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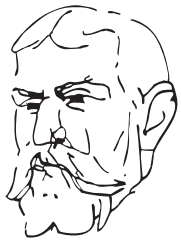

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PRACE ORYGINALNE
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BLOODSTREAM INFECTIONS AND ANTIMICROBIAL RESISTANCE OF RESPONSIBLE PATHOGENS IN UKRAINE: RESULTS OF A MULTICENTER STUDY (2013-2015)

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ABSTRACT

Introduction: Bloodstream infections (BSIs) are associated with high morbidity and mortality worldwide. However data of BSI from Ukraine are scarce.

The aim: To obtain the first national estimates of the current incidence of BSI and antimicrobial resistance of responsible pathogens, and associated mortality in Ukraine.

Materials and methods: A retrospective multicenter cohort study was conducted at the 14 hospitals of Ukraine between January 2013 to December 2015. Definitions of BSIs were adapted from the CDC. The identification and antimicrobial susceptibility of cultures were determined, using automated microbiology analyzer. Some antimicrobial susceptibility test used Kirby - Bauer antibiotic testing.

Results: Among 20,544 patients, 3816 (18.6%) BSIs were observed. The rate of health care associated BSI was 92.4%. Death was reported in 68.4% BSI cases. The predominant pathogens were: *Klebsiella pneumoniae* (25.1%), *Escherichia coli* (17.5%), *Staphylococcus aureus* (9.9%), *Pseudomonas aeruginosa* (8.9%), and *Acinetobacter* spp.(8.5%). The overall proportion of extended spectrum beta-lactamase (ESBL) production among Enterobacteriaceae was 24.8% and of methicillin-resistance in *S. aureus* (MRSA) 38.2%. Vancomycin resistance was observwd in 9.2% of isolated enterococci (VRE). Carbapenem resistance was identified in 33.1% of *P.aeruginosa* isolates and 63.2% of *A. baumannii* isolates. Resistance to third-generation cephalosporins was observed in 14.2% *K. pneumoniae* and *E.coli* 55% isolates.

Conclusions: Healthcare-associated BSIs and antimicrobial resistance of responsible pathogens together with their associated impact on mortality, presents a significant burden to the Ukraine hospital system. Surveillance of BSIs may help to delineate the requirements for infection prevention and control.

KEY WORDS: Bloodstream Infections, Healthcare-associated infection, Mortality, Pathogens, antimicrobial resistance

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INTRODUCTION

Bloodstream infections (BSIs) is associated with major morbidity and mortality [1-4]. Despite the great advances in medical science in the past century, BSI remains a growing public health concern in the modern world. BSI is among the top seven causes of death in many European and North American countries [2]. With an a case fatality rate of 20–50%, BSI have been declared the third most common cause of death in Germany [5]. The incidence of BSI has been demonstrated to vary significantly among regions, and this is in part related to blood culturing rates, population demographic differences and risk factor distribution in regions [1].

Bacterial resistance to antibiotics is increasing and creates a therapeutic challenge for clinicians when treating patients with BSI. Increasing rates of bacterial resistance leads many clinicians to empirically treat critically ill patients with broad-spectrum antibiotics, which can perpetuate the cycle of increasing resistance [6, 7]. Conversely, inappropriate initial antimicrobial therapy can lead to treatment failures and adverse patient outcomes [8].

Nosocomial BSI has particular importance from the public health standpoint. Optimizing the management and empirical antimicrobial therapy may reduce the burden of nosocomial BSI, but prevention is the key element [2]. A thorough knowledge about local epidemiology of resistance may contribute to limiting resistance and may have a significant role in designing effective antimicrobial stewardship policies [9].

BSIs can be caused by a wide variety of microorganisms, commonly *Escherichia coli, Klebsiella* spp., *Staphylococcus aureus, Enterococcus* spp., *Pseudomonas aeruginosa,* other bacteria, and yeast [2-4, 6, 9]. Microorganisms enter the bloodstream through various portals, including dissemination from a previous or concomitant infection and access via surgical sites, intravenous catheters, and other vascular access devices [10].

Among the infection prevention initiatives, surveillance of BSIs is the cornerstone to decrease infection rates in hospitalized patients, and it is considered to be the best way to assure patient safety. Continuous monitoring of BSI rates can be used to assess effectiveness of interventions and provides information which may be used for benchmarking comparison.

To identify BSIs prevention targets and reduce thus disparities between countries, ongoing surveillance is necessary. However, the epidemiology of BSI in Ukraine and associated treatment outcomes are not well studied. National network for the surveillance of HAIs is not in Ukraine. Resources are severely limited in country, creating difficulties implementing surveillance and establishing effective measures for infection control and BSI prevention. However, efforts to improve infection control training and begin HAI surveillance have been underway. Previous reports of BSIs in Ukraine were limited [3, 4].

THE AIM

The objective of this study was to obtain the first national estimates of the current incidence of BSI and antimicrobial resistance of responsible pathogens, and associated mortality in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN AND DATA COLLECTION

This is a retrospective, cohort study of patients with bloodstream infection (BSI) admitted to the 14 regional (tertiary) hospitals (50% adult (3600 beds) and 50% pediatric, total 1200 beds) that are similar in terms of technical equipment (ICU, haematology, surgery) highly specialized personnel, laboratory facilities) of Ukraine between January 1st, 2013 and December 31st, 2015. These hospitals provide care to individuals living within its catchment area (total 24 147 586 populations) and regularly take referrals from other (primary and secondary) hospitals.

All participating hospitals were required to have at least one full-time infection prevention and control professional (doctors), a clinical microbiology laboratory with the capacity to process cultures, and a data collection and reporting manager. The study included all positive blood cultures with recognized bacterial pathogens among patients who were hospitalized during the study period and additional clinical information from a subgroup of patients whose patient records were available to the investigators. Only the first bacteremic episode for each patient was included in the analysis. A standard data collection form was created to extract demographic and clinical data, microbiology (isolated pathogens and their antibiograms) and outcome information from routine patient records.

DEFINITIONS

In our study the CDC (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) definition of BSI was used [11]. Clinically significant bacteremia was defined as at least one positive blood culture together with clinical features compatible with BSI. When the clinical information was not available for judgment, the same organism(s) isolated within 48 h of another positive culture was considered as the same episode. A case of community-acquired BSI (CABSI) was defined as a patient with a positive blood culture from a blood sample drawn < 48 h after hospitalization. Patients were classified as having healthcare-associated hospital-onset BSI (HABSI) when the culture was obtained 48 hours or more after admission. Fatal cases were defined as patients who died in hospital. These data were only available from patients whose clinical records were available.

ETHICS

The Shupyk National Medical Academy of Postgraduate Education ethics committee approved the waiver of informed consent to participate in this study due to its retrospective design. All patient data were anonymised prior to the analysis. According to the Health Research Act of Ukraine, quality assurance projects, surveys and evaluations that are intended to ensure that diagnosis and treatment produce the intended results do not require ethical approval or patient consent.

MICROBIOLOGICAL METHODS

Microbial isolates were identified using standard microbiological techniques, including automated microbiology testing (Vitek-2; bioMe´rieux, France), and antibiotic susceptibility testing was performed by using the disk diffusion method according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). Some antimicrobial susceptibility test used Kirby - Bauer antibiotic testing.

STATISTICAL ANALYSIS

The prevalence of BSIs was reported as the percentage of the total number of patients. BSIs were analysed by type of infection (CABSI and HABSI), which were mutually exclusive. The analysis of statistical data was performed using Microsoft Excel for Windows. Results are expressed as median (range), meanstandard deviation for continuous variables, and number and corresponding percentage for qualitative variables. The primary endpoint was the epidemiology of the micro-organisms isolated in blood samples and their resistance to antibiotics. Comparisons were undertaken using Student's t-test and Pearson's chi-squared test or Fisher's exact test for categorical variables as appropriate. 'Statistical significance was defined as $P<0.05$.

RESULTS

PATIENT CHARACTERISTICS

During the study period (January 2013 and December 2015), 3816 of 20,544 patients were found to have BSIs.

Table 1. Demographics data of patients with bloodstream infections (BSI) in Ukraine (2013-2015)

Characteristics	Total		CABSI		HABSI	
	n	%	*n*	%	*n*	%
All	3816	100.0	519	13,6	3297	86.4
Sex						
Male	1788	46.9	225	43,4	1563	47.4
Female	2028	53.1	294	56,6	1734	52.6
Age						
≤28 days	1298	34.1	0	0	1298	100.0
29 days – 3 years	619	16.3	16	2,6	603	97.4
4 – 12 years	214	5.7	13	6,1	201	93.9
13 – 21 years	168	4.5	13	7,7	155	92.3
22 – 30 years	191	5.1	13	6,8	178	93.2
31 – 39 years	233	6.2	32	13,7	201	86.3
40 – 48 years	119	3.2	33	27,7	86	72.3
49–57 years	160	4.3	12	7,5	148	92.5
58 – 66 years	172	4.6	7	4,7	165	95.3
67 – 75 years	291	7,70	7	2,7	284	97.6
≥75 years	351	9,30	3	0,9	348	99.1

Notes: CABSI, community-acquired bloodstream infections; HABSI, healthcare-associated bloodstream infections.

The prevalence of BSIs was 18.6%. Among these patients, 7.6% (289/3816) CABSI and 92.4% (3527/3816) HABSI were observed. Of the cases of BSIs identified, 2611/3816 (68.4%) died before discharge. The age of the patients was ≤ 28 days to ≥ 76 years. From the confirmed cases of BSIs, 1788/3816 (46.9%) were male and 2078/3816 (53.1%) female. Sensitivity analysis of gender showed no differences between cases with and without clinical outcome (p = 0.053). BSI rate was highest in the age group of ≤28 days (34.1%; 1298/3816) followed by those in the age group of 29 days – 3 years (16.3%; 619/3816). Most patients (86.4%; 3297/3816) had HABSI. Table 1 shows the demographic data of patients with BSI.

HABSI were reported as catheter-related in 41.9% (1478/3527) and secondary to another infection site in 28.9% (1020/3527). For 29.2% (1029/3527) of the bloodstream infections, the origin was unknown, either after clinical ascertainment of possible sources of the infection (17.1%; 603/3527), or because data were missing (12.1%; 426/3527).

MICRO-ORGANISMS CAUSING BSI

A total of 3872 specimens isolated from 3816 patients with BSI. Gram-positive organisms accounted for 26.4% (1022/3872) of all BSIs and gram-negative organisms accounted 71.1% (2752/3872), respectively. Enterobacteriaceae were the most frequently isolated group of organisms among patients with BSI (51.4%, 1989/3872) with the predominant Enterobacteriaceae being *Klebsiella pneumoniae* (25.7%, 973/3872) and *Escherichia coli* (17.5%, 678/33872), followed by *P. aeruginosa* (8.9%; 334/3872), and *Acinetobacter* spp.(8.5%; 328/3872). Among Gram-positive isolates, *S. aureus* was the leading pathogen (9.9%; 382/3872), followed by Coagulase-negative staphylococci (CoNS) (6.8%; 265/3872). Anaerobes were not isolated. *Candida albicans* and nonalbicans fungi accounted for 2.1% (81/3872) and 0.4% (17/3872) of all BSI episodes (Table 2).

The proportions of CABSI and HABSI caused by Enterobacteriaceae were not statistically different (48.1% vs 51.9%, p = 0.23), similar for non-enterobacteriaceae Gram-negative bacteria (19.7% vs 28.2%, p = 0.132). In contrast, Gram-positive bacteria were more frequently identified in CABSI (29.2% vs 14.3%, p = 0.011) and *Acinetobacter* species were more common in HABSI.

ANTIMICROBIAL RESISTANCE

The overall proportion of extended spectrum beta-lactamases (ESBL) production among Enterobacteriaceae was 24.8%. The prevalence of ESBL production among *E. coli* isolates was significantly higher than in *K. pneumoniae* (44.4%, vs 12.4%, p < 0.001). Methicillin/oxacillin resistance was observed in 38.2% *S. aureus* and 44.2% CoNS isolates. Vancomycin resistance was reported in 9.2% of isolated enterococci (VRE). Carbapenem resistance was reported for 33.1% of *P.aeruginosa* isolates and 63.2% of *A. baumannii* isolates. Resistance to third-generation cephalosporins was reported in 14.2% *K. pneumoniae* and *E.coli* 55% isolates.

There was no difference in the proportion of ESBL production in community versus hospital setting among *E.*

Table 2. Distribution of responsible pathogens (n=3872) of bloodstream infections (BSIs) in Ukrainian hospitals (2013-2015)

Types of micro-organisms[a]	Total no. (%) of isolates	95% CI
Gram-positive cocci	1022 (26.4)	25.7 – 27.1
Staphylococcus aureus	382 (9.9)	9.4 – 10.4
CoNS	265 (6.8)	6.4 – 7.2
Staphylococcus haemolyticus	58 (1.5)	1.3 – 1.7
Streptococcus spp.	213 (5.5)	5.1 – 5.9
S. pneumoniae	135 (3.5)	3.2 – 3.8
S. viridans[b]	51 (1.3)	1.1 – 1.5
Beta-hemolytic streptococci	27 (0.7)	0.6 – 0.8
Enterococcus spp.	87 (2.2)	2.0 – 2.4
Other gram-positive bacteria	17 (0.4)	0.3 – 0.5
Gram-negative bacilli	2752 (71.1)	70.4 – 71.8
Enterobacteriaceae	1989 (51.4)	50.6 – 52.2
Klebsiella pneumoniae	973 (25.1)	24.4 – 25.8
Escherichia coli	678 (17.5)	16.9 – 18.1
Serratia marcescens	103 (2.7)	2.4 – 3.0
Enterobacter spp.	97 (2.5)	2.3 – 2.7
Enterobacter aerogenes	56 (1.4)	1.2 – 1.6
Enterobacter cloacae	82 (2.1)	1.9 – 2.3
Non-Enterobacteriacae	763 (19.7)	19.1 – 20.3
Stenotrophomonas maltophilia	63 (1.6)	1.4 – 1.8
Pseudomonas aeruginosa	334 (8.9)	8.4 – 9.4
Acinetobacter spp.[c]	328 (8.5)	8.1 – 8.9
Other gram-negative bacteria	28 (0.7)	0.6 – 0.8
Fungi	98 (2.5)	2.3 – 2.7
Candida albicans	81(2.1)	1.9 – 2.3
Nonalbicans fungi	17 (0.4)	0.3 – 0.5
Total no. of isolates	3872 (100.0%)	

Notes: BSIs, bloodstream infections; CoNS, coagulase-negative staphylococci; CI, confidence interval.
[a]Used 'The Bergey's Manual of Determinative Bacteriology', 9th Edn.
[b]Cases with Viridans group infection had at least two positive blood culture or single positive blood culture plus vegetation on echocardiography.
[c]Including 30 cases with A. baumannii, and 10 cases with A. lwoffii.

coli isolates (53.5% vs 55.3%, p = 1.0). In *K. pneumoniae* isolates, the proportion of ESBL production were higher in HABSI (21.3% vs 6.2%, p = 0.039). Compared with *K. pneumoniae*, *E. coli* isolates were also more frequently resistant to aminoglycosides (23.3%, vs 13.0%, p = 0.031) and fluoroquinolones (31.7% vs 8.3%, p < 0.001).

K. pneumoniae isolates associated with HABSI more frequently showed antibiotic resistance compared to CABSI isolates, though statistical significance was only reached for quinolones, while the pattern of resistance among *E. coli* isolates did not differ between the hospital and community. MRSA rates differed between community and hospital settings, though this did not reach statistical significance (p = 0.074).

IMPACT OF BSI ON INPATIENT MORTALITY

Of the BSI case-patients identified, 2611/3816 (68.4%) died before discharge. Case fatality of BSIs was assessed in the clinical dataset only. Overall case fatality rates among patients infected with Gram-negative and Gram-positive bacteria were 78.7%, and 21.3%, respectively. There was no case of death among patients with mix infections. Case fatality rate in CABSI (27.5%) was lower, but not statistically different from HABSI (36.4%) (p < 0.05). In the most frequent isolates of *P. aeruginosa*, *Acinetobacter* spp., *E. coli, K. pneumoniae,* and *S. aureus*, case-fatality rates were 37.9%, 36.3%, 26.8%, 23.6% and 12.4%. The pathogen-specific hospital mortality rate was significantly greater for *P. aeruginosa* and *Acinetobacter* spp. compared

to Enterobacteriaceae ($p < 0.001$ and $p = 0.008$, respectively). BSIs caused by *E coli* and *Klebsiella* spp. had relatively low mortality, ESBL-producing isolates were associated with a significantly increased mortality. In addition, the mortality rate of carbapenem-resistant gram-negative bacteria (*P. aeruginosa*, *Acinetobacter* spp. and *K. pneumoniae*) was high.

DISCUSSION

This study presents the first national estimates of the current prevalence of BSIs and antimicrobial resistance of responsible pathogens in Ukraine. During the study period (2013-2015) the prevalence of BSIs was 18.6%. Among these patients, 7.6% community-acquired and 92.4% healthcare associated infection were observed. Death was reported in 68.4% BSI cases.

The BSI prevalence by European countries ranged from 4.9% in Latvia to 19.0% in Cyprus. Bloodstream infections were highest in Greece at 18.9%, 16.1% in Netherlands, and 15.8% in Italy and Belgium at 14.0% [12]. The prevalence rate of BSIs in our study was 18.6%. The similar prevalence rate of 16% BSIs was observed in Pakistan [13].

The most frequently reported pathogens of BSIs were common all countries with some rank differences. In our study the predominant pathogens were *K. pneumoniae* (25.1%), *E. coli* (17.5%), *S. aureus* (9.9%), *P. aeruginosa* (8.9%), and *Acinetobacter* spp.(8.5%). *E.coli* is one of the most frequent pathogens causing CABSI and HABSI [14,15]. The highest percentage of *E. coli* was observed in France (26.6%) and the lowest in Cyprus (3.9%). *E. coli* was one of the three most common microorganisms in most of the European countries, except in Cyprus, Denmark, Greece, Romania and UK-Northern Ireland [12]. *S. aureus* is the most significant cause of gram-positive bacteremia in the worldwide [17]. *S. aureus* was most common in Malta (26.5%) and least common in Greece (3.0%). The percentage of enterococci varied between 4.5% in the Czech Republic and Norway and more than 20% of all microorganisms in Denmark and Sweden. *P. aeruginosa* ranged from 0% in Iceland and Latvia to 16.8% in Greece. *Klebsiella* spp. (79.0% of which were *K. pneumoniae*) varied from less than 4% in Iceland, Sweden, UK-England, UK-Northern Ireland and UK-Wales to 17.6% in Greece. The highest percentages of *Candida* spp. were reported from Denmark (19.4%), Iceland (10.8%) and Sweden (10.3%). The percentage of *Enterobacter* spp. was 6% or more in Belgium, Estonia, the Netherlands, Poland and Slovenia. No *Acinetobacter* spp. were reported from nine countries, but in four countries (Latvia, Romania, Bulgaria and Greece), the percentage of these bacteria ranged from 10.6% to almost 17% [12].

During last years, in worldwide clinicians have witnessed a growing incidence of BSIs along with resistance against commonly used antimicrobials [3-10, 12, 13]. Four European countries (Cyprus, Italy, Portugal and Romania) reported the most than 60% of meticillin-resistance in *S. aureus* (MRSA) isolates [12]. Sensitivity varies among MRSA strains, ranging 26–100% in US and 0–92% worldwide [16]. In 2017, 14.9% of *E. faecium* isolates in the European hospitals were reported to be resistant to vancomycin. In 2017, national percentages ranged from 0.0% to 43.9% [18]. In European countries the highest percentage of non-susceptibility to third-generation cephalosporins among Enterobacteriaceae isolates was observed in Greece (63.9%) and Latvia (71.4%) [12]. EARS-Net data indicated that in the EU mean resistance rate *E.coli* isolates was reported for aminopenicillins (58.7%), followed by fluoroquinolones (25.7%), third-generation cephalosporins (14.9%) and aminoglycosides (11.4%) [18]. Three countries reported over 20% of Enterobacteriaceae isolates resistant to carbapenem with the highest level (39.9%) being reported from Greece. Non- susceptibility to carbapenems in *K.pneumoniae* was higher than 50%, Greece (66.7%) and Lithuania (66.7%). The percentage of *P.aeruginosa* non- susceptibility isolates varied from 6.3% in Bulgaria to almost 49.4% in Greece [12]. In the EU, 30.8% of the *P. aeruginosa* isolates reported to EARS-Net for 2017 were resistant to at least one of the antimicrobial groups under regular surveillance (piperacillin ± tazobactam, fluoroquinolones, ceftazidime, aminoglycosides and carbapenems). Carbapenem resistance *P. aeruginosa* was reported in >40% of isolates in Slovakia (47.0%), Latvia (57.1%) and Romania (63.4%). [18]. In EARS-Net database, in 15 countries in the EU from where susceptibility rates for *A. baumannii* were reported >30% of all isolates were resistant to carbapenems (33.4%), fluoroquinolones (37.6%) and aminoglycosides (32.4%). Carbapenem resistance was reported in >60% of isolates in Poland (67.4%), Spain (68.2%), Cyprus (76.0%), Italy (78.7%), Latvia (79.4%), Bulgaria (80.4%), Romania (87.4%), Lithuania (88.5%), Greece (94.8%) and Croatia (86.2%) [18]. In our study the overall proportion of extended spectrum beta-lactamase (ESBL) production among Enterobacteriaceae was 24.8% and of methicillin-resistance in *S. aureus* (MRSA) 38.2%. Vancomycin resistance was observwd in 9.2% of isolated enterococci (VRE). Carbapenem resistance was identified in 33.1% of *P.aeruginosa* isolates and 63.2% of *A.baumannii* isolates. Resistance to third-generation cephalosporins was observed in 14.2% *K. pneumoniae* and *E.coli* 55% isolates.

BSIs are associated with high mortality worldwide. In North America and Europe, the nosocomial BSI case fatality rate ranges from 12 to 32% [2]. Our study shows a death rate of 68.4%; this rate appears higher than those reported by several international studies [2, 5, 19-21]. HABSIs are known to have a higher attributable mortality than infections acquired outside the hospital [23]. Mortality estimates vary with country, and overall in-hospital mortality has been estimated as 15.3% in Ireland [20], 40.0% in Brazil [20], and 28.9% in Vietnam [21]. The differences in mortality rates may be caused by differences in the distribution of pathogens and in the delivery of health care. The prevalence of AMR in Enterobacteriaceae was higher in Brazil [20] and Vietnam [21] than in other countries, and fungal BSIs were a significant contributor to mortality in some reports [20, 22].

In our study, CABSIs had a low mortality risk. BSIs caused by *E coli* and *Klebsiella* spp. had relatively low mortality,

ESBL-producing isolates were associated with a significantly increased mortality. In addition, the mortality rate of carbapenem-resistant gram-negative bacteria (*P. aeruginosa, Acinetobacter* spp. and *K. pneumoniae*) was high. The results suggest that antimicrobial resistance has a poor prognosis in BSIs. Further study is needed to investigate the effect of antimicrobial resistance on patient prognosis.

This study highlights the predominance of Gram negative bacteria and the emergence of multidrug-resistant organisms. Our results confirm some facts reported in many publications like the resistance to antibiotics and mortality.

STUDY LIMITATIONS

The limitations of this study include its retrospective design and conduct at a 58.3% region (14 from 24) in Ukraine. The results may not be representative of other regions of Ukraine with different distributions of antimicrobial resistance of responsible pathogens of BSIs. However, there are no national surveillance data in Ukraine, which compelled us to rely entirely on data from the only existing national retrospective study of BSIs. This investigation provides valuable data as a first study for national surveillance of BSI and potential comparison with data from other countries.

CONCLUSION

Healthcare-associated BSIs and antimicrobial resistance of responsible pathogens together with their associated impact on mortality, presents a significant burden to the Ukraine hospital system. Strategic planning and implementation of BSI surveillance is required in Ukraine.

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PRACE ORYGINALNE
ORIGINAL ARTICLES

PECULIARITIES OF CHANGES IN INDICES OF CALCIUM AND ZINC TRACE ELEMENTS AND MATRIX METALLOPROTEINASE-2 IN PREGNANT WOMEN WITH PERINATAL INFECTIONS

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ABSTRACT

Introduction: The role of calcium and zinc in the body is very high and diverse. Calcium performs a structural and important regulatory function, participates in key physiological and biochemical processes. One such regulation is its coordinated action with zinc, occurring in matrix metalloproteinases (MMP), which play an important role in reproductive processes.

The aim: To study the peculiarities of changes in the levels of calcium, zinc indices in serum of pregnant and umbilical cord blood of newborns and MMP-2 indices in serum of pregnant, depending on the etiology of perinatal infection.

Materials and methods: The study involved 230 pregnant and their newborns, who were divided into clinical groups depending on the pathogen of perinatal infection (PI): Group I - 60 women with viral PI; Group II - 60 women with bacterial PI; Group III - 60 women with combined PI; Group IV (control) - 50 women with a physiological course of pregnancy. The presence of PI is confirmed by the high titre of anti-infective M antibodies and low-avidity Ig G in serum and other biological fluids in pregnant women and their newborns. The study implied determination of the level of calcium and zinc in serum of peripheral blood in pregnant and cord blood of newborns, the level of MMP-2 in serum of peripheral blood in pregnant. The received data was statistically processed using STATISTICA software.

Results: The presence of PIs leads to the development of moderate but consistent hypocalcemia. Bacterial infection has a more pronounced negative effect than a viral infection, whereas the combined infection is most likely to affect the reduction of calcium in the blood serum of pregnant women. In the groups of patients with PI, the average zinc content in serum of pregnant and umbilical cord blood of newborns was reduced in comparison with the control group (1 μmol / l, Kruskall-Wallis test, $p < 0.05$). In all groups of pregnant with PIs, MMP-2 level in blood was elevated with respect to Group IV parameters by about 3-4 times (Kruskall-Wallis test, $p < 0.05$). Assessment of the decrease in the level of trace elements studied in pregnant with PIs showed a statistically significant relationship between the level of MMP-2 and the level of serum calcium in pregnant and PI in newborn (Kruskall-Wallis test, $p < 0.001$).

Conclusions: Taking into account the fact that MMPs belong to Zn- and Ca-dependent proteolytic enzymes, it can be assumed that microelementosis and changes in the level of MMP-2 found in women are interrelated, they are complex and contribute to the creation of favorable conditions for the risk of development of PIs and other complications of the fetus.

KEY WORDS: perinatal infection, pregnant, MMP-2, calcium, zinc indices

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INTRODUCTION

The role of calcium and zinc in the body is very significant and diverse. Calcium performs a structural and important regulatory function, participates in key physiological and biochemical processes [1.2]. One such regulation is its coordinated action with zinc, occurring in the matrix metalloproteinases (MMP), which, in turn, play an important role in embryogenesis, morphogenesis, and in the processes of angiogenesis.

MMPs are homologous proteins that contain Zn 2+ ions in the active center; Ca 2+ ions stabilize the molecule, are secreted by cells in an inactive form, and their catalytic activity is suppressed by specific tissue inhibitors [3].

MMPs as representatives of Zn- and Ca-dependent proteolytic enzymes are able to destroy all protein components of the extracellular matrix – a complex structure that ensures the integrity of the tissues. Adjustable remodeling of the extracellular matrix is necessary for normal growth and development of the body, and the violation of this process leads to the development of various disorders [4].

MMPs, affecting the processes of hydrolysis and removal of components of the extracellular matrix and release of various factors are able to modulate the activity of growth factors and cytokines. MMPs are key enzymes, since the remodeling matrix underlying their wide range of activities is involved in such important processes as proliferation and cell migration.

At the present stage of the development of biomedical science there is an accumulation of information on the effects and mechanism of action of various representatives of MMPs. [5.6]. Thus, MMP-2 is synthesized by mesenchymal cells (fibroblasts), neutrophils, macrophages and monocytes. MMP-2 hydrolyzes elastin, fibronectin, laminin, cleaves collagen types V, VII and X, participates

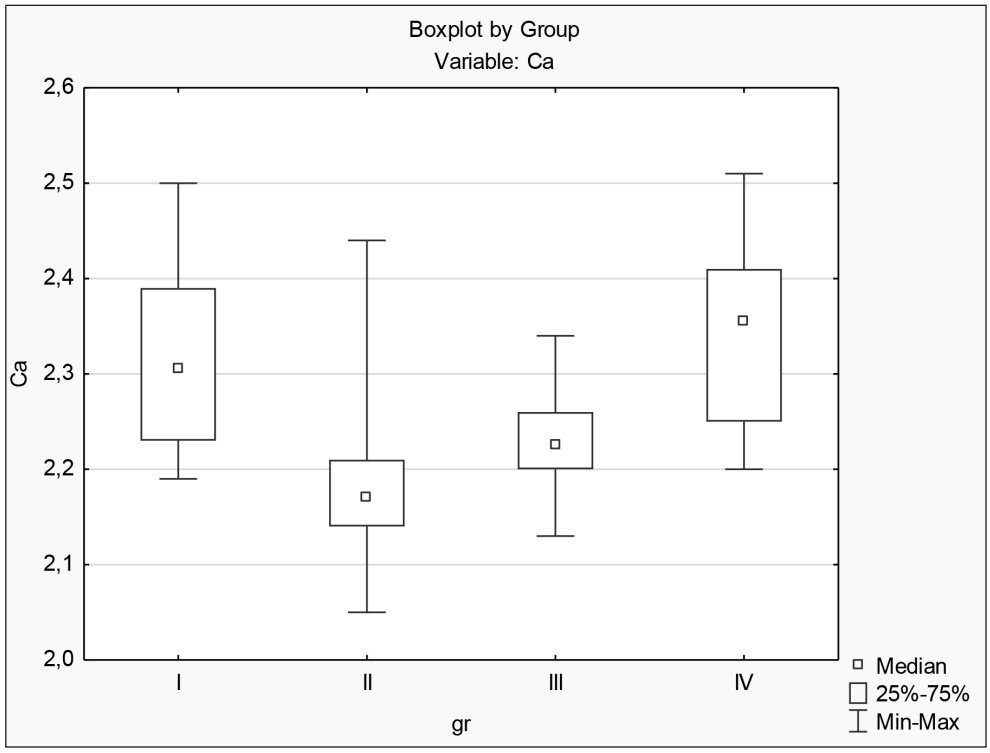

Fig. 1. The level of total calcium in the blood serum of pregnant in clinical groups under study (mmol / l)

in degradation of type IV collagen. In addition, MMP-2 cleaves monocytic chemotactic protein-3 and, as a result, reduces inflammation. MMP-2 affects the permeability of the vascular wall. Another important fact is that MMP-2, along with MMP-7, MMP-9 and MMP-12, can inhibit angiogenesis. This effect is associated with their ability to form angiostatin from plasminogen. [7].

Many studies demonstrate the importance of the MMP family in human reproduction: folliculogenesis, ovulation, formation and regression of the yellow body, implantation and placentation. Adequate expression levels of MMP-2 and MMP-9 are necessary for successful implantation and subsequent positive development of pregnancy [8]. MMP and tissue inhibitors of matrix metalloproteinases are of great importance at the beginning of labor and the destruction of fetal membranes [9]. Abnormally high expression and activity of MMP-1, MMP-2 and MMP-9 is the cause of pathological destruction of the fetal membranes, which causes spontaneous premature birth [10].

There is no doubt about the importance of MMP in reproductive processes. Potential use of integrated assessment of trace elements – calcium and zinc and the level of MMP as biomarkers is promising in view of the outlook for the development of abnormal pregnancy and childbirth which requires further research.

THE AIM

To study the peculiarities of changes in the levels of calcium, zinc indices in serum of pregnant and umbilical cord blood of newborns and MMP-2 indices in serum of pregnant, depending on the etiology of perinatal infection.

MATERIALS AND METHODS

The study involved 230 pregnant women. All of them were divided into three clinical groups depending on the perinatal infectious (PI) agent:

– Group I – 60 women with viral PI and their newborns;
– Group II – 60 women with bacterial PI and their newborns;
– Group III – 60 women with combined PI and their newborns.

The fourth (control) group (IV) included 50 women with a physiological course of pregnancy and their newborns.

The presence of PI was confirmed by the high titre of anti-infective M antibodies and low-dose Ig G in serum and other biological fluids in pregnant and their newborns.

The level of trace elements in the serum of peripheral blood of pregnant and cord blood (CB) of newborns was determined by spectrophotometric method using the diagnostic kits "Filisit-Diagnostika" (Ukraine).

In the blood serum of pregnant women, the level of MMP-2 was determined by the immune-enzymatic method using the human-MMP-2 reagent sets produced by "RD Systems" (USA).

Statistical data processing was performed using the general-purpose data processing software Statistica for Windows version 6.1. To represent the data series, the median was used and the mean value as a measure of the level; standard deviation and quartiles as measures of range; minimum and maximum value for the idea of the overall variability of indices.

To determine the differences between the groups, Mann-Whitney's non-parametric criterion (MWC) was used.

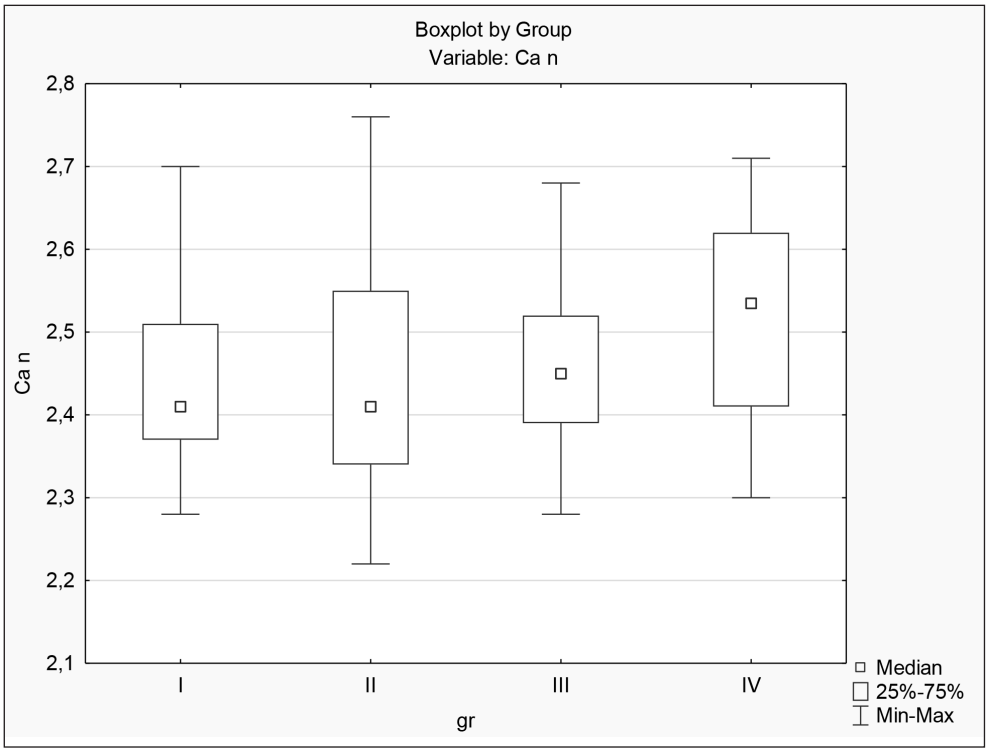

Fig. 2. The total calcium level in the umbilical cord blood of the pregnant in clinical groups under study (mmol / l)

RESULTS AND DISCUSSION

The data on the effect of PIs on the level of calcium in serum of pregnant and CB is shown in Figures 1 and 2.

The above data shows that the mediums and the magnitude of variations in serum calcium levels in all examined groups were within the normal limits [11]. However, at the same time, Group II (interquartile range was 2.21 ÷ 2.25 mmol / l, median value was 2.23 mmol / l) and Group III (interquartile range was 2.13÷2.20 mmol / l), and median an significance was 2.16 mmol / l) were found to have a general trend towards a statistically significant decrease in all indices compared to those in the control group (interquartile range – 2.25 ÷ 2.41 mmol / l, and the median value of this indicator is 2.35 mmol / l), i.e. in patients with a physiological course of pregnancy. At the same time there were features of changes in blood serum indices of patients depending on the type of infection. Group III patients were found to have the lowest level: the median value was 2.16 mmol / l versus 2.35 mmol / l in control (Kruskall-Wallis test, $p < 0.05$). It is noteworthy that the level of calcium in pregnant with bacterial infection (Group II) was lower compared with the group of patients with viral infections (Group I – interquartile range – 2.22 ÷ 2.38 mmol / l, median value – 2.31 mmol / l).

The comparative analysis showed that the level of calcium in Group II was lower compared to Group I. In Group III, hypocalcemia was expressed to a greater extent against Groups I and II. The dependencies are statistically significant, $p < 0.05$ (Kruskall-Wallis test).

Consequently, the findings suggest that the presence of PI leads to the development of moderate but consistent hypocalcemia, with bacterial infection having a more pronounced negative effect than the virus, while the combined infection most significantly affects the reduction of calcium in the blood serum of pregnant women.

The study of the level of calcium in the umbilical cord blood (Fig. 2) showed that in Group IV the interquartile range was 2.41 ÷ 2.62 mmol / l, and the median significance of this indicator was 2.53 mmol / l. In Group I, the following data were obtained: interquartile range – 2.36 ÷ 2.50 mmol / l, median value – 2.40 mmol / l. In Group II, the interquartile range was 2.38 ÷ 2.51 mmol / l, the median value was 2.44 mmol / l, and in Group III, the interquartile range was 2.33 ÷ 2.54, and the median value – 2.41 mmol / l.

Despite the fact that the findings on the level of calcium in CB were within the limits of norm, the tendency to hypocalcemia in the mother indicated a possible risk of development of a decrease in supply of this most important mineral for the fetus.

Zinc is an essential trace element necessary for the development and functioning of the body. Deficiency of zinc in women can lead to various complications of pregnancy, premature birth, some abnormalities in the development of the fetus, including disorders of the formation of the reproductive system of the child. Zinc enhances the immune response in relation to bacteria and viruses, stimulates the processes of antibody formation. Zinc deficiency is associated with a decrease in bactericidal activity of amniotic fluid and CB [12. 13]. In this regard, it was advisable to conduct a study of zinc levels in pregnant women with PIs.

Data on the serum zinc content in pregnant with PIs and their newborns' CB are presented in Figures 3 and 4.

The obtained results show that in Group IV of healthy pregnant serum zinc levels were 16.45-20.0 μmol / l with a

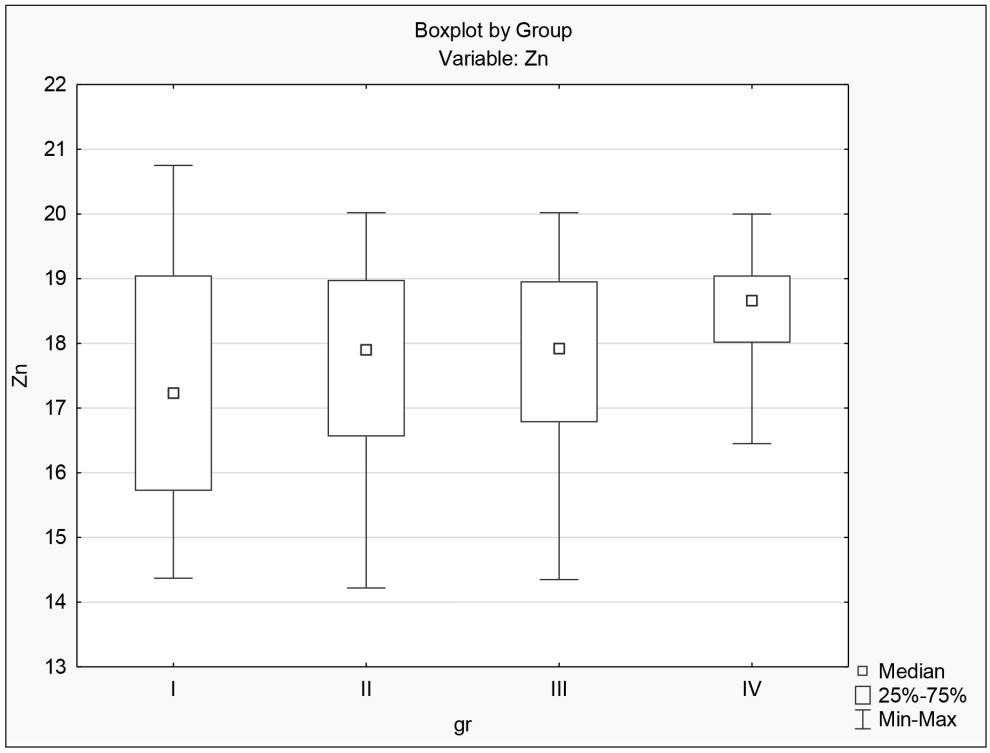

Fig. 3. Zinc level in the blood serum of pregnant in clinical groups under study (μmol / l)

median of 18.66 μmol / l, that is, were at the upper limit of norm. In the groups of patients with PIs, the mean serum zinc content was reduced in comparison with the control group (approximately by 1 μmol / l, Kruskall-Wallis test, $p < 0.05$) (Fig. 3). The differences in zinc content between Group I (interquartile range – 15.71 ÷ 19.04 μmol / l, median value – 17.22 μmol / l), Group II (interquartile range – 16.79 ÷ 18.97 μmol / l , median significance – 17.93 μmol / l) and Group III (interquartile range – 16.55 ÷ 19.00 μmol / l, median value – 17.91 μmol / l) were not detected. In all groups, regardless of the type of infection, the indicator was reduced to the same extent (Kruskall-Wallis test, $p < 0.05$).

A similar picture was observed in CB of the parturients of these groups (Fig. 4). Thus, in Group IV the interquartile range was 21.35 ÷ 23.17 μmol / l, and the median value of this indicator was 22.15 μmol / l. In Group I, the interquartile volume was 19.06 ÷ 22.89 μmol / l, the median value was 21.01 μmol / l. In Group II the interquartile range was 19.07 ÷ 22.68 μmol / l, the median value was 21.69 μmol / l, and in Group III the interquartile range was 19.05 ÷ 22.55 μmol / l, and the median value was 20.67 μmol / l.

The data presented in Fig. 4 demonstrate that in patients of all examined groups the zinc content in CB at 1 μmol / l, (Kruskall-Wallis test, $p < 0.05$) was lower than that of Group IV.

At the next stage of the study, an evaluation of the dependence of the content of MMP-2 on the type of infection in the studied groups was performed using a discriminant analysis of the grouping of variables at a statistically significant level (Kraskaall-Wallis test, $p < 0.01$).

In all groups of pregnant women I-III with PIs, level of MMP-2 in blood was elevated with respect to the parameters of Group IV by about 3-4 times (Kruskall-Wallis test, $p < 0.05$).

In Group II the median index recorded in the groups of bacterial and viral etiology was 30.12 ng / ml, and also in Group I – 31.18 ng / ml with an interquartile range of 29.87 ÷ 33.18 ng / ml and 27.87 ÷ 35.50 ng / ml respectively. The highest mean median – 36.05 ng / ml was recorded in Group III, the interquartile range was 29.84 ÷ 43.29 ng / ml, whereas in the control group the median was 12.79 ng / ml and the interquartile velocity was 10.72 ÷ 15.67 ng / ml (Kruskall-Wallis test, $p < 0.05$). The revealed peculiarities of changes in the level of MMP-2 in the studied groups of pregnant are obviously related to the influence of PI. [14].

Assessment of the decrease in the level of trace elements studied in pregnant women with a PIs showed a statistically significant relationship between the level of MMP-2 and the level of serum calcium of pregnant and newborn's CB (Kruskall-Wallis test, $p < 0.001$).

CONCLUSIONS

The level of trace elements of calcium and zinc is characterized by negative changes in pregnant women with PIs. A more severe deficiency of calcium in pregnant women was found in groups with bacterial or combined infections. At the same time, the zinc content in the groups of patients with PI is lower compared with the norm and does not depend on the type of infection. The obtained data testify that in the blood of pregnant with PIs there is

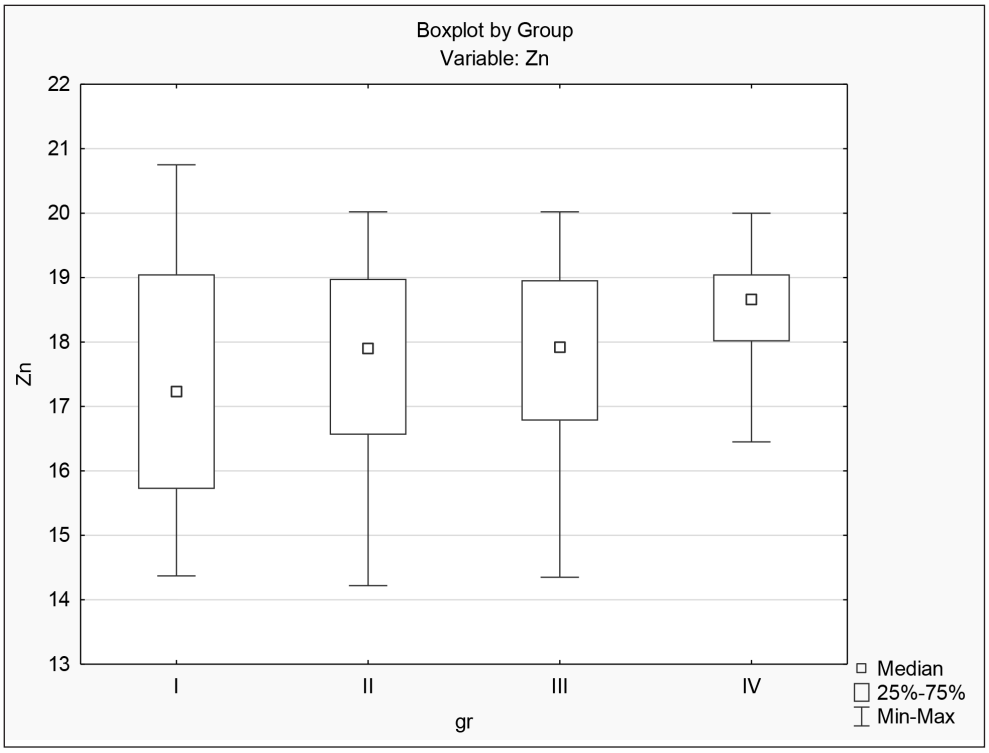

Fig. 4. Zinc level in the umbilical cord blood of pregnant in clinical groups under study (μmol / l)

a decrease in the trace elements important for the body, which is related to the etiology of the PI. In the case of a viral infection, moderate zinc deficiency was observed compared with the control parameters. The presence of bacterial infection caused a more sharp decrease in the level of both investigated minerals in blood serum – calcium and zinc. Minimum values of the minerals under study were recorded in the group with combined infection. CB was also found to have a moderate decrease in the level of these elements, but there was not always a direct correlation between the deficiency of minerals in the mother's blood and in CB.

Taking into account the fact that MMPs belong to Zn- and Ca-dependent proteolytic enzymes [15], it can be assumed that those found in women with microelementosis and changes in the level of MMP-2 are interrelated, complicated and contribute to the creation of favorable conditions for the risk of developing PIs and other complications in the fetus.

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PRACE ORYGINALNE
ORIGINAL ARTICLES

THE INFLUENCE OF URIC ACID LEVEL ON ERYTHROCYTE MORPHOLOGY IN NORMOTENSIVE PATIENTS

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ABSTRACT

Introduction: Hyperuricemia is an independent risk factor for high-normal blood pressure (BP) both in men and women. The effect of uric acid (UA) on erythrocyte morphology in normotensive patients needs further study.

The aim – to evaluate the impact of serum UA level on erythrocyte morphology in normotensive patients.

Materials and methods: Patients were divided into two group according to the UA level: the first group - 38 patients with UA level < 400 mcmol/L; the second group - 42 patients with UA level ≥ 400 mcmol/L. Studies on erythrocyte morphology were conducted using cytological analysis and scanning electron microscopy.

Results: Patients of the 1st group had poikilocytosis level of 4,6%, while type I echinocytes were 3,2%, type II echinocytes – 1,1%, stomatocytes – 1,3%. In the 2nd group, poikilocytosis exceeding 5% was observed in 12 patients with mean values of altered shapes of 12,8±1,2%. In the 2nd group, type I echinocytes was 6,2% (9,4±0,9%) more, type II echinocytes – 1,3% (2,4±0,5%) more, stomatocytes – 0,3% (1,0±0,2%) more. In the study correlation between UA and poikilocytosis was found: in the 1st group – r = +0,21 and in the second group – r = +0,42. In the 1st group, correlation between UA and BP was moderate for SBP – r = +0,34 and weak for DBP – r = +0,29; in the 2nd group: SBP – r = +0,49 and r = +0,35 for DBP.

Conclusions: Direct correlation between uric acid level and poikilocytosis level becomes more intensive when uric acid level exceeds ≥ 400 mcmol/L.

KEY WORDS: uric acid, erythrocyte morphology, normotensive patient

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INTRODUCTION

Among the population of Central and Eastern Europe, hyperuricemia (HU) prevalence is 28% in female and 23% in male [1]. Moreover, HU is an independent risk factor for high-normal BP both in men and women [2]. Meta-analysis of 97824 patients shows that a high UA level can be a reason for AH development [3]. Studies, devoted to the influence of uric acid level in serum on erythrocyte morphology show that there is a relationship between UA level and red cell distribution width (RDW) in patients with AH [4]. However, this issue is still being discussed and needs further study, as periodicals provide information about the absence of the relationship between UA and change in erythrocyte morphology [5]. Incubation of erythrocytes in the solution containing uric acid causes change in morphology with predominance of echinocytosis; therefore, it is reasonable to suppose that the same phenomenon will become obvious in vivo. Pathogenetic mechanism for changing the forms of erythrocytes explains the ability of UA to decrease zeta potential of erythrocytes [6].

THE AIM

The objective is to evaluate the impact of serum UA level on erythrocyte morphology in patients with blood pressure not exceeding reference values.

MATERIALS AND METHODS

The study included 80 normotensive patients that were divided into two groups: first group included 38 patients with UA level < 400 mcmol/L, second group included 42 patients with UA level ≥ 400 mcmol/L. The exclusion criteria were bone and articular pathology and anemia of any nature. Twenty-four-hour blood pressure monitoring in both groups was performed by using ABMP-50 HEACO monitor. Reference values were ≤ 135 mm Hg for average systolic blood pressure (SBP), and ≤ 85 mm Hg for diastolic blood pressure (DBP) [7].

Studies on erythrocyte morphology were conducted using the Romanovsky- Giemsa method with May-Grünwald modification with cytologic analysis of smear and also using scanning electron microscopy. Scanning electron microscopy was performed by using scanning electron microscope РЭИ-106т "SELMI" with low-vacuum chamber. Poikilocytosis was considered to be a state when a number of erythrocytes with the change in shape exceeds 5% from the common pool of erythrocytes [8].

UA level was determined by using biochemistry analyzer Cobas 6000. Roche Diagnostics (Switzerland). Patients enrollment for formation of groups as well as instrumental examinations were conducted in Sumy Laser Clinic LLC (Cooperation Agreement No. 62.14-01.16-21/н).

Table I. Main characteristic of the studied groups M±m

Index, unit of measurement	Investigated groups		P-value
	First group (HU-)	Second group (HU+)	
	n=38	n=42	
DaySBP (mmHg)	120±5	132±4	P_{1-2}<0,001
DayDBP (mmHg)	74±4	82±4	P_{1-2}<0,001
Uric Acid (μmol/L)	326±28	466±32	P_{1-2}<0,001
Poikilocytosis (%)	4,6±0,8	12,8±1,2	P_{1-2}<0,001
Type I echinocytes (%)	3,2±0,4	9,4±0,9	P_{1-2}<0,001
Type II echinocytes (%)	1,1±0,2	2,4±0,5	P_{1-2}<0,001
Stomatocytes (%)	1,3±0,3	1,0±0,2	P_{1-2}>0,05
RDW (%)	11,8%±0,9	13,2±1,0	P_{1-2}<0,001

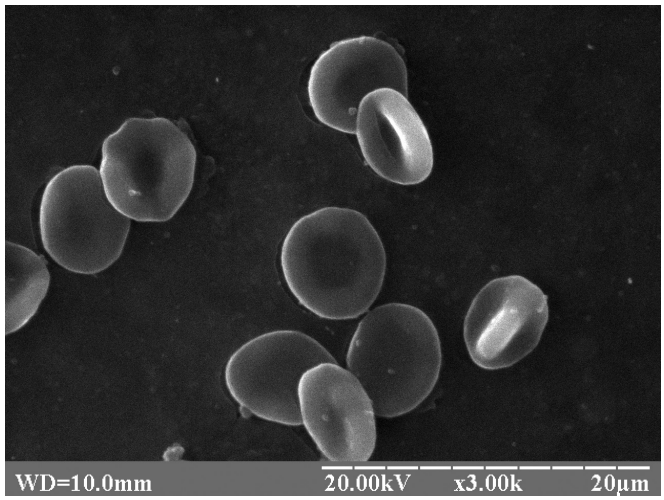

Figure 1. Electronogram of the normotensive patient: poikilocytosis 4,2%. Magnification × 2000

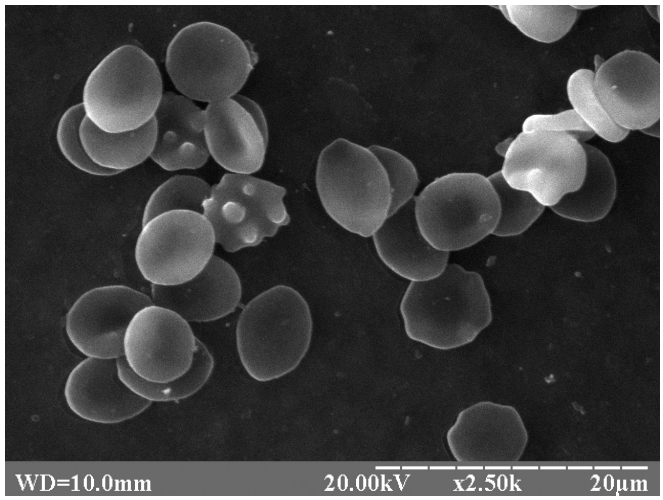

Figure 2. Electronogram of the normotensive patient with hyperuricemia: poikilocytosis 12%. Magnification × 2000

Scientific study was conducted in compliance with international and national legislation on ethics in accordance with the Law of Ukraine No. 690 dated September 23, 2009 "On Approval of Procedure for Conducting Clinical Trials of Medicinal Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of the Ethics Committees". Design of the study with regard to adherence to ethical, moral, and legal principles was approved by Bioethics Committee of Medical Institute of Sumy State University (Protocol No. 15 dated January 15, 2015). Patients of all groups have signed informed consent forms for participation in the study in accordance with World Medical Association's Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". Statistical processing of the obtained results was performed by using Windows 10 - Office Professional Plus software in accordance with Microsoft licensing agreement (Agreement ID: V0731528) with the use of parametric and non-parametric methods of variation statistics. Normality of distribution of the value was checked by using the Shapiro-Wilk test and a method of direct visual evaluation of histograms of proper values.

Quantity values with normal distribution were presented as M ± m. To compare data with normal distribution, parametric tests with evaluation of Student's t-test were used. Correlation analysis was used for evaluation of dependence between variables.

RESULTS AND DISCUSSION

At the baseline, levels of average systolic blood pressure (SBP) and average diastolic blood pressure (DBP) were different: with an increased UA level, the second group had a significantly higher SBP and DBP (table I).

Patients of the first group (HU-) with UA level < 400 mcmol/L had poikilocytosis level of 4,6%, while type I echinocytes were 3,2%, type II echinocytes – 1,1%, stomatocytes – 1,3% (fig.1).

In the second group (HU+), poikilocytosis exceeding 5% was observed in 12 patients with mean values of altered shapes of 12,8±1,2%. In the second group, type I echinocytes was 6,2% (9,4±0,9%) more, type II echinocytes – 1,3% (2,4±0,5%) more, stomatocytes –0,3% (1,0±0,2%) more (fig.2).

In the first group, red cell distribution width (RDW) was 11,8%±0,9; in the second group RDW was 1,4% higher.

The study found a direct correlation between UA level and intensity of poikilocytosis: weak correlation was observed in the first group – r = +0,21 (p<0,05), and moderate correlation was observed in the second group – r = +0,42 (p<0,05). In the first group, correlation between UA level and average blood pressure was moderate for SBP – r = +0,34 and weak for DBP – r = +0,29; in the second group, correlation was moderate for SBP – r = +0,49, and r = +0,35 (p<0,05) for DBP. While studying the relationship between UA level and RDW, one has found weak correlation: r = +0,16 in the first group and r = +0,21 (p<0,05) in the second group.

The results indicate the ability of UA to impact BP level even within reference values. In patients with hyperuricemia, influence of UA level on the values of average BP demonstrates a stronger correlation than that in patients without hyperuricemia. There is a direct relationship between UA level and degree of poikilocytosis that increases when UA level exceeds 400 mcmol/L.

Red cell distribution width is higher in normotensive patients with hyperuricemia, although it does not fall outside the range of reference values. A weak direct correlation between UA level and RDW was established in both groups.

CONCLUSIONS

Increase in uric acid level in normotensive patients has an impact on erythrocyte morphology by increasing poikilocytosis with predominance of type I echinocytes. It is proven that a direct correlation between uric acid level and poikilocytosis degree becomes more intensive when uric acid level exceeds ≥ 400 mcmol/L.

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PRACE ORYGINALNE
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EFFECT OF KALLISTATIN AND GHRELIN ON THE FORMATION OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH CHRONIC PANCREATITIS AND ATHEROSCLEROSIS

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ABSTRACT

Introduction: The article is devoted to the optimization of complex diagnosis of endothelial dysfunction in patients with a combination of chronic pancreatitis and atherosclerosis.

The aim: To study the level and effects of kallistatin and ghrelin on the formation of endothelial dysfunction in patients with chronic pancreatitis and atherosclerosis.

Materials and methods: 54 patients with chronic pancreatitis were examined. The serum kallistatin level was determined by immunoassay using the Human Serpin A4 ELISA Kit from RayBiotech according to the application method. The serum ghrelin level was determined by immunoassay using the Human/Mouse/Rat Ghrelin Enzyme Immunoassay Kit from RayBiotech. Endothelial dysfunction was determined by the method proposed by D.Celermajer.

Results: The study of endothelial-dependent and endothelial-independent vasodilatation is indicative of the presence of a pronounced ndothelial dysfunction in patients with chronic pancreatitis and atherosclerosis, which was manifested by a decrease in their level to 8.7±0.4% and 16.8±0.7%, respectively. The level of kallistatin and ghrelin in patients with chronic pancreatitis and atherosclerosis (15.44 ± 3.97 ng/ml and 276.69 ± 10.06 ng/ml respectively) also confirmed their important role in the formation of endothelial dysfunction in these patients.

Conclusions: The study of ghrelin and kallistatin level in serum can serve as a criterion for determining the severity of chronic pancreatitis and atherosclerosis, the development of endothelial dysfunction, and be a marker for predicting their future course.

KEY WORDS: Chronic pancreatitis, atherosclerosis, endothelial dysfunction, ghrelin, kallistatin

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INTRODUCTION

The endothelium is a multi-level cellular structure that permeates all organs and systems of the body. A significant influence on the endothelium has a state of lipid metabolism. Endothelial cells contain receptors for low-density lipoprotein (LDL), being a natural reservoir for binding their excess. Constantly interacting with peripheral blood cells, the endothelium controls the migration of cells to the depth of the vascular wall. Since blood flow depends on the diameter of the vascular bed, the balance of the coagulation and anticoagulation system factors produced by the endothelium is of fundamental importance [1].

The protective role of kallistatin in the vessels and organs is provided by vasodilation, inhibition of angiogenesis, inflammation, oxidative stress, apoptosis and fibrosis in the tissues of the body. Kallistatin is the key to inhibiting the use of kallikrein tissue and stimulating endothelial nitric oxide (NO) synthase (eNOS), sirtuin 1 (SIRT1), and signaling suppressor of 3 cytokines (SOCS3). Mechanically, kallistatin inhibits vascular inflammation through interaction with a transcription factor such as the Kruppel-like factor 4, which results in increased expression of eNOS and in NO levels in endothelial cells. At the same time, the exhaustion of endogenous kallistatin enhances organs` damage, enhances oxidative stress, inflammation, and fibrosis [2].

The expression and distribution of kallistatin in endothelial and smooth muscle cells of the blood vessels confirm its effect on the cardiovascular system. Increase in oxidative stress and reduction in the bioavailability of NO are important factors contributing to the pathogenesis of such systemic diseases as atherosclerosis, and also create conditions for the progression of the inflammatory process in the pathology of individual organs (including, in chronic pancreatitis) [3].

Ghrelin, as a multifunctional peptide hormone, that participates in the formation of eating behavior, energy balance, regulation of carbohydrate and lipid metabolism, as well as in modulation of the gastrointestinal tract functioning [4]. According to recent studies, ghrelin has potent anti-inflammatory properties by inhibiting proinflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor, and binding of mononuclear cells to human endothelium [5].

THE AIM

The aim of the research – to study the level and effects of kallistatin and ghrelin on the formation of endothelial dysfunction in patients with chronic pancreatitis and atherosclerosis.

Table I. Doppler changes in BA in examined patients with pulmonary arterial hypertension and atherosclerosis, as well as control group

Indicator	Control group (n=30)	Patients on HP	
		I group (n=31)	II group (n=23)
	M ± m	M ± m	M ± m
Diameter of BA at the beginning of the study, mm	4,52±0,04	4,37±0,05	3,99±0,03*
Diameter for 30 seconds of reactive hyperemia, mm	6,42±0,05	5,31±0,03^	3,66±0,02*
Diameter for 60 seconds of reactive hyperemia, mm	6,23±0,08	4,61±0,05	3,88±0,03*
Speed of blood flow by BA, cm / sec	98,6±3,0	80,1±3,5	69,9±3,2*
EDVD (%)	13,8±1,05	10,5±0,7	8,7±0,4*
EIVD (%)	28,2±1,1	22,6±0,3	16,8±0,7*

Note: statistically significant difference between the indices in patients of the II group and the control group: * - p <0,05; statistically significant difference between the indicators in patients from groups I and II: ^ - p <0,05.

MATERIALS AND METHODS

54 patients with chronic pancreatitis underwent examination in the gastroenterological department of the Transcarpathia Regional Clinical Hospital named after A. Novak and in the family outpatient clinic by a gastroenterologist. The control group consisted of 30 practically healthy persons without signs of pancreatic-duodenal zone damage. The patients were from 30 to 61 years old. There were 39 (72.2%) male and 15 (27.8%) female among patients.

The diagnosis of chronic pancreatitis was based on complaints, anamnestic data, laboratory and instrumental methods of examination in accordance with the Marseilles-Roman`s criteria (1989), supplemented by Ya.S. Zimmermann (1995), as well as since the points system M-ANNHEIM.

The diagnosis of atherosclerosis was based on measuring of thickness of the intima-media layer of the carotid artery, the presence of the lipid profile violations and atherogenicity coefficient.

The serum`s kallistatin level (Serpin A4) was determined by immunoassay using the Human Serpin A4 ELISA Kit from RayBiotech, according to the methodology. An analysis of the results was carried out at a wavelength of 450 nm.

Serum ghrelin levels were determined using an enzyme-linked immunosorbent assay according to the implementation method. The human immunoassay kit RayBiotech Human / Mouse / Rat Ghrelin Enzyme Immunoassay Kit was used for the study. Evaluation was performed at a wavelength of 450 nm.

Endothelial dysfunction (ED) was determined according to the method proposed by D.Celermajer through detection of endothelial-dependent vasodilatation (EDVD) of the brachial artery (BA). EDVD was researched through the formation of reactive hyperemia by applying a cuff on distance from the site of the study. The diameter of the BA was measured after 10-15 minutes after rest. As a normal reaction, an increase in the diameter of BA on60-90 seconds against a background of reactive hyperemia was estimated at 10% or more. For the study of endothelial-independent vasodilatation (EIVD), the patient received 0.5 mg of nitroglycerin sublingually (as an endothelial-independent relaxation stimulus of peripheral vessels). Measurement was repeated in 2 and 5 minutes after taking nitroglycerin. EIVD was diagnosed when BA expansion in reactive hyperemia was significantly less than that of nitrates.

All patients were divided into 2 groups: group I included 31 patients with CP without atherosclerosis, group II - 23 patients with CP and atherosclerosis.

The methodology of studies corresponds to the Helsinki Declaration. The statistical processing of the patients` results was carried out using program STATISTICA 10.0 (firm StatSoft Inc., USA).

RESULTS

An ultrasound duplex scan of BA was performed in all patients and the EDVD and EIVD of BA were determined to detect ED. Table I shows the results of this survey.

According to results presented in Table I, the presence of ED was observed in all patients with CP and atherosclerosis. At the beginning of the study, there was a significant decrease in the diameter of the BA to 3.99±0.03 mm in patients with CP and atherosclerosis in comparison with the control group (4.52±0.04 mm) by duplex scanning of the BA. Patients with a CP without atherosclerosis also showed a tendency to decrease in diameter (4.37±0.05 mm), but these data were not statistically significant in comparison with the control group. Also, in patients with CP and atherosclerosis, there were more pronounced changes in the diameter of BA in 30 and 60 seconds of the study compared with the group of patients with pulmonary arterial hypertension without atherosclerosis and control group were observed. The EDVD study also indicates that there is a pronounced ED in patients with CP and atherosclerosis, which was manifested by a decrease in its level to 8.7±0.4% compared with 13.8±1.05% in the control group, respectively. Analyzing the indices of EIVD in patients with CP and atherosclerosis, the changes in comparison with the group of patients with CP (without atherosclerotic lesions) and control group (16,8±0,7% versus 22,6±0,3% in group I and 28.2±1.1% in the control group, respectively).

The serum kallistatin and ghrelin level were studied in all patients to detect the effects of these hormones on the course of these diseases.

Table 2. Comparison of the ghrelin, kallistatin and EDVD parameters in the examined patients

Indexes	Patients with CP without atherosclerosis		Patients with CP and atherosclerosis	
Ghrelin-Kallistatin	r=0,881	p=0,039	r=-0,743	p=0,044
EDVD-Kallistatin	r=0,674	p=0,035	r=-0,635	p=0,005
EDVD-Ghrelin	r=0,706	p=0,024	r=0,675	p=0,002

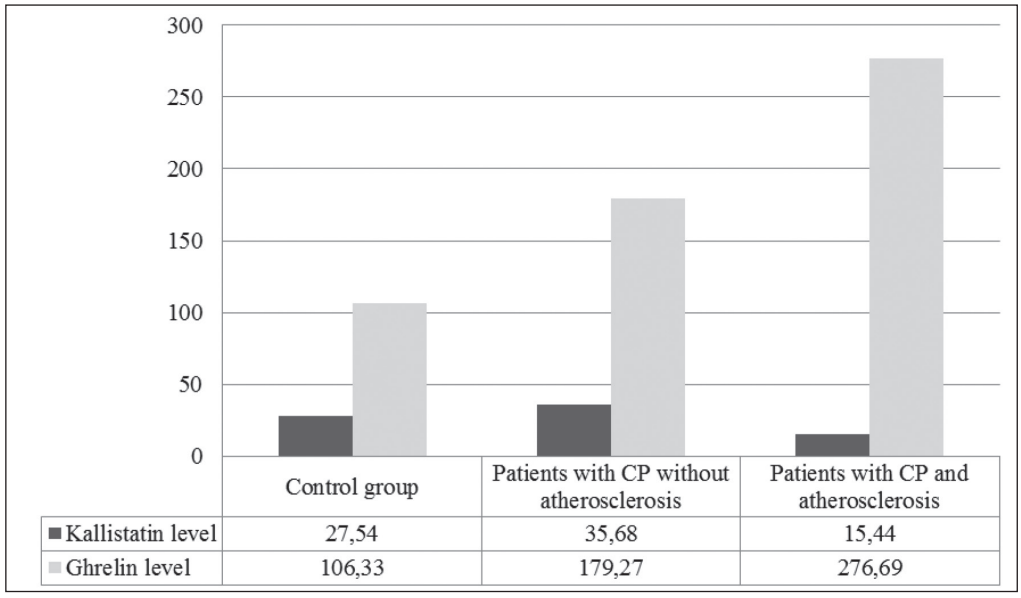

Fig. 1. Changes in the level of kallistatin and ghrelin in patients with CP and the control group

As can be seen from Figure 1, kallistatin level was increased in all patients with CP without atherosclerotic changes (up to 35.68±4.67 ng/ml) compared with the control group (27.54±3.95 ng/ml). Instead, a significant decrease in serum kallistatin (15.44±3.97 ng/ml) level in patients with CP and atherosclerosis, compared to the control group and the group of patients with CP without atherosclerosis were observed. An increase in serum ghrelin level to 179.27±9.84 ng/ml in patients with CP without atherosclerosis and to 276.69±10.06 ng/ml in patients with CP and atherosclerosis compared with the control group (106.33±9.43 ng/ml) were determined.

As shown in Table II, a positive correlation between the level of ghrelin and kallistatin (r = 0.888; p = 0.039), between the level of EDVD and the level of kallistatin (r = 0.674; p = 0.035), and between the level of EIVD and the level of ghrelin (r = 0.706; p = 0.024) were observe. A direct correlation between the level of EDVD and the level of ghrelin in patients with CP and atherosclerosis (r = 0.675; p = 0.002) and a negative correlation between the level of ghrelin and kallistatin (r = -0.743; p = 0.044) and between the level of EDVD and the level of kallistatin (r = -0.635; p = 0.05) were established.

DISCUSSION

In other author's studies of kallistatin was observed to inhibit inflammation in animal sepsis' models, myocardial ischemia-reperfusion, arthritis and salt-induced renal injury, etc. Kallistatin inhibits endothelial cell apoptosis and inflammation-induced organ damage by activating KLF4-eNOS 18, PI3K-AKT-eNOS and AKT-FOXO1 signaling pathways 19 and by preventing tumor necrosis factor-α (TNF-α)-mediated endothelial activation. It was shown that kallistatin inhibits atherosclerotic plaque formation caused by partial left carotid artery (PLCA) ligation in apoE-/- mice. Kallistatin also inhibits in plaques and the liver inflammation in vivo [6]. Other studies have shown kallistatin protective role in vascular aging. Kallistatin's anti-aging effect is mainly attributed to oxidative stress suppression by preventing miR-34a-mediated inhibition of antioxidant gene expression [7].

Due to its pleiotropic activity on energy metabolism, ghrelin has become a topic of great interest for experimental research. Furthermore, ghrelin seems to exert inhibitory effects on pancreatic acinar and endocrine secretory functions [8].

It is the first time when the level and effects of kallistatin and ghrelin on the formation of endothelial dysfunction in patients with CP were studied. Increase in the serum kallistatin level in all patients with CP without atherosclerotic changes confirms the hypothesis about the probable participation of kallistatin in the formation of organism`s protective mechanisms in the chronic inflammatory process in the pancreas, and its level can serve as a new biomarker for the diagnosis of CP. Significant reduction in serum kallistatin level in patients with CP and atherosclerosis provide the opportunity to assume the depletion of quinidine reserves in endothelial and smooth muscle cells of the body as a response to chronic systemic inflamma-

tory process with atherosclerosis and local inflammatory process in the pancreas in patients with CP.

Increase in the serum ghrelin level confirms its important role not only as an orexigenic hormone, but also its role in the pathogenesis of inflammation and oxidative stress in these patients.

Consequently, in response to inflammation (in the case of CP and atherosclerosis), protective mechanisms are triggered in the body, which are aimed in suppressing the inflammatory process. An increase in serum kallistatin levels, the key effect of which is inhibition of the kallikrein-kinin system, is likely to be considered as a response to inflammatory processes in the pancreas and vascular wall, which are aimed in limiting inflammation and preserving the integrity of the endothelial layer. However, with a combined and prolonged course of CP and atherosclerosis, there is an exhaustion of the compensatory possibilities of the organism and, accordingly, a decrease in its level in serum, which facilitates the process of chronicity and the formation of ED in such patients.

CONCLUSIONS

1. In patients with CP and atherosclerosis, an increase in serum ghrelin levels and a decrease in serum kallistatin level on the background of ED are observed with the results of EDVD and EIVD.
2. Patients with CP without atherosclerosis have an increase in serum ghrelin and kallistatin level.
3. The study of the ghrelin and kallistatin level in serum can serve as a criterion for determining the severity of CP and atherosclerosis, the development of ED, and be a marker for predicting their future course.

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MATHEMATICAL MODELING OF THE ELASTIC PROPERTIES OF THE MUCOUS FLAPS IN CONDUCTING PATCHWORK OPERATIONS OF THE ORAL CAVITY

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ABSTRACT

Introduction: To date, there are techniques that allow dental surgeons to restore the lost volume of bone mass, but the level of complications during augmentation remains consistently high. One of the main types of postoperative complications is the exposure of bone augmentate and its infection as a result of ischemic or destructive processes in the mucous shreds, which cover the augmentate, resulting from their overgrowth.

The aim: The purpose of our research was to increase bone augmentation effectiveness in patients with secondary edentulism and to reduce risk of postoperative complications caused by ischemia of the mucous membranes because of their tension by mathematical simulation of tensile limits and permissible deformation for the mucous membranes of the oral cavity.

Materials and methods: As a research method was selected a two-component Mooney-Rivlin model, taking into account the indicators of elasticity and static strength of flat samples in tension, which allows them to perform hyperprime behavior at small and moderate deformations. For computer simulation of epithelial flap deformation during operation by finite element method we used ANSYS software environment.

Results: Since elastic forces are potential, the work of forces does not depend on the way of tension. Only the initial and final states of the sample, i.e. its initial and final forms, play a role.

Conclusions: The flap of 30×25 mm can be stretched and thus it is necessary to eliminate the deficit of fabric up to 5 mm wide in the direction of the Y axis (vertical axis). The relative elongation is $\lambda = 25/20 = 1.25$. The flap tension first occurs in the y direction.

KEY WORDS: flap surgery, elasticity of the mucous flap, stretching of the mucous flap, mathematical modeling

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INTRODUCTION

In modern dentistry, tendency to help patients with secondary edentulism by dental implantation method is more clearly observed [1]. However, this diagnosis is often followed by loss of bone tissue by patients that makes it impossible to widely use dental implants. Today there are techniques that allow surgeons-dentists to restore lost bone volume [3], but degree of complications during bone augmentation remains persistently high. One of the main types of postoperative complications is the bone augmentat exposure and its infection resulting from ischemic or destructive processes in the mucous membranes covering the augmentat due to their overextension [14].

THE AIM

The purpose of our research was to increase bone augmentation effectiveness in patients with secondary edentulism and to reduce risk of postoperative complications caused by ischemia of the mucous membranes because of their tension by mathematical simulation of tensile limits and permissible deformation for the mucous membranes of the oral cavity. The challenge for us was to create a working mathematical model for better planning of surgical intervention.

MATERIALS AND METHODS

The two-component model of Mooney–Rivlin [2, 5] was chosen as a research method to consider parameters of elasticity and static strength using flat tensile specimens and to analyze their hyper-elastic behavior in small and moderate deformations. For computer simulating the process of epithelium graft deformation during an operation, the ANSYS software [14] uses finite element method.

RESULTS AND DISCUSSION

Almost all materials have some degree of elastic properties. This includes biological tissues. If external forces causing a deformation do not exceed a certain limit, then deformation disappears after removing these forces. Hereinafter we will assume that the bodies exposed to the external forces are perfectly elastic, i.e. they completely restore their original form after removing any load.

We will also assume that the elastic body material is homogeneous and continuously distributed throughout the body, so that the smallest element dissected out of the body has the same physical properties as the whole body. To simplify considerations, we will assume that the body is isotropic – its elastic characteristics in all directions are the same.

In general, stress is distributed unevenly over a cross-section (Fig. 1, cross-section *mm*). To get the stress value in the small segment ΔS dissected out of the cross-section *mm* at the point *O*, first we note that the forces acting on this elementary segment from the body part *B* towards the body part *A* can be reduced to the resultant ΔF. Now, if we continuously reduce area of the elementary segment ΔS, then limit value of the ratio $\Delta F/\Delta S$ will give us the stress value in the cross-section *mm* at the point *O*. Boundary direction of the resultant ΔF is the stress direction at this point. In general, the stress vector is inclined to the subjected segment ΔS, and it can be decomposed into two components: normal stress perpendicular to the segment, and tangential stress acting in the segment plane ΔS.

There are two types of the external forces affected on the body. The forces distributed over the body surface, such as pressure of one body to another or hydrostatic pressure, are called surface forces. Forces distributed across the body volume, such as gravity, magnetic forces or (in case of body motion) inertial forces, are called body forces. Surface forces per unit area and body forces per unit volume, so-called volume forces, are decomposed into three components parallel to the Cartesian *x, y, z* coordinate axes.

The letter σ denotes normal stress, and the letter τ – tangential one. Indices are added to these letters to indicate applied stress plane orientation. Let us consider a very small cubic element (Fig. 1) with faces parallel to the coordinate axes. Component designation for the stresses acting on the element faces, as well as the directions considered positive, are shown in Fig. 2. For example, the normal stresses components acting on the element faces perpendicular to the *y*-axis are denoted by σ_y. The index *y* indicates the stresses acting on the segment perpendicular to the *y*-axis. Normal stress is considered positive when it causes element tension, and negative when it causes its compression.

The tangential stresses are divided into two components parallel to the coordinate axes. In this case, two indexes are used – the first one shows normal direction to this plane, and the second one shows the stress component direction. For example, if you again consider the faces perpendicular to the *y*-axis, then component in the *x*-direction is denoted by τ_{yx}, and component in the *z*-direction – by τ_{yz}. Positive directions of the tangential stress components on the boundary of a cubic element are considered to be coincided with the positive directions of the coordinate axes, if tensile stress on the same boundary coincides with the positive direction of the corresponding axis. If the tensile stress has a direction opposite to the positive axis direction, then the positive directions of the tangential stress components change to the opposite. In accordance with this rule, the positive directions of all stress components on the right face of the cubic element (Fig. 2) coincide with the positive directions of the coordinate axes. If the left face of the same element is considered, the positive directions change to the opposite.When considering the elastic body deformations, we will assume that there is a sufficient number of constraints that prevent the body movement as a rigid whole and make it impossible to move the body particles without its deformation.

Displacement of the deformed body particles is decomposed into components *u, v, w,* parallel to the *x, y, z* coordinate axes. It is believed that these components are very small values varying continuously in the body volume.

Relative elongation is noted by ε, and relative shear deformation – by γ. To indicate deformation direction, the same indices are used as for the stress components. Six variables ε_x, ε_y, ε_z, γ_{xy}, γ_{xz}, γ_{yz} are called deformation components:

$$\varepsilon_x = \frac{\partial u}{\partial x}, \qquad \varepsilon_y = \frac{\partial v}{\partial y}, \qquad \varepsilon_z = \frac{\partial w}{\partial z},$$

$$\gamma_{xy} = \frac{\partial u}{\partial y} + \frac{\partial v}{\partial x}, \qquad \gamma_{xz} = \frac{\partial u}{\partial z} + \frac{\partial w}{\partial x}, \qquad \gamma_{yz} = \frac{\partial v}{\partial z} + \frac{\partial w}{\partial y}.$$

Linear relations between stress components and deformation components are called Hooke's law. If you imagine an elementary rectangular parallelepiped with faces parallel to the coordinate axes, it is prone to normal stress exposure σ_x evenly distributed over two opposite faces, as is the case in tension testing. Until reaching the proportionality boundary, relative elongation of the element is given by the formula

$$\varepsilon_x = \frac{\sigma_x}{E},$$

where – *E* elasticity modulus when tensioning.

Such elongation of the element in the direction of the *x*-axis is followed by narrowing in the transverse direction (compression), which is determined by deformation components

$$\varepsilon_y = -\nu\frac{\sigma_x}{E}, \varepsilon_z = -\nu\frac{\sigma_x}{E},$$

where ν – constant called Poisson's ratio. For many materials, Poisson's ratio can be equal to 0.25. For structural steels, it is usually considered to be equal to 0.3.

If the element under consideration is subject to simultaneous action of normal stresses σ_x, σ_y, σ_z, uniformly distributed over its faces, then it is possible to get the following relation by applying the deformation components caused by each of the three stresses:

$$\begin{aligned} \varepsilon_x &= \frac{1}{E}\left[\sigma_x - \nu(\sigma_y + \sigma_z)\right], \\ \varepsilon_y &= \frac{1}{E}\left[\sigma_y - \nu(\sigma_x + \sigma_z)\right], \\ \varepsilon_z &= \frac{1}{E}\left[\sigma_z - \nu(\sigma_x + \sigma_y)\right] \end{aligned} \tag{1}$$

These relations are confirmed by numerous experimental measurements.

In the relations (1), deformations as functions of stresses are completely determined by two physical constants *E* and ν. The same constants are also used to determine relation between shear deformation and tangential stress:

$$\gamma_{xy} = \frac{\tau_{xy}}{G}, \qquad \gamma_{xz} = \frac{\tau_{xz}}{G}, \qquad \gamma_{yz} = \frac{\tau_{yz}}{G},$$

Table 1. Compressive stress value in the direction of the y-axis, where the capillary bed is narrowed.

Vessel	Innerdiameter, μm	Wallthickness, μm	Bloodpressure, mmHg
Capillary	6	1	30

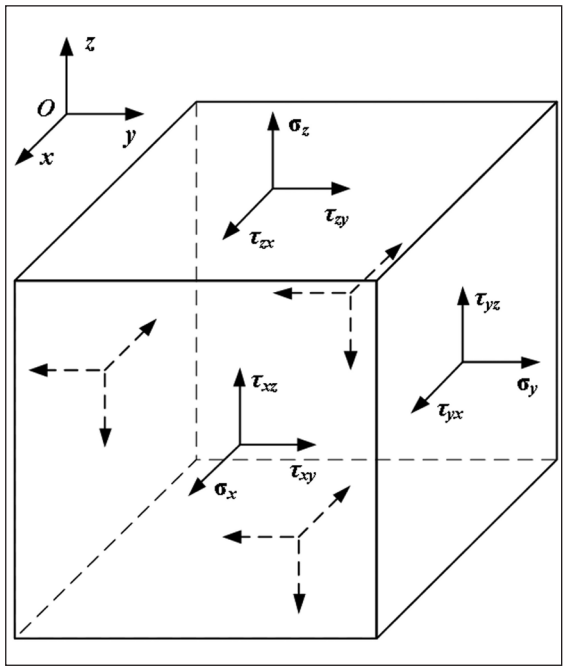

Figure 1. Small cubic element with faces parallel to the coordinate axes.

where $G = \frac{E}{2(1+\nu)}$ – elastic shear modulus or shear modulus. Solving the equation (1) for σ_x, σ_y, σ_z it is possible to find:

$$\sigma_x = \frac{\nu E}{(1+\nu)(1-2\nu)}\left[\varepsilon_x + \varepsilon_y + \varepsilon_z\right] + \frac{E}{1+\nu}\varepsilon_x,$$
$$\sigma_y = \frac{\nu E}{(1+\nu)(1-2\nu)}\left[\varepsilon_x + \varepsilon_y + \varepsilon_z\right] + \frac{E}{1+\nu}\varepsilon_y,$$
$$\sigma_z = \frac{\nu E}{(1+\nu)(1-2\nu)}\left[\varepsilon_x + \varepsilon_y + \varepsilon_z\right] + \frac{E}{1+\nu}\varepsilon_z \quad (2)$$

By the Laplace's law [1], the normal stress component in the circumferential direction σ_θ, which arises in a vessel wall of internal radius r_i when exposed to internal p_i and external pressures, p_o is determined by the formula:

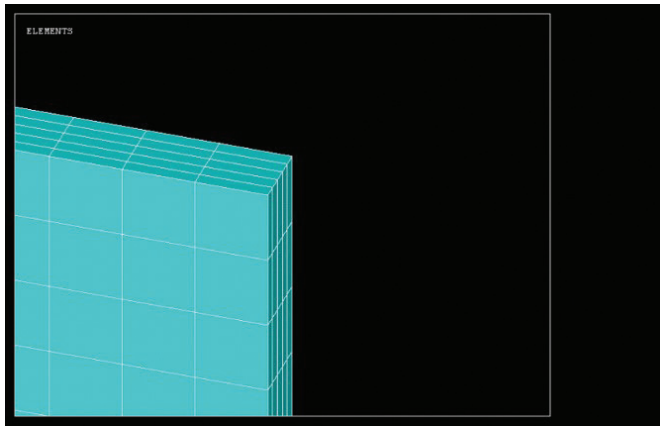

Figure 4. Decomposition of the graft into finite elements.

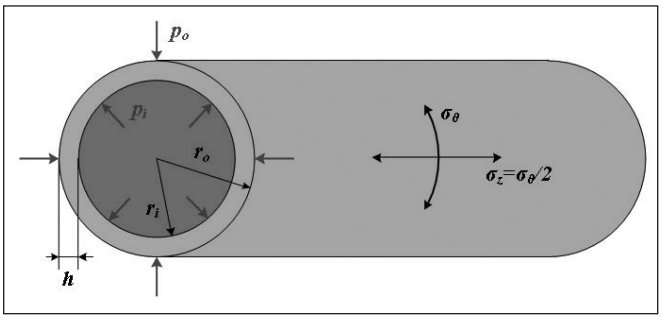

Figure 2. Tensile stress , which is directed along the vessel axis.

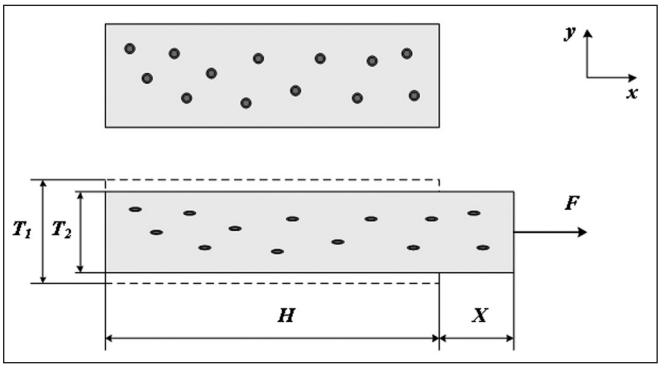

Figure 3. Epithelial cross-section in the direction of the -axis. – tensile force, – initial longitudinal size of the epithelium graft, – longitudinal elongation, and – initial and final thickness of the epithelium.

$$\sigma_\theta = \frac{p_i r_i - p_o r_o}{h} \quad (3)$$

where $h=r_o-r_i$ – thickness of the vessel wall, and r_3 is outer radius, respectively. Tensile stress σ_z, which is directed along the vessel axis, is twice as small as circumferential stress (see Fig. 2).

Formula (3) shows that if external pressure p_o is $p_o \geq \frac{p_i r_i}{r_o}$ (4) then circumferential stress σ_θ in the vessel wall will be negative, i.e. it will be compressive, and cross-section of the vascular bed will accordingly decrease. This is precisely what happens when measuring arterial pressure by the method of M.S. Korotkov: when pumped air pressure in the arm cuff is higher than systolic (maximum) pressure, blood flow through the artery completely stops.

A similar process occurs when tensioning the epithelium graft (see Fig. 3), but in this case, air pressure in the blood pressure cuff acts as internal compressive stress in the *y*-direction.

First, we estimate compressive stress value in the direction of the *y*-axis, where the capillary bed is narrowed, in accordance with the data given for the capillary [2] in the Table 1 by the formula (4):

$$\sigma_y = \frac{p_i r_i}{r_o} \approx 3\ kPa$$

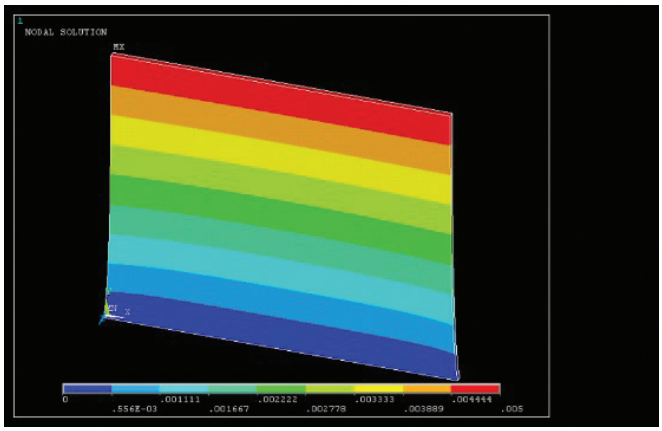

Figure 5. Movement of element nodes in the directions: a) X; b) Y; c) Z.

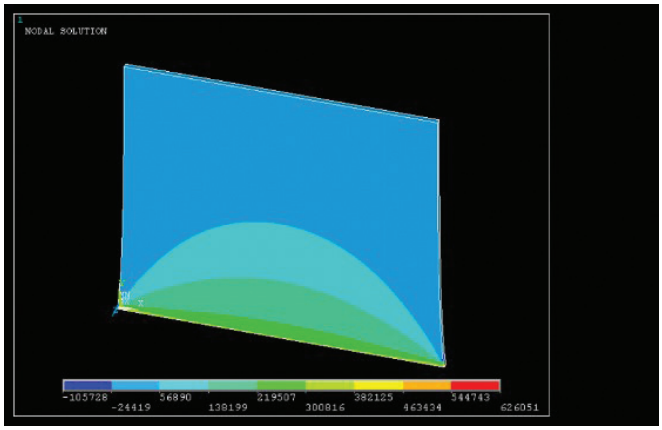

Figure 6. Distribution of stress components in the sample resulting from deformations: a) σx; b) Σy; c) Σz.

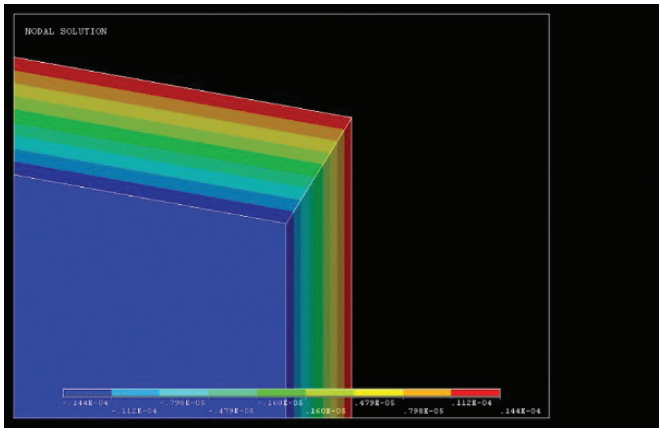

Figure 7. Movement of element nodes in the Z-direction with residual tension of the sample.

Then we will estimate what deformation in the direction of the *x*-axis corresponds to the compressive stress in the direction of the *x*-axis. Let us do it using the formula:

$$\varepsilon_x = -\nu \frac{\sigma_y}{E}$$

Due to high content of water, which is known to be incompressible fluid, Poisson's ratio for soft tissues is close to 0.5 [3-6]. Poisson's ratio for oral mucosa is often equal to 0.45 [5]. It is more complicated to determinate elastic modulus *E*, its value varies in the very wide range from 0.01 to 20 MPa [5.7-10]. Elastic modulus values 1 to 5 MPa [5] are the most often used in practice. Let us take the average value of elastic modulus of 3 MPa for evaluation. Evaluation of deformation gives:

$$\varepsilon_x = 0{,}135$$

Thus, if the size deficit is 3 mm, then longitudinal size of the epithelium graft *H* (detachment value) is 22.2 mm.

The evaluation is fairly approximate. For more accurate calculations, it is necessary to solve equations (1) and (2) using numerical methods, i.e. finite element method. This is the purpose of our further research.

Simulation results for tensioning the epidermis graft in size (width × height × thickness) = 30 × 20 × 0.5 mm using finite element method.

The graft is tensioned to the size (width × height) = 30 × 25 mm. This eliminates the necessary tissue deficit of 5 mm wide in the direction of the Y-axis (vertical axis). At the same time relative elongation is λ = 25/20 = 1.25. Initially, graft tension occurs in the Y-direction.

As we can see in the figure, due to incompressibility of the sample material (volume conservation), when the sample is elongated in the Y-direction, its thickness in the X- and Z-directions decreases. Numerical values are shown in Figure 5.

Figure 5 shows, that maximum sample thinning in the direction of the X-axis is 2 × 0.624 = 1.248 mm. And in the direction of the Z-axis is 2 × 0.0124 = 0.0248 mm.

The stresses arising in the sample are shown in Figure 4.

In Figure 6, a minus sign of a stress component indicates compressive stress, and a plus sign – tensile stress. Figure 6 shows that Z-component of the stress σz is practically negative (-44.04 kPa) in the whole sample volume.

In order to cover clearances in the X-direction resulting from the sample thinning in this direction, it is necessary to tension the sample in the X-direction.

In the residual state, the sample changes its geometric dimensions only in the Y- and Z-directions. In this case, the sample is tensioned in the Y-direction and is compressed in the Z-direction: the maximum thinning in the Z-direction is 2 × 0.0144 = 0.0288 mm (see Fig. 7).

By distribution of the stress components σx and σy in the sample (see Fig. 7) arising from residual tension of the sample, we can evaluate the angle of tensile force direction when applying it to the sample corners. It is obvious that this angle will vary depending on the initial sample geometry and its geometry after deformation.

$$\operatorname{tg}\theta = \frac{\sigma_x}{\sigma_y}$$

Now, we can calculate the angleθ:

$$\theta = \operatorname{arctg}\left(\frac{\sigma_x}{\sigma_y}\right)$$

The values of the stress components are: σ_x = 275 kPa, σ_y = 1.515 MPa. Calculation gives the following:

$$\theta = \text{arctg}\left(\frac{2{,}75 \times 10^5}{1{,}515 \times 10^6}\right) = \text{arctg}\left(\frac{2{,}75 \times 10^5}{1{,}515 \times 10^6}\right) = 10{,}3°$$

CONCLUSIONS

Calculation shows that work of forces does not depend on tension way, because elastic forces are potential. Only initial (original) and final states of the sample, i.e. its initial and final shapes, are important. Required tissue deficit up to 5 mm wide in the direction of the Y-axis (vertical axis) can be eliminated by tensioning the graft of 30 × 25 mm. At the same time relative elongation is λ = 25/20 = 1.25. Initially, graft tension occurs in the Y-direction. Hence, it is possible to increase effectiveness of bone augmentation in patients with secondary edentulism and to reduce a risk of postoperative complications caused by ischemia of the mucous graft when tensioning. Mathematical simulation according to the proposed system allows you to calculate permissible tensile force and permissible deformation of the mucous grafts in the oral cavity.

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PRACE ORYGINALNE
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INFLUENCE OF TRIMETAZIDINE AND LEVOCARNITINE ON CLINICAL COURSE, STRUCTURAL AND FUNCTIONAL CHANGES AND MYOCARDIAL FIBROSIS IN PATIENTS WITH MYOCARDIAL INFARCTION

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ABSTRACT

Introduction: Modern strategies of STEMI/NSTEMI management, that include revascularization by coronary stenting, bypass grafting, nowadays are used in 30-40% of urgent patients of such category. The prevalent part of patients is treated by administration of the optimal drug therapy.

The aim of the research was to study the influence of trimetazidine and levocarnitine on the clinical course of STEMI/NSTEMI.

Materials and methods: 100 patients with STEMI/NSTEMI were included into the research. Depending on the therapy scheme, patients were divided into three groups and the control one. Determination of the key parameters was performed initially after hospitalization and at the day of patient discharge.

Results: Promising results were shown while slowing the myocardial fibrosing. Limiting of the infarcted and `stunned` myocardium area resulted in ejection fraction increase, increase of the myocardial reserve, measured by echocardiographic indexes.

Conclusions: Decreasing of myocardial fibrosing can be potentiated by the pharmacological postconditioning as well as limiting of the necrotic myocardium area and increase of viable myocardium area. Pharmacological postconditioning is effective and save, that can be proved by the absence of any serious complications.

KEY WORDS: myocardial infarction, revascularization, postconditioning, postinfarction remodeling

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INTRODUCTION

The main cause of cardiovascular mortality in Ukraine remains the ischemic heart disease (IHD) and takes 68.8% of total cardiovascular deaths. 25% of adult population in Ukraine suffer from IHD [23]. The most dangerous is myocardial infarction (MI) (STEMI and NSTEMI) which is confirmed in more than 50.000 new patients annually. Despite all achievements in STEMI/NSTEMI diagnostics and treatment, the high mortality level still exists – 12-15%. Despite availability of percutaneous coronary intervention, the number of `non-revascularized` patients is still high – around 40-60%. It can be explained by the late emergency call-up, extension of the time interval between first medical contact and hospitalization, deficit of accessible regional reperfusion centers, absence of patient's informed concern to conduct the procedure.

PROBLEM STATEMENT AND ANALYSIS OF THE LATEST RESEARCH

Modern strategies of STEMI/NSTEMI management, that include revascularization by coronary stenting, bypass grafting, nowadays are used in 30-40% of urgent patients of such category. The prevalent part of patients is treated by administration of the optimal drug therapy. The coronary blood flow restoration itself paradoxically leads to myocardial injury and enlargement of the lesion zone up to 50% – so called reperfusion injury phenomenon, that is realized through the endotoxicity of reactive oxygen species, endothelial cells and macrophage activation [1-3].

During the ischemia, lack of oxygen leads to quick ATP stockpile depletion, which is crucial in maintaining cellular homeostasis. Cardiomyocytes are rich with mitochondria, so they use the biggest part of endogenic ATP stockpile. Myocardial demand in ATP can only be covered by aerobic glycolysis. Insufficient provision of myocardium with energy leads to increased myocardial vulnerability by ischemia [4].

Result of lasting ischemia is accumulation of toxic metabolites, high concentration of cytoplasmic Ca^{++} and cardiomyocyte swelling. All factors lead to opening of the mitochondrial permeability transition pore (mPTP) that regulates the permeability of mitochondrial inner membrane. As the result, all pro-apoptic factors are released and trigger programmed cellular death. Together with the reactive oxygen species, all mentioned above worsens myocardial injury [1,5-6].

"Myocardial remodeling" term was proposed as the characteristic of the myocardial response to infarction and chronic heart failure development [2]. Post infarction remodeling develops in 30% of patients with MI and has negative prognostic value as it is a predictor of chronic

heart failure [7-8]. Remodeling process starts after the ischemic loss of cardiomyocytes and matrix metalloproteases (MMP) activation. Previously inactive MMP`s destroy local extracellular matrix and coronary microcirculation [9-10] with subsequent of dead cardiomyocytes with the fibrous `scar` tissue produced by local myofibroblasts [11-12]. Specific matrix proteins (such as fibronectin) induce fibroblast differentiation and promote deposition of non-fibrillar collagen in the site of necrosis [13-15].

One of the possible ways of potentiating of the standard STEMI/NSTEMI treatment scheme can be recently discovered mechanism of preconditioning and postconditioning. It is proved that these processes are aimed on the adaptation of myocardium to ischemia and protection of myocardium from metabolic damages because of the lasting cycle of ischemia-reperfusion [16]. All known mechanisms of myocardium conditioning converge to the prevention of opening of the mPTP, which is crucial and leads to imminent cell death by apoptosis and can be triggered by brief episodes of ischemia-reperfusion cycles (ischemic conditioning) or pharmacologically (pharmacological conditioning) [16]. Extracellular adenosine is most evidentially based drug known to trigger pharmacological conditioning of myocardium. It acts as cytoprotective modulator in physiological and pathological conditions in response to organic or cellular stress, including myocardial ischemia [17]. Nowadays, the influence of trimetazidine is actively studied in clinical practice, so as levocarnitine, that is endogenously synthetized aminoacid and plays significant role as a cofactor in fatty acids metabolism that results in ATP synthesis [18-20] and leads to reducing of the reperfusion arrythmias and angina pectoris frequencies [20-21].

THE AIM

The objective of the research was to study the influence of trimetazidine and levocarnitine on the clinical course of STEMI/NSTEMI.

MATERIALS AND METHODS

100 patients with STEMI/NSTEMI were included in the research. The diagnosis of STEMI and NSTEMI was verified according to the Fourth universal definition of myocardial infarction [ESC-2018]. 25 patients, which formed the control group, received standard therapy. The main group of patients was divided into three subgroups depending on the addition to the standard scheme: 1st subgroup (25 patients) received 30 mg of trimetazidine (domestic production drug `Trimetazidine-Darnitsa`) 3 times per day orally in addition to the standard therapy; 2nd subgroup (25 patients) received 20 mg of l-carnitine (domestic production drug `Tivor-L` - l-carnitine mixture with l-arginine) in 1 infusion per day, for 8-12 infusions per course as addition to the standard scheme; 3rd subgroup (25 patients) received both of drugs in the same doses as the addition to the standard scheme. Average age of included patients was 63.6±0.80 years. 64% of patients were men and 36% - women. All patients underwent through standard clinical examinations (clinical monitoring of STEMI/NSTEMI signs – dynamics and changes of the pain syndrome, signs of peripheral hypoperfusion), ECG in 12 standard leads (auxiliary lead systems where used on demand), transthoracic echocardiography with detailed visualization of segmental myocardial contraction (including calculation of special indexes: index of contractile function of myocardium – ICF; index of remaining myocardial reserve – IRMR). ICF was calculated by dividing stroke volume (SV) to end-systolic volume (ESV). IRMR was calculated with the help of I. Sledzevska's (2012) method as the end-systolic volume divided to the end-diastolic volume (ESV/EDV; normally 0.38±0.01 units). In case of ICF lowering to <25-10% after the treatment, the scheme was considered ineffective. In case of IRMR was < 0.45, sufficient myocardial reserve was observed; 0.45-0.55 meant restrictions of the myocardial reserve; >0.56 meant serious restrictions of myocardial reserve. Index of myocardial mass of the left ventricle (IMMLV) was used to characterize the structural changes in myocardium. Also, the laboratory marker of cardiac fibrosis (serum fibronectin) was studied.

Segmental myocardial contractility was studied on the 16 – segment model of the left ventricle with the help of transthoracic echocardiography and calculation of the Wall Motion Score Index (WMSI). Segments with normal kinetics were awarded with 1 point, hypokinesis – 2 points, akinesis – 3 points and dyskinesis – 4 points correspondingly. Total summary of all 16 segment points was divided onto 16 and the result (WMSI) was used to calculate the left ventricle ejection fraction (LVEF) and compare with one, calculated during the transthoracic echocardiographic examination by Simpson's method. LVEF by WMSI was calculated using the next formula: LVEF=0.93-(0.26 × WMSI).

Statistical analysis included data processing on the Statistica software, using methods of parametrical and non-parametrical statistics, Student's t-criterium, relative risk with confidence intervals calculation, odds ratio calculation and Pearson's correlation coefficient.

RESULTS AND DISCUSSION

Results of the clinical monitoring after treatment course showed regression of the pain syndrome in 60% of patients of the control group, 84% of patients in both 1st and 2nd subgroups and 92% in the 3rd subgroup. Table I shows that patients of the 1st subgroup had slightly increased LVEF (by Simpson): from 48.43±0.609% to 51.27±0.785% ($p<0.05$), 3rd subgroup showed better dynamics of the EF: from 47.46% to 52.35% ($p<0.05$), while control group did not show credible results: from 48.05% to 48.65% ($p>0.05$). ICF in the 1st subgroup increased from 0.94±0.02 units to 1.06±0.03 units. Even better results were observed in the 3rd group: from 0.90 units to 1.09 units ($p<0.05$). On the contrary, the control group did not show credible results. IRMR showed tendency to decrease in 1st and 3rd subgroups: from 0.51 to 0.48

Table I. Dynamics of the main indexes before and after the treatment course

Index	Control group		Main group					
			1st subgroup		2nd subgroup		3rd subgroup	
	Before	After	Before	After	Before	After	Before	After
LVEF	48,05 [44,15-50,28]	48,65 [46,77-50,60] +1.2% p=0.26	48,43±0,609	51,27±0,785 +5.8% p=0.006	51,25±1,143	53,56±1,214 +4.5% p=0.17	47,46 [45,27-49,65]	52,35 [49,53-55,72] +10.3% p=0.0003
ICF	0,92 [0,79-1,01]	0,94 [0,87-1,02] +2.1% p=0.26	0,94±0,023	1,06±0,034 +12.7% p=0.006	0,98 [0,90-1,17]	1,08 [0,97-1,36] +10.2% p=0.18	0,90 [0,83-0,99]	1,09 [0,98-1,26] +21.1% p=0.0003
IRMR	0,51 [0,49-0,55]	0,51 [0,49-0,53] -0% p=0.26	0,51±0,006	0,48±0,008 -5.9% p=0.006	0,50 [0,45-0,52]	0,48 [0,42-0,50] -4% p=0.17	0,53 [0,50-0,55]	0,48 [0,44-0,50] -9.5%; p=0.0003
IMMLV	151,21 [137,63-167,79]	129,84 [118,25-167,47] -14.2% p=0.000	200,63±6,149	158,13±5,042 -21.2% p=0.000	162,65±7,477	168,72±6,697 +3.7% p=0.54	142,93 [129,39-155,41]	137,78 [128,73-154,31] -3.7% p=0.54
Fibronectin	2,24±0,131	2,43±0,124 +8.4% p=0.29	1,89 [1,76-2,16]	1,90 [1,78-2,20] +0.5% p=0.72	1,76±0,095	1,66±0,081 -5.7% p=0.44	1,72 [1,47-2,14]	1,39 [1,12-1,74] -19.2% p=0.01

Table II. LVEF dynamics after the treatment course

Group	LVEF dynamics	
	via Simpson's method	via WMSI
Control group	↑ 1,3% (p=0,36)	↓ 23,1% (p=0,001)
1st subgroup	↑ 5,2% (p<0,001)	↓ 0,8% (p=0,56)
2nd subgroup	↑ 4,0% (p=0,004)	↑ 2,4% (p=0,14)
3rd subgroup	↑ 10,1% (p<0,001)	↑ 9,7% (p<0,001)

and from 0.53 to 0.48 units correspondingly (p<0.05) that mean more effective involvement of the remaining myocardial reserves. 2nd subgroup and control group did not show credible results. IMMLV credibly decreased in 1st subgroup of the main group and in control group: from 200.63 to 158.13 g/kg/1.73^2 and from 151.21 to 129.84 13 g/kg/1.73^2 correspondingly (p<0.05) what proved the regression of postinfarction hypertrophy and remodeling of left ventricle. Cardiac fibrosis credibly slowed by 19,2% in 3rd group (p<0.05) evaluated by the serum fibronectin level. In the control group this exponent grew up in 24 patients out of 25.

While analyzing the WMSI dynamics, only 20% of patients of the control group had positive dynamics – decrease of WMSI what equals LVEF increase. In the 1st subgroup such dynamics was observed in 64% of patients, in 2nd – in 44% and in 3rd subgroup – 84% of patients. Figure 1 shows the WMSI dynamics in 1st, 2nd and 3rd subgroups of the main group. Table II shows the dynamics and of the LVEF in all subgroups. After analyzing both LVEF measurement methods, correlation coefficient equaled r =0.76, approximation credibility equaled R^2=0,57 (see Fig.2).

The summary of all results indicates on the reducing of the infarction size at the expense of restriction of the `scar` zone and increase of the viable myocardium area. Achieved result shows that WMSI has better prognostic value than routine LVEF measurement.

According to our data infarction size under the influence of trimetazidine reduced by 25%, what is slightly better result, than one achieved in the AMISTAD-II clinical trial with intravenous adenosine usage (2005), where the infarction size reduced by 16% (p=0.023). This type of dynamics was observed in case of 70 μg/kg/min adenosine dose usage.

According to N. Vatutin and V. Kolesnikov (2013) [22], LVEF increased from 54.7±7.8% to 58.7±8.6% (p<0.05) as the result of adenosine course treatment (900 mg orally, daily). Our research showed 5.2% increase of LVEF (p<0.05) after the course of trimetazidine and l-carnitine combined usage.

So, achieved results can be comparable with previous researches (AMISTAD-II, 2005; Vatutin N., Kolesnikov V., 2013). However, the effectiveness of trimetazidine postconditioning in our research was higher because of l-carnitine potentiation.

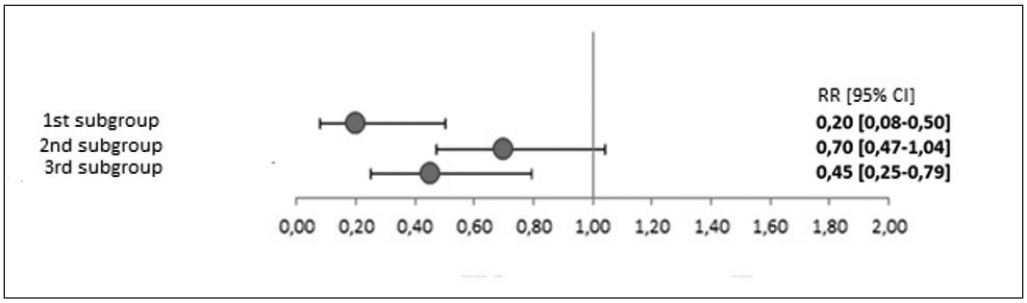

Figure 1. WMSI dynamics after the treatment course.

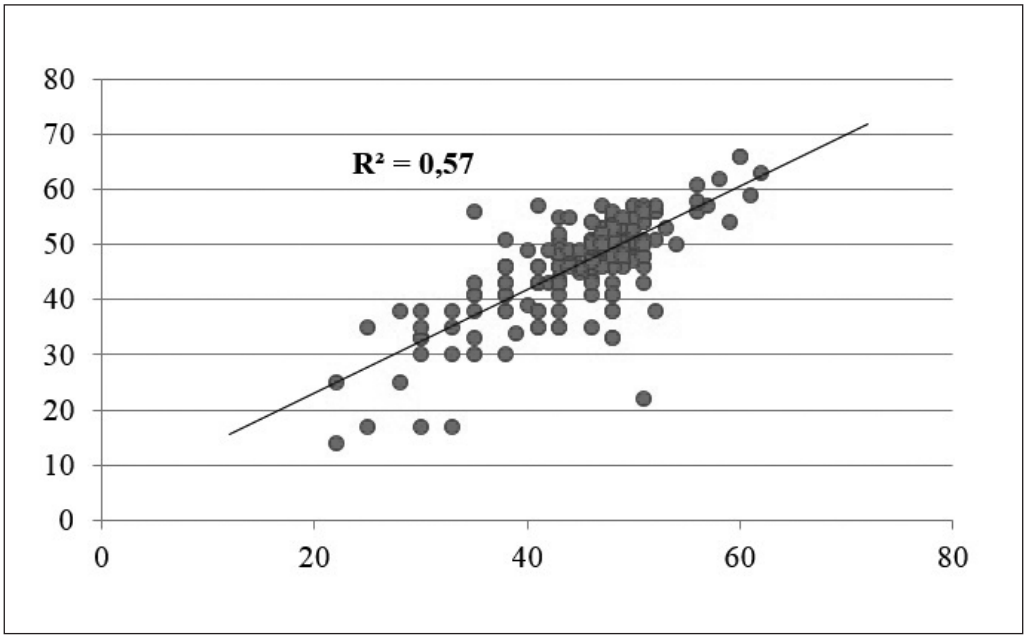

Figure 2. LVEF dispersal diagram (via Simpson's method and via WMSI).

CONCLUSIONS

Trimetazidine is an effective way to increase the myocardial contractility, correct excessive fibrosis, decrease the size of the myocardial infarction at the expense of limitation of the `scar` zone, increase of the viable myocardium area. L-carnitine was not as effective in case of solitary addition to the treatment scheme. Treatment effectiveness essentially increases in case of two drugs addition to the therapy scheme. Cardiac fibrosis in postinfarction period can be slowed down by combined usage of both researched drugs. Positive influence of drugs combination on myocardial remodeling and ventricular hypertrophy was also observed. Application of both drugs did not cause any serious side effect, so it is safe and well tolerated.

Prospects of further researches. A comprehensive research of myocardial postconditioning can be performed to identify the effect of postconditioning in patients that underwent urgent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) with more severe myocardial reperfusion injury.

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PRACE ORYGINALNE
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IMPACT OF RISK FACTORS OF ISCHEMIC HEART DISEASE ON THE DEVELOPMENT OF ACUTE CORONARY SYNDROME, PLATELET ULTRASTRUCTURE, AND ASPIRIN RESISTANCE

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ABSTRACT

Introduction: Risk factors of ischemic heart disease have an impact on blood cell apoptosis, platelets in particular, and their calcification. 5-40% of patients with high cardiovascular risk have anti-platelet drug resistance. The study of the morphofunctional status of platelets in patients with acute coronary syndrome is relevant and requires further research.
The aim: to find out the impact of various risk factors for coronary heart disease on ultrastructural changes in platelets and the causes of their resistance to antiplatelet drugs.
Materials and methods: 36 patients with acute coronary syndrome and risk factors such as arterial hypertension, dyslipidemia, type 2 diabetes mellitus, smoking, alcohol abuse, and occupational hazards were examined. The mean age of patients was 56±5.6 years. The control group consisted of 10 apparently healthy people. Functional state and ultrastructure of platelets were studied using electron microscopy.
Results: Most platelets of patients in the control group were discoid without pseudopods with evenly distributed platelet and dense granules. Platelets of patients with acute coronary syndrome were mostly activated, as evidenced by the presence of pseudopods, as well as moderate concentrations of platelet granules in their central region. In the study group of patients, part of platelets was aggregated, osmiophilic, and vacuolated with signs of microclasmatosis of the pseudopods. Particular attention should be paid to platelets with signs of calcification, as evidenced by their excessive osmiophilic property and manifestations of apoptosis.
Conclusions: The presence of ischemic heart disease risk factors in acute coronary syndrome patients leads to platelet calcification and activation of blood cell apoptosis. With the use of electron microscopy, we detected degenerative changes of platelets and their calcification, which in the future may lead to the development of resistance to aspirin and require new oral coagulants.

KEY WORDS: acute coronary syndrome, risk factors, ultrastructure, apoptosis, platelets

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INTRODUCTION

According to ultrastructure, there are four forms of human cell death, in particular, cardiomyocytes (CMCs): necrosis, typical apoptosis without degeneration, apoptosis with degeneration and secondary necrosis, and severe cellular degeneration [1-2]. Apoptosis is a programmed death [2,4]. Typical ultrastructural changes that initiate apoptosis mainly include cell shrinkage and the appearance of small, compact mitochondria; cytoplasmic vacuolization; DNA fragmentation with the presence of nuclear heterochromatin deposits; karyorrhexis (fragmentation and decay); the disintegration of cells into apoptotic bodies, as well as their phagocytosis by macrophages. Apoptosis is divided into physiological, which predominates in the early postnatal period and partially remains throughout human life, and pathological – under the impact of various pathological processes, particularly, in ischemia and CMC reperfusion in ischemic heart disease (IHD) [2-4].

It was found that the number of endogenous physiological factors such as nitric oxide, reactive oxygen intermediates, increased concentration of ions (Ca^{2+} and Mg^{2+}) and adenine nucleotides (ADP, ATP) affects the intensity of apoptosis processes [2,4,6]. Calcium ions are known to have a direct effect on CMC apoptosis in IHD [4]. The increase of their concentration in cell cytosol can be due to excessive penetration of Ca^{2+} from the intercellular space through the plasma membrane, as well as because of disturbance of intracellular homeostasis due to dysfunction of mitochondria and endoplasmic reticulum. An increase in intracellular Ca^{2+} in these circumstances contributes to the initiation of apoptosis processes, which provides reasons to consider it an important marker and one of the initiators of this process [4-5,7].

Antiplatelet drugs are known to inhibit activation, adhesion, and aggregation of platelets (PLTs) due to their effect on platelet mediators, namely, thromboxane A2 and ADP, by blocking surface GPIIb/IIIa receptors. However, the existence of PLT resistance to aspirin and clopidogrel is known since IHD patients may have a myocardial infarction, stroke, or sudden cardiac death, despite the administration of these antiplatelet drugs [8]. So far, the causes of aspirin resistance have not been completely established, although it is known that there is resistance to aspirin in 5-40% of patients, and to clopidogrel – in 20% of cases [8-9]. In this regard, it is relevant to find out the causes of the PLT resistance to these drugs.

We live in an "era of visualization" since it is important to see changes occurring at the ultrastructural level in different cells of the human body. Therefore, the study of the morphofunctional status of PLTs in patients with acute coronary syndrome (ACS) is relevant and important in relation to aspirin resistance.

THE AIM

The aim of the study is to investigate the impact of various IHD risk factors on ultrastructural changes in PLTs, which may predetermine their resistance to antiplatelet drugs.

MATERIALS AND METHODS

36 patients with ACS who underwent inpatient treatment in the cardiology department for patients with myocardial infarction of Lviv Clinical Municipal Communal Emergency Hospital were examined. They included 28 male and 8 female patients. The mean age of patients was 56±5.6 years. Arterial hypertension (AH) was found in 76.1% of people, dyslipidemia – 56.6%, type 2 diabetes mellitus – 40.2%, smoking – 58.4%, alcohol abuse – 40.6%, occupational hazards (soldering, welding, electroplating, job related to varnish, paint, acids and alkalis, harsh chemical, organic plastics, and dust pollution) in 48.8% of patients. The control group consisted of 10 apparently healthy people. Both groups are comparable by age and gender. In all cases, complaints and risk factors for the development of IHD, as well as anamnesis morbi and vitae were analyzed in detail. The objective clinical study was conducted, including ECG and echocardiography (Echo-CG), as well as coronary angiography or multidetector row spiral CT and electron microscopic study of PLTs.

Ultrastructural studies of platelets in venous blood were studied using electron microscopy. To do this, 9 ml of fasting blood was collected from the patient's basilic vein into a siliconized vial, where it was mixed with a 2% solution of sodium citrate in a ratio of 9:1 and centrifuged for 10 minutes at 150 G to form a pellet. The supernatant blood was transferred to a clean vial and centrifuged for 10 minutes at 300 G to precipitate "white" blood cells, including PLTs. The resulting material was washed with a cacodylate buffer and transferred to a 1% osmium solution for 60 minutes to fix it. After this, the cell pellet was washed in a cacodylate buffer, followed by dehydration in alcoholic solutions of increasing concentration (30, 50, 70, 90%), and in 100% acetone for 10 min. Subsequently, the resulting "film" with blood cell samples was placed in a mixture of epon-araldite, which was polymerized in gelatin capsules at a temperature of 60°C. Ultra-thin slices were prepared on UMTP-3 ultramicrotome using diamond blades. Prior to the study, blood cells were contrasted with lead citrate according to the E. Reynolds method [1]. Contrast slices were studied and photographed using a UEMV-100-K electron microscope magnified 3000 to 12000 times.

RESULTS

In the ultrastructural study of blood cells, PLTs were predominantly discoid in patients from the control group. They were circumscribed by the cytoplasmic membrane and had similarities in size, configuration, the electron-optical density of the cytoplasm and contained an ordinary set of organelles, in particular, individual mitochondria, platelet and dense granules, open tubular system, microtubules, and microfilaments. PLTs predominantly comprised 10% of the "old" platelets that contained a small number of organelles. The "young" PLTs accounted for about 15% of the total number. They were the largest in size and contained a significant number of organelles. The "classical", medium-sized PLTs with a moderate number of organelles (10-15 α-granules, 2-3 dense granules, 1-3 mitochondria) and no pseudopods, which did not interact with each other, prevailed in apparently healthy people (Fig. 1).

PLTs of patients with ACS mostly had classical signs of activation, which were manifested by the accumulation of platelet granules in their central region and the presence of microvilli (Fig. 2). Some of them were partially or completely degranulated, which was not observed in the control group. Moreover, PLTs formed numerous projections (pseudopods) that contacted among themselves and with other blood cells, forming cellular associations or conglomerates.

In patients with ACS in the presence of type 2 diabetes, significant polymorphism of PLTs and a significantly increased electron-optical density of the cytoplasm (Fig. 3) was detected due to their calcification. Damaged, calcified (osmiophilic) plates with degenerative changes were dominant, indicating their reduced functional capacity, and thus, obviously, resistance to antiplatelet drugs. PLTs in diabetes mellitus (DM) were predominantly hyporesponsive, which was manifested by their rounded shape and reduced number of granules in some platelets in the presence of destructive changes of cells that "agglutinated", as well as by the destruction and detachment of pseudopods. On the other hand, the fusion of the cytomembranes of the adjacent platelets and their pseudopods indicate the increased PLT adhesion in DM. Adhesion of PLTs to adjacent leukocytes was also observed. Similar changes were observed in patients with hypertension and dyslipidemia.

Changes in PLTs had certain peculiarities in patients abusing alcohol. PLT swelling and increased PLT size was dominant, as well as degenerative changes in organelles, indicating a decrease in their functional properties, but increased adhesion similar to that observed in patients with diabetes (Fig. 4). Part of PLTs showed signs of carbohydrate dystrophy (hibernation), manifested by the accumulation of an excessive number of glycogen granules, mainly in the central part of the platelets, which caused a decrease in their functional properties.

In an ultrastructural study of the blood of patients exposed to occupational hazards such as soldering, welding, electroplating, job-related varnish, paint, acids and alkalis, harsh chemical, organic plastics, and dust pollution, PLTs were found to have different shape and size, with

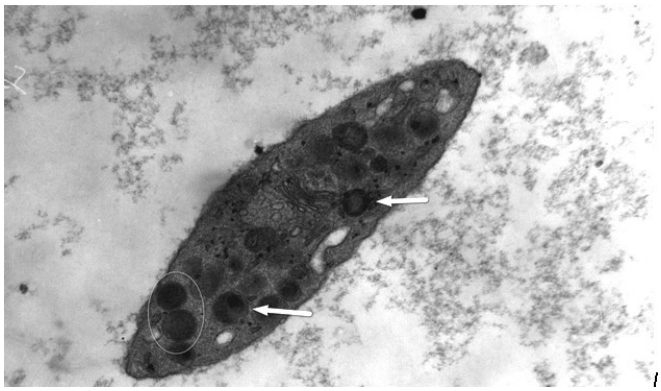

Fig. 1. Discoid platelet ultrastructure containing a large number of α-granules (→) and dense granules (0). Venous blood. Control study. Magnification x 12000.

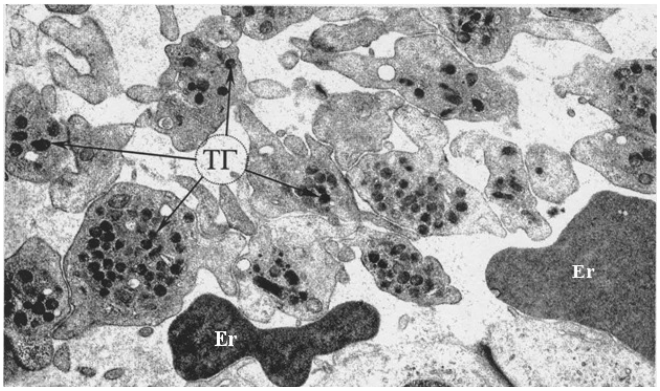

Fig. 2. Platelet ultrastructure in venous blood of a patient with the acute coronary syndrome. ТГ – thrombocyte granules. Er – red blood cells. Magnification x 7000.

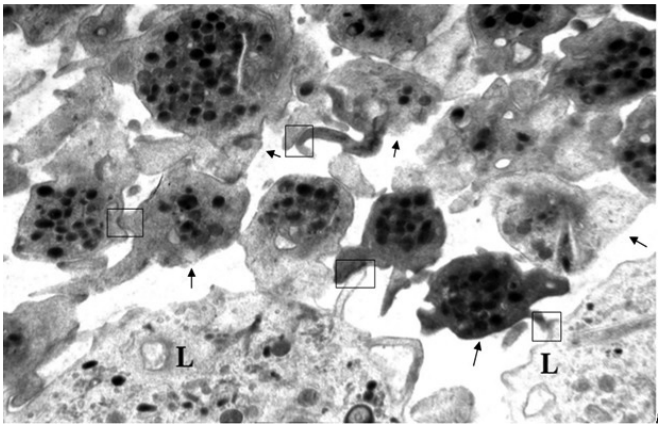

Fig. 3. Ultrastructure of abnormal, different sizes adhering (▭) titer PLTs (→) with evidence of calcification, apoptosis and secondary necrosis. Destroyed leucocyte (L). Acute myocardial infarction. Diabetes mellitus. Magnification x 6000.

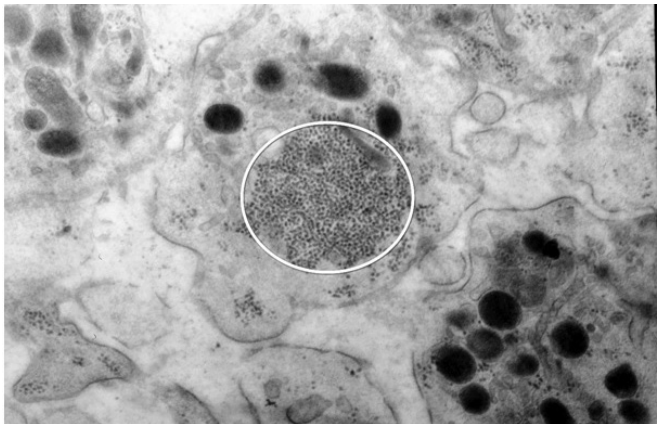

Fig. 4. Significant swelling and structural and functional heterogeneity of platelets under the influence of excessive doses of alcohol. Partial degranulation (0) in the settings of reduced functional activity of the platelets as a result of their hibernation (accumulation of glycogen). Recurrent myocardial infarction. Cardiac insufficiency. Magnification x 12000.

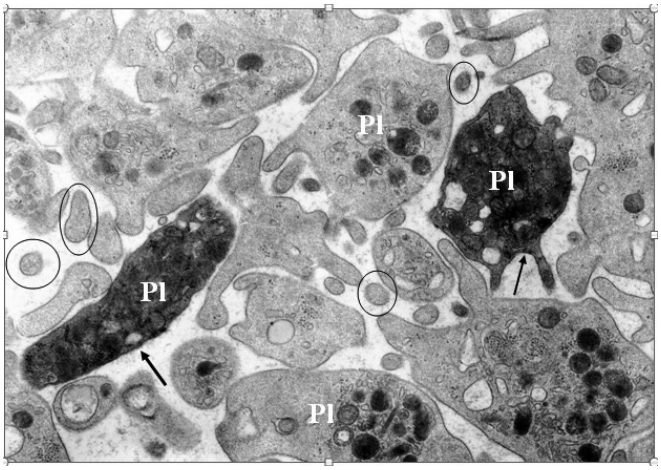

Fig. 5. Significant platelet polymorphism (Pl) with microclasmatosis of some pseudopods (0). Platelets of significant electron-optical density (→) as signs of their calcification.
Magnification x 8000.

the microclasmatosis of some pseudopods. Some PLTs had a significant electron-optical density, indicating their calcification (Fig. 5).

DISCUSSION

PLTs are the smallest, discoid blood akaryocytes (platelets). Their diameter is 1.5-3.0 microns. They are much smaller in size than erythrocytes, lymphocytes, monocytes, and leukocytes. According to electronic microscopy, the internal structure of PLTs consists of 4 zones: peripheral, sol-gel, organelle and membrane zones [10-11,13].

Under physiological conditions, PLTs freely circulates in the bloodstream among other cells and do not adhere to each other or to the intact endothelium. However, under the influence of various IHD risk factors (diabetes, alcohol abuse, occupational hazards), which led to ACS, PLTs become adhesive, agglutinate together and adhere to the damaged surface of the endothelial cells, leading to circulatory disorders, and also undergo degranulation, which is the reason for the release of vasoconstrictors and hemotoxic substances (derivatives of arachidonic acid), which obviously contributes to coronary circulatory disorders and development of blood clots [1,12,15].

The PLT cytoplasm normally contains α-granules comprising V, VIII, XIII blood clotting factors, the von Willebrand factor and fibrinogen, as well as dense β-granules containing ADP, serotonin, ATP, and calcium ions; in addition – lysosomes containing hydrolytic enzymes and peroxisomes (containing catalase) [11-13].

When activated, PLTs acquire a spherical shape, become rounded, pseudopods appear. PLT aggregation occurs when they are in contact with the damaged endothelium, collagen fibrils of the subendothelial layer of blood vessels, as well as with leukocytes. Thrombin, ADP, thromboxane A2, adrenaline, immune complexes, and fatty acids are known to contribute to PLT aggregation. During aggregation, platelet granules concentrate in the center of the cells, and subsequently, their degranulation begins [12-14]. The degranulation of individual PLTs mainly is not accompanied by thrombosis and does not lead to damage of endothelial cells. However, the degranulation of a significant number of PLTs promotes the formation of blood clots or platelet aggregates and is accompanied by spasm of arterioles, as well as swelling and endothelial damage. The presence of fibrin on the membranes of the aggregated blood cells is the morphological manifestation of blood clots [12].

According to the results of our studies, most of PLTs of patients in the control group were discoid without pseudopods, with evenly distributed platelet and dense granules. PLTs of patients with ACS were mainly activated, as evidenced by the presence of pseudopods and the concentration of platelet granules in their central part (with well-preserved functional activity). In the study group of patients with such IHD risk factors as DM, occupational hazards, alcohol abuse, as well as the presence of corticosteroids, 20-80% of PLT had signs of increased adhesion, with a tendency to aggregation, as well as degenerative changes that consisted of their vacuolization, microclasmatosis of the pseudopods.

Particular attention should be paid to PLTs with signs of calcification of the cytoplasm, as evidenced by its excessive osmiophilic property (visually elevated electron-optical density of the PLT cytoplasm) and manifestations of apoptosis. The indicated ultrastructural changes in PLTs were specific to patients with such IHD risk factors as diabetes, smoking, occupational hazards, elderly age, and alcohol abuse. In all these cases, due to the damage of mitochondria, Ca^{2+} homeostasis was affected and the overload of the cellular cytoplasm with Ca^{2+} ions, which apparently led to a reduced functional capacity of PLTs, their degeneration, calcification, and apoptosis, - thus, leading to resistance to aspirin and other antiplatelet drugs (clopidogrel, ticagrelor).

Disturbances of morphological and functional changes in the PLTs of patients with DM and AH are manifested by increased PLT adhesion, their propensity to aggregation and destruction, increased tendency to form aggregates and microthrombosis. Under these conditions, the PLT production of thromboxane A2 and other vasoconstrictors increases, the PLT production of prostacyclin and other vasodilators is inhibited. Under these conditions, damage to the PLT membranes and their adhesion increases [12,15].

CONCLUSIONS

The presence of such IHD risk factors as type 2 diabetes mellitus, smoking, alcohol abuse and occupational hazards in ACS patients leads to calcification and increased adhesion of PLTs, activation of apoptosis and destruction of these blood cells. With the help of electron microscopy, we detected degenerative changes of PLTs, their hibernation, dystrophy, degeneration, calcification, resulting in resistance to aspirin and other antiplatelet drugs, and requiring new oral anticoagulants (rivaroxaban) for patients at high risk of developing IHD and ACS. Under such ultrastructural changes of PLTs, there is a high risk of cardiovascular complications, in particular, the development of myocardial infarction, angina pectoris, stent thrombosis or sudden death due to coronary artery thrombosis.

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Authors' contributions:
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PRACE ORYGINALNE
ORIGINAL ARTICLES

INFLUENCE OF OPEFERA ON THE COLON MOTILITY OF RATS IN THE CONDITIONS OF PROLONGED GASTRIC JUICE HYPOACIDITY

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ABSTRACT

Introduction: Gastric hypohlorhydria is the result of inflammatory process in the intestine caused by dysbiosis. Multiprobiotics significantly improve the colon's motility. Not only probiotics, but also synbiotics are used to eliminate dysbiosis.

The aim of the work was to study the effect of Opefera on spontaneous and stimulated contractile activity of the colon in rats.

Materials and methods: The studies were carried out on 30 white rats, divided into 3 groups. The rats of group I served as controls; they daily received water for injections for 28 days. Group II rats received omeprazole daily for 28 days and rectally - water. Rats of group III were given omeprazole and Opefera simultaneously during 28 days. On the 29th day the colon motility was examined by the balonography method [13]. To do this, the "Jaguar" automated unit was used. For statistic data processing, Student's t-criterion for independent samples was applied.

Results: In the group of rats, which received omeprazole and Opefera simultaneously during 28 days, the index of motor activity increased compared to the group of rats given omeprazole only. Thus, application of the Opefera drug enhances the spontaneous and stimulated motility of the colon, suppressed by prolonged hypochlorhydria of gastric juice.

Conclusion: The Opefera drug stimulates spontaneous and stimulated motility of the colon, suppressed by prolonged hypochlorhydria of gastric juice. Opefera application is expedient in patients with prolonged hypochlorhydria of various genesis to normalize the colon contractile activity.

KEY WORDS: hypochlorhydria, colon motility, synbiotic, omeprazole

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INTRODUCTION

Previously, we have shown that the effect of prolonged reduction of gastric juice acidity in rats is the suppression of spontaneous and stimulated contractile activity of the colon in rats. It is proved that this is the result of the inflammatory process in the intestine, caused by hyperhastrinemia and dysbiosis, which leads to hypoacidity of gastric juice. Multiprobiotics of the "Symbiter" group, by eliminating dysbiosis and reducing the inflammatory process, greatly improved the colon motility, although no complete recovery was observed [1].

To eliminate dysbiosis, not only probiotics, which are living microorganisms that have a positive effect on human health, normalize the composition and function of the gastrointestinal tract microflora, but also prebiotics are used. Prebiotics (food ingredients such as fructooligosaccharides or inulin) are not digested by enzyme systems of the stomach and intestine [3]. However, they are hydrolyzed by enzymatic systems of the colon microflora. This leads to the growth of bifidum- and lactobacilli in the colon [5, 7].

The literature analysis showed that there are currently no data on the effect of synbiotic drugs, which represent a rational combination of probiotics and prebiotics, on the motility of the stomach and colon under the conditions of prolonged gastric juice hypoacidity.

Our attention was drawn by the Opefera synbiotic drug (pharmaceutical company "World Medicine"), which includes live lyophilized bacteria (1.94 10^9): *Lactobacillus rhamnosus* (0.5 10^9 CFU), *Lactobacillus plantarum* (0.2 10^9 CFU), *Streptococcus thermophiles* (0.5-10^9 CFU), *Lactobacillus acidophilus* (0.5 10^9 CFU), *Bifidobacterium spp*. (*Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium infantis*) (0,24 10^9 CFU), *Saccharomyces boulardii* (65 mg), wild chamomile dry extract (*Matricaria chamomilla L.*) - 50 mg and inulin - 200 mg.

Chamomile is known for its anti-inflammatory, antidiarrheal, antioxidant [10, 15], anti-tumor [8], neuroprotective [9], anti-allergic [4] and antimicrobial properties [11]. It is known that essential oil of chamomile has a disinfectant effect, eliminates formation of gases and relieves pain, weakens inflammatory processes and normalizes the impaired function of the gastrointestinal tract [6, 14].

Inulin, being a prebiotic, has a positive effect on the bifidobacterial microflora of the digestive tract [12]. We hypothesized that Opefera can be a promising means for the normalization of the colon motility under the conditions of prolonged gastric juice hypochlorhydria.

THE AIM

The purpose of the work was to study the effect of Opefera on spontaneous and stimulated contractile activity of the colon in rats with omeprazole-induced hypochlorhydria of gastric juice.

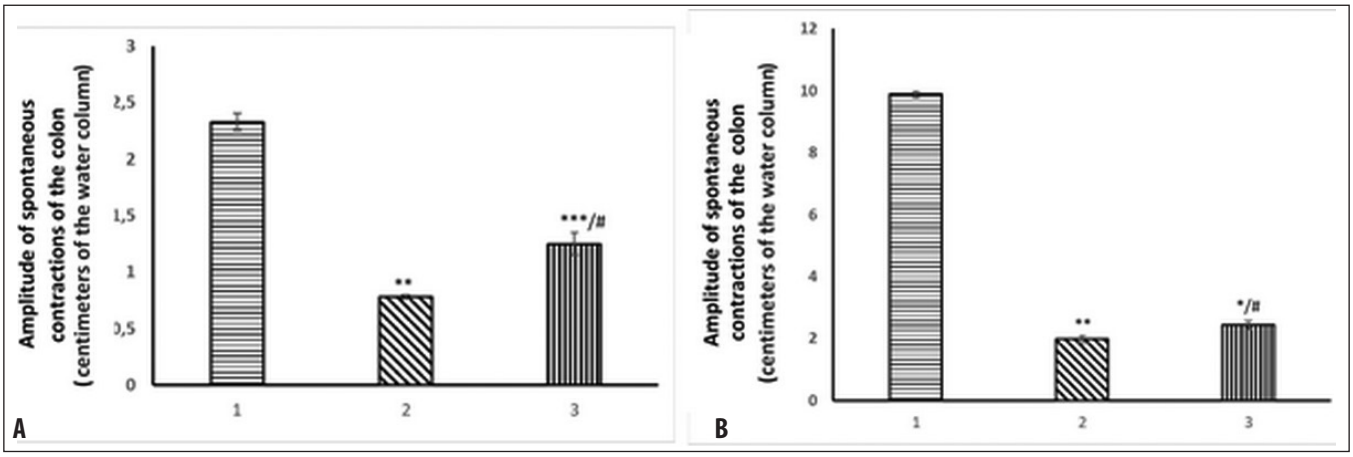

Fig. 1. Amplitude of spontaneous (A) and carbacholin-stimulated (B) contractions of the colon (M + m, n = 10):
1 - control group of rats;
2 - group of rats after 28 days of omeprazole daily administration;
3 - group of rats after 28 days of omeprazole and Opefera daily administration;
* - p <0.05, ** - p <0.01, *** - p <0.001 compared to the control group rats;
# - p <0.05 compared to rats given omeprazole over 28 days.

MATERIALS AND METHODS

Experiments have been carried out in compliance with the general principles of bioethics according to the international recommendations of the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes [Strasbourg, 1986] and approved by the First National Congress on Bioethics of Ukraine (September 2001).

The studies were carried out on 30 white nonlinear rats, divided into 3 groups, weighing 180-200 g. The rats of group I served as controls; they were intraperitoneally (i/p) and rectally daily injected 0.2 and 0.5 ml of water for injections for 28 days. Group II rats received omeprazole (produced by Sigma-Aldrich, USA) (14 mg/kg, once a day) daily for 28 days and rectally 1.0 ml of water.

Rats of group III were administered omeprazole (5 mg / kg, rectally three times a day) and Opefera simultaneously during 28 days. To do this, a capsule of Opefera with a mass content of 350 mg was opened and dissolved in 350 ml of warm water. That is, 5 ml of the solution contained 5 mg of Opefera. According to the weight of the rats, the volume of rectal administration of the solution did not exceed 1 ml. Rectal administration is due to the fact that the capsule does not dissolve in the proximal gastrointestinal tract.

On the 29th day of the experiment, animals were narcotised with urethane (1.1 g/kg, i/p) and the colon motility was examined by the balonography method [13]. To do this, the colon was injected with a latex balloon filled with 0.8 ml of water and connected to the "Jaguar" automated unit. The unit is a modification of the classical balonographic method with the use of modern registration methods, i.e. the ink-writing dual-channel recorder is replaced with a computer with the corresponding software. It is proved that balloons of the similar volume (called miniature ones) do not stimulate the colon motility by themselves. After a 20-minute equilibration period, within 2 hours, the spontaneous motor activity of the colon was recorded. After this, rats were given a standard motility stimulator with a non-selective agonist of carbacholin acetylcholine receptors at a dose of 10 μg/kg and the motility continued to be recorded for another 2 hours. Duration of carbacholin action is 1.5-2 hours.

Statistical data processing was performed using the statistical software package StatisticSoft 6.0. Due to the small volume of samples, the Shapiro-Wilk's W-test was used to check the distribution to normal. The probability of type I error was α> 0.05. Since the data obtained were distributed according to the normal law, parametric methods for comparing the samples were used. For statistic processing of parametric data, Student's t-criterion for independent samples was used. For our data, we took the level of significance p <0.05. The mean (M) and the standard error of the mean (m) were calculated.

RESULTS

As a result of our studies, we have shown that in the control group rats, the frequency of spontaneous contractions in the stomach was 3 contractions per minute, with a mean amplitude of these contractions being 2.33 + 0.08 cm H_2O (fig. 1A).

After 28 days of omeprazole administration, frequency of the colon spontaneous contractions did not change, and the amplitude of spontaneous contractions decreased to 0.78 + 0.02 cm H_2O or by 66.5% (p <0.01) (fig. 1A).

Under the conditions of simultaneous administration of omeprazole and Opefera synbiotic, the amplitude of spontaneous contractions increased to 1.25 + 0.10 cm H_2O or by 60.2% (p <0.05) compared to the group of rats given omeprazole only. However, under these conditions, the amplitude of spontaneous contractions remained at the level of 46.4% (p <0.001) less than the same index in the control group (fig. 1A).

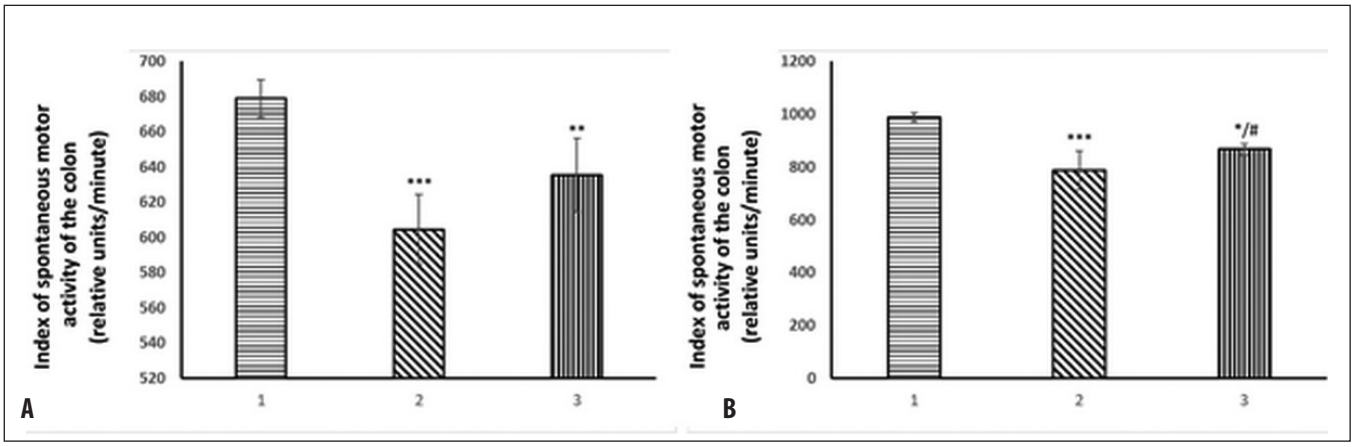

Fig. 2. Index of spontaneous (A) and stimulated carbacholin (B) motor activity of the colon (M + m, n = 10):
1 - control group of rats;
2 - group of rats after 28 days of omeprazole daily administration;
3 - group of rats after 28 days of omeprazole and Opefera daily administration;
** - p <0.01, *** - p <0.001 compared to the control group rats;
# - p <0.05 compared to the rats given omeprazole over 28 days.

Administration of carbacholin to the control group rats stimulated a pronounced contractile response of the colon, which, on the background of unchanged frequency of contractions, was characterized by an increase in the amplitude of contractions to 9.89 + 0.10 cm H_2O (fig. 1B).

In the group of rats who received omeprazole for 28 days, the stimulatory effect of carbacholin on the contractile activity of the colon smooth muscles was significantly weaker compared to that in the control group: the contractions amplitude was reduced by 80% (p <0.01) and was 1.98 ± 0.13 cm H_2O (fig. 1B).

In the group of rats, which were administered omeprazole and Opefera simultaneously during 28 days, the carbacholin-stimulated amplitude of contractions increased up to 2.44 + 0.13 cm H_2O which was by 23.2% (p <0.05) more compared to the group of rats given omeprazole only.

Consequently, the Opefera drug amplified the amplitude of spontaneous and carbacholin-stimulated contractions of the colon under the conditions of the gastric juice hypochlorhydria.

Further we have shown that in the control group rats, the index of motor activity was 678.9 + 10.8 RU/min (fig. 2A). After 28 days of omeprazole administration, the index of spontaneous motor activity decreased to 604.6 ± 19.9 RU/min, or by 10.9% (p <0.05) compared to the control group rats (fig. 2A).

In the context of the simultaneous administration of omeprazole and Opefera synbiotic, the growth rate of the spontaneous motor activity index was statistically insignificant compared to the group of rats, which was administered omeprazole only within 28 days (fig. 2A).

When stimulating the colon motor activity by carbacholin, the index of motor activity was 988.4 + 15.6 RU/min (fig. 2B). After 28 days of omeprazole administration, the index of stimulated motor activity decreased by 20.3% (p <0.001) and amounted to 788.1 ± 73.1 RU/min.

In the group of rats, which received omeprazole and Opefera simultaneously during 28 days, the index of motor activity stimulated by carbacholin increased to 867.7 + 20.5 RU/min or 10.1% (p <0. 05) compared to the group of rats given omeprazole only (fig. 2B).

Thus, application of the Opefera drug enhances the spontaneous and stimulated motility of the colon, suppressed by prolonged hypochlorhydria of gastric juice.

DISCUSSION

The performed studies are original due to impossibility of carrying out such experiments in humans. However, the results can be extrapolated to people due to, primarily, similar mechanisms of the gastrointestinal tract motility regulation. Secondly, all preclinical studies are carried out on animals, among which one of the species being rats.

The mechanism of Opefera stimulating action on the colon motility is, obviously, associated with the elimination of dysbiosis. Dysbiosis may be the cause of the intestinal motility disorder, as the decrease in symbionic microflora leads to violation of the colon motility regulation, primarily by reducing the formation of short-chain fatty acids [2]. Elimination of dysbiosis weakens the inflammatory process in the colon, which occurs on the background of gastric juice hypoacidity. This, in its turn, leads to a reduction in the release of proinflammatory cytokines (interferon-γ, interleukin-1β and tumor necrosis factor-α), which inhibit the motility of the colon.

CONCLUSIONS

The Opefera drug stimulates spontaneous and stimulated motility of the colon, suppressed by prolonged hypochlorhydria of gastric juice. A conclusion has been made on the expediency of Opefera application in patients with prolonged hypochlorhydria of various genesis for normalization of the colon contractile activity.

Prospects for further research are to clarify the quantitative and qualitative composition of the colon microflora in rats with gastric juice hypoacidity and in the use of synbiotics.

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DOES ULTRASOUND-GUIDED TRANSVERSUS ABDOMINIS PLANE BLOCKADE DECREASE PERIOPERATIVE OPIOIDS IN MORBID OBESE PATIENTS UNDERGOING LAPAROSCOPIC SURGERY?

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ABSTRACT

Introduction: The recent recommendations have luck of information about regional anesthesia as one of the ERAS key component within the structure of multimodal analgesia in obese patients .The Ultrasound- guided Transversus abdominis plane blockade (USG- TAP-blockade) is a new regional anesthetic technique to reduce peri-operative pain for many abdominal surgeries.

The aim of this study is to assess the efficiency of analgetic action of USG- TAP-blockade in morbid obese (MO) patients undergoing laparoscopic surgery (LS).

Materials and methods: 90 MO patients were assigned to one of two equal groups; The first group (n1=45) included patients who underwent LS surgery in the lower abdomen and in the pelvis, second group (n2=45) included patients, who underwent LS surgery in the upper and middle part of the abdominal cavity. All patients had bilateral USG- TAP-blockade with systemic analgesia .The primary efficacy end point- reduction of the intraoperative dose of opioids, the need for rescue analgesia in the first 6 postoperative hours.

Results: The fentanyl intravenous dose in n1=55 was considerably decreased : 1.34 ±0.15 μg / kg /h vs 2.2±0.18 μg / kg /h in second group , (p=0.032). The pain level by VAS in patients in both groups, in average, did not exceed 4 points within the first post-operative day, and there was no need in life-saving analgesia with narcotic analgetics.

Conclusion: The USG- TAP-blockade has analgetic and opioid-sparing advantages in MO patients undergoing laparoscopic surgery in the lower abdomen and in the pelvis and may be a part of the efficient multimodal analgesia within ERAS in that patient's group.

KEY WORDS: ERAS, morbid obesity, ultrasound- guided TAP- blockade, multimodal analgesia

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INTRODUCTION

The laparoscopic methods in surgery and the principles of enhanced recovery after surgery (ERAS) of individuals afflicted by morbid obesity (MO) have been already proved, and should be considered as a standard of surgical aid for this group of patients [1,9] . Multimodal approach in peri-operative analgesia is the ERAS program mandatory component.

Notwithstanding the good analgetic effect, narcotic analgetics represent a considerable risk and danger for individuals with MO: risk of hyperalgesia, negative effect on immune system, increase of post-operative nausea and vomiting (PONV), and the most important – respiratory disorder in patients with sleep apnea syndrome.

According to ERAS protocols, it is necessary to minimize the use of opioids in patients with MO [1]. As a rule, the opioid load is minimized due to multimodal analgesia using the local anesthesia, nonsteroidal anti-inflammatory drug (NSAID), paracetamol and regional anesthesia. It is regrettable that the epidural anesthesia is not always technically possible for MO patients, and it has risks to cause post-operative complications resulting in prolongation of hospitalization [3-5]. Thus, the recent recommendations have no data on regional anesthesia as one of the ERAS key component within the structure of multimodal analgesia in obese patients [6]. Precisely for this reason, notwithstanding that the opioid-free anesthesia protocols already exist [7-8] , the development of alternative schemes of peri-operative anesthesia in this group of patients in general surgery remains extremely urgent.

The Ultrasound- guided Transversus abdominis plane blockade (USG- TAP-blockade) gains wide popularity nowadays. TAP blockade is an afferent block of the anterior abdominal wall , was first described by Rafi in 2001 and involves blockade of the T7-L1 intercostal, subcostal, ilioinguinal and iliohypogastric nerves that provide sensory innervation to the anterior abdominal wall [13] . The technique involves analgesic agent introduction into the lateral abdominal wall and between the internal oblique and transversus abdominis muscles . The classic blind method is associated with several complications [14] , therefore, it has largely been replaced by USG- TAP blockade, first described by Hebbart et al. [15].

There are many studies confirming the efficiency and safety of this technique for patients with normal and excess weight [11-12]. But there are a few data on TAP-blockade

efficiency in MO patients during general laparoscopic surgeries [2]. Therefore, we presupposed that bilateral USG -TAP blockade might decrease pain and peri-operative dose of opioids during surgeries on abdominal cavity lower section in this group of patients.

THE AIM

The aim of this study is to asess the efficiency of analgetic action of bilateral USG- TAP blockade in MO patients undergoing laparoscopic surgeries.

MATERIALS AND METHODS

The study included 90 patients with MO: 42 men and 48 women which underwent laparoscopic surgery. Inclusion criteria: age 18 years, body mass index (BMI) ≥40 kg / m2 or ≥35 kg / m2 in the presence of comorbid pathology. 17 patients underwent laparoscopic (LS) appendectomy, 10 - LS transabdominal preperitoneal hernioplasty with inguinal hernia , 8 - LS conservative myomectomy, 10 - LS ovarian cystectomy, 10- LS gastric sleeve resection, 22 - LS cholecystectomy, 13- LS transabdominal preperitoneal hernioplasty with postoperative ventral hernia .

Patients were randomly assigned to one of two equal groups; The first group (n1=45) included patients who underwent surgery in the lower abdomen and in the pelvis, second group (n2=45) included patients who underwent surgery in the upper and middle part of the abdominal cavity. All patients had bilateral ultrasound- guided transversus abdominis plane blockade with systemic analgesia . The primary efficacy end point- reduction of the intraoperative dose of opioids, the need for rescue analgesia in the first 6 postoperative hours. The secondary endpoints included hospital stay. The following indicators were also evaluated: parameters of intraoperative hemodynamics, indicators of early postoperative rehabilitation, indicators of postoperative pain by VAS, the frequency of episodes PONV.

All patients during the operation had a combined inhaled low-flow anesthesia with sevoflurane in combination with preventing multimodal analgesia , multimodal PONV prevention [18] and thromboprophylaxis.

Used method of anesthesia - multicomponent balanced anesthesia with the following method: premedication – ondansetron 8 mg, dexketoprofen - 50 mg, paracetamol 1000 mg , pantoprazole - 40 mg intravenously(i.v.). The induction of propofol – 1.5-2.0 mg / kg fractionally until the clinical symptoms of anesthesia, fentanyl 0.005% -0.1-0.2 mg i.v.. Tracheal intubation after relaxation against atracurium benzilate or rocuronium bormid . Support for anesthesia: oxygen-sevoflurane mixture FiO2 - 50-55%, sevoflurane – MAC 0,6-0,8 at a flow no more than 1 l/min. BIS parameters were maintained at the level of 40-55. For intraoperative anesthesia patients had bilateral USG- TAP blockade with systemic analgesia by fentanyl.

Technique of USG- TAP Blockade : procedures were performed under a combined inhaled low-flow anesthesia with sevoflurane.

The ultrasound probe (Shenzhen Mindray Bio-Medical Electronics Co Ltd., M5 ADP1210-01, China) was placed on the lateral abdominal wall in the mid-axillary line between the lower costal margin and iliac crest. Using ultrasound allowed accurate deposition of the local anesthetic in the correct neurovascular plane. A spinal needle G 25 was advanced using in-plane technique between the aponeurosis of the internal oblique and transversus abdominis muscles. With intermittent aspiration, 20 mL of local anesthetic (0.25% bupivacaine) was deposited in the TAP on each side and seen as a hypoechoic shadow pushing the two layers apart .

The level of postoperative pain was determined on the visual-analytical scale (VAS) [10]. The assessment of pain by VAS was performed for the first time on the operating table, immediately after the tracheal extubation, then at 2, 4, 6, 12 and 24 hours after the operation twice (before and 30 minutes after anesthesia).

Interpreting of VAS scale:

0 - no pain;

1-3 points - mild pain;

4-5 points - moderate pain;

6-9 points - severe pain;

10 points - the strongest pain.

Interpretation of anesthetizing results:

1) no pain - 0 points;

2) adequate pain relief - 1-4 points;

3) additional pain relief (moderate pain) - 5 points;

4) it is necessary to use narcotic analgesics (severe pain) - 6 -10 points.

PONV rate was recorded during the first 24 hours of the postoperative period. In order to objectivize the clinical significance of nausea, the scale of the PONV manifestations of the intensity of clinical manifestations, consisting of four points, where 0 - corresponded to the absence of PONV, 1 - manifestation of nausea, 2 - presence of vomiting, 3 - development of repeated vomiting, was used. In the case of two or more episodes of vomiting, ondansetron was administered intravenously at a dose of 4-8 mg [9,10] .

In the early postoperative period, patients continued to receive multimodal analgesia and perioperative thromboprophylaxis with compression stockings and LMWH.

The statistical processing of the study results was carried out using the statistical analysis package MedCalc v. 18.11 (MedCalc Software Inc, Broekstraat, Belgium).

RESULTS

Baseline patient characteristics are shown in Table 1.

There was no statistically significant difference in gender, age, body mass index, ASA classification and comorbidities.

Indicators characterizing hemodynamics and gas exchange during surgery are presented in Table 2.

The presented data testify that the indices of hemodynamics, adequacy of oxygenation and ventilation in both groups do not considerably differ between themselves during operation and have been within intra-operative

Table 1. Baseline characteristics

Variables	Group 1 (n1=45)	Group 2 (n2=45)	P
Female gender	26 (57 %)	24 (53 %)	0.08
Age (years)	43.32 (±11.05)*	41.46 (± 11.73)*	0.618
BMI	42 (35-48)**	41 (36-45)**	0.018
ASA grade			0.335
ASA I	0 (0.0%)	0 (0.0%)	
ASA II	33 (73%)	34 (75%)	
ASA III	12 (26 %)	10 (22 %)	
ASA IV	0 (0.0%)	1 (2 %)	
Hypertension	30 (54 %)	42 (76 %)	0.223
Diabetes mellitus II	12 (26 %)	15 (33 %)	0.205
OSA	2 (4 %)	3 (6 %)	0.162

*-Values are mean (± standard deviation)
**-Values are median (interquartile range)

Table 2. Indicators of hemodynamics and gas exchange in the perioperative period

Variables / period	In the mind		Trocars installation		The main stage of operation		The end of operation	
	Group 1 (n1=45)	Group 2 (n2=45)	Group 1 (n1=45)	Group 2 (n1=45)	Group 1 (n1=45)	Group 2 (n1-45)	Group 1 (n1=45)	Group 2 (n1=45)
Systolic blood pressure, mm Hg	157 (139-168)*	160 (135-170)*	125 (110-130)**	142 (135-150)**	127 (115-135)*	125 (120-130)*	118 (112-125)*	120 (120-130)*
Diastolic blood pressure, mmHg	100 (85-100)*	100 (80-100)	73 (68-80)**	95 (85-105)**	80 (60-80)*	70 (70-80)*	80 (60-80)*	70 (60-80)*
Heart rate, beats/min	82 (72-97)*	85 (78-88)*	67 (62-74)**	92 (88-107)**	70 (64-76)*	67 (57-77)*	84 (80-87)*	73 (69-77)*
SPO2, %	98 (95-98)*	96 (94-99)*	98 (97-100)**	94 (92-96)**	99 (99-100)*	98 (97-99)*	98 (98-100)*	97 (96-100)*
Et CO2, mm Hg	38 (36-39)*	37 (37-38)*	37 (35-39)**	40 (39-41)**	38 (37-39)**	38 (36-40)*	40 (39-42)*	39 (38-40)*

* - Comparison of the central tendencies of the two independent populations, the statistically significant differences (p≥0.05, W Wilcoxon test, multiple comparison, Kruskal-Wallis test, Xi square test) between parameters in the 1 st and 2 nd groups;
** - statistically significant differences (p≤0.05, T Wilcoxon test, multiple comparison, Kruskal-Wallis test) of the parameters in the comparison groups.

stress-norm, except the trocars installation period. The heart rate in this operative time in second group had a static meaningful tendency to tachycardia, hypertension, decrease of oxygen saturation values and increase of Et CO2 that witnessed the insufficient analgesia. Therefore, the second group patients needed the increase of fentanyl intravenous dose and additionally local infiltration anesthesia at trocar entry points unlike the first group patients.

The values characterizing early patient recovery after surgery are given in table 3. The values have been estimated from zero sevoflurane end-expiratoryconcentration and the last relaxant introduction after 30 minutes at the earliest.

As it is clear from table 3, data in both groups are reliably different, except the pain level by visual analog scale (VAS) during awakening. In group1(n1=45) the recovery time of spontaneous breathing, eye opening and extubation was reliably shorter in comparison with the group29n2=45) analog values; probably it is stipulated by the fact that the fentanyl intravenous dose in first group was considerably decreased : 1.34 ±0.15 μg / kg /h vs 2.2±0.18 μg / kg /h in control group, (p=0.032).

Extubation in both groups was done on surgical table, so there was no need for prolongated artificial pulmonary ventilation. At that, the level of post-operative pain on surgical table by VAS in both groups was minimum 0-1 point.

Dynamics of the level of postoperative pain by VAS in the first day after surgery is presented in Table 4.

As it can be seen from the given data, the pain level values by VAS in the first group patients were reliably lower within the first four hours after surgery, probably due to TAP-block extended analgetic action. There were no statistically meaningful distinctive features between the groups under study as to average pain points within the first 6, 8, 12 and 24 hours after surgery. At the pain threshold up to 5 points by VAS, the nonsteroidal anti-inflammatory drugs (dexketoprofen, ketarolac) and paracetamol have been used

Table 3. The values characterizing early patient recovery after surgery

Variables	Group 1 (n1=45)	Group 2 (n2=45)	P
Opening eyes, min	4 (3-6)**	8 (8-9)**	0.02
Effective spontaneous breathing, min	2 (1-3)**	6 (4-7)**	0.01
Extubation, min	4 (3-6)**	8 (8-10)**	0.01
Tthe level of postoperative pain for VAS	0 (0)*	1 (0-2)*	0.1

* - Comparison of the central tendencies of the two independent populations, the statistically significant differences (p≥0.05, W Wilcoxon test, multiple comparison, Kruskal-Wallis test, Xi square test) between parameters in the 1 st and 2 nd groups;
** - statistically significant differences (p≤0.05, T Wilcoxon test, multiple comparison, Kruskal-Wallis test) of the parameters in the comparison groups .

Table 4. Parameters of the level of postoperative pain for VAS in the first 24 hours after surgery.

Postoperative hours	Group 1 (n=45)	Group 2 (n=45)	p
2 hours	1 (1-3)**	3 (3-5)**	0,001
4 hours	2 (3-4)**	4 (4-5)**	0,003
6 hours	3 (3-5) *	4 (3-5)*	0,14
8 hours	2 (2-4)*	3 (2-4)*	0,23
12 hours	2 (2-5)*	3 (3-6)*	0,13
24 hours	2 (2-4)*	2 (3-4)*	0,069

* - Comparison of the central tendencies of the two independent populations, the statistically significant differences (p≥0.05, W Wilcoxon test, multiple comparison, Kruskal-Wallis test, Xi square test) between parameters in the 1 st and 2 nd groups;
** - statistically significant differences (p≤0.05, T Wilcoxon test, multiple comparison, Kruskal-Wallis test) of the parameters in the comparison groups at 2 and 4 postoperative hours;

as pain relief drugs, and above 5 points – narcotic analgetics (promedol) [10]. After the above-mentioned laparoscopic surgeries the pain level by VAS in patients in both groups, in average, did not exceed 4 points within the first post-operative day, and there was no need in life-saving analgesia with narcotic analgetics correspondently.

The PONV values have been considerably lower in first group: 2,3 ± 0,9 vs 3,1 ± 0,9; p <0,0001.

As to the values of hospitalization duration, there was no statistically meaningful difference between the groups: 2.76 ± 0.56 days vs 2.74 ± 0.6 days, p= 0.87.

DISCUSSIONS

The obesity is one the principal problems of the present day in the whole world. The patients with MO have very variable co-morbid conditions that complicate considerably their post-operative period. Therefore, the decrease of general dose of opioids, pain control, and early mobilization are the most important components in treatment of this group of patients.

It is known that postoperative pain after laporoscopic surgery presents three components: parietal pain associated to the damage in the abdominal wall during the insertion of the ports, visceral pain and the pain associated to the pneumoperitoneum, causing a diaphragmatic irritation. It has been estimated that after laparoscopic surgery, parietal pain represents 50–70% of the total pain, visceral pain (10–20%), and the pain related to the pneumoperitoneum 20–30% [16-17].

Our study has proved opioid-sparing advantages of USG-TAP blockade in MO patients during laparoscopic interference on abdominal cavity lower sections, having practically halved the fentanyl intra-operative dose, which have positive effect on the speed of spontaneous breathing recovery and cognitive functions in the first-group patient. Insufficient performance of the USG- TAP blockade in the second group is more likely to be associated with the development of afferent blockade at a level below the trocar insertion area, which is confirmed by the dynamics of VAS pain level in first postoperative day.

In the early postoperative period, patients in both groups did not complain of pain associated with the effect of pneumoperitoneum on the diaphragm. Therefore, despite the absence of an intraoperative opioid- sparing effect in the second group, the bilateral TAP blockade in the second group was effective as component of postoperative analgesia

CONCLUSIONS

The USG-TAP blockade has analgetic and opioid-sparing advantages in MO patients in laparoscopic surgeries . It is a practically implemented low-invasive method in MO patients and may be a part of the efficient multimodal analgesia within ERAS in MO patients who undergone laparoscopic operation on abdominal cavity lower sections.

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KALLIKREIN-KININ SYSTEM DISBALANCE IN CHRONIC PANCREATIS IN COMBINATION WITH METABOLIC SYNDROME

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ABSTRACT

Inroduction: Disbalance of kallikrein-kinin system, which is present in patients with chronic pancreatitis, is quite often associated with metabolic syndrome.

The aim: to study and compare the status of kallicrein-kinin system in patients with chronic pancreatitis compared with patients with comorbidity of chronic pancreatitis and metabolic syndrome.

Materials and methods: All patients were divided into two groups: I group included 58 patients with chronic pancreatitis in combination with metabolic syndrome; II group included 32 patients with chronic pancreatitis. . Indicators of kallicrein-kinin system in blood plasma were determined by chromatographic method.

Results and conclusions: Worse condition of kallicrein-kinin system was observed in patients with metabolic syndrome.

Patients with chronic pancreatitis with comorbidity with metabolic syndrome established more pronounced activation of the system of general and specific proteolysis with statistically significantly higher rates of proteolytic activity of plasma, kallikrein, α_1-protease inhibitor and kininase-II ($p<0.05$) relative to patients with chronic pancreatitis.

KEY WORDS: chronic pancreatitis; stable coronary artery disease; disbalance; kallikrein-kinin system

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INTRODUCTION

Chronic pancreatitis (CP) is one of the most common, rapidly progressing disease of pancreas (up to 70.0 %) with a high incidence of temporary disability and primary disability (up to 15.0 %). The negative effect of CP on the basal metabolism system has long been known. It is established that in 19.5 % of patients with gastroenterological pathologies, including pancreatitis, there is stable coronary metabolic syndrome (MS). The combination of CP and MS is characterized by a progressive course with increasing of the functional insufficiency of pancreas and the development of disorders in the kallikrein-kinin (KKS) system [1-2].

The system of general and specific proteolysis (or KKS) is a regulatory link that aims to adapt the body to the constantly changing environment of the environment. Currently KKS are among the most intensively investigated humoral proteolytic systems of the body [3-4]. One of the reasons for interest in this system is its multifunctionality due to the special properties of kallikrein (KK) and the formation of this enzyme family of highly active peptides (kinins), which have a huge spectrum of biological action [5-6]. Adaptation processes of the body are regulated by a complex of proteolytic systems and are determined by the persistence of biochemical homeostasis [7-8]. The versatility of the KKS is due to its close relationship with the four most important humoral proteolytic systems: coagulation, fibrinolytic, renin angiotensin and complement system [9-11].

The status of KKS indicators also reflects the activity of inflammatory response in the body, the state of microcirculation, the severity of the disease. The system of general and specific proteolysis is one of the central systems that regulates homeostasis and performs adaptive-protective reactions [12-13]. In the development of biochemical disorders that accompany many diseases of the internal organs plays an important role in the KKS disbalance. Under physiological conditions, the activity of proteolytic enzymes is balanced with the level of proteinase inhibitors. In chronic inflammatory conditions, including pancreatitis, there is a violation of the dynamic equilibrium between proteases and their inhibitors. An increase in the amount and activity of tissue-derived proteolysis enzymes leads to a "protease explosion", which causes hypertrophic, fibrinolytic systems and KKS to be hyperactivated. Subsequently, changes caused by the development of destructive and inflammatory changes throughout the body, including in the pancreas and cardiovascular system. That is why the study of the status of KKS in patients with comorbid course of CP and MS is relevant.

THE AIM

To study and compare the status of kallicrein-kinin system in patients with chronic pancreatitis compared with patients with comorbidity of chronic pancreatitis and metabolic syndrome.

MATERIALS AND METHODS

The study was conducted at the Department of General Practice – Family Medicine, I. Horbachevsky Ternopil State Medical University (within 2016-2017).

To achieve this goal, 90 patients were screened for CP. The patients were divided into two groups: I group included 58 patients with CP in combination with MS; II group included 32 patients with CP. They were comparable to the etiological factor, socio-economic conditions and nutrition. Also, the influence of the alcohol factor was excluded. Among patients, there were 46 (51.2 %) male age (49.9±8.7) years and 44 female (48.8 %) age (52.65±6.2) years. The average duration of CP was (12.4±4.3) years, MS – (4.2±1.1) years. The average level of glucose in CP+MD group was (5.7±1.19) mmol/L. The control group consisted of 20 healthy individuals. Patient examination was carried out with their consent. The study did not include patients with moderate to severe DM requiring insulin, severe arterial hypertension, cancer and somatic illness in the stage of decompensation. The studies meet the requirements of the Helsinki Declaration of the World Medical Association «Ethical principles for medical research involving human subjects as the object of study» opinion of the Committee on bioethics SHEI «Ternopil State Medical University by I. Horbachevsky of MPH of Ukraine» № 41/2017.

The diagnosis of CP was verified on the basis of the generally accepted classification in Ukraine proposed by the Scientific Research Institute of Medical Sciences of Ukraine, which corresponds to the Marseilles-Roman classification according to the «Unified clinical protocol of primary, secondary (specialized) medical care and medical rehabilitation of patients with chronic pancreatitis» approved by Order of the Ministry of Health of Ukraine № 638 dated 10.09.2014. All of the patients under study had a lipid metabolism [14]. The diagnosis of SCAD was established according to guidelines from the National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association (AHA) when at least 3 of the 5 MS criteria were diagnosed [15].

The patients were comparable in age, sex, duration of CP, the frequency of diagnostic criteria for MS. Indicators of KKS in blood plasma were determined by chromatographic method [16]. Specific proteolysis was evaluated by the content of KK, PKK (prekallikrein), α_2-MG (α_2-macroglobulin), and kininase-II. Non-specific proteolysis was evaluated by the level of PAP (proteolytic activity of plasma) and α_1-IP (α_1-protease inhibitor) in blood plasma.

Statistical processing of the received data was performed on a personal computer using standard software packages of Microsoft Excel and with help of the computer program Statistica for Windows version 6.0 (Stat Soft inc., USA).

RESULTS

Table I shows the results of the obtained indicators of general and specific proteolysis in the comparison groups that characterize the state of KKS.

A statistically significant higher PAP level was found in patients with CP in combination with MS relative to the CP group and the control group. This indicates activation of total proteolysis in such patients. Also, the analysis of KKS indices in patients with MS with CP showed activation of specific proteolysis (or kininogenesis) by a statistically significantly higher level of the proteolytic enzyme KK relative to the group of CP and control group. There was a decrease in the level of inactive precursor KK – PKK in patients with CP + MS relative to the CP group by 20.95 % and 49.11 % relative to the control group.

The level of α_1-IP in patients with MS as an enzyme that controls the activity of proteolysis due to the binding of proteolytic enzymes of exo- and endogenous origin, was statistically significantly increased in the group of CP by 13.79 % and 40.43 % relative to the control group. Patients with MS were also found to have a statistically significant decrease in α_2-MG relative to the CP group and the control group. This indicates the depletion of the body's inhibitory protection.

With regard to kininase-II activity, its level in patients with MS was statistically significantly lower relative to this indicator of the CP group by 14.98 % and 43.20 % and relative to the healthy group. This indicates a weakening of the body's protective reactions due to excessive kinogenesis. Therefore, activation of KKS indicators confirms the presence of inflammatory process in the body of patients with CP in the phase of clinical remission, with a tendency to increase it more depending on the presence of MS.

DISCUSSION

The analysis of KKS indices in the subjects patients showed activation of specific proteolysis and nonspecific proteolysis in the two comparison groups, however, more significant activation of proteolysis was noted in the group of patients with SCAD. A more intense increase in the level of KK was observed in groups of patients with CP+ SCAD, which is 1.26 times higher than the level of this indicator relative to the group of patients with isolated CP ($p<0,001$). A similar tendency was observed for the level of α1-IP – its level in persons with the presence of SCAD is 1.14 times higher than the level of this indicator in group CP. Such changes in the body of patients indicate the simultaneous activation of both specific and nonspecific proteolysis both in our study and in comparison with the world literature [17]. Also, individuals of the CP+SCAD group showed such dynamics of indicators, which indicated a weakening of the body's protective reactions due to excessive kinogenesis [18]. The level of kininase-II in patients in the main group was lower by 1.18 times compared with patients in the HP group. The concentration of α2-MG in the CP+SCAD group also decreased (1.98 times compared with the comparison group) ($p<0,05$).

Therefore, the enlightened dynamics of the indicators indicate more significant simultaneous activation of specific and nonspecific proteolysis in groups of patients with the presence of SCAD compared with patients with isolated CP. A more significant decrease in the level of kininase-II and α2-MG in the CP+SCAD group indicates a weakening of the body's protective reactions due to excessive kinogenesis.

Table I. Indicators of general and specific proteolysis in comparison groups

Indicator	Comparison group		
	Control group (n=20)	CP (n=32)	CP+SCAD (n=64)
PAP, mmol / (h·L)	31,83±0,71	47,99±1,20 (p<0,001)*	55,63±0,52 (p<0,001)* (p<0,001)**
KK, μmol / (min·L)	52,15±1,43	140,81±1,45 (p<0,001)*	177,44±1,00 (p<0,001)* (p<0,001)**
PKK, μmol / (min·L)	72,57±1,21	46,72±0,99 (p<0,001)*	36,93±0,43 (p<0,001)* (p<0,001)**
α1-IP, g/L	1,41±0,02	1,74±0,02 (p<0,001)*	1,98±0,03 (p<0,001)* (p<0,001)**
α2-MG, g/L	1,50±0,03	0,89±0,02 (p<0,001)*	0,45±0,01 (p<0,001)* (p<0,001)**
The activity of kininase-II, μmol / (min·L)	269,84±1,74	180,27±1,12 (p<0,001)*	153,27±1,31 (p<0,001)* (p<0,001)**

Note: * – statistical-significance concerning indicators of the control group; ** – statistical-significance concerning indicators of CP group.

CONCLUSIONS

Patients with chronic pancreatitis with comorbidity with metabolic syndrome established more pronounced activation of the system of general and specific proteolysis with statistically significantly higher rates of proteolytic activity of plasma, kallikrein, α_1-protease inhibitor and kininase-II ($p<0.05$) relative to patients with chronic pancreatitis. It indicates a greater activation of inflammation-catabolism processes in patients with chronic pancreatitis with the presence of metabolic syndrome.

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RELATIONSHIP BETWEEN IDIOPATHIC SCOLIOSIS OF THE SPINE AND DENTOGNATHIC ANOMALIES IN ADOLESCENTS

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ABSTRACT

Introduction: According to the data of the national statistics, the disease of the musculoskeletal system among the teenagers takes the third place among the main types of diseases. So, we decided to analyze and study the connection between the idiopathic scoliosis of the spine and dentognathic anomalies in children aged 12-15 years old in Uzhhorod (Ukraine).

The aim: To determine the characteristic violations of the dentognathic system in adolescents with idiopathic scoliosis of the spine, taking into account the anatomical type of lesion.

Materials and methods: 225 people were examined, including 190 girls and 35 boys. All patients were under the control of an orthopedic physician.

Results: The most common type of scoliosis is found to be thoracolumbar, which is noted in 114 patients. As a result of analysis it was found that the most characteristic disorders of the dentognathic system in patients with thoracolumbar scoliosis were distal bite (80 ± 2.0%), sagittal gap (37.5 ± 2.1%), deep bite (22.5 ± 2.3%). In the group of healthy children, without scoliosis, the prevalence of dentognathic anomalies is 2.6 times lower than in patients with idiopathic adolescent scoliosis.

Conclusions: Regardless of the localization of deformation in the spine under scoliosis, all the groups of patients are characterized by the following signs: sagittal gap, shortening of the upper dentition, distal bite, crowding of the teeth on the lower jaw.

KEY WORDS: age group 12-15 years, scoliosis, dentognathic anomalies, spine, bite

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INTRODUCTION

According to the data of the national statistics, the disease of the musculoskeletal system among the teenagers takes the third place among the main types of diseases. They are mainly scoliosis, flat foot, rheumatoid arthritis and others. According to the investigations, the prevalence of posture and scoliosis disorders among the children varies from 5% to 46% [1]. Scoliosis leads to the serious spine and chest deformations and it tends to the progress of the disease especially when the child stops growing. Scientific researches of the last years have showed that the metabolic osteopathy occurs mainly in the childish period [2]. Children who suffer from scoliosis have problems with biotransformation of the main structural components of the connected tissue, caused by the integral reaction of the organism to the combination of the two pathologies: osteopenia and scoliosis. Modern scientific literature confirms that osteopenia, which accompanies scoliosis, progresses in peak periods of intense growth and regresses in the post-adolescence period, indicating the importance of violations of the morphofunctional state of bone tissue in the pathogenesis of scoliosis [3,4]. The symptoms of the osteopenia are: the decrease of the minerals and the mineral density of the bone tissue, the changes in the metabolism that lead to the progress in the spine's deformations. The dentofacial system as a part of the musculoskeletal system faces the same metabolic changes that the bone tissue of our organism does [5,6].

The dentognathic anomalies are widespread among children who have problems with their posture (1,5 times frequency) and in 2,5 times more frequent among the children who suffers from the scoliosis. Among the children who suffers from the scoliosis the dentognathic anomalies occur from 69 to 82,5 % [7]. Some authors consider that this is because of the wrong fixed facts about the influence of the postural reflexes on the development of the occlusion anomalies. In those patients, the position of the head changes, the sublingual bone is distal, which in turn contributes to the distal shift of the mandible, the tongue loses contact with the palate, lies at the bottom of the oral cavity, there is a decrease in the tone of the *m. orbicularis oris*. When the mineralization in the bone tissue decrease the form of the bones changes as well. As a result, posterior occlusion, transversal anterior occlusion and aggregation of the teeth develop [8].

THE AIM

Aim of research – to determine the characteristic violations of the dentognathic system in adolescents with idiopathic scoliosis of the spine, taking into account the anatomical type of lesion.

MATERIALS AND METHODS

225 children have been examined at the age of 12 to 15 (190 of them were girls (84,4±3,3%) and 35 - were boys (15,6±2,1%).

All patients were under the control of an orthopedic physician.

In studying the spine deformity, the subjects analyzed: anatomical type of deformation; side of arc of deformation; degree of deformation severity; the value of the arc curvature of the spine [9].

In the course of investigation great attention was paid on: the type of the closure of dental raws in three positions (sagittal, horizontal and vertical); the dentognathic anomalies of the dental raws and of the separate teeth; the defect in functions and esthetics.

The position of the occlusion and of the separate teeth has been investigated by means of the Angle's classification and WHO recommendations (1997) [10].

All calculations were performed on a PC using a licensed software for operating system Windows and standard software package STATISTICA 6.1. Statistical data processing was carried out using Student's probability *t*-test.

RESULTS

According to the anatomical types, the patients who suffer from scoliosis have been divided into 3 groups: with thoracic deformation, thoracolumbar deformation, lumbar deformation. The fourth group was almost healthy children without deformations. As a result, the most frequent type of scoliosis turned out to be a thoracolumbar one (114 patients suffering it). The data of the prevalence of the patients who suffer from scoliosis is in the Table 1.

Groups of patients were formed in accordance with the revealed orthopedic symptom complex, with the following characteristics of the violations of the dentognathic system.

The evaluation of the occlusion among the patients of the Group 1 (the thoracic deformation) has showed that the most frequent type of teeth occlusion in the sagittal position is the 2 classification according to Angle's classification. The distal occlusion occurred among 29 patients (63,0 ± 2,0%). Neutral occlusion has been examined among 11 patients (23,9 ± 2,2%).

Sagittal gap has been examined among 17 patients (36,6 ± 2,1%). The deep bite occurred among 9 patients (19,6 ± 2,3%). In the course of investigation, the cross occlusion appeared to be among 5 patients (10,9 ± 2,6%). On the level of the dental rows in the sagittal position the most frequent is the decrease of the lower raw (12 people - 26,1 ± 2,2%) and the upper one (9 people – 19,6 ± 2,3%). In the horizontal position the narrowing of the upper dental row has been investigated (11 people - 23,9 ± 2,2%). The lack of the placement of the front dental row has been found among 28 people (60,9 ± 2,1%). Diastema on the lower and upper jaws has been examined among 6 children (13,0 ± 2,4%). The replacement of the central line has been examined among 17 patients (36,9 ± 2,1%), deformation of the spine on the right (40 people - 86,9 ± 2,0%), it has been also examined the shifting of the central line of the lower jaw on the left among 6 patients (13,0 ± 2,4%) and on the right only in 2 cases (4,3 ± 4,3%).

As a result of the research it have been found out that the most frequent deformation of the dentofacial system is among the patients with the thoracic scoliosis: distal occlusion (57,8 ± 5,9%), sagittal gap (38,3 ± 5,7%), deep bite (18,4 ± 4,6%).

The Group II of patients with left-sided and right-side thoracolumbar scoliosis of the spine was 114 persons (50.7 ± 2.0%). Right-hand localization of the spine deformity is characteristic for 47 (41,2 ± 2,0%), left-handed for 67 patients (58,8 ± 2,0%).

In assessing the bite in the sagittal plane in Group II, it was found that distal bite is characterized for 68 people (59.6 ± 2.0%). In the 10 patients (8.8 ± 2.2%) mesial bite was detected. Sagittal gap was found in 59 patients (51,8 ± 2,0%). In the vertical plane deep bite was predominant (32 people - 28,1 ± 2,0%), open bite was detected in 12 examined (10,5 ± 2,2%). In the study of occlusion in a horizontal plane was established a cross bite in 8 persons (7,0 ± 2,3%). Extension of the upper dentition was diagnosed in 13 patients (11,4 ± 2,2%), the lower dentition in 5 people (4,4 ± 2,6%). The shortening of the upper dentition was detected in 14 patients (12,3 ± 2,1%), shortening the lower tooth row - in 29 cases (25,4 ± 2,0%). At the level of dental rows in the horizontal plane, the narrowing of the upper dental arc was characterized for 20 surveyed (17.5 ± 2.1%). The deficit of place (mainly the front group of teeth) was diagnosed in 48 patients (42,1 ± 2,0). In 49 people (43 ± 2.0%) oral displacement was noted, and 28 patients (24.6 ± 2.1%) had a vestibular displacement of teeth. The diastema and the trema on the upper and lower jaw were noted in 25 (21,9 ± 2,1%) and 19 (16,7 ± 2,1%) patients respectively. The deficit of the place for teeth was noted in 22 cases (19,3 ± 2,1%).

The Group III - the scoliosis of the lumbar spine is represented by a group of 40 patients, which is 17.8 ± 2.0 % from all the examined patients. It was found that in 13 patients was neutral bite (32,3 ± 2,2%), in 32 (80 ± 2,0%) - distal. Sagittal gap was observed in 15 patients (37,5 ± 2,1%). Deep bite was diagnosed in 9 people (22.5 ± 2.3%). In the sagittal plane at the level of dentition, the shortening of the lower tooth row was observed in 8 patients (20 ± 2.3%), the shortening of the upper dentition was observed in 6 persons (15 ± 2.4%), the extension of the upper dentition had 8 (20 ± 2.3%). At the level of dental rows in the horizontal plane, the narrowing of the upper dental arc was determined in 10 people (25 ± 2,2%). In studying the state of individual teeth, vestibular displacement was detected in 15 people (37,5 ± 2,1%), oral displacement of the anterior teeth - in 22 (55 ± 2,1%). The diastema and the trema were noted in 8 (20 ± 2,3%) and 2 (5 ± 4,3%) patients respectively. The deficit of the place of teeth was in 18 surveyed (45 ± 2.1%). The displacement of the middle line is characteristic for 19 people (47,5 ± 2,1%).

As a result of the analysis of the obtained data, it was found that the most characteristic disorders in the Group IV (practically healthy children without scoliotic spine deformation) were distal bite (24 ± 2.6%), sagittal gap (16 ± 2.8%), deep bite (12 ± 3,2%), shortening of the lower tooth row (16 ± 2,8%), oral position of the teeth (12 ± 3,2%).

Table 1. The prevalence of the patients who suffer from scoliosis

Group of patients	Examined boys		Examined girls		Total amount of examined patients	P±m %
	Abs.	%	Abs.	%		
I - Thoracic scoliosis	7	15,2±2,4	39	84,8±2,0	46	20,4±2,0
II - Thoracolumbar scoliosis	18	8±2,1	96	42,7±2,0	114	50,7±2,0
III - Lumbar scoliosis	6	2,7±2,4	34	15,1±2,0	40	17,8±2,0
IV - Control group (Almost healthy children)	4	1,8±2,8	21	9,3±2,1	25	11,1±2,1
Total amount	35	15,6±2,0	190	84,4±2,0	225	100

DISCUSSION

As a result of analysis of the obtained data, it was found that the most characteristic disorders of the dentognathic system in patients with lumbar scoliosis were distal bite (80 ± 2.0%), sagittal gap (37.5 ± 2.1%), deep bite (22.5 ± 2.3%).

The analysis of the comparison of distal occlusion prevalence in the groups of patients with different types of scoliosis allowed to establish that the most commonly distal bite met with the thoracic scoliosis.

However, the degree of severity of bite violations, the characteristic symptom of which is the sagittal gap between dental rows, is highest in patients with thoracolumbar scoliosis. Deep bite is most commonly encountered in patients with deformation of the lumbar part of spine.

The deficiency of the place for the teeth was most often noted in patients with lumbar and thoracic deformation of the spine.

These studies are in accordance with what affirmed by Lippold et al. (2003), [11] that the scoliotic curves occur in the frontal plane and - through the head posture that is tilted sideways -play an important role in the development of the different dentofacial asymmetries.

Shifting of the central line of the lower jaw on the left is noted for thoracic scoliosis.

Frequency of dental anomalies does not depend on the severity of scoliosis deformation and is 100%.

In such patients, the main type of disruption of bite is distal closure of dental rows. At the level of the dentition, violations such as shortening of the upper dentition, shortening of the lower tooth row, narrowing of the upper tooth row are detected.

In the group of healthy children, without scoliosis, the prevalence of dentognathic anomalies is 2.6 times lower than in patients with idiopathic adolescent scoliosis. Segatto *et al.* (2008) analyzed also other occlusal characteristics of the frontal region of dental arch and found some other significant differences between the scoliotic and the health groups. In particular, the subjects with scoliosis showed a significant higher overjet and a higher midline deviation respect to the control group. Then, the scoliotic group was characterized by lower overbite compared to the determined mean values (3.10 mm) of the control health group [12].

In addition to the studies that compared scoliotic to healthy subjects, other investigations underlined a relation between the occlusion and the vertebral column alignment, also in not scoliotic subjects [13].

CONCLUSIONS

Regardless of the localization of deformation in the spine under scoliosis, all the groups of patients are characterized by the following signs: sagittal gap, shortening of the upper dentition, distal bite, crowding of the teeth on the lower jaw, predominantly in the anterior. Dentist during the examination of children and adolescents knowing violation of the dentition, which most commonly found in scoliosis may recommend the patient to see a orthopedic - traumatologist doctor to detect scoliosis.

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MASTERING YOUR BODY AND YOUR HEALTH RESOURCES: FROM THEORETICAL SCIENTIFIC DEVELOPMENTS TO INDIVIDUAL COMPREHENSION

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ABSTRACT

Introduction: The phenomenon of "health", being studied on an interdisciplinary basis, does not appear as the property that automatically belongs to the subject, since it is not inherited by the "natural" property, but is regarded as something that everyone needs to master the same way as the outside reality, in other words, to constantly teach your body to different movements, actions, types of activities, to know the resources of their own health and to develop their ability to serve them throughout their lives as a certain ability.
The aim of the study is to provide theoretical substantiation and experimental verification of the appropriateness of considering health in the context of the inner world of man as a process of mastering the body and resources of his own health. Also in clarifying the factors that negatively affect the health of people aged 13 to 60 years.
Materials and methods: in the work, a set of methods is used: general scientific (analysis, synthesis, comparison, systematization, generalization) and empirical (observation, conversation, questionnaires).
Results: consideration of the phenomenon of "health" is carried out with an emphasis on the inner world of man, in particular on the natural, social and spiritual grounds. It has been established that the content of the inner world exists in the child from the very moment of its birth and is unknowingly expressed by it in various types of activity (crying, movements). The formation of a natural origin is caused by the gradual ripening of various structures of the nervous system, which causes the transition from disorderly movements to clear and harmonious and the process of mastering his body on the basis of mastering one or another action, types of activity. The social origin, occurring and often changing under the influence of human interaction with others, is to a large extent caused by the improvement and deterioration of health. For the formation of a spiritual beginning, it is important to contemplate the spirituality of others (the attitude to health as a social and personal value) and the discovery of a spiritual principle in itself.
Conclusions: educational activity of teachers, aimed at understanding people of different ages in the process of mastering the body and resources of their own health, will serve the formation of their inner world, the conscious elevation of health to the rank of personal values and the understanding of the essence of health as the ability of a person which is used throughout his life.

KEY WORDS: health, body mastering, resources of someone's own health, internal world of a person

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INTRODUCTION

The field of health attracted and still attracts the attention of the person and comprehensively pondered over it, from the process of its formation as a reasonable person (Homo sapiens), continuing in the reproduction of numerous human generations, branching in the progressive development of man as the Homo educates and deepening in the process of reproduction of evolutionarily acquired by man in the coming generations.

In the dimensions of the past and modern, in philosophical treatises, theories of scientists from different fields of knowledge and in the thoughts of ordinary citizens differently interprets the essence of health, unevenly characterized by the "internal picture of health", variously determined by the semantic basis of knowledge in objects and subjects of scientific research, revealing the biological, physiological, physical, medical, spiritual, psychological, social, educational, etc. essence of health, more and more comprehensive determines the internal and external factors of health state, in-depth analyzes what causes changes both in the direction of improvement of health, and in the direction of its deterioration, etc.

Mainly the field of health causes the appearance of various branches of cognition. This is physiology and medicine, and psychology, and ... This process continues to this day, manifested in the formation and development of such branches of knowledge as psychophysiology, neurophysiology, neuroendocrinology, psychogenetics, psychoneuroimmunology, psychopharmacogenetics, normal neuropsychology, psychology of the bodily subject and so on. But despite the powerful human concentration on the field of health, this branch of knowledge is increasingly occurs in different perspectives, modifications, in relation to the dynamic conditions of the development of society, scientific developments in medicine, ecology, sociology, anthropology, andragogy, etc., giving rise to the new and

new aspects for in-depth analysis and formulation of meaningful for perception of the realm of health reasons and practical recommendations for medical, treatment and rehabilitation, improving, strengthening, preventive, educational, etc. activities.

In the context of our study, we use the definition of the concept of "health" that was developed by the working group of the World Health Organization and is presented in this context [4]: health is the degree of ability of an individual or group, on the one hand, to realize their aspirations and to meet the needs, and, on the other hand, to change the environment or co-operate with it. Analyzing this formulation, we emphasize the fact that health in modern trends is revealed in the context of psychological work, which thoroughly explores different aspects of human aspirations and needs, takes into account the belonging of man to society and to nature. This is manifested, firstly, in the classification of society and nature in open systems with complex, nonlinear, unstable relationships and attitudes; and secondly, in the consideration of "the development of man and nature as a single interrelated, cooperative process of co-evolution" [2, p. 353]. And, therefore, the medical and educational foundations of health are based on the study of man as an integrity, determined using the category-conceptual apparatus of various branches of knowledge and the workings of scientists to interpret the essence of certain problems, issues, developments, inventions related to health.

THE AIM

The purpose of this work is to justify the need for interdisciplinary consideration of the phenomenon of health, in particular the use of scientific developments relating to the human inner world and its psycho-physiological development in ontogenesis to explain the process of mastering their own body and health resources.

Hypothesis of research: human awareness of health unfolds as a process of mastering your body and resources of your own health.

Objectives of the study: 1) to characterize the inner world of man as a mental entity; 2) analyze the manifestations of the formation of the natural, social and spiritual principles in the inner world of man; 3) summarize the results of the respondents' questionnaire on the multidimensional understanding of the phenomenon of "health"; 4) to systematize factors which, according to respondents, cause a negative impact on their health; 5) form conclusions about the educational activities of educators, aimed at understanding people of different ages of the process of mastering their body and resources of their own health in accordance with the natural, social and spiritual principles of the human inner world.

MATERIALS AND METHODS

We used a range of methods: general (theoretical analysis, synthesis, comparison, systematization, generalization) and empirical (observation, conversation, questionnaires). To conduct the research 381 respondents in three age groups were involved: the first group - respondents aged 13 to 19 years; second group - respondents aged 19 to 35; the third group - respondents aged 35 to 60 years. Separation of these groups was made on the basis of periodization of mental development of a person, developed by E. Erickson [3].

RESULTS AND DISCUSSION

Fundamental to this study was the reasoning of O. Zaporozhets [4]; that the inherited health of the individual is not a property that automatically belongs to the subject, since the body of the individual, the resources of his health should be mastered in the same way as the external reality. These considerations of scientists confirm the involvement of the human psyche to explain the processes that affect its health.

The process of mastering the body (in other words, the body in its external physical forms and manifestations) and the resources of its own health (which is used in the body to maintain physiological processes, provide activity, ability to work, adapt, etc.) will be considered in the context of the external and the inner world in relation to a person. Firstly, let's emphasize the characteristics of these worlds. To the characteristics of the external world M. Papucha [5] includes a considerable level of complexity, a high degree of nonlinearity, orderliness, structuring (hierarchical), ability to productivity, development and self-development. In relation to the inner world of man, the characteristics of complexity, structuring, high degree of nonlinearity and self-development (self-organization) are complemented by the characteristic of self-controllability (self-control).

The inner world of man comes from a system that is self-organizing and has a high degree of nonlinearity. Its essence and existence are not conditioned only by the fact that the external world is internalized, but is built on the basis of self-management. Managing your own inner world is not always the same efficiency. In the periods of age and life crises, psychotrauma, severe somatic disorders, the seizure of a person with some feelings, as well as mental disorders, this process can be stopped for a relatively short period of time. The inner world in the process of functioning does not remain unchanged, but constantly restructured, completed, transformed into a structured integrity. Therefore, in the works of L. Vygotsky [6], S. Maksymenko [7], M. Papucha [5], the inner world of man is regarded as a structural, dynamic, complex entity capable of self-development and empirically studied as integrity.

According to M. Papucha [5], the structures of his own inner world are created by the man himself. In the generalized form, they can be correlated with three independent principles, such as:

- natural (the natural development of the psyche is provided by maturation);
- social (the line of socio-cultural development of the psyche manifests itself in the appropriation (internalization) (internalization - "the formation of internal structures of the human psyche through the assimilation of structures of external social activity" [8]);

- spiritual (the line of spiritual development of the psyche consists in the contemplation and discovery of the source of the universal spiritual principle (in our understanding, this is the rise of a particular person's health to the rank of personal values on the basis of contemplating the attitude of others to health as a social and personal value).

In order to reveal the process of mastering the body and the resources of own health, it is important that, in the opinion of S. Maksymenko [7], the content of the inner world itself exists in a small child from the very moment of his birth and is unpackaged by it, but represents what is called unconscious. These instances, needs, images that are not understood, but they are causing activity. The inner world is not represented to the child, at the same time, the child, not knowing about it, expresses his inner world with different kinds of activity (crying, movements).

According to I. Sikorsky [9], the first germs of the inner world as a special and entirely real content and the first "outbreaks" of consciousness is that the child constantly strives to repeat the new movements, positions of the body. Recurrence, on the one hand, is associated with the simultaneous occurrence of internal experiences, but on the other hand, it enables one to study new movements and positions of the body, to get used to them, to make them their own.

The process of mastering the body and resources of someone's own health begins immediately after birth. The line of natural development of the psyche begins to manifest itself in the disordered movements of the limbs of the newborn. In the further regulation of movements, the growing role belongs to the cerebral cortex. In scientific papers [10-15] there is a question of establishing a balance of muscle activity, the appearance of the first grasping movements of the hand towards a visible subject, the gradual development of locomotor movements (crawling, getting up, walking), which are promoted by processes that intensively occur in the first year of child's life relates to the maturation of the cerebellum, striatum and other structures of the central nervous system. The process of self-management and personal health resources unfolds consistently. After fixing the movements that arose as a result of generalized excitation with the action of complex visual, auditory and other stimuli, there is a transition to the differentiation of those motor acts that lead to the acquisition of new visual, tactile, vestibular, kinesthetic stimuli (for example, the capture of the subject's hand, the lifting of the head).

The process of mastering the body, namely: motor acts of hands (movement in the direction of the subject, the capture of the subject, experience of the tactile sensation) begins from a two-month age. Uncertain grasping movements with frequent misses as a result of repeated repetition exercises gradually change on smooth, confident movements not only with a precise approach to the subject, but also with the prior adjustment of the fingers of the hand to the shape of an object that a ten-month-old child intends to seize, or with the implementation of grasping movements "blindly" with a prior purposeful targeting to a liked item.

The process of mastering the body and the resources of the own health at the age from 1 to 8 months unfolds in the directions [11] from fixing the movements of the reverse from the back to the side (from the abdomen to the back) and transposition (the motor act caused by the corresponding movements of the adult), to the formation and consolidation of repeated and inherited movements (crawling, walking, sitting, getting up, lowering with the use of a subject as a support, etc.).

For revealing the line of socio-cultural development of the psyche in the context of mastering the body and the resources of someone's own health, the work of O. Leontiev is significant [16]. A psychologist, analyzing the attitude of a small child to people and the subject environment, characterizes him as undifferentiated, since the child, without separating some people (some subjects) from others, reveals a relation to them, which has a pronounced objective, extraneous character. In the process of development of the child, this objectity persists, but the attitude of the child to people and the subject environment becomes different. Mainly these changes-transformations form the internal essence of the crisis of three years, "I will do myself". Further ontogeny is characterized by overcoming the child's alienation in relations with people and the emergence of some of them "equally-human" subject relations. Further ontogenesis, which covers all the next stage of life, is accompanied by an overwhelming majority of cases of a state, manifested in alienation from objects and phenomena of objectivity, and in some cases, a state that is a higher level of human existence compared with the state of alienated objectivity, namely: overcoming the alienation and "admitting" the world to oneself, entering with him in a relationship of kinship and deep penetration of the world.

The line of spiritual development of the psyche appears as a complex process. According to the scientific paper of S. Maksymenko [7], when the inner world of the child is formed, it changes immediately, since formation is at the same time a development. The scientist points out that the thought, expressed (embodied), always "pulls" a different opinion. At the same time, the initial opinion is refined, complicated or simplified, that is, it always changes. An expression of the interior always leads to its same change. Internal in a person always exists; it concerns his development-complication.

The process of mastering the body and resources of own health in the context of the line of spiritual development of the psyche can be illustrated by an example of ontogenetic development of the properties of nerve processes [11, 15]. Children are born, usually with a weak type of nervous system. With the formation of the main mechanisms of neuroimmunodenic regulation in the child's body, the dynamics of strength, balance and mobility of the nervous processes, which is manifested in the gradual growth of the strength of the nervous processes, is parallel and conjugated. In early ontogeny there is a protracted increase in the strength of the excitation process compared with the strength of the braking process. This is manifested in the disequilibrium of the neural processes with the predominance of the force of the excitation process by the end

of adolescence. In general, the average indicators of the properties of nerve processes in adolescents correspond to the average adult performance.

Consequently, the content of the inner world, existing in a small child from the beginning of his birth, suffers the intense development in the age from 0 to 3 years, caused by processes occurring in the autonomic parts of the nervous system [11, 15]. Those or other influences of factors of the environment cause the corresponding reactions of the organism and the change of vegetative functions (complications of digestive processes, reduction of sleep duration, etc.).

Formation of the content of the inner world in the age-old gap of 4-10 years is manifested in the predominance of psychomotor functions and in establishing subordinate relationships between subcortical and cortical brain neurostructures. Such changes in the child's body contribute to the further process of body and health self-care. In a given age-line reaction to the action of environmental factors is carried out mainly in the motor form.

The next essential stage of mastering the body and health resources is the age range of 7-12 years. In this ontogenesis period, the child reacts to the influences of factors of the outside world predominantly emotionally. It causes the development of the inner world of the child on the basis of the formation and complication of its subjective experience, namely: its emotional components.

Subsequent stage of mastering the body and personal health resources are deployed in the age range of 12-16 years. The inner world of the child undergoes further building up against the background of the child's achievement of a sufficiently high level of psychophysical development and mental maturity. At this stage, the ontogenesis of mastering the body and personal health resources is accompanied by a neuro-psychological response to stimuli of the external world, and the process of this response is determined by the individual characteristics of one or another child.

In adolescence, mastering the body and personal health resources arises, according to E. Erickson's considerations [3], as the discovery of the uniqueness of their bodily being, the experience of the state of well-being and the physical self-image as an awareness of the value of their "selves". In adulthood, body and health resources deploy in the process of activity, aimed at ensuring and maintaining productivity during its implementation, despite various stimuli, including those that will affect the emotional sphere.

Mastering the body and the resources of the own health has the general features that are caused by the double nature of the inner world and are independent of age. According to Papucha [5], the inner world of man is both a structure and a process, in other words, it appears both as a structured process and as a procedural structure. The inner world of the human is ordered, since it has stable components and structural indicators (so-called "points of reference"). Also, the inner world of man is a constant flow (namely, a process), during which the new structures appear, exist, performing certain functions and collapse, leaving a part that becomes stable. In other words, various processes characterize the inner world of man, namely: ordering, development, complication, dynamism. These processes have a pronounced individual character that significantly distinguishes the health of one person from the health of another.

The above-mentioned theoretical scientific developments [4-16] identified the empirical component of the study, which aimed at establishing respondents' understanding of the phenomenon of "health", the process of mastering their body and their own health resources; identification of factors that have a negative impact on the health of respondents.

The survey involved respondents aged 13 to 19 (Group I), 19 to 35 years (Group II) and 35 to 60 years (Group III). The division into groups is carried out taking into account the periodization of E. Erickson [3]. The analysis of the personal data showed that the respondents from the three groups treat health using a variety of keywords, namely:

- state of well-being, physical and mental condition, working condition (I group of respondents);
- balance in all systems of the organism, feeling of pleasure, state of the organism, when a person feels satisfied, absence of chronic diseases, mental, physical harmony (II group of respondents);
- value, happiness, pleasure (III group of respondents).

The process of mastering the body of the respondents from all three groups correlates with the first year of life of a child and interprets how to master the child's actions to sit, crawl, walk, etc.

All the respondents described the resources of their own health as: complete; gradually exhausted; restorative and non-renewable (depending on how they are used in excessive, intense and prolonged labor); those that are more heavily inherited from parents.

According to the respondents' considerations, various factors have a negative impact on health. Based on generalization of the questionnaire, the factors determined by the respondents are organized in the following content lines:

- receipt of information from others (under the term "others" we mean other people from the family, collective, group social communities that are spontaneously and (or) purposefully formed in the conditions of the global information space;
- interaction with others;
- an emotional experience of the influence of the social environment on the "I";
- social conditions in which you need to work;
- time parameter specified by others for the performance of certain actions (activities);
- living conditions of life;
- influence of the natural environment, namely: atmospheric phenomena;
- biological, physical, chemical factors;
- previous changes in the physiological and mental state of a person developing as a result of intense or prolonged activity;
- influence of the nature of physiological functions on the performance of work;
- dissatisfaction with physiological needs.

Table 1. Results of the ranking of content lines of factors influencing the health of respondents of three age sections

Content lines of the factors influencing the health of respondents	from 13 to 19 years	from 19 to 35 years	from 35 to 60 years
receipt of information from others	9	10	10
interacting with others	10	10	10
the emotional experience of the influence of the social environment on the «I»	10	10	9
social conditions in which you need to work	9	10	10
time parameter specified by others to perform certain actions (activities)	9	10	10
living conditions of life			
influence of the natural environment, namely: atmospheric phenomena	3	7	10
biological factors	5	7	9
physical factors	3	7	10
chemical factors	6	6	8
previous changes in the physiological and mental state of a person developing as a result of intense or prolonged activity	6	9	9
the influence of the nature of physiological functions on the performance of work	5	9	7
dissatisfaction with physiological needs	6	9	6

As shown in Table 1 on each of the three groups of respondents, these factors acquired a certain rank. Based on the analysis of the location of respondents from factors 1 to 10, it is possible to distinguish common trends, which, according to respondents' considerations, have a significant impact on their health.

The analysis of factors that have a negative impact on the health of respondents is carried out in the context of finding out the influence of these factors on the natural, social and spiritual origin of the structures of their own inner world, which testifies the following: the above-mentioned factors are caused in age segments from 13 to 19 years, from 19 to 35 years and from 35 to 60 years influence on the social basis of the structures of the internal world of all three groups of respondents, since the content of the factors relates to a person as a highly organized and self-regulating developing system. in society and developing society, interacting with others. The respondents identified the factors that we arranged in the following content lines:

- receipt of information from others - news, calls;
- interaction with others - conversation, relationships in the family, the team;
- emotional experience of influence of social environment on the "I" - general mood (microclimate) in a collective (at home); the behavior of others; events that are emotionally "charged" or exhausting; reaction of the environment;
- social conditions in which work has to be performed: shortage of time; high responsibility for the results of work; the importance of the case; lack of work experience; the need to perform work quickly and without errors; the amount of work that needs to be done; a busy and loaded day with a new job added; load (number of tasks to be done in one day);
- time parameter specified by others for the performance of certain actions (activities): the urgency of the work.

Groups of respondents aged 19 to 35 and between 35 and 60 years also pointed to other factors that have an impact on their health. These factors also influence the formation of the social basis of the structures of their own inner world and are disclosed in the following content lines:

- previous changes in the physiological and psychological state of a person developing as a result of intense or prolonged activity: preliminary fatigue; accumulation of fatigue; tiredness during work;
- dissatisfaction with physiological needs: feeling hungry, feeling sleepy.
- conditions of life: construction of problems; how to get to work; the lack of opportunity to stay alone and relax normally.

The explanation is explained by the fact that the intensification of physiological processes to perform certain activities, ensuring the regulation of functional reserves of the body and the implementation of a protective function to protect it from excessive loads and depletion with age requires much more time to restore the ability to implement the planned.

Respondents aged 19 to 35 also pointed to the factors that we have summarized in such a content line as the effect of the nature of physiological functions on performance. These factors were presented by respondents in the following contexts: I feel better in the morning, therefore, in the early hours, I will perform one or another work better and feel less tired; after dinner I feel a surge of strength, doing work in this period I feel less tired; I work most efficiently in the evening, so fulfilling the responsible work in the morning is very depleting me.

Another list of factors was found in questionnaires of age-old respondents from 35 to 60 years and sorted in content lines:

- influence of the natural environment, namely: atmospheric phenomena (in the interpretation of respondents it is weather);
- biological factors: microbes (fungi) caused by frequent diseases, which, according to respondents, are preceded by a feeling of tiredness, exhaustion, anxiety);
- physical factors: noise, humidity, change in barometric pressure;
- chemical factors: the composition of the air in the room (very much feels the decrease in the amount of oxygen in the room and the presence of unpleasant odors).

CONCLUSIONS

The study leads to some generalizations.

1. Understanding that the "natural" health inherited by the individual is not a property that automatically belongs to the subject, since the body of the individual, the resources of his health must be mastered in the same way as the external reality (O. Zaporozhets [4]) causes the human psyche, in particular its inner world, to explain the processes affecting its health.
2. According to the scientific achievements of L. Vygotsky [6], S. Maksymenko [7], M. Papucha [5], the inner world of man is considered as a structural, dynamic, complex entity, capable of self-development and empirically studied as integrity. The complexly structured inner world determines the functioning and development of man as a whole.
3. According to M. Papucha [5], the structures of their own inner world are created by the very man and conditionally correlated with three independent principles: natural (the line of natural development of the psyche is provided by maturation); social (the line of socio-cultural development of the psyche manifests itself in the appropriation (internalization), spiritual (the line of spiritual development of the psyche consists in contemplation and discovery in the original universal general spiritual principle).
4. According to S. Maksymenko [7], I. Sikorsky [9], the meaning of the inner world exists in a small child from birth, is not represented to her and represents what is called unconscious. The child unknowingly expresses the inner world by different kinds of activity (crying, movements).
5. The process of self-management and self-care begins immediately after the birth of the child. The line of natural development of the psyche begins to manifest itself in the disorderly movements of its extremities, and gradually this natural beginning becomes clear and coherent as a result of the body's absorption, in particular, by various movements, actions, types of activity. These processes are caused by the gradual maturing of various structures of the nervous system as the most important coordinating activity of other biological systems of the organism, the homeostatic system, which ensures the adequacy of the reactions of the organism to irritation coming from the external and internal environments.
6. Ontogeny development and interaction with other people, according to M. Papucha [5], are the most "structured" situations, in other words, situations in which the structures of the inner world arise and change more often.
7. The results of the experimental part of the study showed that the respondents aged 13 to 60 years in the highest degree of health are affected by different aspects of interaction with others, in particular: the receipt of information from others; interaction with others in the family, team; emotional experience of the influence of social environment on the "I"; social conditions in which to work; time parameter defined by others to perform certain actions (activities).
8. At the age from 19 to 60 years, experiencing a state of health is hampered by a feeling of weakness, laziness, impotence, a sense of physiological discomfort, the occurrence of which respondents associate with fatigue, its accumulation and fatigue.
9. Respondents between the ages of 19 and 35 pointed to the dependence of the state of health (as the degree of ability of an individual or group, on the one hand, to realize their aspirations and satisfy needs, and on the other hand, to change the environment or co-operate with it) from the period day, because they are differently experienced and able to work in the morning, afternoon and evening hours.
10. Educational activities of teachers, aimed at understanding people of different ages in the process of mastering their body and resources of their own health, will serve the formation of the three principles of their inner world, in particular:

- the natural principle - based on the awareness of significance for the process of mastering the body and resources of own health not only in the first year of life (as defined by respondents of this study), but the whole process of ontogenetic development, when a person is aware of various activities and actions in their composition;
- social principle - education and self-education of the corresponding personal qualities and features, including stress-sustainability, moderation, analyticity, etc.;
- spiritual principle - intensive "germination" of a healthy way of life in people of mature and old age, conscious increase of health to the rank of social and personal values, contemplative and active attitude towards the health of younger generations.

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PATIENT PATHWAYS AS A TOOL OF IMPROVEMENT IN MANAGEMENT OF URGENT AND SCHEDULED HEALTH CARE FOR KIDNEY STONE DISEASE

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ABSTRACT

Introduction: Urolithiasis is one of the most common urological pathologies, which has a significant socio-economic burden on the health care system.

The aim: To develop patient pathways based on the current guidelines on urolithiasis, and to assess the effectiveness of kidney stone management within health care system of Ukraine.

Materials and methods: There were analyzed: national and international regulatory documents (12 units); 890 patient records (confirmed urolithiasis) in seven inpatient public health care facilities and private one in Ivano-Frankivsk region; 282 control cards of follow-up examination in seven public outpatient facilities in Ivano-Frankivsk region; 129 patient records in Truskavets health resort (residents of Ivano-Frankivsk region).

Used methods: bibliosemantic, epidemiological, modeling, biostatistical, pharmaco-economical analysis and peer review.

Results: It was established that national protocols on urgent and scheduled medical care for urolithiasis require renewal. Founded on world, national and personal experience, patient pathways were created as a sequence of outpatient and inpatient care for urolithiasis, which clarified the criteria for hospitalization, the scope and type of facility for delivery the necessary care, taking into consideration the peculiarities of the patient's medical state, the size and location of stone. It was shown that the lack of high-quality clinical protocols of medical care on urolithiasis leads to the irrational use of resources, especially in district health care facilities.

Conclusion: The proposed patient pathways are an effective tool for assessment of effectiveness and identification the ways of improvement in management of medical care for patients with urolithiasis.

KEY WORDS: Urological health care management, urolithiasis, patient pathway

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INTRODUCTION

Urolithiasis is one of the most widespread urological pathologies, which ranks second in prevalence, third – in mortality rate, and fourth – in disability rate from urinary system diseases [1, 2].

The socio-economical importance of urolithiasis is also enhanced by the fact that it usually affects people of young working age [3].

In addition, the peculiarities of the course of the disease (acute beginning, serious medical state with exacerbations and a tendency to re-stone formation) cause a high need for expensive inpatient, in particular surgical, treatment. Today, 30-40% of patients of urological departments and up to 70% of emergency department are patients with urolithiasis [4, 5].

The scope of the socio-economic burden of disease is also indicated by the calculation of expenses for urolithiasis treatment in the developed countries of Europe. Therefore, in Italy and the UK, these costs are on average 150 million Euros per year. In Germany, the cost of inpatient treatment of urolithiasis reaches 600 million Euros per year. In general, the treatment of urolithiasis in Western Europe costs about 2 billion Euros per year and according to experts' forecasts, these costs will only increase [6, 7].

It is known that the reduction of the burden of financial expenses is possible only after rational organization of urgent and scheduled health care founded on the principles of evidence-based medicine [8, 9].

THE AIM

To develop patient pathways based on the current guidelines on urolithiasis, and to assess the effectiveness of kidney stone management within health care system of Ukraine.

MATERIALS AND METHODS

It was analyzed:

- national legislation documents on health care for urolithiasis and requirements of creation medical and technological standards in health care system (7 units) [10, 11-14];

- clinical guidelines on urolithiasis of the European and American associations of urology [15-17];
- patient records on urolithiasis in health care facilities in Ivano-Frankivsk region: six central district and city hospitals (625 units), Regional Clinical Hospital (157 units), and private Diagnostic and Treatment Center (108 units);
- control cards of follow-up examination of the same district health care facilities and Ivano-Frankivsk city polyclinics № 2 (282 units), but except Regional Clinical Hospital and private Diagnostic and Treatment Center because the post-treatment control does not provide there (only surgery treatment);
- patient records with urolithiasis of Ivano-Frankivsk region residents, who were under sanatoria treatment on the basis of "Truskavetskurort" (129 units), as the existing Ukrainian protocols (2004, 2007, 2008) recommend the inclusion of sanatorium and resort treatment in the metaphylaxis of urolithiasis recurrence.

Used methods: bibliosemantic, epidemiological, modeling, biostatistical, pharmaco-economical analysis and peer review

In particular, experts (average work experience - 35.6 years) - two professors and an associate professor at the Department of Urology of the Ivano-Frankivsk National Medical University, as well as two urologists of the highest qualification category - were involved in the peer review of a data from medical records. Developed by the authors, medical and organizational technology of delivery urgent and scheduled health care for urolithiasis (patients pathways) was discussed, hospitalization criteria were agreed and was reached a consensus on the list of diagnostic examinations and treatment strategy, based on which an assessment of data from documentation was made.

RESULTS AND DISCUSSION

It was established, that the national protocols (2004, 2007, 2008) [10-12], are outdated, do not fully meet the requirements of the orders of the Ministry of Health of Ukraine since September 28, 2012, No. 751 and December 29, 2016, No. 1422 on the creation of medical and technological standards and regulations of health care system [13, 14] and therefore do not comply with the principles of evidence-based medicine and as result do not described in details.

Therefore, based on them, as well as on the current clinical guidelines of the European and American associations of urology [15-17], on data from other and our own research, we developed the medical and organizational technologies of urgent (Fig. 1) and scheduled health care on nephro- (Fig. 2) and ureterolithiasis (Fig. 3). It allowed creating the patient pathways based on the principle of sequence of outpatient and inpatient care for urolithiasis, to specify the criteria for hospitalization, to determine the scope and conditions of the necessary care delivery, taking into consideration the individual peculiarities of the medical state of the patient, the size and location of the concrement.

In addition, it was proposed a medical and organizational technology for the development and correction of an individual program of metaphylaxis (Fig. 4), based on the stratification of the risk of recurrence, which depends on the analysis of composition of calculus and the presence of relevant risk factors.

Is known, most often the first manifestation of urolithiasis is an attack of renal colic (Fig. 1).

According to the last scientific advancements, disease management program, including the level and the amount of medical care, depends of the severity of the symptoms.

If there are signs of uncomplicated kidney stone disease, namely: pain back pain accompanied by nausea, vomiting, changes in the urine (hematuria), impaired urinary elimination (dysuria), passage of stones, the aim of medical care is a primary anesthesia. Further, in order to verify the diagnosis and to exclude „acute abdomen", the patient undergoes basic examinations, namely: urine test, blood test, blood creatinine test), as well as ultrasound examination (as the primary procedure). In case of any diagnostic difficulties, it is necessary to provide excretory urography or even better – computed tomography (CT), which today is considered as the "gold standard", but significantly more expensive than ultrasound examination.

The specified list of medical services at the time lasts several hours, and therefore should be given on an outpatient basis.

After removal of pain and clarification of the diagnosis, the patient is directed to a routine consultation with an urologist to determine further treatment tactics.

Patients with urolithiasis need hospitalization only in case of complicated course of disease (pain, which is not relieved after taking analgesics for 2-4 hours, fever, and anuria) or if patient is in risk group: in case of pregnancy, elderly age (over 60 years), having single kidney, transplanted kidney. Such patients require urgent urological consultation, medical care and round-the-clock observation in hospital.

In addition to basic examinations also mandatory examinations are: CT of the kidneys and ureters and laboratory tests – coagulation test, determination of the level of electrolytes and uric acid in the blood serum, urine culture to check for flora and antibiotic sensitivity.

Inpatient treatment for complicated urolithiasis continues until kidney function normalizes and, according to research Lotan Y., et al (2012), an average term of treatment lasts 8-10 days [7].

Further tactics in treatment of the patients with urolithiasis (as in the normal course of disease as after improvement after complications) depends on the location and size of the stone. At the same time, minimized surgical intervention using low-impact methods is today recognized as a priority method of therapy.

In case, when a stone is located in renal pelvis or the upper or middle calyx of the kidney (Fig. 2), ≤ 20 mm in size, Extracorporeal Shock Wave Lithotripsy (ESWL) is the operation of choice, which does not require hospitalization of the patient and is carried out on an outpatient basis.

However, there are contraindications to the ESWL: hemorrhagic diathesis, deformation of the musculoskeletal system, obesity, aortic aneurysm, anatomical obstruction of the ureter distal to the stone, stone density more than 1000 HU, stone > 20 mm. In these cases, other minimally invasive methods of stone crushing are used: Percutaneous Nephrolithotomy (PCNL), or flexible ureteronephrolithotripsy (RIRS – Retrograde Intrarenal

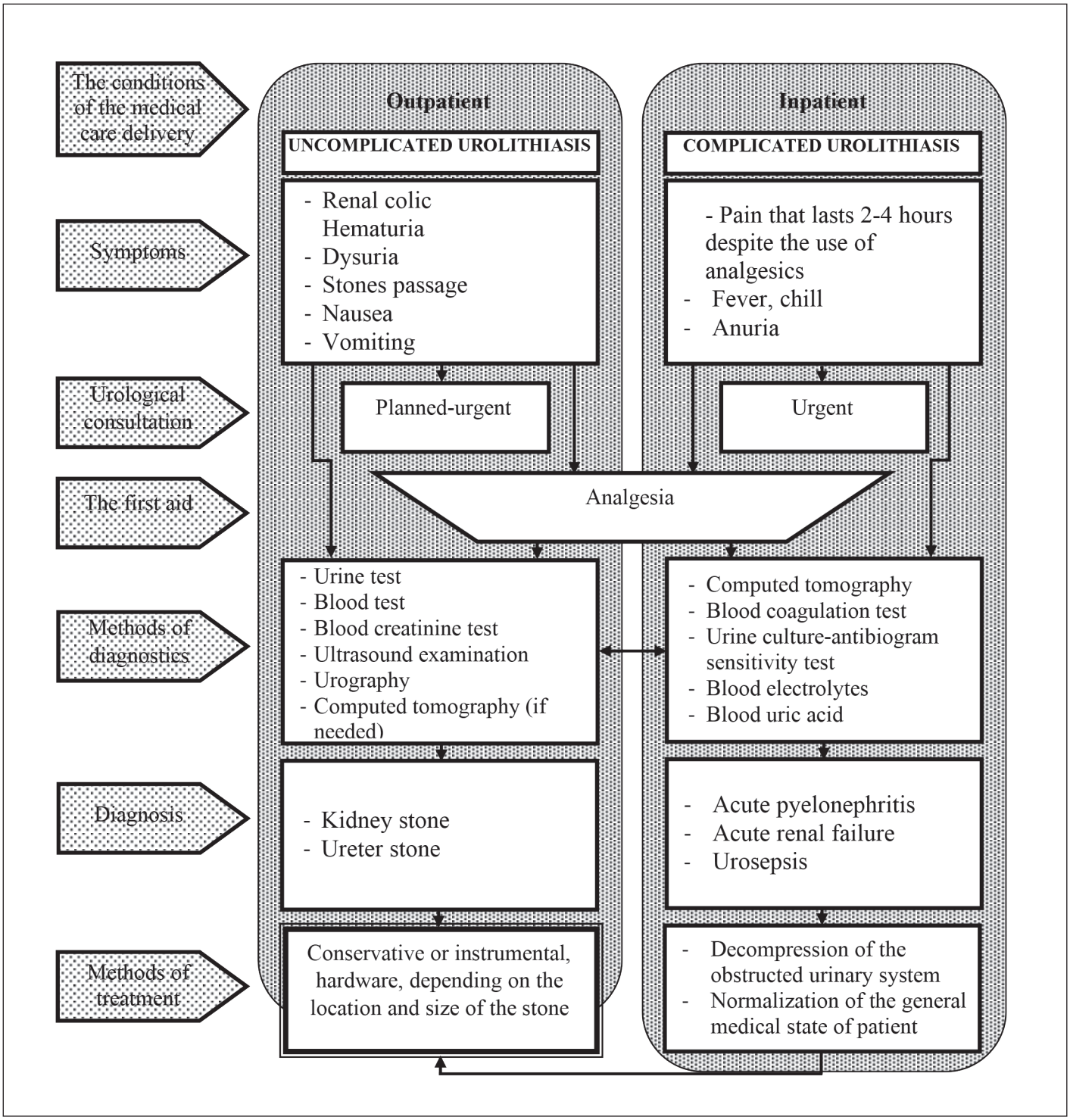


Fig. 1. Medical and organizational technology of creation patient pathways with renal colic

Surgery assisted by Flexible Ureterorenoscopy), which are carried out exclusively in the in-patient departments and require expensive equipment, especially flexible RIRS. Despite this, when patient has hemorrhagic diathesis, multiple kidney stones up to 20 mm in size, congenital disorders (horseshoe-shaped kidney), obesity and deformation of the musculoskeletal system, flexible RIRS considered as surgery of choice. In addition, a flexible RIRS should use for those who have contraindications to PCNL: an atypical interposition of the intestine or a tumor in the way of access to a calculus.

As already noted, in case of the presence the stone located in renal pelvis or the upper or middle calyx of the kidney (Fig. 5.2) > 20 mm in size operations of choice are PCNL or RIRS.

If the kidney stone is located in the lower calyx and its size is ≤ 10 mm, then surgical intervention is carried out only if there are clinical symptoms (pain, changes in urine, etc.) and the surgery of choice is the ESWL. If patient has no symptoms, active dynamic monitoring is recommended for 2-3 years, the

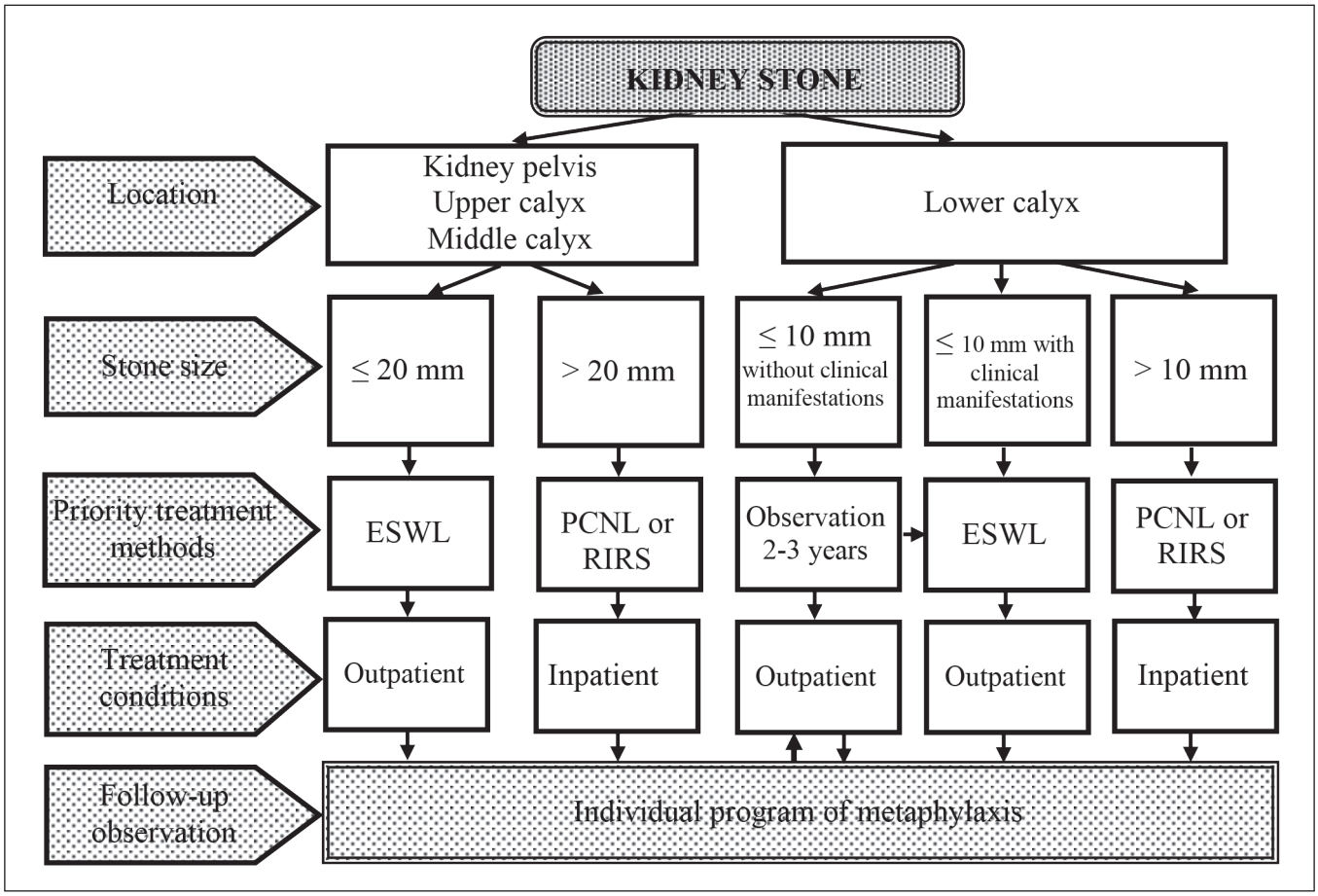


Fig. 2. Medical and organizational technology of creation patient pathways with nephrolithiasis

program of which is based on periodic (twice a year) medical follow-up observation (urological consultation, blood and urine tests, ultrasound test, CT) and conservative therapy aimed at promoting stone passage (α-blockers). In case of a stone passing during this time or its increase in size, ESWL is recommended.

For patients, who have a stone of the lower calyx of the kidney exceeding 10 mm, the methods of choice are PCNL or RIRS.

In addition to modern minimally invasive surgical interventions, kidney stones can be removed by laparoscopic or open surgery. Indications for such operations are: ineffectiveness of the ESWL, PCNL, RIRS; stone of complex shape (coral); anatomical abnormalities (stricture of the pyeloureteral segment, calculus in the diverticulum of the calyx, especially the anterior, calculus in the abnormally located kidney, when access to it in the ESWL is difficult); severe obesity; deformation of the musculoskeletal system; contracture and persistent deformation of the pelvis and legs, which limits the use of minimally invasive interventions; accompanied open surgery; the patient's wishes.

For patients with ureterolithiasis, the choice of a priority treatment method also depends on the location and size of the ureteral stone (Fig. 3).

For small stones (≤ 10 mm) without significant clinical manifestations, conservative treatment is used. At the same time, the period of observation and expectation of unaided stones passage is significantly shorter than with similar in size kidney stones – only 2-4 weeks.

If there is no effect or are small stones, but with clinical manifestations, surgical intervention is carried out: for a stone ≤ 10 mm in the upper third of the ureter – ESWL; for stone ≤ 10 mm in the middle and lower thirds of the ureter – ureterolithotripsy (URS – Ureteroscopic Lithotripsy).

For stones > 10 mm, regardless of their location, it is recommended to conduct URS. When the stones come into the bladder, cystolithotripsy is used to remove it.

It should be emphasized that the stones of the kidneys and ureters (those that passed unaided or were removed surgically) should be sent to the laboratory for determination their composition (oxalates, phosphates, urates, etc.) using infrared spectroscopy or X-ray diffraction (Fig. 4).

This is due to the fact that after the stone passage or remove, each patient in order to prevent re-stone formation and to rehabilitate renal function should be given an individual program of metaphylaxis. For this, based on the results of the analysis of the composition of the stone and general blood and urine tests (if possible – parathyroid hormone), as well as the presence of risk factors, the risk of re-stone formation is assessed.

General preventive recommendations are given to low-risk patients: 1) fluid intake (2.5–3L per day); 2) diet (a balanced diet with plenty of vegetables and fiber, salt and animal protein restriction and other diet recommendations depending on the composition of the stone and test results); 3) lifestyle (maintenance of a normal body weight, sufficient physical activity;

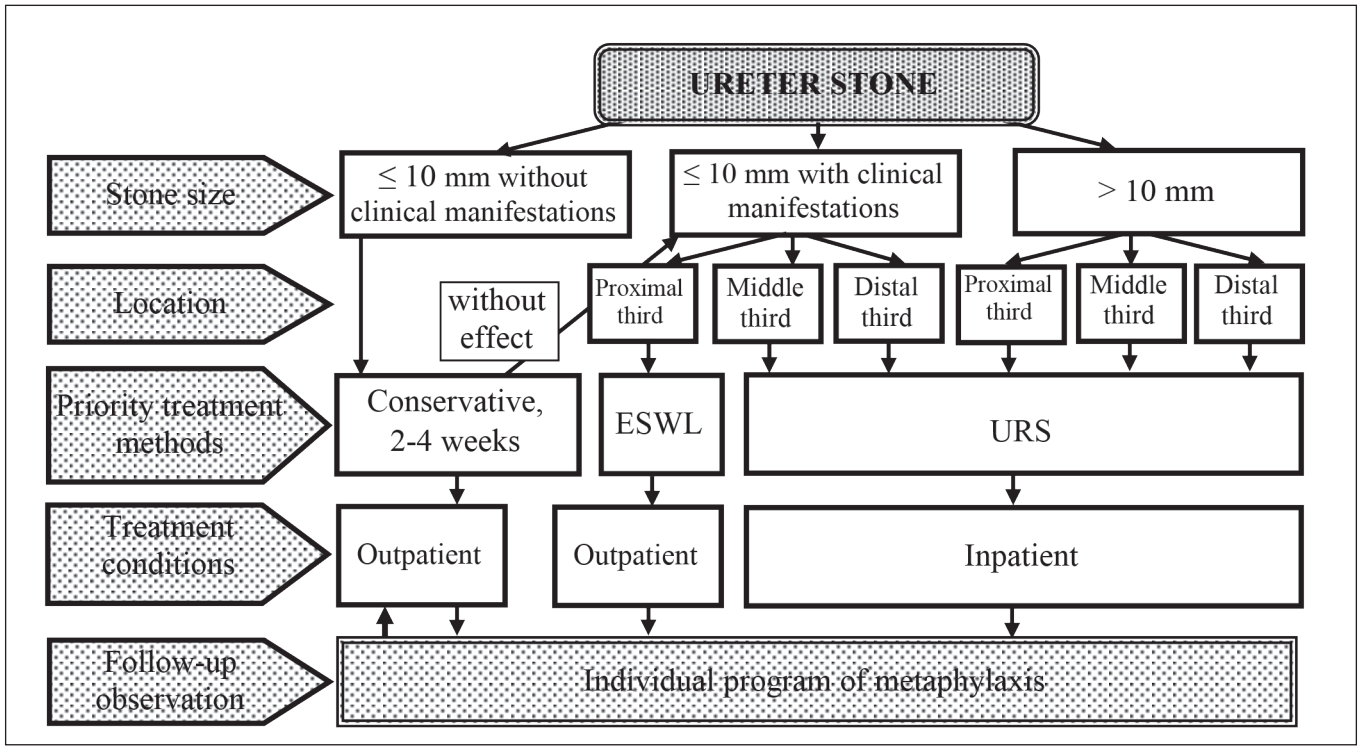


Fig. 3. Medical and organizational technology of creation patient pathways with ureterolithiasis

avoidance of stress and dehydration of the body); 4) sanatorium treatment (preferably once a year); 5) control (once a year): tests (blood, urine, salt metabolism), ultrasound test or urography (if necessary – CT) and urological consultation.

Patients are related to high risk-group of recurrence of urolithiasis, if the results of stone analysis show brucite (calcium phosphate), uric acid, urate or infectious stone and if there are risk factors for re-stone formation: obesity, arterial hypertension, burdened genetic history, congenitally disorders of the urinary system, chronic pyelonephritis, hyperparathyroidism, lengthy immobilization after bone fractures.

In this case, medication-assisted treatment is added to the general preventive measures, aimed at the normalization of urine, as well as the correction of risk factors. Control urine test should be done after 3 months from the start of therapy. If urine is normal, next control test is in a year. If there is no progress, correction of medical treatment and control urine tests should be provided once a quarter until optimal result will be achieved.

In our opinion, developed on the basis of current clinical guidelines of the world leading associations of urology, patient pathways will facilitate urologists of healthcare facilities, mainly of the secondary level, to develop individual patient pathways. As a result, this will ultimately help to meet the needs of the population, improve medical services and optimize the organization of urological care in general.

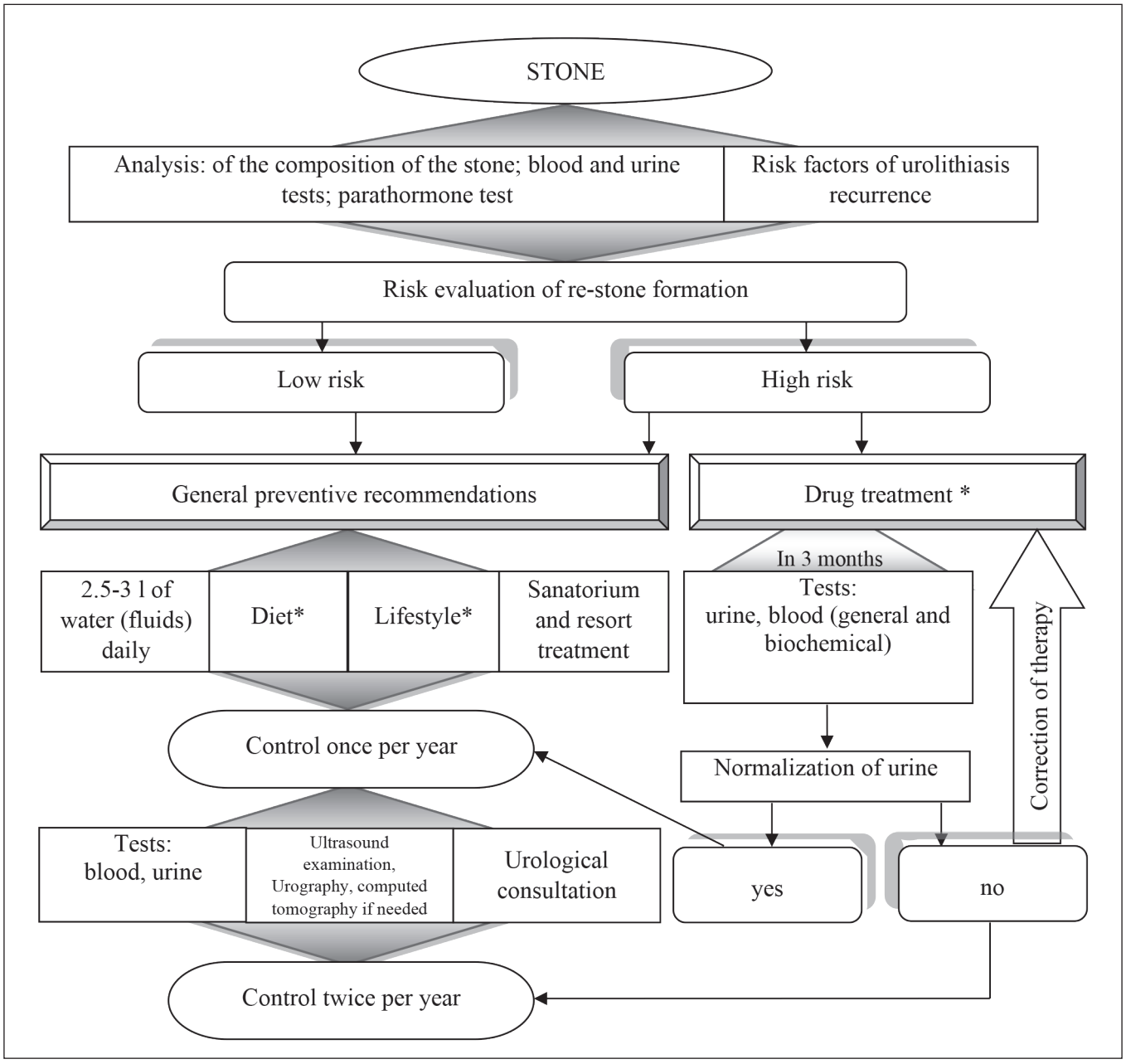
Based on the obtained patient pathways, it was conducted an assessment of the regional urological services capacity for assurance the access patients with urolithiasis to modern medical care.

It has been established that the lack of high-quality unified clinical protocols of medical care for urolithiasis leads to the irrational use of resources [18-20].

In particular, the analysis of the medical records display that medical care provided to patients with urolithiasis in the district health care facilities did not at all measure up to current clinical guidelines and protocols. The majority of patients in health care facilities of second level were hospitalized unreasonably (80.5%), stayed in hospital in average 11.4 days, when no surgical intervention was provided (90.7%), the diagnosis was not confirmed (38.9%), excessive tests (23.4%) and medicines were prescribed (an average of 7.1 medicines and 1138.27 UAH per patient, 62.1% of drug duplication, 46.9% medicines on the list and 40.0% of all prescriptions were non-essential).

Significant reserves for improvement the treatment and diagnostic process were also revealed in the Regional Clinical Hospital, where the average length of stay of a patient with urolithiasis was 8.1 days, only 38.9% of patients was hospitalized with referral from a physician, 78.3% of them were operated on (22. 2% obsolete surgical procedures and palliative technologies, with an average wait 1.9 days for surgery), unreasonably hospitalized were 21.7%, 19.1% at moment of discharge had not confirmed diagnosis, many of them received excessive tests (11.5%) and medicines (6,9 medicines and 2261.11 UAH per patient, 51.0% of duplication, 42.9% of medicines on the list and 31.9% of prescriptions were non-essential).

It was found out that the inpatient treatment of urolithiasis was the most adequate in the private health care facility, where all patients were operated on (with an average wait 0.3 days), were treated for an average 1.4 days, without unnecessary tests and with minimal medication-assisted treatment (3.8 medicines with an average cost of 260.76 UAH per patient, without duplication and the smallest parts of doubtful prescriptions both



Note: * - Depending on the composition of the stone and the results of the tests

Fig. 4. Medical and organizational technology for the development and correction of an individual program of metaphylaxis

in the list of drugs and among the list of prescriptions – 15.4 % and 15.9% respectively).

According to results of peer review of control cards of follow-up observation in public district health care facilities, it was found that only 55.0% of patients with urolithiasis adhered to the recommended frequency of follow-up examinations by an urologist, 47.6% - required laboratory tests, and 39.8% - ultrasound test. In the background of quite frequent inpatient treatment (an average of 0.4 cases of hospitalization per year), only half of the patients (51.1%) underwent surgery, a high percentage of patients had advanced urolithiasis (15%), frequent complications (12.4%) and recurrence (11.8%) [21].

According to the analysis of patient records in Truskavets resort, it has been shown that the selection of patients for sanatoria treatment, the full coverage of their examinations and, especially, treatment, also do not correspond to the current regulatory documents. At the same time, the sanatorium treatment is characterized not only by the incomplete volume of standard methods, but also by the excessive prescription of additional procedures, which are not mentioned in clinical guidelines [22].

Thus, the results of the study convincingly show that the organization of urological care in the region, in particular in public health care facilities, requires improvement.

The introduction of developed medical and organizational technologies of urgent and scheduled health care for patients

with urolihiasis (Fig. 1-4) during the study in observed health care facilities of the region confirmed its medical, social and economic efficiency. Improvement of the medical-diagnostic process has allowed to reduce the rate of unreasonably hospitalized (by 5.3-9.7%), to shorten the length-stay in hospital (by 1.2-1.4 days), including before surgical treatment (by 0.3-0.4 days) and to increase the coverage of patients by post-treatment observation (by 21.2 – 21.8%).

CONCLUSION

It has been established that the national protocols on urgent and scheduled medical care for urolithiasis require renewal.

Founded on world, national and personal experience, patient pathways were created as a sequence of outpatient and inpatient care for urolithiasis, which clarified the criteria for hospitalization, the scope and type of facility for delivery the necessary care, taking into consideration the peculiarities of the patient's medical state, the size and location of stone.

It was shown that the lack of high-quality clinical protocols of medical care for urolithiasis leads to the irrational use of resources, especially in district health care facilities.

The proposed patient pathways are an effective tool for assessment of effectiveness and identification the ways of improvement in management of medical care for patients with urolithiasis.

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Conflict of intrest:

Authors declare no conflict of interest

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PRACE ORYGINALNE
ORIGINAL ARTICLES

PERSONALITY TRAITS OF PATIENTS SUFFERING FROM CONGENITAL HEART DEFECTS

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ABSTRACT

Introduction: Personality traits of patients suffering from congenital heart defects

The work presents a research project carried out in John Paul II Hospital, The Clinical Department of Cardiac and Vascular Diseases with the Intensive Cardiac Surgeon Division Institute of Cardiology, Collegium Medicum of the Jagiellonian University in Cracow, with participation of patients with congenital heart defects.

We aimed to assess personality traits of clients suffering from congenital heart defects, in a group of women and men, younger, under 40 years old and older than 40 years old, with PFO and ASD before and after surgery.

The aim: identify specific personality traits of patients with congenital heart defects and to check the psychological functioning of patients by examining: the level of anxiety, impulsiveness, tendency to risk-taking, empathy, neuroticism, extraversion, psychoticism and lying.

Material and methods: We performed a psychological clinical assessment and conducted the psychological tests like EPQ-R(S) by Hans J. Eysenck and Sybil G. Eysenck, IVE by Hans J. Eysenck and Sybil G. Eystenck, STAI by C. D. Spielberger, R. L. Gorsuch, R. E. Lushene describing personality traits of patients.

Results: Patients (F=29, M=21), adult, with ASD and with PFO, with the level of education: basic, vocational, secondary, incomplete higher, higher; inhabiting: village, city up to 40 thousand residents, a city with a population of 41-61 thousand, and a city with a population of 60 thousand; civil status: single, married, divorced, widow/widower, separated; being: students, unemployed persons, working persons, pensioners, retirees.

Conclusions: The presented results and their statistical analyses showed specific personality traits of patients with congenital heart defects.

KEY WORDS: personality, personality traits, congenital heart defects, PFO, ASD, neuroticism, extraversion, psychoticism, lying, impulsiveness, tendency to risk-taking, empathy, anxiety as current state, anxiety as personality trait

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INTRODUCTION

Congenital heart defects are caused by abnormal development of the circulatory system in the fetal life or its inhibition, which may in turn be a consequence of the mother's bad habits during the pregnancy, primarily in the first trimester of pregnancy, such as: viral infections, drugs used; or depend on genetic factors. There are heart defects that do not cause any indisposition [1]. However, there are those that bring to the life of a sick person a number of ailments, which cause that the patient feels badly not only physically, but also mentally. The aim of the article is to identify specific personality traits of patients with congenital heart defects and to check their psychological functioning by examining: the level of anxiety, impulsivity, risk-taking, empathy, neuroticism, extraversion, psychoticism and lying.

The justification for the choice of this topic is the desire to become familiar with specific personality traits of patients with congenital heart defects, curiosity about how ill persons function and are psychologically adapted, the level of anxiety, impulsivity, risk propensity, empathy, neuroticism, extraversion, psychoticism and lies, examining effects on the occurrence of possible or already existing psychiatric disorders caused by the existence of a heart defect and an attempt to answer the question: *Do patients with congenital heart defects have specific personality traits?*

In the absence of available literature on the subject, the project can be considered pioneering.

CONGENITAL HEART DEFECTS

In order to recognize a heart defect, the physician first of all applies listening to the murmurs created above the heart with a characteristic location and type for a specific defect, as well as the analysis of changes in the image of the heart, electro and phonocardiological changes, or measurement of blood pressure. Example symptoms of congenital heart defects: tremor of a chest, the so-called cat's murmur, sometimes there is also a problem with too high blood pressure of the patient and others. Congenital defects may

cause too slow physical development of the child, while too rapid flow of blood through the lungs may cause frequent respiratory infections [1].

Characteristic symptoms of congenital heart defects are: effort dyspnoea, which may be accompanied by cough caused by stagnation in the lungs. There are also possible disorders of the cerebral circulation, which in turn may cause recurrent loss of consciousness or convulsions [1].

For diagnostics there are also used: one or two-dimensional echocardiography - to detect defects in the atrial septal or inter-ventricular septum; contrast echocardiography, which is particularly useful in the diagnosis of leaks [1].

Depending on the degree of cardiac dysfunction caused by congenital heart disease, ill persons may be at risk of: heart failure, endocarditis, cardiac arrhythmias, often fatal. Treatment of heart defects focuses on surgical treatment. Congenital malformations can be divided into defects without leakage and defects with leakage [1].

CONGENITAL HEART DEFECTS IN ADULTS

Congenital heart defects in adults are divided into:
1. Non-cyanotic heart disease with a leak at the level of:
a. the atria,
b. the ventricles,
c. the great arteries.
2. Cyanotic heart disease with a leak:
a. with reduced pulmonary flow,
b. Eisenmenger syndrome.
3. Valve defects:
a. atrio-ventricular valves,
b. valves of arterial trunks.
4. Others:
a. pathology of systemic veins,
b. lungs veins,
c. arterial trunks.

Birth defects that can be found in an adult: bicuspid aortic valve, aortic valve coarctation, valvular stenosis, atrial septal defect, patent ductus arteriosus, ventricular septal defect, Fallot tetralogy, Eisenmenger's syndrome, congenital corrected arterial trunks, left atrioventric valve regurgitation, Ebstein anomaly, Uhl's anomaly, subvalvular narrowing of the left ventricle outflow pathway, Valsava sinus aneurysm, coronary fistula, pulmonary arteriovenous fistula [3].

ATRIAL SEPTAL DEFECT ASD

Latin: defectus septi interatrialis, English: atrial septal defect – ASD

Atrial septal defects can be divided into:
a. secondary opening, occurring in about 70% of patients with congenital heart disease - ASD II,
b. primary opening - partial loss of the atrio-ventricle septum, occurring in about 15% of patients with congenital heart defects - ASD I,
c. main vein, occurring in about 7% of patients with congenital heart defects - ASD sv,
d. coronary sinus, occurring in about 1% of patients with congenital heart defects - ASD cs [3].

ASD is one of the most common heart defects in adults, it is twice as common in women as in men, also in combination (about 30%) with trisomy 21 in the Down Syndrome [3].

The leakage of oxygenated blood from the left to the right atrium is caused by the loss of the atrial septum [3].

SIGNS AND SYMPTOMS OF CONGENITAL HEART DEFECTS OF ADULTS

Patients with congenital heart disease usually do not report any complaints or report only minor discomforts. These defects are most often diagnosed at the moment of echocardiographic examination, less frequently by means of magnetic resonance or computed tomography. At the age of about 40, patients experience reduced physical capacity to cope with exercise, palpitations, atrial fibrillation. Over the years and uncontrollable heart defects, symptoms such as fatigue, dyspnoea, enlarged liver, central cyanosis, edema may appear [3].

Patients may be qualified for percutaneous surgical operation closing the defect, whereas patients with a small leak do not require any recommendations or special treatment. The latter can take advantage of all the charms of life, taking up activity in sport, pregnancy is also not contraindicated, the solution without the need of Cesarean cutting; on the other hand, pharmacologically treated persons may be exposed to danger while diving or being at high altitudes [3].

PATENT FORAMEN OVALE PFO

Latin: *foramen ovale apertum*, English: patent foramen ovale PFO

PFO occurs in about 20% or even 30% of adults, most often it is diagnosed accidentally, during additional tests in patients at a young age after a stroke. PFO may lead to leakage from the right to the left atrium, possibly causing embolism, especially in the presence of an atrial septal aneurysm.

One of the visible symptoms of the obstruction of the orifice can be asymptomatic stroke at an early age [3].

VENTRICULAR SEPTAL DEFECT

Latin: *defectus septi interventricularis*, English: ventricular septal defect VSD

Diagnosed in about 10% of patients with congenital heart defects, consisting of leakage of blood oxygenated from the left to the right ventricle, and sometimes to the right atrium. Uncontrolled can lead to heart failure [3].

PATENT DUCTUS ARTERIOSUS PDA

Latin: *ductus arteriosus persistens*, English: patent ductus arteriosus - PDA

Congenital heart defect, associated with complications arising during the rubella, from which a pregnant woman

suffered - I trimester of pregnancy, consisting of the connection of the left pulmonary artery with the aorta. Characteristic symptoms are: leakage, exercise dyspnoea, palpitations [3].

TETRALOGY OF FALLOT

Latin: *tetralogia Falloti*, English: tetralogy of Fallot

The most common cyanosis defect after the patient reaches the first year of life. Patients complain about symptoms such as in the case of previous heart defects as well as chest pains. Characteristic symptoms may also be: rod-shaped squares, pronounced nails [3].

EISENMENGER SYNDROME

Latin: *syndroma Eisenmengeri*, English: Eisenmenger syndrome

If untreated, it can lead to pulmonary arterial hypertension. It exists as a complication of diagnosed congenital malformations, most of them being leaky. Patients report a feeling of lack of air, sometimes also fainting, unconsciousness [3].

RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

It involves the development of changes in the pulmonary valve [3].

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

This is the most common defect in approximately 2% of adults with congenital heart disease and this is the so-called bilipler valve, occurring about 4 times more often in men [3].

AORTIC COARTATION

Latin: coarctatio aortae; stenosis isthmi aortae, English: aortic coartation

This disadvantage is primarily the narrowing of the aorta. 2-5 times more often in men compared to women, often combined with Turner syndrome. Hypertension, as well as headaches, are characteristic for this defect [3].

The congenital heart defects highlighted above are only some of the existing ones.

HEART DEFECTS WITHOUT LEAKAGE

The following are briefly discussed heart defects without leakage, such as: stenosis of the main aorta, congenital pulmonary stenosis, dextrocardia and Ebstein syndrome [1].
Narrowing of the main artery
Congenital narrowing of the pulmonary artery
Dextrocardia
Ebstein syndrome

HEART DEFECTS WITH LEAK

This section will discuss heart defects with leakage such as: ventricular septal defect, atrial septal defect, persistent arterial duct Botalla [1]

Ventricular septal defect - Defectus septi ventriculorum, consists in the flow of blood from the left to the right ventricle, which may cause its growth, as well as increased blood flow through the small circulation. A characteristic symptom is the appearance of a loud systolic murmur. To diagnose this disadvantage, one can use a radiological examination that can determine the widening of the pulmonary artery trunk as well as an electrocardiographic examination indicating the total or partial block of the right bundle of the His bundle [1].

Atrial septal defect - Defectus septi atriorum - ASD, consisting of a complete absence of atrial septum - with a very severe heart defect or partial omission of the oval hole valve [1].

PSYCHOLOGY IN CARDIOLOGY - PSYCHOCARDIOLOGY

Cardiology has its achievements in the work of psychologists. Already in 1961 a psychological studio was established thanks to Zdzisław Askanas, who was tasked with a holistic approach to the treatment and rehabilitation of patients with ischemic heart disease. Currently, heart disease is one of the most serious epidemiological problems. Cardiovascular disease is one of the most common causes of death (about 400 people per 100,000 people). Most often, these are such diseases in which the participation of psychological factors has been detected [4].

Psychocardiology deals primarily with the course of treatment or rehabilitation of cardiological disorders, as well as the psychosocial factors themselves affecting the emergence of the above-mentioned disorders. It also focuses primarily on improving the patient's quality of life. Psychocardiology has developed over the years. W. Harvey already pointed out in his works how much influence emotions have in the emergence of cardiological problems. One by one W. Osler described factors such as time pressure, today you could say workaholism; that may affect coronary vascular changes to a greater extent than lack of moderation in food and drink [5].

Cardiology has its achievements in the work of psychologists. It should be mentioned that Poland was one of the first countries to focus on psychological problems of patients suffering from cardiovascular diseases [5].

Already in 1961, on the initiative of Professor Askanas, the first psychological laboratory was established in the department of cardiology, whose task was a holistic approach to the treatment and rehabilitation of patients with coronary heart disease [6, 7].

Thanks to Professor Zdzisław Askanas /1910-1974/, a Polish doctor, cardiologist, academic teacher at the Medical Faculty of the Medical University of Warsaw, the creator and the first Head of the First Chair and Clinic of Cardiology at the Medical University of Warsaw, in

1962 the founder of the Central Cardiovascular Disease Clinic, and in 1965 the founder of the Institute of Cardiology in Warsaw introduced many innovative methods in cardiology. Professor Askanas was a teacher of many outstanding Polish cardiologists. He also created the Warsaw Academic School of Cardiology, in which his students were concentrated [6, 7].

Throughout his life he was characterized by great enthusiasm for his actions, dedication to work and consistency. Professor Askanas›s desperation resulted in very effective teaching, many thematically diverse scientific works, and above all extremely caring, patient-oriented care, development of very specialized care for initially internist patients, which has been focused on cardiological patients over the years [6, 7].

It was on the initiative of professor Asnanas in the Cardiology Clinic in Warsaw that a multidisciplinary team was created, dealing with all cardiological patients, consisting of doctors, nurses, diagnostics, epidemiologists, rehabilitators and psychologists [6, 7].

The use of psychological methods in cardiology and their gradual implementation were dealt with by: doc. Stanisław Siek), Henryka Ostrowska, Jan Tylka, Barbara Dębska, Józef Latoch and Marek Mordyński [6, 7].

The efforts of the team of prof. Askanas aimed at early rehabilitation of cardiac patients and quickly restoring their full fitness [6, 7].

The scientist's achievements have been noticed not only in Poland but also abroad, and are still used in modern cardiology [6, 7].

Psychological intervention in a cardiological patient is based on the patient's own work, which requires a lot of involvement in the process of change; conducted therapy by professionals, including interviews with the patient, regarding family structure, psychosocial factors [5].

The development of ischemic heart disease, as a model cardiological disease, is associated with deepening depression as well as stress, low level of support or low socioeconomic status [5].

It is necessary to remember how cardiological therapy of the patient affects his mental state. We can mention a number of psychopathological disorders, such as: disorders: consciousness, mood (manic, depressive), sleep, sometimes also psychotic - e.g. after using cardiological drugs [8].

PERSONALITY DETERMINANTS OCCURRING IN PATIENTS WITH CONGENITAL HEART DEFECTS

In psychology, the concept of type A personality is known. type A behaviour pattern, considered to be one of the causes of cardiovascular disease. This is one of the psychological risk factors of the above-mentioned group of somatic diseases. The creators of the theory are Friedman and Rosenman. Patients with this type of behaviour are ambitious, focused on success, achieving everything that is possible in the shortest possible time, often hostile, with excessive reactivity, they are often hostile to other people regardless of the situation, as one of temperamental traits, expressiveness. Type A behaviour is most common in people with coronary artery disease and may be the cause of a heart attack [4].

However, the question is what personality traits are characterized by adults suffering from congenital heart disease? There are very few such studies.

Of course, not only psychological factors have an impact on the development of health-related illnesses, but also the lifestyle is of great importance here. These include: cigarette smoking, a rich diet, raising cholesterol levels, stress and inability to deal with it, lack of support from loved ones and the environment in which patients live and work [4].

The tasks that should be completed are primarily the health education of patients. Psychological help is needed not only because personality traits or other psychological factors are risk factors for cardiovascular disease, but also because the treatment and rehabilitation themselves are a source of stress [4].

There are known studies on the rehabilitation of patients after myocardial infarction. It is important to remember that the rehabilitation of a cardiac patient involves work in an interdisciplinary team: cardiologists, psychologists, and physiotherapists. It should also be remembered how important psychological assistance is to the patient before starting treatment, during hospital treatment, but also after leaving hospital. Psychological therapy is carried out in this case in order to minimize the negative effects of the disease, establish an attitude towards illness and health, solve family problems or professional problems [4].

However, the question arises: What personality traits are characteristic of adults suffering from a congenital heart defect? There are very few such studies. There are studies on the personality traits of children, adolescents suffering from congenital heart defects, but there is a lack of studies on the personality traits of adults and their impact on quality of life. There are known studies showing a lower level of extroversion (causing a worsening of emotional functioning) in people aged 15-20 years suffering from congenital heart defects, compared to healthy people. Patients were examined to determine the level of extraversion, diligence, agreeableness, openness and neuroticism. It was also shown that girls achieved high scores in conscientiousness, while boys achieved low scores in neuroticism; as well as the fact that sick youth are less socially and emotionally adapted than healthy youth. It has also been shown that a higher level of extraversion is a good predictor of a higher level of quality of life, better emotional and social functioning. Similarly with the obtained low level of neuroticism or a higher level of conscientiousness. It was also shown that patients could not cope with stress. Most importantly, the above research helps in predicting the quality of life of patients in the future [9].

Personality traits such as optimism or conscientiousness, openness to experience are "cardioprotective" to a large extent prevent the development of cardiovascular

diseases. Optimism is one of the positive personality traits, understood as a tendency to anticipate good experiences in the future, protecting against coronary heart disease, especially in the elderly. These patients also reported less pain after surgery. Conscientiousness is a predictor of longevity in healthy people. The same applies to openness to experience [10].

Due to the fact that the work is pioneering, research hypotheses have been adopted on the basis of the correlation between the occurrence of cardiovascular diseases and personality type A.

THE AIM

Objective: To show personality traits typical of patients with congenital heart defects.

The aim of the work is to resolve the issue of personality specifics, and thus the different characteristics of people who suffer from congenital heart defects. Therefore, the following questions should be answered: Is there a relationship between personality traits and the occurrence of a congenital heart defect? What personality traits are characteristic for patients with congenital heart defects?

Adopted hypotheses:

Personality traits in psychological terms of patients with congenital heart defects.

Patients with congenital heart disease are characterized by high extraversion and low anxiety.

Patients with congenital heart disease are characterized by high empathy and low psychoticism.

Patients with congenital heart defects are characterized by low impulsivity and low risk propensity.

Women with congenital heart disease are characterized by low psychoticism and high anxiety as a condition.

Men with congenital heart defects are characterized by high levels of neuroticism, high levels of lying and average level of empathy.

MATERIALS AND METHODS

The examined group are patients with congenital heart defects, adult men, adult women, and the research area is John Paul II Hospital In Cracow, The Clinical Department of Cardiac and Vascular Diseases with the Intensive Cardiac Supervision Subdivision, Institute of Cardiology, Collegium Medicum of the Jagiellonian University in Cracow, John Paul II Hospital. The study involved 50 adults, including 29 women and 21 men, undergoing surgery In John Paul II Hospital In Cracow in the field of heart defects such as ASD and PFO, in age groups 0-19 years, 20-34, 35-49, 50-64, 65-74, 75-89 and over 90 years, with the level of education: basic, vocational, secondary, incomplete higher, higher; inhabiting: village, city up to 40 thousand residents, a city with a population of 41-61 thousand, and a city with a population of 60 thousand; civil status: single, married, divorced, widow/widower, separated; being: students, unemployed persons, working persons, pensioners, retirees.

The research was carried out personally by psychologist Adrianna Skoczek. Psychometric analysis was performed by quantitative and qualitative interpretation of psychological tests along with statistical calculation using the Statistica 12 program.

USED METHODS

Psychological tests:

EPQ-R (S) - Hans J. Eysenck and Sybil G. Eysenck [2]; consisting of 48 questions, examines the level of neuroticism, extraversion, psychoticism, lies

IVE - Hans J. Eysenck and Sybil G. Eystenck [11] consists of 54 questions, examines impulsiveness, risk-taking, empathy

STAI C. D. Spielberger, R. L. Gorsuch, R. E. Lushene [12] - consisting of 40 questions, examines the level of anxiety as a state and as a trait

STATISTICAL ANALYSIS TOOLS

In the studies, qualitative and quantitative traits were assessed. The analysis of each of them has its own specificity, which consists in applying adequate statistical tools to comparisons. In order to characterize the structure of the variables studied, basic descriptive statistics were calculated in the form of position and variability measures. The verification of the normality of distributions of the analysed variables was carried out using the Shapiro-Wilk test. In order to determine the strength of the link between the variables, the vectors of the Spearman's rank correlation coefficients were calculated. Non-parametric Significance Test of Mann-Whitney U Differences was used as well as nonparametric analysis of Kurskall-Wallis variance and multiple comparison tests. The structure index was calculated for variables measured in rank and nominal scales. A significance level of 0.05 was assumed for all analyses. All analyses were performed using the Statistica v.12 package.

RESULTS

The analysis of the test results was started from the short characterization of the analysed sample due to the qualitative variables for which the structure indices were calculated.

42% of men and 58% of women participated in the study (Fig.1).

40% of respondents declared their secondary education, 26% vocational, 22% higher, and 6% basic and incomplete higher (Fig. 2).

50% of respondents declared a village as a residence, 24% a city over 61 thousand residents and 14% city to 41 thousand residents and 12% city from 41-61 thousand residents (Fig. 3).

46% of the female respondents were married, 30% of male respondents were married, 10% were in bachelor and 8% were maids, 4% were divorced and 2% were widows (Fig.4).

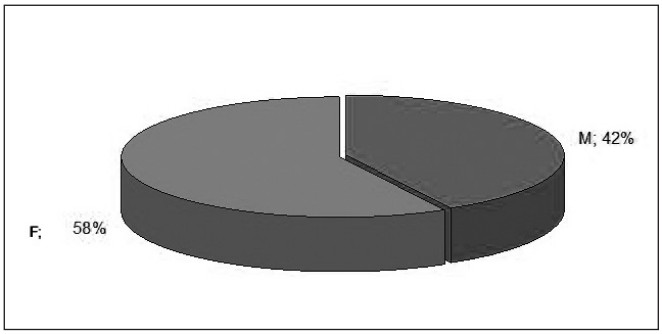

Fig. 1. Sex

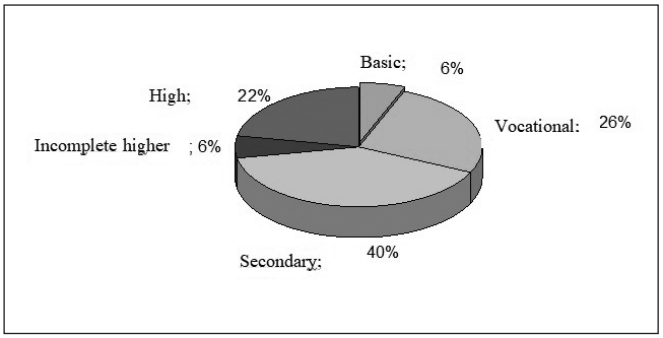

Fig. 2. Level of education

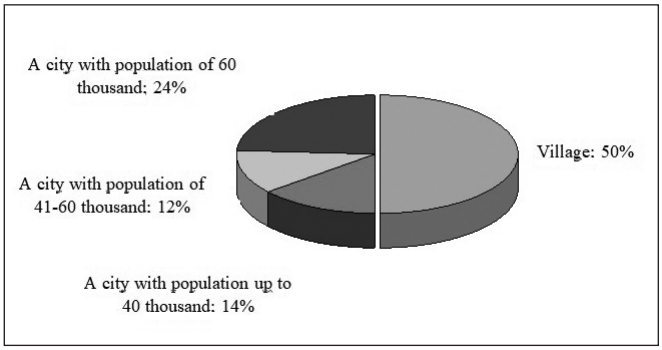

Fig. 3. Place of residence

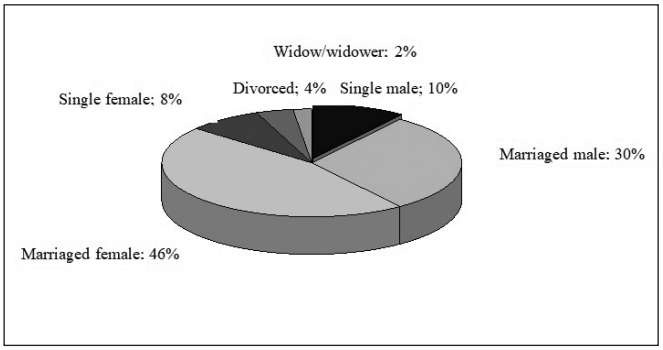

Fig. 4. Marital status

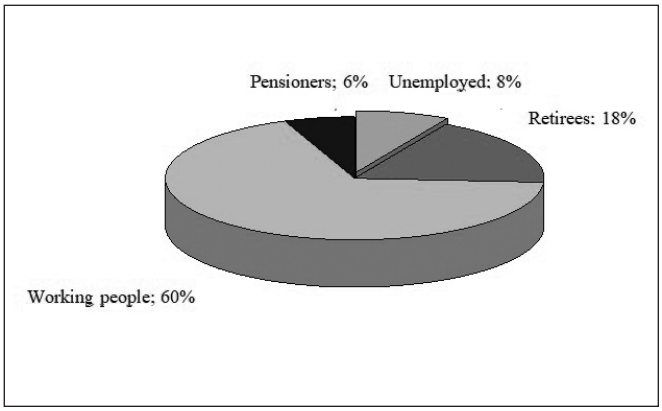

Fig. 5. Work

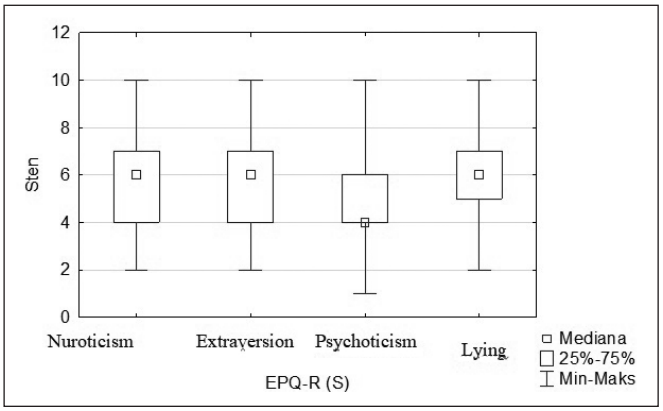

Fig. 6. Categorized box chart of EPQ-R(S) results obtained in the whole group.

68% of respondents were working people, 18% were pensioners and 8% were unemployed and 6% were retired (Fig. 5).

DESCRIPTIVE STATISTICS

The median age in the analyzed group is 47 years, the minimum age is 22 years and the maximum age is 68 years.

TEST RESULTS FOR THE ENTIRE SAMPLE

The analysis of the results allowed to state that the highest sten scores in the EPQ-R (S) test occurred in the neurotics median = 6, the extraversion median = 6 and the median lie = 6 (mean results). The highest results in the IVE test occurred in the case of empirical median = 6.5 (high score) and in the STAI test the highest score occurred for anxiety as sten 5 (average score).

TEST RESULTS FOR MEN

The analysis of the results allowed to state that the highest sten scores in the EPQ-R (S) test occurred in the median = 6 (median results). The highest results in the IVE test occurred in the case of empirical median = 6 (average score) and in the STAI test the highest score occurred for anxiety as sten 6 (average score).

Table 1. Value p for multiple (double-sided) comparisons; Sten (Sheet6) Independent variable (grouping): EPQ-R (S)

Variable	Average	Median	Minimum	Maximum	Standard deviation	Coefficient of variation
age	46.28	47.00	22.00	68.00	12.48	26.96

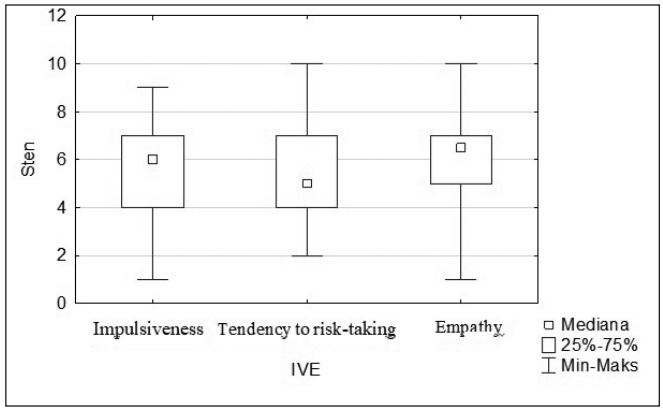

Fig. 7. Categorized box chart of IVE results obtained in the whole group.

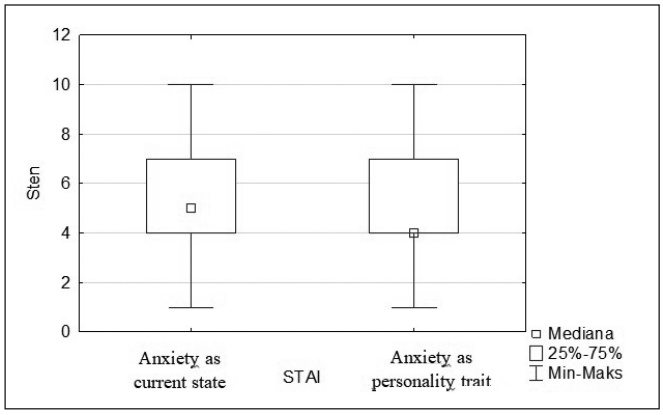

Fig. 8. Categorized box chart of STAI results obtained in the whole group.

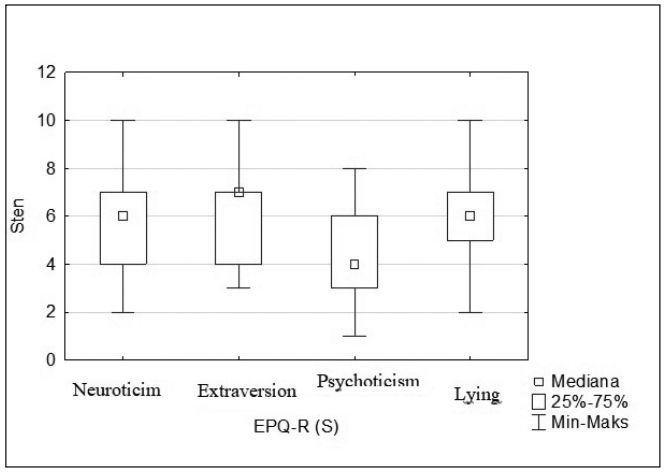

Fig. 9. Categorized box chart of EPQ-R(S) results obtained in the group of man.

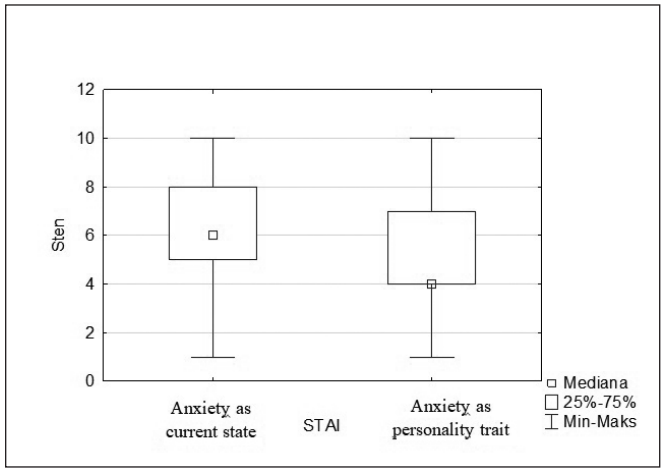

Fig. 10. Categorized box chart of EPQ-R(S) results obtained in the group of woman.

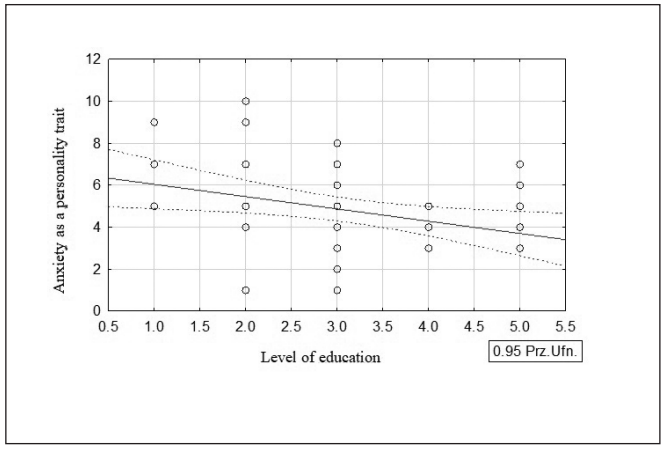

Fig. 11. Correlation of Spearman's rank order (level of education and ankiety as a trait). The correlation coefficients determined are significant with p <.05000.

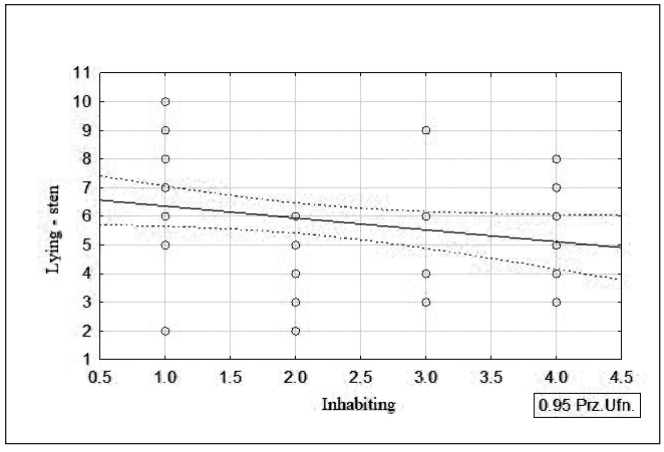

Fig. 12. Correlation of Spearman's rank order (inhabiting and lying trait). The correlation coefficients determined are significant with p <.05000.

TEST RESULTS FOR WOMEN

The analysis of the results allowed to state that the highest sten scores in the EPQ-R (S) test occurred in the extraversion median = 7 (high result). The highest results in the IVE test occurred in the case of empathy median = 7 (high result) and in the STAI test the highest score occurred for anxiety as a state and as a trait 6 (average score):

1. Neuroticism is clearly the strongest characteristic of people with congenital heart defects.
2. Extraversion is characteristic of people suffering from congenital heart disease.
3. Psychotism is not characteristic of people with congenital heart defects.
4. The lie is characteristic of people with congenital heart defects.

Subsequent analyses were aimed at verifying whether there are significant differences between the results converted into stents for individual EPQ-R (S), IVE and STAI tests. For this, Anova Kruskala-Wallis and the Mann-Whitney U test for the STAI test were used (Tab. 1).

Kruskal-Wallis test: H (3, N = 200) = 11.63656 p = 0.0087 (Fig. 6).

The analysis provided the basis for finding significant differences H (3, N = 200) = 11.63 p = 0.0087. In the analyzed group extraversion was significantly higher than psychotism p = 0.046 and the results of the lie were statistically significantly higher than psychoticism.

There were no significant differences between item values in the IVE test: H (2, N = 150) = 4.28; p = 0.12 (Fig.7).

There were no significant differences between item values in the STAI test: p = 0.09 (Fig. 8-9).

The same analyses were carried out by women and men:

1. Empathy is clearly the strongest characteristic of women with congenital heart defects.
2. Neuroticism is characteristic of women with congenital heart defects.

There were no significant differences in the case of women between items in the EPQ-R (S) test. Kruskal-Wallis test: H (3, N = 116) = 5.52 p = 0.14 (Fig. 10):

1. A high level of psychoticism is characteristic of men suffering from congenital heart disease.
2. Extraversion is not a characteristic feature for men with congenital heart defects.

The analysis provided the basis for finding significant differences H (3, N = 84) = 8.80; p = 0.032. In the analyzed group extraversion for men was significantly higher than psychotism p = 0.027 and the results of the lie were statistically significantly higher than psychoticism:

1. A lie is characteristic of women with congenital heart defects.
2. Impulsivity is not a characteristic feature of women suffering from congenital heart disease.

There were no significant differences between the items' values for women in the IVE test: H (2, N = 87) = 2.31 p = 0.31.

Inclination to risk is characteristic for men with congenital heart disease.

There were no significant differences between the items' values for men in the IVE test: H (2, N = 63) = 1.85 p = 0.40

Anxiety as a condition is characteristic of women suffering from congenital heart disease.

In the case of women, the results of the variable anxiety as a state were statistically significantly higher than the results of anxiety as a trait p = 0.032.

1. Anxiety as a trait is not a characteristic feature for men with congenital heart defects.

In men, there were no significant differences between the results of anxiety variables as a state and anxiety as a trait of> 0.05.

Subsequent analyzes were aimed at verifying whether gender significantly differentiates the results of EPQ-R (S), IVE and STAI.

The analysis of the results did not give grounds for stating that the sex significantly differentiates the results of EPQ-R (S), IVE and STAI tests p> 0.05.

Another analysis aimed at verifying whether the age is significantly statistically related to the results of tests carried out for this purpose, the Spearman rank correlation coefficient was applied.

There were no statistically significant associations between age and results of the analyzed tests p> 0.05.

Another analysis aimed at verifying whether education is significantly statistically related to the results of tests carried out for this purpose, the Spearman's rank correlation coefficient was applied.

Correlation of Spearman's rank order. The correlation coefficients determined are significant with p <.05000

The analysis allowed to find a statistically significant negative average correlation between the variables Education & Anxiety as a trait - sten R = -0.39; p = 0.005. Along with the increase in the level of education, the level of anxiety as a trait decreases (Fig. 11).

Another analysis aimed at verifying whether education is significantly statistically related to the results of tests carried out for this purpose, the Spearman's rank correlation coefficient was applied.

Correlation of Spearman's rank order. The correlation coefficients determined are significant with p <.05000

The analysis made it possible to find a statistically significant negative average correlation between the variables Place of location & Lie - sten R = -0.33; p = 0.02. With the increase in the place of residence, the level of the variable lie decreased (Fig. 12).

Another analysis aimed to verify whether marital status significantly differentiates the analyzed results of EPQ-R (S), IVE and STAI tests

Analysis of the results did not give grounds for stating that marital status significantly differentiates the results of the analyzed tests by p> 0.05.

The next analysis was to verify whether the work significantly differentiates the analyzed results of EPQ-R (S), IVE and STAI tests

The analysis of the results did not give grounds for stating that the work significantly differentiates the results of the analyzed tests by p> 0.05.

DISCUSSION

The analysis of the research results allowed to state that the highest sten results in the EPQ-R (S) test occurred in neu-

roticism, extraversion and a lie. The highest results in the IVE test occurred in the case of empathy, while in the STAI test the highest results occurred for anxiety as a condition.

In the case of men, they obtained the highest sten scores in the EPQ-R (S) test on the lie scale. The highest results in the IVE test occurred in the case of empathy, while in the STAI test the highest results occurred for anxiety as a condition.

In the case of women, they obtained the highest results in the EPQ-R (S) test on the extraversion scale. The highest results in the IVE test occurred in the case of empathy, and in the case of the STAI test the highest results occurred for anxiety as a condition and as a trait:

1. Neuroticism is clearly the strongest characteristic of people with congenital heart disease.
2. Extraversion is characteristic of people suffering from a congenital heart disease.
3. Psychoticism is not characteristic of people with congenital heart disease.
4. Lying is characteristic of people with congenital heart disease.
5. Empathy is clearly the strongest characteristic of women and men with congenital heart disease.
6. Neuroticism is characteristic of women with congenital heart disease.
7. A high level of psychoticism is characteristic of men suffering from a congenital heart disease.
8. Extraversion is not a characteristic feature for men with congenital heart disease.
9. Lying is characteristic of women with congenital heart disease.
10. Impulsiveness is not a characteristic feature of women suffering from congenital heart disease.
11. Anxiety as a condition is characteristic of women suffering from a congenital heart disease.
12. Anxiety as a trait is not a characteristic feature of men with congenital heart disease.

The analysis gave rise to significant differences. In the analyzed group, extraversion for men was significantly higher than psychoticism and the results of lies were statistically significantly higher than psychoticism. There were no significant differences between the values of items for women in the IVE test. Tendency to risk is characteristic for men with congenital heart disease. There were no significant differences between the values of items for men in the IVE test.

In men, no significant differences were found between the results of the variables anxiety as a condition and anxiety as a trait $p > 0.05$. Analysis of the results did not give grounds to conclude that gender significantly differentiates the results of the EPQ-R (S), IVE and STAI tests $p > 0.05$. There were no statistically significant correlations between age and the results of the analyzed tests $p > 0.05$. As the level of education increases, the level of anxiety as a feature decreases. Place of residence influenced the level of the variable lie. Analysis of the results did not give grounds to state that marital status significantly differentiates the results of the analyzed tests $p > 0.05$. The analysis of the results did not give rise to the conclusion that the work significantly differentiates the results of the analyzed tests $p > 0.05$.

CONCLUSIONS

Research on the relationship between congenital heart defects and personality traits of people suffering from congenital heart defects are very important in the everyday practice of every doctor. The well-being of a patient with a congenital heart disease requires interdisciplinary care consisting of specialists from various fields, such as doctors, nurses, midwives, physical therapists, psychologists, and nutritionists [5].

Due to scarce scientific data on this issue, and mainly concerning ischemic myocardial disease, as a model unit in cardiology, activities that could lead to the establishment of the aforementioned relationship should be intensified. This subject is dealt with in psychocardiology focused on: health promotion, psychoprophylaxis, facilitating the prevention, early detection and treatment of cardiological diseases, alleviating the consequences of diagnosis, therapy of cardiological diseases. The activities of psychocardiologists are also directed at the education of members of a multidisciplinary, cooperating therapeutic team; conducting scientific research in the field of psychology, sociology and medicine, because the results of the above-mentioned individual studies can contribute to the emergence of effective methods in the fight against cardiovascular diseases [5].

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PRACA POGLĄDOWA
REVIEW ARTICLE

MEASLES OUTBREAKS: THEY ARE PREVENTABLE BUT KEEP PROGRESSING DANGEROUSLY

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ABSTRACT

Introduction: During last year's, Ukraine and other European countries are facing outbreaks of well-known and emergency infections. Particularly alarming is the increase in the incidence of measles, which may be the result of a sharp decline of immunization that leads to the accumulation of susceptible individuals in the population.

The aim was to assess the incidence of measles and the vaccination coverage for measles during last 5 years among children of Sumy region of Ukraine and factors due to which it is unable to be reached the required level of MMR-vaccination.

Review: Statistical data shown the vaccination coverage rates was dangerously low in Sumy region of Ukraine last 5 years. It began to decrease starting from 2013 year. measles vaccination coverage in 2013 was below 50%, reaching a staggering minimum of ~ 30 % in 2014 and 20 % in 2015. According to our research (questioning), the targeted vaccination coverage for measles was unable to be reached due to several factors, such as the active refusal of parents to vaccinate their children or partly the lack of sufficient vaccine supplies.

Conclusions: MMR-vaccination uptake in Sumy Region is still below World Health Organization target. In the period 2014-2016, the level of children immunization was critically low and the concept of herd immunity was lost. This is the main reason for the ongoing measles outbreak in 2018. It is of the utmost importance that all medical professionals, physicians, researchers, educators, and governments of Ukraine unite to combat the anti-vaccination movement.

KEY WORDS: vaccination coverage, measles, measles outbreaks, children

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INTRODUCTION

Immunization is a proven tool for controlling and eliminating life-threatening infectious diseases and is estimated to avert between two and 3 million deaths each year. It is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine. Vaccines stimulate the body's own immune system to protect the person against subsequent infection or disease [1].

Immunization is one of the most cost-effective health investments, with proven strategies that make it accessible to even the most hard-to-reach and vulnerable populations.

However, during last years Ukraine and other European countries are facing outbreaks of well-known and emergency infections. Particularly alarming is the increase in the incidence of vaccine preventable diseases, which may be the result of a sharp decline of immunization that leads to the accumulation of susceptible individuals in the population [1, 2, 8].

WHO documents identified key aspects of modern immunization policies, one of which states that vaccine preventable diseases, can be eliminated locally without global eradication of the causative microorganism. Key to this achievement is more than 95% population immunity [2, 3].

Ukrainian vaccination schedule is familiar to the European immunization scheme and includes vaccination antigens of 10 infections (in the USA, France, the UK and Italy against 12 infections, in Germany – 13, in Poland - against 11) [4, 5]. One of these infections is measles. The measles virus is exceptionally contagious and spreads easily among susceptible individuals. To prevent outbreaks, at least 95% immunization coverage with two doses of measles-containing vaccine is needed every year in every community, as well as efforts to reach children and adults who missed routine vaccination in the past. Many factors contribute to suboptimal immunization coverage and the spread of measles. To prevent outbreaks and eliminate measles, countries need to sustain high national and subnational immunization coverage with two doses of measles-containing vaccine, as well as identify and address all pockets of underimmunization among their populations.

THE AIM

Aim is to assess the incidence of measles and the vaccination coverage for measles during last 5 years among children of Sumy region of Ukraine.

MATERIALS AND METHODS

Methods of immunization provides according to Ministry of health care of Ukraine order No. 595 from 16.09.2011 (the last edition – 03.07.2018) [4] which defines the no-

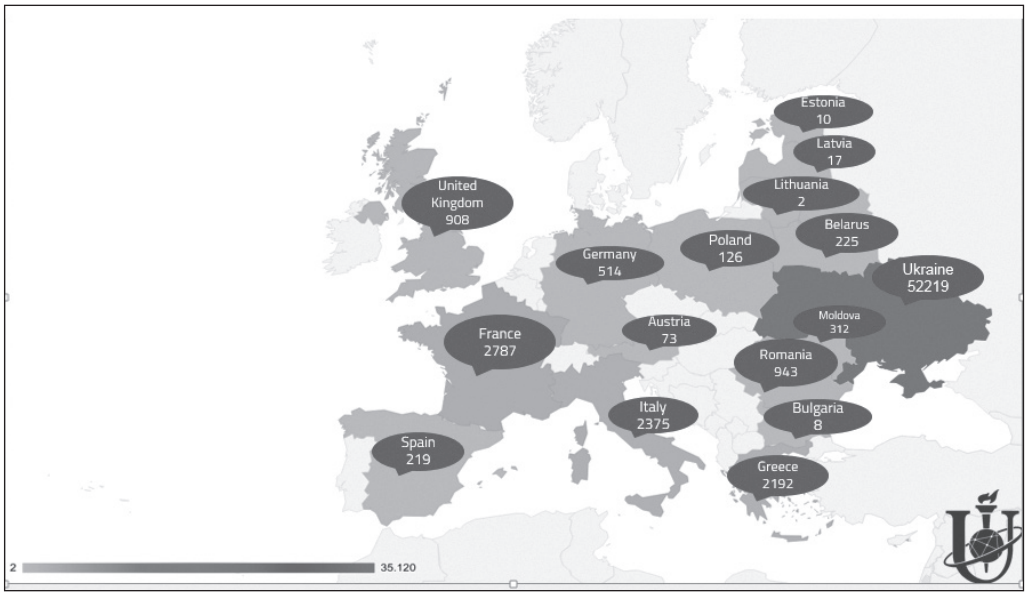

Fig. 1. Measles outbreaks in European countries in 2018 (according to monthly country reports for January to December 2018 received as of 01 February 2019).

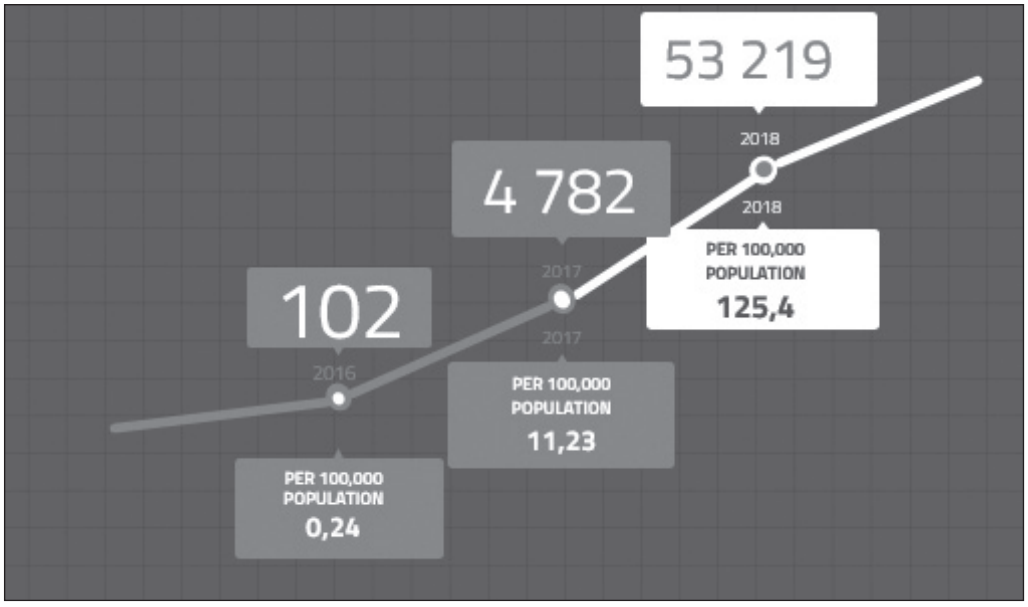

Fig. 2. Measles outbreaks in Ukraine (2016-2018)

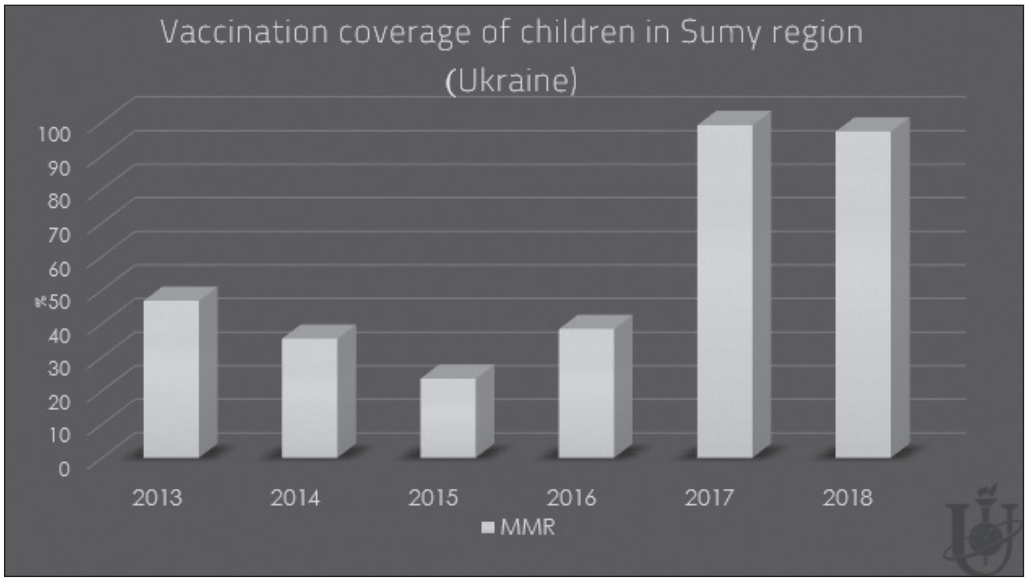

Fig.3. Vaccination coverage of children in Sumy region (Ukraine) in 2013-2018 (%)

menclature, age, and intervals between doses of antigens administered.

State Statistical Reporting Form No. 2 "Report on Certain Infections and Parasitic Diseases", and No. 6 "Report concerning Persons of Selected Age Groups Immunized to Infectious Diseases" were used as main data sources.

Some countries in European Region have seen over 1000 infections in children and adults in 2018 (France, Georgia, Greece, Italy, UK and Ukraine). Measles killed 72 children and adults in the European Region in 2018.

REVIEW AND DISCUSSION

According to measles data for the year 2018 released today, some countries in Europe have seen over 1000 infections in children and adults this year. Ukraine has been the hardest hit, with over 50 000 people affected (Fig. 1). Measles-related deaths have been reported in all of these countries [7].

The total number of people infected with the virus in 2018 was the highest this decade: 3 times the total reported in 2017 and 15 times the record low number of people affected in 2016.

Last year Ukraine is seeing a record number of measles cases. In 2018, health officials reported the highest number of measles cases during all the time of Ukraine's independence, with more than 50000 people infected (Fig. 2). Previous outbreaks of measles in Ukraine were registered in 2006 and 2012.

The vaccination coverage was dangerously low during last years in Sumy According to the information of Sumy region, the vaccination coverage rate began to decrease starting from 2013 year. For example, measles vaccination coverage in 2013 was below 50%, reaching a staggering minimum of ~ 30 % in 2014 and 20 % in 2015 (Fig. 3). According to our research (questioning), the targeted vaccination coverage for measles (>95%) was unable to be reached due to several factors, such as the active refusal of parents to vaccinate their children or even the lack of sufficient vaccine supplies. Even people favorable to vaccination can be confused by the ongoing debate, leading them to question their choices. Many parents lack basic knowledge of how vaccines work, as well as access to accurate information explaining the importance of the process. The declining trends in vaccination coverage in the context of the recent measles epidemics have also constituted the basis for recurrent discussions about mandatory immunization and during 2017-2018, this index was to be improved, however it still reveals in quite low level and it was still below WHO target. As such, even if the government provides the vaccines, which are part of the national immunization program (including the MMR), free of charge, parents can still opt out without having to legally justify this action. It is known examples do exist of countries where vaccination coverage has been increased by a more explicit form of legal enforcement (school entry laws or substantial financial incentives/penalties) [9, 10].

Last two years more children in Sumy Region are being vaccinated against measles than three years before, so progress has been uneven, leaving increasing clusters of susceptible individuals unprotected, and resulting in a record number of people affected by the virus in 2018.

In 2018, in Sumy region, 312 people suffered from measles, including 211 adults and 101 children. Fatal cases are not registered. The vast majority of these patients were not vaccinated against measles.

Measles cases spike globally due to gaps in vaccination coverage. The resurgence of measles is of serious concern, with extended outbreaks occurring across regions, and particularly in countries that had achieved, or were close to achieving measles elimination.

According to the Centers for Disease Control and Prevention, one in 20 children with measles develops pneumonia and one in 1,000 develops encephalitis (brain swelling that can cause brain damage). Pregnant women with measles are at greater risk of having premature or low-birth-weight babies. Two in 1,000 children who contract measles will die [6]. According to the World Health Organization, in countries where measles vaccination is not routine, it is a significant cause of death.

CONCLUSIONS

Rutine immunization uptake in Ukraine is still below WHO target. The main reason for the ongoing measles outbreak was low vaccination coverage by the MMR vaccine. One of the main reason is the active refusal of parents to vaccinate their children that was spurred with the release of a report that claimed the MMR vaccine was linked to autism. The findings have been debunked but some parents have remained skeptical as the rates of autism continue to rise at an unprecedented rate, with no known cause. Because of this collective immunity among children decreased to a critical level.

Currently Ukraine's immunization program works to regain high immunization coverage and stop measles outbreaks.

Also strict monitoring of the implementation of the immunization schedule by medical institutions at all levels are recommended to improve vaccination status of Ukrainian children. The rise of anti-vaccination movements in Ukraine and other countries of Europe adduces a dire threat to people's health and the collective herd immunity. People of all ages have fallen victim to recent outbreaks of measles. This vaccine preventable disease was to be eliminated that, but made a comeback as a direct consequence of not reaching the immunization threshold for MMR vaccines. These outbreaks not only put a strain on national healthcare systems but also lead to severe complications and cause fatal casualties. Therefore, it is of the utmost importance that all medical professionals, physicians, researchers, educators, and governments of Ukraine unite to combat the anti-vaccination movement. There must be a strong accent on helping parents develop trust in health professionals and relevant authorities, educating them on the facts and figures, debunking the myths diffused by the anti-vaccination movements, and even introducing legislation that promotes vaccination.

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PRACA POGLĄDOWA
REVIEW ARTICLE

INNOVATIVE AND INTERACTIVE TEACHING METHODS AS A MEANS OF OPTIMIZING THE EDUCATIONAL PROCESS OF HIGHER MEDICAL EDUCATION

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ABSTRACT

Introduction: The public need prompts the modern school to find new ideas and technologies, to share and adopt the advanced pedagogical experience. Achieving the ultimate goal of the educational process in universities is training of highly qualified and competitive specialists in health care.

The aim of the study is to assess the results of using the innovative and interactive teaching methods implemented in the national system of higher medical education.

Materials and methods: Official documents; the academic studies of leading Ukrainian scientists-pedagogues; textbooks and manuals on pedagogy, the results of our own pedagogical practice.

Conclusions: The widespread adoption of digital technologies into the educational process at clinical and theoretical departments of medical universities significantly simplifies the assimilation of the disciplines, optimizes and generalizes the results of the educational process. The innovative path of education development is a "social elevator" that raises people to higher levels of social development.

KEY WORDS: innovative teaching methods, interactive teaching methods, educational process, higher medical school

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INTRODUCTION

The Law of Ukraine on Education No. 2145-VIII dated 05.09.17 states that the person is the highest value of society, and the objectives of teachers at the all stages of his formation as an individual are the realization of talents, intellectual, creative and physical abilities, formation of values which are necessary for successful self-realization of competences, to foster responsible citizens, capable of conscious social choice and directing their activities for the benefit of other people and humanity in general [1]. Ukraine as a European country possesses valuable acquisitions of national pedagogical thought, substantially changes the "knowledge policy" and social priorities in education, forms a fundamentally new "developing" paradigm of upbringing and education by involving new methods of the educational process that would stimulate the development of student's personal characteristics. The implementation of modern methods aims to form a responsible person capable of thinking critically, processing a large amount of diverse information, distinguishing principal things from secondary, having skills of self-education, self-development and self-control, the ability to use the acquired knowledge for the creative meeting the challenges [2]. Thus at this time in Ukraine a new educational policy is being formed, in which modern innovative pedagogical technologies are implemented, the main benchmark of which is the implementation of new, interactive methods of upbringing and education [3].

These changes are preceded by Ukraine's aspiration to become an equal member of the European community, which causes comprehensive reform not only in the organization of the educational process, but also in scientific and research activities in educational institutions. All of that requires the research work in educational institutions to be led to a qualitatively higher level and aligned with European dimensions and standards [4].

Obviously, the public need prompts the modern school, its teachers and pedagogues, scientists to find new ideas and technologies, to share and adopt the advanced pedagogical experience. Certainly, nowadays it raises the issue of competent and professional specialist for the high school. Therefore, the important and pressing issue for higher education today is creating of such a High-Tech Information and Communication, Science and Education Environment in which the student is engaged on a daily basis throughout the entire period of study at university. The Environment should meet the needs of the information society, the current level of science and technology development, world educational standards, and promote the formation of information and communication compe-

tencies of all participants in the educational process from professor to student [5].

The problem concerning the content of education is exacerbated by sharp (dramatic) increase in the information flow, which faces the universities the need for prompt retrieval and use of information. Implementation of computers into the educational process, as well as new information and multimedia technologies requires a qualitatively new approach to the problem of the content of education [4].

It should be noted that in recent years the interest of ukrainian teachers and academicians has grown significantly in the introduction the latest innovative and interactive technologies into the educational process which are aimed at realization of advanced methods of teaching and upbringing of today's youth. In particular, great attention was focused on this problem by many leading Ukrainian scholars such as A. Aleksyuk, V. Andrushchenko, K. Bakhanov, I. Dychkivska, V. Kremin, A. Pekhot, A. Pometun, O. Saukh, V. Khiminets and others [6,7,8,9,10,11,12,3,4]. Their scientific works are focus on the importance of introducing the latest innovative technologies into the educational and pedagogic process of the student youth for upgrading and renewal of the national education, raising it to the European level in order to promote the overall social development.

The above-mentioned changes concern medical universities and lead to a correction of teaching both theoretical and clinical disciplines [13]. Achieving the ultimate goal of the education in universities is training of highly qualified and competitive specialists in health care. It is possible by summing up deep theoretical knowledge, practical skills acquired both at the undergraduate stage of medical education, and continuous postgraduate skills development during practice. Therefore, the mission of the teachers in medical universities is not only to provide knowledge but studying to interpret information correctly [14].

THE AIM

The aim of the study is to assess the results of using the innovative and interactive teaching methods implemented in the national system of higher medical education, thus enabling more efficient solution of complex task of development of the creative person ready to meet the challenge of the constant professional growth of a Ukrainian doctor under close integration of Ukraine into European and world community.

Reconstitution of a holistic view of the Ukrainian educational system reform in this period, identifying leading trends in it, priority-setting and perspective directions of its formation and development - these are the main tasks and content of our study.

MATERIALS AND METHODS

The source of the research contains official documents (lows, orders, decrees, directions etc.); the academic studies of leading Ukrainian scientists-pedagogues on the given problem; scientific sources (monographs and dissertations); textbooks and manuals on pedagogy, as well as the work of teachers-reformists of the late nineteenth and early twentieth centuries, the results of our own empirical studies.

To assess the didactic aspects of the problem, we used a set of routine scientific methods: theoretical analysis, synthesis, comparison, systematization, generalization.

REVIEW AND DISCUSSION

Exploring the essence of pedagogical innovation, it should be noted that it is a fairly young science. An analysis of foreign scientific materials on pedagogy suggests that the study of innovations, as a component of pedagogy, began in the 1960s [15].

The concept of "innovation" includes a form of organization of innovation activity; a set of new professional actions of the teachers aimed at solving the actual problems of education and teaching from the standpoint of person-centered education. It includes changes in educational practice, providing, distribution and use of new practical means in the technology, pedagogy, scientific research and the results of the innovation process The development of pedagogical innovation in Ukraine is associated with mass socio-pedagogical movement, caused by contradictions between social needs for the development and functioning of educational institutions on the one hand, and the realities of educational establishments at that time on the other [9].

A clear example of this problem is the new IFOM exam introduced by Ministry of Health of Ukraine for the 3rd year medical students as an obligatory part of curriculum in higher medical educational establishments of Ukraine in 2018-2019. The exam is developed by one of the world's most authoritative attestation councils - National Board of Medical Examiners (NBME) is an independent, not-for-profit organization that serves the public through its high-quality assessments of healthcare professionals. It has become a real challenge for both students and teachers, as the academic system in Ukrainian medical universities varies from European and world. To foster a student, and then a doctor who can cope with such a challenge, Bukovinian state medical university (BSMU) has improved the educational process with a variety of innovative methods: adaptation of units of measurement, intensification of cross-curricular integration, terminology (symptoms in English), modern methods of diagnostics including biochemical, genetic engineering, use of modern treatment and diagnostics protocols, increase of the share of computer testing for evaluation of student success, unifying methods practical skills and diagnostics.

Expanding the essence of the innovation process in the modern Ukrainian education and pedagogy, the academic I. Dychkivska draws attention to the specific features of innovative learning. In particular, she noted that the development of systems and content of training in today's world takes place in the context of global educational trends (megatrends), the most notable of which are the widespread and continuous education as its new quality, the importance of education for the individual and society,

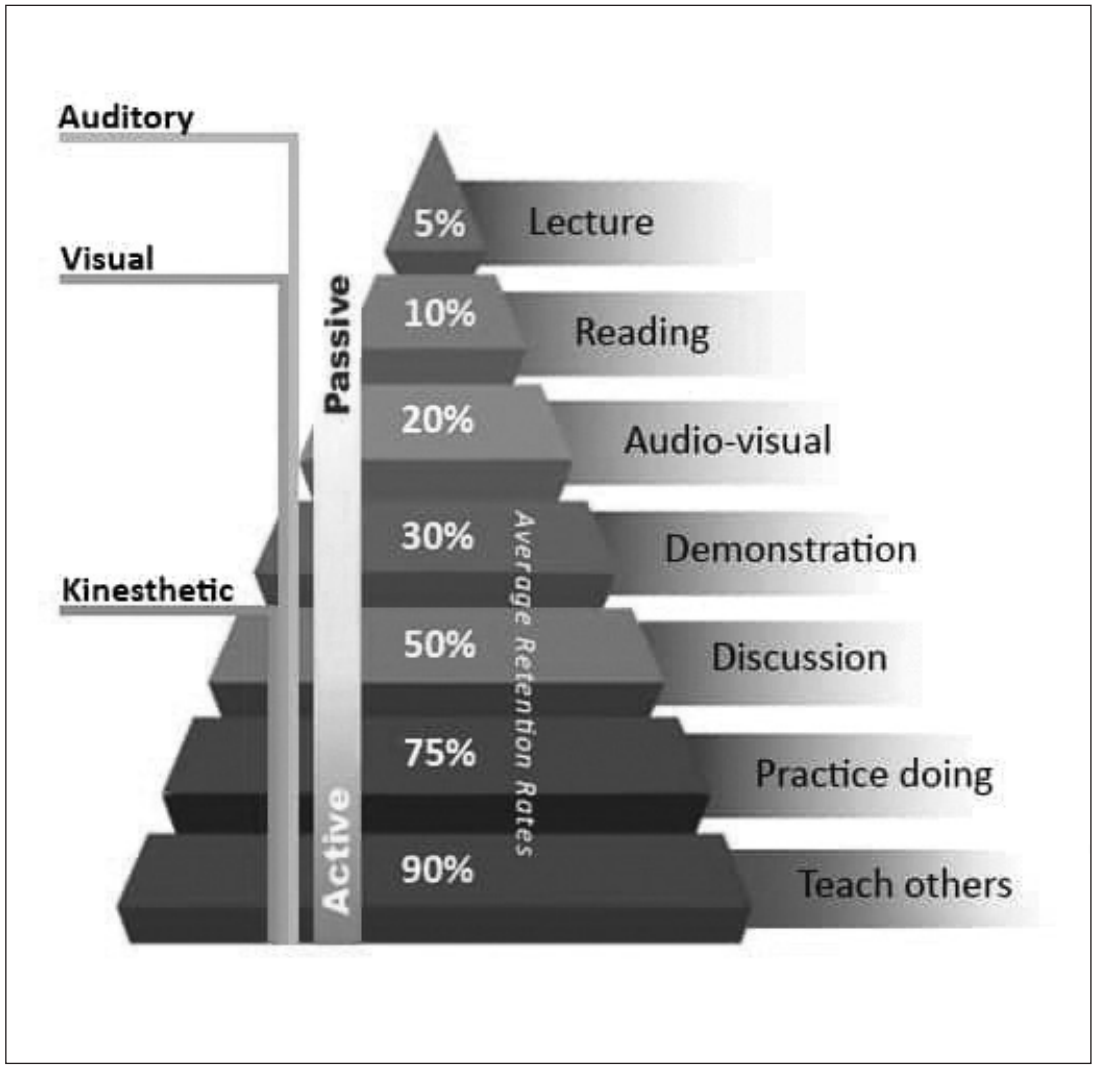

Fig. 1. Learning Pyramid

focusing on active development of a person's cognitive activity; adaptation of the educational process to the needs of the individual, the driving towards training on personality, providing opportunities for self-revelation [9].

Academician I. Zyazun in this context emphasizes that the meaning and purpose of modern education should be a constantly developing person, his spiritual growth, harmonization of his relationship with himself, the other people, and the world. Among other things, he emphasizes that the system of education is created for an individual, it is functioning and developing in its interests, it serves the national purpose of personality development and ideally – for the humans' happiness [16].

As it is referred in the studies of American scientists R. Karnika and F. Macelroya, most students only remember about 10% of information they read, 20% of information they heard, 30% of what they saw, 50% of what they heard and saw, 80% of what they spoke aloud, but they retain nearly 90% of what they learn through their own activity [17,18]. Visually this can be represented as the "learning pyramid"(Fig. 1).

This can be achieved using interactive methods, in particular: 1) a heuristic conversation; 2) discussion; 3) "brainstorming"; 4) round-table discussion; 5) "business game"; 6) competition of practical works; 7) socio-psychological training.

Interactive learning is a special form of cognitive activity that forms comfortable learning conditions in which the student appears not as an "object" but as a full-value "subject" of the learning process. Interactive engagement with basic conceptual positions learning based on interactive communication preclude the dominance of any participant the educational process either student or teacher [12,19]. Analyzing our own experience of teaching clinical disciplines in medical universities, we can note that the use of round tables, partly with the elements of the heuristic conversation and "brainstorming" leads to the optimization of the educational process [20], namely the growth of both the current level of knowledge, aptitudes and practical skills, and results of the final module control. It should also be stressed that productivity is determined by the differentiated use of these methods depending on the topic of practical classes. For instance, when studying the ECG basics the main problem is the confusion of the large amount of knowledge that students gained on theoretical disciplines and during preparation to practical classes. Therefore, the teacher's task is giving

students a clear algorithm of the ECG interpretation that the correct answer can be obtained by passing all the steps in the correct order, starting from the definition of the rate and rhythm to analysis of the waves and intervals. For the realization of these objectives we used the "round-table" method to increase the effectiveness of theoretical knowledge assimilation by considering them in various scientific aspects through joint debate and reaching a consensus in solving a problem. Interactive learning is just aimed at boosting cognitive activity by means of communication between group of students and teacher for solving a common educational problem [21, 22]. Sometimes, during the discussion, elements of a heuristic conversation should be used, in particular by asking students some questions teacher can put them in the right frame of mind. For further studies, when students are familiar with the normal ECG and have in-depth understanding of the algorithm of ECG interpretation, it is useful to use more complex methods, including the "brainstorming" proposed by Alex Osborne. The scientist noticed that in the situation when there is no teacher's pressure and criticism, some people start generating a huge number of ideas, while others, owing to the features of their thinking, are more inclined to analyze and critically assess other people's ideas and their development. Thus, two groups of students are formed: "ideas men" which put forward the idea and versions, and "critics" whose task is to analyze and assess the ideas, in our case concerning correct interpretation of the ECG. It is important for "critics" to analyze all opinions carefully (comments, assumptions, conclusions) without omitting none of them. In case of making wrong suggestions or conclusion the critics should explain why the claim is wrong and defend their positions. It should be noted that this kind of cooperation is very effective in teamwork of medical students, the number of which in one academic group varies from 10 to 14 persons. The "brainstorming" method activates all activities and maximizes the process of assimilation of the material.

The importance of acquiring a complex competency by contemporary university graduates which enables introduction of innovative technologies into educational and pedagogical process of the younger generation deserves to be mentioned. First of all it should be noted that the main competences (civic, social, general cultural, informational, special subject-oriented, healthcare) have the following characteristic features:

- multifunctionality (enables a person to solve various problems and achieve important goals as in daily life as in professional and social life);
- multidimensionality (includes various mentation and intellectual skills);
- subject superiority and disciplinarity (can be applied in various situations in the professional, social and household spheres);
- dynamism (dependence on the society and individual priorities thus having a mobile nature) [23].

Based on personal experience we can illustrate the effectiveness of competent approach in teaching bioorganic and biological chemistry in medical universities [24].

1. The bioorganic and biological chemistry course forms the competencies that are required both for studying other disciplines and in the professional activity of the future doctor.
2. The module-rating system allows the student to realize the need for systematic work in the study of discipline and to adjust their academic performance, which is the main prerequisite for getting qualitative education.
3. For successful study of bioorganic and biological chemistry student should be involved into the educational process as much as possible, developing his creative abilities and teaching techniques of solving professional problems by studying their mechanisms at molecular level.
4. Business games, practical classes in the form of competitions, the use of logical-meaning systems build up students 'cognitive abilities: independence of thinking, creativity, ability to solve problems which increase students' creativity, allow them to integrate the knowledge gained in the study of different subjects, establish interdiscipline links, induct their interest in science, scientific research, help to join scientific and theoretical положення with the clinical practice.
5. Studying elective course on clinical biochemistry emphasizes the medical thrust of biological chemistry, promotes increasing knowledge of students further professional activity.

The need for specialist competences resulted from the fact that, when introducing pedagogical innovations and exploring new ideas in an educational institution, one should act in a comprehensive manner, involving all levels of the educational process: methodological, theoretical, methodical and technological.

Research activity of the educational institutions is related to the development of both ideas and ways of their practical implementation. The source of ideas is practice, that is the activity of a pedagogical stuff and individual teacher [4].

The research activity and implementation of new ideas by educational institution is carried out in two directions: methodological and technological. The technological direction of the university's activities in the realization of ideas and their research is related with the implementation of new methods and technologies of education, as well as the management of the educational institution [11,25]. Practice admits that technological direction of research can be an inexhaustible source of facts and ideas that enrich pedagogy and enable the personal growth of teachers [26]

The methodological direction of the research activity is related to the independent development of educational institutions of new pedagogical ideas, goals, tasks, forms of work, functions, methods and principles, regularities of organization and implementation of the educational process [4].

It should be noted that the effectiveness of innovations depends largely on the innovation potential of universities, namely on the ability to create, accept and implement innovations. The appropriate model of innovation activity of modern universities is just created with emphasis on the

innovative potential. The initial level of the model reveals the potential for innovative activity, the second level - the ability of the educational institution to implement a particular innovation [27].

CONCLUSIONS

To increase the efficiency of innovative technologies implementation into educational process, guided by the law of Ukraine "On Innovative Activities" [28] and the Order of the Ministry of Education and Science of Ukraine "On Amendments to the Regulations on the Procedure of Innovative Educational Activities" [29] instead of "one-size-fits-all" approach the individual characteristics of each ward should be considered that is a personal approach while using the appropriate innovative methods and technologies.

1. Questions about the possibilities and ways of managing innovative pedagogical systems remains open. The specificity of this process is clear because innovative systems are based on the creativity phenomenon.
2. The widespread adoption of digital technologies into the educational process at clinical and theoretical departments of medical universities significantly simplifies the assimilation of the disciplines, optimizes and generalizes the results of the educational process.
3. Innovative forms and methods allow to integrate the knowledge gained in the study of various subjects, and to establish interdisciplinary linkages, enhance students' interest in science, research, help to link scientific and theoretical facts with the clinic, facilitating the development of practical skills.
4. Innovative technologies in medical colleges should be represented more widely through by means of distance learning programs. The training of the undergrad of the medical faculties should be complex and include not only a practical component, but also a variety of innovative pedagogical techniques and teaching methods.
5. The innovative path of education development increases the relevance of intellectual and creative resources, which together fulfill the role of "social elevator", which lifts people to higher levels of society.

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PRACA POGLĄDOWA
REVIEW ARTICLE

PUBLIC-PRIVATE PARTNERSHIP AS AN INVESTMENT AND INNOVATION TOOL FOR MEDICAL FACILITIES: A CASE OF UKRAINIAN HEALTHCARE

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ABSTRACT

This paper summarizes the scientific discussion on the issue of public-private partnership in healthcare sector. The main purpose of research is to analyze the public-private partnership as the progressive form of innovative and investment mechanism in Ukrainian healthcare sector, taking into the consideration international experience in this sphere. The key methods used in the conducted research are data analysis, summarization and comparison. The data synthesis and analysis are the basic value-added elements of this research, which could help to find out the main prospective of PPP-model use in Ukrainian healthcare sector. The object of research is the group of countries such as USA, UK, Canada, and BRIC countries, because namely they are the most progressive in public-private partnership in health care. Practical importance of the scientific research results lies in defining the general principles of public-private partnerships and a set of criterion for its efficiency estimation. Also, the worldwide experience was analyzed in this research and main challenges for its implementation in Ukrainian healthcare practice were considered. It is important for the further development of the healthcare sphere, and improvement of the healthcare facilities' activity in Ukraine. Further research directions are aimed at study of the specific issue of public-private partnership, such as circumstances for creating alliances between private and public actors from a strategy perspective, explore the impact of incentive mechanisms and risk management procedures on health service performance throughout the extended project life-cycle, and to create conducive environments to foster inter-project learning.

KEY WORDS: public-private partnership, health management, health care, medical facility, innovative development

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INTRODUCTION

Nowadays innovation is usual phenomenon for most economic spheres, generally concentrating in private and industrial sectors. But nevertheless the modern society understands its role for public and social sectors, because of increased competition. As we know, social agencies are considered to be conservative, bureaucratic and slow-growing. Such situation is driven, inter alia, by its main goal, which is to increase the welfare of society, without taking into consideration the financial component.

In recent years the society began to recognize the necessity and the benefit of the close interaction between the private and public sectors, and healthcare is not an exception. We can see the notable examples, which are of great benefit to both parties – private and public.

LITERATURE REVIEW

Nowadays, public-private partnership (PPP) is one of the most promising models for financing successful healthcare innovations. By combining public interest with private-sector research and development, PPP can inject new life into stalled projects and delivered innovative solutions to numerous industries – especially healthcare.

A recent literature review of public-private partnership examined its emerging themes of interest for health research [1].The main argument for widespread use of PPP all around world and, especially, Europe, that by promoting increased diversity of provision and contestability, it allows to secure better quality of infrastructure and services at optimal cost and risk allocation [2].

Scientists and practitioners from different disciplines have focused on this topic, among which are the fields of health policy and management, accountancy, finance and public management, etc.

A. Venkat Raman and James Warner Björkman has proven the importance of PPPs in the healthcare sector as the political, financial and innovative tool, given the systemic deficiencies in government health programs as well as the spiraling costs of an expensive, inequitable, and often unregulated private sector [3].They have focused on Indian healthcare sector, nevertheless they have shown the experience of other developing countries and how the private sector there is tapped to deliver healthcare services to poor and under-served sections of society through collaborative arrangements with the government.

We can mention the following significant studies on the public-private private partnership in healthcare [4; 1; 5].

Among the national scientists we can point out the following scientific works [6; 7; 8; 9; 10; 11; 12; 13; 14; 15], in which legal, organizational, economic and financial gears of PPP are considered.

THE AIM

The main goal of this paper is to analyze the public-private partnership as the progressive form of innovative and investment mechanism in Ukrainian healthcare sector, taking into the consideration the international experience in this sphere.

MATERIALS AND METHODS

Our analysis was conducted in two parts. In Part 1 the international publications related to the PPP theme were researched, among which the experience of PPP in USA, Great Britain, India, and Canada was the central one. It was made with a purpose to analyze foreign experience and to learn what we can adopt in our Ukrainian realities. In Part 2 we focused on the scientific works of the domestic authors to analyze Ukrainian experience of building public-private partnerships, especially in healthcare field.

The key methods used in this research are data analysis, summarization and comparison. The data synthesis and analysis are the key value-added elements of this research, which could help to find out the main prospective of PPP-model use in Ukrainian healthcare sector.

REVIEW AND DISCUSSION

BASIC PRINCIPLES OF PUBLIC-PRIVATE PARTNERSHIPS

As it is defined in [16], the public-private partnership is "ongoing agreement between government and private sectors organizations in which the private organization participates in the decision-making and production of a public good or service that has traditionally been provided by the public sector and in which the private sector shares the risk of that production".

World Bank Institute defines public-private partnership as "a long-term contract between a private party and a government agency, for providing a public asset or service, in which the private party bears significant risk and management responsibility" [17].

If we research the category of "partnership", we can say, it is a joint ownership of a program or proposal by two or more parties to achieve a common goal. Thus, it is a higher level of collaboration [18].

We can emphasize the following principles of public-private partnership: (a) joint action of both parties at all stages; (b) complimentary roles of the parties, which means expectation of each other are clarified and stabilized; (c) creation of the temporary system; (d) continuous open communication process; (e) collaborative activities used for policy development, program support and delivery of government programs; (f) contractual arrangements for long-term perspective. Usually PPP involves two or more parties.

The main feature of PPP, compared with the traditional approach to funding, is that it "bundles investment and service provision in a single long-term contract" [19]. Duration of such contract is usually 20 years or more. While this period, the parties can manage and control the assets, usually in exchange for user fees, which are its compensation for the investment and other costs [19].

An implication of PPP is that there is a cooperative investment of resources and therefore joint risk-taking, sharing of authority, and benefits for all parties.

Also we can state, that PPP is a relationship involving sharing of power, work, support and/or information with others for the achievement of joint goals and/or mutual benefits [20].

PUBLIC-PRIVATE PARTNERSHIP'S ACTIVITY IN HEALTH CARE

Today governments spend increasing portions of their budgets on health care, since health spending is growing much faster than inflation. Exacerbated by the global recession and financial crisis, governments face frighteningly gaping deficits. Public health system is usually not able to provide significant investments to its sustainable development, to deliver healthcare infrastructure, including buildings, large-technology systems, clinical services, and associated non-clinical maintenance and facility-managements services immediately, thus it needs to seek for the different finding sources, among which the private funds are.

PPP is health care is a specific strategy to achieve better community health. Also the policy aim of PPPs is to achieve higher efficiency by bundling investments, infrastructure and medical services delivery [19], drawing on a business experience and financial resources of private sector. Additionally, it helps public healthcare sector to receive unique resources and capabilities for innovative activities and improving quality of health services. General model of PPP in healthcare is presented in fig. 1.

Literature review shows, that the potential benefits from the PPP in health care are: (1) freedom to allow public sector to concentrate on, for example, the provision of clinical services; (2) increased efficiency in project delivery realized by the private sector (Barlow et al., 2013); (3) solution for public-sector capital shortage; (4) value for money (VfM) consideration; (5) introduction of healthcare market efficiency; (6) risk transfer.

But nevertheless, we see that PPP can slow down the process and improvements because of (a) limited contractor capacity in comparison with project size; (b) high capital and transaction costs throughout the project life-cycle; (c) limited integration between clinical services model and infrastructure design and delivery; and (d) limited innovation in new-build healthcare PPPs [4]; (e) limited competition due to a small number of contractors; (f) relationship management problems; (g) inappropriate risk allocation. The main critic of PPP is that such partnerships are "essentially political symbols and political choices" [1].

Thus, the main challenges of PPP in health care are the following: (a) cost containment; (b) effective use of private resources; (c) logical diversion of public resources; (d) synergy to reduce duplication; (e) resource mobilization.

One of the main instruments for PPP's regulation is risk management. The issue of risk management in PPPs attracts much attention; moreover the questions of risk allocation between partners are urgent. Among other types of risk, which can arise while PPPs, are dysfunctional effects

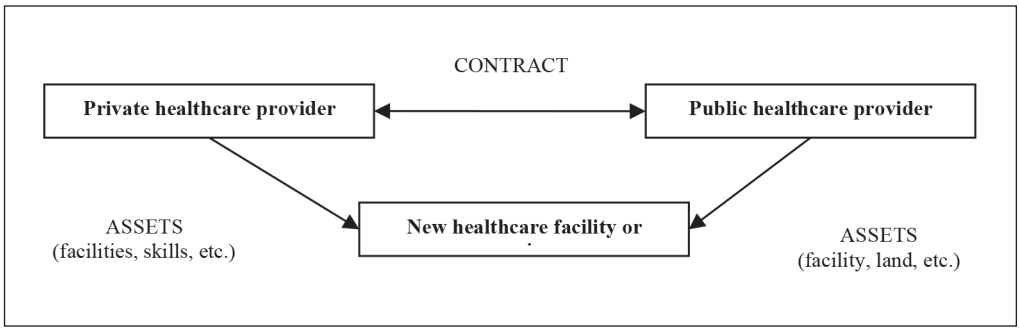

Figure 1. General model of PPP in healthcare
Source: (Health Research Institute, 2010).

Table 1. Typical set of players included in service-based PPP

Operations	Funding	Legislation	Monitoring / consulting organizations
Hospital Providers	Financial / Industrial	State health authorities	Independent consultancies
Insurers	Infrastructure funds	State health authorities	Non-governmental organizations
IT	Banks	Regional commissions	Financial
Medical devices		National health insurance boards	Legal
Pharmaceutical Companies		Members of the Legislative Assembly	Technical advisers
Construction			
Facilities management			

Source: (Health Research Institute, 2010).

of lengthy and expensive contracts negotiation periods, risk and benefit sharing between partnering organizations and across all PPP's network, quantification at the outset of inter-organizational relations and so on. Also the risk at the PPPs is related to a limited degree of market competition due to a small number of bidders and market entries barriers. Contracting parties could face barriers such as a lack of management and contract negotiation skills, high participation costs, high project values, project risks and demands on management time [1].

Each public-private partnership is defined by a set of the organizations involved. The dependencies among the partners must be considered thoroughly. Table 1 categorizes the range of players that are typically involved in a service-based PPP project in which clinical services are included.

These organizations all play critical roles in successful PPPs: from ensuring an appropriate legislative framework that allows PPPs to take place, to funding institutions prepared to invest in project companies, experienced advisory capability to assist both public and private sectors navigate these complex transactions, and strong service providers that are able to assume the service obligations and manage the risks associated with them [21].

MAIN INDICATORS OF PUBLIC-PRIVATE PARTNERSHIP'S EFFICIENCY

Traditionally PPPs are measured by a common yardstick called Value for Money (VfM). In some cases, the calculation is called a Public Sector Comparator. Many governments are required to publish VfM calculations (both monetary value and percentages) to justify the value a PPP is delivering compared to traditional government procurement. Calculation procedures of this indicator are presented in table 2.

But, in our opinion, VfM should be one of a set of metrics used for comparing public-private partnership projects. As PPPs expand into improving care delivery and patient outcomes, governments and the private sector must agree upon more complex measurements that address both short-term and long-term goals. Such measures allow governments to target even larger savings and align quality goals. The problem is that the health production function is complex. This makes it difficult to demonstrate quality, or even effectiveness, in health care interventions.

Success factors can be clearly defined in the contracts, but they are often missing from many PPP contracts, and that leads to conflict. Table 3 provides a high-level view of types of performance metrics gathered through PPP projects globally.

Table 2. Value for Money calculation

Estimated cost of the public sector delivering the project	$100 million
Expected cost of private sector delivering the project	$95 million
Difference in cost	$5 million
Value for money	5%

Source: (Health Research Institute, 2010).

Table 3. Examples of used PPP performance metrics

Patient Satisfaction	Organisational / Clinical Performance Workforce	Performance
Pain level after X amount of days following a procedure	Number of admissions, Surgeries	Timely reporting
Waiting times	Provider cancellation of elective care operation for non-clinical reasons	Average of sick days of staff
Evaluation of catering	Patient safety indicators	Ratio of credentialed staff
Evaluation of cleanliness	Infection rates	Diagnostic reporting within one week of test
Evaluation of interaction with staff	Emergency readmission rates	-
-	Wait times	-
-	Provider failure to ensure that "sufficient appointment slots"	-
-	Penalty for wrong-site surgery	-

Source: formed by authors.

However, performance metrics are meaningless without comparables. Wide variation exists in how medicine is practiced and how clinicians, drugs and medical resources are used, even within a single city.

WORLDWIDE EXPERIENCE OF BUILDING PUBLIC-PRIVATE PARTNERSHIPS IN HEALTHCARE SECTOR

Nowadays healthcare sector worldwide is under the pressure of increasing its efficiency and quality. It is seeking for the new ways of its development and new types of funding resources. Thereby, the public-private partnership model becomes in-demand in health care. It gives a lot of opportunities to the healthcare facilities at the different levels. The most important is it helps to build healthcare infrastructure faster, without great public finances losses.

Summarizing all existing world experience in healthcare PPPs, we can highlight next Most common models:

- Franchising;
- Leasing;
- Concessions;
- Build-operate-transfer;
- Branded clinics;
- Contracting out;
- Contracting in;
- Social marketing;
- Donations;
- Social club partnerships;
- Involvement of corporate sector.

The public-private partnership model is highly developed in the UK, USA and Canada. PPPs are particularly important in building healthcare infrastructure facing limited government financial funds. A Harvard Kennedy School Review report counts 48 major PPP infrastructure transactions in the USA between 2005 and 2014 with a worth of $61 billion. Of these, 40 closed – that is more than 80% of the total, with a value of $39 billion. In 2016, the U.K.'s National Audit Office reported a 15-year average of $5.8 billion annually in PPP capital investment. Its economy is about one-sixth the size of the one in the USA [22].

Special attention is paid to health care. Thus, since 2012, spending on health care in the USA has risen to more than 17% of GDP, and it is expected to rise to about 20% by 2020 – reflecting an older population and an increase in requests for treatment, a rise in chronic conditions and expensive tests inspired by certain advances in technology [22].

In accordance with [22], Canada has also a strong record in health care PPPs: between 2003 and 2011, there were more than 50 public-private hospital projects, valued at $12.3 billion. These partnerships enable a community to combine the resources and medical expertise of the public sector with the operational and environmental specialties of the private sector.

Thus, we are of the option of marc Mitchell, professor at the Harvard School of public health, that "public-private partnerships in health care are inevitable". It is because of "constantly rising prices, changing disease patterns and increasing use of sophisticated technology for diagnosis and treatment" [22]. PPP model allows public sector to share the risk of building healthcare infrastructure with private one.

According to PwC estimates, by 2020, infrastructure spending for OECD (Organization for Economic Cooperation and Development) and BRIC (Brazil, Russia, India, and China) will increase to $ 397 billion, among which only 5% for healthcare infrastructure, and the biggest part is non-infrastructure spending.

Countries with the highest spending growth are China (166 %) and India (140%).

The examples of PPP in the global level of health care are:
- Global Alliance for Vaccine and Immunization;
- Global Polio Eradication Initiative;
- European Partnership Project on Tobacco Dependence;
- UNAIDS/Industry Drug Access Initiative;
- Stop TB Initiative;
- Roll Back Malaria;
- so on.

MAIN CHALLENGES OF PUBLIC-PRIVATE PARTNERSHIP IN HEALTH CARE: LESSONS FOR UKRAINE

I. Paying to entice competition: In countries where government provides all or most of clinical services, private partners can be disruptive. And, private partners may avoid markets where government health systems have an inbuilt competitive advantage (such as subsidized pension benefits that cannot be replicated within the private sector). For that reason, government often may have to pay more initially to entice private partners to enter the market in the hope of gaining long-term savings.

Example: When the UK decided to create a PPP for selected surgical procedures, it accepted that it had to pay private organizations more to spark their interest in competing with National Health Service's providers. The idea was that competition would increase productivity and lower costs in the long run. It would also offer patients more choice. The initial strategy was successful as private partners captured about 20% of the market. The UK is now in the process of re-letting the first wave of contracts, estimated at £1.2 billion, and the rates paid will be the same as NHS.

II. Labour costs: When PPP projects include clinical services – or even if they do not – partners must confront workforce costs, which can be between 50% and 75% of health spending. Healthcare is a labour-intensive industry, and in many countries, it is heavily unionized with rigid compensation structures. In some countries, the public sector pays more or offers more benefits than the private sector. In others, the opposite is true (e.g., Ukraine). Labour markets must be addressed by both sides. Labour laws and unions may need to be more malleable to foster the growth of PPPs. To reach a high service quality, medical facilities need to attract the best physicians and academics and PPP can support this by offering a more attractive working environment while minimizing the risk of brain drain.

Example: In Austria, 75% of hospital costs are in labour and nearly every hospital is owned by the government. Employees are civil servants who have a job for life, making PPPs difficult to implement, beyond the basic infrastructure model. The government opened a window of opportunity, however, with one PPP project, the Psychosomatic Centre in Eggenburg, because those services are outside the government healthcare plan.

III. Transparency: PPP players need to clearly articulate their motives and the benefits they can deliver. Strong partnerships require keeping both sides honest. Independent monitoring also helps keep the partnerships sustainable. The oversight function is critical for PPPs, especially in low-income countries. In the higher income countries, it's less of a stretch for the public sector to hold up its end of the partnership. That's not trivial, even when it's just a building. But, when you get to a 20-year agreement to provide clinical services, the government has to be able to provide competent oversight of performance against very specific benchmarks over a long period of time. These functions are a challenge for all governments at all income levels. But, it's even more of a challenge for low- and middle-income governments, where the capacity is sometimes fragile.

Example: In Australia, the Australian Council of Healthcare Standards publishes quality standards for all hospitals, allowing the public to review the performance of public, private and PPP facilities.

IV. Technology: Today's world is one of robotic surgery, point-of-care diagnostics, and telehealth. Technology is moving so quickly that it can be difficult to forecast costs and demand. In service-based PPPs, private partners are required to provide the consistent levels of technology throughout the life of the contract. Benchmarking against a group of peer hospitals is one way of measuring and ensuring that consistency. The latest technology is a major cost driver, but one that both patients and physicians demand in PPPs that include the provision of clinical services. Under the PPP scope, long-term partnerships will drive a more efficient use of resources, including optimizing technology deployment, clinical training to end users, a wider use of professional services, all of which will aim to provide better quality of healthcare for the patients.

Example: Tongji University of Shanghai, Siemens Project Ventures and the German private hospital chain Asklepios have signed a PPP contract to construct a 250-bed hospital at a cost of more than €100 million. Once the license is approved, the hospital is expected to open within two years [21].

CONCLUSIONS

In view of foregoing, we can make a conclusion that private-public partnership can combine the strengths of private organizations, such as innovation, technical knowledge and skills, managerial efficiency and entrepreneurial spirit, and the role of public organizations, including social responsibility and justice, public accountability and local knowledge, to create an enabling environment for delivering high quality healthcare infrastructure and services for the society. Through this partnership public and private sectors can realize benefits such as

creation of jobs, educational development, incentives for innovation and competition, and health infrastructure development.

Nowadays, in the modern Ukrainian realities public-private partnership is an efficient alternative to the traditional system – public provision, including outsourcing, performance agreements and management contracts, and privatization, including build-own-operate, divestiture by license, sale and private supply. Ukraine just needs to have a will to implement such worldwide experience and to follow the rules for building successful PPPs.

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PRACA POGLĄDOWA
REVIEW ARTICLE

MEDICAL NEGLIGENCE SUBJECT TO CRIMINAL LAW

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ABSTRACT

Introduction: Legal liability for medical negligence should contribute to the protection of patients' rights to life and health. At the same time, unreasonably strict sanctions against physicians should be analyzed much closely. More balanced model of such liability requires serious in-depth research.

The aim of the article is to stimulate discussion about the necessity to improve the criminal legislation and judicial practice of criminal liability execution.

Materials and methods: This study is based on the analysis of international law, WHO documents, jurdicial practice and statistics, criminal and medical law legal doctrine (29 laws and papers, 97 court judgments were analyzed). Dialectical, comparative, analytic, synthetic and system analysis research methods were used, also for interpretation purposes.

Conclusions: An effective legal mechanism should ensure the timeliness and thoroughness of the investigation and prosecution of each case of medical negligence to prevent the recurrence of such consequences in the future. Legal liability (civil, disciplinary or criminal) for medical negligence is a necessary part of this mechanism. The inevitability of criminal punishment rather than its severity should be recognized as a core for the medical negligence prevention concept. That's why the long-term imprisonment for medical negligence as a form of punishment should be recognized as socially unreasonable, it cannot improve the protection of patients' life and health but leads to significant negative social complications instead.

KEY WORDS: medical negligence, medical mistake, patient rights, legal liability, criminal punishment

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INTRODUCTION

The criminal liability of medical practitioners for improper performance of professional duties, which entailed serious consequences for the patient, causes serious discussion among physicians and lawyers. Medical practice refers to activities that are constantly associated with the risk of harm to life and health of the patient. The physician conducting treatment intervenes in the functioning of organs and tissues of the human body, affects the activity of body systems (nervous, circulatory, reproductive, etc.). In many cases, saving the patient's life requires the physician to make a decision with some level of profession risk. If such a risk is justified, then in the event of adverse consequences, these circumstances exempt person from criminal liability.

It should be noted that the expectations of the patient and his relatives do not always coincide with the real possibilities of treatment. Very often such expectations are overstated. Undoubtedly, modern medicine is capable of solving many complex tasks of saving lives and restoring the health of patients. However, the complexity and in many cases stochasticity, unpredictability, or low predictability of pathological processes of the human body cause a high level of risk of medical activity. At the same time, as medical research shows, in many cases, the death of a patient or causing significant harm to his health is the result of medical mistakes. So, according to a study by researchers at Johns Hopkins University School of Medicine which was published on 03 May 2016 at BMJ that medical mistakes should rank as the third leading cause of death in the U.S., after heart disease and cancer? The authors of this research, prof. Martin Makary and research fellow Michael Daniel based on an analysis of prior research, estimate that more than 250,000 Americans die each year from medical mistakes [1]. As stated by World Health Organization (WHO), 2017, making health care safer, it is commonly reported that around 1 of 10 hospitalized patients experience harm, with at least 50% preventability [2].

Another factor that significantly affects the situation with holding physicians liable for their medical mistakes is a sharp increase in the number of lawsuits filed by patients against physicians and medical facilities in democratic countries. So, according to Christian Nordqvist, in the United States, there are between 15,000 and 19,000 medical malpractice suits against doctors every year [3]. Polish researchers reported that the number of such cases from the beginning of the 1990s to 2016 has six times increased, but only about 20% of cases revealed deviations made by doctors in the performance of their duties [4]. Researchers from Germany also noted a significant increase in such requirements and, as a result, an increase in the cost of insurance and legal services in the health sector [5].

Thus, the complexity and ambiguity of approaches to the legal assessment of medical negligence, as well as the choice of legal sanctions that the state establishes and applies for this offense, indicates that the scientific research of medical negligent subject to criminal law is timely and necessary.

THE AIM

The purpose of the article is to raise awareness and stimulate discussion about the necessity of criminal legislation and judicial practice improving in medical negligence sphere.

MATERIALS AND METHODS

This study was conducted in 2019 and is based on the International Covenant on Economic, Social and Cultural Rights, The European Social Charter, The Oviedo Convention on Human Rights and Biomedicine, European Convention for the Protection of Human Rights and Fundamental Freedoms, case law of European Court of Human Rights (ECHR), documents of WHO, criminal and medical legislation of countries such as Germany, Ukraine, Poland, Latvia, the Ukrainian General Prosecutor's Office and Supreme Court data on the criminal liability of those who committed crimes in the field of medical safety, legal doctrine in the field of criminal and medical law. Totally 29 laws and papers, 97 court judgments were analyzed.

Dialectical, comparative, analytic, synthetic and system analyses research methods were used, also for interpretation purposes.

REVIEW AND DISCUSSION

The International Covenant on Economic, Social and Cultural Rights (art. 12, p. 1) provides that the States Parties to the present Covenant recognize the right of everyone to the enjoyment of the highest attainable standard of physical and mental health [6]. The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology, which was ratified by twenty-nine of the Council of Europe member States, provides that: parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality (art. 3); any intervention in the health field, including research, must be carried out in accordance with relevant professional obligations and standards (art. 4); the person who has suffered undue damage resulting from an intervention is entitled to fair compensation according to the conditions and procedures prescribed by law (art. 24); parties shall provide for appropriate sanctions to be applied in the event of infringement of the provisions contained in this Convention (art. 25) [7].

Article 2 of The European Convention on Human Rights says that everyone's right to life shall be protected by law [8]. The ECHR has interpreted this sentence, which ranks as one of the most fundamental provisions in the Convention and also enshrines one of the basic values of the democratic societies making up the Council of Europe, requires the State not only to refrain from the "intentional" taking of life, but also to take appropriate steps to safeguard the lives of those within its jurisdiction (see: cases of Mccann and Others v. the United Kingdom § 147 [9], Lopes De Sousa Fernandes v. Portugal, § 164 [10], Calvelli and Ciglio v. Italy, § 48 [11], and Vo v. France, § 88 [12], Byrzykowski v. Poland, § 104 [13]).

So, in the case of Byrzykowski v. Poland, it was established that on 11 July 1999 the applicant's 27-year-old wife was about to give birth to their child. She was admitted to a hospital of the Wroclaw Medical Academy at 8 p.m. As there was no progress in the delivery and the child showed signs of heart distress, on 12 July 1999 at 10 a.m. a decision was taken to perform a caesarean section. Epidural anesthesia was administered, as a result of which she falls into a coma. All resuscitation efforts failed. The applicant's wife was subsequently transported to the intensive therapy unit, where she died on 31 July 1999. A child H. was born by a caesarean section, suffering from serious health problems, mostly of a neurological character. He requires permanent medical attention. Despite the fact that criminal, disciplinary and civil proceedings, after almost seven years no final decision in any of these proceedings has been given. In these circumstances, the Court concludes that there has accordingly been a procedural violation of Article 2 of the European Convention for the Protection of Human Rights and Fundamental Freedoms. It was awarded the applicant EUR 20,000 as a compensation of non-pecuniary damage and EUR 2,000 for the costs and expenses incurred before the domestic courts and before the Court, EUR 850 paid to the applicant as compensation of legal aid, plus any tax that may be chargeable on that amount [13].

The ECHR considers that the positive obligations require States to make regulations compelling hospitals, whether public or private, to adopt appropriate measures for the protection of their patients' lives. They also require an effective independent judicial system to be set up so that the cause of death of patients, whether in the public or the private sector, can be determined and those responsible medical professionals made liable (see: cases of Byrzykowski v. Poland, § 104 [13], Lopes De Sousa Fernandes v. Portugal, § 166 [10]). However, this provision cannot and should not be understood as the need in each case to establish strict measures of criminal liability for medical negligence. In this regard, the court emphasizes that: «if the infringement of the right to life or to personal integrity is not caused intentionally, the positive obligation imposed by Article 2 to set up an effective judicial system does not necessarily require the provision of a criminal-law remedy in every case. In the specific sphere of medical negligence the obligation may for instance also be satisfied if the legal system affords victims a remedy in the civil courts, either alone or in conjunction with a remedy in the criminal courts, enabling any liability of the doctors concerned to be established and any appropriate civil redress, such as an order for damages and for the publication of the decision, to be obtained. Disciplinary measures may also be envisaged." (The case of Byrzykowski v. Poland, § 105 [13]).

Particular attention should be paid to the conclusions of the court in the case of Byrzykowski v. Poland, § 117 that, apart from the concern for the respect of the rights inherent in Article 2 of the Convention in each individual case, more general considerations also call for a prompt

Table 1. Criminal punishment for medical negligence under the criminal laws of Germany, Latvia, Poland and Ukraine

Consequences of medical negligence	Criminal punishment			
	The Criminal Code of Germany [14]	**Act of 6 June 1997, Penal Code, The Republic of Poland [15]**	**The Criminal Law of The Republic of Latvia [16]**	**The Criminal Code of Ukraine [17]**
The moderate (medium gravity bodily) injury of the victim	Imprisonment* not exceeding three years or a fine (Sec. 229)	a fine, the penalty of imprisonment or the penalty of deprivation of liberty for up to one year (Art. 157 § 3)	imprisonment for a term up to one year or temporary imprisonment, or community service, or a fine (Sec. 138 p. 1)	deprivation of the right to occupy certain positions or engage in certain activities for a term up to five years, or correctional labor for a term up to two years, or restraint of liberty for a term up to two years, or imprisonment for the same term (Art. 140 p. 1)
The moderate (medium gravity bodily) injury to a minor	imprisonment not exceeding three years or a fine (Sec. 229)	a fine, the penalty of imprisonment or the penalty of deprivation of liberty for up to one year (Art. 157 § 3)	imprisonment for a term up to one year or temporary imprisonment, or community service, or a fine (Sec. 138 p. 1)	restraint of liberty for a term up to five years, or imprisonment for a term up to three years, with deprivation of the right to occupy certain positions or engage in certain activities for a term up to three years (Art. 140 p. 2)
Serious (grievous) bodily injury of the victim	imprisonment not exceeding three years or a fine (Sec. 229)	imprisonment for up to 3 years (Art. 156 § 2)	imprisonment for a term up to one year or temporary imprisonment, or community service, or a fine (Sec. 138 p. 1)	deprivation of the right to occupy certain positions or engage in certain activities for a term up to five years, or correctional labor for a term up to two years, or restraint of liberty for a term up to two years, or imprisonment for the same term (Art. 140 p. 1)
Serious (grievous) bodily injury to a minor	imprisonment not exceeding three years or a fine (Sec. 229)	imprisonment for up to 3 years (Art. 156 § 2	imprisonment for a term up to one year or temporary imprisonment, or community service, or a fine (Sec. 138 p. 1)	restraint of liberty for a term up to five years, or imprisonment for a term up to three years, with deprivation of the right to occupy certain positions or engage in certain activities for a term up to three years (Art. 140 p. 2)
The death of the victim	imprisonment not exceeding five years or a fine (Sec. 222)	imprisonment for a term of between 3 months and 5 years (Art. 155)	imprisonment for a term up to five years or temporary imprisonment, or community service, or a fine (Sec. 138 p. 2)	deprivation of the right to occupy certain positions or engage in certain activities for a term up to five years, or correctional labor for a term up to two years, or restraint of liberty for a term up to two years, or imprisonment for the same term (Art. 140 p. 1)
The death to a minor	imprisonment not exceeding five years or a fine (Sec. 222)	imprisonment for a term of between 3 months and 5 years (Art. 155)	imprisonment for a term up to five years or temporary imprisonment, or community service, or a fine (Sec. 138 p. 2)	restraint of liberty for a term up to five years, or imprisonment for a term up to three years, with deprivation of the right to occupy certain positions or engage in certain activities for a term up to three years (Art. 140 p. 2)

* Given the differences in terminology used in criminal laws, the term "imprisonment" is used with the same meaning as the term "deprivation of liberty".

examination of cases concerning death in a hospital setting. This is because the knowledge of facts and possible errors committed in the course of medical care should be established promptly in order to be disseminated to the medical staff of the institution concerned so as to prevent the repetition of similar errors and thereby contribute to the safety of users of all health services.[13]

Summarizing the analysis of international law, as well as the practice of the ECHR, it should be concluded that it is the duty of States to establish an effective legal mechanism to investigate each case of medical negligence, which has led to serious consequences. The purpose of such an investigation is, first and foremost, to protect the human right to life by reducing the number of cases of medical negligence. The legal liability of health professionals is a necessary part of such a mechanism, but the ECHR has indicated that such liability does not necessarily have to be only criminal, but may be civil or disciplinary. Priority in addressing these issues should not be given to the severity of legal sanctions, but to the timeliness and thoroughness of the investigation and prosecution of each case of medical negligence, in order to prevent the recurrence of such consequences in the future.

An analysis of the legislation of Germany, Latvia, Poland and Ukraine has shown that in all of these States medical

negligence, which has resulted in the death of a patient or serious harm to his or her health, is considered a crime committed through negligence. At the same time, there are two approaches to establishing criminal liability for this crime. In Germany and Poland, for example, criminal law does not provide for special rules establishing liability for medical negligence, and the general rules on negligent homicide or serious injury to health by negligence apply to such cases. Another approach takes place in Latvia and Ukraine, where the criminal codes have a special provision that provides for liability for the improper performance of duties by medical personnel. There are also significant differences in the types and limits of punishment provided for in the criminal legislation of these countries for medical negligence (Table 1).

An analysis of the data presented in Table 1 shows that in those States where medical negligence is criminalized in a separate article of the criminal law (Latvia, Ukraine), the punishment for this crime is less severe. This is due to the fact that the legislator takes into account that medical activity is associated with a high risk of harm to the patient as a result of medical mistake. At the same time, in States where the criminal law does not distinguish medical negligence as a separate article and liability for this crime is incurred according to the norms providing for liability for causing death or bodily injury through negligence (Germany, Poland), sanctions are stricter because they do not take into account the specifics of such crimes committed by medical professionals.

An analysis of the judicial practice of Ukraine in cases of medical negligence (Article 140 of The Criminal Code of Ukraine (CCU) "Improper performance of professional duty by a member of a medical or pharmaceutical profession") showed that the courts, as a rule, do not apply criminal punishment in the form of imprisonment. Physicians and other medical professionals were either sentenced to other types of punishment or were released from punishment or from serving it.

Thus, the study analyzed 75 court decisions included in the Unified State Register of Court Decisions of Ukraine for the period from 2007 to June 2019, according to which 80 medical workers were charged with medical negligence under Article 140 of the CCU, including 78 doctors and 2 nurses; 13 medical workers (16%) were found innocent and acquitted, 67 (84%) - guilty. 19 (28 %) persons have been sentenced to actual punishment, including 4 to imprisonment, 6 to restriction of liberty, 1 to correctional labor, 7 to deprivation of the right to engage in medical activities and 1 to a fine. 48 (72 %) were exempt from execution of their sentences, including 15 on probation, 16 on amnesty and 17 due to limitation period. Of the 67 persons convicted of medical negligence, only 4 (6 %) were sentenced to imprisonment for a period not exceeding 2 years and 6 months, while the remaining 63 (96 %) were sentenced to other penalties or released from serving their sentences.

Other researchers also point out that in Ukraine there is a steady tendency to impose punishments that are not related to imprisonment or release from serving a sentence for medical negligence. So, Valentyn Franchuk, Svitlana Trach Rosolovska, Petro Selskyy et al in the article *Analysis of Final Judgements in Cases of Medical Negligence Occurred in Ukraine* indicate that imprisonment for these crimes for a period of 1 to 2 years was assigned only in 5,9% [18]. The same tendency is confirmed by Alesia Gornostay, Alona Ivantsova and Tetiana Mykhailichenko in the article *Medical Error and Liability for it in some Post-Soviet Countries (Belarus, Kazakhstan, Moldova, Ukraine).* In their opinion, such a loyal attitude of judges to physicians who commit medical negligence takes place not only in Ukraine, but also in post-Soviet countries such as Belarus, Kazakhstan and Moldova [19]

Thus, the judicial practice of Ukraine follows the path of imposing a medical negligence penalty in the form of imprisonment only in extreme, exceptional cases, mainly limiting it to milder measures of influence or even freeing such persons from serving their sentences.

Although there is a strong tendency in European countries that medical negligence is rarely punished by imprisonment, Polish criminal law is being proposed to be amended to radically change the criminal penalty for this crime. As was already mentioned, in Poland The Penal Code does not contain a separate article on liability for medical negligence resulting in serious consequences, and in such cases the rule on causing unintentional death (Art. 155) or serious injury to health (Art. 156, § 2 and 157, § 3) applies.

Given that the sanction of Article 155 of the Penal Code of Poland establishes a sentence of imprisonment of 3 months to 5 years, this allows the court to impose a milder sentence than imprisonment for medical negligence, which led to the death of the patient. Thus, Article 37a states that if the law provides for a punishment of imprisonment of no more than 8 years, a fine or restriction of liberty may be applied instead. Under Article 66 the court may conditionally discontinue the criminal proceedings, but this shall not be applied to the perpetrator of an offence for which the statutory penalty exceeds 5 years of imprisonment [15].

On June 13, 2019, The Sejm of the Republic of Poland adopted a draft law amending the Penal Code and some other laws, which provides for extensive reform of the criminal law [20]. One of the proposed changes is a significant increase in sanctions for causing unintentional death. So, according to § 1 of Art. 155 for this crime it is proposed to establish a punishment from one year to 10 years of imprisonment, and if death is caused to more than one person (§ 2 of Art. 155) - from 2 to 15 years of imprisonment. This document, which in the opinion of leading Polish scientists contains numerous technical and legal defects [21], has not yet been signed by the President of Poland and therefore has not entered into force.

Obviously, in the event of these amendments to Article 155 of the Polish Penal Code, the only possible punishment for medical negligence resulting in death of a patient will be imprisonment. The application of a milder punishment (fine or restriction of liberty) in accordance with Art. 37a, as well as probation on the basis of Art. 66 will become impossible.

These novelties in Poland are actively discussed and critically evaluated by many specialists in both medicine and law. Referring to representatives of the medical community, the changes in the Penal Code contain threats to physicians, who may be subjected to extremely severe criminal punishments for negligent offences in the performance of their professional duties, if this has led to the death of a patient. Pessimistically predicting the consequences of such innovations, Polish physicians first of all note that such actions of the state can push medical stuff to massively refuse to perform their duties in situations where there is a risk of patient's death. Accordingly, this will significantly reduce the quality and efficiency of medical care provided to the population of the country and will have a negative impact on the right to health care in Poland. Experts point to another potential problem that may also have a negative impact on Polish health care: the strengthening of labor migration processes of Polish physicians to countries where the legislation is less rigid (or more balanced) in terms of criminal liability for adverse effects of treatment [22].

It should be noted that attempts to solve complex social problems by increasing the severity of punishments for offences are quite common. However, scientific research shows that such a way is counterproductive, as it leads to the emergence of new negative social phenomena, the overcoming of which requires significant material and non-material costs. The effectiveness of criminal law influence is not increased by toughening punishments, but by increasing its inevitability. Thus, as early as 1764 the outstanding Italian lawyer and economist Cesare Bonesana di Beccaria in "An Essay on Crimes and Punishments" wrote: "The certainty of a small punishment will make a stronger impression, than the fear of one more severe, if attended with the hopes of escaping; for it is the nature of mankind to be terrified at the approach of the smallest inevitable evil, whilst hope, the best gift of Heaven, hath the power of dispelling the apprehension of a greater; especially if supported by examples of impunity, which weakness or avarice too frequently afforded." [23, p. 94, 95]. Nobel Laureate-economist Gary S. Becker in his work "Crime and Punishment: The Economic Approach" on the basis of his mathematical calculations, concludes that in counteracting crime, "optimal" decisions are interpreted to mean decisions that minimize the social loss in income from offenses. The author wrote that if there is not a high level of probability of criminal prosecution, then increasing the severity of punishments will not lead to the desired result, but at the same time significantly increase public spendings on combating crime [24, p. 207-209]. A theory of the limits of the penal sanction defends prof. Douglas Husak in his study "Overcriminalization. The limits of the Criminal Law." [25].

One of the authors of this article, Prof. N. Gutorova, justifies in her researches that the purpose of criminal law regulation is, first of all, to prevent the commission of new crimes by applying such measures of influence, which cause minimal damage to society. [26] The legislator should be guided by this when establishing sanctions for crimes, especially when it comes to crimes in the field of professional and official activity. It should be taken into account both the specifics of the perpetrators of such crimes, as well as the specifics of the crimes themselves [27].

The above suggests that the criminal punishment in the form of long-term imprisonment for medical negligence cannot objectively lead to a reduction in the number of such crimes, and, accordingly, improvement of the protection of patients life and health, but will have a negative impact on the health care system as a whole, as well as on the activities of individual physicians.

CONCLUSIONS

1. Medical negligence is a very common negative social phenomenon in the world. In order to protect the human right to life states are obliged to establish an effective legal mechanism to investigate each case of medical negligence, which has led to serious consequences. Such a mechanism should, first of all, ensure the timeliness and thoroughness of the investigation and prosecution of each case of medical negligence, in order to prevent the recurrence of such consequences in the future. Legal liability for medical negligence is a necessary part of this mechanism, but it should not be only criminal, but also civil or disciplinary.
2. The criminal laws of Germany, Latvia, Poland and Ukraine establish that medical negligence, which led to the death of a patient or causing serious harm to his or her health, entails criminal liability for a negligent crime. There are two ways to establish such liability: 1) by formulating a separate norm in the criminal law (Latvia, Ukraine); 2) by applying the rules on liability for the negligent homicide or serious injury to health by negligence (Germany, Poland). In the criminal laws of states where there is a separate rule on medical negligence, sanctions for this crime are milder.
3. An analysis of the judicial practice of Ukraine in cases of medical negligence for the period from 2007 to July 2019 showed that in most cases (96%) the sentence of imprisonment was not applied, or medical professionals were released from serving the sentence.
4. The inevitability of criminal punishment rather than its severity should be recognized as a core for the medical negligence prevention concept. That's why the long-term imprisonment for medical negligence as a form of punishment should be recognized as socially unreasonable, it cannot improve the protection of patients' life and health but leads to significant negative social complications instead.

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PRACA POGLĄDOWA
REVIEW ARTICLE

INFORMATIONAL AND PSYCHOLOGICAL TECHNOLOGIES DEVELOPMENT OF EDUCATIONAL COMPETENCIES IN MEDICAL E-EDUCATION

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ABSTRACT

Introduction: The article analyses systematized ideas on e-education as informational-psychological technology of educational competencies development applied to medical education. In the widest sense, e-education is interpreted as use of internet for learning. Such aspects of this informational-psychological technology, as virtual educational environment and subjects of educational process (e-student, educational technologist, librarian, teacher) are examined in the article.

The aim. On the basis of the above information, one can formulate the purpose of the article, which is to present systematized representations of e-learning as an informational and psychological technology for the development of educational competencies in the process of postgraduate medical education.

Materials and methods: In the work is used a range of methods: content analysis, bibliosemantic, systematic approach, analysis of products of activity.

Review: Features of e-education are explored as an adaptive educational technology in the process of medical education and retraining. Target-orientation is emphasized as key important principle of effective informational-psychological technology of educational competencies development. Virtual educational environment is researched as the computer-integrated e-learning, which typically includes wide set of various tools for effective delivery of e-educational content to the audience, which improves co-operation and management. The article proves that structural and contentual dimensions of e-teaching make fundamental influence on what can or can't take place within e-educational process and even on how teachers and students build their own knowledge within e-courses, build that they what do (not) know, and the process of this construction. It is mentioned that the role of content within the e-educational environment can acquire many various forms, including educational materials, reference sources, as well as any practice-related materials, like scientific articles or clinical protocols and instructions. Some most typical functions, instruments and services, usually available in a virtual educational environment, are described in the article.

Conclusion is made about considerable potential of e-education as an effective informational-psychological technology of educational process in medical education.

KEY WORDS: e-education, informational-psychological technologies, medical education, learning competencies, development

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INTRODUCTION

For centuries, various technologies (books, pens, paper, cinema, radio or television) have been used as additions and improve the learning process. In most cases, these technologies were not originally created as educational, but in time they were successfully borrowed by teachers who did not refuse to take good chance to improve their teaching skills. Computers and the Internet are one of the newest technologies used in education, and it is thanks to this novelty is technology has become known as e-learning.

The introduction of new technologies also generates new social tensions, and e-learning has not become an exception here. Some people want to use new technology simply to deal with existing activities more effectively or faster, while others are trying to master new ways of thinking and new approaches that are available with the appearance of e-learning. At the same time, the main focus is learning rather than technology itself, is the main goal of the educational process among medical workers (as a consequence of healthcare, the best results for patients). It should be taking into consideration in mind that it is not always possible to accurately predict the results of the application of new technology in the learning process.

Intuition often adds motivation for both sides of the learning process – for teachers how to teach and for students how to study. The use of technologies to support learning is not always essential set of tools. It is more appropriate to apply creativity and adaptability to fast changing information flow, which includes changes in training and retraining of specialists in the medical sector.

In the broadest sense, e-learning is the use of the Internet for learning. However, such a laconic definition isn't fully embrace all details and important aspects of e-learning. Although the content and methods of teaching the material are also important, e-learning (also often referred to as online learning) is not a simple file-sharing document in an online format for a group of listeners through the Internet. E-learning necessarily includes a pedagogical approach from the teacher, which implies its flexibility, activity and student-orientation; communication and especially interaction between

teachers and students are encouraged through means of asynchronous computer-mediated communication [1].

Any e-learning discipline can be conducted exclusively online or combine online communication with face-to-face communication (the combination of these two types is commonly referred to as mixed e-learning) [2]. Online subject can be organized in such a way as to completely exclude the interaction of the listener with another person (except for the examiner). The course can be personalized, where materials and teaching methods are adjusted to the needs, demands and rhythm of training a small group of listeners (up to one single listener) [3]. Students can be at a considerable distance from the teacher or use computer classes at their university / academy, work with educational materials from their home or open public space.

Thus, it is obvious that our initial definition gives some explanation of the phenomenon of e-learning, but there is a lack of full understanding of the whole complexity of ways and methods of the new technology with older, more traditional approaches.

It should be noted that the concept of e-learning is often used by people who are not directly involved in online studding and / or teaching and they can use it in the wrong way, which can bring together a variety of approaches, practices and techniques, many of which are not relevant computer-mediated learning. Therefore, it is critically important to clearly outline the concept of e-learning and distinguish it from many other, sometimes related, roles, identities, goals, and activities [4].

THE AIM

On the basis of the above information, one can formulate the purpose of the article, which is to present systematized representations of e-learning as an informational and psychological technology for the development of educational competencies in the process of postgraduate medical education.

MATERIALS AND METHODS

In the work is used a range of methods: content analysis, bibliosemantic, systematic approach, analysis of products of activity.

REVIEW AND DISCUSSION

Let's start with an e-student - the main figure of the entire e-learning process. An e-learner is any person who obtains some learning activities online. What is often united in the concept of e-learning does not always fully and completely cover the whole set of student learning choices, but rather concerns a certain set of educational material and planned training activities prepared by a teacher in advance by or an educational institution. Real e-learning is something that the listener is dealing with, and it often happens outside of the teacher's sight and even beyond its reach in general. If we really are interested in understanding the concept of e-learning then it should be takin g into consideration that it is the listener in the learning process who really wants and does, and that only a small proportion of these desires and lessons will coincide with the materials and activities previously selected as educational. If necessary, this will include using Google, Wikipedia or the Google Academy to search for materials, research, or just general queries; instant messengers and / or Skype for communicating with colleagues in training or other listeners, and blogs or social networks like Facebook to create and create informal collections of materials, which were found or created in the process of learning or training (something like e-portfolio).

An e-listener is more independent compared to a traditional student, still uses materials and techniques that are created and chosen by teachers or (independently) by individual students or groups of students.

The existence of e-learning as a concept in general, however, depends critically on a separate set of activities and practices that form "e-Teaching." The structure and content of e-teaching has a fundamental impact on what may or may not occur within the educational process and even on how teachers and students build their own knowledge about what they (do not) know and exactly how it is happening. To a certain extent, this link between e-learning and e-teaching has been described in the Snider's concept of "hidden curriculum" [5]. Considering e-teaching, one can more clearly see its dependence on the role of the teacher and the curriculum as a whole, since e-teaching requires highly qualified and motivated teachers.

The roles of the student, the teacher and the educational institution in the process of e-learning vary both among themselves and from the same role in the traditional face-to-face co-presence paradigm. Understanding these updated roles is critical for the successful implementation of e-learning at any institution.

Additional difficulty of e-teaching is that the novelty of this methodology does not provide educational institutions with certainty as how to support and motivate e-teachers at the level of traditional teachers. For example, efficiency factors such as working hours, academic rankings and titles, or positions within an institution are the only line of traditional teaching against e-teaching, evaluating the apparent formal merits of the first and, vice versa, neglecting and leaving the most invisible majority of the achievements of the latter.

It is possible not only to point out e-learning and e-teaching as a couple of different (though rather close to each other) concepts, but also to isolate such relatively autonomous parts of the educational online matrix:

1) E-logistics and e-management. Many e-learning applications actually strengthen the managerial and logistical direction of the learning environment rather than improve the cognitive development of the student's learning material. This is especially noticeable in medicine, where managing placement and transfer of students, compilation of schedules, preparation and processing of exam results, signing up in the training groups, tracking the training material and the filling of the training groups, as well as many other aspects of planning and non-academic communication with students.

Outside the educational process and educational institution as such - are, however, essential prerequisites for student training. Broadly speaking, there are many institutions where the education system can and must be connected to independent centers for managing human, time and material resources.

2) E-community as an embodiment of a deeply rooted human desire to cooperate, share and inspire in diverse, collaboratively distributed activities. The so-called "Revolution Web 2.0" has captured many unexpectedly how much others are involved in creating content (Wikipedia, personal or group blogs), file sharing (video services such as YouTube) and Internet communication (Facebook and asynchronous instant messengers). Although participation in the medical community is an important part of any student's socialization process, it may be quite controversial that how online engagement is learning by itself. However, it should be taken into account that the level of the students' comprehension in the process of learning is not only a formally learned material for the examinations but also that which has been internalized and further developed in the role models of these students in society. There is no doubt that a wide-ranging, controversial discussion of this issue will continue as the e-community develops as one of the key, nongovernmental concepts of e-learning and e-training.

The new multimedia environment includes not only e-students and e-tutors, but also many e-managers and e-support staff. The role of an educational technologist and e-librarian should also be mentioned separately.

Educational technologist is a specialist, whose presence in medical education is a direct consequence of the transition to computer-mediated learning and teaching. Technologists usually work as mediators, facilitators, developers and debuggers of all hardware in the learning environment, in particular their professional responsibility and competencies combine both technical areas (programming) and creative (animation) and educational development (writing manuals or instructions). One of the most important roles played by them is to smooth the contradictions between what teachers want and what is technically realizable, including the possibility of introducing or not implementing a specific technology.

The recent revival of the e-librarian as an updated form of the ancient traditional profession fully reflects the numerous changes in the roles and even identities of information professionals in the modern world, which in turn led to a rethinking of the traditional role and place of a librarian in a higher education institution. Typically, these e-librarians are expanding traditional forms of engagement with key topics of the learning process through evidence-based practice, literature, verification and selection of information, which in turn effectively helps both students and teachers in dealing with online resources, including electronic versions of journals and databases. An e-librarian maintains a balance between a traditional physical library and its online counterpart.

The significance and importance of the concept of e-learning can be grasped more deeply through consideration through the binary opposite of "process or phenomenon", namely, whether the focus should be on digital content or on a computer-mediated learning process [6]. The importance of these different points of view is understandable: within a particular curriculum or program, the first is access to educational materials (content), then even the structure of the curriculum may reflect such a principled idea by focusing on access to certain materials, attributed or accessible a certain teacher (a group of teachers). Creating and sharing content is becoming a dominant aspect of such a system, while management of learning processes (discussion in forums or in group chats) acts as a component of less significant importance. On the other hand, if the curriculum or the program - first of all, involvement in various activities, then the focus obviously shifts to the planning, discussion and monitoring of participants' activities, both individually and within the educational subgroups. The creation of content itself occupies in such system not the most important place. While most virtual learning environments can be effectively used for each of the approaches described, local development software (for example, within a single university or a group of universities) shows better involvement in the local academic culture and worldview.

For greater clarity and understanding, we mean "content" as a material used by students in addition to those specified in the curriculum of a discipline; it can be sites, forums, electronic bookshops, etc.

The role of content in the e-learning environment can take many forms, including teaching materials, reference materials, and any materials from the field of practice, such as scientific articles or clinical protocols and instructions.

The materials of the course are probably the most popular kind of content that is associated with e-learning; formed mainly on the basis of teaching aids and lecture slides, these materials have relatively low orienting value (the review of slide by listeners without the possibility of access to the discussed subject often turns the discussion into wholly meaningless), while ensuring structured and sustainable access to information in the training course or discipline [7].

Another key source of educational content at an educational institution is its library. Rapidly changing for the flexible challenges of the digital reality the modern medical e-library usually provides access to content in the form of electronic versions of books (such as reference books, textbooks), magazines, collections of bibliographic data (for example, PubMed) and science-based databases (Scopus, Web of Science). Interestingly, even traditional publications on paper (for example, textbooks) are being now issued along with electronic versions or multimedia content applications (images, animations).

In the end, the Internet as a whole is a huge potential source of content for e-learning. The World Wide Web has many sites that are directly or indirectly useful and suitable for e-learning purposes, although they do not always and with not due regard refers to the enforcement of intellectual property rights (IPR) and the authenticity of published materials. The power of search engines such as Google or Google-based Academy makes searching such content rel-

atively simple and understandable. It is important, however, to remember that search algorithms are usually targeted to content with the most numbers of views, rather than to quality, but it can be not popular - which greatly affects the search strategies of students [8]. In recent years, the burst of popularity of online encyclopedias, and Wikipedia, in particular, has transformed openly-available knowledge bases with shared-distributed authorship into a key element of the e-learning curriculum.

The idea of schematization of the curriculum is not completely new, but in the online environment, the use of databases to draw links between the various elements of the curriculum reveals the potential of the technology. For example, the online curriculum can be interactively connected to e-learning content, profiles of other students and teachers in educational institutions or external resources, teaching assignments, etc., also displaying many other subtle and not immediately noticeable connection between the elements of the system. After implementation, this type of integrated scheme provides much better monitoring of the learning activities of individual listeners and entire groups.

While e-learning has a large number of different tools, the most common approach is to use integrated tools and services, known as "Virtual Learning Environments" (VLE), "Learning Management System" (LMS), and "Course Management System" (CMS) [1]. The differences between the specific implementation of these three concepts are rather insignificant, which makes it possible to use them as synonyms.

At the beginning of the introduction of e-learning technologies, such integrated systems required the student to be physically present at a workplace (university computer class), but now the vast majority of them use standard browsers, both on mobile and on stationary devices, anywhere outside the educational institution. Although the main purpose of integrated e-learning platforms is shared, there are a number of differences. Some, such as Blackboard or WebCT, are commercially available, some like Moodle or Sakai, are free software or open source software; and many other platforms are developed specifically for local needs, conditions and queries.

Most integrated platforms provide work with a separate training course or module, requiring students and teachers of the same kind of registration to access the module / course. Participants get access to a variety of tools, content and functionality in their role (teacher or listener). Typically, the system can control the accessibility of educational materials based on a variety of criteria, such as date / time, membership in groups, activity level, task execution, performance, etc.

Below are some of the most typical features, tools and services that are typically available in the VLE. It should be noted, however, that not all of the above will necessarily be available in each specific VLE, the possibilities of which can vary considerably from system to system, and some of these functions may have other names or combine with each other.

1. The main resources, that is, the curriculum or methodological complex, contain general reference information such as teacher contacts, a description of the discipline, requirements for the choice of this discipline, the objectives of the course, the main time frame and the basic list of literature to the course, which includes, in particular, the short (educational manual) or an extended version (textbook) of the content of the discipline. The function of sending short important messages by teachers may also work, although on some systems such announcements or warnings can also be immediately sent to the e-mail and / or mobile number indicated on the profile of the listener.
2. Zones for placement of educational content contain references to materials and presentations to the course, links to other resources (including external, that is, outside of this VLE), audio and video records, etc. - that would be occupied a lot of place in the traditional paper library. By giving teachers the ability to upload content and manage access to it, the content area can be subdivided into subdivisions, each for a specific part or topic of the course, for different teachers or groups or for any other possible sharing of e-learning participants. It also includes areas for student content and electronic versions of written assignments for checking and / or assessment by teachers, incl. with the function of tracking the missed deadline for writing work. Another popular feature is the ability to leave students comments or notes on pages of educational materials.
3. Most systems allow users to search for keyword-based materials. Some systems automatically return the student to the place in the learning process that was during the last session of the VLE when they login in this system. A glossary or online dictionary with expanded explanations is often available. Such auxiliary functionality can be especially useful for students of the first years of study, to whom it may be badly influenced by a large number of confusing terms and concepts.
4. Boards of e-advertisements, also known as e-mail, boards or simply forums, are the key means of asynchronous, computer-mediated communication between participants in the e-learning process. Asynchronous communication in this case means placing one of the participants in the message to which other participants write answers after a certain time, thus forming asynchronously long topics of communication as structural elements of the forum. Usually, in each topic and / or message, the time of the placement is given, which enables readers, if necessary, to trace the chronology of both the mainstream of the discussion and the side branches. Forums can be public, that is, accessible to anyone within an educational institution or even the Internet as a whole, or private, with access only for certain groups of participants. Often, it is useful to provide a separate unit or topic for discussion of issues that concern community members, but are not directly related to the learning process, so that students do not flood the other forums with irrelevant information or simple comments. Many learners prefer forums, which enables to send the new replies to the forum on personal e-mail, which allows you to read, not responding to messages and not going to the VLE; at the same time, an interesting discussion motivates the students to

choose one or another online course or even e-learning as a form of education in general and to maintain active participation throughout the course.

5. Chat channels are used for synchronous communication when listeners are physically separated from each other, but they want a simultaneous discussion. Chat channels can be difficult to manage, but with reasonable use and flexible moderator policies, they can become an effective means of academic discussion [9]. Usually, conversations in the chat channel are recorded (stored) in a text file, which should remind students that their conversations will not be lost forever at the end of the chat session. Some chat channels provide private conversations between individual members; others are equipped with a virtual board for drawings and writings.
6. Blogs usually exist in the form of a personal online diary guided by one person but available for public reading. Each new post is added from the previous posts, and readers can add their own comments to the messages.
7. Online encyclopedias, in particular the famous Wikipedia, consist of a plurality of web pages which are created and filled up immediately in the browser by the shared-distributed activities of the participants. Text formatting is quick and easy, and participants do not require special knowledge, including HTML markup. Participants can edit and rewrite written by others while preserving the history of corrections and, accordingly, the possibility of canceling the changes. In the field of education, online encyclopedias are widely used to teach and develop skills of group writing, including course projects, databases or project documentation. Although some Wikipedia (including Wikipedia itself) are open to editing by any of the participants, most of the specialized educational Wikipedia, including in the field of medical education, provide limited editing opportunities, especially for novice participants.
8. Some systems support online testing and / or examinations using a variety of issues, such as multiple choice, comparison and rankings, with a single word or sentence, etc. Most answers to questions (other than fully open responses) can be automatically evaluated online; this toolkit provides polls and surveys. After completing training tasks, most departments have an appropriate section where teachers put their grades and results of student work (including the transfer of results from non-electronic media).
9. Online Portfolio allows students to create online storage for their work / study materials and records (including external resources links), documents and audio files like podcasts.
10. There are several other additional tools, such as podcasts, news feeds (RSS), personal student cabinet, image database, etc.
11. The last but not the least: such systems provide a range of logistics tools, including scheduling (training calendar, curriculum), placement of learning groups and classes, and other forms of user activity management.

CONCLUSIONS

The Virtual Learning Environments (VLE) offer an integrated learning environment for e-learning, and typically include a wide variety of tools for developing learning competencies, including effective conferencing with the audience, cooperation and management. Although some people consider the very concept of the VLE to be limited, it mostly meets the needs of both e-students and e-teachers. In those areas where the VLE can't effectively meet certain educational needs (in particular, in the teaching of practical medical disciplines), this can be achieved through the implementation of additional programs and services.

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PRACA POGLĄDOWA
REVIEW ARTICLE

EKSPERYMENTY MEDYCZNE W POLSKIM SYSTEMIE OCHRONY ZDROWIA

MEDICAL EXPERIMENTS IN POLISH HEALTH CARE SYSTEM

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WYŻSZA SZKOŁA INFORMATYKI I ZARZĄDZANIA W RZESZOWIE, RZESZÓW, POLSKA

STRESZCZENIE

Rozwój nauk medycznych związany jest z przeprowadzaniem eksperymentów medycznych. Jednakże ciągle wzbudzają one obawy społeczne. Każdego roku w Polsce przeprowadza się eksperymenty medyczne z udziałem człowieka i uczestniczą w nich lekarze. Szczególnym rodzajem eksperymentu medycznego są badania kliniczne. Prawo reguluje zasady wykonywania eksperymentów medycznych. Celem artykułu jest przedstawienie uwarunkowań prawnych prowadzenia eksperymentów medycznych w polskim systemie ochrony zdrowia.

SŁOWA KLUCZOWE: eksperyment medyczny, badanie kliniczne, lekarz, zgoda, prawo

ABSTRACT

The development of medical sciences is associated with conducting medical experiments. However, they raise social concerns. Every year in Poland, medical experiments are carried out with the participation of man and doctors participate in them. Clinical trials are a special type of medical experiment. The law regulates the principles of performing medical experiments. The purpose of the article is to present the legal conditions for conducting medical experiments in the Polish healthcare system.

KEY WORDS: medical experiment, clinical trial, doctor, consent, law

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WSTĘP

Rozwój nauk medycznych związany jest m.in. z przeprowadzaniem eksperymentów medycznych. Każdego roku w Polsce przeprowadza się eksperymenty medyczne z udziałem człowieka. Część z nich to badania kliniczne nowych produktów leczniczych. Według danych przedstawianych przez Prezesa Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych (URPL) w latach 2011–2018 w Polsce zarejestrowano od 400 do 450 badań klinicznych rocznie [1]. Obecnie obserwowany jest znaczny ich wzrost, tylko w pierwszym półroczu 2019 r. liczba zgłoszonych wniosków w sprawie badań klinicznych wzrosła o 40% w porównaniu do 2018 r., do czego przyczyniło się m.in. uproszczenie w Unii Europejskiej procedury rejestracji badań klinicznych. Wśród złożonych w 2018 roku wniosków o rozpoczęcie badań klinicznych największą grupę stanowią wnioski o rozpoczęcie badań prowadzonych w onkologii (aż 29%). Inne dziedziny medycyny to: neurologia (11%), dermatologia (8,5%), gastroenterologia (7%), kardiologia (5%), reumatologia (4%), choroby płuc (5%), diabetologia (3,5%), nefrologia (3%), psychiatria (4%), ginekologia (2%), okulistyka (2%) [2].

Eksperyment (łac. *experimentum*) powszechnie oznacza próbę, doświadczenie. Eksperyment to w świetle *Słownika języka* polskiego pod redakcją Doroszewskiego próba realizacji nowatorskiego pomysłu, doświadczenie naukowe przeprowadzone w celu zbadania jakiegoś zjawiska [3]. W polskim systemie prawnym nie ma ustawowej definicji eksperymentu medycznego. Eksperymentem powszechnie określa się próbę, zwłaszcza przeprowadzaną po raz pierwszy; realizację nowatorskiego pomysłu; doświadczenie; celowe wywołanie jakiegoś zjawiska (lub jego zmiany) w sztucznych, zwykle laboratoryjnych, warunkach w celu zbadania i wyjaśnienia jego przebiegu. Eksperymentem jest tylko czynność, tzw. nowatorska, taka, której dotąd w dziejach nie przeprowadzono lub przeprowadzono tak niewiele razy, że jej wyników nie można uznać za powtarzalne. Mimo braku definicji normatywnej eksperymentem medycznym może być nazwane tylko takie działanie badawcze, które prowadzone jest zgodnie z ogólnie przyjętymi zasadami badań naukowych, w szczególności w ściśle określonych, celowo dobranych, precyzyjnie kontrolowanych i dających się wielokrotnie powtarzać warunkach. Eksperymentem medycznym nie jest zatem niezaplanowane jednorazowe zastosowanie przez lekarza nowatorskiej czy niekonwencjonalnej metody leczenia w celu ratowania życia lub zdrowia pacjenta [4].

Ze względu na zagrożenia i możliwości nadużyć, jakie wiążą się z problematyką eksperymentu medycznego jest

ona przedmiotem regulacji licznych aktów normatywnych prawa międzynarodowego i krajowego zarówno o charakterze prawnym, jak i deontologicznym. Podstawowe regulacje prawa międzynarodowego dotyczące eksperymentów medycznych zawiera Konwencja o Ochronie Praw Człowieka i Godności Istoty Ludzkiej wobec Zastosowań Biologii i Medycyny, a ponadto art. 7 Międzynarodowego Paktu Praw Obywatelskich i Politycznych z 1966 r. (Dz. U. z 1977 r. nr 38;poz. 167). Ogólnie uznanym międzynarodowym standardem są Zasady Dobrej Praktyki Badań Klinicznych (ang. *Good Clinical Practice*), znajdujące swoje odzwierciedlenie na gruncie polskiego prawa w rozporządzeniu Ministra Zdrowia z 2 maja 2012 w sprawie Dobrej Praktyki Klinicznej (Dz. U. z 2012; poz. 489). Do uczestnictwa lekarzy w eksperymentach medycznych odnosi się także Kodeks Etyki Lekarskiej (rozdział II).

Głównym celem niniejszego artykułu jest przedstawienie i analiza uwarunkowań prawnych prowadzenia eksperymentów medycznych w polskim systemie ochrony zdrowia. Celem szczegółowym artykułu jest wskazanie roli lekarza w przeprowadzaniu eksperymentów medycznych.

W niniejszej pracy dokonano przede wszystkim analizy aktualnie obowiązujących norm prawnych dotyczących eksperymentów medycznych, w tym badań klinicznych, w aspekcie zasad wykonywania zawodu lekarza. W pracy zastosowano metodę analityczno-syntetyczną, a także wykorzystano dane statystyczne, w szczególności Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych.

RODZAJE EKSPERYMENTÓW MEDYCZNYCH

Eksperymenty medyczne związane są z wykonywaniem zawodu lekarza i jako takie zostały uregulowane najdokładniej w ustawie o zawodach lekarza i lekarza dentysty z dnia 5 grudnia 1996 r. (t. jedn. Dz.U. 2019; poz.537) art.21 i n. Powyższa ustawa o zawodach lekarza i lekarza dentysty zwana w skrócie u.z.l. nie definiuje pojęcia eksperymentu medycznego, a jedynie określa podział eksperymentów medycznych na dwie ich kategorie tj.:

1. eksperymenty lecznicze (terapeutyczne),
2. eksperymenty badawcze(naukowe).

Należy przyjąć, że powyższa ustawa określa generalne rodzaje eksperymentów medycznych, jakie mogą być prowadzone w Polsce. W świetle art. 21 u.z.l. eksperymentem leczniczym jest wprowadzenie przez lekarza nowych lub tylko częściowo wypróbowanych metod diagnostycznych, leczniczych lub profilaktycznych w celu osiągnięcia bezpośredniej korzyści dla zdrowia osoby leczonej. Może on być przeprowadzony, jeżeli dotychczas stosowane metody medyczne nie są skuteczne lub jeżeli ich skuteczność nie jest wystarczająca. Eksperyment leczniczy ma więc na celu polepszenie zdrowia człowieka i jest często jedyną szansą wyleczenia. Natomiast eksperyment badawczy ma na celu przede wszystkim rozszerzenie wiedzy medycznej. Może być on przeprowadzany zarówno na osobach chorych, jak i zdrowych. Przeprowadzenie eksperymentu badawczego jest dopuszczalne wówczas, gdy uczestnictwo w nim nie jest związane z ryzykiem albo też ryzyko jest niewielkie i nie pozostaje w dysproporcji do możliwych pozytywnych rezultatów takiego eksperymentu. Samo prowadzenie eksperymentu badawczego nie może być utożsamiane z celem *stricte* leczniczym. Zadaniem eksperymentatora nie jest bowiem wyleczenie konkretnego pacjenta. Priorytetem przy eksperymencie badawczym, na co wyraźnie wskazuje jego definicja, jest wyeliminowanie ryzyka dla uczestników eksperymentu lub chociaż doprowadzenie do sytuacji, w której ryzyko jest niewielkie wobec oczekiwanych konsekwencji poznawczych [5]. Ocena stosunku ryzyka do spodziewanych korzyści ma charakter subiektywny i jest sprzężona z osobą eksperymentatora, z jego subiektywną oceną.

Ustawodawca jednoznacznie określa, że celem eksperymentu leczniczego musi być korzyść dla zdrowia osoby leczonej (korzyść lecznicza). Nie można jednakże wykluczyć, że w tym przypadku nie mogła zostać osiągnięta równocześnie korzyść poznawcza. Jednakże przeprowadzenie eksperymentu leczniczego wyłącznie w celach poznawczych jest prawnie niedopuszczalne [6]. Natomiast celem eksperymentu badawczego jest przede wszystkim korzyść poznawcza. Każdy eksperyment związany jest nieodłącznie z ryzykiem. Ryzyko stanowi konieczny element instytucji prawnej eksperymentu także medycznego. Ryzyko jest na ogół postrzegane w kategoriach negatywnych, jako działanie, które wiąże się z pewnym niebezpieczeństwem i może przynieść niekorzystne lub niepożądane skutki [7]. Ryzyko wiąże się z niepewnością w realizacji działań, osiągnięcia zamierzonych celów. W eksperymencie badawczym margines dopuszczalnego ryzyka jest znacznie węższy niż w przypadku eksperymentu leczniczego, którego celem jest korzyść lecznicza dla pacjenta. Eksperyment leczniczy jest podejmowany w interesie pacjenta, dlatego też ocena skali dopuszczalnego ryzyka i jego relacji w stosunku do oczekiwanych korzyści musi być dokonana pod tym kątem. Będzie ona uzależniona od rozmiaru niebezpieczeństwa dla zdrowia, któremu eksperyment będzie przeciwdziałać [8]. Jak słusznie zauważa Sakowski, niezbędne wydaje się być porównanie przewidywanych negatywnych konsekwencji wynikających z rozwoju choroby i przeprowadzenia eksperymentu leczniczego. W oparciu o to należy dokonać oceny, co będzie bardziej „opłacalne" dla osoby leczonej.

Szczególnym rodzajem eksperymentu medycznego jest badanie kliniczne. Zgodnie z art. 2 ustawy z dnia 6 września 2001 r. – Prawo farmaceutyczne (t. jedn. Dz. U. z 2019; poz.499) badaniem klinicznym jest każde badanie prowadzone z udziałem ludzi w celu odkrycia lub potwierdzenia klinicznych, farmakologicznych, w tym farmakodynamicznych skutków działania jednego lub wielu badanych produktów leczniczych lub w celu zidentyfikowania działań niepożądanych jednego bądź większej liczby badanych produktów leczniczych czy śledzenia wchłaniania, dystrybucji, metabolizmu i wydalania jednego lub większej liczby badanych produktów leczniczych, mając na względzie ich bezpieczeństwo i skuteczność.

Nie należy zapominać, że badanie kliniczne może być prowadzone także z użyciem wyrobu medycznego. Ozna-

cza to, że w ramach badań klinicznych prowadzonych z udziałem ludzi wyodrębnia się dwa ich rodzaje, tj.: badania kliniczne produktów leczniczych oraz badania kliniczne z użyciem wyrobów medycznych. W świetle prawa badanie kliniczne jest więc rodzajem eksperymentu badawczego, ale o ściśle określonych regułach i zasadach przeprowadzania.

Z definiowaniem eksperymentu medycznego powiązane jest także zagadnienie terapii/procedury *off label use*. Określenie to odnosi się do pozarejestrowego stosowania leków. Zgodnie z doktryną stosowanie leków w terapii innej niż określona w procesie autoryzacji rynkowej, określa się mianem zastosowania pozarejestracyjnego (ang. *off-label use*), czyli w sposób niezatwierdzony przez organ upoważniony do rejestracji leku [9]. Pozarejestrowe stosowanie leków polegać może na odmiennym niż wskazany w Charakterystyce Produktu Leczniczego (ChPL) sposobie jego podania, na podaniu innej grupie wiekowej czy zastosowaniu leku w innej aniżeli wynikało to z rejestracji jednostce chorobowej. W polskim prawie co do zasady stosować można wyłącznie leki dopuszczone do obrotu. Możliwość stosowania leku poza wskazaniami rejestrowymi jest zagadnieniem niezwykle złożonym, zarówno pod względem prawnym, jak i etycznym. Stosowanie leków *off label use* ma coraz powszechniejsze zastosowanie w praktyce lekarskiej szczególnie w onkologii. Część doktryny odnosi podstawy prawne powyższej procedury do regulacji ustawy o zawodzie lekarza dotyczącej eksperymentu medycznego-leczniczego [10].W takich wypadkach podmiot, który zamierza zastosować lek poza wskazaniami rejestracyjnymi, powinien spełnić wymogi, jakie ustawodawca nakłada na podmiot odpowiedzialny za eksperyment medyczny. Stosowanie produktów leczniczych poza ChPL ma istotne znaczenie w kontekście refundacji produktów leczniczych przez Narodowy Fundusz Zdrowia. Zagadnienie leczenie *off label use* dotyczy tylko produktów leczniczych i jako takie, a także wymagające obszerniejszych rozważań pozostaje zasadniczo po zakresem niniejszego artykułu.

WARUNKI WYKONYWANIA EKSPERYMENTÓW MEDYCZNYCH

Polskie prawo określa warunki wykonywania eksperymentów medycznych. Regulacje dotyczące eksperymentów medycznych znajdują się w różnych aktach normatywnych przede wszystkim rangi ustawowej a podstawowym z nich jest ustawa o zawodach lekarza i lekarza dentysty z 5 grudnia 1996 r. (t. jedn. Dz.U. 2019; poz.537). Do eksperymentów medycznych odnosi się także bezpośrednio najwyższy akt prawny w hierachii źródeł prawa w Polsce, tj. Konstytucja. Bowiem art. 39 Konstytucji RP wskazuje, iż nikt nie może być poddany eksperymentom naukowym, w tym medycznym, bez dobrowolnie wyrażonej zgody. Eksperymenty medyczne stanowią także przedmiot regulacji prawa karnego. Kodeks karny w art. 27 § 2 stanowi, że eksperyment jest niedopuszczalny bez zgody uczestnika, który musi zostać należycie poinformowany o spodziewanych korzyściach i grożących mu ujemnych skutkach oraz o prawdopodobieństwie ich powstania, jak również o możliwości odstąpienia od udziału w eksperymencie na każdym jego etapie. Eksperyment medyczny (czyli kontratyp ryzyka nowatorstwa) stanowi okoliczność wyłączającą odpowiedzialność karną. Podstawą wyłączenia bezprawności czynu realizującego znamiona przestępstwa jest działanie w celu przeprowadzenia eksperymentu poznawczego, leczniczego, technicznego lub ekonomicznego.

Wszystkie akty prawa międzynarodowego i polskiego, odnosząc się do kwestii eksperymentu medycznego na człowieku, uzależniają dopuszczalność jego przeprowadzenia przede wszystkim od zgody osoby w nim uczestniczącej. Natomiast niektóre z tych aktów, stanowiące ich nowszą generację, uzależniają dopuszczalność eksperymentu medycznego także od zgody innego podmiotu lub podmiotów, a w szczególności od pozytywnej oceny projektu przez specjalną komisję etyczną. W Polsce jednym z wymogów legalności eksperymentu medycznego jest uzyskanie pozytywnej opinii komisji bioetycznej. Działają one przy okręgowych izbach lekarskich, wyższych uczelniach medycznych albo wyższych uczelniach z wydziałem medycznym oraz przy medycznych jednostkach badawczo-rozwojowych.

Generalne warunki przeprowadzania eksperymentów medycznych zarówno leczniczych, jak i badawczych określa ustawa o zawodach lekarza i lekarza dentysty z dnia 5 grudnia 1996 roku. Przede wszystkim zgodnie z powyższą ustawą eksperyment medyczny może być przeprowadzany, jeżeli spodziewana korzyść lecznicza lub poznawcza ma istotne znaczenie, a przewidywane osiągnięcie tej korzyści oraz celowość i sposób przeprowadzania eksperymentu są zasadne w świetle aktualnego stanu wiedzy i zgodne z zasadami etyki lekarskiej. Eksperyment leczniczy powinien być stosowany tylko wyjątkowo, gdy uznane środki i metody lecznicze nie pozwalają na wyleczenie pacjenta i gdy ryzyko zastosowania eksperymentu będzie proporcjonalne do oczekiwanych korzyści.

Eksperymentem medycznym powinien kierować lekarz posiadający odpowiednio wysokie kwalifikacje [11]. Nie jest to jednak zbyt precyzyjne sformułowanie. Wydaje się zasadnym dokładniejsze określenie przez prawodawcę wymogów dla takiego lekarza – przykładowo minimalnego doświadczenia zawodowego czy też posiadania adekwatnej specjalizacji.

Fundamentalną przesłanką dopuszczalności eksperymentu medycznego jest zgoda jego uczestnika. Z prawem do zgody na uczestnictwo w eksperymencie medycznym nierozerwalnie związane jest prawo uczestnika do uzyskania odpowiednich informacji. Osoba, która ma być poddana eksperymentowi medycznemu, musi być uprzednio poinformowana o celach, sposobach i warunkach przeprowadzenia eksperymentu, spodziewanych korzyściach leczniczych lub poznawczych, ryzyku oraz o możliwości odstąpienia od udziału w eksperymencie w każdym jego stadium [12]. Ponadto w przypadku gdyby natychmiastowe przerwanie eksperymentu mogło spowodować niebezpieczeństwo dla życia lub zdrowia jego uczestnika, lekarz obowiązany jest go o tym poinformować. Lekarz

ma obowiązek poinformować o skutkach normalnych, typowych. Dopiero odpowiednio poinformowana osoba może wyrazić zgodę na uczestnictwo w eksperymencie.

Zgodnie z art. 25 u.z.l. przeprowadzenie eksperymentu medycznego wymaga pisemnej zgody osoby badanej mającej w nim uczestniczyć. W przypadku niemożności wyrażenia pisemnej zgody, za równoważne uważa się wyrażenie zgody ustnie złożone w obecności dwóch świadków. Zgoda pacjenta musi być powzięta (wewnętrzny akt decyzji) i zakomunikowana (uzewnętrzniona) oraz być uprzednia (przykładowo wyrażona przed zabiegiem, a nie w jego trakcie lub po nim). Ponadto zgoda musi mieć charakter pozytywny (co oznacza, że brak sprzeciwu nie jest zgodą). Zgoda własna pacjenta to typowy przypadek, który odnosi się do pełnoletnich i nieubezwłasnowolnionych uczestników eksperymentu. Zgoda zastępcza natomiast dotyczy przede wszystkim osób małoletnich, ale także osób ubezwłasnowolnionych. W świetle u.z.l. udział małoletniego w eksperymencie medycznym jest dopuszczalny tylko za pisemną zgodą jego przedstawiciela ustawowego. Za pacjenta małoletniego należy uważać, posługując się definicją negatywną, osobę, która nie jest pełnoletnia. Pacjentem małoletnim jest osoba fizyczna, która nie ukończyła lat 18 (wyjątek: kobiet, które zawarły za zezwoleniem sądu związek małżeński po ukończeniu lat 16). Za osoby małoletnie czynności prawne wykonują generalnie tzw. przedstawiciele ustawowi. Należy wyróżnić dwie kategorie przedstawicieli ustawowych tj.:

1. rodziców (reprezentują interesy biologicznych i przysposobionych dzieci),
2. opiekunów prawnych (reprezentują interesy sierot oraz dzieci niepodlegających władzy rodzicielskiej oraz osób ubezwłasnowolnionych) [13].

Zgodnie z art. 98 §1 ustawy z dnia 25 lutego 1964 r. – Kodeks rodzinny i opiekuńczy (t. jedn.: Dz. U. z 2017; poz. 682) zwanej w skrócie kodeksem rodzinnym, rodzice są przedstawicielami ustawowymi dziecka pozostającego pod ich władzą rodzicielską. Natomiast art. 97 kodeksu rodzinnego stanowi, że jeżeli władza rodzicielska przysługuje obojgu rodzicom, każde z nich jest obowiązane i uprawnione do jej wykonywania (co dotyczy realizowania m.in. funkcji przedstawiciela ustawowego). Jednakże o istotnych sprawach dziecka (a za istotną sprawę należy uznać m.in. sprawę jego leczenia) rodzice rozstrzygają wspólnie, a w braku porozumienia między nimi rozstrzyga to zagadnienie sąd opiekuńczy. Nie każda czynność medyczna musi być uznana za „istotną sprawę dziecka", co nieraz podnoszono już w polskim piśmiennictwie bioetycznym, ale wiele tych czynności taki charakter ma w tym niewątpliwie jego udział w eksperymencie medycznym. Mimo że ustawa o zawodzie lekarza wymaga zgody „przedstawiciela ustawowego" na udział małoletniego w eksperymencie, to zdaniem autorki z uwagi na powyższe przepisy kodeksu rodzinnego należy uznać za słuszne, a także konieczne uzyskiwanie zgody od dwóch przedstawicieli ustawowych dziecka, tj. obojga jego rodziców posiadających władzę rodzicielską.

Jeżeli żadnemu z rodziców nie przysługuje władza rodzicielska albo jeżeli rodzice są nieznani, ustanawia się dla dziecka opiekę (konkretną osobę jako opiekuna prawnego). Opiekuna prawnego zarówno dla osób małoletnich, jak i ubezwłasnowolnionych wyznacza orzeczeniem sąd. Fakt posiadania opiekuna prawnego przez pacjenta powinno się odnotować w jego dokumentacji medycznej. W przypadku gdy przedstawicielem ustawowym osoby małoletniej jest opiekun prawny, należy rozważyć istotną w praktyce jego zdolność do samodzielnego udzielania zgody na udział małoletniego, którego jest opiekunem w eksperymencie. Problem powyższy należy rozpatrywać w aspekcie art. 156 kodeksu rodzinnego, zgodnie z którym opiekun powinien uzyskiwać zezwolenie sądu opiekuńczego we wszelkich ważniejszych sprawach, które dotyczą osoby lub majątku małoletniego. Zdaniem autorki udział małoletniego w eksperymencie medycznym należy uznać bezspornie za „ważniejszą sprawę" w rozumieniu powyższego przepisu i dlatego też opiekun prawny powinien uzyskać uprzednie zezwolenie sądu opiekuńczego, żeby potem sam mógł wyrazić skuteczną zgodę.

W praktyce często występuje „zrównywanie" zarówno przez personel medyczny, jak i przez bliskich pacjentów dwóch odrębnych podmiotów, tj. opiekuna prawnego i opiekuna faktycznego. Dlatego też istotne jest wyjaśnienia pojęcia opiekun faktyczny. Zgodnie z definicją ustawową za opiekuna faktycznego należy uważać osobę sprawującą, bez obowiązku ustawowego, stałą opiekę nad pacjentem, który ze względu na wiek, stan zdrowia albo stan psychiczny opieki takiej wymaga (art.3 ust.1. pkt.1 ustawy o prawach pacjenta i Rzeczniku Praw Pacjenta). Podkreślić należy, że tylko przedstawiciel ustawowy (rodzic lub opiekun prawny) może wyrazić legalną zgodę na udział osoby małoletniej w eksperymencie medycznym. Opiekun faktyczny nie może wyrazić skutecznie takiej zgody. W świetle przepisów kodeksu rodzinnego należy przyjąć, iż powyższą zgodę powinni wyrazić oboje rodzice, jeżeli posiadają pełnię władzy rodzicielskiej (są przedstawicielami ustawowymi dziecka). Jeżeli małoletni ukończył 16 lat lub nie ukończył 16 lat a jest w stanie z rozeznaniem wypowiedzieć opinię w sprawie swego uczestnictwa w eksperymencie, konieczna jest także jego pisemna zgoda (jest to tzw. zgoda kumulatywna). W powyższej sytuacji konieczne jest uzyskanie zgody podwójnej: pacjenta i przedstawiciela ustawowego.

Poza uzyskaniem zgody od osób uprawnionych udział małoletniego w eksperymencie badawczym jest dopuszczalny tylko, jeżeli spodziewane korzyści mają bezpośrednie znaczenie dla zdrowia małoletniego, a ryzyko jest niewielkie i nie pozostaje w dysproporcji do możliwych pozytywnych rezultatów. Za problematyczną należy uznać kwestię oceny skali ryzyka a także spodziewanych korzyści. Zważywszy m.in., iż ryzyko związane jest immanentnie z eksperymentem medycznym. Ponadto wątpliwości może wzbudzać przyjęta przez ustawodawcę przesłanka bezpośredniego znaczenia dla zdrowia małoletniego. Czy należy ją odnieść do tego małoletniego uczestnika eksperymentu badawczego, czy też do zdrowia jakiegokolwiek małoletniego i małoletniego w ogólności [14]. Zdaniem autorki należy ją raczej odnieść do konkretnej osoby – małoletniego mającego być uczestnikiem danego eksperymentu badawczego. Jednakże w piśmiennictwie i w praktyce funkcjonowania

komisji bioetycznych spotykane jest także odniesienie do zdrowia małoletnich w ogólności.

Bezspornie należy przyjąć, iż eksperyment badawczy z udziałem osoby małoletniej powinien mieć jedynie wyjątkowy charakter. W świetle ustawy o zawodzie lekarza (art.25 ust.3) eksperyment badawczy z udziałem małoletniego nie jest dopuszczalny, gdy istnieje możliwość przeprowadzenia takiego eksperymentu o porównywalnej efektywności z udziałem osoby posiadającej pełną zdolność do czynności prawnych.

Poza osobami małoletnimi obowiązek uzyskania przez personel medyczny zgody tzw. zastępczej odnosi się także do osób ubezwłasnowolnionych całkowicie. Procedura dotyczy tylko eksperymentów leczniczych. W świetle u.z.l. w przypadku osoby całkowicie ubezwłasnowolnionej zgodę na udział tej osoby w eksperymencie leczniczym wyraża także jej przedstawiciel ustawowy. Ubezwłasnowolnienie oznacza pozbawienie lub ograniczenie zdolności do czynności prawnej konkretnej osoby fizycznej w wyniku orzeczenia sądu. Instytucja ubezwłasnowolnienia uregulowana jest w kodeksie cywilnym (art.13,16) a procedura sądowa orzekania o nim w kodeksie postępowania cywilnego (art. 544-560). Powinno ono być wyrazem troski, pomocy i opieki wobec osób, które nie potrafią same się o siebie zatroszczyć i pomóc sobie. Ustawodawca w kodeksie cywilnym wyodrębnia dwa rodzaje ubezwłasnowolnienia, tj.: całkowite (art.13) i częściowe (art.16). Przesłanki w obydwu powyższych wypadkach pozostają zbliżone. Pierwsza przesłanka ubezwłasnowolnienia dotyczy wieku osoby mającej być ubezwłasnowolnioną. Ubezwłasnowolnić całkowicie można tylko osobę, która ukończyła lat 13 (gdyż wcześniej i tak nie posiada zdolności do czynności prawnych), a częściowo tylko osobę pełnoletnią. Druga przesłanka ma charakter medyczno-biologiczny i jest związana przede wszystkim ze stanem zdrowia psychicznego konkretnej osoby. Ubezwłasnowolnienie całkowite, jak i częściowe, może nastąpić tylko z powodu choroby psychicznej, niedorozwoju umysłowego albo innego rodzaju zaburzeń psychicznych. Trzecia przesłanką w przypadku ubezwłasnowolnienia całkowitego jest brak możliwości kierowania swoim postępowaniem, a w przypadku ubezwłasnowolnienia częściowego konieczność pomocy w prowadzeniu spraw. Pacjenci ubezwłasnowolnieni, podobnie jak pacjenci małoletni, mają swych przedstawicieli ustawowych. Przedstawiciele ustawowi decydują m.in. w sprawach dotyczących udzielania świadczeń zdrowotnych. Dla ubezwłasnowolnionego całkowicie sąd ustanawia opiekę, chyba że pozostaje on jeszcze pod władzą rodzicielską. Opiekun prawny ustanowiony przez sąd opiekuńczy jest przedstawicielem ustawowym osoby ubezwłasnowolnionej całkowicie. Opiekun sprawuje pieczę nad osobą i majątkiem pozostającego pod opieką; podlega przy tym nadzorowi sądu opiekuńczego. Zgodnie art. 175 kodeksu rodzinnego do opieki nad ubezwłasnowolnionym całkowicie stosuje się odpowiednio przepisy o opiece nad małoletnim, dlatego też za adekwatne do omawianej sytuacji należy uznać zastosowanie art. 156 kodeksu rodzinnego i wcześniej przedstawione w artykule rozważania na temat zezwolenia sądu opiekuńczego poprzedzającego wyrażenie zgody przez opiekuna prawnego na udział małoletniego w eksperymencie medycznym.

Opieka nad ubezwłasnowolnionym całkowicie ustaje z mocy prawa w razie uchylenia ubezwłasnowolnienia lub zmiany ubezwłasnowolnienia całkowitego na częściowe. Dla osoby ubezwłasnowolnionej częściowo ustanawia się kuratelę. Ustawodawca nie określił, nawet ogólnie, kompetencji kuratora – w praktyce zazwyczaj określa je sąd. Udział osób ubezwłasnowolnionych częściowo w eksperymentach leczniczych w aspekcie formalnym(uprawnionego do wyrażania zgody) nie został wprost uregulowany przez ustawodawcę w przepisach dotyczących bezpośrednio eksperymentów medycznych a zawartych w ustawie o zawodzie lekarza. Natomiast nie mogą oni uczestniczyć bezwzględnie w eksperymentach badawczych. Brak bezpośrednich regulacji dotyczących zasad udziału osób częściowo ubezwłasnowolnionych w eksperymentach leczniczych stanowi lukę w prawie i prowadzi do wątpliwości, a w konsekwencji do rozbieżności opinii na temat ich statusu. Część doktryny, wśród nich także M. Safjan, uważa że osoby te, jako mające ograniczoną zdolność do czynności prawnych, samodzielnie wyrażą zgodę na eksperyment(wniosek ten wyprowadza on a contrario z treści art. 25 ust. 4 u.z.l.) [15]. Autorka uważa, że problem jest bardziej złożony i jako taki wymaga bezpośredniej regulacji szczególnie, iż osoby ubezwłasnowolnione częściowo z mocy samego prawa (kodeks cywilny) potrzebują pomocy do prowadzenia swoich spraw. Pomoc powyższa może dotyczyć także tak istotnej kwestii jak podjęcie racjonalnej decyzji o udziale w eksperymencie leczniczym. Problem należy rozpatrywać także w aspekcie tzw." dostatecznego rozeznania".

Jeżeli osoba ubezwłasnowolniona całkowicie jest w stanie z rozeznaniem wypowiedzieć opinię w sprawie swojego uczestnictwa w eksperymencie leczniczym, konieczne jest ponadto uzyskanie pisemnej zgody tej osoby (zgoda kumulatywna/podwójna). W przypadku gdy przedstawiciel ustawowy odmawia zgody na udział chorego w eksperymencie leczniczym, można zwrócić się do sądu opiekuńczego, właściwego ze względu na siedzibę podmiotu przeprowadzającego eksperyment, o wyrażenie zgody. Ponadto w przypadku osoby, która ma pełną zdolność do czynności prawnych, lecz nie jest w stanie z rozeznaniem wypowiedzieć opinii w sprawie swego uczestnictwa w eksperymencie, zgodę na udział tej osoby w eksperymencie leczniczym wyraża sąd opiekuńczy właściwy ze względu na siedzibę podmiotu przeprowadzającego eksperyment. Należy zauważyć, że w świetle obowiązujących regulacji prawnych dotyczących zgody na udział w eksperymencie medycznym jego potencjalny uczestnik może nie mieć zdolności do czynności prawnych, a mieć rozeznanie umożliwiające podjęcie decyzji w sprawie eksperymentu lub też odwrotnie, mając zdolność do czynności prawnych, może nie dysponować rozeznaniem umożliwiającym wyrażenie zgody. Zwrot „z rozeznaniem" ma podstawowe znaczenie dla przyjęcia zdolności do wyrażenia zgody samodzielnej a także w ramach zgody kumulatywnej. Dostateczny stan rozeznania oznacza, że podmiot fak-

tycznie posiada możliwość rozpoznania znaczenia zgody i świadomego jej wyrażenia. Rozeznanie łączy się więc ściśle z dojrzałością i stanem psychicznym pozwalającym na wyrażenie z pełną świadomością zgody na czynność medyczną [16]. Jednakże, określenie „osoby niezdolnej do rozeznania znaczenia eksperymentu medycznego" nie jest w przepisach do końca jednoznaczne i może w praktyce wzbudzać wątpliwości. Wydaje się, że za powyższą osobę można uznać, pacjenta nieprzytomnego, upośledzonego czy też chorego psychicznie nieposiadającego orzeczenia o ubezwłasnowolnieniu (ale też sama choroba psychiczna/upośledzenie nie powinna stanowić takiej podstawy).

Przedstawiciel ustawowy osoby małoletniej ma prawo nie tylko do wyrażania zgody na jej udział w eksperymencie medycznym, ale także odmowy(podobnie jak sam uprawniony potencjalny uczestnik eksperymentu). Ponadto zgodnie z art. 27 u.z.l. osoba lub inny podmiot uprawniony do udzielenia zgody na eksperyment medyczny może ją cofnąć w każdym stadium eksperymentu. Lekarz powinien wówczas eksperyment przerwać.

Co istotne zgodnie z art.25 ust.8 u.z.l. w przypadkach nie cierpiących zwłoki i ze względu na bezpośrednie zagrożenie życia, uzyskanie zgody uczestnika (lub zgody zastępczej) nie jest konieczne. Za bezprawne należy uznać jednak przeprowadzenie eksperymentu wbrew woli pacjenta. Regulacja powyższa może budzić zastrzeżenia z uwagi na brak jasnego określenia, jakich eksperymentów dotyczy ten przepis. W konsekwencji za dopuszczalne można by uznać działanie bez zgody uczestnika nie tylko w przypadkach eksperymentu leczniczego, ale i badawczego. Taką interpretację należałoby wykluczyć jako niezgodną z Konstytucją (art.39), która zabrania uczestnictwa w eksperymentach naukowych bez dobrowolnej wyrażonej zgody. Dlatego też omawiany przepis odnosić można tylko do eksperymentów leczniczych.

Ustawodawca wymaga formy szczególnej dla wyrażania zgody na eksperyment medyczny. Przeprowadzenie eksperymentu medycznego wymaga bowiem pisemnej zgody osoby badanej mającej w nim uczestniczyć. Wyjątkowo, zgoda pisemna może być zastąpiona zgodą ustną. W przypadku bowiem niemożności wyrażenia pisemnej zgody, za równoważne uważa się wyrażenie zgody ustnie złożone w obecności dwóch świadków. Zgoda tak złożona powinna być odnotowana w dokumentacji lekarskiej.

Reasumując, zgoda na udział w eksperymencie, aby była prawnie skuteczna musi być uprzednią, poinformowaną i wyrażoną przez uprawniony podmiot oraz mieć formę pisemną. Jeśli chodzi o eksperyment medyczny, to przepisy wyraźnie przewidują możliwość wycofania zgody przez pacjenta. Zgoda może być odwołana przez pacjenta w każdym stadium eksperymentu. Poza wycofaniem zgody przez uczestnika, przerwanie eksperymentu może być wynikiem prawnego obowiązku ciążącego na lekarzu, zgodnie z którym lekarz prowadzący eksperyment leczniczy ma obowiązek przerwać go, jeżeli w czasie jego trwania wystąpi zagrożenie zdrowia chorego przewyższające spodziewane korzyści dla chorego. Natomiast lekarz prowadzący eksperyment badawczy ma obowiązek przerwać go, jeżeli w czasie jego trwania nastąpi nieprzewidziane zagrożenie zdrowia lub życia osoby w nim uczestniczącej.

Prawodawca ogranicza lub wyklucza możliwość udziału w eksperymentach medycznych niektórych kategorii osób w szczególności małoletnich, kobiet w ciąży, a także dzieci poczętych, osób ubezwłasnowolnionych oraz osób pozbawionych wolności[17]. Kobiety ciężarne i karmiące mogą uczestniczyć wyłącznie w eksperymentach badawczych pozbawionych ryzyka lub związanych z niewielkim ryzykiem. Natomiast ich udział w eksperymencie leczniczym uzależniony jest od dodatkowej wnikliwej oceny ryzyka dla matki i płodu. Eksperymenty badawcze na kobietach ciężarnych należy ograniczyć do działań, które nie dotykają płodu[18]. Będą to np. badania polegające na analizie próbek moczu, krwi.

W świetle art. 26 u.z.l. dzieci poczęte(płody, embriony), osoby ubezwłasnowolnione (orzeczeniem sądu) oraz osoby pozbawione wolności nie mogą uczestniczyć w eksperymentach badawczych. Przy okazji należy zwrócić uwagę na lakoniczność regulacji dotyczących eksperymentów medycznych na dzieciach poczętych. Za bezsporną należy uznać jedynie powyższą regulację dotycząca zakazu ich udziału w eksperymentach badawczych. Natomiast brak jest zasadniczo określenia zasad ich udziału w eksperymentach leczniczych. Jak słusznie zauważa Haberko ustawodawca powinien określić zasady podejmowania decyzji i wyrażania zgody na działania lecznicze o charakterze eksperymentu medycznego w stosunku do płodu [19].

Należy przyjąć, że wykluczenie możliwości udziału w eksperymencie badawczym dotyczy zarówno osób ubezwłasnowolnionych całkowicie, jak i częściowo i nie ma na nie wpływu ewentualna zgoda ich przedstawiciela ustawowego czy też sądu. Ma ono charakter bezwzględny.

Zgoda na przeprowadzenie eksperymentu medycznego jest jedną z podstawowych przesłanek jego dopuszczalności, jednakże prawidłowo udzielona zgoda nie legalizowałaby eksperymentu, w którym nie byłyby zachowane jego pozostałe warunki prawne (np. brak opinii komisji bioetycznej). Niezbędnym warunkiem legalności przeprowadzenia eksperymentu medycznego w świetle polskiego prawa jest także uzyskanie pozytywnej opinii komisji bioetycznej. Bowiem zgodnie z art. 29 u.z.l. eksperyment medyczny może być, bowiem przeprowadzony wyłącznie po wyrażeniu pozytywnej opinii o projekcie przez niezależną komisję bioetyczną. Powyższa komisja bioetyczna wyraża opinię o projekcie eksperymentu medycznego, w drodze uchwały, przy uwzględnieniu kryteriów etycznych oraz celowości i wykonalności projektu. Skład i sposób funkcjonowania komisji bioetycznych został określony w rozporządzeniu Ministra Zdrowia z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznej (Dz. U. nr 47, poz. 480). Komisje bioetyczne funkcjonują przy okręgowych izbach lekarskich, wyższych uczelniach medycznych albo wyższych uczelniach z wydziałem medycznym oraz przy medycznych jednostkach badawczo-rozwojowych. Komisje bioetyczne powoływane są w celu wyrażania opinii o projekcie eksperymentu medycznego. Komisję

bioetyczną powołuje się na okres kadencji trwającej trzy lata. Członkami komisji bioetycznej są:
1. lekarze specjaliści,
2. po jednym przedstawicielu innego zawodu, w szczególności: duchowny, filozof, prawnik, farmaceuta, pielęgniarka, posiadającego co najmniej 10-letni staż pracy w zawodzie.

Komisja bioetyczna wybiera ze swego składu przewodniczącego komisji będącego lekarzem i zastępcę przewodniczącego komisji niebędącego lekarzem. Podmiot powołujący komisję bioetyczną ustala skład komisji w liczbie członków od 11 do 15.

Postępowanie przed komisją bioetyczną rozpoczyna złożenie wniosku przez zainteresowanego wydaniem opinii. Do wniosku o wyrażenie opinii o projekcie eksperymentu medycznego, należy dołączyć:
1. projekt eksperymentu medycznego,
2. informację przeznaczoną dla osób poddanych eksperymentowi medycznemu, zawierającą szczegółowe dane o celach i zasadach przeprowadzenia eksperymentu medycznego, spodziewanych dla tych osób korzyściach leczniczych i innych oraz ryzyku związanym z poddaniem się eksperymentowi,
3. wzór formularza zgody pacjenta, poddanego eksperymentowi medycznemu,
4. wzór oświadczenia o przyjęciu warunków ubezpieczenia,
5. wzór oświadczenia składanego przez osobę poddaną eksperymentowi medycznemu, w którym wyraża ona zgodę na przetwarzanie danych związanych z jej udziałem w eksperymencie przez osobę lub inny podmiot przeprowadzający eksperyment medyczny.

W aspekcie trybu postępowania przed komisją bioetyczną należy zwrócić uwagę na pewne odmienności proceduralne (m.in. poszerzona treść wniosku) związane z jedno- lub wielośrodkowym charakterem eksperymentu a uregulowane w rozporządzeniu Ministra Zdrowia z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznej (Dz. U. nr 47, poz. 480). Komisja bioetyczna wyraża opinię nie później niż w terminie 3 miesięcy od dnia otrzymania kompletnej dokumentacji eksperymentu. Przewodniczący komisji bioetycznej powinien przekazać bezzwłocznie uchwałę wyrażającą opinię podmiotowi zamierzającemu przeprowadzić eksperyment medyczny i kierownikowi podmiotu leczniczego, w którym ma być prowadzony ten eksperyment. W przypadku opinii negatywnej uprawnionym podmiotom przysługuje prawo do wniesienia odwołania do Odwoławczej Komisji Bioetycznej. Zadaniem Odwoławczej Komisji Bioetycznej jest rozpatrywanie odwołań od uchwał komisji bioetycznych. Środki finansowe przeznaczone na finansowanie działalności komisji bioetycznej pochodzą z opłat wnoszonych przez podmiot zamierzający przeprowadzić eksperyment medyczny.

Pozytywną opinię komisji bioetycznej należy uznać za warunek *sine qua non* legalności każdego eksperymentu medycznego [20]. Powinna ona zostać wyrażona uprzednio, tj. przed rozpoczęciem jakiejkolwiek czynności medycznej w procedurze realizacji eksperymentu (przed jego rozpoczęciem).

BADANIE KLINCZNE PRODUKTÓW LECZNICZYCH JAKO SZCZEGÓLNY RODZAJ EKSPERYMENTU MEDYCZNEGO

Badania kliniczne produktów leczniczych uregulowane są bezpośrednio w ustawie z dnia 6 września 2001 r. – Prawo farmaceutyczne (t. jedn. Dz. U. z 2019;poz.499) zwanej w skrócie pr. farm. Jak wcześnie wskazano zgodnie z art. 2 pkt 2 ustawy z dnia 6 września 2001 r. – Prawo farmaceutyczne badaniem klinicznym jest każde badanie prowadzone z udziałem ludzi w celu odkrycia lub potwierdzenia klinicznych, farmakologicznych, w tym farmakodynamicznych skutków działania jednego lub wielu badanych produktów leczniczych, lub w celu zidentyfikowania działań niepożądanych jednego lub większej liczby badanych produktów leczniczych bądź śledzenia wchłaniania, dystrybucji, metabolizmu i wydalania jednego lub większej liczby badanych produktów leczniczych, mając na względzie ich bezpieczeństwo i skuteczność. Głównym celem prowadzenia badań klinicznych jest w praktyce potwierdzenie, że lek, który trafia w ręce lekarzy i pacjentów jest bezpieczny i skuteczny. Art. 37a ust. 2 pr. farm. wyraźnie stanowi, że badanie kliniczne produktu leczniczego jest eksperymentem medycznym z użyciem produktu leczniczego przeprowadzanym na ludziach w rozumieniu przepisów ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty. Co oznacza, że badanie kliniczne produktów leczniczych stanowi szczególny oraz uregulowany normatywnie rodzaj eksperymentu medycznego. W badaniach klinicznych generalnie występują trzy podstawowe podmioty, tj. badacz, sponsor oraz uczestnik badania. Zgodnie z definicją legalną badaczem jest lekarz albo lekarz dentysta, jeżeli badanie kliniczne dotyczy stomatologii, posiadający prawo wykonywania zawodu na terytorium Rzeczypospolitej Polskiej oraz odpowiednio wysokie kwalifikacje zawodowe, wiedzę naukową i doświadczenie w pracy z pacjentami, niezbędne do prowadzonego badania klinicznego, odpowiedzialny za prowadzenie tych badań w danym ośrodku; jeżeli badanie kliniczne jest prowadzone przez zespół osób, badacz wyznaczony przez sponsora, za zgodą kierownika podmiotu leczniczego w rozumieniu przepisów o działalności leczniczej, w którym prowadzone jest badanie kliniczne, jest kierownikiem zespołu odpowiedzialnym za prowadzenie tego badania w danym ośrodku [21]. Do obowiązków badacza prowadzącego badanie kliniczne w danym ośrodku należy w szczególności: zapewnienie opieki medycznej nad uczestnikami badania klinicznego, monitorowanie zgodności przeprowadzanego badania klinicznego z zasadami Dobrej Praktyki Klinicznej oraz zgłaszanie sponsorowi ciężkiego niepożądanego zdarzenia badanego produktu leczniczego. Od 1 czerwca 2019 roku, co jest nowym obowiązkiem ustawowym (art. 3 ustawy z dnia 21 lutego 2019 r. o zmianie ustawy o świadczeniach opieki zdrowotnej finansowanych ze środków publicznych oraz niektórych innych ustaw Dz.U. z 2019; poz. 399), badacz lub właściwy podmiot leczniczy musi poinformować właściwy oddział wojewódzki Narodowego Funduszu Zdrowia o numerze PESEL uczestnika badania klinicznego, a w przypadku jego braku – o numerze dokumentu potwierdzającego jego tożsamość, w terminie

14 dni od dnia włączenia do badania. *Ratio legis* nowelizacji polega na umożliwieniu NFZ kontroli zakresu świadczeń opieki zdrowotnej, które są udzielane uczestnikom badania klinicznego i są finansowane ze środków publicznych.

Zgodnie z definicją legalną uczestnikiem badania klinicznego jest osoba, która po poinformowaniu o istocie, znaczeniu, skutkach i ryzyku badania klinicznego wyraziła świadomą zgodę na uczestniczenie w badaniu; dokument potwierdzający wyrażenie świadomej zgody przechowuje się wraz z dokumentacją badania klinicznego [22].

Badania kliniczne, w tym badania dotyczące biodostępności i biorównoważności, planuje się, prowadzi, monitoruje i raportuje zgodnie z wymaganiami Dobrej Praktyki Klinicznej (GCP). Zgodnie z ustawą prawo farmaceutyczne, badanie kliniczne produktu leczniczego, musi być bezwzględnie prowadzone zgodnie z GCP, która zapewnia standard określający sposób planowania, prowadzenia, monitorowania, dokumentowania oraz raportowania wyników badań klinicznych prowadzonych z udziałem ludzi. Dobrą Praktyką Kliniczną jest w rozumieniu normatywnym zespół uznawanych przez społeczność międzynarodową wymagań dotyczących etyki i jakości badań naukowych, przy prowadzeniu badań klinicznych, gwarantujących ochronę praw, bezpieczeństwo, dobro uczestników tych badań oraz wiarygodność ich wyników. Szczegółowe wymagania Dobrej Praktyki Klinicznej określa obecnie rozporządzenie Ministra Zdrowia z dnia 2 maja 2012 r. w sprawie Dobrej Praktyki Klinicznej (Dz. U. z 2012 r., poz. 489). Zgodnie z powyższym rozporządzeniem badanie kliniczne musi być:

1. uzasadnione wynikami badań przedklinicznych oraz, jeżeli dotyczy, danymi uzyskanymi z wcześniejszych badań klinicznych z badanym produktem leczniczym;
2. uzasadnione naukowo i opisane w protokole badania klinicznego;
3. oparte na zasadach etycznych;
4. prowadzone przez osoby posiadające odpowiednio wysokie kwalifikacje zawodowe, wiedzę naukową i doświadczenie w pracy z pacjentami, niezbędne do prowadzenia badania klinicznego, oraz w sposób gwarantujący jego właściwą jakość;
5. przeprowadzane w ośrodku badawczym.

W świetle art.37b ust.2 pr. farm. badanie kliniczne przeprowadza się, uwzględniając, że prawa, bezpieczeństwo, zdrowie i dobro uczestników badania klinicznego są nadrzędne w stosunku do interesu nauki oraz społeczeństwa, jeżeli w szczególności:

1. porównano możliwe do przewidzenia ryzyko i niedogodności z przewidywanymi korzyściami dla poszczególnych uczestników badania klinicznego oraz dla obecnych i przyszłych pacjentów, a komisja bioetyczna oraz Prezes Urzędu uznali, że przewidywane korzyści terapeutyczne oraz korzyści dla zdrowia publicznego usprawiedliwiają dopuszczenie ryzyka, przy czym badanie kliniczne może być kontynuowane tylko wtedy, gdy zgodność z protokołem badania jest stale monitorowana;
2. uczestnik badania klinicznego, a w przypadku gdy osoba ta nie jest zdolna do wyrażenia świadomej zgody – jej przedstawiciel ustawowy, podczas przeprowadzonej przed badaniem klinicznym rozmowy z badaczem lub z członkiem jego zespołu, zapoznali się z celami, ryzykiem i niedogodnościami związanymi z tym badaniem klinicznym oraz warunkami, w jakich ma ono zostać przeprowadzone, a także zostali poinformowani o przysługującym ich prawie do wycofania się z badania klinicznego w każdej chwili;
3. przestrzegane jest prawo uczestnika badania klinicznego do zapewnienia jego integralności fizycznej i psychicznej, prywatności oraz ochrony danych osobowych;
4. uczestnik badania klinicznego, a w przypadku gdy osoba ta nie jest zdolna do wyrażenia świadomej zgody – jej przedstawiciel ustawowy, po poinformowaniu go o istocie, znaczeniu, skutkach i ryzyku badania klinicznego wyraził świadomą zgodę na uczestniczenie w badaniu; dokument potwierdzający wyrażenie świadomej zgody przechowuje się wraz z dokumentacją badania klinicznego;
5. przewidziano postępowanie zapewniające, że wycofanie się uczestnika z badania klinicznego nie spowoduje dla niego szkody;
6. sponsor i badacz zawarli umowę obowiązkowego ubezpieczenia odpowiedzialności cywilnej za szkody wyrządzone w związku z prowadzeniem badania klinicznego.

Bardzo istotny dla bezpieczeństwa (w tym dochodzenia roszczeń) uczestników badań klinicznych jest prawny obowiązek posiadania przez badacza/sponsora ubezpieczenia odpowiedzialności cywilnej za szkody wyrządzone w związku z prowadzeniem badania klinicznego. Jednakże uregulowanie tego obowiązku w art. 37b ust. 2 pkt 6 nie do końca jest precyzyjne i wzbudza zastrzeżenia co określenia osoby/osób zobowiązanych, a tym samym liczby (jedna czy dwie) wymaganych polis OC. Standardowo to sponsor zapewnia badaczowi polisę OC (sponsor zawiera umowę z ubezpieczycielem, która to umowa obejmuje zarówno sponsora jak i badacza). Ubezpieczeniem OC jest objęta odpowiedzialność cywilna badacza i sponsora za spowodowanie uszkodzenia ciała, rozstroju zdrowia lub śmierci uczestnika badania klinicznego w wyniku działania lub zaniechania ubezpieczonego bądź osób, za które ponosi on odpowiedzialność, w okresie trwania ochrony ubezpieczeniowej, wyrządzone w związku z prowadzeniem badania klinicznego.

W świetle prawa farmaceutycznego (art. 37j) za szkody wyrządzone w związku z prowadzeniem badania klinicznego odpowiedzialny jest sponsor i badacz. Odpowiedzialność za szkodę jest odpowiedzialnością cywilną i wiąże się z odpowiedzialnością majątkową dłużnika (winnego naprawienia szkody). W przypadku doznania uszczerbku na zdrowiu, przy spełnieniu przesłanek odpowiedzialności cywilnej uczestnik badania klinicznego może domagać się zapłaty odszkodowania z pieniędzy z zawartej polisy. W przypadku szkody poniesionej przez uczestnika w związku z udziałem w badaniu, lecz niezawinionej przez badacza, sponsora lub osoby, za które badacz lub sponsor ponoszą odpowiedzialność, szkoda taka nie będzie objęta ubezpieczeniem badacza i sponsora [23].

Szczegółowe regulacje w zakresie omawianego ubez-

pieczenia OC zawiera rozporządzenie Ministra Finansów z dnia 30 kwietnia 2004 r. w sprawie obowiązkowego ubezpieczenia odpowiedzialności cywilnej badacza i sponsora (Dz.U. Nr 101, poz. 1034 z późn. zm.). Zasadny obowiązek posiadania polisy OC należy uznać za jeden z podstawowych prawnych elementów ochrony uczestników badania klinicznego.

Uczestnik badania klinicznego może w każdej chwili bez szkody dla siebie wycofać się z badania klinicznego. Uczestnika badania klinicznego, podmiot wskazany w wymaganiach Dobrej Praktyki Klinicznej, informuje o możliwości uzyskania dodatkowych informacji dotyczących przysługujących mu praw.

Badanie kliniczne z udziałem małoletnich może być prowadzone po spełnieniu dodatkowych wymogów [24]. Szczegółowe zasady prowadzenia badań klinicznych małoletnich określa rozporządzenie Ministra Zdrowia z dnia 30 kwietnia 2004 r. w sprawie sposobu prowadzenia badań klinicznych z udziałem małoletnich (Dz. U. nr104; poz.1108).

W badaniach klinicznych, z wyjątkiem badań klinicznych z udziałem pełnoletnich, którzy mogą wyrazić samodzielnie świadomą zgodę, i zdrowych uczestników badania klinicznego, nie mogą być stosowane żadne zachęty ani gratyfikacje finansowe, z wyjątkiem rekompensaty poniesionych kosztów.

Badanie kliniczne można rozpocząć, jeżeli komisja bioetyczna wydała pozytywną opinię w sprawie prowadzenia badania oraz Prezes Urzędu wydał pozwolenie na prowadzenie badania klinicznego. Badania kliniczne prowadzone są w czterech etapach (fazach). Każda faza musi zakończyć się wynikiem pozytywnym, aby można było przejść do kolejnej. Badania kliniczne możemy podzielić na badania nieterapeutyczne (faza I, badania dostępności i równoważności biologicznej), badania terapeutyczne typu poznawczego (faza II), badania terapeutyczne typu potwierdzającego (faza III) oraz badania terapeutyczne w warunkach praktyki klinicznej (faza IV) [25]. Za szkody wyrządzone w związku z prowadzeniem badania klinicznego odpowiedzialny jest sponsor i badacz. Do badań klinicznych badanego produktu leczniczego w zakresie nieuregulowanym w ustawie prawo farmaceutyczne stosuje się przepisy o eksperymencie medycznym, o którym mowa w rozdziale IV ustawy o zawodzie lekarza.

Reasumując, cel prowadzenia badań klinicznych polega na ocenie możliwości dopuszczenia badanej substancji do obrotu lub na zmianie (w tym rozszerzeniu) zastosowania badanej substancji. Wyniki badań klinicznych stanowią między innymi element wniosku o dopuszczenie leku do obrotu. Polska postrzegana jest jako kraj z dużym potencjałem w zakresie możliwości prowadzenia badań klinicznych. Przemawia za tym duża populacja pacjentów, dobrze wykwalifikowani specjaliści oraz stosunkowo niskie koszty [26].

PODSUMOWANIE

Medycyna dla swojego rozwoju wymaga bezspornie badań doświadczalnych, eksperymentalnych. Czynności podejmowane w procesie eksperymentowania naukowego bezpośrednio lub pośrednio służą empirycznemu zweryfikowaniu teoretycznych założeń czy hipotez, poznaniu nowych praw dotyczących ludzkiego ustroju, dotychczas mało znanych [27]. Eksperymenty są narzędziem postępu nauk medycznych, dają szanse lepszego zwalczania chorób, ale związanego z nimi ryzyka nie da się uniknąć.

Badania kliniczne będące rodzajem eksperymentu medycznego stanowią fundament współczesnej medycyny, są warunkiem dostępu pacjentów do nowoczesnych terapii i wpływają znacząco na poszerzenie zawodowej wiedzy lekarzy. Pacjenci uczestniczący w badaniach klinicznych bezpłatnie korzystają z najnowocześniejszych terapii oraz opieki medycznej o podwyższonym standardzie. Sam fakt wzięcia udziału w procesie kwalifikacji do badania klinicznego daje szansę na odbycie bezpłatnych badań przesiewowych, które często pozwalają na wczesną diagnozę innych niebezpiecznych schorzeń.

Eksperyment medyczny może być przeprowadzany, jeżeli spodziewana korzyść lecznicza lub poznawcza mają istotne znaczenie, a przewidywane osiągnięcie tych korzyści oraz celowość i sposób przeprowadzania eksperymentu są zasadne w świetle aktualnego stanu wiedzy i zgodne z zasadami etyki lekarskiej. Eksperyment leczniczy powinien być stosowany tylko wyjątkowo. Uprzednio należałoby przeprowadzić wiele prób laboratoryjnych na organizmach żywych. Do prawnych warunków dopuszczalności eksperymentu medycznego należą: istotna korzyść lecznicza lub poznawcza, uprzednia i pisemna zgoda odpowiednio poinformowanego uczestnika eksperymentu oraz pozytywna opinia komisji bioetycznej. Ponadto celowość i sposób przeprowadzania eksperymentu powinny być zasadne w świetle aktualnego stanu wiedzy i zgodne z zasadami etyki lekarskiej. Powyższe wszystkie warunki dopuszczalności eksperymentu muszą być utrzymane na początku i w trakcie realizacji eksperymentu medycznego (przez cały czas do jego zakończenia).

Stosowanie nowych metod czy środków niesie ze sobą niebezpieczeństwo dla konkretnych osób poddających się doświadczeniu i może skutkować naruszeniem dóbr prawnych tych osób. W konsekwencji eksperymentu może dojść do uszczerbku na zdrowiu i życiu osób biorących w nim udział albo do stworzenia bezpośredniego niebezpieczeństwa dla ich zdrowia lub życia [28]. Zagrożeniom tym trzeba zapobiegać przez odpowiednie uregulowania prawne dotyczące dopuszczalności eksperymentów. Najistotniejsze jest, aby wszystkie rodzaje eksperymentów medycznych były prowadzone w praktyce z poszanowaniem praw ich uczestników. Priorytetem powinno być dla badaczy bezpieczeństwo zdrowotne uczestnika eksperymentu. Generalnie lekarz prowadzący eksperyment leczniczy nie może narażać pacjenta na ryzyko istotnie większe niż to, które grozi osobie niepoddanej takiemu eksperymentowi.

Obecnie w ustawie o zawodzie lekarza podobnie jak w innych aktach normatywnych brak jest definicji eksperymentu medycznego i dlatego należy postulować jej wprowadzenie przez ustawodawcę. Ponadto jeśli chodzi o ocenę regulacji zawartych w ustawie o zawodzie le-

karza to krytycznie należy ocenić to, iż w kwestii osób ubezwłasnowolnionych częściowo ustawa nie zawiera żadnych uregulowań, które wprost odnosiłyby się do tych podmiotów. Dlatego też *de lege ferenda* należy postulować wypełnienie tej luki w prawie. Ponadto jednoznacznego określenia wymaga kwestia zasad udzielania zgody zastępczej w przypadku osób małoletnich podlegających władzy rodzicielskiej obojga rodziców (zgoda obojga rodziców jako przedstawicieli ustawowych), a także osób małoletnich oraz ubezwłasnowolnionych całkowicie posiadających opiekuna prawnego (uprzednie zezwolenie sądu opiekuńczego). Ponadto rozważenia wymaga wzmocnienie normatywne ochrony płodów/embrionów.

Regulacje dotyczące eksperymentów medycznych znajdują się w różnych aktach normatywnych, co stanowi pewien problem. Za zasadne należy uznać uchwalenie jednej ustawy poświęconej kompleksowo eksperymentom medycznych w tym badaniom klinicznym. Od pewnego czasu planowane jest uchwalenie nowej ustawy jednakże dotyczącej tylko badań klinicznych (rządowy projekt takiej ustawy miał m.in. trafić jesienią 2018 do konsultacji społecznych). W Dzienniku Urzędowym Ministra Zdrowia z 14 sierpnia 2019 r. opublikowane zostało zarządzenie Ministra Zdrowia z dnia 14 sierpnia 2019 roku w sprawie powołania Zespołu do spraw opracowania projektu ustawy o badaniach klinicznych produktów leczniczych stosowanych u ludzi. Uchwalenie ustawy o badaniach klinicznych związane jest z rozporządzeniem Parlamentu Europejskiego i Rady nr 536/2014 w sprawie badań klinicznych produktów leczniczych stosowanych u ludzi. Powyższe rozporządzenie nie stanowi regulacji kompletnej i tylko w części ujednolica prawo badań klinicznych na terenie Unii Europejskiej. Prawodawca unijny pozostawił bardzo wiele zagadnień do uregulowania przez poszczególne państwa członkowskie. Dlatego też polska ustawa będzie pełniła funkcję komplementarną w stosunku do wyżej wskazanego rozporządzenia.

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PRACA POGLĄDOWA
REVIEW ARTICLE

GASTROINTESTINAL INSUFFICIENCY SYNDROME IN INTENSIVE CARE OF NEWBORN: LITERATURE REVIEW

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ABSTRACT

The research analytical study of scientific publications in Cochrane Library, Medline, Scopus, Pubmed, Google Scholar databases for the period from 2008 to 2018 was conducted. Modern views on the course of critical states are increasingly considering this process as the uniform mechanism with universal pathogenetic links that lead to the formation of multiple organ lesions, including the digestive system lesions. The contingent of newborns is the patients of high risk of this syndrome occurrence. The frequency of gastrointestinal insufficiency in neonatology makes 80%. The anatomical and functional features of newborns contribute to the development of the syndrome of gastrointestinal insufficiency. There is no clear classification, diagnostic and treatment algorithm of this syndrome. The residual stomach volume measurements when feeding, the abdominal circumference and intraabdominal pressure measurements are used as markers of gastrointestinal insufficiency syndrome in newborns. The additional methods are available X-ray, dopplerographia, electrogastrographia, manometria, phonenterographia, the studies of the fatty-acid-binding proteins, zonulin, β-defensins, calprotectin. The therapy of the gastrointestinal insufficiency syndrome in newborns include the evacuation of pathological intestinal content, detoxification, stimulation of intestinal motility, elimination of mesenteric blood flow violations, restoration of the intestinal microbiota, adequate energoplastic and cyto-energy homeostasis.

KEY WORDS: newborns, gastrointestinal insufficiency syndrome, intensive care

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INTRODUCTION

A critical state means a state of a patient in which there are disturbances of physiological functions and violation of activity of separate systems that can't be corrected by self-regulation and require partial or complete correction or replacement, which is the goal of intensive care. Modern views on the course of critical state increasingly consider this process as a single mechanism with universal pathogenetic links that lead to the formation of multiple organ lesions [1]. There is no exception to the digestive system.

The GIS is considered not only a composite component, but also a driving force for the formation of multiple organ lesions. The frequency of this syndrome in Neonatal Intensive care Departments is equal to 80% [2].

At present, the term "GIS" refers to the inhibition of intestinal function below the minimum required for the absorption of macronutrients and / or water and electrolytes, requiring intravenous administration of admixtures to maintain health and / or growth [3]. This definition makes it possible to consider precisely the contingent of newborns as patients at high risk for the implementation of this syndrome, because according to the World Health Organization definition, inadequate nutrition is a determining factor in the delay of physical and mental development, morbidity, disability and mortality of newborns [4].

In addition, the anatomical and functional features of newborns contribute both to the development of the GIS and to the implementation of the pathological processes caused by it at the organism level. Thus, the gastrointestinal tract (GIT) has an imperfect system of the intestinal passage, fermentative system that is non-adapted for active nutrition, incomplete bacterial colonization, high intestinal permeability due to active pinocytosis of enterocytes, which leads to a high probability of bacterial translocation and immunogenic loading by macromolecular peptides from the intestine. In addition, it is known that the normal values of intra-abdominal pressure in children are proportionally less in the age aspect than in adults. And although there is currently no clear values of this indicator in the neonatal period, a faster development of such a pathological state as intra-peritoneal hypertension, which is accompanied by deepening of splanchnic hypoperfusion, bacterial translocation and respiratory failure, should be expected in newborns [5-7].

On the part of the immune system, it is advisable to emphasize its incompleteness, which promotes bacterial translocation with the development of systemic reactions, in particular - the non-formation of local immunity of the intestinal wall with the absence of production of secretor immunoglobulin A. In addition, the activity of anti-inflammatory cytokines (interleukins 4, 10, transforming growth factor-β, the level of proliferation of T-lymphocytes, the cytotoxicity of natural killers) is directly proportional to the gestational age of the child, while fetal monocytes and macrophages are capable of producing pro-inflammatory cytokines (factor of tumor-α necrosis, interleukins 6.8)

already in the beginning of the first trimester of pregnancy, and at the time of birth, their activity reaches the level of an adult and almost does not undergo changes during the prenatal period.

Reducing the number of circulating neutrophils, increasing the proportion of lymphocytes, monocytes, eosinophils, immunoregulatory index (CD4/CD8), decreasing the ability of neutrophilic granulocytes to adhesion, aggregation, incontinence of L-selectin expression and adhesion molecules, promote the activation of phlogogens caused by their development in the GIT inclusively, which result in leukocyte migration to the center of inflammation and decrease of their ability to reduce phagocytosis [5, 7-9].

In the conditions of the GIS, a special role in destabilization of the patient's state is played by the peculiarities of the energy-plastic provision, the essence of which is reduced to high energy-plastic needs for growth and physical development and the special needs of the composition of nutrienites, in particular - amino acids, some of which (histidine, cystine, cysteine, taurine) is partially or completely essential in the neonatal period [7].

Finally, unlike adults the GIS, as other organ lesions, in newborns can be formed even intrauterine, which excludes the possibility of its prophylaxis and determines the severity of lesion [5, 10-12].

THE AIM

Order to substantiate the scientific research directions for optimization of the tactics of intensive care of the gastrointestinal insufficiency syndrome (GIS) in newborns.

MATERIALS AND METHODS

A search analytical study of scientific publications in Cochrane Library, Medline, Scopus, Pubmed, and Google Scholar databases from 2008 to 2018 has been conducted.

REVIEW AND DISCUSSION

Despite the high frequency and medical and social significance of the formation of GIS in newborns, at present there is no clear classification, but therefore, no diagnostic and treatment algorithm of this syndrome in newborns as well. Actually, the development of these standards is inadequately coordinated in case of patients of elder age. There are classifications of the GIS, which are based on clinical, laboratory, video-laparoscopic, radiological, sonographic, and morphological data [13-17].

For example, for the past three decades the European Society for Clinical Nutrition and Metabolism (ESPEN) has identified 26 different classifications of the GIS in the scientific literature [18].

Such data is confirmed by the opinion of the European Society of Intensive Care Medicine (ESICM) that the monitoring and management of GIT problems continues to be based on a comprehensive assessment of various gastrointestinal symptoms and food intolerance, although this approach involves a large level of subjectivity. However, such an opinion did not prevent its authors from proposing their own classification of the GIS, based on clinical diagnostics, taking into account intra-abdominal pressure [19]. Due to its accessibility and practicality, this classification should obviously have a significant prevalence among clinicians. It should be noted that according to its principles it is similar to the classification of ulcerative-necrotic enterocolitis in newborns [20], and therefore it can be adapted for neonatal practice.

In clinical neonatology, the measurements of gastric residual volume during feeding, abdominal circumference and, less commonly, intra-abdominal pressure, which is mainly used in intensive care in adult patients, are used as the markers of the GIS [6, 21, 22].

The relation to the above studies is controversial. So, for example, ESICM considers it necessary to take into account the severity of intra-abdominal pressure in case of the GIS of the 3rd -4th grades, but does not consider this criterion to be compulsory the case of the GIS of the 2nd grade while at the same time not diminishing its diagnostic value. The residual volume of the stomach, which is one of the imaging of the test for tolerance to enteral load, can increase intra-abdominal hypertension on the one hand and is one of the means of its prevention on the other hand. At the same time there are no clear requirements for conducting this test in the accessible literature. In addition, not all authors consider the residual volume of the stomach, as well as the dynamics of abdominal circumference, as criteria of high diagnostic significance [19, 23-26].

Contradictions regarding the clinical diagnostics of the GIS in newborns require additional clinical information that can be obtained by methods of instrumental and laboratory diagnostics.

The X-ray method is one of the oldest instrumental methods for assessing the state and registration of motor activity in the GIT. For the latter, its use is currently limited, since the process of studying the motor activity of the GIT requires a certain time, and hence - a significant dose of X-ray irradiation. The main method for determining the intestinal blood flow is the Doppler sonography of the upper mesenteric artery. There is a strong direct correlation between clinical manifestations of increased tolerance to enteral nutrition with disturbances of intestinal blood supply, and high vascular resistance in the basin of the upper mesenteric artery in the first day of life allows predicting tolerance to enteral nutrition in the early neonatal age. Another method for evaluating the functional activity of the GIT organs is electrogastroenterography. With this type of research, electrical biopotentials arising during the contractions of the muscles of the intestinal walls are recorded. The study of electrogastrographic indices also gives an opportunity to adequately assess the motor-evacuation function of the intestine. An alternative method for evaluating intra-abdominal microcirculation is the use of the mean capillary intra-abdominal pressure [27-29].

Phonoenterography is based on the registration of acoustic activity of different sections of the GIT in condition-

al-graphic reproduction. It is known that hypoxic-ischemic lesions of the central nervous system in newborns in case of any type of feeding are accompanied by disturbances of the motor-evacuation function of the intestine, which are manifested by changes in the strength of contractions of the intestinal wall, incidence of peristaltic waves and average duration of the peristaltic wave on the phonoenterogram. When performing this method, some difficulties took place while using electromechanical devices for the registration of acoustic phenomena in the abdominal cavity, which hindered the interpretation of the results obtained, limiting the possibilities of this methodology. Nowadays, due to the use of computer technologies, new opportunities of the method have appeared. The minimum sizes of perceptive microphones allow them to be used for a long time at different parts of the abdomen of the patient at the same time, which gives more accurate results of the study; the software allows to separate external noise; the recording acoustic noises in patients of different gestational age is more comfortable [30, 31].

Among the laboratory methods for diagnosing the condition of the intestinal wall and mechanisms for its immune protection in newborns the following elements may be used: protein, which binds fatty acids and is a marker of ischemic intestine damages; zonulin, which shows the permeability of the intestine; lactoferrin , which is an indicator of microbiotic activity; ß- defensin, which is considered a marker of immune-competence of the intestinal glycocalyx; calprotectin, which indicates the activity of local immunity, etc. [32-35].

The strategy of intensive care of the GIS in newborns traditionally is of a pathogenetic orientation. So, under the condition of the GIS development, the focus of endotoxicosis and infectioning in the lumen of the GIT organs is formed. The main effect on it involves the evacuation of pathological intestinal contents and detoxification [36].

In order to stimulate intestinal motility, anticholinesterase drugs are often used, which are aimed at blocking pathological nerve impulses and reducing sympathetic hypertonus. Their disadvantage is short-term action and electrolyte imbalance. Prokinetics (metoclopramide, domperidone, erythromycin) became widespread as they have not only a stimulating effect on peristalsis, but also regulatory effects of the movements coordination [37].

Treatment of the disorders of mesenteric blood flow depends on etiologic reasons, which can be divided into two groups: occlusive and non-occlusive. Occlusive disorders (thrombotic, embolic) are characterized by a rapid development of the pathological state upon the scheme: ischemia -heart attack - peritonitis, with mainly surgical and antithrombotic treatment. Non-occlusive disorders associated with inadequacy of mesenteric blood flow occur due to spasm of the intestinal vessels, hypovolemia, and low cardiac output, which is more common in patients of Intensive care Departments. The therapeutic tactics is represented mainly by the elimination of the pathophysiological cause, appointment of drugs of sympathomimetic, cardiotonic and vasopressor action, infusion of glucose-salt and colloidal solutions according to general principles. The selection of drugs for use is based on the hemodynamic profile [38, 39].

The problem of the adequacy of the intestinal microbiota composition acutely occurs in newborns, since the GIT after birth only begins to be inhabited by microorganisms, and its own protective mechanisms are not able to restrain the growth of pathological microflora. In addition, flatulence, which is caused by changes in the intestinal gas composition due to changes in intestinal flora in newborns, is one of the causes of the intra-abdominal pressure increase. The correction of dysbacteriosis, which necessarily takes place in the development of the GIS, is carried out in accordance with general principles, using bacterial drugs (prebiotics, probiotics), ferments providing digestion and immunotropic therapy, aimed at restoring their own protective systems of the organism [40, 41].

An important factor in the GIS treatment is an adequate energy-plastic provision. Complete parenteral nutrition is dangerous for the development of atrophy of the intestinal mucosa with inhibition of antimicrobial protection and the possible development of a bacterial translocation syndrome. Enteral nutrition that is inadequate due to the quality composition can be a cause of both intra-and extra-intestinal abnormalities. Thus, the use of enteral mixtures with a high content of simple hydrocarbons leads to a change in the intestinal flora composition, which results in the acidification of the internal environment of the organism, since lactate is one of the end products of bacterial fermentation of hydrocarbons in the intestine [42, 43].

Another method of cytoenergetics recovery is the direct introduction of energy-intensive substances that are involved as metabolites in the Krebs cycle. The effect of these drugs on the energy supply of cells was studied both in adults and children (including newborns) in cases of mitochondrial diseases and post-hypoxic lesions and multiple organ insufficiency syndrome. But in available literature there are no data on their use in newborns precisely with the GIS. Nevertheless, taking into account the results of the clinical studies of cases with lesions of other organs and systems, one can expect the effectiveness of using drugs created on the basis of phosphatidylcholine, carnitine, glutamine and amber acid. The latter is not only a participant in the sixth Krebs cycle reaction, but is also metabolised without oxygen and transported to the mitochondria without requiring energy consumptions, which is advantageous in conditions of hypoxia and initial hypoergosis [44].

CONCLUSIONS

Despite the high medical and social significance of the GIS problem, there are no generally accepted classification as well as the clear clinical criteria of this syndrome in newborns in critical state. It is important to develop a system for classification of enteral insufficiency in newborns, which will allow to systematize the clinical manifestations of this syndrome and combine them into clinical groups. The problem of expedi-

ency and effectiveness of instrumental, laboratory and diagnostics methods and specific therapy of the GIS in neonatal intensive care requires further detailed and in-depth study.

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PRACA POGLĄDOWA
REVIEW ARTICLE

ORGANIZATION OF DERMATOVENEROLOGIC MEDICAL CARE: DOMESTIC REALITIES AND WORLD PRACTICE (REVIEW OF LITERATURE)

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ABSTRACT

Introduction: In Ukraine, more than 2 million citizens need dermatovenerologic care each year. The incidence and prevalence rates of skin diseases and sexually-transmitted infections remain stable and the number of people with disabilities resulting from chronic skin conditions increases annually. Both in Ukraine and across the globe, there is an increasing demand for cosmetic care. Therefore, studying the current state of organizing dermatovenerologic care in the context of healthcare reforming in Ukraine with regard to the domestic and world experience is relevant.

The aim: To examine the experience in organizing dermatovenerologic care in Ukraine and the developed countries.

Materials and methods: We used the methods of systematic approach and system analysis of laws and regulations in Ukraine, the data from the websites of healthcare institutions, materials of sectoral statistical reporting and scientific sources on the subject**.**

Conclusions: Given the domestic experience, the elements of world models of organizing dermatovenerologic care are used in Ukraine. However, the general practitioners' contribution to detecting skin diseases is negligible and the statutory regulation of dermatovenerologic and cosmetic care is obsolete. This requires taking measures at all governance levels in order to optimize dermatovenerologic and cosmetic care in Ukraine.

KEY WORDS: Skin diseases, dermatovenerologic care, organization

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INTRODUCTION

Reforming the healthcare in Ukraine requires some modifications in the organization of the entire system. They are connected with functional interrelationships, structural components, resources provision, statutory regulation of operation of healthcare institutions, which provide medical care to the population according to their profile, specialization, type of medical care provided and form of ownership.

In Ukraine, according to the Order of the Ministry of Health of Ukraine dd. 19.12.1997, No. 359, "Nomenclature of medical specialties", as amended by the Order of the Ministry of Health of Ukraine dd. 31.10.2018, No. 1973 (z1294-18), there are 124 medical specialties by whose profile corresponding networks of healthcare institutions operate. As indicated in Art. 33 of the Act of Ukraine "Fundamentals of Ukrainian healthcare legislation" (amended on 01.01.2019), healthcare institutions are divided into institutions of primary, secondary, tertiary medical care, emergency, palliative care, rehabilitation. Articles 16, 17 of the same Act show that by legal form healthcare institutions can be state, municipal, private or based on a joint form of ownership.

One of the most demanded specialties in Ukraine is dermatovenerology. Scientists believe that in recent decades skin diseases and sexually-transmitted infections have been an urgent medical and social problem. More than 2 million citizens need annual dermatovenerologic care. The percentage of first registered diseases of skin and subcutaneous tissue in overall incidence in 2015-2017 was 5.85-5.87%, respectively; and in the prevalence of all diseases – 2.6%. Sexually-transmitted infections, leprosy, and AIDS, which fall within the competence of the dermatovenerologic care, are recognized legislatively as socially dangerous infectious diseases [1]. The number of patients with chronic severe skin diseases, which result in disability, grows each year. Due to their visual signs, skin lesions reduce the quality of patients' life significantly. It adversely affects their labor, social activity and mental condition and forces them to self-isolation [2-4]. Manifestations of stigma and discrimination against such patients are commonly widespread. Therefore, the issues of optimizing the organization of dermatovenerologic care are relevant within the context of healthcare reforming in Ukraine given the acquired domestic and world experience.

THE AIM

To study the experience of organizing dermatovenerologic care in Ukraine and the developed countries.

MATERIALS AND METHODS

The aim of the research was achieved using systematic approach and system analysis of laws and regulations in Ukraine, the data from the websites of healthcare institutions, materials of sectoral statistical reporting and scientific sources on the subject.

REVIEW AND DISCUSSION

A systematic analysis of the data on the network of healthcare institutions providing dermatovenerologic care in Ukraine has shown that it covers almost all types of medical care and functions in different forms of ownership.

So, while developing common practice – family medicine, dermatovenerologic care should be provided in primary care facilities [5-7]. However, according to scientific observations, the population's needs in dermatovenerologic care are not fully met in these institutions yet: in the overall structure of visits to a general practitioner – family doctor, the percentage of such patients' visits was quite low in 2015 – 0.25-0.3% depending on the region, and sexually-transmitted infections were not detected at all [8]. Although in Ukraine the group practice of primary healthcare has been introduced, which is considered to be the most effective among mono- and mixed ones, only 6.0-26.0% patients with dermatoses were detected by family doctors in different regions in 2016. It should be noted that the staffing level of general practitioners in Ukraine remains almost twice lower than in European countries with highly developed primary healthcare systems, in particular, the percentage of staffing by general practitioners – family doctors was 72.0% in 2017, which, of course, affects the level of detecting diseases by them [9-12]. In general, the average percentage of visits due to the diseases of skin and subcutaneous tissue was 1.2% in 2018 in the structure of all outpatient visits [13].

The largest volume of medical care for patients with dermatovenerologic profile is provided in secondary healthcare institutions (territorial medical association "Dermatology", Kyiv; city dermatovenerologic dispensaries; offices of outpatient-polyclinic institutions); and tertiary ones (regional dermatovenerologic dispensaries, regional dermatovenerologic hospitals, university clinics, the Institute of Dermatology and Venereology of the National Academy of Medical Sciences of Ukraine). According to [14], in 2008 there were 81 dermatovenerologic dispensaries in Ukraine, in 2014 - 57, in 2016 - 55, 33 of them had ward beds. The number of beds of dermatovenerologic profile decreased from 6324 to 3376; as of 01.12.2017 there were 2107 (for adults) and 484 for children. Such statistics displays the general trends in the healthcare regarding streamlining the ward bed fund, in particular, the widespread introducing such outpatient forms of medical care as day-patient departments at dispensaries.

In addition to the dispensaries, there were 3 dermatovenerological hospitals in the network (Kyiv, Odessa, Izmail in Odessa Region) as of 01.01.2019.

In outpatient-polyclinic institutions, medical care is provided to patients by dermatovenerology offices, the number of which decreased from 945 in 2008 to 758 in 2014; in 2016 there were 790 of them.

The number of dermatovenerologists has decreased slightly – from 2819 people, including 151 children's doctors or 0.66 per 10 thousand of population in 2014, to 2,659 people, including 142 children's doctors, or 0.63 per 10 thousand of population in 2017. The staffing level of physicians by individuals was 97.3% in 2014 and 93.8% in 2017 and remained one of the highest rates among the doctors with different specialties [15, 16].

The activities of healthcare institutions providing specialized dermatovenerologic care are directly regulated by the Order of the Ministry of Health of Ukraine dd. 07.06.2004 No. 286 "On improving dermatovenerologic care of the population of Ukraine". The Order is valid as amended on 04.07.2016 [17]. The Order defines the main goal of dermatovenereologic service – improving the quality and efficiency of providing medical care to patients with dermatovenerologic pathology, further developing and improving the functioning of the dermatovenereologic service.

As indicated in the Order, this goal can be achieved, in particular, by adhering to the standards and methods of diagnosing and treating skin diseases and sexually-transmitted infections, instructions for preventing transfusion syphilis for dermatovenerologic dispensaries and other prevention and treatment facilities, implementing a list of actions to detect sexually-transmitted infections in the network of prevention and treatment facilities.

According to the Order, a dermatovenerologic dispensary, as the basic structural unit of the dermatovenerologic service, is a specialized prevention and treatment facility intended to provide high-quality specialized advisory-diagnostic and preventive-treatment dermatovenerologic care to the population under outpatient and inpatient treatment. The structure of the dispensary makes it possible for structural units to operate; they are funded from the budget and are supported by a special fund. The latter can carry out periodic preventive medical examinations, functional diagnostics, treat parasitic skin diseases, conduct anonymous examination and treatment, provide cosmetic care, and organize the inpatient activity at home.

The analysis of the websites of Ukrainian dermatovenerologic dispensaries, both state and municipal institutions, showed that in general their activity complies with the legislative requirements and covers:

- treating all skin diseases by ICD-10 (L00-L99): category XII. "Diseases of the skin and subcutaneous tissue"; category II "Neoplasms" (C43-C44) "Melanoma and other malignant neoplasms of skin", (D22) "Melanocytic nevi" (D23) "Other benign neoplasms of skin";
- treating infections with a predominantly sexual mode of transmission (A50-A64);
- providing advisory-diagnostic care and promoting healthy lifestyles among the population;
- carrying out preventive and anti-epidemic measures to prevent spreading of skin infections and sexually-transmitted diseases;

- managing the activity of health facilities of any ownership on the respective territory regarding advisory, diagnostic, preventive-treatment care to the population with skin diseases and infections with a predominantly sexual mode of transmission;
- introducing modern technologies for prevention, diagnosis and treatment of skin diseases and infections with a predominantly sexual mode of transmission;
- functioning as clinical sites of dermatovenerology departments at higher education institutions of Ukraine;
- participating in scientific researches and implementing scientific programs and projects according to their profile.

Attention should be drawn to the activity type of dermatovenerologic dispensaries which has been in strong demand among the population in recent years – cosmetic care to the patients with skin lesions, which led to cosmetic defects. Such care is provided on a self-supporting basis in many dermatovenerologic dispensaries (Zaporizhzhia, Ivano-Frankivsk, Lviv, Mykolaiv Regional Dispensary and Kyiv City Dispensary No. 1, Kyiv City Dispensary No. 4, Kharkiv City Dispensary No. 5).

The provision of cosmetic care is also carried out in state and municipal cosmetology hospitals (Dnipro, Kryvyi Rih, Lviv), which operate on a self-supporting basis, and by 418 individual entrepreneurs who work on the basis of private medical practice (as of 01.01.2019).

The activity of the structural subdivisions of dermatovenerologic dispensaries, as well as private institutions, providing cosmetic care, are additionally regulated by the Order of the Ministry of Health of the USSR dd. 28.12.1982 No. 1290 "On measures for improving cosmetic care to the population" [18]. The range of services may include such diseases as seborrhea, hair diseases, acne, hypertrichosis, hirsutism, benign neoplasms (nevi, atheromas, fibromas, keratomas, papillomas, hemangiomas, warts, keratosis), vascular dermatosis (rosacea, perioral dermatitis), pigmentation disorders – hyperpigmentations (chloasmas, freckles), depigmentations (vitiligo), impregnation of skin by foreign particles, scars of various origins, wrinkles, congenital and acquired deformations of face parts (nose, auricles, eyebrows, lips, eyelids), excessive face skin, deformation of breasts, anterior abdominal wall, etc. It is known that these diseases cause cosmetic defects of skin, and therefore, contribute to the emergence of mental disorders, social self-isolation, stigma and patients' lower quality of life.

At the same time, it is obvious that the legal framework for regulating cosmetic care in Ukraine has been used since the Soviet period and therefore is obsolete. There is no such specialty as "Cosmetology" [19], although it is recognized by all leading dermatologists of Ukraine, European countries and the USA. The materials of Ukrainian scientific periodicals, the activities of professional medical associations and scientific forums recognize this specialty to be as the one which was put into real practice; this is confirmed by scientific periodicals approved by the Ministry of Education and Science of Ukraine: "Dermatovenerology. Cosmetology. Sexual pathology" of the non-governmental organization "Association of dermatologists, venerologists and cosmetologists of Dnipropetrovsk Oblast" and the state establishment "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine"; "Ukrainian Journal of Dermatology, Venereology, Cosmetology" of Bohomolets National Medical University and Ukrainian Association of Dermatologists and Cosmetologists.

According to the official websites, the following separate courses, which are taught at the departments of many medical universities of Ukraine, in addition to the main discipline "Dermatology and venereology", are the evidence for the recognition of cosmetology as a sub-specialty of dermatovenerology: "Cosmetology", "Medical cosmetology", "Workshop on practical cosmetology", "Physiotherapy in cosmetology" (Bohomolets National Medical University, Ivano-Frankivsk National Medical University, Danylo Halytsky Lviv National Medical University, Kharkiv National Medical University, Zaporizhzhia State Medical University). The Department of Dermatovenerology at Shupyk National Medical Academy of Postgraduate Education, Kyiv, holds a series of informing and internship "Cosmetology in the practice of a dermatovenereologist", which gives the right to obtain a state recognized certificate and provide cosmetic care [20].

The annual growth of demand for cosmetic care is also evidenced by the flourishing market of cosmetology services in the world and in Ukraine. According to the report "World Preview 2018, Outlook to 2024" prepared by the analytical company "Evaluate Pharma", in 2017 the sales of dermatological products worldwide was 12.9 billion USD, and by 2024 it will have grown to 30.3 billion USD (average annual growth is 13%). According to US statistics, in 2018 skin care products were the most popular among other health and beauty products and amounted to 5021.1 million USD [21]. In Ukraine, for several years running cosmetics sales have been increasing in quantitative and monetary terms, namely from 30 billion UAH in 2015 to 36 billion UAH in 2016. In February 2019, the total sales of cosmetic products at pharmacies were 497.7 million UAH for 6.9 million packages, the indicator increased by 42.5% in monetary equivalent and by 22.1% in kind over the relevant period of 2018 [22]. 181 companies deliver equipment for cosmetic procedures to Ukraine, 22 companies deliver laser technologies, 5 companies deliver the equipment for tanning salons.

This undoubtedly requires elimination of contradictions between statutory regulation and the realities of the activities of institutions of any ownership in cosmetic care sphere, since the issues arise regarding availability to the population, consumer protection, prevention of treatment complications, coordination in the work of various healthcare professionals (dermatovenerologists, oncologists, plastic surgeons, allergists, endocrinologists, obstetrician-gynecologists, pediatricians and others).

The world experience in organizing dermatovenereologic care is evidence of two of its models. The first model is typical of such advanced countries as Germany, France, where the specialty "dermatovenerology" exists, there is no system of referral to

specialists, so a patient has direct access to them, without referral from a general practitioner, there is a sufficiently high number of dermatovenerologists (in France, one dermatovenerologist per 25 thousand of population, in Germany – per 16 thousand of population.). The second model was developed in the United Kingdom, the USA and the English-speaking countries where the specialties "Dermatology" and "Venereology" are separated, the "goalkeeper" system functions, which means that patients can access a specialist only with the referral from a general practitioner – a family doctor. The number of dermatologists and venerologists is low (in the UK – 1 dermatologist per 120 thousand of population) [23-26].

Taking into account the results of reforming primary and secondary medical care, Ukraine has a model containing the elements of both world ones: the specialty "dermatovenerology" includes two specialties, the staffing level of specialists for the population is high, the system of "goalkeeper" has been introduced, when the first stage in diagnosing skin diseases and sexually-transmitted infections should be the visit to a primary healthcare physician.

However, the Ukrainian Association of Dermatovenerologists and Cosmetologists believes that in the context of changes in healthcare, the organization of dermatovenerologic service operation is imperfect, particularly with respect to statutory regulation of the interaction and coordination of physicians of all specialties and institutions of any ownership that may be involved in detecting, diagnosing and treating skin diseases and sexually-transmitted infections, the range and term of service provision, their clear separation depending on type of medical care, professional level of specialists. [27, 28].

CONCLUSIONS

1. The survey showed that healthcare reforms in Ukraine affected, in particular, dermatovenerologic care. The ward bed fund was streamlined at impatient departments while the structure of the dermatovenereology service and staffing were preserved. The dermatovenerologic dispensary remains the leading institution which delivers specialized dermatovenerologic care; the level of dermatovenerologist staffing by individuals remains high, which is 93.8%. General practitioners – family doctors are involved in initial examination of patients with skin lesions and sexually-transmitted infections, following the example of healthcare systems in the developed countries worldwide (the USA, the UK).
2. At the same time, it was found that the contribution of general practitioners to the detection of skin lesions and sexually-transmitted infections is negligible; statutory regulation of dermatovenerologic care needs to be improved with respect to coordination of the activities of doctors of all specialties and institutions of any ownership that may be involved in detecting, diagnosing and treating skin diseases and sexually-transmitted infections; it is necessary to solve the issue of the formal status of the specialty "Cosmetology" and update the regulatory framework of cosmetic care.
3. The directions for future research are the scientific substantiation, development and implementation of an optimized model of dermatovenerologic care into healthcare in Ukraine with regard to the results of this review, the acquired domestic and world experience.

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