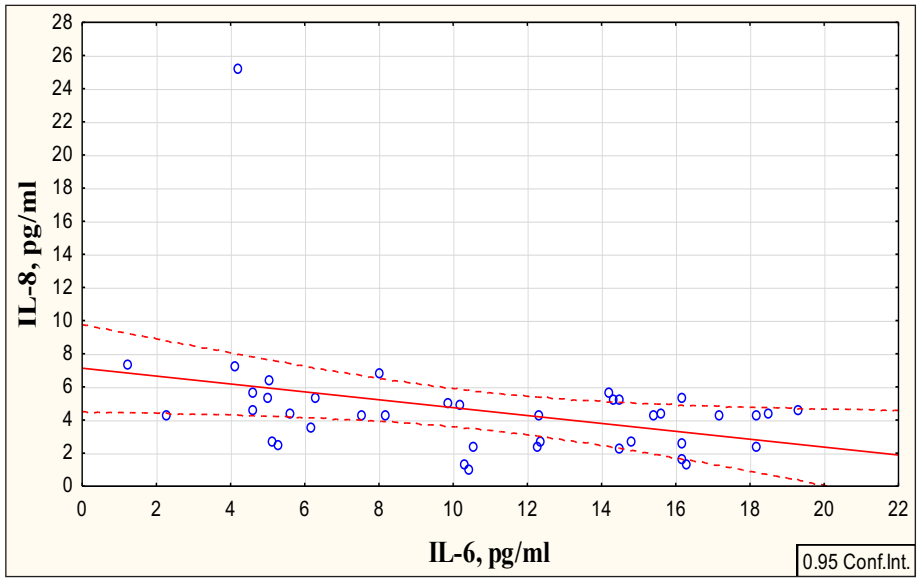

Fig. 5. Correlation between IL-6 and IL-8 levels in the blood of examined newborns

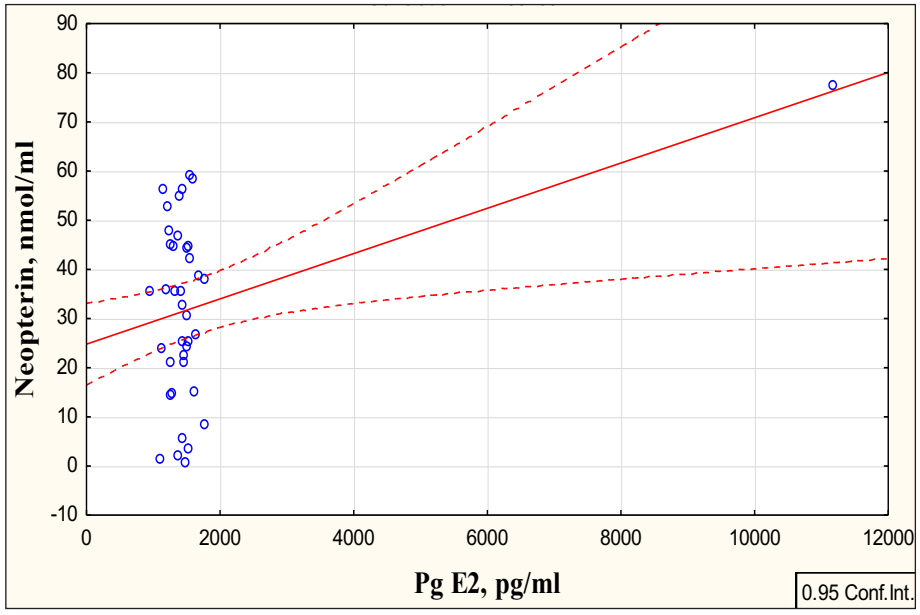

Fig. 6. Correlation between Neopterin and Prostaglandin E2 levels in the blood of examined newborns

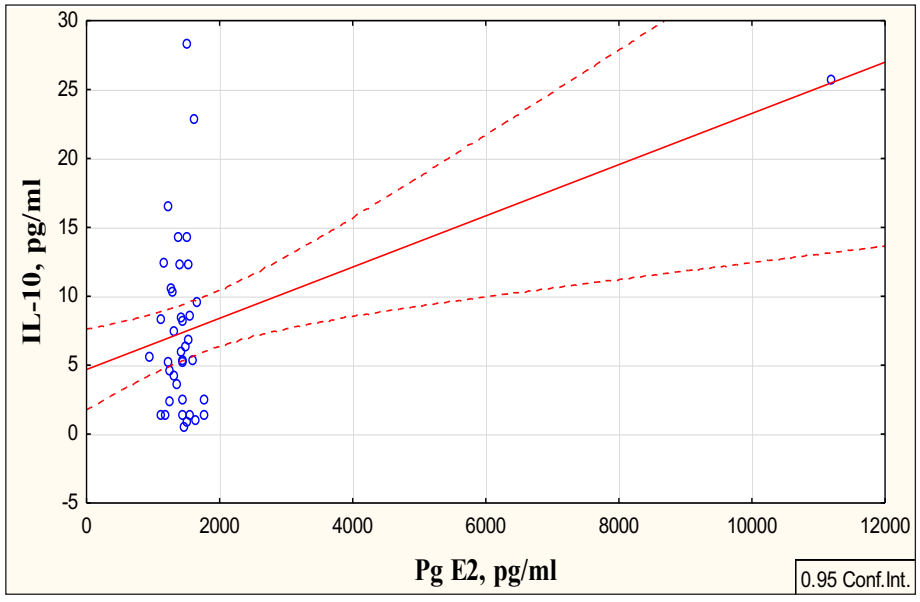

Fig. 7. Correlation between IL-10 and Prostaglandin E2 levels in the blood of examined newborns

distribution of T lymphocytes, neutrophils and monocytes. This action is defensive in nature. [8]. According to our data (Fig. 5). , there is a correlation relationship of the middle level (r = 0.44), which presents the unidirectionality of the interaction of biologically active substrates.

Consider the correlogram of the relationship between the levels of Neopterin and Prostaglandin E2 in the blood of examined newborns (Fig. 6.).

In the inflammatory process, an important role belongs to the mediators of inflammation – cytokines. However, the concentration of separate cytokines reflects only a limited view of the interaction between them and immunocompetent cells. Therefore, it is best to measure the level of Neopterin. Neopterin is a substance that is synthesized by monocytes and macrophages under the influence of interferon γ and to a lesser extent by activated vascular endothelial cells. Neopterin plays a role in the mechanism of cytotoxic action of activated macrophages. Its concentration reflects the combined effect of different cytokines on the population of monocytes / macrophages. Prostaglandins have an extremely wide range of physiological effects, are among the most active biological substances, which perform three main functions in the body: supportive, molecular, mediatory. The participation of prostaglandins in the inflammatory process has been proven. They are able to change the activity of enzymes, affect the synthesis of hormones and adjust their action on various organs and tissues. Imbalance in synthesis leads to the development of various diseases[8]. Thus, prostaglandins F2 and E2 are formed in the tissues of the respiratory tract, in particular E is synthesized in the lung tissue in the bronchi and can cause contraction of the bronchial muscles. Prostaglandins can be attributed to intracellular low molecular weight regulators, but they are also active in the extracellular space. Correlation analysis (Fig. 6.).of the obtained results showed positive dependences of the average level of Neopterin concentration on PgE2 (r = 0.39, p = 0.02).

Consider the correlogram of the relationship between the levels of IL-10 and Prostaglandin E2 in the blood of examined newborns (Fig. 7).

According to our data(Fig. 7)., there are significant correlations between the levels of IL-10 and Prostaglandin E2. In inflammation, PgE2 is involved in all processes that lead to the classic signs of inflammation: redness, swelling, pain. It also has immunomodulatory properties and effects on growth, bone structure, which is especially important for infants. IL10 suppresses the production of almost all proinflammatory cytokines, inhibits the adhesion of leukocytes to the endothelium and inhibits the secretion of superoxide radicals and cytokines, inhibits the effect of interferon on the synthesis of neopterin by monocytes / macrophages. The increase in the level of the anti-inflammatory cytokine IL10 can be explained by the increase in the secretion of this cytokine in response to the increased content of pro-inflammatory cytokines in the serum [8,12].

According to the results of correlation analysis, a positive moderate relationship between Pg E2 and IL-10 (r = 0.44, p = 0.006) was presented.

DISCUSSION

Modern research shows that the most common intrauterine infection of the fetus is caused by viral infections of the mother. The range of viruses that cause congenital pathology is constantly expanding. In addition to rubella, HSV, CMVand some others. Pathogens of infectious diseases of the mother during pregnancy are especially dangerous for the fetus, because the fetus lacks both active and passive immunity to microorganisms, which determines the development of the infectious process. Because most of the diseases of pregnant women that leading to IUI occur in subclinical, latent form with activation of the process in any violation of homeostasis, it complicates the clinical diagnosis. Thus, diagnostics based on clinical manifestations only, without involvement of specific microbiological studies, leads to diagnostic errors in 90-95% of cases. It is known that cytokines have a wide range of biological properties – interact with each other, form a universal network that triggers and regulates the cascade of inflammatory, immune-metabolic processes – both local and systemic, aimed at neutralizing and eliminating pathogens. Markers of inflammatory response in newborns diagnosed IUI present changes at all levels, The values of the cytokine profile parameters are within the reference values but have significant differences from the data of the control group according to our data. The levels of other inflammatory mediators (γ-IFN Procalcitonin Neopterin TNF-α, Pg E2) exceeded the upper limit of the reference values in 1,3,3, 25, 4 times, respectively, and significantly differed from the data of the infants control group. Immunological immaturity of the newborn can lead to a violation of the response to infectious agents. Various infectious agents can act as «primary affect» of sepsis as a complex pathological process involving the organism, and each of the infections has its own characteristics of the pathological process, therefore curent changes in infectious circumstances make new demands on research. It has been proven that intrauterine infection has a negative effect on the homeostatic parameters of infants[6], in particular, on the indicators of the inflammatory response of the child's organism. Symptomatic inflammatory biomarkers can be used to identify the pathological condition of the infant, in addition to routine laboratory tests, for early correction of VUI. This delay in identifying affected infants can lead to long and unnecessary therapy, the emergence of resistant strains of microorganisms, increased treatment costs and, in particular, a higher risk of complications such as cerebral palsy or intraventricular hemorrhage.

CONCLUSIONS

1. The values of the parameters of the cytokine profile (IL-1, IL-6, IL-8, IL-10) varied within the reference values, but with significant differences with the values of the control group, which was 1,2; 4; 10; 6 times, respectively.
2. The levels of inflammatory mediators (γ-IFN Procalcitonin Neopterin TNF-α Pg E2) differed significantly from the data of the control group of infants and exceeded the upper limit of the reference values by 1,3; 3; 25; 4 times, respectively.

3. According to the correlation analysis, there are positive correlations of medium level: IL 1 and procalcitonin (r = 0.33); IL 6 and IL10 (r = 0.44); IL 10 and prostaglandin E2 (r = 0.44); neopterin and prostaglandin E2 (r = 0.39), which indicates synergism in the performance of biologically active processes.
4. Negative correlations of moderate degree were observed between the following parameters: IL 1 and gestational age of infants (r = -0.36); IL 6 and IL 8 (r = -0.34); γ-IFN and TNF-α (r = -0.43), which indicates the diversity of interactions between participants in the inflammatory response of the organism.

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Conflict of interest:

The Authors declare no conflict of interest.

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A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

ORIGINAL ARTICLE

CHANGES IN SERUM GHRELIN AND ITS RELATIONSHIP WITH OF BODY MASS INDEX IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE AND SPONDYLOARTHRITIS

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ABSTRACT

The aim: To determine the features of changes in serum ghrelin levels and its relationship with the body mass index in patients with GERD and spondyloarthritis (SpA) with lesions of the cervical and thoracic spine.

Materials and methods: The examined patients included 80 patients with SpA with cervical and thoracic spine lesions in combination with GERD. The examined patients with SpA with predominant cervical and thoracic spine lesions were divided into two groups depending on the clinical course of GERD, namely: group I included 33 (41.2%) patients with typical esophageal manifestations of GERD (13 males (39.4%), 20 females (60.6%)), and group II consisted of 47 (58.8%) patients with atypical extraesophageal manifestations of GERD (among them were 17 (36.2%) males and 30 (63.2%) females).

Results: All patients were tested for serum ghrelin by enzyme-linked immunosorbent assay. Analysis of clinical manifestations of atypical GERD (group II patients) revealed that most often patients with SpA of the cervical and thoracic spine were diagnosed with dental and otolaryngological masks of reflux disease (40.4 % and 25.5 % of patients, respectively). Maximum serum ghrelin levels were detected in patients with SpA with cardiac GERD (355.02 ± 4.75 ng/ml), while minimum values were found in patients with dental signs of reflux disease (298.17 ± 5.16 ng/ml – $p < 0.05$).

Conclusions: 1. In patients with SpA with cervical and thoracic spine lesions, GERD often has atypical symptoms (mostly dental and otolaryngological forms in 40.4% and 25.5% of patients). 2. In patients with SpA with esophageal clinical signs of GERD, normal weight or underweight is more common, while in patients with extraesophageal forms of GERD overweight or obesity of varying severity prevails. 3. In patients with SpA and GERD, an increase in serum ghrelin levels was found in patients with cardiac manifestations of reflux disease (355.02 ± 4.75 ng/ml). 4. The relationship between BMI changes in patients with SpA and GERD and increased serum ghrelin levels was found, namely: in group II patients with overweight and obesity a direct correlation was found, and in group I patients with underweight an inverse correlation was fund.

KEY WORDS: esophageal, extraesophageal manifestations of gastroesophageal reflux disease, spondyloarthritis, body mass index; ghrelin

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INTRODUCTION

Ghrelin is an orexigenic hormone that regulates neuronal chains that modulate food intake and energy expenditure by binding to specific receptors in the brain [1, 2]. It has a variety of metabolic effects on physiological processes in the body, such as food regulation and satiety, modulation of energy expenditure through regulation of brown fat thermogenesis, regulation of lipid levels and obesity in general, glucose metabolism, inflammation, effects on endothelial dysfunction and many others [3]. Ghrelin, by stimulating growth hormone secretion, may also stimulate increased calorie intake, weight gain, and obesity by activating hypothalamic orexigenic neuropeptide Y (NPY) [4]. Thus, ghrelin is associated with conditions associated with hyperlipidemia, weight gain, abnormal body composition, and fat accumulation [5].

Ghrelin is produced mainly by P/D1 cells of the mucous membrane of the fundus of the stomach [2]. Ghrelin circulates in the human body in two main forms: acylated (about 5.0 % of total ghrelin) and deacylated (about 95.0 % of total ghrelin), which have potential differences in metabolic effects. [4]. Ghrelin as a multifunctional peptide hormone, is involved in the formation of eating behavior, energy balance, regulation of carbohydrate and lipid metabolism, as well as modulation of gastrointestinal function (it stimulates the secretion of hydrochloric acid and affects the motor activity of various digestive systems) [6].

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 [7]. 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% [8, 9]. 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 [10].

The search for new factors that play a role in the formation of GERD is especially relevant in patients with

polymorbid pathology, the treatment of which requires medications that may adversely affect the condition of the mucous membrane of the upper gastrointestinal tract, as well as its functional activity. Therefore, the study of the clinical course, as well as factors and levels of various biologically active substances that may play an important role in the pathogenetic mechanism of GERD in patients with combined pathology, including inflammatory lesions of the spine, namely spondyloarthritis (SpA), is an extremely relevant problem of modern clinical medicine.

THE AIM

The aim of the study is to determine the features of changes in serum ghrelin levels and its relationship with the body mass index in patients with GERD and spondyloarthritis with lesions of the cervical and thoracic spine.

MATERIALS AND METHODS

The examined patients included 80 patients with SpA with cervical and thoracic spine lesions in combination with GERD who were hospitalized in Rheumatology and Gastroenterology 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, as well as underwent dental treatment at Dental Plus Clinic in the period of 2019-2022. All studies were performed 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.

The control group included 20 healthy individuals: 9 males (45.0%) and 11 females (55.0%) without musculoskeletal and upper gastrointestinal tract lesions. The average age was 48.8 ± 4.1 years.

All patients were examined using general clinical, anthropometric, instrumental and laboratory methods. To verify the diagnosis, attention was paid to the nature of the complaints and medical history. In anthropometric research, height and waist circumference were determined, and body mass index (BMI) was calculated. According to WHO recommendations, the patients were distributed depending on the BMI, at which BMI 16.0 or less indicates a pronounced deficit of body weight; 16.0-18.5 underweight; 18.5-24.9 normal weight; 25.0–29.9 overweight; 30.0-34.9 obesity Class 1; 35.0-39.9 obesity Class 2; 40.0 and more obesity Class 3 (morbid obesity) [11].

The diagnosis of GERD 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. Also, 24-hour pH monitoring according to Prof. V.N .Chernobrovy's method was performed. The Los Angeles (LA) classification (1998) was used for endoscopic assessment of the degree of damage to the esophagus: Grade A – single erosion ≤5 mm; Grade B – ≥1 erosion> 5 mm long that does not occupy the entire space between 2 adjacent folds of the esophagus; Grade C – ≥1 erosion that occupies the entire space between ≥2 folds of the esophagus and ≤75% of the perimeter of the esophagus; and Grade D – erosions or ulcers occupying ≥75% of the esophageal perimeter [12].

The diagnosis of SpA was established on the basis of diagnostic criteria of the American College of Rheumatology (ACR, 2018) and the European League Against Rheumatism (European League Against Rheumatism, EULAR, 2018) [13, 14].

All patients were tested for serum ghrelin by enzyme-linked immunosorbent assay (ELISA) using a test system from BioChemMac, RayBio® Human/Mouse/Rat Ghrelin Enzyme Immunoassay Kit.

The examined patients with spondyloarthritis with predominant cervical and thoracic spine lesions were divided into two groups depending on the clinical course of GERD, namely: group I included 33 (41.2%) patients with typical esophageal manifestations of GERD (13 males (39.4%), 20 females (60.6%), with the average age 49.8 ± 5.2 years), and group II consisted of 47 (58.8%) patients with atypical extraesophageal manifestations of GERD (among them were 17 (36.2%) males and 30 (63.2%) females, with the average age 46.7 ± 4.9 years).

The inclusion criteria were as follows: the presence of clinical symptoms (typical and atypical) of GERD, detection of FEGDS changes in the esophageal mucosa characteristic of GERD, and spondyloarthritis of the cervical and thoracic spine.

The exclusion criteria were as follows: functional or organic diseases of the esophagus, stomach and duodenum, non-erosive form of GERD, Barrett's esophagus, Helicobacter pylori positive patients, and patients with psychiatric and oncological diseases.

Analysis and processing of the results of the examinations was carried out by the computer program Statistics for Windows v.10.0 (StatSoft Inc, USA) using parametric and non-parametric methods of evaluation of the results.

RESULTS

The leading clinical manifestations of lesions of the upper gastrointestinal tract in patients of group I (with typical esophageal manifestations of GERD) were acid regurgitation, heartburn and dysphagia. As shown in Figure 1, esophageal signs of GERD were diagnosed in 41.2 % of patients, while atypical clinical forms of reflux disease were detected in 58.8 % of SpA patients.

Analysis of clinical manifestations of atypical GERD (group II patients) revealed that most often patients with SpA of the cervical and thoracic spine were diagnosed with

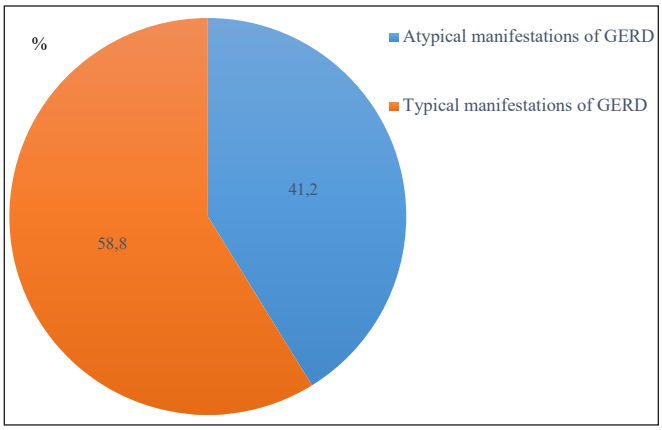

Fig. 1. Distribution of the examined patients with SpA depending on the clinical form of GERD

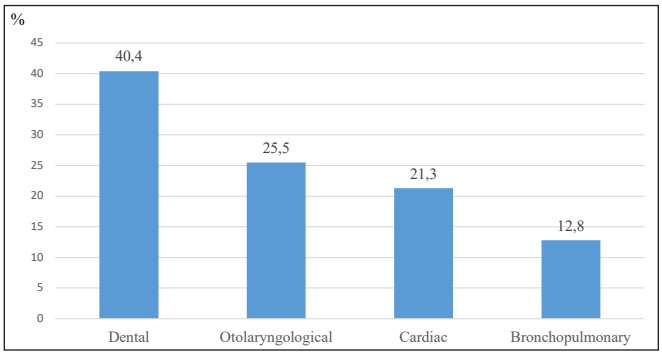

Fig. 2. Distribution of the examined SpA patients of group II depending on atypical clinical forms of GERD

dental and otolaryngological "masks" of reflux disease (40.4 % and 25.5 % of patients, respectively) – Fig.2. At the same time, dental signs of GERD were manifested by dental caries, stomatitis and periodontitis. Otolaryngological changes, which were considered atypical manifestations of GERD, were indicated by sore throat, hoarseness of voice, lump in the throat, as well as chronic coughing.

Cardiac form of GERD, manifested by chest pain along the esophagus, heart failure, as well as its bronchopulmonary "mask", which was clinically manifested by dry cough and sleep apnea, was found in 21.3 % and 12.8 % of patients.

Determination of BMI allowed to establish differences in body mass in the examined patients with SpA with different clinical forms of GERD – Table I.

Patients with SpA with a typical clinical course of GERD (group I) more often had normal BMI and overweight (45.5 % and 24.2 % of patients). Obesity I and II was found in only 9.1 % and 3.0 % of patients. Also, underweight was 7.9 % more often found in patients of group I ($p < 0.01$) than in patients with atypical clinical forms of GERD. Group II patients most often had overweight (34.0% of subjects), as well as obesity of Class 1 and Class 2 (25.5 % and 17.1 %, respectively). Thus, SpA patients with atypical clinical forms of GERD are more likely to be overweight and obese (Class 1-2), while patients with typical esophageal manifestations of reflux disease are more likely to be diagnosed with normal or overweight or underweight.

Table I. Distribution of examined patients with SpA and different clinical forms of GERD depending on BMI

Indicator	Examined patients with SpA.	
	group I (n=33)	group II (n=47)
Underweight (BMI: 16.0 – 18.5)	18.2 % **	4.3 %
Normal weight (BMI: 18.5 – 24.9)	45.5 % **	19.1 %
Overweight (BMI: 25.0 – 29.9)	24.2 %	34.0 % *
Obesity Class 1 (BMI: 30.0 – 34.9)	9.1 %	25.5 % *
Obesity Class 2 (BMI: 35.0 – 39.9)	3.0 %	17.1 % **

Note: the difference between the indicators in the examined patients of groups I and II is statistically significant: * – $p < 0.05$; ** – $p < 0.01$.

Determination of ghrelin levels in the blood serum revealed differences in its level in the patients we examined for SpA depending on different clinical forms of GERD – Table II.

A significant increase in serum ghrelin levels was found in patients with SpA and GERD. In patients with SpA with esophageal manifestations of GERD its level was 223.21 ± 4.16 ng/ml against 105.11 ± 3.25 ng/ml in the control group ($p < 0.05$), while in patients with atypical forms a 3.0-fold increase was detected ($p < 0.01$).

Further analysis determined the differences in the level of this orexigenic hormone depending on the clinical course of atypical manifestations of GERD and established a dependence on changes in BMI in patients with SpA – tables III and IV.

Maximum serum ghrelin levels were detected in patients with SpA with cardiac GERD (355.02 ± 4.75 ng/ml), while minimum values were found in patients with dental signs of reflux disease (298.17 ± 5.16 ng/ml – $p < 0.05$). Almost the same serum ghrelin levels were found in patients with SpA with otolaryngological and bronchopulmonary signs of GERD.

In patients of group I, ghrelin levels correlated with BMI, which corresponds to normal weight and overweight and inversely correlated with underweight. In patients with SpA with atypical manifestations of GERD, a relationship was found between increased ghrelin levels and obesity Class 1-2, as well as BMI which corresponded to overweight ($r = 0.72$; $p < 0.05$).

The results of an experimental study by Kraft EN et al. (2019) indicate that ghrelin and its isoforms directly affect fatty acid oxidation and lipolysis. This may be the reason why patients with UCTD with high ghrelin levels have an asthenic constitution and poor nutrition. In particular, their BMI was often lower than normal. The results of this study also show that ghrelin stimulates the transport of fatty acids, affecting not only lipolysis but also skeletal muscle. Probably because f this, patients with UCTD are characterized by proximal muscle weakness, hypotension and /

Table II. Serum ghrelin levels in patients with SpA and GERD and the control group

Indicator	Controlgroup (n=20)	SpA patients	
		Typical form of GERD (n=33)	Atypical form of GERD (n=47)
Ghrelin, ng/ml	105.11±3.25	223.21±4.16 *	316.77±3.89 **, ^

Note: a statistically significant difference was found between the control group and the examined patients: * - p <0.05;** - p <0.01;statistically significant difference between indicators in patients of group I and group II: ^ - p <0.05.

Table III. Serum ghrelin levels in patients with SpA and GERD and control group

Indicator	SpA patients of group II (with atypical forms of GERD) (n = 47)			
	Dental (n=19)	Otolaryngological (n=12)	Cardiac (n=10)	Broncho-pulmonary (n=6)
Ghrelin, ng/ml	298.17±5.16	305.70±5.26	355.02±4.75*	308.04±4.25

Note: a statistically significant difference was found between the indicators in patients with dental and cardiac "masks" of GERD: * – p<0.05.

Table IV. Comparison of changes in serum ghrelin levels in patients with SpA and GERD with BMI

Indicator	Ghrelin levels (ng/mL)	
	group I (n=33)	group II (n=47)
Insufficient weight	r= -0.60; p<0.05	-
Normal weight	r= 0.56; p<0.05	-
Overweight	r= 0.64; p<0.05	r= 0.72; p<0.05
Obesity Class 1	-	r= 0.70; p<0.05
Obesity Class 2	-	r= 0.52; p<0.05

or malnutrition. According to the same authors, ghrelin does not independently change lipolysis, but, apparently, there are some additional sites for the regulation of lipid oxidation, which need to be further investigated [Kraft EN, Cervone DT].

DISCUSSION

Scientific research of pathogenetic mechanisms of GERD formation at comorbid pathological states is carried out, including its combination with backbone lesions of various genesis. At the same time, of great interest are studies aimed at determining the effect of various biologically active substances on the tonus of the lower esophageal sphincter (LES) with subsequent formation of GERD. It is known that such peptide hormones as ghrelin, adipokines, which regulate food intake, also play an important role in the formation of GERD, due to their effect on gastric acid secretion and gastrointestinal motility [15].

The results of experimental studies by Nahata M. et al. (2012) indicate an increase in peripheral ghrelin levels in rats with GERD against the background of reduced gastric emptying, food intake and antral motility [16]. The results of experimental studies in recent years (Kraft EN et al., 2019) indicate that ghrelin and its isoforms directly affect fatty acid oxidation and lipolysis. The authors explain this by the fact that patients with undifferentiated connective tissue dysplasia have high ghrelin levels, an asthenic constitution and underweight. The results of this study also show that ghrelin stimulates the transport of fatty acids, affecting not only lipolysis but also skeletal muscle. The authors believe that ghrelin does not independently change lipolysis, but, apparently, there are some additional sites for the regulation of lipid oxidation, which need to be further investigated [17].

The results of the study also indicate high serum ghrelin levels in patients with SpA in combination with GERD. At the same time, the maximum values were registered in patients with atypical course of GERD (its increase of 3.0 times – p <0.01), especially in the cardiac "mask" of reflux disease (increase of 3.4 times – p <0.01). The results of our study also indicate a relationship between an increase in serum ghrelin levels and an increase in BMI, mainly in patients with atypical forms of GERD.

In the group of patients with SpA and GERD who have clinically typical esophageal signs, there was also an increase in ghrelin levels (2.1 times – p <0.05 compared with the control group). In this group of patients, ghrelin levels were negatively correlated with BMI, which corresponded to underweight (-0.60; p <0.05) and coincided with the results of Kraft EN et al.

Thus, the mechanism of GERD formation and features of its clinical course is multifactorial, but not fully understood process, especially in patients with comorbid conditions. Further research is needed in this direction to understand the processes underlying the lesions of the upper gastrointestinal tract in patients with comorbid conditions, especially lesions of the spine of inflammatory origin (in SpA). Particular attention needs to be paid to the detection of atypical forms of GERD, such as dental, otolaryngological and cardiac "masks" for their timely correction.

CONCLUSIONS

1. In patients with SpA with cervical and thoracic spine lesions, GERD often has atypical symptoms (mostly dental and otolaryngological forms in 40.4% and 25.5% of patients).
2. In patients with SpA with esophageal clinical signs of GERD, normal weight or underweight is more common,

while in patients with extraesophageal forms of GERD overweight or obesity of varying severity prevails.
3. In patients with SpA and GERD, an increase in serum ghrelin levels was found in patients with cardiac manifestations of reflux disease (355.02 ± 4.75 ng/ml).
4. The relationship between BMI changes in patients with SpA and GERD and increased serum ghrelin levels was found, namely: in group II patients with overweight and obesity a direct correlation was found, and in group I patients with underweight an inverse correlation was fund.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

POTENTIAL RISKS OF THE SPREAD OF ANTIBIOTIC-RESISTANT MICROORGANISMS AND ANTIBIOTIC-RESISTANCE GENES IN POTABLE WATER – HUMAN ORGANISM CHAIN

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ABSTRACT

The aim: Determination of circulation interrelations between antibiotic-resistant microorganisms of *Enterobacteriaceae* family and their resistance genes in clinical strains and potable water samples taken in Uzhhorod and Uzhhorod district.

Materials and methods: We carried out generic identification of the microorganisms isolated from clinical samples of the oral cavity of 64 patients suffering from periodontal inflammatory diseases, and potable water samples taken from sources of public centralized and decentralized water supply; the isolated microorganisms were tested for antibiotic sensitivity by the Kirby-Bauer disc diffusion method according to EUCAST. With the help of molecular-genetic methods, the total DNA of potable water was isolated and tested for the presence of the following genetic resistance determinants: carbapenems *bla*NDM; *bla*OXA48-like; tetracyclines *bla*Tet-M; cephalosporins *bla*CTX-M.

Results: In the microbiota of the clinical material and potable water samples, the same spectrum of microorganisms belonging to *Enterobacteriaceae* family dominated; the isolated bacteria showed a high resistance level to beta-lactam antibiotics and to natural antibiotic preparations. The highest level of resistance was established for microorganisms isolated from well water samples, where genetic resistance determinants to *bla*CTX-M cephalosporins and *bla*Tet tetracyclins were also revealed.

Conclusions: The obtained results proved high probability of the spread of antibiotic-resistant microorganisms and their genetic resistance determinants via potable water.

KEY WORDS: antibiotic resistance genes, oral cavity, potable water, water sources

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INTRODUCTION

The wide spread of the use of antibiotics for various branches of medicine and economy and lack of any legally valid perfect system of regulation of reasonable use of antibiotic preparations have led to a growing level of antibiotic resistance [1].

During the COVID-19 pandemic, the demand for antimicrobial preparations soared up, which fact only worsened the situation with confronting the development of resistance to antibiotics [2-4]. The lack of efficient antimicrobial preparations throws the progress of medicine back for decades, increases the risk of growing of the number of incurable infectious diseases, and makes it impossible to perform many hi-tech surgeries [5, 6].

The spread of resistant strains in environmental objects (surface and soil waters, bottom deposits, wastewaters, soils) where a large-scale exchange with resistance determinants takes place between clinical strains and natural bacteria, attracts increasingly greater attention of researchers [7]. The spread of poly- and multiresistant bacteria, pharmaceuticals in environmental objects may serve as a potential source of entry of genetic resistance determinants to human organisms via food chains [8,9]. The existing out-dated water treatment facilities and imperfect potable water treatment techniques fail to interfere with the spread of genetic resistance determinants on their way to the customers, which causes heightened academic interest to study the possible spread of resistance genes via potable water [10].

THE AIM

The purpose of the given scientific paper is to determine the circulation interrelations of antibiotic-resistant microorganisms of *Enterobacteriaceae* genes and their resistance genes in clinical strains and potable water samples taken from sources of public centralized and decentralized water supply within the city of Uzhhorod and areas adjacent thereto.

MATERIALS AND METHODS

Samples for microbiological study of tap-water were taken from 2 monitoring sites in Uzhhorod located in different parts of the city (48.632576, 22.283702; 48.622222, 22.250806), and from 3 sources of decentralized water supply (water wells) located in the village of Velyky Berezny (48.885283,22.452778), on the outskirts of the town of Perechyn (48.729388, 22.448340), and in the village of Storozhnytsia (48.600345, 22.238672). Clinical isolates

were isolated from the oral cavities of patients suffering from periodontal inflammatory diseases (n=213). The microorganisms of *Enterobacteriaceae* family were identified with the study of morphological characteristics on Hottinger's broth, and their further differentiation was carried out on selective media (Ploskirev's, Endo's, bismuth sulphite agar). The generic and specific attribution of the microorganisms was performed with the help of biochemical tests (Enterotest 24 and Enterotest 16) made by Erba Lachema, the Czech Republic. The antibiotic sensitivity of the isolates was determined by by the Kirby-Bauer disc diffusion method according to EUCAST (European Committee on Antimicrobial Susceptibility Testing). The isolates were tested for antibiotic sensitivity with the use of the following discs with antibiotics: ceftriaxon (30 mg), ampicillin (10 mg), ceftriaxon (30 μg), meropenem (10 μg), cefuroxim (30 μg), imipenem (10 mg), amycacin (30 μg), ciprofloxacin (5 μg), gentamycin (10 μg), levofloxacin (5 μg), norfloxacin (10 μg), gatifloxacin (5 μg), ofloxacin (2 μg), lomefloxacin (30 μg), tetracyclin (30 μg) and doxicycline (10 μg) made by Farmaktyv and HiMedia. As control test culture, *Escherichia coli* ATCC 25922 strain was used to check the quality of the media, discs with antibiotics, and the testing precision.

IDENTIFICATION OF GENETIC RESISTANCE MARKERS FROM METAGENOMIC DNA OF WATER SAMPLES

The water samples (500 ml – 1000 ml) were filtered through a sterilized membrane filter (Millipore, USA) with pore size 0.22 μm. Total DNA was extracted from the membrane filter with the help of modified method from hexadecyltrimethylammonium bromide (CTAB) according to Andronov's method [11]. The isolated metagenomic water DNA was studied with the help of polymerase chain reaction for the presence of resistance genes, using Litex reagent set (Russia) to identify the following genetic determinants: carbapenems – *bla*NDM; *bla*OXA48-like; tetracyclines – *bla*Tet-M; cephelosporines – *bla*CTX-M. The testing was carried out with the use of the DTPrime Amplifier (DNA Technology, Russia), according to the Manufacturer's Manual. The molecular genetic studies were performed on the basis of the private laboratory of Madicover Medical Centre, Lviv. The microbiological studies were carried out on the basis of the Microbiological Laboratory, Department of Genetics, Microbiology and Plant Physiology, Biological Faculty, Uzhhorod National University.

RESULTS

The spread of antibiotics via the food chain is an increasing problem of today. Globalization in the use of antibiotic substances in products of animal origin, migration of antibiotics and leftovers of pharmacological preparations in natural waters lead to the increase of the share of antimicrobial preparations in the environment.

The studies of microbiota of different biotopes of the oral cavity of Uzhhorod residents showed that *Enterobacteriaceae* family bacteria characterized by resistance to a wide spectrum of antibiotic preparations were isolated in 30% cases. The specific spectrum of the microorganisms isolated from the oral cavity of 64 patients (the total number of the studied samples of biomaterial n=213) suffering from inflammatory diseases of periodontium tissues is presented in Figure 1.

Based on the results of the microbiological water analysis, domination of *Enterobacteriaceae* family bacteria was established for microbial associations of water samples taken from centralized and decentralized water facilities. Microorganisms of *Escherichia spp*, *Citrobacter spp*, and *Enterobacter spp* genera were observed in three out of the 12 water samples taken from centralized water supply systems; bacteria of *Citrobacter spp, Escherichia spp, Klebsiella spp,* and *Enterobacter spp* genera were found in five out of the 10 water samples taken from wells (Fig.2).

The spectrum of opportunistic microorganisms isolated from potable water samples and human organism indicates to a possibility of existence of common sources of bacterial entry and their migration, which constitutes a menace to the spread of genetic resistance determinants between humans and the environment.

The *Enterobacteriaceae* family microorganisms isolated from the oral cavity manifested a high level of resistance to antibiotic preparations. According to the analysis of the obtained antibiograms, the highest resistance level was established for macrolides, tetracyclines and unprotected beta-lactams (Fig.3).

The highest susceptibility indices were established for III-IV generation cephalosporins and II-III generation phthorchinolons.

The microorganisms isolated from central water supply sources showed the highest resistance to natural antibiotics and, compared with the bacteria isolated from well water, were susceptible to most of the tested antibiotics (Fig.4).

The enteric bacteria isolated from decentralized water supply sources were characterized by a high level of resistance to tetracyclines, aminoglycosides, unprotected beta-lactams and cephalosporins (Fig.5).

Following the research results, a similar generic spectrum of Gram-negative microorganisms was isolated from potable water samples and from the oral cavity, of which the most widely spread were bacteria of *Escherichia spp, Klebsiella spp, Citrobacter spp* and *Enterobacter spp* genera characterized by a similar antibiotic resistome, which indicated to a possible migration of microorganisms between the human organism and the environment.

Following the results of the molecular genetic studies, metagenomic DNA was isolated from potable water samples and tested for presence of the following antibiotic resistance genes: *bla*NDM; *bla*OXA48-like; *bla*Tet-M; and *bla*CTX-M.

It was established that no resistance genes were revealed in the well water samples from Velyky Berezny; this site is located in the high-mountain area which is referred to environmentally congenial regions. From total DNA of the well water

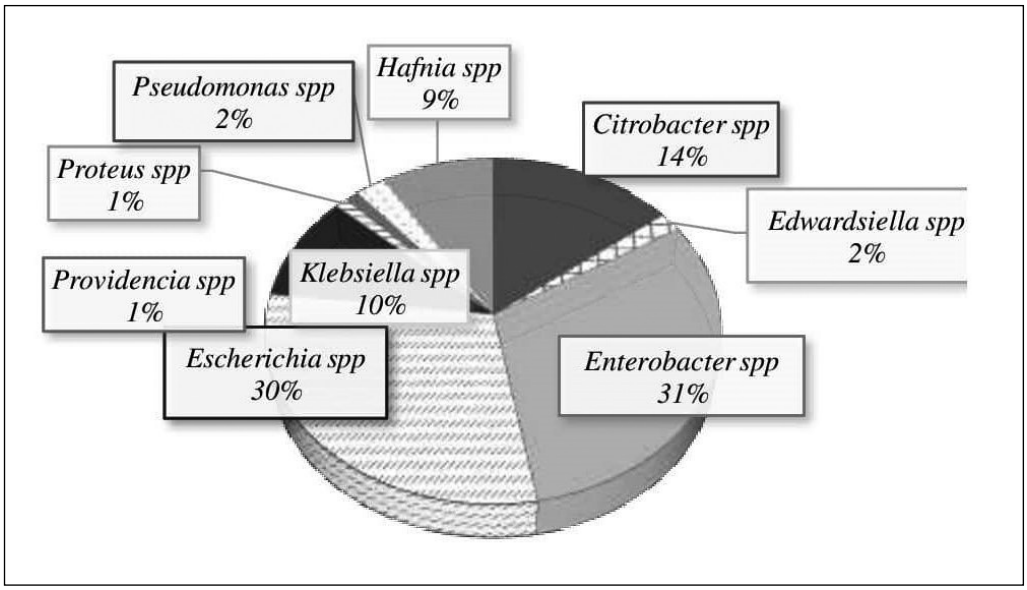

Fig.1. Specific spectrum of the microorganisms isolated from the oral cavity

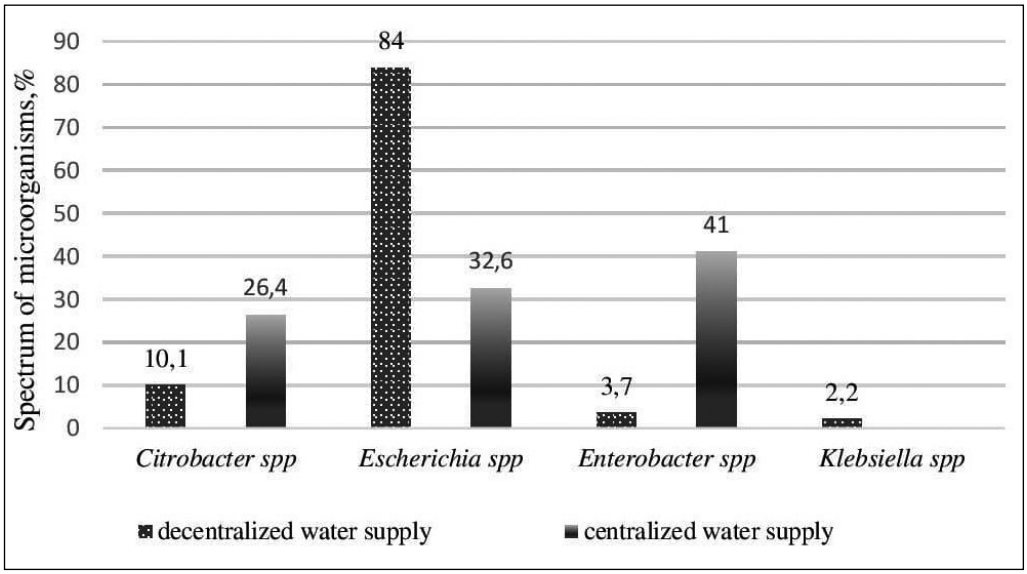

Fig.2. Microorganisms isolated from water samples taken from centralized and decentralized water supply, the city of Uzhhorod.

located in Perechyn, *bla*Tet genes were isolated. The presence of genetic resistance determinants in the well water may have been caused by a number of different reasons, including undue sanitary state of the wells, pollution of the adjacent areas, ignoring the need of regular disinfection according to sanitary requirements, incorrect disinfection, etc. It is known that water disinfection with the use of chlorine may work as a trigger, enhancing the development of resistance to medicines [12].

From the well water samples taken in Storozhnytsia, *bla*CTX-M-type genes were isolated; this site is located in a more densely populated area than the previous ones, and it is located in breach of sanitary requirements – first of all, not above the subsurface water flow which causes regular pollution of the well.

In the water samples taken from centralized water supply sources, no genetic resistance determinants were revealed.

The obtained results have proved a significant spread of genetic resistance determinants in potable water used for household needs.

DISCUSSION

The increasing spread of antibiotic resistant microorganisms is causing a global menace to public health. The excessive use of antimicrobial preparations in various fields has caused a significant growth in the spread of antibiotics in different environments. The obtained data of microbiological studies indicated to the domination of the same spectrum of microbiota belonging to *Enterobacteriaceae* family in potable water and clinical samples. The isolated representatives of Gram-negative microorganisms (*Citrobacter spp, Escherichia spp, Klebsiella spp* and *Enterobacter spp*) were opportunistic bacteria, and as such they could be agents of infectious diseases; their availability in potable water sources indicates to the imperfection of the techniques used to treat potable water. The out-dated and worn water pipelines, and violation of the rules of arrangement and maintenance of water wells and individual water boreholes increase the risk of bacteria's entering potable water. Suchlike circulation of opportunistic microorganisms is

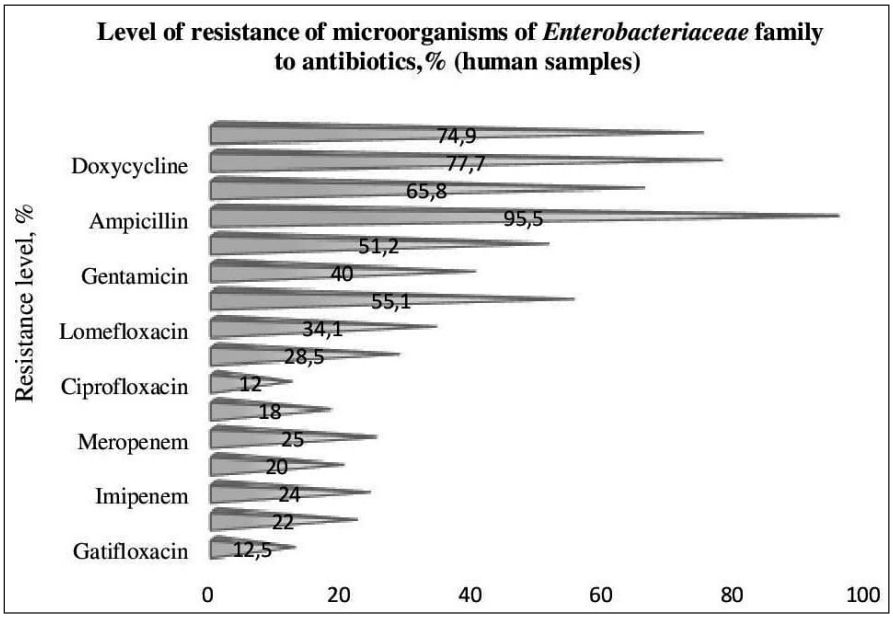

Fig. 3. Level of resistance of microorganisms isolated from human oral cavities

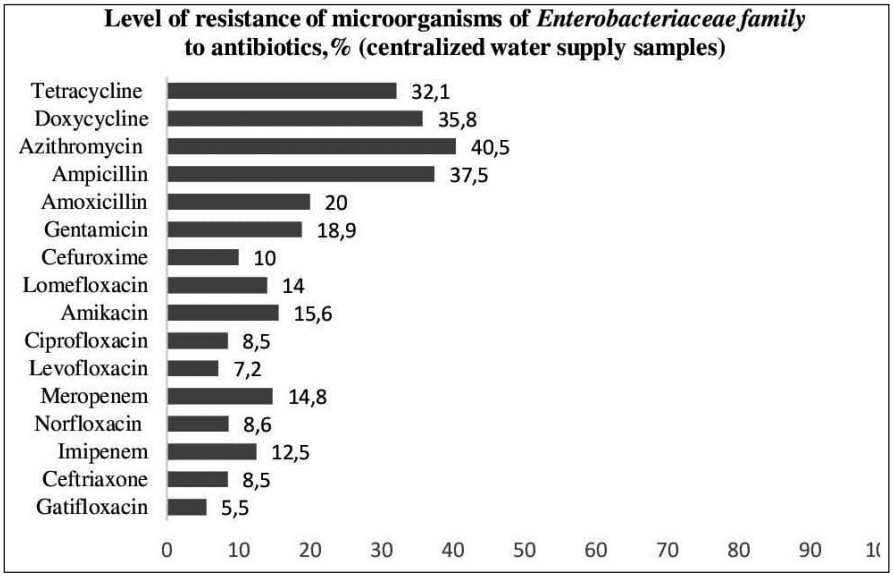

Fig.4. Level of resistance of microorganisms isolated from centralized water supply samples.

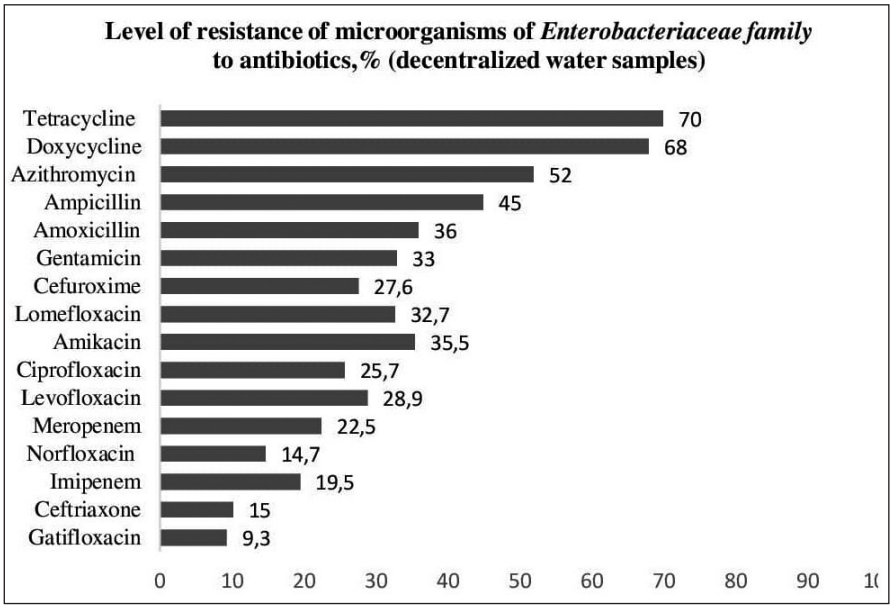

Fig. 5. Level of resistance of microorganisms isolated from decentralized water supply samples.

a source for the spread of genetic antibiotic resistance determinants.

According to the research results, the microorganisms isolated from clinical samples and water showed significant resistance to natural antibiotics, such as tetracycline, ampicillin and gentamycin, as well as to beta-lactam antibiotics. The highest susceptibility to antibiotics was registered among the enteric bacteria isolated from well water characterized by a high level of resistance to phthorchinolons (levofloxacin, ciprofloxaxin, lomefloxacin), beta-lactam antibiotics, and to natural antimicrobial preparations. The growth of the share of microorganisms resistant to new-generation antimicrobial preparations in decentralized water supply sources may be caused by the violation of disinfection processes, in particular incorrect calculation of application of disinfectants. An excessive amount of disinfectants, among which bleach powder is the most frequently used agent, may create favourable conditions for the exchange of resistance genes between bacteria by means of natural transformation [13, 14].

The obtained results of molecular genetic studies proved these assumptions, because it was in the water samples taken from the wells that genetic determinants of *bla*CTX-M and *bla*Tet resistance whose spread constitutes serious risks for human health were revealed.

Our previous studies indicated to the circulation of antibiotic resistant isolates with the water from natural ecosystems, in the doctor – patient chain, and via patients' and doctors' personal hygiene items [15,16]. The revealed regularities are of importance for the development of a perfect antibiotic resistance prevention system, and rational application of antibiotics and antiseptics [17] with due regard to their susceptibility, and search for alternative antimicrobial means [18].

The circulation of genetic resistance determinants in the food chain, in particular in water, opens the door for the humankind to return back to the pre-antibiotic era [19-21].

CONCLUSIONS

1) A spectrum of microorganisms similar to *Enterobacteriaceae* family was established for the contents of microbiota of potable water and clinical material samples, viz.: *Citrobacter spp, Escherichia spp, Klebsiella spp* and *Enterobacter spp.*
2) The reviewed resistomes of representatives of *Enterobacteriaceae* family revealed a high level of antibiotic resistance in decentralized water supply sources and in clinical samples.
3) According to the results of molecular genetic studies, no genetic resistance determinants were established for water samples taken from centralized water supply sources, but cephalosporin – *bla*CTX-M and tetracycline – *bla*Tet resistant genes were revealed in well water samples.
4) The obtained results proved the spread of antibiotic resistant microorganisms and their genetic determinants via potable water, and justified the expediency of strengthening of control over the spread of genetic resistance determinants in potable water supply sources.

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ORIGINAL ARTICLE

IMPROVEMENT OF CARDIAC FUNCTION AFTER WEIGHT LOSS PROGRAM AMONG YOUNG WOMEN

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ABSTRACT

The aim: To determine the difference between body composition and hemodynamics indices at baseline and after the weight loss program.

Materials and methods: The subject of this study was 13 young women. The weight and body composition were measured by the bio-impedance method. Hemodynamics indices were measured by the method of the thoracic rheography. The measurement of body composition and indices of hemodynamics were performed at the beginning of the weight loss program and 2 months later. The participants underwent 45 minutes per day of moderate-intensity physical activity 3 times a week.

Results: The percentage of body fat decreased in 3.9±0.37% from baseline (p=0.01) and the level of visceral fat - 1.54±0.14 units (p=0.001) respectively. Indices of hemodynamics were improved after the weight loss program. Firstly, the index of cardiac output was reduced in 1.43±1.09 l/min (p=0.019) after 2 months of the weight loss program. Secondly, the indices of peripheral resistance also have been improved. Moreover, the index of workload of left ventricle has decreased from 3.56 to 2.7 kg/m/m2 (p=0.035).

Conclusions: Our results demonstrated the improvement of indices of hemodynamics due to the normalization of body composition among young women after weight loss program.

KEY WORDS: body composition; weight loss; central hemodynamics

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INTRODUCTION

Obesity continues to be a worldwide problem, which increases tremendously at the current time. Nowadays, obesity is not the only dilemma among adults, but the youth generation is also suffering from it. Ten percent of school-aged children around the world are being overweight [1]. According to the WHO data in 2016, 39% of women and 39% of men aged 18 and over were overweight [2]. In particular, obesity is associated with diabetes mellitus, cardiovascular diseases, certain forms of cancer, sleep apnea, and other breathing disorders, etc. Obesity is defined by a body-mass index of 30 kg/m^2 or greater, but it does not take into account the level of skeletal muscle and adipose tissue distribution [3]. Previous researches showed that people with different levels of skeletal muscle and intra-abdominal fat could have similar BMI, but different metabolic effects on health [4]. For instance, visceral fat has a positive correlation with the metabolic abnormalities in comparison with fat in a lower part of the body, which has a negative connection with the metabolic disturbance. That is why, people with normal weight, but with central obesity have the same high risk of cardiovascular diseases as people with obesity or overweight with central obesity [5]. Moreover, central obesity could trigger the pathophysiological mechanism of insulin resistance. As a result, the young adult will be at a high risk to suffer from diabetes mellitus [6]. A lot of evidence suggests that physical activity could reduce the deteriorating influence of visceral fat on the human body. Skeletal muscles due to the physical activity, produce myokines that have anti-inflammatory effects on the cardiovascular system. For example, interleukin -6 (IL-6), which is increased after physical activity, is responsible for increasing glucose uptake and fat oxidation in muscles. Moreover, it increases glucose production during exercise in the liver and, enhances lipolysis in the adipose tissue [7].

The intercorrelation of muscle and adipose tissue in the human body could play an important role in its physical and functional condition.

THE AIM

Firstly, the aim of our study was to determine the body weight and its composition at the baseline and after a 2-month weight loss program. Secondly, to determine the values of hemodynamics indices at the baseline and after a 2-month of weight loss program. Thirdly, to find the connection between the indices of body composition and hemodynamics ones.

MATERIALS AND METHODS

The subject of this study was 13 young women with age from 18 to 25, who studies on the medical faculty #2 of Uzhhorod national university. The participants did not have any acute and chronic diseases. Firstly, they were informed consent about the further procedures of the study. We followed all rules of the WMA Declaration of Helsinki in the research project.

The weight, body mass index (BMI, kg/m^2), the percentage of body fat (BF, %), the percentage of fat-free mass (FFM, %), and the index of visceral fat (VF, un.) were measured by bio-impedance analysis with using body-analizator Tanita BC-601.

Mean arterial pressure (MAP, mmHg), stroke volume (SV, ml/beat), stroke volume index (SVI, ml/m^2/beat) cardiac output (CO, l/min), cardiac index (CI, l/min/m^2), systemic vascular resistance (SVR, dynes-sec/cm^{-5}), systemic vascular resistance index (SVRI, dynes-sec/cm^{-5}/m^2), the workload of the left ventricle (WLV, kg/m), the workload of the left ventricle index (WLVI, kg/m/m^2) were measured by the method of thoracic rheography. 'REOKOM' is the medical device, which we used for the measurement of hemodynamics indices.

The measurement of thoracic rheography requires 2 tape electrodes (one coil). One coil of potential electrodes should be placed around the neck, closer to the clavicle. Another one should be placed on the lower part of the chest, below the xiphoid process. The current electrodes should be placed around the head at the level of the forehead and above the left ankle joint. Since the rheograph is completed with double tape electrodes (coils), then in each of the four used in this case the coils will be involved only one tape [8]. Current cables of the remote unit of the RVG.1 rheograph (white marking) are connected to any of the tapes of the coil installed above the left ankle joint and to any of the tapes of the coil placed on the patient's head. Potential cables RVG.1.1 of the remote unit RVG.1 of the rheograph (red marking) are connected to the lower tape of the coil installed on the neck of the patient and to the upper tape of the coil installed on the patient's chest. The potential cables RVG.1.2 (green marking) are connected to one of the used potential electrodes using a special splitter, together with the corresponding potential cable of the first channel.

The measurement of body composition and indices of hemodynamics were performed at the beginning of the weight loss program and 2 months later. The participants underwent 45 minutes per day of moderate-intensity physical activity 3 times a week. They followed the individualized dietary strategy, which suggested a caloric deficit of 500 kcal/day.

Data were analyzed with a t-t for dependent samples and the multiple linear regression method. All statistical analyses were performed using the program Minitab.

RESULTS

Firstly, were performed the multiple linear regression to find the connection between BMI and the indices of body composition (table I).

Multiple linear regression was calculated to identify the connection between the dependent variable BMI and independent predictors BF, VF, FFM. Our regression model was statistically significant (p=0.001), the predicted R^2 for this model was 13.96%. The statistically significant connection BMI had only with VF (p=0.035). The coefficient of the visceral fat told us that increasing of visceral fat in 1 unit could lead to the increasing of BMI in 1.38 kg/m^2 (table II).

Regression Equation:

BMI = 20 + 0.16 BF+ 1.385 VF – 0.10 FFM

Our data showed that the average weight among participants was 79.38±12.04 kg and BMI=29.25±3.66 kg/m^2, which was identified as overweight. The body weight and body composition changes were evaluated after 2 months of weight loss program and are presented in table III. To investigate this statistically, we calculated the difference by t-test dependent samples.

Participants lost a mean of 5.49±2.02 kg (p=0.008). Furthermore, the percentage of BF decreased by 3.9±0.37% from baseline (p=0.01) and the level of VF 1.54±0.14 units (p=0.001) respectively. The data reveal significant enhancement in FFM – 4.88±0.32% (p=0.001). Also, we observed changes for hemodynamics indices after the weight loss program (table VI).

DISCUSSION

It is well known that there is a sex difference according to fat distribution. In comparison to men women have a higher percentage of body fat, which mainly deposit in the subcutaneous area. That is why the fat, which is accumulated in the gluteal-femoral area has a positive influence as in the metabolic processes as in the cardiovascular system [9]. According to our data women had increased level of visceral fat. We could predict that this happened due to the low physical activity and junk food consumption. The loss weight program helps to reduce the level of visceral adipose tissue in 1.54±0.14 units.

Our data also address that indices of hemodynamics were prone to improvement in participants. Firstly, we received the reduction of WLV in 1.65±0.27 kg/m (p=0,024) after 2 months of the weight loss program. Secondly, the CI as the CO significantly decreased in 1.29±0.56 l/min/m^2 and in 1,43±1,09 l/min respectively (p=0,031; p=0,019). Thirdly, the indices of SVR and SVRI increased significantly after the weight loss program. SVR increased in 424±36 dynes-sec/cm^{-5} and SVRI increased in 630±146 dynes-sec/cm^{-5}/m^2. These results go beyond previous reports, showing that the weight loss program, which includes aerobic exercises and dietary intervention, produced clinically important and significant improvement of body composition and hemodynamic indices [10,11].

Increased BMI, which is related to overweight or obesity (OW/OB), is associated with hemodynamic overload. As a result, people with OW/OB are likely to have higher CO, due to enlarged stroke volume and an increase of heart rate [12]. According to our data, while participant lost their weight the index of CO reduced. Firstly, our results support the previous findings that weight and adipose tissue reduction may provide with the improvement of the left ventricular function by decreasing the volume of overload and CO [13]. Secondly, we could predict that LV geometry and its workload have a connection with hemodynamic

Table I. Regression Summary for dependent variable BMI

Model Summary					
		S	R-sq	R-sq(adj)	R-sq(pred)
		1.86059	80.59%	74.12%	13.96%
Source	**DF**	**Adj SS**	**Adj MS**	**F-Value**	**P-Value**
Regression	3	129.376	43.1254	12.46	0.001
BF, %	1	0.061	0.0612	0.02	0.897
VF, un.	1	21.183	21.1834	6.12	0.035
FFM, %	1	0.023	0.0229	0.01	0.937
Error	9	31.156	3.4618		
Total	12	160.532			

Table II. Results of multiple linear regression according to the coefficients

Coefficients					
Term	**Coef**	**SE Coef**	**T-Val ue**	**P-Value**	**VIF**
Constant	20	118	0.17	0.870	
BF, %	0.16	1.19	0.13	0.897	101.61
VF, un.	1.385	0.560	2,47	0.035	2.93
FF, %	-0.10	1.25	-0.08	0.937	101.37

Table III. Comparison of indices of body composition after the weight loss program

Body composition	baseline	after 2 month	p-value
Weight, kg	79.38±12.04	73.89±10.02	0.008
BMI, kg/m^2	29.25±3.66	27.6±3.11	0.001
BF, %	37.95±4.57	34.05±4.2	0.01
FFM, %	58.78±4.32	63.66±4	0.001
VF, units	6.77±1.64	5.23±1.78	0.001

Table VI. Comparison of hemodynamics indices after the weight loss program

Indices of hemodynamics	baseline	After 2 months	p-value
MAP, mm Hg	91.67±7.11	92.2±4.33	0.746
SVI, ml/m^2/beat	44.84±14.90	40.22±15.19	0.441
CO, l/min	5.32±1.96	3.89±0.87	0.019
CI, l/min/m^2	3.00±0.97	2.29±0.41	0.031
SVR, dynes-sec/cm^{-5}	1388±418	1812±382	0.011
SVRI, dynes-sec/cm^{-5}/m^2	2415+697	3045+551	0.028
WLV, kg/m	6.31±2.59	4.66±2.32	0.024
WLVI, kg/m/m^2	3.56±1.3	2.70±0.56	0.035

components due to the Frank-Startling law and non-hemodynamic components (body composition). That is why increasing of CO and disproportional increment of body size due to the adipose tissue could lead to augmentation of the index of WLV [14].

In our findings, we observed that OW participants were likely to have lower SVR in the presence of increased CO. To some extent, this scenario has a temporary adaptive mechanism for the prevention of an increase of blood pressure, but mainly it is insufficient [15]. Other studies showed a similar association between these hemodynamics indices [16]. There is a reason to suspect, that increased level of visceral fat and subcutaneous fat in the trunk decreases artery compliance [17]. Increased CO due to the augmented blood flow leads to the rising of preload. At the same time, the overproduction of adipocytokines by visceral fat reduces NO-mediated vasodilatation, which leads to an increase in blood pressure and afterload.

After the weight loss program, SVR increased, whereas CO reduced. We could hypothesize that reducing CO, respectively, leads to the increasing in SVR. To our mind, such changes in SVR talk about the improvement of the vasomotor activity after the weight loss program. We have not received a statistically significant difference according to the index MAP

(p=0.746). That is why, during the whole period of the weight loss program, women had constant MAP. The MAP was based on the increased level of CO and decreased level of SVR before the weight loss program. The same level of the MAP mainly was based on the CO, which has decreased, and the SVR, which has increased after the weight loss program. We could suppose, that the reduction of the visceral fat during the weight loss program has prevented the irreversible changes of the SVR, and has improved the vasomotor activity of the vessels.

The % of FFM mostly describes the physical person's activity. After 2-months of the weight loss program, the % FFM has been improved. The skeletal muscle pump facilitated the venous return and as a result, the myocardium requires less force for contraction [18]. Exercise training changes the geometry of the heart and improves the pump capacity of the heart [19]. Adaptive remodeling of the heart typically occurs with the preservation of the contractility function of the heart through the oxidative energy production and by omitting fat acid oxidation [20]. Steam from this, the index of WLV decreased significantly from 3.56±1.3 to 2.70±0.56 kg/m/m^2, so we could predict that the power of contraction of LV will be more economical.

CONCLUSIONS

1. According to the results of the multiple linear regression, the reduction of the visceral fat will influence on the reduction of the BMI.
2. According to our data, body composition has been improved after the weight loss program. The visceral fat has reduced in 1.54±0.14 units and FFM has increased in 4.88±0.32 %.
3. The CO has decreased in 1,43±1,09 l/min and SVR has increased in 424±36 dynes-sec/cm^5, which together have optimized the functional condition of the cardiovascular system.

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ORIGINAL ARTICLE

ULTRAMORPHOMETRIC CHARACTERISTICS OF ACINI AND MICROVASCULATURE OF THE PANCREAS IN THE PRESENCE OF MODERATE DEHYDRATION

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ABSTRACT

The aim: The objective of our study was to evaluate the features of ultramorphometric characteristics of exocrine parenchyma and microvasculature of the pancreas in the presence of moderate dehydration by means of an experiment in laboratory rats.

Materials and methods: The experiment involved 20 mature white male rats divided into 2 groups: control and experimental (10 rats each). In the experimental group, moderate dehydration was simulated, i.e. the animals were deprived of water for 7 days, while the control rats were provided with a normal water supply during the study. Pancreatic parenchyma samples were fixed in phosphate-buffered glutaraldehyde solution and post-fixed in osmium tetroxide solution, dehydrated and embedded in a mixture of epoxy resins. Ultrastructural analysis was performed using JEOL JEM-1230 transmission electron microscope (Japan).

Results: Pancreatic electron microscopy in the presence of moderate dehydration demonstrated statistically significant changes in exocrinocytes area and exocrinocyte nucleus area which increased by 8.02% ($p = 0.028$) and 40.28% ($p < 0.001$), respectively. Among the vessels of microcirculation, the largest changes occurred in the capillaries: their lumen narrowed by 22.34% ($p = 0.002$) as compared with the control group. The cytoplasm of endothelial cells contained a large number of vacuoles and micropinocytotic vesicles.

Conclusions: Among the organelles of exocrinocytes, mitochondria appeared the most vulnerable to the effects of dehydration. They demonstrated polymorphic changes: a part of the mitochondria was hypotrophic and had partially reduced cristae, and another part was hypertrophic.

KEY WORDS: pancreas, dehydration, ultrastructure, morphometry

Wiad Lek. 2022;75(4 p2):998-1001

INTRODUCTION

Nowadays, water is considered not only a natural resource but also a factor having social significance, since the availability of sufficient amount of proper quality water is one of the main milestones of safe living conditions and development of a country [1]. Most countries of the world, including Ukraine, entered the XXI century with a set of environmental, global, and regional problems [2]. The most threatening among them are the depletion and deterioration of water resources, i.e. sources of drinking water. Today, about 1.1 billion people on Earth still do not have permanent, secure access to water supply [3]. Insufficient water intake causes a pathological condition that is accompanied by metabolic disorders and has significant consequences for population health and working capacity.

In recent decades, there has been a high growth rate of the digestive system and endocrine system diseases, which optimize the fluid volume in the body [4]. The main reasons for the development of these diseases are not only genetic factors but rather the lifestyle and external adverse factors, such as intoxication, radiation, gravity load and hypoxic stress, salts of heavy metals, injuries, etc. [5], to which the pancreas is very sensitive.

The issue of morphofunctional changes in the pancreas under the influence of various exogenous factors is important for both clinicians and morphologists. Despite the significant amount of work devoted to this problem, many issues still remain debatable, in particular, the changes in the pancreatic morphology under the influence of various types of dehydration. Taking into account the abovementioned facts, we can assume that experimental and clinical studies on the different types and degrees of dehydration will help clinicians predict the course of pancreatic diseases and provide adequate treatment.

THE AIM

The objective to study the features of ultramorphometric characteristics of acini and microvasculature of the pancreas in the presence of moderate dehydration by means of an experiment in mature laboratory rats.

MATERIALS AND METHODS

To achieve this objective, the experiment involved 20 mature white male rats kept in a stationary vivarium. The experimental study was performed in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986); the Declaration of Helsinki of

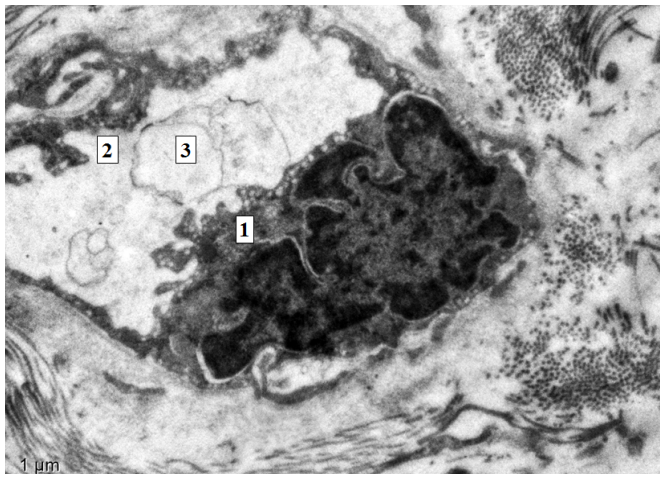

Fig. 1. Rat pancreatic capillary. Dehydration, Day 7. Endothelial cell cytoplasm (1), endothelial cell cytoplasmic processes (2), membrane structures (3). Contrast enhancement with uranyl acetate and lead citrate according to Reynolds method. x8000

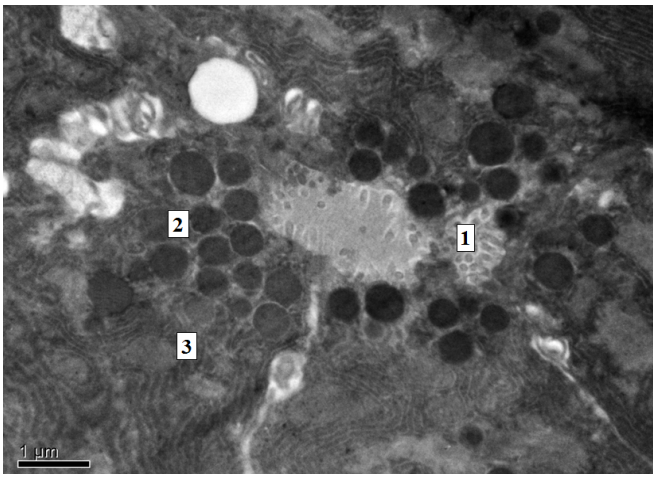

Fig. 2. Rat pancreatic acinus. Dehydration, Day 7. Acinar lumen (1), secretory granules (2), hypotrophic mitochondria (3). Contrast enhancement with uranyl acetate and lead citrate according to Reynolds method. x8000

Table I. The results of ultramorphometric studies of the pancreas in rats

Parameter	Control group (n = 10)	Dehydration (n = 10)
PA, μm²	983.4 ± 67.1	1058.8 ± 63.1
EA, μm²	149.5 ± 3.1	161.5 ± 4.5
ECA, μm²	138.7 ± 4.7	146.5 ± 4.4
ENA, μm²	10.7 ± 0.4	15.01 ± 0.4
N/C ratio, %	8.2 ± 0.9	10.2 ± 0.4
Da, μm	16.34 ± 0.49	14.49 ± 0.48
Dc, μm	7.92 ± 0.28	6.15 ± 0.30
Dv, μm	19.41 ± 0.59	15.89 ± 0.40

Note: The resulting values were presented as M ± m.

the General Assembly of the World Medical Association (1964–2000); the General Ethical Principles for Animal Experiments approved by the First National Congress on Bioethics (Kyiv, 2001); and the Law of Ukraine "On Protection of Animals From Cruelty" (2006).

Animals were divided into two groups: the control group (10 rats) and the experimental group (10 rats). In the experimental group, moderate dehydration was simulated according to the model of A. D. Sobolieva [6], i.e. the animals were deprived of water for 7 days. The control rats were provided with a normal water supply during the study. Upon reaching the required degree of dehydration, the animals were sacrificed using thiopental anesthesia overdose.

For ultrastructural examination, pancreatic samples were fixed in 4% phosphate-buffered glutaraldehyde solution and post-fixed in 1% OsO_4 solution, dehydrated, and embedded in a mixture of epoxy resins (epon and araldite). Ultrathin sections (40–60 nm) were performed on UMTP–6M ultramicrotome using glass knives. Contrast enhancement of ultramicrosections on copper grids was performed for 15 minutes with a 2% solution of uranyl acetate, followed by a lead citrate solution for 30 minutes according to Reynolds method. Ultrastructural analysis was performed using JEOL JEM-1230 transmission electron microscope (Japan). All measurements of ultrastructural components were performed using SEO Image Lab 2.0 electronic program. During the study, the following parameters were evaluated: pancreatic acini area, exocrinocytes area, exocrinocyte cytoplasm area, exocrinocyte nucleus area, the nuclear-cytoplasmic ratio of exocrinocytes, the inner diameter of arterioles, capillaries, and venules.

The results of ultramorphometric studies were analyzed by means of statistical methods using IBM SPSS Statistic 21 statistical program. The digital data were tested for normality of the distribution using the Kolmogorov-Smirnov test. Mean values were presented as M ± m. The Mann-Whitney test was used to compare the parameters in the experimental and control groups. Values of $p < 0.05$ (≤ 5%) were considered statistically significant.

RESULTS

The microscopical study in the control rats revealed that the pancreatic parenchyma was represented mainly by exocrine tissue – conical pancreatic acini, with the apical parts directed towards the secretory ducts, where the intercalated ducts of the pancreas originate from. The average size of the pancreatic acini was 983.4 ± 67.1 μm. In the acinar parenchyma, the islets of Langerhans of different shapes and sizes were seen. In the center of the pancreatic islets, there were β-cells that were localized close to each other and had oval or round shape and a light cytoplasm, while on the periphery of the islet, smaller and fewer α- and D- cells were observed. The average size of the islets of Langerhans was 13934.1 ± 688.3 μm. Endocrine cells were clearly separated from exocrine cells by connective tissue consisting of reticular, collagen, and elastic fibers.

On Day 7 of the experiment (upon reaching the average degree of dehydration), the cytoplasmic processes and cy-

toplasm of pancreatic capillary endothelial cells contained a large number of vacuoles and micropinocytotic vesicles. The luminal surface of endothelial cells had a significant number of cytoplasmic processes and reniform nodules. Endothelial cell nuclei had invaginations of the nuclear envelope and marginally placed chromatin (Fig. 1). Capillary lumens obtained irregular shape and significantly narrowed by 22.34% ($p = 0.0001$) vs. control group and contained thin membrane structures. Collagen fibers in the pericapillary zone generally maintained an orderly arrangement. The diameter of arterioles decreased by 11.32% ($p = 0.0001$), and the diameter of venules – by 18.12% ($p = 0.0001$) (Table I).

The lumens of the acini were narrowed and contained fine-grained secretory material. The acini area increased by 7.66% ($p > 0.05$) vs. the control group. The microvilli of the apical part of acinocytes were well visualized, but somewhat deformed. On the periphery of the apical cytoplasm, there were accumulations of electron-dense secretory granules of regular round shape; closer to the central part of the cell, large and irregularly shaped vacuoles were visualized. A part of mitochondria was hypotrophic and had partially reduced cristae; still, another part of mitochondria appeared to be hypertrophic (Fig. 2).

Exocrinocytes area and exocrinocyte cytoplasm area increased by 8.02% ($p = 0.028$) and 5.54% ($p = 0.326$). Exocrinocyte nucleus area and the nuclear-cytoplasmic ratio of exocrinocytes increased by 40.28% ($p < 0.001$) and 29.11% ($p = 0.96$) which is presented in Table I.

DISCUSSION

Today, there are a large number of scientific studies devoted to the study of the pathology of the pancreas, however, in the modern literature there are no systematized data on the direct anatomical and physiological features of the structure of this organ under the influence of various types of dehydration on the pancreatic parenchyma. The sources contain a lot of data on the influence of various factors on the structure of the pancreas, in particular, the group of authors P.N. Zamyatin, V.N. Likhman et al. [9] studied ultrastructural changes in pancreatic cells after modeling blunt trauma, the researchers noted changes in the structure of the pancreas, both dystrophic and destructive, revealed mitochondrial dysfunction in the form of focal lysis of membranes and granular endoplasmic reticulum, found that some of the mitochondria were hypotrophic and had partially reduced cristae, however, there were also those that were, on the contrary, hypertrophied.

A group of authors [10] studying the effect of opioids, such us nalbuphine, on the pancreatic parenchyma noted pronounced structural changes in the microvasculature in the form of micro- and macroangiopathy, followed by profound destructive changes that led to disorganization of the pancreatic tissue, which is consonant with our studies - a decrease in the area of arterioles, venules and capillaries, the gaps of which have acquired an irregular shape.

Back in 2008, a group of researchers in their work studied the effect of heavy metal salts on the pancreatic parenchyma [12]. The authors noted pronounced morphological changes in the pancreas, the intensity of which was associated with the duration of the experiment, first of all, they found mitochondrial edema with a decrease in the number of cristae, vacuolization of cisternae of the granular endoplasmic reticulum, clarification of the nuclear matrix, and chromatin condensation, however, further studies in this direction were not carried out. We have revealed a similar relationship between changes in the structure of the pancreas depending on the duration of dehydration, with the progression of the process, the cytoplasmic processes of the endothelial cells of the pancreatic capillaries and their cytoplasm contained a large number of vacuoles and micropinocytic vesicles, the nuclei of endothelial cells were with invagination of the nuclear membrane and marginally located chromatin.

In 2017, data were published on the effect of changes in water and electrolyte balance on the morphogenesis of the organ of the gastrointestinal tract - tongue [12]. The authors noted destructive processes in the microvessels, which were full-blooded, the walls were edematous, and their lumens were enlarged, which is consonant with the results of our studies.

CONCLUSIONS

Analysis of the exocrine parenchyma in the presence of moderate dehydration demonstrated statistically significant changes in exocrinocytes area and exocrinocyte nucleus area which increased by 8.02% ($p = 0.028$) and 40.28% ($p < 0.001$), respectively.

Analysis of ultramorphometric characteristics of the pancreas showed a significant decrease in the diameter of arterioles, capillaries, and venules among the vessels of microcirculation, but the largest changes occurred in the capillaries: their lumen narrowed by 22.34% ($p = 0.002$) as compared with the control group. The cytoplasm of endothelial cells contained a large number of vacuoles and micropinocytotic vesicles.

Among the organelles of exocrinocytes, mitochondria appeared the most vulnerable to the effects of dehydration. They demonstrated polymorphic changes: a part of mitochondria was hypotrophic and had partially reduced cristae, and another part was hypertrophic.

Prospects for future research. It is planned to study the features of ultramorphometric parameters of the pancreas in the presence of cellular dehydration of various degrees.

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ORIGINAL ARTICLE

ASSOCIATIONS OF POLYMORPHISMS *NOS3-T-786C, MTHFR-C667T, P2RY12-T-744C, (GPIBA) -C482T* AND GENE INTERACTIONS IN MACROANGIOPATHIES IN PATIENTS WITH COMBINED HYPERTENSION AND TYPE DIABETES MELLITUS 2

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ABSTRACT

The aim: To establish the role of allelic polymorphisms *NOS3-T-786C, MTHFR-C667T, P2RY12--744C, (GPIbα)-C482T* in the development of vascular lesions in patients with hypertension and diabetes mellitus type 2.

Materials and methods: The study included 100 patients with hypertension and diabetes mellitus type 2 (main group) and 50 patients without type 2 diabetes (control group). Patients underwent echocardiography, color duplex scanning of extracranial, brachiocephalic and femoral vessels. The distribution of allelic polymorphisms was investigated by isolation DNA from leukocytes and polymerase chain reaction (PCR).

Results: The risk of vascular damages increases 2-fold when carrying all 4 risk alleles in monozygotic genotypes of polymorphic loci in patients with hypertension with concomitant type 2 diabetes ($p<0,05$). In gene-gene interaction, the values of contributions and directions of interaction between alleles of polymorphic loci are established ($p<0,05$). Genes create a paired hierarchy of interaction according to their functional activity; the largest contribution to the probable vascular damage depends on the allelic polymorphism *NOS3-786CT* ($p<0,05$), the lowest - on the allelic polymorphism *P2RY12-744CC (H2H2)*. The genetic polymorphism of the *MTHFR* gene is independent of the influence of other studied polymorphisms ($p<0,05$); the genes *P2RY12-744CT* and *GPIbα 482CT* act synergistically with the gene *NOS3-786CT*, being in a weak negative interaction with each other.

Conclusions: Phenotypic manifestations of endothelial dysfunction may be modified by allelic polymorphism of genes associated with endothelial and platelet functions with the risk of vascular complications.

KEY WORDS: arterial hypertension, diabetes mellitus type 2, angiopathy, candidate genes

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INTRODUCTION

Multifactorial endothelial damage is reflected by the presence of a significant number of biochemical markers, including a decrease in the synthesis of nitrogen monoxide and its metabolites [1]. Therefore, the gene that are responsible for the production of endothelial nitrogen monoxide synthase (NOS3) is considered a candidate gene for the development of hypertension (AH) and type 2 diabetes mellitus (DM) complications. [2]. Given the role of nitrogen monoxide in the involvment of vascular damage in the combined course of hypertension and type 2 diabetes, the study of the association of allelic polymorphism of the NO-synthase gene is important for predicting the severity of polypathology and the effectiveness of antihypertensive therapy.

Hyperhomocysteinemia is a proven risk factor for thrombosis [3]. A slight excess of homocysteine evels is much more common and is associated with mutations and polymorphisms in the methylenetetrahydrofolate reductase gene. (*MTHFR*) [4]. Carrying the *MTHFR 677T* allele under certain conditions may cause hyperhomocysteinemia and increase the risk of arterial thrombosis [5].

According to Aga Q.A.A. et al. [6], the contribution of genetic factors to the variability of platelet reactivity is about 30%. Functional evaluation of the effect of polymorphic variants of the GRIbα gene on the rate of thrombosis was performed only in some small studies [7]. Other studies have shown that the occurrence of H2-haplotype is associated with increased platelet ADP dependent aggregation with different concentrations of inducers, which may be due to increased platelet ADP receptor expression [8]. The association of the haplotype of H2 presence with peripheral vascular thrombosis and the development of peripheral arterial damage in the absence of other influencing factors (smoking, weight gain, hyperlipidemia, etc.) was also determined [9].

THE AIM

The aim of the study was to establish the role of allelic polymorphisms *NOS3 - T-786C, MTHFR - C667T, P2RY12 -T-744C, (GPIbα) - C482T* in the development of vascular lesions of vessels with medium caliber in patients with hypertension and diabetes mellitus type 2.

Table I. Distribution of gene polymorphisms and their correspondence to Hardy-Weinberg equilibrium

Gene	Poly-morphism	Genotype	Distribution of genotypes in the control group		p1 for χ2, p2 Fisher's exact	Distribution of genotypes in the main group		p1 for χ2, p2 Fisher's exact
			N	%		N	%	
NOS3	*T-786C*	**-786CC**	4	8	p1=0,25 p2=0,35	15	15	p1<0,01 p2<0,01
		-786CT	26	52		72	72	
		-786TT	20	40		13	13	
MTHFR	C667T	667CC	21	42	p1=0,18 p2=0,26	19	19	p1<0,01 p2<0,01
		667CT	25	50		69	69	
		667TT	4	8		12	12	
P2RY12	*T-744C (H1/H2)*	-744TT (H1H1)	25	50	p1=0,51 p2=0,73	37	37	p1=0,15 p2=0,21
		-744TC (H1H2)	22	44		53	53	
		-744CC (H2H2)	3	6		10	10	
GPIbα	*C482T*	482CC	16	32	p1=0,06 p2=0,08	4	4	p1<0,01 p2<0,01
		482CT	30	60		86	86	
		482TT	4	8		10	10	

Note: Genotypes that are potential risk factors for vascular lesions in hypertension and type 2 diabetes are highlighted in bold

MATERIALS AND METHODS

The study included 100 patients with hypertension and diabetes mellitus type 2 (main group) and 50 patients with hypertension without type 2 diabetes (control group). Verification of the diagnosis of hypertension was performed using the criteria recommended by the European Society of Hypertension and Cardiology, verification of diabetes was carried out on the basis of WHO criteria. All representatives belonged to the general population of Ukrainians in Chernivtsi region (Northern Bukovyna).

The distribution of alleles of polymorphic regions was investigated by isolation of genomic DNA from peripheral blood leukocytes and subsequent amplification by polymerase chain reaction (PCR) on the amplifier "Amply-4L". All patients underwent echocardiography, color duplex scanning of extracranial vessels, duplex scanning of brachiocephalic and femoral vessels on the EnVisor HD device (Philips, USA). Attention was paid to the presence of stenotic lesions of large vessels, assessment of intraluminal diameter of vessels and thickening of the complex of intima-media walls of large vessels for verification of macroangiopathies.

For statistical analysis of the obtained results we used a a programe packages Statistica for Windows 8.0 (Stat Soft inc., USA), WinPEPI 11.43 (School of Public Health and Community Medicine, Hebrew University, Israel), MDR 3.0.2 (Perelman School of Medicine of the University of Pennsylvania, USA), GMDR 0.7 (Department of Psychiatry and Neurobehavioral Sciences University of Virginia, USA).Values are presented in the frequencies (percentage of observations to the total number of subjects). DeFinetti online programs (https://ihg.gsf.de/cgi-bin/hw/hwa1.pl) (Institute of Human Genetics, Helmholtz Center, Munich, Germany) were used to study the associations of genetic polymorphisms. Comparison of the frequency of alleles and genotypes was performed using the criterion χ2 of maximum likelihood (ML χ2) and modification of the exact Fisher's test (mid-p). At level of $p<0,05$ discrepancies were considered statistically significant.

RESULTS

At the initial stage of the study, the distribution of genotypes of polymorphisms of genes of 4 loci, respectively, according to the Hardy-Weinberg equilibrium in the main and control groups were calculated. The results of the compliance analysis are presented in table I.

In the control group there was no statistical deviation from Hardy-Weinberg equilibrium. In contrast, the genotype distribution of the main group polymorphisms for the *NOS3*, *MTHFR* and *GPIbα* genes was characterized by a probable deviation from Hardy-Weinberg equilibrium, and no statistically significant deviation from equilibrium was found for the *P2RY12* gene polymorphism.

A monolocus analysis of the associations of alleles and genotypes of the corresponding polymorphisms with the risk of vascular damage of the elastic type in patients with hypertension and concomitant type 2 diabetes showed the presence of changes between the main and control groups. Tests of associations of allelic polymorphism T-786C of the NOS3 gene are presented in table II.

The variability of the -786C allele was associated with an increased risk (2.55-fold increase) (Table II) of large vessel damage in the examined patients compared with the control. The main group also differed in the level of

Table II. Association of T-786C alleles of the NOS3 gene in patients with macrovascular lesions in hypertension and diabetes mellitus compared with control

Simple frequency of alleles	The degree of heterozygosity	The degree of homozygosity	Allelic positivity	Linear trend (Armitage's test)
		Allele risk 2 (T)		
[1]<->[2]	[11]<->[12]	[11]<->[22]	[11]<->[12+22]	General OR
OR=0,49 95%CI=0,30-0,81 χ2=7,77 p=0,005	OR=0,74 95%CI=0,23-2,43 χ2=0,25 p=0,62	OR=0,17 95%CI=0,05-0,64 χ2=7,59 p=0,006	OR=0,49 95%CI=0,16-1,57 χ2=1,48 p=0,22	OR=0,38 χ2=11,4 p<0,001
		Allele risk 1 (C)		
[2]<->[1]	[22]<->[12]	[22]<->[11]	[11+12]<->[22]	General OR
OR=2,02 95%CI=1,23-3,33 χ2=7,77 p=0,005	OR=4,27 95%CI=1,86-9,77 χ2=12,58 p=0,003	OR=5,77 95%CI=1,56-21,28 χ2=7,59 p=0,006	OR=4,46 95%CI=1,98-10,05 χ2=14,16 p<0,001	OR=2,55 χ2=11,4 p<0,001

Table III. Association of C667T alleles of the MTHFR gene in patients with macrovascular lesions in hypertension and diabetes mellitus compared with control

Simple frequency of alleles	The degree of heterozygosity	The degree of homozygosity	Allelic positivity	Linear trend (Armitage's test)
		Allele risk 2 (T)		
[1]<->[2]	[11]<->[12]	[11]<->[22]	[11]<->[12+22]	General OR
OR=1,77 95%CI=1,18-2,65 χ2=7,61 p=0,006	OR=3,05 95%CI=1,59-5,6 χ2=11,60 p=0,006	OR=3,32 95%CI=1,17-9,44 χ2=5,32 p=0,02	OR=3,09 95%CI=1,63-5,84 χ2=12,48 p<0,001	OR=1,98 χ2=10,04 p=0,002
		Allele risk 1 (C)		
[2]<->[1]	[22]<->[12]	[22]<->[11]	[11+12]<->[22]	General OR
OR=0,57 95%CI=0,38-0,85 χ2=7,61 p=0,006	OR=0,92 95%CI=0,35-2,42 χ2=0,53 p=0,86	OR=0,30 95%CI=0,11-0,86 χ2=5,32 p=0,02	OR=0,64 95%CI=0,25-1,63 χ2=0,89 p=0,35	OR=0,49 χ2=10,04 p=0,002

Table IV. Association of T-744C (H1 / H2) alleles of the P2RY12 gene in patients with macrovascular lesions in hypertension and diabetes mellitus compared with controls

Simple frequency of alleles	The degree of heterozygosity	The degree of homozygosity	Allelic positivity	Linear trend (Armitage's test)
		Allele risk 2 (T) (H2)		
[1]<->[2]	[11]<->[12]	[11]<->[22]	[11]<->[12+22]	General OR
OR=1,48 95%CI=0,88-2,49 χ2=2,16 p=0,15	OR=1,62 95%CI=0,80-3,31 χ2=0,25 p=0,62	OR=2,52 95%CI=0,56-9,01 χ2=1,37 p=0,24	OR=1,70 95%CI=0,86-3,39 χ2=2,32 p=0,13	OR=1,53 χ2=2,45 p=0,12
		Allele risk 1 (T)(H1)		
[2]<->[1]	[22]<->[12]	[22]<->[11]	[11+12]<->[22]	General OR
OR=0,68 95%CI=0,40-1,14 χ2=2,16 p=0,15	OR=0,72 95%CI=0,18-2,88 χ2=0,21 p=0,64	OR=0,44 95%CI=0,11-1,78 χ2=1,37 p=0,24	OR=0,57 95%CI=0,15-2,19 χ2=0,67 p=0,41	OR=0,65 χ2=2,45 p=0,12

heterozygosity (OR = 4.27; 95% CI = 1,86 – 9,77; p<0,05) from the control, which explained the deviation of the frequency of genotypes from Hardy-Weinberg equilibrium.

Analysis of the associations of alleles of the *C667T* polymorphic locus of the *MTHFR* gene showed a constant difference in the "risk" allele of T in patients with hypertension with concomitant type 2 diabetes. Adjusted for the linear trend, the odds ratio (OR) is 1,98 (p = 0,002), table III. The model is also characterized by an increased degree of heterozygosity and the presence of allelic positivity in

Table V. Association of C482T alleles of GPIbα gene in patients with macrovascular lesions in hypertension and diabetes mellitus type 2 compared with control

Simple frequency of alleles	The degree of heterozygosity	The degree of homozygosity	Allelic positivity	Linear trend (Armitage's test)
		Allele risk 2 (T)		
[1]<->[2]	[11]<->[12]	[11]<->[22]	[11]<->[12+22]	General OR
OR=1,84 95%CI=1,13-3,00 χ2=6,01 p=0,014	OR=11,46 95%CI=3,55-37,01 χ2=22,34 p<0,001	OR=10,00 95%CI=2,03-49,28 χ2=8,99 p=0,003	OR=11,29 95%CI=3,53-36,15 χ2=22,62 p<0,001	OR=3,29 χ2=13,33 p<0,001
		Allele risk 1 (C)		
[2]<->[1]	[22]<->[12]	[22]<->[11]	[11+12]<->[22]	General OR
OR=0,54 95%CI=0,33-0,89 χ2=6,01 p=0,014	OR=1,15 95%CI=0,34-3,93 χ2=0,05 p=0,83	OR=0,10 95%CI=0,02-0,49 χ2=8,99 p=0,003	OR=0,78 95%CI=0,23-2,63 χ2=0,16 p=0,69	OR=0,29 χ2=13,33 p<0,001

Table VI. GRS for two-locus, three-locus, and four-locus models of vascular complications in patients with hypertension and diabetes type 2

Genes with polymorphic loci	OR and 95% CI	χ2, p
MTHFR	1,62 (0,50 – 5,32)	0,56; 0,46
MTHFR+ NOS3	1,94 (0,80 – 4,60)	2,25; 0,13
MTHFR+ P2RY12	1,73 (0,70 – 4,67)	1,36; 0,24
MTHFR+GPIbα	1,48 (0,61 – 3,80)	0,75;0,39
NOS3+P2RY12	2,05 (0,83 – 5,46)	2,40; 0,12
NOS3+GPIbα	1,75 (0,73 – 4,45)	1,57; 0,21
P2RY12+GPIbα	1,54 (0,61 – 4,17)	0,81;0,37
MTHFR+ NOS3+P2RY12	2,08 (0,96 – 4,71)	3,45;0,063
MTHFR+ NOS3+GPIbα	1,87 (0,87 – 4,11)	2,56;0,11
NOS3+ P2RY12+GPIbα	1,91 (0,88 – 4,32)	2,65; 0,4
MTHFR+P2RY12+GPIbα	1,67 (0,76 – 3,79)	1,63;0,20
MTHFR+NOS3+P2RY12+GPIbα	2,07 (1,05 – 4,32)	3,96; 0,046

Table VII. Models of gene-gene interactions in patients with vascular lesions of large caliber in the combined course of hypertension and diabetes mellitus type 2

Combinations of polymorphisms in the model	Training balance accuracy	Testing balance accuracy	Test the significance of the model (sign (p) test)	Reproducibility of the model (CV consistency)
MTHFR+NOS3+P2RY12+GPIbα	0,82	0,76	9(0,011)	10/10
NOS3+ P2RY12+GPIbα	0,78	0,77	10(0,001)	10/10

the main group (respectively 3,3 and 4,8 times at p<0,001).

The ratio of alleles of the ADP receptor gene (*T-744C, P2YR12*) in patients was quite uneven: in 63,5% ± 3,15% of cases the presence of *-744T* allele, in 36,5% ± 3,15% - *-744C*-allele (p<0.05). The distribution of genotypes in the main group (H1/H1; H1/H2; H2/H2) of carriers of this polymorphism was determined as follows: H1/H1 homozygotes accounted for 37,0% of cases, homozygotes with the presence of the "risk" allele - H2/H2 – 10,0 %, heterozygotes H1/H2 – 53,0% (p<0,05), table IV.

The frequency distribution of alleles of the platelet glycoprotein receptor gene (*C482T, GP1bα*) was more uniform than the alleles of the P2RY12 receptor. Thus, the *482C* allele was found in 90% of patients (its frequency in the group – 47,0 ± 1,8%), and the *482T* allele - in 96% of patients (total frequency in the group – 5,0 ± 1,8%). However, the analysis of associations of the *C482T* polymorphic locus of the *GPIbα* gene revealed a probable excess of the T allele frequency in patients with hypertension with concomitant type 2 diabetes (OR = 3,29 in the trend test, increasing the degree of heterozygosity for the allele " risk ", increase in the degree of allelic positivity (p<0,001)), table V.

Thus, based on data analysis, it can be assumed that allelic polymorphisms of the *NOS3*, *MTHFR*, and *GPIbα* genes can be considered as genetic markers of markers associated with vascular damage in the general cohort of patients with combined hypertension and type 2 diabetes.

Our monolocus analysis of allelic polymorphisms of four genes revealed a significant difference (p<0,05) in reducing the incidence of "protective" alleles and genotypes in pa-

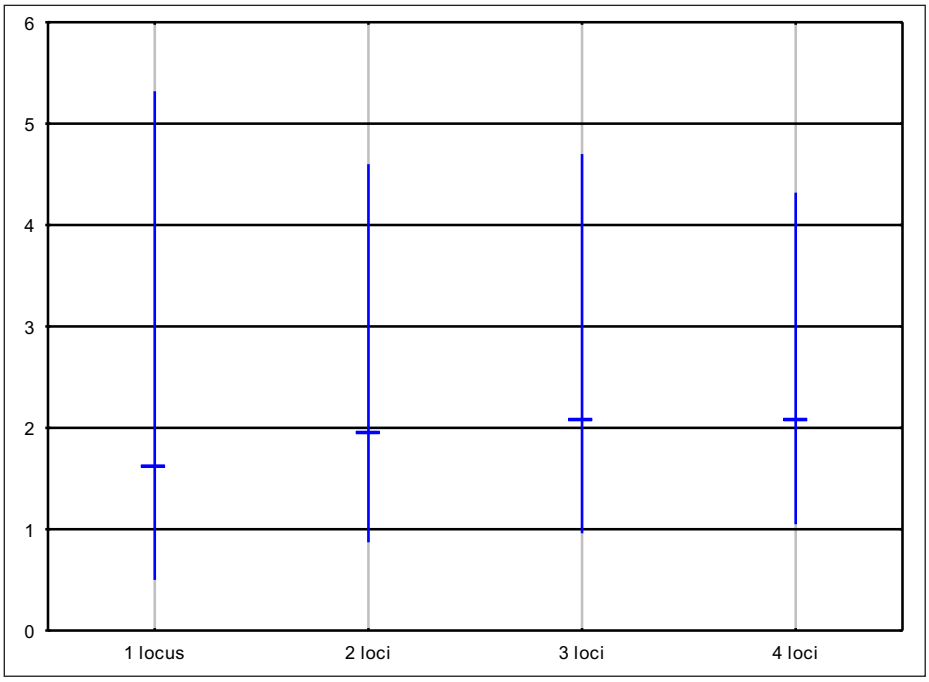

Fig. 1. Changes in the GRS index depending on the frequency of interaction of polymorphic loci of genes responsible for endothelial dysfunction.
Note: GRS for the models with different number of loci (from 1 to 4). The estimation of risk of macrovascular damage in patients with hypertension and diabetes mellitus type 2 (OR (95% CI)).

tients with hypertension and diabetes with macrovascular lesions, but monolocus analysis of the frequency of "risk" alleles and genotypes found only a tendency to increase their frequency in patients of the main group (p> 0,05).

To validate gene interactions, analysis was performed using the Genetic Risc Score (GSR) interlocus conjugation model. According to this model, in the main and control group for the *GPIbα* gene the frequency of "risk" alleles was 53% and 38%, for the *P2RY12* gene - 36% and 28%, for the *NOS3* gene - 51% and 34%, for the MTHFR gene - 46% and 33%, with a total median frequency of 48,5% for the main group and 33,5% for the control group. On average, there were 1,33 alleles per person in the control group, and 1.86 alleles in the main group, which was in 1,42 folds greater (t = 3.07; p = 0,022; p = 0,04 by median Mood test). Thus, in contrast to the single-locus model of allelic polymorphism, carriers of "risky" allelic polymorphisms simultaneously for all 4 genes significantly (p<0,05) increases the likelihood of macrovascular complications, which depends on multilocus gene interaction. GRS values for complications dependent on genotype interactions were calculated from models of two, three and four-gene interactions. Indicators of the ratio of chances (OR) with confidence intervals and the corresponding frequencies of risk genotypes are given in table VI.

Thus, the overall risk of macrovascular complications in patients with hypertension and diabetes mellitus 2 is a measure of the effect of a combination of polymorphisms of the four so-called "risky" alleles, of course, without considering the possible influence of additional polymorphisms or mutations in patients' genotypes.

Changes in the GRS index depending on the type of multiple model (including loci of models *MTHFR* (1 locus), *MTHFR* + *NOS3* (2 loci), *MTHFR* + *NOS3* + *P2RY12* (3 loci), *MTHFR* + *NOS3* + *P2RY12* + *GPIbα* (4 loci)) are illustrated in fig. 1.

Given that the regions of the studied polymorphisms are located on different chromosomes, it is possible that there is an epistatic or complementary interaction of the genes included in our analysis with each other. To evaluate these types of interactions, namely, how mononucleotide polymorphisms affect each other's function, we modeled the interaction of nucleotide polymorphisms by the method of multifactorial dimensional reduction (MDR). According to the analysis of this method in the sample of sick and healthy people, the optimal models of combinations of gene interactions were determined, with the establishment of their accuracy and reproducibility. Forced Search Algorithm was used to analyze the interaction models, which assessed the nature of genotype combinations in the direction of the development of macrovascular complications in patients with hypertension and type II diabetes. As a result, we selected 2 models with the highest degree of reproducibility (10/10 - 100%) - for three loci of polymorphism and for four loci of polymorphism, table VII.

Thus, the risk of developing macrovascular complications in patients with hypertension and diabetes mellitus type 2 associated with allelic polymorphism depends not only on the type of monolocus polymorphism, but has a more complex nature of dependence due to intergenic multidirectional interactions.

DISCUSSION

Analysis of current literature data on the association of different polymorphic markers of the eNOS gene and hypertension shows contradictions. For example, in a Canadian study, an association of the polymorphic allele *-786T> C* with the risk of developing hypertension was found, but in Japanese studies, the existence of this association was not confirmed [10]. The polymorphic variant of the *Glu298Asp* gene in the eNOS gene has been shown to be associated with the risk

of acute myocardial infarction [11], coronary artery disease (CAD) [12], AH [13]. The minisatellite polymorphism eNOS 4a / 4b has been studied in detail. In the Chinese population, allele 4a is defined as an independent risk factor for atherosclerosis and diseases that are accompanied by impaired formation of nitrogen monoxide, including hypertension [14]. However, in another study, on the contrary, the protective role of the 4a allele in the development of stroke in patients with hypertension [15]. Genotypes *eNOS-786C / C* and allele *eNOS-922G* in case-control studies were more common in patients with hypertension compared with the control group [16].

An association with arterial thrombosis depending of the *C667T* polymorphism of the *MTHFR* gene has been found in Chinese populations [17], Turkish population [18], Polish population [19], in Italians [20].

CONCLUSIONS

1. The risk of vascular damages increases 2-fold when carrying all 4 risk alleles in monozygotic genotypes of polymorphic loci in patients with hypertension with concomitant type 2 diabetes (p<0,05).
2. In gene-gene interaction, the values of contributions and directions of interaction between alleles of polymorphic loci are established (p<0,05). Genes create a paired hierarchy of interaction according to their functional activity; the largest contribution to the probable vascular damage depends on the allelic polymorphism *NOS3-786CT* (p<0,05), the lowest - on the allelic polymorphism *P2RY12-744CC (H2H2)*.
3. The genetic polymorphism of the *MTHFR* gene is independent of the influence of other studied polymorphisms (p<0,05); the genes *P2RY12-744CT* and *GPIbα 482CT* act synergistically with the gene *NOS3-786CT*, being in a weak negative interaction with each other.

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REVIEW ARTICLE

RESOURCES OF CARDIOLOGICAL CARE (ON THE EXAMPLE OF THE KYIV REGION OF UKRAINE)

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ABSTRACT

The aim: To analyze the network, resources of outpatient clinics in the Kyiv region (Ukraine) that provide cardiac care.

Materials and methods: With the help of the medical - statistical method the analysis of the network of outpatient clinics of the Kyiv region which render cardiological medical care and their resources in dynamics from 1995 to 2019 was carried out. During the analysis the methods of statisticalgrouping, compilation, generalization, statisticalcomparisonwere used. The materials for the analysis were the data of reporting statistical forms № 20 "Report of the treatment and prevention institution" and form № 17 "Report on medical staff" of the Kyiv region individual institutions and districts, as well as statistical directories of the information-analytical center.

Conclusions: On the basis of the analysis of the network, resources and activity of outpatient clinics of the Kyiv region that provide cardiac care the existing problems of this type of care were revealed. The provision of cardiac diagnostic tests over five years did not change, which is proved by analysis made. It is established that at the present stage of providing high-quality and affordable cardiac medical services within the existing system of cardiac outpatient care to the population of the Kyiv region has great difficulties and needs to be solved.

KEY WORDS: network, resources and activities of outpatient clinics; cardiac care provision

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INTRODUCTION

The leading role in maintaining and strengthening the health of the population belongs to outpatient care in which up to 90% of patients who seek medical care must begin and complete their treatment [1]. And, first of all, it concerns the availability and quality of cardiac care, including its high-tech types, as currently, diseases of the circulatory system (DCS) remain the leading cause of death and disability in most European countries, including Ukraine [2]. This determines their significant medical, social and socio-economic importance [3-5].

As the experience of many countries shows, the effectiveness of the cardiological service functioning, the provision of high quality medical aid depends on the use of promising organizational and advanced medical technologies, the level of training of highly professional personnel, their economic incentives [6].

Under Ukrainian current economic conditions, associated with the reduction of public investment opportunities, there is growing interest in alternative forms of social facilities financing. There are a lot of examples of such an alternative form of financing – this is public-private partnership.

An urgent problem of this country health care system is the need to move it to progressive models of development that ensure the structural efficiency of medical sector [7].

To solve this problem it is necessary to conduct a comprehensive analysis of outpatient clinics activities, evaluation of their experience. High cardiac morbidity requires the improvement of outpatient care facilities that provide cardiac aid, introduction of new organizational forms of medical care, introduction of advanced technologies.

THE AIM

The aim was to analyze the network, resources of outpatient clinics in Kyiv region that provide cardiac care.

MATERIALS AND METHODS

With the help of the medical - statistical method the analysis of the network of out-patient clinics of the Kyiv region which render cardiological medical care and their resources in dynamics from 1995 to 2019 is carried out. During the analysis the methods of statistical grouping, compilation, generalization, statistical comparison were used. The materials for the analysis were the data of reporting statistical forms № 20 "Report of the treatment and prevention institution" and form №17 "Report on medical staff" of individual institutions and districts in the Kyiv region, as well as statistical directories of the information-analytical center.

REVIEW AND DISCUSSION

The analysis of the network, staffing of the cardiology service of Kyiv region in 2014-2019 showed that cardiac care for the

Table I. Cardiology consulting rooms of Central District Hospitals

Name of the region	Number of consulting rooms
Kyiv region (total)	27
District	24
Bila Tserkva	1
Boguslavsky	1
Boryspil	1
Borodyansky	1
Brovarsky	2
Vasylkivsky	1
Vyshgorod	1
Ivankivsky	1
Kyiv-Sviatoshynskyi	2
Makarivsky	1
Myronivsky	1
Obukhov	1
Pereyaslav-Khmelnytsky	1
Rokytnyansky	1
Skvyrsky	1
Tarashchansky	1
Tetiivsky	2
Fastivsky	1
Bila Tserkva	2
Irpin	1
Fastiv City Hospital	1
Regional institutions on the territory of Kyiv	1
Region children's hospital №1 (Boyarka)	1
Region children's hospital №2 (Bila Tserkva)	1

population of the mentioned area is provided by the cardiological consulting rooms of Central District Hospitals (CDH) (Table I), which had 38 outpatient positions of cardiologists (by 01.01. 2019). During 2014 - 2019 there were no significant changes in the network of cardiac offices of the Kyiv region.

Thus, there are a total of 27 cardiology consulting rooms in the Kyiv region, and 24 of them are in the districts of the region and 3 in regional institutions.

In total, from 2014 to 2019, there were 102.75 positions of cardiologists in the Central District Hospitals, including 38.00 positions in outpatient clinics and 64.75 positions in hospitals (Table II).

There were no cardiologists' positions inStavyshche, Polissya districts and Rzhyshchiv by the end of 2018.

For 15 years (1995 – 2014) the number of cardiologists decreased from 108 persons in 1995 to 79 in2014 in the Kiev region, but then from 2014 to 2019 on the contrary it increased to 91 by 2019.

Dynamic analysis of the state of the cardiology network in the Kyiv region from 2014 to 2019 showed that the development of the material and technical base of the cardiology service in the Kyiv region is insufficient.

Besides In the Kyiv region there is also a downward trend in cardiac beds, which in 1995 numbered 1160, i. e. 6.1 per 10 thousand of population; in 2014 - 710, which corresponds to 4.08 per 10 thousand of population, and in 2019 year - 513, which corresponds to 2.97 per 10 thousand of population of the region. In fact, the reduction was almost 56%, i. e. in the Kyiv region every second cardiac bed was reduced.

From 29 districts of the Kyiv region 10 districts are equipped with minimal diagnostic equipment for the diagnosis of cardiac pathology (Table III).

In 14 districts there are no echocardiographs, in 16 districts they do not work, or there are no bicycle ergometers, and from 8 districts which have bicycle ergometers, in three they are 1982-1985 years of release. Only 3 districts of the region, Kyiv Regional Hospital №2 and Kyiv Regional Cardiology Dispensary, can perform daily ECG and blood pressure monitoring. Of the 15 districts, i.e. a half do not have the opportunity to conduct blood tests for lipids. Holter ECG and blood pressure monitoring of patients can be performed only in 4 districts of the region, Kyiv Regional Hospital N 2 and Kyiv Regional Cardiology Dispensary.

The dynamics of indicators of cardiological diagnostic tests for five years shows that almost nothing has changed for the better, and BEM and CRFC became less.

The Kyiv region of Ukraine remains practically the only one in the country where a cardiac surgery center which carries out methodical work with the network of cardiac Central District Hospitals.

For a number of years, cardiovascular diseases and exacerbations of their chronic forms occupy one of the leading places in the structure of the general morbidity of the population of Ukraine. Increasingly, cardiovascular diseases are registered in people of young working age, which causes significant economic damage. The proportion of diseases of the circulatory system remains stably high, and diseases of the circulatory system continue to occupy a leading place in the structure of total mortality of the population.

Therefore, the provision of highly specialized cardiological care to the population of the country and, in particular, the Kiev region should be one of the priority tasks of public health.

Improving medical care for patients with cardiovascular diseases will require equipping specialized medical and preventive institutions with medical diagnostic equipment, modernizing hospitals in medical and preventive institutions of a cardiological profile. increasing the volume of specialized (interventional and cardiac surgery) types of care for cardiological patients.

The use of all types of emergency care for cardiological patients (medication, endovascular, cardiac surgery) requires appropriate staffing and regulatory and methodological support.

.It is also necessary to improve the continuity in the provision of medical care at the outpatient and polyclinic stages, which will help reduce mortality and disability.

Table II. Number of outpatient positions of cardiologists in the Kyiv region

Job title	Including in the polyclinic (outpatient clinic) dispensary, consultations	
	full-time employees	Position held
Kyiv Region	38.00	35.75
Districts	31.00	28.75
Baryshivsky	0.25	0.25
Bila Tserkva	1.00	1.00
Boguslavsky	1.00	1.00
Boryspil	1.50	1.00
Borodyansky	1.00	1.00
Brovarsky	2.00	2.00
Vasylkivsky	1.75	1.75
Volodarsky	0.50	0.50
Vyshgorod	1.25	1.25
Zgurivsky	0.50	0.50
Ivankivsky	1.00	1.00
K-Sviatoshynsky	3.50	3.50
Kagarlytsky	0.50	0.00
Makarivsky	1.00	1.00
Myronivsky	1.00	1.00
Obukhov	0.50	0.50
P-Khmelnytsky	1.00	1.00
Polissya	0.00	0.00
Rokytnyansky	1.00	1.00
Skvyrsky	1.00	1.00
Stavyshchansky	0.00	0.00
Tarashchansky	0.50	0.50
Tetiivsky	1.00	1.00
Fastiv	1.00	1.00
Yagotinsky	1.00	1.00
Bila Tserkva , town	4.00	4.00
Irpin, town and Bucha, town	1.50	1.50
Berezan, town	0.00	0.00
Rzhyshchiv	0.00	0.00
Region hospital №2	2.50	2.50
Region cardio dispensary	4.50	4.50

Table III. Dynamics of indicators of provision of cardiological diagnostic examinations, 2014 -2018

N	District	ECG	EchoCG		BEM		PCCS		Holter		Angiography
		2014-2018	2014	2018	2014	2018	2014	2018	2014	2018	2014-1018
1	Total by districts	30	15	16	14	8	0	0	3	4	1
2	Total, regional	2	2	2	2	2	2	1	2	2	1
3	Total by district	32	17	18	16	10	3	1	6	6	2

CONCLUSIONS

It is established that at the present stage of providing high-quality cardiac medical services within the existing system of cardiac outpatient care to the population of the Kyiv region has great difficulties. The problem of organizing cardiac care for the rural population of Kyiv region does exist and needs to be solved.

Prospects for further research. The results obtained will be used in substantiation of conceptual directions of

improvement of cardiac outpatient care to the population of the Kyiv region and development of functional-organizational model of the regional center of cardiology and cardiac surgery on the principles of public-private partnership (PPP).

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REVIEW ARTICLE

LEGAL OBLIGATIONS IN THE CONTEXT OF HUMAN ORGANS AND TISSUES TRANSPLANTATION

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ABSTRACT

The aim: To highlight and analyze the nature of certain legal obligations occuring in the process of human organs and tissues transplantation, in particular, the following obligations: compliance with regulatory and medical requirements for organ and human tissues transplantation, obtaining the donor's consent for organs and tissues transplantation, organs or tissues transplantation on a non-commercial basis.

Materials and methods: Methodologically, this work is based on the system of methods, scientific approaches, techniques and principles with the help of which the realization of the research aim is carried out. There have been applied universal, general scientific and special legal methods.

Conclusions: Analyzed regulatory and medical requirements, indicate the complexity of the transplant process, as well as the need for strict compliance with established regulations and rules. For the whole complex transplant procedure, one of the key points is the donor's consent (disagreement) to remove anatomical materials from him. The obligation to perform organ or tissue transplantation on a non-commercial basis has a dual purpose: first, to prevent offenses and legal violations in this area; secondly, to determine as transparently and clearly as possible the list of costs incurred by the donor in connection with the organs and tissues removal and subject to reimbursement, the procedure for such reimbursement and its reasonable, acceptable and sufficient amount.

KEY WORDS: obligations, law, transplant, donor, recipient, donation

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INTRODUCTION

Several years of experience in transplantation have demonstrated the importance of this institute in medicine, as well as the need for its proper regulation at the level of international and national legislation [1]. At the present stage, transplantation of human organs and tissues should be an effective means of saving lives, restoring health and having a significant effect on the duration and quality of population life. As the medical procedure itself is complex in nature, the need to identify and further study the legal responsibilities of the transplant procedure is of particular importance. After all, they show the need for participants' increased responsibility and strict compliance with legal requirements in the relevant activities. Responsibilities allow us to emphasize the importance of acting in accordance with the existing legislation considering medical intervention. In this study, we will focus on the justification of certain legal obligations arising from the connections in the field of human organs and tissues transplantation.

THE AIM

The aim of the work is, therefore, to study and analyze the nature of certain legal obligations occuring in the process of human organs and tissues transplantation, in particular, the following obligations: compliance with regulatory and medical requirements for organ and human tissues transplantation, obtaining the donor's consent for organs and tissues transplantation, organs or tissues transplantation on a non-commercial basis.

MATERIALS AND METHODS

Methodologically, this work is based on the system of methods, scientific approaches, techniques and principles with the help of which the realization of the research aim is carried out. There have been applied universal, general scientific and special legal methods. In particular, the formal-legal method, which is used to study the internal form of legal phenomena and processes, allowed to formulate the concept of relevant legal obligations in the field of transplantation on the basis of generalization and identification of features. The object of the formal legal method is the sources of law at all levels, the law and the legal systems. In turn, the comparative law method, which involves comparing legal phenomena having similar properties, allowed us to identify common and different aspects that reveal the nature of our legal obligations within different national legal orders (based on a comparison of legal regulations of some foreign states, including Ukraine).

REVIEW AND DISCUSSION

Obligation to comply with regulatory and medical requirements for human organs and tissues transplantation . We

consider this responsibility to be one of the most important and fundamental, as it emphasizes the complexity of the transplant process, as well as the need to take into account legal requirements and medical indications for its proper implementation.

According to the Convention on Human Rights and Biomedicine, removal of organs or tissues from a living donor for transplantation is possible only for the recipient treatment, as well as in the absence of the required organ or tissue of the deceased and other (alternative) treatment [2]. In turn, based on the Additional Protocol regulations of the Convention on Human Rights and Biomedicine on human organs and tissues transplantation, as well as the content of other international instruments, it is possible to identify the following requirements without which transplantation is impossible, namely:

1) removal of organs and tissues from a living donor is allowed only for the recipient therapeutic purposes, provided that the deceased does not have the required organ or tissue, as well as if there is no alternative method of treatment [3]; such a procedure can be used only after a careful assessment of the feasibility and effectiveness of other therapies [4];

2) transplantation intervention is possible only if professional duties are performed and professional standards are observed [3]; removal of organs and tissues should be carried out in appropriate places, in particular, in public or private medical institutions that are provided with the necessary personnel and equipment [5]; the doctor performing the transplant must have special medical knowledge and techniques through special training, education and practice [4]; relevant professionals should take all reasonable steps to minimize the health risks of transplant participants.

3) removal of organs and tissues is possible only in the absence of a serious risk to the life and health of the donor [3]; in case that such a risk still exists, removal may be carried out only when it is justified by the donor's motivation, family ties to the recipient and medical indications; at the same time, the state is allowed to prohibit such seizures [5];

4) the donor is provided with information about the purposes, nature, consequences and risks of organs and tissues removal, as well as his rights and guarantees provided by law;

5) for the organs and tissues removal from a deceased person it is necessary, first of all, to certify his death, as well as to obtain consent due to the prescribed by law [3]; organs and tissues removal from a deceased person is not allowed if there were obvious or previous objections, including taking into account the religious or philosophical beliefs of such person [5].

With regard to the death certificate of the deceased, whose organs and tissues will be removed for transplantation to the recipient, the Declaration of the World Medical Assembly on human organ transplantation requires the statement of two or more independent doctors (each of them) who do not participate in the transplantation procedure. At the same time, physicians should be guided by the scientific methods and criteria known at the time, as well as ethical requirements and professional standards [4]. According to the WHO Guidelines for Transplantation of Human Cells, Tissues and Organs, such rules, as well as the fact that doctors establishing the death of a person, should not be physicians of potential organs and tissues recipients, are aimed at preventing conflicts of interest between health professionals [6].

The above requirements that must be met during transplantation can be also found in national legislation. Thus, the Federal Law of Germany «On Donation, Collection and Transplantation of Organs and Tissues» establishes the following conditions under which it is possible to take organs and tissues from a living donor for transplantation to another person: first, the donor has reached adulthood and has legal capacity; secondly, the transplantion, according to the doctor, is able to support the recipient and cure him of a serious illness, prevent exasperations or alleviate symptoms; thirdly, the intervention must be performed by a physician [7].

Under Argentine federal law on transplantation, it can only be performed by a doctor or a team of doctors who are registered and authorized by the judicial authorities. For such doctors, their accreditation, training and experience in this field are examined . Organs and tissues removal from a living donor is possible only if he is 18 years old, and if the recipient is his blood relative or was adopted to the 4th generation, or a wife (husband), or a person who, without being a wife (husband), is in relationship with the donor for at least 3 years on an ongoing basis. In the case of underage donors, they may donate their organs and tissues with the prior consent of their legal representative and are recipients relatives. A doctor's opinion on such a possibility is also required for a transplant [8].

Therefore, the Tajikistan Republic legislation of presupposes the following: first, the transplant can be performed only for the recipient's health reasons and in case of the alternative treatment method absence, that is comparable in degree of effectiveness; secondly, the donor voluntarily and consciously agreed to donate organs and tissues; thirdly, the donor is warned about possible complications for his health after his organs and tissues removal; fourth, the donor has undergone a full medical examination and there is the medical council conclusion on the possibility of organs and tissues removal; fifth, the donor is warned about the consequences of his disagreement during the final period of organs and tissues preparation for transplantation. In the case of a living donor, the transplant must be genetically related to the recipient, except in the case of a bone marrow transplant [9].

As for Ukrainian legislation, transplantation is possible only if the necessary medical indications are provided, as well as the voluntary consent of an informed person with legal capacity is given: at the same time, medical evidences are established by the doctors council of that health care institution where the patient is being treated or being in dispensary. Withdrawal of anatomical materials from the donor is carried out only with the appropriate conclusion of the medical council, provided after a complete medical

examination of the donor, and if the damage to his health is less than the danger to the recipient life [10].

OBLIGATION TO OBTAIN THE DONOR'S CONSENT FOR ORGANS AND TISSUES TRANSPLANTATION

To a greater extent, we will pay attention to the cases of obtaining consent for a posthumous transplant. Foreign practice in this regard has developed two main models (approaches) to the formation of the preconditions for its implementation:

1) «presumption of consent» (opt-out) (objection model) – according to which the removal and further organs and tissues use of the deceased is carried out provided that he has not objected to it during his life, or if such objections are not expressed by his relatives or legal representatives; this model is provided by the laws of Belarus, Israel, Spain, Austria, Great Britain and others;

2) «presumption of dissent» (opt-in) (informed consent model) – according to which the removal and further organs and tissues use of the deceased is carried out provided that he clearly expressed his informed consent to such actions after death, or if members of his family agree; thus, the lack of the donor or his relatives consent means the refusal of the transplant; this model is used, in particular, in the United States, Denmark, Ukraine, Portugal, Australia, Canada and other countries [11].

Under the opt-out model, states apply either «soft» or «hard» law. In the case of «soft» one – family members of the deceased may refuse to transplant his anatomical materials. In case of hard – organ transplantation is allowed for everyone who has not given up on it for life [12].

At the same time, the approaches we have given concerning giving consent are quite debatable. On the one hand, the presumption of consent approach can be justified by the fact that it helps to improve the coverage of needs for donor organs and tissues among the population of a country. On the other hand, let us agree with M. Laszewska-Helrigel that such a commitment cannot be justified by the public interest. The obligation of the state to protect the lives of recipients cannot be used as an excuse. The opt-in model better meets the needs of society. It does not impose any additional obligations on citizens. Moreover, the researcher adds, the experience of countries around the world does not prove a significant increase in the number of donors on the opt-out model. Other methods can be implied for this [13].

It should be added that for several decades, informed consent to medical intervention has been considered an international standard, enshrined in the Convention on Human Rights and Biomedicine, the European Charter of Patients «Rights, the World Medical Assembly's Declaration on Patients» Rights and a number of other international instruments. Yes, Art. 5 of the Convention on Human Rights and Biomedicine regulates the legality of any medical intervention only after voluntary and informed consent. The relevant consent may be revoked at any time by the person. Giving consent is preceded by the person receiving information about the purpose, nature, risks and consequences of the intervention. However, the Convention prohibits the organ or tissue removal from a person who is unable to consent. In this case, as an exception, prescribed by law, a regenerative tissue can be removed from such a person, if: first, the recipient of the donor is a brother or sister; second, there is no compatible donor who is able to give consent; third, transplantation aims to save the patient's life; fourth, there are no objections from a potential donor [2].

Therefore, the issue of consent (disagreement) for the transplantation of anatomical materials is stipulated in the national legislation on transplantation. After all, this is a key prerequisite for «starting» the process.

Swiss federal transplant law requires a lifelong donor to transplant after his or her death. If there is no such consent or disagreement, the medical institution must first ask the immediate relatives of the deceased whether they were aware of their consent for life. If such information is not known, the transplant may be performed with the consent of the deceased donor's close relatives. If there are no such relatives or they cannot be contacted, the transplant cannot be performed. Provided that the deceased left the decision to transplant his organs and tissues to a trustee, it is his will that must be accepted by the medical institution, and it has priority over the decision of close relatives [14].

Under German federal transplant law, a person has the right to consent to a transplant of his or her organs and tissues, to refuse to do so, and to transfer the right to make a decision in this regard to a trustee. Such consent may include the specification about certain organs and tissues. At the same time, consent to transplantation can be given to people who turned 16, and refusal – to those who turned 14 [7]. Interestingly, a person who turned 16 must indicate in his medical policy his readiness to become organs and tissues donor after death. Upon agreement, the potential donor receives a special certificate, which he undertakes to carry. If such a certificate is found in the documents of the deceased, it is possible to take organs and tissues without asking relatives [15]. At the same time, consent for organs and tissues transplant from a deceased donor may be given by his close relatives if they have had personal contact with the deceased during the last two years before death. This information is obtained by a doctor. Close relatives must still adhere to the deceased's will regarding his or her intended intention to become an organ and tissue donor. The doctor is obliged to inform the close relatives about this. In the event of a dispute between close relatives over a donation decision, they may be given a reasonable period of time to reconcile their positions. If they have not agreed on one decision, the differences can be considered by the court [16].

According to the law on transplantation in Belarus, a person who does not want to become a donor of his organs and tissues after death submits an application to the state health care organization. In the case of underage people, such a statement is submitted by their legal representatives. If the person is not able to make an informed decision due

to health reasons, the statement of disagreement is submitted to the other spouse or close relative (parents, adoptive parents, children, siblings, grandparents, grandchildren). Moreover, public health organizations have the right to dispose deceased organs without his will or without his close relatives or legal representatives decision, if they have not shown in the manner, prescribed by law, their negative attitude to organ and tissue transplantation. Statements of refusal to be a donor are entered in a special Unified Register [17]. At the same time, before the organs and tissues collection from the donor, the employees of the state health care organization should check the information whether the authorized persons did not receive a statement of disagreement to participate in the transplant before death and whether they came from another spouse, close relatives or legal representatives of the statement of disagreement with organs and tissues donation of the deceased, addressed to the state health care organization or the State Committee of Forensic Science, after the death of the donor [18].

South African health law provides for the right of a person over the age of 16 to donate his or her organ or tissue in a will or in a document signed by him or her and at least two witnesses, or in an oral statement in the presence of at least two witnesses. Such a will or document should specify the institution or person of the recipient, as well as which organ or tissue can be used after death. Provided that no specific gifted person is identified, the donation will be considered invalid [19].

Ukrainian legislation establishes the possibility of seizing anatomical materials from an adult individual only in the presence of his voluntary and conscious consent to donate. Such consent shall be given in a written form. It should be noted that consent is given after the doctor has provided objective and accessible information to the potential donor about the possibility of complications for his health, as well as about his rights as a donor.With regard to posthumous donation, a note on the consent or disagreement of a person may, if he wishes, be included in the passport of a citizen of Ukraine and (or) a driver's license. An adult has the right to appoint an authorized representative, who after his death will agree to the removal of anatomical materials from his body. Such a representative must also give his or her voluntary consent to such authorization. If during his lifetime the person did not consent or disagree with the posthumous donation, did not appoint an authorized representative, consent to remove from his body anatomical materials for transplantation after determining his condition as irreversible, death is requested by the transplant coordinator from the other spouse or close relatives of the deceased. In the absence of the latter, consent to the seizure is requested from the person who undertook to bury the deceased [10].

OBLIGATION TO PERFORM ORGAN OR TISSUE TRANSPLANTATION ON A NON-COMMERCIAL BASIS

Adherence to the principle of de-commercialization in the process of transplantation is of paramount importance, especially in view of a number of international organizations that regularly record and publish reports and other news of human rights violations whose anatomical material has been the subject of commercial agreements. One of the means of counteracting such illegal actions should be the proper consolidation at the international and domestic levels of the obligation to perform transplantation on a non-commercial basis, ie without the purpose of obtaining financial or other benefits.

Thus, the Convention on Human Rights and Biomedicine clearly sets out the rule prohibiting financial gain from the human body or its parts (Article 21) [2]. The Additional Protocol to this Convention supplements this prohibition with possible exceptions. The point is that various payments are allowed that do not represent a financial benefit, in particular: compensation for loss of earnings and other costs of a living donor incurred through participation in the transplant procedure; compensation in case of unforeseen damage due to removal of organs and tissues from a living donor; payments for legitimate medical or related technical services provided in connection with transplantation [3].

Thus, today the problem of trade in human organs and tissues for transplantation is one of the leading and is the subject of attention and solution of the World Medical Assembly. In particular, in one of its resolutions WHA63.22, the international organization recommended that the following: to promote the system of altruistic donation of human organs and tissues and raise public awareness in this regard; to encourage health professionals to report on the practice of receiving financial benefits from transplantation; to ensure transparent and fair distribution of organs and tissues, as well as free access to transplantation; to promote the application of international best practices in transplantation to ensure the safety and effectiveness of donation; to conduct international cooperation in the collection of data on transplantation practice, etc [20].

The Istanbul Declaration on Transplant Tourism and Organ Trade is also dedicated to this issue. The primary purpose of transplantation should be to provide medical care to ensure the health of both the donor and the recipient, while financial gain or other material factors should not influence the decision to perform the procedure. In general, transplant tourism is the movement of organs, donors, recipients or transplant professionals across jurisdictional boundaries for the purpose of transplantation. It should be distinguished from medical tourism, which implies the importance of ensuring the interests and well-being of both the living donor and the recipient. While the medical «resource» used by transplant tourism is the exploited living donor [21].

Organ trafficking and transplant tourism, according to the Istanbul Declaration, must be banned because they do not respect the principles of justice, equality and respect for human dignity. The prohibition of such forms of activity should include, in particular: all forms of advertising, all forms of mediation, purchase and sale of organs, transplant tourism. It should also provide for penalties for such activities [22].

The WHO Guidelines for the Transplantation of Human Cells, Tissues and Organs (Principles 5, 7, 8) contain requirements for the non-financial benefit of transplantation. Particular attention should be paid to principle № 8, according to which all medical institutions and specialists should be prohibited from receiving any payment in excess of the reasonable amount of remuneration for services for transplantation and supply of human organs and tissues. To obtain this, health authorities should control the amount of fees for these services to prevent situations where such fees are a veiled form of organs and tissues remuneration. In addition, all institutions and individuals involved in the transplant process should be accountable for all payments associated with the provision of such services [6].

In addition, some researchers rightly emphasize the need to adopt at the UN level a single mandatory convention act that would prohibit commercial relations in the field of transplantation, as well as streamline the transplantation procedure [23].

For now, let's turn to the analysis of the relevant legal provisions of foreign countries, which establish the principle of de-commercialization in the implementation of transplantation. Thus, the Indian Law on Human Organ Transplantation of 1994 prohibits the human organs removal for commercial purposes; contains norms aimed at preventing the realization of such a goal; regulates the issue of brain death, after which it is possible to remove organs and tissues; establishes liability for violation of its requirements [24]. Article 143 of the Health Code of the Republic of Tajikistan [9] prohibits the human organs and tissues sale. Article 17 of the Federal Law of Germany on Transplantation explicitly prohibits trade in organs or tissues intended for therapeutic treatment. It is possible to obtain a reasonable reward for the measures necessary for the purpose of therapeutic treatment, in particular, for the removal, preservation, further processing, protection against infections, storage and transportation of organs or tissues [7]. By enshrining the obligation to de-commercialize transplantation, Swiss law allows for a symbolic gesture of gratitude that is not seen as a financial benefit or advantage [14].

Polish transplantation legislation stipulates that no payment, other material or personal benefits may be claimed or accepted for organs or tissues taken from a donor. Reimbursement of expenses incurred in connection with the transplant procedure is not a fee and does not constitute property or personal gain. In addition, the list of costs to be reimbursed and the procedure for such reimbursement are clearly defined. Article 20 of the Law of Ukraine «On the Application of Transplantation of Human Anatomical Materials» prohibits the conclusion or offer of contracts involving the purchase and sale of human anatomical materials. Advertising of human anatomical materials, except for social ones, aimed at promoting transplantation is also prohibited [25].

CONCLUSIONS

Thus, we have identified and researched the following legal obligations in the light human organs and tissues transplantation: compliance with regulatory and medical requirements for organs and tissues transplantation; obtaining the donor's consent for organs and tissues transplantation; organ or tissue transplantation on a non-commercial basis.

1. Analyzed regulatory and medical requirements, indicate the complexity of the transplant process, as well as the need for strict compliance with established regulations and rules. The legislator (at the international and national levels), setting mandatory requirements for transplantation, must first and foremost be guided by the principles of expediency and justification of their implementation in order to balance the rights of donors and recipients, maximize preservation and improve their quality of life.
2. For the whole complex transplant procedure, one of the key points is the donor's consent (disagreement) to remove anatomical materials from him. Each state chooses its own method (opt-in or opt-out model) and mechanisms for obtaining the necessary will of the person – the predominant is either individual or public interest.
3. The obligation to perform organ or tissue transplantation on a non-commercial basis has a dual purpose: first, to prevent offenses and legal violations in this area, as anatomical materials cannot be traded or enriched; secondly, to determine as transparently and clearly as possible the list of costs incurred by the donor in connection with the organs and tissues removal and subject to reimbursement, the procedure for such reimbursement and its reasonable, acceptable and sufficient amount. In the sense of the second mentioned goals, of course, it is also a necessary practice on the part of states to promote the development of human organs and tissues altruistic donation system and to raise public awareness in this regard.

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REVIEW ARTICLE

HOLISTIC APPROACH IN COMMUNICATION SKILLS TEACHING OF MEDICAL STUDENTS

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ABSTRACT

The aim: To analyze the relevance of communicative competence in medical practice and to choose the best pedagogical methods by improve communication skills in future doctors through the use of a holistic approach in teaching.

Materials and methods: Sociological, informational and analytical research methods were used in the research.

Conclusions: The holistic direction in education promotes partnership between a student and a teacher, the achievement of mutual understanding and trust, better commitment and motivation to learn. The use of feedback forms helps to recognize and understand the needs and feelings of each student, work effectively with diversity, motivates the teacher to continuous self-development and self-improvement. Modern teaching methods such as working in small groups, Storytellling and role-play according to students are more valid in mastering the communicative competence of the future doctor.

KEY WORDS: holistic learning, communication skills, doctor's communicative competence

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INTRODUCTION

Educational processes in the era of globalization require the use of such learning technologies that would be aimed at forming a holistic picture of the world, preparing students for life in a dynamically changing environment [1,2]. The issue of a holistic approach in education in modern conditions has become very relevant. A student in holistic education is perceived as a holistic person in need of harmonious learning and development. The teacher does not focus only on the content of the subject, but pays attention to the relationship with students, preferring a partnership model of relations, recognizes and understands the needs and feelings of students, open to the views of each person with constructive resolution of conflicts arising from diversity, shows flexibility, ready for constant self-development and self-improvement [3,4]. The basic principles of holistic learning are: connectedness – the transition from a fragmentary approach in learning to an approach that creates connections at each level of learning; inclusion – application of a wide range of educational approaches for people with different needs; balance – recognition and support of complementary aspects of personality (for example, analytical and intuitive thinking) [3].

Acquisition by students of basic competencies that form a highly qualified specialist occupies a special place in the training of medical workers [5]. Communicative competence is one of the basic competencies of a doctor [6]. Competences are best learned using modern methods of education, taking into account holistic approaches that will include in the active learning process all participants, considering the individual needs of each student [7]. Therefore, we can confidently state the fact of the need to identify the most effective and efficient techniques for mastering communicative competence as a component of quality professional training of physicians.

THE AIM

The aim of this study was to analyze the relevance of communicative competence in medical practice and to choose the best pedagogical methods by improve communication skills in future doctors through the use of a holistic approach in teaching.

MATERIALS AND METHODS

Sociological, informational and analytical research methods were used in the research.

REVIEW AND DISCUSSION

Employees of the Department of Primary Health Care and General Practice-Family Medicine have developed and implemented in the educational process for fourth-year students of the Medical Faculty a selective subject of Communicative Skills in Medical Practice." According to the work program, the subject consists of 3 credits, the total number of hours – 90, of which – 30 hours of practical classes and 60 hours of individual work. Fourth-year students attended ten two-hour practical classes over two

semesters. The first five lessons learn the basics of communication in medical practice: the definition of communication, the basic models of communication between doctor and patient, technology and basic counseling skills, communication barriers. The next five classes are devoted to studying the structure of counseling, working with different types of patients, informing bad news, motivational counseling and prevention of emotional burnout. Students were recommended to practice the acquired skills while performing practical work at clinical departments.

Because the study of selective subject was based on a holistic approach to learning, students were asked to complete an anonymous feedback form upon completion of the course. The questionnaire was compiled and agreed by the teachers of the department and included 10 items. The form contained questions related to students' impressions of studying the subject, preferences, needs for future learning and professional activities and wishes to optimize the study of the subject. The analysis of the survey revealed that 33 students (97.0 %) out of 34 respondents noted the importance of studying communication skills for the future doctor. To the question "Do you think that a doctor's communication skills are no less important than his professional qualifications?" 26 respondents answered yes, 8 – partially yes. According to students' thought, the most important parts of the subject are mastering the basic techniques of effective counseling – 30 (88.2 %), knowledge and adherence to the structure of counseling – 26 (76.5 %), the ability to have difficult conversations and inform bad news – 22 (64.7%), knowledge of the peculiarities of counseling "special" patients – 17 (50 %).

To the question "What format of studying the subject do you consider the most optimal?" only 5 students (14.7 %) indicated distance learning, 17 respondents (50 %) prefer traditional, live study of the subject and 12 respondents (35.3%) – for a mixed format of study.

Several questions of the questionnaire concerned the choice of acceptable methods of educational process. The majority, 29 students (85.3 %) noted the high efficiency of work in small groups in mastering the subject, 26 students (76.5 %) were impressed by the use in practical classes of storytelling, stories of clinical cases from real practice with emotional impact, motivational, cognitive sphere of the listener, 25 students (73.5 %) – for group work with a presentation on Google disk with the joint creation of a syllabus, 20 students (58.8 %) noted the role play as the best technique in mastering the subject. At the same time, only 8 respondents (23.5 %) showed commitment to solving situational problems and watching educational videos in practical classes.

Several items of the questionnaire contained questions related to the continuation of study and improvement of students' communicative competence. In the answers to the questionnaire, all respondents indicated the need to improve their communication skills in the future, and 32 students out of 34 (94.1 %) will recommend the study of selective subjects to their colleagues. The majority of students, 22 persons, consider it necessary to continue studying the prevention of emotional burnout of health professionals in the future. 18 students plan to improve their leadership skills. For 19 respondents it is important to continue studying the topics of empathy and humanity in the work of a physician. 19 respondents plan to study the peculiarities of communication in the work process with colleagues, nursing stuff, as well as with representatives of the health care facility administration. For 15 respondents, the study of the peculiarities of communication with critically ill patients in the provision of palliative care is considered promising.

To improve communicative competence, almost all respondents plan to study individually, using special literature, watching available videos on the Internet, passing free distance webinars and trainings. At the same time, 10 respondents (30.3 %) are going to attend thematic improvement courses in the future and only 4 (12.1 %) are ready to attend paid courses and trainings.

Thus, the successful acquisition of communication skills by students requires holistic approaches to learning, which involves the search and selection of new pedagogical methods and technologies [7,8]. Only in this case, mastering the communicative competence important for a medical worker will be effective and motivate the student to improve the acquired skills.

CONCLUSIONS

The holistic direction in education promotes partnership between a student and a teacher, the achievement of mutual understanding and trust, better commitment and maintaining motivation to learn. The use of feedback forms helps to recognize and understand the needs and feelings of each student, work effectively with diversity, motivates the teacher to continuous self-development and self-improvement. Modern teaching methods such as working in small groups, storytellling and role-playing according to students' thought are more valid in mastering the communicative competence of the future doctor.

In the future, we plan to develop objective tools and methods for assessing the acquired communication skills of the student.

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REVIEW ARTICLE

THE ROLE OF ADAPTIVE-STRESS RESPONSE IN THE PATHOGENESIS OF PERIODONTAL DISEASES

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ABSTRACT

The aim: The purpose of this work is to analyze the literature data of scientific research of Ukrainian and foreign scientists to assess the pathogenetic mechanisms of the adaptive stress response to the condition of periodontal tissues.

Materials and methods: Bibliosematic and analytical methods were used in the trial. The materials of the trial are international experience in studying the pathogenetic mechanisms of the interaction of psycho-emotional disorders and the development of periodontal lesions.

Conclusions: Chronic stress and depression suppress the immune system, cause the hormonal imbalances, lead to metabolic disorders in tissues and increase the risk of dystrophic and inflammatory processes in periodontal tissues, which in turn lead to reduced masticatory function, tooth loss, severe emotional instability and significant reduction in quality of life. Psycho-emotional disorders in patients slow down the treatment of inflammatory processes in periodontal tissues and contribute to the early recurrence. Thus, the problem of studying the adaptive stress response of the organism requires further research for deeply understaningits role in the etiology and pathogenesis of dental diseases and justify effective treatment and prevention measures for its correction.

KEY WORDS: periodontal tissues, generalized periodontitis, psychoemotional stress, adaptation, maladaptation, psycho-emotional disorders

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INTRODUCTION

Modern man is under the constant influence of unfavourable factors, including natural, techno-genetic, informational and psychological ones. Experimental and clinical studies show that increased emotional impressibility affects the metabolic and physiological processes of organs and systems of the human body, in particular periodontal tissues, which leads to inflammatory-dystrophic changes [1-3]. Health condition often depends on a person's ability to adapt to environmental conditions, and the effectiveness of the regulatory function of adaptation depends on the state of the body and mind. Overstain of adaptive mechanisms leads to diseases in the case of intensive and long-term effects of stimuli on the human body. As a result, it develops a violation of homeostasis, starting a chain of adaptation, depending on the level of activity of adaptive reactions, which, in turn, occur at the cellular, subcellular and molecular levels in the form of resistance, and at high intensity and long-term negative influence leads to the development of maladaptation [4, 5]. In the case of maladaptation a violation of the higher autonomic centers of vasomotor regulation occurs, the tone of the parasympathetic division of the autonomic nervous system increases, which leads to a steady decrease in total peripheral vascular resistance [6-9]. In conditions of maladaptation, there is often a strengthening of personality qualities. In particular, the main clinical manifestation of the syndrome of psycho-emotional stress is anxiety of various degrees, which leads to increased stress reactions, the development of distress and various psychosomatic diseases [10].

THE AIM

The purpose of this work is to analyze the literature data of scientific research of Ukrainian and foreign scientists to assess the pathogenetic mechanisms of the adaptive stress response to the condition of periodontal tissues.

MATERIALS AND METHODS

Bibliosematic and analytical methods were used in the trial. The materials of the trial are international experience in studying the pathogenetic mechanisms of the interaction of psycho-emotional disorders and the development of periodontal lesions.

REVIEW AND DISCUSSION

The main biochemical and physiological changes in the body under stressful situations are determined mainly due to the action of adrenaline and noradrenaline. Unlike adrenaline, norepinephrine is produced not only by the adrenal glands but also by neurons in the sympathetic nervous system. Thus, the mobilization of the body's reserve capacity in stressful situations depends on its activity. The

parasympathetic nervous system helps to preserve and accumulate energy reserves. A person's reaction to psychological stressors is individual and depends on many factors - the general condition of the body, its psychological characteristics [12]. An important role in the development of metabolic and hemodynamic disorders during psychophysiological loading is played by the lack of such compounds as tocopherol acetate, retinol acetate, vitamins B and ascorbic acid, which may be explained by their participation in antiinflammatory, antioxidant, osteotropic, immunomodulatory, capillary-strengthening, membrane protective mechanisms of development in pathological process[13]. Excessive stress in combination with violation of any organs and tissues under the influence of irritants can lead to failure of adaptation, as prolonged increase in catecholamines and stress hormones leads to nitrogen imbalance, destruction of cellular structures, promoting to the development of trophic disorders [11, 14-16].

Diseases of the maxillofacial area are often considered separately from the patient's personality, and if their relationship to somatic health is still taken into account, then the psychological, socio-psychological and social aspects of dental pathology remain without proper attention from researchers and clinicians. At the same time, the involvement of psychophysiological factors in the development of any pathological process and their importance for therapeutic action no longer needs proofs, which necessitates a systematic, comprehensive, interdisciplinary approach to the diagnosis and treatment of human health disorders, including dental [17-20].

Chronic stress syndrome is especially dangerous at a young age, as most people are exposed to bad habits (smoking, drinking, etc.) that can affect oral health. Stress caused by psychosocial factors can violate the lifestyle and hygiene of the oral cavity and affect the microbial ecology of the periodontium [21].

While it is well established that chronic psychologic stress can have significant deleterious systemic effects, only in recent decades have begun to explore the biochemical, microbial, and physiologic impacts of chronic stress diseases on oral tissues. Currently, chronic stress is classified as a «risk indicator» for periodontal disease[1, 5].Modern scientific studies have proven the relationship between psychological stress and periodontal disease, as periodontal tissues are highly sensitive to stressors [22-24]. Clinicians consider appropriate to distinguish a separate nosological unit – «periodontal emotional stress syndrome» [25]. Many scientists study the influence of stress on the pathological process in periodontitis, the functional state of the brain in periodontitis, structural changes of periodontal nerves in its lesions and attach importance to such factors as emotional stress, chronic psycho-emotional stress affecting periodontal tissuetrophism [26-28].

In the pathogenesis of stress periodontal damage the reactions of the salivary glands have the sense, which respond by changing the secretion of hormones, mediators and other biologically active substances, which leads to changes in immune homeostasis of the oral cavity. Cytokines and other humoral mediators of inflammation are powerful activators of the central stress response. Glucocorticoids, which are released under their influence, can regulate the involvement of immune cells in inflamed tissues to help the body in coping with psychological stress [26, 29].

Increased secretion of steroid hormones, in particular cortisol, causes in the oral cavity: gangrenous ulcers under the influence of viruses and bacteria due to immune deficiency; temporomandibular bruxism - with grinding or clenching of teeth; dryness in the mouth due to decreased salivation; gingivitis due to poor hygiene (56% of young people surveyed said that stress affected their ability to brush their teeth effectively, both with a brush and floss) [30]. Due to its immunosuppressive effect, stress also leads to slow healing of connective and bone tissue, apical migration of connective epithelium and the formation of periodontal pockets [31]. It is also one of the reasons for increasing the processes of lipid peroxidation (LPO) and weakening antioxidant protection and hemocirculatory disorders, reducing the synthesis of the organic matrix and enhancing bone resorption [32, 33].

Activation of LPO is the main mechanism of stress lesions of periodontal tissues with disruption of cell and subcellular membranes, and hence cell metabolism in general. Stress activation of LPO also initiates the damage of connective tissue, which is the substrate of periodontium and is characterized by weakened, compared to other tissues, antioxidant protection [34-36]. Fibroblasts have affinity receptors for cortisol and respond to glucocorticoids by reducing the synthesis of collagen and glycosaminoglycans. Acute stress stimulates the degradation of connective tissue biopolymers, as evidenced by increased blood levels of oxyproline [37]. In addition, there is an increase in the activity of anti-inflammatory enzymes - NO synthase and cyclooxygenase-2, which leads to increased oxidative processes due to the production of peroxynitrite and the release of radicals in the synthesis of prostaglandins. The dependence of the levels of LPO products and periodontal tissue damage under stress on the nature of emotional response and typological features of the nervous system has been established. Under the influence of adverse environmental factors, the intensity of free radicalprocesses increasessharply, the antioxidant defence system is gradually depleted, which leads to the development of inflammatory-dystrophic process in periodontal tissues [38].

Psycho-emotional stress causes microcirculatory disorders and metabolic disorders in periodontal tissues [34]. Vascular dilatation, which occurs under stress, contributes to the pathological deposition of blood, which leads to impaired blood supply to periodontal tissues [38, 39]. In turn, the spastic reaction of blood vessels restricts blood flow to the tissues and promotes the development of ischemic damage to periodontal tissues. Deterioration of blood supply to periodontal tissues is directly dependent not only on the severity of periodontitis, but also on the depth of autonomic disorders with a predominance of the sympathetic system [40].

An important intermediate link that implements the pathogenic effects of chronic psycho-emotional stress are autonomic disorders. There is a direct relationship between the functional state of the autonomic nervous system and the severity of periodontitis. A number of authors have found that one of the causes of diseases of the oral cavity is a combination of vascular changes with impaired autonomic regulation [17, 23]. The study of the dynamics of autonomic parameters in patients with generalized periodontitis shows an increase in sympathotonic activity of the higher nervous system and decrease it after treatment. Comparative evaluation of the complex of autonomic reactions revealed a connection between the activity of the sympathetic nervous system, disorders of psychoemotional state (decreased levels of health, activity and mood) with quantitative changes in ultrasound hemodynamics of the main vessels of the dental system in patients with generalized periodontitis [12, 40].

CONCLUSIONS

Chronic stress and depression suppress the immune system, cause the hormonal imbalances, lead to metabolic disorders in tissues and increase the risk of dystrophic and inflammatory processes in periodontal tissues, which in turn lead to reduced masticatory function, tooth loss, severe emotional instability and significant reduction in quality of life. Psycho-emotional disorders in patients slow down the treatment of inflammatory processes in periodontal tissues and contribute to the early recurrence. Thus, the problem of studying the adaptive stress response of the organism requires further research for deeply understaningits role in the etiology and pathogenesis of dental diseases and justify effective treatment and prevention measures for its correction.

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REVIEW ARTICLE

CURRENT APPROACHES TO DIAGNOSIS AND TREATMENT OF HIRSCHSPRUNG DISEASE IN NEWBORNS AND INFANTS (LITERATURE REVIEW AND FIRST-HAND EXPERIENCE)

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ABSTRACT

The aim: To analyze the current state of the issue of Hirschsprung disease in newborns and infants on the basis of literature data and first-hand experience.

Conclusions: 1. Hirschsprung disease should be suspected in all newborns with late meconium passage. 2. The main methods of diagnosing Hirschsprung disease in newborns and infants are the assessment of anamnestic data, clinical manifestations and features of the clinical course of the pathology, contrast enema, morphological examination of rectal biopsies and immunohistochemistry for ACE. 3. The presence of enterocolitis in newborns and infants should raise suspicion of Hirschsprung disease. 4. Low intestinal obstruction, perforation of the cecum, ascending or terminal small intestine, and peritonitis in the first days of a child's life may be complications of Hirschsprung disease. 5. In newborns and infants, early diagnosis of Hirschsprung disease and timely surgical correction by one-stage surgery help improve treatment outcomes

KEY WORDS: Hirschsprung disease, newborns, diagnosis, transanal endorectal pull-through

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INTRODUCTION

Hirschsprung disease in newborns and infants is a complex problem of modern pediatric surgery. The improvement in the treatment of children with Hirschsprung disease in the last decade has been due to advances in understanding the etiology and pathogenesis of the disease, improving diagnostic methods and developing surgical methods of correction. Increased awareness of Hirschsprung disease and improved diagnosis have significantly reduced the age of detecting Hirschsprung disease in recent times, but there are often cases of late diagnosis of the disease in newborns. Thus, the issue of early diagnosis of this pathology and timely treatment of newborns and infants remains relevant today [1-3].

It is the late diagnosis of Hirschsprung disease in newborns that has necessitated a more in-depth study of this issue.

THE AIM

The aim is to analyze the current state of the issue of Hirschsprung disease in newborns and infants on the basis of literature data and first-hand experience.

REVIEW AND DISCUSSION

CURRENT VIEWS OF THE ETIOPATHOGENESIS OF HIRSCHSPRUNG DISEASE IN NEWBORNS

A review of the literature indicates that the issues of etiology and pathogenesis of Hirschsprung disease are no longer considered controversial. The etiology of Hirschsprung disease is represented by cellular and molecular abnormalities in the enteric nervous system development and disorders of crest-derived cells migration to the intestinal tract. Neuroblasts first appear in the esophagus after the 5th week of gestation. These cells migrate in a craniocaudal direction into the intestine between 5 and 12 weeks of gestation. The form of Hirschsprung disease depends on the time and place of migrating neuroblast stop. An early delay in cell migration leads to an extensive aganglionosis [4, 5]. The pathogenesis of Hirschsprung disease is based on the obstruction of the narrow part of the large intestine, where peristaltic waves are not formed due to the absence of parasympathetic ganglion cells. Aganglionosis, cholinergic hyperinnervation, failure of nerve supply by nitric oxide synthase, disruption of interstitial cells of Cajal are all involved in the pathogenesis of Hirschsprung disease [4, 6]. There are many factors contributing to the development of Hirschsprung disease. These include extracellular matrix component damage, neurotrophic disorders, molecular damage to nerve cells, etc. [7]. Hirschsprung disease is a neurocristopathy, a tissue developmental anomaly due to defective migration of neural crest cells [5].

An increased risk of children being born with Hirschsprung disease among relatives of patients with this disease, association of Hirschsprung disease with other congenital anomalies (heart, central nervous system, genitourinary system), syndromes and chromosomal disorders (Waardenburg-Shah syndrome, Bardet-Biedl syndrome, Mowat-Wilson syndrome, Down syndrome) prove the presence of genetic factors in the etiopathogenesis of

Fig 1. Characteristic appearance of a newborn suspected of having Hirschsprung disease.

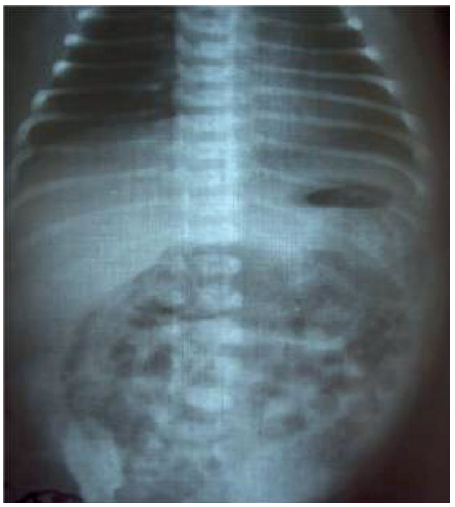

Fig 2. Toxic dilatation of the colon in Hirschsprung-associated enterocolitis in a newborn child.

the disease. We have the clinical case of the boy T. with Hirschsprung disease, whose mother had an operation for a similar disease in her childhood. Today it is known that mutations in 10 genes are associated with Hirschsprung disease, among which the RET protooncogene, the glial cell line-derived neutrophilic factor (GDNF) gene, the neurturin (NRTN) gene, the endothelin receptor type B (EDNRB) gene, and the endothelin 3 (EDN3) gene are the most studied [8, 9, 10]. The increased risk of children being born with Hirschsprung disease among relatives of patients with this disease, association of Hirschsprung disease with other congenital malformations, syndromes and chromosomal abnormalities prove the presence of genetic factors in the pathogenesis of the disease.

CLINICAL FINDINGS

Hirschsprung disease in newborns is manifested by signs of low intestinal obstruction due to the presence of aganglionic segment of varying length of the distal colon: failure to pass meconium for 48 hours after birth, progressive bloating, vomiting bile, restlessness, enteral nutrition disorders, etc. [11]. Most newborns with Hirschsprung disease are usually full-term babies with delayed passage of meconium (more than 24 - 48 hours of life). The complicated course of Hirschsprung disease in newborns is manifested by enterocolitis and/or cecal perforation and peritonitis. Hirschsprung disease is often accompanied by loose stools, the presence of which indicates enterocolitis, which is the most common cause of mortality. The appearance of a newborn with Hirschsprung disease is shown in Figure 1.

Enterocolitis in Hirschsprung disease in newborns is a severe complication that can develop in the pre- and postoperative period. Approximately 5-42% of infants with Hirschsprung disease develop enterocolitis [12]. It is manifested by symptoms of fever, colic-like abdominal pain, intoxication, bloating, diarrhea, sometimes with blood. Despite numerous studies, there is still no complete understanding of the etiology of enterocolitis. There are the following theories in this regard:

1. Proximal colon distention, which leads to intestinal stasis, and even greater distention in dynamics, mucosal ischemia and bacterial invasion. However, this theory does not explain the occurrence of enterocolitis in the distal from stoma part of the intestine, or the histological finding of enterocolitis even in the aganglionic segment
2. Long-segment aganglionosis, which is common in newborns and characterized by a more pronounced proximal obstruction with greater pressure, increasing bacterial stasis and proximal distention. However, numerous studies indicate a correlation between aganglionic segment length and the prevalence of enterocolitis
3. Mucin production is significantly reduced in newborns, which leads to the intestinal mucosal barrier damage and bacterial translocation
4. Reduced production of secretory immunoglobulin A, which provides an immunological barrier in the gastrointestinal tract of the child, resistance to bacteria and eliminates bacterial translocation, that is, immature mucosal immunity in newborns
5. An increase in the number and activity of macrophages during inflammation of the intestinal wall leads to disruption of the interstitial cells of Cajal responsible for the rhythmic contractions of the intestinal peristaltic activity.

DIAGNOSIS

The diagnosis of Hirschsprung disease is based on X-ray examination of the colon, biopsy of the mucosa and submucosa of the rectum and colon, where aganglionosis, hypertrophied nerve fibers and hyperproduction of acetylcholinesterase (ACE) are detected. Microbiological study reveals Clostridium difficile in most cases [13]. Differential diagnostic search is performed with congenital

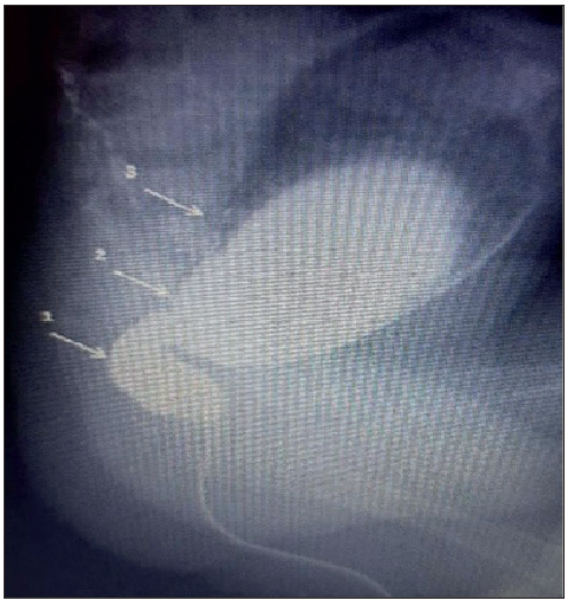

Fig. 3. Contrast enema radiograph in a newborn with Hirschsprung disease. Note the narrowed aganglionic segment – 1, transition zone – 2, and suprastenotic dilatation of the colon – 3.

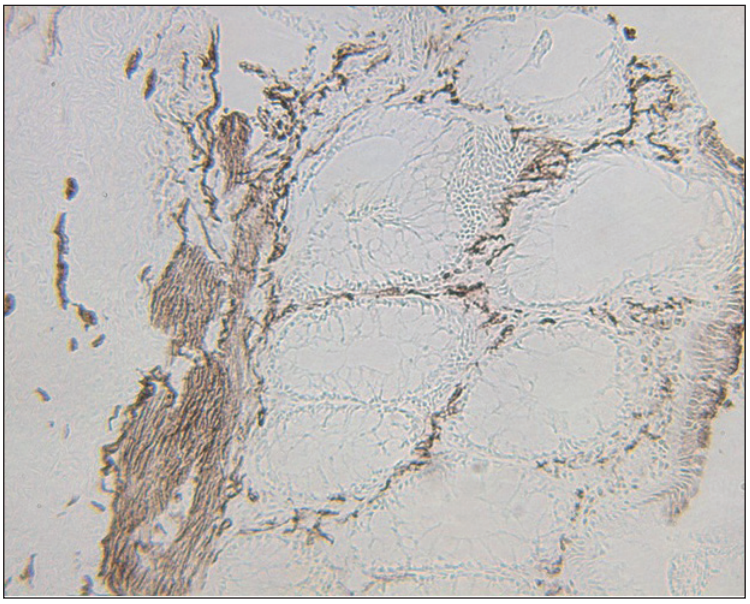

Fig. 4. Rectal mucosal biopsy sample shows the presence of numerous nerve fibers between crypts with high ACE activity, forming a dense network in some places. In the proper and muscular mucous plates there is also a dense network of thickened brightly colored tortuous cholinergic nerve fibers. Ganglia are absent.

malformations of the small intestine (atresia, malrotation, meconium ileus), congenital malformations of the colon (rectal malformations, small left colon syndrome), hypothyroidism, sepsis, metabolic disorders, etc.

Extensive intestinal pneumatosis, dilatation of the colon can be seen on the plain radiograph of a newborn child with Hirschsprung disease. In case of evident enterocolitis, the signs of toxic dilatation of the colon can be found (Figure 2). Complicated Hirschsprung disease can be characterized by signs of low intestinal obstruction or intestinal perforation with free gas in the abdominal cavity [14, 15].

The signs of Hirschsprung disease during contrast enema are pathological narrowing of the distal colon, funnel-shaped transition zone and distention of the proximal colon (Figure 3). In some newborns (approximately 10%), funnel-shaped transition zone and proximal colonic distention may be indistinct. By 1 month of age, the risk of false-positive and false-negative results increases almost 3 times [1, 11]. Contrast enema in newborns is performed using water-soluble contrast at a dilution of 1:3 in the volume of 20 ml/kg. Excess contrast use should be avoided. The anterior and lateral X-ray films should be necessarily taken when filling the intestine and after defecation. The contrast material should be injected into the large intestine in small portions to gradually fill all its segments. The intestine is examined in different projections. The aganglionic segment is more easily seen in the lateral projection.

Contrast enema is a highly informative method of diagnosing Hirschsprung disease in newborns. It is important not to perform colon lavage and digital rectal examination before contrast enema, as this may contribute to radiographic distortion and give false-negative data [William J.Cochran. MSD Manual. 2019. Professional Edition].

It is important to note that full-thickness biopsy in newborns is technically sophisticated to perform, while rectal mucosal biopsy is a technically simple procedure. In addition, the absence of aganglionic cells in the distal section of the anal canal is a normal variant, thus a biopsy in newborns is performed 1 cm above the dentate line.

A classical morphological examination reveals the absence of ganglion cells in the nerve plexuses of the intermuscular and submucosal layers of the rectum when stained with hematoxylin-eosin.

Histochemical analysis of rectal mucosal biopsy reveals the presence of acetylene-positive hypertrophied nerve fibers, which confirms Hirschsprung disease (Fig. 3). Histochemical reaction to ACE for the diagnosis of Hirschsprung disease in newborns has a sensitivity of 91%, specificity of 100%, false-negative result is observed in 8% of cases.

Newborns, especially premature and not fully developed ones, can have reduced number of nerve fibers in the intestinal wall even in Hirschsprung disease, so a decrease in the level of ACE – positive fibers in newborns can lead to a false-negative result. However, despite these limitations, rectal biopsy is more sensitive and specific than contrast enema and anorectal manometry combined.

TREATMENT

Confirmation of the diagnosis of Hirschsprung disease is an indication for surgical treatment. Success in anesthesiology and resuscitation of newborns, successful developmental care have made it possible for pediatric surgeons to perform one-stage correction of Hirschsprung disease in an uncomplicated form of the disease and the absence of total aganglionosis. This involves pulling through the aganglionic segment, performing transanal resection and colorectal anastomosis, that is de la Torre procedure, which is today considered the gold standard in the surgical treat-

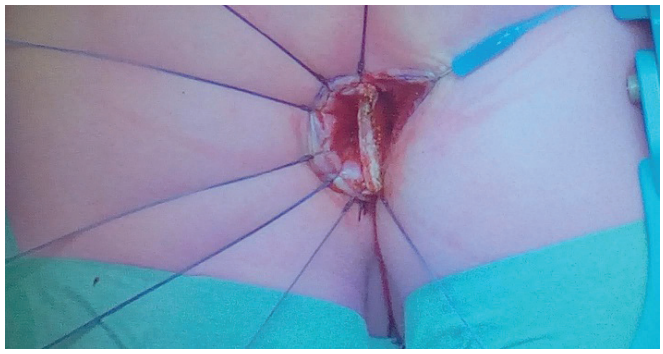

Fig. 5. Transanal mobilization of the rectum in Hirschsprung disease.

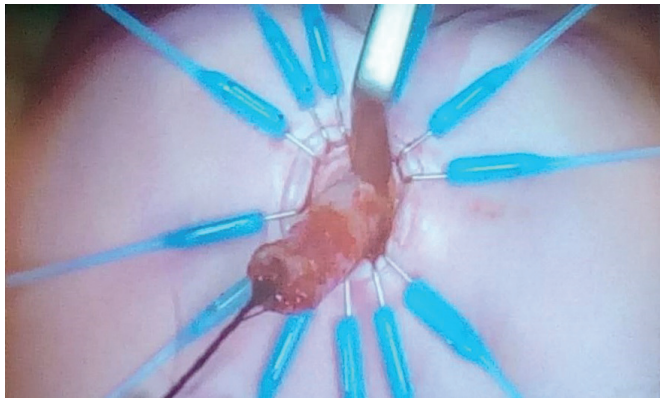

Fig. 6. Transrectal mobilization of the gut for resection.

Fig. 7. Direct colorectal anastomosis after transendorectal pull-through and colon resection in Hirschsprung disease.

ment of newborns and infants with Hirschsprung disease [16-18]. The main stages of the de la Torre procedure are presented in Figures 5, 6, 7.

Most medical institutions and centers today perform pull-through radical operation in the neonatal period with good results and a minimum number of complications. Since in newborns it is possible to quickly cope with the dilation of the colon by washing it, then during the operation the diameter of the pulled-through colon is almost normal, which makes it possible to apply an optimal anastomosis and promotes healing without dehiscence and infection. The main contraindications to primary transanal pull-through in newborns are the following:

- severe congenital anomalies;
- severe enterocolitis;
- severe dilatation of the proximal colon;
- serious general medical condition of a child,

Radical one-stage surgical treatment of Hirschsprung disease by de la Torre in newborns and infants is becoming more widespread and improves the results of treatment.

The postoperative period in newborns and infants is mostly without complications, provided that appropriate surgical approach is adhered.

CONCLUSIONS

1. Hirschsprung disease should be suspected in all newborns with late meconium passage.
2. The main methods of diagnosing Hirschsprung disease in newborns and infants are the assessment of anamnestic data, clinical manifestations and features of the clinical course of the pathology, contrast enema, morphological examination of rectal biopsies and immunohistochemistry for ACE.
3. The presence of enterocolitis in newborns and infants should raise suspicion of Hirschsprung disease.
4. Low intestinal obstruction, perforation of the cecum, ascending or terminal small intestine, and peritonitis in the first days of a child's life may be complications of Hirschsprung disease.
5. In newborns and infants, early diagnosis of Hirschsprung disease and timely surgical correction by one-stage surgery help improve treatment outcomes.

Directions for future research: immunohistochemical study of calretinin (calretinin is negative in Hirschsprung disease) and on the detection of nerve fibers containing nitric oxide (no nitric oxide in the aganglionic zone).

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REVIEW ARTICLE

IMPLEMENTATION OF ENHANCED RECOVERY AFTER SURGERY PROTOCOL FOR METABOLIC SURGERY PATIENTS (LITERATURE REVIEW)

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ABSTRACT

The article reviews the literature highlighting modern views on the issues of postoperative rehabilitation of patients after metabolic surgical interventions. The concept of accelerated postoperative recovery of patients is presented as a single integral system of principles, means and methods of multidisciplinary work in the perioperative period aimed at reducing the time of hospitalization of patients and reducing the financial costs of the healthcare system. The separate components of the protocol of accelerated postoperative recovery from the standpoint of evidence-based medicine are analyzed, an emphasis is made on its specificity in metabolic surgery. The key role of laparoscopic access at the present stage of development of metabolic surgery is emphasized. Specific risk factors have been identified in patients with obesity, type 2 diabetes mellitus and metabolic syndrome, which can affect the effectiveness and safety of surgical treatment, especially in conditions of early discharge from the hospital. Attention is focused on the extremely important, but still controversial positions of the protocol, requiring further research to form a better evidence base and clear practical recommendations. The promising directions of scientific research for improving both the system of accelerated postoperative recovery as a whole and its individual elements are demonstrated. Electronic databases of Scopus and PubMed were searched using keyword searches. The analysis of the literature has shown the feasibility of introducing, systemic use and further improvement of the protocol for accelerated postoperative recovery in metabolic surgery.

KEY WORDS: metabolic surgery, enhanced recovery after surgery

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INTRODUCTION

According to the WHO data, in 2016 the number of overweight adults in the world exceeded 1.9 bln persons (39% of population of our planet aged over 18), among whom 650 mln (13%) were suffering from obesity. The above statistical data coupled with catastrophic dynamics of this illness spread allowed the professionals to characterise the problem of overweight as a "non-infectious pandemic" of today's world [1].

The proven overall negative medical and social effects of obesity and related numerous illnesses and metabolic disorders (primarily cardiovascular pathologies and type 2 diabetes) [1,2] became a powerful impetus to develop new approaches to metabolic syndrome treatment.

One of the most effective modern methods of treatment of such patients is metabolic surgery. Metabolic surgery is a group of surgical procedures performed on gastrointestinal tract organs in order to change topographic anatomy thereof, digestion processes physiology and impacting incretin condition of gaster and intestines and allowing weight loss, correction of diseases collateral to obesity and metabolism disorders. At the same time, one of the main "target areas" of the above surgery became treatment of type 2 diabetes [3].

Over the last decade, metabolic surgery continued to demonstrate rapid and consistent evolution, where an important role had implementation of laparoscopic access to Enhanced Recovery After Surgery protocol (ERAS), among other achievements [4]. Development of ERAS became a logical result of fast-track surgery concept evolution proposed by Kehlet et al. in the 90s of the last century and used for colorectal surgery. Intensive research proving effectiveness (including cost-effectiveness) and safety of the above approach led to quite expeditious implementation of ERAS in practically all surgery areas [5].

According to the definition, ERAS (Enhanced Recovery After Surgery) is a multimodal integrated patient management system aimed at reducing postoperative stress, accelerating physical and psychological recovery, reducing financial burden on national healthcare systems, primarily

by reducing the time of patients' stay in hospitals [6].

ERAS consist of separate elements (principles, means and methods of multidisciplinary management of patients during preoperative, intraoperative and postoperative periods), which due to their synergy ensure achieving the above goals. It is also worth noting that ERAS system is implemented according to the "all or nothing" principle, which means that it's proper functioning is possible only when implementing in practice all of its elements without any exceptions. First general recommendations on the use of ERAS in metabolic surgery, which were published in 2016 [6], are undoubtedly require close analysis mostly due to the specific nature of patients and goals of the metabolic surgery.

THE AIM

The aim of this study was to analyse the literature data highlighting modern views on the issues of postoperative rehabilitation of patients after metabolic surgical interventions.

REVIEW AND DISCUSSION

PREOPERATIVE PERIOD

INFORMATION, EDUCATIONAL AND CONSULTATIVE WORK WITH A PATIENT.

The main goal of preoperative period in ERAS system is comprehensive preparation of the patient for the surgery. The objective is to correct not only physical, but also mental condition of the patient via consultation and awareness-raising work with the patient, which is advisable to be commenced 2-3 months before surgery [5]. Such "early commencement" of information and educational support of potential candidates for surgical treatment is, on the one hand, explained by a broad range of issues, requiring to be addressed, and on the other hand, by mental particulars of patients most evident in type 2 diabetes patients. Such patients very often demonstrate cognitive disorders, poor attention and memory [7], anxiety at the stage of waiting for the surgery, which leads to the fact that they absorb only 10% of information provided by the doctor during a single consultation. Therefore, in view of the above, it seems logical to organise a series of consultations with repeated addressing of important issues whenever necessary.

During the preoperative period, a patient should receive comprehensive information on contemporary metabolic surgery procedures and on specific surgery planned to be conducted. A particular emphasis should be placed on the high level of safety of modern metabolic surgery, particulars of anaesthetic support, absence in most cases of the need for prolonged stay in a hospital, the possibility of solving most issues remotely with a 24/7 support by calling a designated contact telephone number, and the rules of conduct at home [8].

The expected positive effect of the surgery without omitting any possible complications and adverse effects of the surgery should be explained to the patient in details. There should be also further detailed discussion on the success factors of the surgery, realisation of which in many aspects relies on the actions of the patient, such as diet correction, particulars of postoperative monitoring, change of lifestyle, possible drug support for avoiding postoperative deficiency conditions [9].

At present, due to the lack of randomised clinical research, the positive impact of the above information and awareness-raising work with the patient on the rate of complications, duration of stay in a hospital, anxiety levels and mental discomfort, cannot be deemed proven. However, it can be stated with certainty that in the process of such interaction, preconditions for assessment and correction of patient's compliance, if necessary, are created. This is due to the fact, that many elements of ERAS at the preoperative stage that are aimed at improving patient's physical condition, concurrent diseases and prevention of perioperative complications, require specific actions to be taken by the patient on their own. Strive to follow all doctor's recommendations demonstrated by taking specific actions is the most evident proof of patient's readiness to work towards achieving the planned result [10].

PREOPERATIVE DIET AND WEIGHT LOSS.

Recommendations on weight loss as an element of metabolic surgery preparation seem logical due to several reasons. In particular, preoperative weight loss allows broadening the range of physical activity of the patient and the possibility to improve functional reserves of the cardiovascular and respiratory systems respectively [11]. Decrease of visceral fat in the abdominal cavity and size of the left part of liver facilitates visualisation of the operating field and the use of laparoscopic surgery technique [12]. Preoperative decrease of the body mass index and creation of potentially conducive conditions for the decrease of the surgery duration may be perceived to a certain extent both as prevention of rhabdomyolysis syndrome and venous thromboembolism [12].

The key instrument in excess weight loss is the low-calorie and very low-calorie diet with limiting daily energy value of meals up to 1,000–1,200 kcal and 800 kcal respectively and provision of energy needs of a patient by predominantly or solely with proteins for a period of 2 to 4 weeks [13]. At the same time, patients suffering from type 2 diabetes require specific attention due to increased risk of hypoglycaemia as a result of intake of standard doses of blood glucose lowering drugs [7].

In general, results of many research papers show that preoperative decrease of body mass index leads to significant decrease of the rate of early complications after the surgery and, in addition to the above, is a prognostic factor for more substantial weight loss during the following postoperative period [14].

PHYSICAL EXERCISES.

An important factor of preoperative preparation is physical exercises aimed at increasing functional reserves of the body in order to ensure quick recovery after the surgery-in-

duced stress. Positive impact of physical exercises on the postoperative course is theoretically connected to the improvement of cardiovascular reserves (increase of systolic discharge and decrease of heart rate (HR)), improvement of endothelial function and oxygen consumption, increase of muscle mass [15].

Results of a range of randomised controlled research in the field of colorectal surgery proved a correlation between the physical exercises (4 to 8 weeks on average) and the decrease of postoperative complications, the hospital mortality, shortening the duration of inpatient treatment and physical rehabilitation of patients. At the same time, it is worth noting that in some papers the reliability of such a correlation is in fact denied [16].

The above non-homogeneity of the obtained results, lack of randomised clinical research in this area, doubts in the correctness of projection of the available data on the metabolic surgery, still do not allow reaching unambiguous conclusions on the exact impact of physical exercises on rapid postoperative recovery of such patients. It is worth pointing out among important, but still unsolved issues, insufficient structuring of training programs, the need to bring them in line with the physical capabilities of a specific patient, and organisation of professional control over the completion of the set exercises [16].

ALCOHOL AND SMOKING.

Strict recommendations regarding refraining from smoking at least 30 days prior to the surgery are based on very reliable evidence confirming significant increase of postoperative complications and mortality among smokers [17].

According to the results of numerous research papers, the negative impact of alcohol abuse (3 and more doses of 12 grams of ethanol each) on the course of postoperative period was also found, as well as improved treatment results in colorectal surgery when a patient refrained fully from alcohol consumption at least 1 month prior to the surgery. The particulars of patients and surgery procedures in the metabolic surgery requires much longer period (from 1 to 2 years) of refraining from alcohol consumption. However, confirmation or refutation of this hypothesis requires further research [18].

GLUCOCORTICOIDS.

Preoperative prescribing of glucocorticoids in the ERAS system is explained by its anti-inflammatory and antiemetic action. A number of research papers demonstrated that use thereof leads to decrease of surgical complications rate and the duration of inpatient treatment of patients. At the same time, in order to prevent postoperative nausea and vomiting, it is deemed sufficient to perform bolus injection of 2.5–5 mg of dexamethasone 90 minutes prior to administration of general anaesthesia [19]. However, according to the actual data, such doses of drugs are not enough to suppress the systemic inflammatory response syndrome after surgery. At the same time, use of 8–10 mg of dexamethasone leads to significantly increased risk of hypoglycaemia and, as a result, infectious postoperative complications. Contra-insular effects of glucocorticoids are especially important to consider in respect of type 2 diabetes patients and substantiate the need of systematic monitoring of proper correction of hypoglycaemia level for such patients during the perioperative period [20]. In general, the particulars of patients in metabolic surgery call for the need to conduct further research aimed at performing objective assessment of the risks and benefits of preoperative administration of glucocorticoids.

CARBOHYDRATES LOAD.

Utilisation of carbohydrates load method consisting in consumption of 200–300 ml of isosmolar sweet drinks 2-3 hours prior to the surgery is aimed at reducing the phenomenon of postoperative insulin resistance and protein loss. According to the results of a number of meta-analyses, such approach allows reducing the duration of stay in a hospital after "large-scale" abdominal surgeries [21].

In addition, the need and potential risks of carbohydrates load used for type 2 diabetes patients is of particular interest. A series of conducted research proved that the above patients demonstrated the same time of gastric emptying as patients without diabetes and without the increase of the aspiration complications rate. However, postprandial peak levels of glycaemia among type 2 diabetes patients were significantly higher, and the time of glucose levels regression to the initial levels was longer (up to 180 minutes) than demonstrated by patients without carbohydrate metabolism disorders [22].

The above issues also require further study, in particular in respect of impact of the carbohydrates load on the rate of postoperative complications among patients suffering from diabetes – in particular among patients suffering from gastrointestinal forms of diabetic autonomic neuropathy, who may have significantly longer time of gastric emptying [23].

PREOPERATIVE FASTING.

Approaches to patient food intake immediately prior to the surgery in the context of ERAS are becoming more liberal. Data of actual research demonstrate that food intake 6 hours and 300 ml of liquid 2 hours prior to the administration of anaesthesia does not increase the gastric volume and does not significantly affects the acidity of the residual gastric content in comparison with patients who fasted throughout the night prior to the surgery [21]. Identical data were obtained also from baseline studies when comparing sub-populations of type 2 diabetes patients (including those with gastrointestinal neuropathy) and patients without diabetes. Therefore, the hypothesis on the increased risk of aspiration complications occurrence due to liberalisation of food intake regime prior to the surgery, is now considered to be effectively refuted.

However, contemporary original literature sources still indicate the need to conduct further research, especially in

respect of diabetes patients in order to form recommendations with higher level of evidence reliability [24].

INTRAOPERATIVE PERIOD

LAPAROSCOPIC SURGERY

Prioritisation of laparoscopic access in bariatric/metabolic surgery is now deemed to be a proven fact and is explained by lower rate of postoperative complications, reduced duration of stay in a hospital and recovery period, significantly lower levels of postoperative pains and better cosmetic effect in comparison with "open" surgeries. Discussion on potential advantages of "open" surgery related to the possibility of tactile dissection and more unobstructed performance of supporting procedures, was essentially closed in the beginning of the XXI century. Since 2011 and till now, almost 100% of metabolic surgeries in the world are performed laparoscopically. Possible problems at the stage of mastering the techniques, especially in respect of patients with morbid super-obesity, can be eliminated very quickly by gaining experience. Significant impact of carboxypneumoperitoneum on the duration of postoperative recovery also was not proven [25].

At present, minimally invasive surgery techniques actually became central and key element of ERAS, which allow realising its main principles to the fullest extent [25].

NASOGASTRIC INTUBATION

Routine use of nasogastric tubes in order to prevent failure of gaster sutures and gastroenteric anastomosis, postoperative gastrostasis, enteroparesis, was deemed to be quite appropriate until recently. However, according to the results of the latest research that included also bariatric patient population, placing nasogastric tube does not lead to a decrease in the rate of the above complications, does not significantly affect the duration of recovery of active vermicular movement and passage, and does not reduce the period of patients' stay in a hospital. Moreover, according to some authors, use of gastric tubes during a postoperative period facilitates nausea occurrence rate, increased rate of bronchopulmonary and intra-abdominal complications [26].

Therefore, at present the optimal approach in ERAS system is the utilisation of gastric tubes when needed, predominantly only in an intraoperative manner with following removal thereof immediately after the completion of the surgery [26].

ABDOMINAL DRAINAGE

The practice of routine (mandatory, preventive) abdominal drainage, which was traditionally based on the need of early diagnostics of intraabdominal complications (primarily failure of stapler sutures line or anastomosis and postoperative bleeding), now is reasonably questioned [27]. A number of authors demonstrated that routine use of drainage in metabolic surgery not only does not decrease, but on the contrary increases the rate of the above complications, repeated surgery and hospitalisations, creates preconditions for occurrence of inflammatory processes in the abdominal area [27] while not affecting significantly the rate of early infection occurrence. At the same time, absence of pathological discharge through the drainage from the abdominal cavity cannot reliably eliminate the possibility of postoperative complications.

Even though the level and quality of evidence still do not allow reaching unambiguous conclusions on the expedience of preventive drainage of patient abdominal cavity after metabolic surgeries, at present there is a quite high possibility of the fact that approaches to drainage will become more selective and indications for use thereof will be significantly limited [28].

STANDARDISATION OF ANAESTHETIC PROTOCOL

Comprehensive use of ERAS is possible only if certain standardised principles of anaesthetic management of a patient throughout the surgery are complied with. At present, the key principles include positioning of a patient on the operating table with elevation of the upper body (reverse Trendelenburg position or "beach chair position"), which, especially in the event of pneumoperitoneum, improves breathing biomechanics, allows avoiding using opioids of prolonged effect, which in turn allows avoiding adverse effects associated with the use thereof (including the so-called "opioid paradox" and drug addiction), adherence to the strategy of restrictive targeted infusion therapy in order to safeguard the patient from hypervolemia [29]. No less important is also the infiltration of trocar puncture sites of the abdominal wall with local anaesthetics and using the regional anaesthesia methods (in particular, TAP- and RS-blocks), prevention of intraoperative hypothermia (including heating of carbon dioxide for pneumoperitoneum), controlling the depth of anaesthesia via conducting Bispectral index monitoring [30].

At the same time, in respect of options for the regional anaesthesia, it is worth note the following. Even though according to the ERAS, the most optimal procedure for performing "open" abdominal surgeries is still deemed to be thoracic epidural analgesia, the use of this method in the metabolic surgery is significantly limited due to quite high rate of complications caused as a result thereof. At the same time, findings of a number of scientific papers allow us to conclude that while using laparoscopic access, the safe and efficient alternative to the above anaesthesia option is the use of multilevel afferent blocks of the abdominal wall, which can be performed under ultrasound or laparoscopic control. The data obtained require further confirmation in randomised clinical research [31, 32].

POSTOPERATIVE PERIOD

EARLY PATIENT ACTIVATION AND THROMBOPROPHYLAXIS.

In view of the rapid increase in the number of metabolic surgeries performed annually around the globe, it can be

said that even considering low overall level of mortality, the number of deaths in contemporary metabolic surgery makes tens of thousands of cases [33]. Among those deaths, over 50% are due to thromboembolic complications. Taking into account the fact that ERAS provides for shortening the duration of stay in a hospital, the majority of venous thromboembolic episodes currently occur at the ambulatory stage, most often during the first month after the surgery [33]. Therefore, the issue of thromboprophylaxis in the metabolic surgery undoubtedly remains pertinent.

It is worth noting that for patients suffering from obesity and metabolic syndrome, a characteristic pathogenetic feature is a prothrombotic state. This dictates the need for in-depth assessment of patients prior to the surgery and individual assessment of venous thromboembolic episodes occurrence risks. The optimal strategy is aimed at prevention of the above complications among those patients and at present comes to the combination of mechanical compression (compression stockings/socks or intermittent pneumatic compression of the lower extremities) and using drugs for prevention of such episodes during implementation of ERSA protocols (laparoscopic surgery and patient early activation within 4–6 hours after the surgery). Preventive use of cava filters did not prove decrease in the venous thromboembolic episodes rate among obese patients and therefore is considered impractical at present [34].

In-depth study of pharmacological prevention of thromboembolic complications has proven the advantage of low molecular weight heparin drugs (the most studied among those drugs is deemed to be enoxaparin) over the use of unfractionated heparin. According to the current recommendations, drug-based prevention of venous thromboembolic episodes for obese patients is advisable to commence 12–36 hours prior to the surgery with the first postoperative administration of enoxaparin not earlier than 6 hours after the surgery and maintaining the administration intervals of 12 hours (twice a day). A single subcutaneous dose of the drug in metabolic surgery is 3,000–4,000 anti-Xa IU for patients within the VTE low-risk group, and 4,000–6,000 anti-Xa IU for patients within the VTE high-risk group [35].

The issue of using low molecular weight heparin drugs is still subject to discussion. Advocates of prolonged thromboprophylaxis (up to 28 days of postoperative period) substantiate their position by significant (from 0.3 to 2.2%) increase of venous thromboembolic episodes rate during the period from 7 to 30 day after the surgery [33].

At the same time, recent research papers do not show the increased rate of the above complications when using so-called "restrictive" prevention strategy utilising low molecular weight heparin drugs only during the hospital stage (1-3 days) when utilising comprehensive ERAS principles. Among those principles, the biggest role has laparoscopic access, reducing the duration of the surgery and patient early activation (within 4-6 hours after the surgery) [4].

European recommendations of perioperative prevention of venous thromboembolic episodes when performing surgery on obese patients state that optimal duration of administration of low molecular weight heparin drugs for the majority of patients, with due regard of the above contradictions, is 10–15 days [34].

Prospects of solving the above problem may be related to individualisation of the thromboprophylaxis programme, which is based on achieving anti-factor Xa target preventive levels for each specific patient and utilisation of Xa factor selective inhibitors [35].

MULTIMODAL ANALGESIA

Multimodal analgesia within the ERAS system provides for utilisation of a combination of simultaneous systemic and regional mechanisms for pain management, synergistic interaction between which leads to significant increase of analgesic effect and allows administering lower doses of each of the pharmacological agents compared to other modes of analgesia.

Such approach, which is based on different-level (peripheral and central) effect on forming and transmission of pain impulse, allows reducing the risks of side effects of each specific drug and minimising or avoiding at all administration of opioid analgesics [36]. An important factor in ERAS system is objective assessment of the pain syndrome acuity using contemporary graded scales for assessment thereof, since being guided solely by patient's subjective sensation leads in most cases to underestimation of the pain and essentially makes it impossible to implement an important *pre-emptive* principle (proactive analgesia) [36].

Basic analgesia during early postoperative period according to the multimodal analgesia protocol is achieved via a combination of paracetamol (daily dose of up to 4 g/day) and one of non-steroidal anti-inflammatory drugs (selective or non-selective) [37]. No less important for ensuring "pain comfort" after the surgery are the above-mentioned regional afferent blocks of the abdominal wall [31]. When analgesia level is insufficient, it is appropriate to use opioids for pain relief (the so-called "rescue analgesia"). At the same time, the decision to use opioid analgesics in the metabolic surgery must be carefully weighed with due regard for its suppressive effect on the respiratory centre (especially for patients with obstructive sleep apnoea syndrome. It is advisable to move as early as possible from parenteral to oral administration of analgesics in order to decrease the rate of catheter-caused or infectious complications [36].

PREVENTION OF POSTOPERATIVE NAUSEA/VOMITING

Postoperative nausea is a significant problem in the metabolic surgery affecting, according to the data of various authors, 18–82% of patients and quite often is the cause of repeated hospitalisation or postponement of discharge from a hospital [38]. Current research and practical recommendations developed based on thereof, are focused on multimodal approach to prevention of postoperative nausea and vomiting using a combination of antiemetic drugs based on assessment of risk factors for each specific

patient [39]. The above strategy provides for prioritised use of propofol for induction and maintenance of anaesthesia, minimisation of opioids utilisation (including implementation of non-opioid protocol) during and after the surgery, restrictive option of infusion therapy [39]. Randomised clinical research conducted in the recent years on the use of antiemetic drugs evidence significant advantages of preventive use of haloperidol/dexamethasone/ondansetron combination in comparison with combination of only two drugs or monotherapy [39].

It is worth noting that despite compiled systematic best practices, the problem of postoperative nausea and vomiting in the metabolic surgery remains far from the final solution and requires further study.

FOOD INTAKE DURING POSTOPERATIVE PERIOD

ERAS system in the abdominal surgery field stipulates renewal of oral food intake as soon as possible: renewal of water intake – in 2-3 hours after the end of the surgery, consumption of liquid and semi-liquid food – on the first postoperative day with a gradual concentration of food density throughout several weeks or months. According to the results of recent studies, such an approach ensures reducing the perioperative stress, the rate of postoperative complications and mortality, facilitates rapid recovery of peristaltic action of the intestinal tract, shortens the duration of inpatient treatment [40].

Even though the above principles are currently being actively implemented in the metabolic surgery, the majority of authors acknowledge that for complete understanding of the risk/benefit balance of early renewal of food intake, further conduct of randomised clinical research is necessary [4].

It is worth noting that type 2 diabetes patients require more careful attention during the food intake renewal stages, since combination of early incretin (proinsular) effects of the surgery, decrease of body weight, forced diet and food intake regime may significantly affect the carbohydrate metabolism regulation. All of the above, especially in view of administration of anti-diabetic drugs without proper correction of its dosage and treatment regimen, may lead to undesirable hypoglycaemia episodes [40]. Therefore, careful glycaemia monitoring and addition into the multidisciplinary team of an endocrinologist, are important factors of the overall success within ERAS system.

CONCLUSIONS

Implementation of modern approaches allowed for significant improvement of the results of metabolic surgeries and bringing it as close as possible to the concept of "one-day surgery". Indeed, as contemporary literature sources analysis shows, the duration of hospitalisation in modern metabolic surgery centres is within the range of 1 to 3 days, while sometimes patients are even discharged on the same day of the surgery. Such reduction of time of stay in the hospital and transition to "remote patient follow-up", on the one hand, fits perfectly the essence of the ERAS and becomes even more relevant amidst the COVID-19 pandemic, while on the other hand, puts forth even more strict requirements to the quality of hospital care services. At the same time, specific features of type 2 diabetes patients indicate the need for their separation into a specific group. This is important because the above-mentioned patients face additional inherent perioperative risks, which may, inter alia, be related to the implementation of both individual elements of ERAS and ERAS system as a whole.

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CASE STUDY

CASE STUDY: MAJOR DUODENAL PAPILLA CANCER COMPLICATED BY ACUTE PARACANCROTIC NECROTIZING PANCREATITIS

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ABSTRACT

The given paper describes a case of treating adenocarcinoma of the papilla of Vater diagnosed as the cause after an episode of acute pancreatitis. The etiology of acute pancreatitis was considered idiopathic until the onset of complaints caused by tumor growth. The volume of radical surgery has changed intraoperatively due to the detection of infected limited necrotic clusters, didn't diagnosed both laboratory and instrumentally. Pathomorphological conclusion: considering clinical data, low-grade (G3) adenocarcinoma of the major duodenal papilla, which developed from pre-existing tubular villous adenoma of the duodenum or intraampullary papillary neoplasia (IAPN). Predicting the early detection of MNPs after AP episode requires further research by improving imaging techniques, introducing new non-invasive techniques and investigating circulating biomarkers. The scope of surgery for patients with clinically significant complications of tumor growth and identified competing diagnosis at the target site should be individually decided and weighed. Infected pancreatitis in the late stages requires careful diagnosis.

KEY WORDS: pancreatitis, periampullary tumor, idiopathic pancreatitis

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INTRODUCTION

While the leading position in the etiology of acute pancreatitis (AP) is occupied by gallstones and alcohol, rarer causes of the disease, such as drugs, trauma, congenital features of the pancreatic duct, tumors, etc., require additional measures for achieving best clinical outcome and prevention in standard diagnosis and treatment. The frequency of detection of malignant neoplasms of the pancreas and periampullary zone (MNP) as a cause of pancreatitis according to various sources varies from 1 to 10% [1-9].

Analyzing the probable predictors of MNP development [5,6], the pathophysiology of AP development in patients with later detected MNP can be considered in two ways:

A) Already developed tumor tissue, being associated with the pancreatic duct, obstructively initiates the development of AP, with treatment and diagnosis being stopped at inflammatory changes, postponing the standard way of treatment and follow-up depending on the severity of AP. Kimura et al. [6] also reported the release of specific chemical mediators during the growth and development of tumor tissue that trigger inflammatory changes in the gland.

B) Damage to the tissue of the pancreas after the acquisition of inflammatory changes in the form of a single or recurrent episode of AP, or the development of chronic pancreatitis, which can be considered as oncogenetic changes. [10]

Peculiarities of acute pancreatitis (AP) manifestation in the presence of pancreatic tumors and anatomical structures located in the area of papilla of Vater has not been reliably studied. The main mechanism of AP is driven by tumor obstruction of the main pancreatic duct (MPD), which leads to the release of enzymes into the pancreatic tissue (PT), while Pelletie et al. argue that with slow growth of pancreatic tumors, compression of MPD does not occur, as a result, AP develops less common.

MNPs diagnosed a few months after the first episode of AP are manifested by a resectable stage of the disease. However, in some cases timely diagnosis of MNP is delayed due to initially incorrect diagnosis, which worsens survival.

AP in pancreatic cancer is more common in patients older than 40 years with no alcohol abuse and gallstones in past medical history (4). Published studies reveal an increase in the 5-year survival rate of patients with a history of pancreatic cancer and a primary episode of AP by 16-23% compared with patients without an epizode. (5) Predicting the early detection of MNPs after AP episode requires further research by improving imaging techniques, introducing new non-invasive techniques and investigating circulating biomarkers.

The given paper describes a case of treating adenocarcinoma of the papilla of Vater diagnosed as the cause after an episode of acute pancreatitis.

CASE REPORT

Female patient I, born in 1954, was hospitalized in the surgical department at the clinical base of the General Surgery Department №1, Bogomolets National Medical

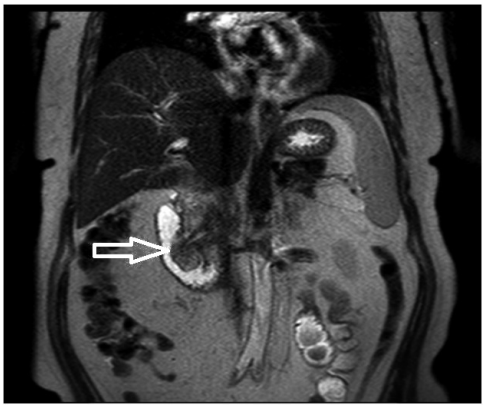

Fig 1. MRI of the patient's abdominal organs after temporary biliary stenting. The arrow highlights the tumor.

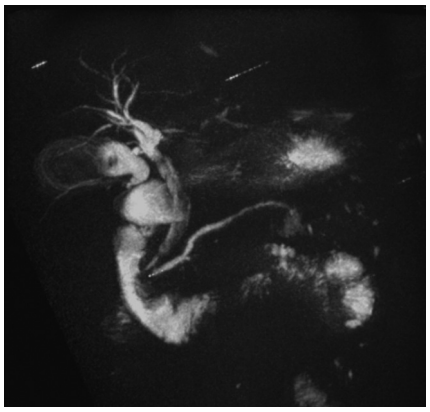

Fig 2. MRHPG after temporary biliary stenting.

Fig 3. CT scan three months after radical surgery.

University, due to urgent indications with complaints of skin yellowing and sclera and fever up to 38 C with moderate pain in the epigastrium with a previous diagnosis of mechanical jaundice and cholangitis.

From the anamnesis it was known that four months ago before the patient was hospitalized for acute pancreatitis for 17 days. Following the protocol volume of examinations, alimentary, biliary and hypertriglyceride genesis of the attack was then excluded. The diagnosis was: Acute idiopathic necrotizing pancreatitis, moderate severity; acute fluid collections. Conservative pancreatotropic therapy was performed according to the protocol and dosing regimens. Due to prolonged febrile fever and elevated levels of C-reactive protein (143.6 mg / l) and procalcitonin (1.7 IU) amid sonographic dynamic monitoring, the patient received two courses of antibiotic therapy with further improvement and reduction of C-reactive protein (CRP) and procalcitonin. After the treatment the patient's condition improved without invasive intervention and the patient was discharged for outpatient treatment with a predicted formation of walled-off necrosis. CT of the abdominal organs and FGDS were suggested among a number of other recommendations. Over the next four months before hospitalization with the mechanical jaundice, the patient was not examined for unknown reasons.

In reference to the episode of mechanical jaundice, at the time of hospitalization hyperbilirubinemia up to 258 μmol / l with elevated levels of transaminases (ALT - 480 U / l, AST - 425 U / l) was detected. The level of C-reactive protein was 114 mg / l.

Ultrasound examination of the abdominal cavity and pelvis revealed signs of ectasia of the common bile duct, enlarged pancreatic head, diffuse changes in the liver parenchyma and pancreatic tissue, without free fluid in the abdomen and pelvis.

According to the absolute indications for therapeutic and diagnostic purposes, after instrumental and laboratory examination with a diagnosis of mechanical jaundice and cholangitis endoscopic papillosphincterotomy, EPST were performed. Endoscopically - in the area of the mouth of the p.Vateri growth of the type of "cauliflower", the tumor-like formation extends to the distal choledochus. Choledoch stenting with 8.5 Fr plastic stent and p.Vateri biopsy were performed. The patient was diagnosed with p.Vateri tumor complicated by mechanical jaundice and cholangitis. According to morphological data after endoscopic biopsy villous adenoma p.Vateri was diagnosed.

Amid further therapy after normalization of bilirubin level the patient underwent MRI of the abdominal cavity (Fig. 1). Thus, in Vater's papilla there is a a formation of 23x17 mm, which exophytically penetrates into the lumen of the duodenum, moderately heterogeneous contrast. The distal segments of the choledochus and virsung duct are amputated in the thickness of the formation (Fig.2). The virsung duct is moderately ectasified to 4.5 mm.

After symptomatic treatment, the patient's condition improved; she was diagnosed with: Vater's papilla neoplasm. (Histologically villous adenoma P.Vateri). Mechanical jaundice. Acute cholangitis, Grade I (Tokyo Guidelines 2018). Partial obstruction of the duodenum. Acute necrotic pancreatitis, Walled-off necrosis. (disease duration - 4 months.) Cardiosclerosis of the aorta and coronary vessels. Hypertension stage II, grade 1, risk 3, high. CH I. Diabetes mellitus, stage of compensation, insulin independent variant.

Then, surgical treatment was planned as the next stage in the treatment of the disease after one month of endobiliary stenting with general condition considered as satisfactory and normalization of C-reactive protein and procalcitonin. Due to inability to reliably exclude the malignant nature of the tumor and the description of MRI images, it was planned to perform pancreatoduodenal Whipple resection. However, the volume of surgery was changed intraoperatively due to the detection of infected limited necrotic clusters. The following procedures were performed: Papillectomy, cholecystectomy, hepaticojejunostomy on the Brown loop, pancreatic necrosectomy, sanitation and drainage of the abdominal cavity, drainage of the omental sac. Intraoperatively: a tumor of the major duodenal papilla was contoured through the duodenum, covering the duodenum and disrupting the passage through it. In the area of the distal part of the pancreas, a demarcated

cluster was revealed: pancreatic sequesters were removed, necrosis affected the body and tail of the pancreas.

Intraoperative culture of pancreatic sequestration detected K.oxytoca * 10^5, sensitive to gentamicin, ceftazidime, ceftazidime-avibactam, cefepime, amikacin, levofloxacin, meropenem. Intraoperative culture of bile and endobilar stent found E. coli * 10^6, E. faecalis * 10^5, Kl. pneumoniae * 10^5 sensitive to gentamicin, ceftazidime-aviabactam, meropenem.

Intraoperative express biopsy was performed: Vater's papilla adenocarcinoma.

Microscopic description of the surgical macropreparation: "Duodenal wall tissue with complexes of invasive tumor, formed by layers of epithelioid and focal elongated cells with signs of significant pleomorphism / atypia. In some areas, the formation of single glandular cribrous structures is determined by tumor cells, which corresponds to low-differentiated G3 adenocarcinoma. The tissue of invasive neoplasia directly borders on the exophytic epithelial formation of tubular-villi / papillary structure with the presence of intraepithelial neoplasia / dysplasia of the intestinal type of low and high degree, corresponding to tubular villous adenoma or intraampullary papillary neoplasia.

Pathomorphological conclusion: considering clinical data, low-grade (G3) adenocarcinoma of the major duodenal papilla, which developed from pre-existing tubular villous adenoma of the duodenum or intraampullary papillary neoplasia (IAPN).

During further inpatient treatment, the patient received antibiotic therapy with amikacin intravenously. The postoperative period was complicated by the development of gallbladder bed abscess: in 10 days after surgery, according to CT with intravenous amplification, there was visualized limited accumulation of fluid content 53x39mm in the gallbladder bed, which spread to the parenchyma of Sg4b \ Sg5 contrasting. Puncture and drainage of the abscess under ultrasound control were performed. According to the microbiological study, E. coli * 10^7, Kl.pneumoniae * 10^7, sensitive to meropenem were detected: sanation and antibiotic therapy were performed with further condition improvement.

Diagnosis: Cancer of the major duodenal papilla pT-3NxM0 G3 (low-grade adenocarcinoma amid IAPN) II stage cl.group 2, Partial duodenal obstruction. Cholangitis. Acute necrotic paracancrous infected pancreatitis. Walled-off necrosis. (The duration of the disease was 5 months). Gallbladder bed abscess (condition after ultrasound puncture and drainage) IHD: cardiosclerosis of the aorta and coronary vessels. Hypertension stage II, grade 1, risk 3, high. CI I. Type 2 diabetes mellitus, stage of compensation, non-insulin dependent variant.

After the treatment, the patient was discharged from the hospital in a satisfactory condition. The condition improved and complaints leveled. The postoperative period lasted 28 bed-days.

Further on, the patient received three cycles of adjuvant chemotherapy Gemcitabine / Capecitabine, further treatment was discontinued due to the development of toxic hepatitis. Three months and one year after radical surgical treatment, CT control was performed with no recurrence detected (Fig. 3).

Problems in the diagnosis and timely initiation of MNP therapy may be related to the simplified post-hospital management of patients with acute pancreatitis who have suffered from its mild form. Konur and co-authors [4] comparing the severity of Balthazar of AP in patients with and without MNP, reported a mild disease in more than 80% of patients with MNP. Similar conclusions can be drawn for patients with AP who did not undergo surgery or whose condition improved significantly during the minimally invasive procedure. However, in a study by Shaoyun et al. [1], 83% of patients with AP and MNP underwent surgery, including tumor biopsy. Even if there is no history of gallstone disease and alimentary genesis, hypertriglyceridemia or surgery, patients are rarely re-examined, being limited to such preventive measures as, strict adherence to prescribed diet and enzyme replacement therapy. And in the case of diagnosed gallstones or hypertriglyceridemia, subsequent treatment and follow-up examination after discharge from the hospital have certain limitations due to the focus on a particular metabolic pathology. The authors suggest a greater prevalence of AP on the background of MNP due to problems with additional examination of patients with AP in the anamnesis. The same features can explain variation in the prevalence of idiopathic pancreatitis, which occupies up to 10% in the etiology of AP [8]. Routine ultrasound during inpatient treatment of patients and after treatment of AP and assessment of pancreatic size without clear visualization of the tumor in some cases can distort the conclusion amid patients' absence of measured cancer markers and other instrumental research methods. Kimura et al. [6] report that MNP cannot be ruled out even if the main pancreatic duct does not dilate in patients with acute pancreatitis, and that induction of AP in patients with MNP is not limited to spread to the main duct / its obstruction. Accordingly, the pathophysiology of this etiological factor is considered today.

In a cohort study held in 2018 [9], among almost 50,000 patients with AP, only 1.1% were diagnosed with MNP after the disease, and more than half (56%) of them in the period from two months to five years. The characteristics of the patients in this study indicate the presence of concomitant pathology and alcohol abuse in most patients, and the etiology is not related to gallstones (58%). Among the patients studied, the number of recurrent episodes of AP was also indicated, and among them 99% of those with recurrence of AP in the next two years were diagnosed with MNP – i.e. undiagnosed MNPs caused recurrent episodes of "idiopathic" AP.

What are the ways of choosing the right amount of surgery for this group of patients, when periampullary malignancy and the consequences of necrotic infected pancreatitis are simultaneously diagnosed? Given that infected limited necrotic accumulations were detected in the patient only during surgery, with normal levels of CRP and procalcitonin, as well as absent in the description of preoperative MRI signs of infection, the amount of radical intervention was changed, i.e. limited. The

erroneous exclusion of infection of pancreatic necrosis in the preoperative period could be explained by lower body reactivity due to the age - normal values of CRP and procalcitonin were accompanied by a satisfactory assessment of the general condition. The lack of MRI data for infection can be explained by the incorrectly chosen method of instrumental diagnosis, when the primary task was to confirm the tumor process. Individual approach, vigilance in the initial diagnosis and weighted risk assessment [11] play a key role in this case.

CONCLUSIONS

The case study describes the experience in treatment of malignant neoplasms of the major duodenal papilla in the patient with previous paracancrotic pancreatitis.

In the given case, loss of one of the instrumental types of follow-up examination (endoscopy), not indicated to the patients with idiopathic acute pancreatitis on admission, emphasizes the importance of increased diagnostic attention during outpatient or inpatient management of patients with the most common pancreatic disease.

The question of absolute indications for endoscopic interventions in patients with acute pancreatitis remains open. In the absence of signs of choledochal obstruction and gallstone disease over the initial hospitalization, endoscopic examination would be crucial in the early detection of a major duodenal papilla tumor, and as it later became clear, the etiology of the acute pancreatitis attack.

Predicting the early detection of MNP amid AP requires further research by improving imaging techniques, introducing new non-invasive techniques, investigating circulating biomarkers, revising clinical strategy.

The scope of surgery for patients with clinically significant complications of tumor growth and identified competing diagnosis at the target site should be individually decided and weighed.

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CASE STUDY

ASEPTIC MENINGITIS AS AN EXTRAHEPATIC MANIFESTATION OF HEPATITIS C: A CLINICAL CASE PRESENTATIONIN A WHITE YOUNG FEMALE EUROPEAN ADULT

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ABSTRACT

We aimed to provide a clinical case presentation of aseptic meningitis as an extrahepatic manifestation of hepatitis C. A 28-year-old ladyhas been admitted to the Regional Clinical Center of Neurosurgery and Neurology, Uzhhorod City, Ukraine, with mild meningeal signs and symptoms upon admission. Complex neurological, clinical, laboratory, and imaging examination was performed within 24 hours of admission. Mononuclear pleocytosis of the cerebrospinal fluid and positive express test on HCV were discovered. The patient was treated and showed full recovery. Specific neurological features of aseptic meningitis as an extrahepatic manifestation of hepatitis C in a young white adult were reported, described, and analyzed.

KEY WORDS: meningitis; extrahepatic; hepatitis C; HCV

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INTRODUCTION

An estimated up to 3% of the world's population is living with hepatitis C virus (HCV) infection [1]. Being one of the main causes of chronic liver disorders,such as progressive liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma, HCV is also responsible for extrahepatic manifestationsinvolving the skin, kidneys, salivary glands, eyes, thyroid, cerebrovascular, and immune systems [2-6] The severity of liver damage due to the disease doesn't correlate with extrahepatic manifestation [7] but the mortality rate is higher in HCV patients with extrahepatic complications [8-11]. However,little to no data are published about aseptic meningitis as an extrahepatic manifestation of hepatitis C [12].

Worldwide, the hepatitis C virus (HCV) infection is a leading cause of liver-related mortality, causing about 700 000 deaths each year [13]. An estimated 71.1 million people are chronically infected with HCV [14, 15].

THE AIM

We aimed to provide a clinical case presentation of aseptic meningitis as an extrahepatic manifestation of hepatitis Cin a white young female European adult.

CLINICAL CASE

We have provided a complex clinical, neurological, laboratory, and instrumental analysis ofan extrahepatic manifestation of hepatitis Cin a white young female European adult admitted to the Regional Clinical Center of Neurosurgery and Neurology, Uzhhorod City, Ukraine.

A twenty-eight-yers-oldlady presented to the primary care physician complainingof intense headache, photosensitivity, severe general weakness, dizziness, and nausea. Considered herselfsick for about 2 weeks, when she rapidly developed a headache, general weakness, and mild fever up to 37.5° Celsius. Received outpatient care, with little improvement. A week ago the intensity of the headache increased dramatically. The patient turned tothe Regional Clinical Center of Neurosurgery and Neurology and was hospitalized to clarify the diagnosis.

MEDICAL HISTORY

The patient's allergic history is negative and she has had no blood transfusions in the last 5 years. The patient does not smoke and does not take any recreational drugs or medications. Tuberculosis, typhoid and paratyphoid dysfunction, dysentery, malaria, venous diseases, and HIV infection were excluded. Hepatitis C since 2016.Denies any surgical interventions. There was no family history of any neurological disorder.

VITALS UPON ADMISSION

Upon admission to the department, the patient showed a normal general condition. The respiratory rate was 16

breaths per minute, oxygen saturation was 99%, and blood pressure was 110/70 mm Hg. A heart rate of 70 beats per minute and a temperature of 36.6° C.

CLINICAL EXAMINATION

The skin and visible mucous membranes were clean, heaving a healthy appearance, pinkish. Moderate facial hyperemia. Peripheral lymph nodes were not palpable. Vesicular respiration in the lungs, no wheezing. The liver was slightly enlarged +2 cm. There were no traces of non-drug injections. No edema. The abdomen was soft and painless on palpation.

NEUROLOGICAL STATUS

The patient was conscious and available for productive contact. Understood the addressed language and followed instructions. Anxious, low mood. Own language was preserved. Meningeal signspresented questionable stiffness in the occipital muscles. Eye slits D = S, pupils D = S. Movements of the eyeballs were in full. No diplopia. The face was symmetrical. Swallowing was not disturbed. The pharyngeal reflex and muscle tone in the extremities were preserved. Muscle strength in the extremities was diffusely reduced to 4.5 points. Tendon reflexes from the arms were high, and symmetrical, from the legs were high also, D = S.Left pathological carpal reflex was present. Surface sensitivity was not impaired. Pelvic functions with no issues. The patient was unsteady in Romberg's posture but the gaitwas intact.

LABORATORY AND INSTRUMENTAL EXAMINATION RESULTS

MRIof the brain upon admission was without pathological changes. Cerebrospinal fluid on TORCH infection was negative. Cerebrospinal fluid analysis: protein 0.38, glucose - 2.80, cell count 120 (57% lymphocyte, 43% neutrophil), erythrocyte 8-10, light yellow color, slightly cloudy. Cerebrospinal fluid samples were found positive for HCV RNA by polymerase chain reaction. Bacteriological analysis of cerebrospinal fluid - negative.Express test on HCV - positive. Blood for borreliosis - negative.

Within three days after admission: General cerebrospinal fluid analysis: protein 0.69, glucose - 4.20, cell count 199 (98% lymphocyte, 2% neutrophil), erythrocyte 20-30, color light yellow, slightly cloudy;MRI of the brain: signs of intravenous hypotension.

DIAGNOSIS

Aseptic meningitis as an extrahepatic manifestation of hepatitis C with mild paresis of the third pair of the right craniocerebral nerve, cephalic, and asthenic syndrome.

DISCHARGE

After treatment, clinical and laboratory improvements were noted: no complaints were voiced, and meningeal signs were not detected. However, mononuclear pleocytosis of the cerebrospinal fluid and an increased ALT persisted. The patient was discharged from the hospital in good condition under the supervision of a neurologist and an infectious disease specialist at the place of residence.

DISCUSSION

HCV has a large public health impact across the world. The prevalence of infection is soaringin lower and middle-income countries. The highest is in Egypt 4.4-15.0%, Gabon 4.9-11.2%, Uzbekistan 11.3%, Cameroon 4.9-13.8%, Mongolia 9.6-10.8%, Pakistan 6.8%, Nigeria 3.1–8.4%, and Georgia 6.7% [16]. In contrast, in high-income countries, the prevalence of chronic HCV is below 2% [17, 18].

HCV infections are mainly caused by high-risk exposures and behaviors among specific populations (men who have sex with men, intravenous drug users, people with multiple sexual partners, people who had cosmetic practicessuch as tattooing, people who had blood transfusions, blood products, or organ donations, unsterile dental equipment, etc).No vaccine against hepatitis C exists and no effective pre- or post-exposure prophylaxis is available [1]. However, viral eradication reduces the rate of extrahepatic deaths significantly[19-21].

Reported extrahepatic manifestations of HCV represent a wide spectrum of disorders, such as mixed cryoglobulinemia, associated vasculitis with multi-organpathology, porphyria cutanea tarda, lichen planus, autoimmune and/or lymphoproliferative disorders,fatigue, depression, cognitive impairment,insulin resistance, diabetes mellitus, accelerated atherosclerosis, cardiovascular, renal, central nervous system diseases, and increased cardiovascular disease morbidity and mortality [22-26]. However,data about meningitis as an extrahepatic manifestation of hepatitis C is very limited [12, 27].

HCV infection is an independent predictorof stroke and cerebrovascular death [28]. HCV viral load is independently associated withearly, asymptomatic carotid atherosclerosis [29]. However, there are only single reports of incidence of acute aseptic meningitis as an extrahepatic manifestation of hepatitis C [12, 27].

Viral meningitis is the most common form of meningitis worldwide [30]. Viral infection causes the inflammation of the meninges with an associated abnormal cell count in the cerebrospinal fluid [31]. Appropriate and timely evaluation is critical. As in the above-described clinical case, meningitis typically presents with the acute onset of fever, headache, photophobia, neck stiffness,nausea, vomiting, and signs of meningeal irritation [32]. Enteroviruses (Coxsackie or Echovirus groups) are the most common cause of viral meningitis across all age groups [33]. Herpes viruses that cause meningitis include herpes simplex virus 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6. Other viral causes include adenovirus, lymphocytic choriomeningitis virus, influenza, parainfluenza, and mumps [33]. Arboviruses that can cause viral meningitis include West Nile virus, Zika, chikungun-

ya, dengue, LaCross, Saint Louise encephalitis, Powassan, and eastern equine encephalitis virus [32]. The flavivirus family (HCV) is very rarely mentioned in the literature as the etiological agent of meningitis [34, 35].

CONCLUSIONS

HCV infection can cause significant extrahepatic manifestations and should beconsidered a systemic disease rather than a single (liver)disease [24]. Over 30 different conditions have been associated with chronic HCV infection. In general, the appearance of extrahepatic manifestations of HCV infection is unpredictable. The severity ofthese disorders does not necessarily correlate with theseverity of hepatic disease because even in cases of quietlyactive chronic hepatitis, as in the presented clinical case, a substantial interruption of healthand quality of life can occur. HCV should be considered in differential diagnoses of patients with meningitis.

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The Authors declare no conflict of interest.

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