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ORIGINAL ARTICLE

CONTENTS

Preliminary study of the influence of maternal and neonatal NOS3 (rs1799983), IL1B (rs1143634) genes variants and their intergenic interaction on the development of hypoxic-ischemic encephalopathy in newborns in the context of treatment planning

Yuliia Cherniavska[1], Alina Davydenko[2], Valerii Pokhylko[1], Liliia Fishchuk[3], Zoia Rossokha[3]

[1]DEPARTMENT OF PEDIATRICS NO1 AND NEONATOLOGY, POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

[2]DEPARTMENT OF ANESTHESIOLOGY AND INTENSIVE CARE, POLTAVA STATE MEDICAL UNIVERSITY, POLTAVE, UKRAINE

[3]EXPERT-ANALYTICAL MEDICAL CENTER FOR MOLECULAR GENETICS, SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: To determine the influence of maternal and neonatal variants of the eNOS (G894T, rs1799983) and IL1B (C3953T, rs1143634) genes and their intergenic interactions on the development of HIE in newborns.

Materials and Methods: The study included a cohort of 105 newborns and their 99 mothers. Determination of variants of the genes eNOS (G894T, rs1799983) and IL1B (C3953T, rs1143634) was carried out for the patients of study groups.

Results: The frequency of detection of the 894TT genotype by the eNOS gene was increased in newborns with severe asphyxia (p=0.018) and in their mothers (p=0,0057). Further analysis of intergenic interactions, performed in mother-child pairs, revealed an increased frequency of the neonatal 894GG (eNOS)/ maternal 3953C (IL-1B) genotype combination in the comparison group versus the group of newborns with HIE (p=0.007).

Conclusions: The significance of the intergenic maternal combination of 894GG/3953CT genotypes for the eNOS and IL1B genes and the intergenic combination of neonatal 894GG (eNOS)/maternal 3953CT (IL-1B) genotypes in the development of HIE in newborns has been proven. Associations of maternal and neonatal 894TT genotypes for the eNOS gene with the development of severe asphyxia, bradycardia, and respiratory failure were found in newborns with HIE.

KEY WORDS: neonates, hypoxic-ischemic encephalopathy, NOS3 (rs1799983), IL1B (rs1143634), intergenic interaction

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INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is a disease with heterogeneous manifestations, most often diagnosed in the neonatal period, and is one of the main causes of severe long-term neurological deficit. According to the data, HIE is one of the main causes of disability in children, and is the leading cause of death in children under the age of 5 [1].

The main mechanisms of neuronal tissue damage are: hypoxia, decreased perfusion with subsequent decrease in cerebral perfusion pressure, inflammation and oxidative stress [2]. It is claimed in the results of some research that cerebral perfusion pressure in newborns almost does not depend on arterial blood pressure (BP), since the external work of the heart in infants is mainly isometric [3]. In critical conditions, there is a violation of autoregulation, while brain perfusion becomes completely dependent on systemic hemodynamics [4].

Currently, it is known that endothelium regulates vascular tone through the release of vasodilator and vasoconstrictor factors and modulates the contractile activity of smooth muscle cells. Nitric oxide (NO) belongs to endothelial dilatation factors. Nitric oxide prevents adhesion and aggregation of platelets, adhesion of monocytes, protects the vascular wall and prevents remodeling of vessels in various pathological conditions [5]. NOS (NO synthase), which catalyzes the biosynthesis of NO, is found in endothelial cells, astrocytes, and neurons. There are three isoforms of NOS: nNOS (neuronal NOS), which regulates synaptogenesis and remodeling and is Ca2+ dependent; eNOS (endothelial NOS), which regulates vascular tone, especially vasodilation, and is also

dependent on Ca2+; iNOS (inducible NOS), which is present in macrophages and astrocytes and is Ca2+ independent.

It has been established that disruption of cerebral blood flow during perinatal HIE is associated with NO activity [6]. The role of NO in the pathogenesis of ischemic brain damage is dual: protective and detrimental, depending on the NOS isoform and the cell type that produces NO. Under oxidative stress, NO produced by nNOS leads to neuronal death, causing mitochondrial damage, energy loss, and subsequent disruption of calcium homeostasis [6]. The endothelial form of NOS has a neuroprotective function, which is realized through NO-mediated enhancement of brain perfusion [7].

In neonates with HIE, the variability of the *eNOS* gene (synonymous name – *NOS3*), which encodes endothelial NOS, can affect both the activity of the enzyme and the formation of NO, which can lead to different clinical outcomes depending on the severity of perinatal HIE. Despite the key role of endothelial dysfunction in the pathogenesis of cerebral blood circulation disorders, there is almost no information about the nature of changes in the vasoregulatory systems of newborns with HIE and potentially possible intergenic interactions.

It should be noted that the concentration of NO can change under the influence of cytokines [8]. In particular, under conditions of hypoxia and inflammation, the cytokine interleukin-1 beta (IL-1β) activates iNOS, which dramatically increases NO production and, accordingly, potentiates brain damage after ischemic perinatal asphyxia [9]. In an in vitro study, it was shown that stimulation of IL-1β production reduced the level of *eNOS* expression in human aortic endothelial cells [10].

On the other hand, the pro-inflammatory cytokine IL-1β itself plays an important role in the development of various pathological, in particular, neurological, conditions of newborn children. Thus, there is convincing evidence that excessive production of IL-1β is a leading component of the development of inflammation and subsequent brain damage in newborns with encephalopathy [11]. Increased levels of IL-1β were observed in newborns with asphyxia, which was accompanied by impaired cerebral metabolism and subsequent developmental delay [12, 13].

Considering the importance of eNOS and IL-1β in the development of HIE, the study of gene variants encoding these proteins and affecting their functional state is extremely relevant. Studying these gene variants and their interactions will help to better understand the mechanisms underlying the disease and may provide new opportunities for developing treatment strategies.

AIM

Therefore, the aim of this study was to determine the influence of maternal and neonatal variants of the *eNOS* (G894T, rs1799983), *IL1B* (C3953T, rs1143634) genes and their intergenic interactions on the development of hypoxic-ischemic encephalopathy in newborns.

MATERIALS AND METHODS

The study was conducted in 2022-2023 in the neonatal intensive care unit. The study included a cohort of 105 newborns with a gestational age of 25 to 42 weeks and their 99 mothers.

The main group of the study included 45 newborns (including 4 twins), hospitalized in the intensive care unit after birth with a diagnosis of «hypoxic-ischemic encephalopathy of newborn» (P91.6 according to ICD-10), aged from 1 day to 28 days of life, according to the severity of the condition, as well as 40 of their mothers (one mother refused to participate in the study).

The comparison group consisted of 60 randomly selected otherwise healthy newborns, without HIE (including 1 twin) and their 59 mothers.

Exclusion criteria of the study were: the presence of congenital malformations, genetic diseases, and parents' refusal to participate in the study.

The study was conducted in accordance with the Declaration of Helsinki. The permission of the ethical committee was obtained for the study. The parents gave their informed consent to participate in the study.

The primary registration forms of the Ministry of Health of Ukraine No. 003/o "Medical records of a hospital patient" were used as medical documentation, and the corresponding individual study cards were formed in accordance with study design. The study was conducted within the framework of the initiative research of the Department of Pediatrics No. 1 with Neonatology "To develop clinical and laboratory criteria, methods for predicting and preventing metabolic disorders in young children", No. 0120U102856.

MOLECULAR GENETIC ANALYSIS

The research was carried out using the buccal epithelium as a biological material. Material was collected using disposable sterile brushes and stored and transported in tubes with the preservative «DNA/RNA Shield» (Zymo Research, USA). DNA was isolated using a commercial kit «Quick-DNA Mini Prep Plus Kit» (Zymo Research, USA). Determination of variants of the genes *eNOS* (G894T, rs1799983) and *IL1B* (C3953T, rs1143634) was carried out by the method of polymerase chain reaction with subsequent analysis of polymorphism of the

Table 1. Basic clinical characteristics of newborns and their mothers

Basic clinical indicators of newborns		Research groups		p
		Main group (n=45)	Comparison group (n=60)	
Gestational age, weeks		32,8±4,5	39,0±1,5	<0,0001
Birth weight, g		2164,9±1034,8	3328,9±470,4	<0,0001
Body length, cm		44,3±7,4	51,2±2,8	<0,0001
Gender	Female, n (%)	17 (37,8%)	29 (48,3%)	0,32
	Male, n (%)	28 (62,2%)	31 (51,7%)	
Apgar scale, 1st minute,scores		6 [5; 7]	8 [7; 9]	<0,0001
Apgar scale, 5th minute, scores		7 [6; 8]	9 [8; 9]	<0,0001
Basic clinical indicators of mothers		**Main group (n=40)**	**Comparison group (n=59)**	
Average age, years		27,3±5,5	28,5±5,3	0,34
Obesity, n (%)		9 (23,1%)	7 (11,9%)	0,17
Cardio-vascular diseases, n (%)		6 (15,0%)	7 (11,9%)	0,76
Thyroid gland diseases, n (%)		4 (10,0%)	4 (6,8%)	0,71
Kidneys diseases, n (%)		8 (20,0%)	4 (6,8%)	0,06
Preeclampsia, n (%)		15 (37,5%)	9 (15,3%)	0,016
TORCH-infections, n (%)		17 (42,5%)	4 (6,8%)	<0,0001
Infectious diseases, n (%)		11 (27,5%)	-	
Miscarriage threat, n (%)		18 (45%)	-	
Fetoplacental insufficiency, n (%)		13 (32,5%)	9 (15,3%)	0,052
Polyhydramnios, n (%)		10 (25,0%)	3 (5,1%)	0,0058

length of restriction fragments [14, 15]. Amplification was carried out using the DreamTaq Green PCR Master Mix kit (Thermo Scientific, USA) and primers (Metabion, Germany), restriction – using specific restriction endonucleases (Thermo Scientific, USA).

STATISTICAL ANALYSIS

Statistical processing of the obtained results was carried out using the IBM SPSS Statistics v27 application program package. Qualitative data are presented as absolute numbers and percentages. Quantitative data are presented as mean±standard deviation (if the data followed a normal distribution) and as median [25th quartile; 75th quartile] (if the data did not follow a normal distribution). Fisher's exact two-tailed test was used to compare qualitative data. When comparing basic clinical characteristics, the distribution of the studied variables was first checked for normality using the Kolmogorov-Smirnov test. Then, depending on the obtained results, one-way ANOVA or the Mann-Whitney test was used to compare the data. The group of newborns (main group and comparison group) was considered the independent factor, and the studied characteristic was considered the dependent variable. In all cases, the differences were considered statistically significant at $p<0.05$.

RESULTS

During the analysis of the basic and clinical indicators of the experimental groups, it was determined that the average GA in the main group was 32.8±4.5, and in the newborns of the comparison group – 39.0±1.5. In addition, mothers of newborns in the main group had a complicated obstetric history (Table I).

Preeclampsia, polyhydramnios, and TORCH-infections were diagnosed significantly more often in mothers of newborns in the main group. In the neonatal period, the newborns of the main group were diagnosed with clinical signs of moderate (17.8%) and severe (8.9%) asphyxia, RDS (60%), respiratory disorders (82.2%), respiratory (33.3%) and heart (24.4%) failure, intraventricular hemorrhages (40%), pulmonary hypertension (82.2%) and bradycardia (13.3%). In the newborns of the main group, non-invasive (95.6%) and invasive (68.9%) lung ventilation, surfactant replacement therapy (68.9%) were conducted.

Table II presents the distribution of genotypes and allele frequencies for the *eNOS* (G894T, rs1799983) and *IL1B* (C3953T, rs1143634) gene variants in mothers of the comparison and main groups.

The analysis of genotype and allele frequencies for the eNOS and IL1B genes did not reveal statistically significant differences between the mothers of the

Table 2. Frequency of genotypes and alleles distribution for the eNOS and IL1B genes among mothers in the study groups

Gene (variant)	Genotype, allele	Mothers of comparison group, n=59	Mothers of main group, n=40	p
eNOS (G894T, rs1799983)	894GG	32 (54,2%)	18 (45,0%)	0,42
	894GT	24 (40,7%)	16 (40,0%)	1,00
	894TT	3 (5,1%)	6 (15,0%)	0,15
	894G	88 (0,75)	52 (0,65)	0,16
	894T	30 (0,25)	28 (0,35)	
IL1B (C3953T, rs1143634)	CC	32 (54,2%)	28 (70,0%)	014
	CT	24 (40,7%)	11 (27,5%)	0,20
	TT	3 (5,1%)	1 (2,5%)	0,65
	C	88 (0,75)	67 (0,84)	0,16
	T	30 (0,25)	13 (0,16)	

Table 3. Frequency of genotypes and alleles distribution for the eNOS and IL1B genes among newborns in the study groups

Gene (variant)	Genotype, allele	Neonates, comparison group, n=60 (%)	Neonates, main group n=45 (%)	p value
eNOS (G894T, rs1799983)	894GG	30 (50,0%)	17 (37,8%)	0,24
	894GT	25 (41,7%)	25 (55,6%)	0,17
	894TT	5 (8,3%)	3 (6,7%)	1,00
	894G	85 (0,71)	59 (0,66)	0,45
	894T	35 (029)	31 (0,34)	
IL1B (C3953T, rs1143634)	3953CC	35 (58,3%)	31 (68,9%)	0,31
	3953CT	20 (33,3%)	12 (26,7%)	0,53
	3953TT	5 (8,3%)	2 (4,4%)	0,70
	3953C	90 (0,75)	74 (0,82)	0,24
	3953T	30 (0,25)	16 (0,18)	

comparison and main groups. These results suggest that these maternal genetic variants, on their own, are not associated with the risk of HIE in neonates.

Table III displays the distribution of genotypes and allele frequencies for the studied *eNOS* and *IL1B* gene variants in neonates from both the comparison and main groups.

For both genes, the analysis revealed no statistically significant differences in the distribution of genotypes and alleles between neonates in the comparison group and the main group. These findings suggest that, in this cohort, the genotypes and alleles of the studied variants of the *eNOS* and *IL1B* genes alone do not significantly contribute to the genetic predisposition to HIE in neonates.

After that, we evaluated the effect of *eNOS* and *IL1B* gene variants on the course of the neonatal period in newborns of the main group, the risk of developing neonatal syndromes, and the need for medical interventions.

An association of the G894T variant of the *eNOS gene* (both neonatal and maternal) with the risk of developing severe asphyxia in newborns was found. The frequency of detection of the 894TT genotype by the *eNOS* gene was increased in newborns with severe asphyxia (50.0% vs. 2.4%: p=0.018) and in their mothers (75.0% vs. 7.5%: p=0, 0057).

An association between G894T variant of the *eNOS* gene (both in newborns and in mothers) and an increased risk of neonatal bradycardia were also found. Thus, the frequency of 894TT genotype was higher in newborns with bradycardia (33.3% vs. 2.6%: p=0.043) and in their mothers (66.7% vs. 5.5%: p=0.0015).

Among mothers of newborns with HIE, who were diagnosed with respiratory failure in the early neonatal period, an increased frequency of the 894TT genotype for the G894T variant of the *eNOS* gene was found, in particular, it was observed in 33.3% compared to 3.4% of cases (p=0.013) in mothers of comparison group, whose children didn't experience respiratory failure. In newborns with respiratory failure, a significant increase in the frequency of the 894TT genotype was also observed (20.0% vs. 0.0%: p=0.032).

In the study of intergenic interactions, no influence of neonatal combinations of genotypes on the

development of HIE in newborns was found, but an increase in the frequency of the maternal combination of genotypes 894GG/3953C for the *eNOS* and *IL1B* genes was detected in the comparison group, in contrast to the mothers of the main group (27.1% vs. 2.5%: p=0.001), that is, this maternal combination of genotypes can reduce the risk of developing HIE in newborns.

Further analysis of intergenic interactions, performed in mother-child pairs, revealed an increased frequency of the neonatal 894GG (*eNOS*)/maternal 3953C (*IL-1B*) genotypes combination in the comparison group versus the group of newborns with HIE (27.1% vs. 5.0%: p=0.007), i.e. they showed a protective effect against the development of HIE.

DISCUSSION

As a result of the research, no associations of the *eNOS* and *IL1B* genes variants with the development of HIE were found, instead, associations of maternal and neonatal genotypes 894TT for the *eNOS* gene with the development of severe asphyxia, bradycardia and respiratory failure in newborns with hypoxic-ischemic encephalopathy were detected.

The G894T variant (rs1799983) in exon 7 of the *eNOS* gene is one of the most common and causes the substitution of glutamine for asparagine at position 298 of the eNOS protein sequence. This substitution is conservative, but the presence of this variant has nevertheless been shown to lead to the generation of protein products with different susceptibilities to cleavage, suggesting that G894T has a functional effect on the eNOS protein [16]. The results of a meta-analysis have shown that the G894T variant affects the production of nitric oxide, in particular, it was determined that carriers of the T allele had lower levels of NO (which is equivalent to lower levels of nitrates/nitrites) [17]. Research by Sofowora et al. indicates that the clinical significance of this genetic variant can be manifested only in the presence of endothelial dysfunction [18].

That is why the G894T variant of the *eNOS* gene has been actively studied in various pathological conditions in newborn children. In particular, it was established that the frequency of the T allele can be a risk factor for pulmonary hypertension in newborns with congenital heart defects [19]. The association of the G894T variant with the risk of development and severity of respiratory distress syndrome in preterm infants was also shown [20]. In a study by Szpecht et al. it was found that premature newborns with the GT genotype had a 3.4 times higher risk of intraventricular hemorrhage [21]. In our study, we got the associations with other pathological conditions in neonates with HIE, but they most fully characterize endothelial dysfunction that occurred in the early neonatal period and increased neurological damage, occurred in the antenatal and intranatal periods. It is worth mentioning that the 894TT genotype, in turn, is associated with low levels of NO, which is critically important for the normal development and functioning of the vascular system of both the fetus and the newborn.

Clinical studies and preclinical animal models have shown dramatic increases in systemic levels of cytokines, particularly IL-1β, as a result of perinatal brain injury caused by severe asphyxia [22]. It should be noted that activity of IL-1β and its biological functions are mediated by variants of the *IL1B* gene. In particular, the variant C3953T (rs1143634) in exon 5 of the *IL1B* gene is one of the most studied. Although this variant is synonymous (or "silent", that means, it does not lead to an amino acid substitution in the protein sequence), in vitro it was demonstrated that individuals with the TT genotype secreted significantly higher levels of IL-1β than individuals with the CT and CC genotypes [23].

Despite the potential clinical significance of the C3953T variant, no associations with the risk of complications such as sepsis, intraventricular hemorrhage, and bronchopulmonary dysplasia were found in the examined newborns [24-26]. In our study, there was also no significant effect of the C3953T variant of the *IL1B* gene on the risk of developing HIE and other pathological conditions in newborns with HIE. However, during the analysis of intergenic interaction (combinations of both maternal and neonatal genotypes), a decrease in the frequency of the maternal combination of genotypes 894GG/3953C for the *eNOS* and *IL1B* genes in the main group was revealed, i.e. a protective effect with regard to the risk of HIE in newborns (in the presence of the 894GG genotype for *eNOS*, as mentioned, reveal higher levels of NO, and with the heterozygous variant – genotype 3953CT for the *IL1B* gene, the level of the cytokine IL-1β is moderately increased)**.** Considering the fact that high levels of IL-1β cytokine were noted in newborns with various pathological conditions [27], it is possible that, in certain clinical situations, the influence of the maternal factors also takes place here – that is, the vertical transfer of maternal immune cells [28]**.** But the increase in the frequency of distribution of the maternal heterozygous variant 3953CT for the *IL1B* gene, which we found in combinations with both maternal and neonatal 894GG genotypes for the *eNOS* gene in the comparison group, indicates the presence of an underestimated and unstudied protein interaction, when with sufficient production of NO, a certain

increase in the level of pro-inflammatory cytokines can block potential negative effects associated with excessive reactions in this pathogenetic link during the development of pathological conditions.

The maternal and neonatal intergenes interactions, we have studied, open up the new opportunities in the formation of new approaches to neuroprotective treatment. As it is known, arginine is a substrate for eNOS and subsequent NO production. It has been detected that hypoargininemia is quite common among premature babies and there are already positive results regarding arginine therapy [29]. As for the regulation of cytokine levels, trimethylglycine can be a promising substance, as it is able to inhibit the production and release of IL-1β [30]. But taking into account the increase in the frequency of heterozygosity 3953CT for the *IL1B* gene in the comparison group and the potential protective effect against the development of HIE when combined with the 894GG genotype for the *eNOS* gene, we need further large-scale studies. For the use of both arginine and trimethylglycine, it is necessary to know the genotype-mediated dose-dependent effect of these amino acids and the need for other macro- and micronutrients, since the pathogenesis of HIE is multicomponent and it is necessary to avoid unwanted clinical effects during treatment**.** Experimentally, with the use of NG-monomethyl-L-arginine, an inhibitor of NOS, it was confirmed that among cytokines only IL-1β directly affects the formation of NO [31]. Therefore, with the simultaneous use and, accordingly, with the protein interaction of trimethylglycine and arginine, there will be the conditions for sufficient production of NO. Given the increase in arginine intake and NO production, the processes contributing to endothelial dysfunction will be inhibited.

In our opinion, the use of arginine and trimethylglycine in pregnant women and some time after childbirth can be effective in the prevention of HIE, especially in the case of complicated obstetric medical history. Thus, these amino acids will exert their biological effects even at the stage of fetal development, and after birth the child will receive them with mother's milk. But it is also worth strengthening the prevention and treatment of HIE by correcting mitochondrial dysfunction. It should be noted, that it is much easier to choose the dosage of a certain drug or biologically active compound for mothers. Mostly all therapeutic doses are already known and it is possible to track the blood levels of these substances, adjust them with the usage of genotyping, and achieve the optimal genotype-mediated dose-dependent effect. In the nearest future genotyping of mothers and newborns, especially with complicated obstetric anamnesis, can be used for personalized treatment tactics to minimize neurological consequences in newborns with HIE.

CONCLUSIONS

The significance of the intergenic maternal combination of 894GG/3953CT genotypes for the *eNOS* and *IL1B* genes and the intergenic combination of neonatal 894GG (eNOS)/maternal 3953CT (IL-1B) genotypes in the development of HIE in newborns has been proven. Associations of maternal and neonatal 894TT genotypes for the *eNOS* gene with the development of severe asphyxia, bradycardia, and respiratory failure were found in newborns with HIE**.** Further studies of intergenic and interprotein interactions of the axis eNOS – IL1β (arginine – trimethylglycine) are necessary to make a prediction and strategy of neuroprotective personalized treatment of HIE in newborns.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Yuliia Cherniavska
Department of Pediatrics No1 and Neonatology,
Poltava State Medical University,
23 Shevchenko St., 36000, Poltava, Ukraine
email: ycherniavska32@gmail.com

ORCID AND CONTRIBUTIONSHIP
Yuliia Cherniavska: 0000-0002-4522-7538 B D
Alina Davydenko: 0000-0002-4042-644X B D
Valerii Pokhylko: 0000-0002-1848-0490 A E F
Liliia Fishchuk: 0000-0001-9999-7389 B C D
Zoia Rossokha: 0000-0002-4767-7364 A E F

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

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ORIGINAL ARTICLE

CONTENTS

Immunohistochemical evaluation of GATA-3 in patients with urinary bladder cancer

Randa Saad Hameed[1], Rihab Hameed Almudhafar[2], Liwaa Hussein Mahdi[2]

[1]DEPARTMENT OF BASIC SCIENCES, COLLAGE OF DENTISTRY, UNIVERSITY OF KUFA, KUFA, IRAQ

[2]DEPARTMENT OF GENERAL PATHOLOGY AND FORENSIC MEDICINE, COLLAGE OF MEDICINE, UNIVERSITY OF KUFA, KUFA, IRAQ

ABSTRACT

Aim: To analyze expression levels of GATA-3 in bladder tumor tissues and to prove a relation between expression of GATA-3 and clinicopathological characteristics of bladder tumors, including patient age, sex, tumor grade, and muscle invasion.

Materials and Methods: Forty formalin fixed paraffin embedded (FFPE) tissue blocks obtained from bladder tumor by transurethral resection are collected from teaching hospitals at Al-Najaf governorate. Those blocks are stained by using hematoxylin and eosin stain. Histopathological features were examined and then immunostained by GATA-3.

Results: Evaluation of GATA-3 expression in urothelial carcinoma, revealed GATA-3 test was (positive) in thirty-four samples of urothelial carcinoma, while GATA-3 test was (negative) in twenty-one samples of urothelial carcinoma. Correlation of GATA-3 with other variables (age, sex, and grade) was a statistically non-significant.

Conclusions: GATA-3 is an Immunohistochemical sensitive marker to diagnose urothelial carcinoma. GATA-3 expression showed non-significant relation with age, gender and histopathological parameters and its expression has been observed to be lost or reduced in substantial proportion in relation to urothelial carcinoma. This alteration or down regulation of GATA-3 is correlated with higher tumor grade and stage.

KEY WORDS: urothelial carcinoma, GATA-3, immunohistochemistry

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INTRODUCTION

Urinary bladder cancer (UBC) is a disturbing malignant disorder which participates about three percent to the recent development of cancer field [1]. In Iraq, urinary bladder cancer was considered the fifth cancer from the top ten cancers with percentage about 7.48% and the incidence rate was about 4.29 depending on Iraqi cancer registry 2021. The etiology and pathogenesis can be related to environmental and occupational agents. The heavy smoking habit is threating which induces cellular transformation through a proinflammatory effect [2]. Chronic inflammation is a strong agent in cancer of urinary bladder. It gives different of mediators like, cytokines and chemokines, which enhance proliferation and angiogenesis of tumor cell. In addition, it releases mutation generating reactive oxygen species to stimulate changes in microenvironment of tumor cell favouriting its metastasis [3]. The transformation of normal urothelial cell to a neoplastic one occurs through complicated sequences of molecular proceedings termed as epithelial plasticity. At early stages, these alterations are reversible. This process is started with epithelial mesenchymal transition (EMT) transcription factors. The differentiation of mesenchymal stem cells can be into a variety of cell types involving endothelial cells, and fibroblasts which induce growth of autocrine [4]. The carcinogenesis of urothelium is molecularly classified into two different pathways resulting in two variant prognostic and morphological subtypes, that are non-muscle invasive (papillary) and the muscle-invasive types [5]. The non-invasive papillary carcinoma drives from normal urothelial as the proliferative proceedings; beginning with hyperplasia, then neoplasia of papillary urothelium; bladder cancer with non-muscle-invasive (NMI-BC) with a little percentage (10–15%) to the part of non-invasive (high-grade) and urothelial carcinoma (invasive). Although there is a little tendency for muscle-invasive, it has potential of recurrence. The primary changes of genes influence tyrosine kinase receptor, fibroblast growth factor receptor-3 (FGFR-3) that stimulates growth of cell [6]. On the other hand, most

Table 1. Demographic and clinical characteristics of studied groups

Variable	Subgroup	Absolut (n)	%
Age group (years)	Less than 67	20	50
	Over 67	20	50
Sex	Male	31	77.5
	Female	9	22.5
Grade	Low	22	55
	High	18	45
Muscle invasion	Present	13	32.5
	Absent	27	67.5

Table 2. Relationship among studied groups according to immunohistochemistry of GATA-3

		GATA 3		Total	P-value
		Positive (n=34)	Negative (n=6)		
Age group (years)	Less than 67	18 (90%)	2 (10%)	20(100%)	0.7
	Over 67	16 (80%)	4 (20%)	20(100%)	
Sex	Male	27 (87.1%)	4 (12.9%)	31(100%)	0.6
	Female	7 (77.8%)	2 (22.2%)	9(100%)	
Grade	Low	18 (81.8%)	4 (18.2%)	22(100%)	0.8
	High	16 (88.9%)	2 (11.1%)	18(100%)	
Muscle invasion	Present	11 (84.6%)	2 (15.4%)	13(100%)	0.9
	Absent	23 (85.2%)	4 (14.8%)	27(100%)	

of invasive carcinoma drives from multiple genetic alterations of tumor suppressor genes involving p53, p16, and Rb that makes a basis for series of disordered growth of tissue to carcinoma in situ (CIS) followed by non-invasive (high grade) to muscle-invasive urothelial carcinoma. Both types have frequent mutations, and primitive missing of heterozygosis that locates on the chromosome 9, that acts a means to yield irregularities of genes which enhances a development of changes in gene [7]. GATA3 (GATA binding protein 3) is one of six types of family of a zinc finger transcription factor, and it has a critical function in activating, controlling cell growth, maturation, and differentiation of numerous cell and tissues types [8, 9] involving luminal part of glandular epithelial cells of the mammary gland, T lymphocytes, thymocytes, kidney, sympathic nervous system and hair follicles of the skin [10, 11]. GATA3, defined as precise marker of urothelial carcinoma of bladder, and it shows a high expression in works of Yuk et al. [12], and Wang et al. [13]. In spite of GATA3 is appeared more in bladder carcinoma, its high appearance may unfavorably suppress development of malignant cells in bladder carcinoma [14]. While, more expression of GATA3 indicates a low tumor grade and stage but a high recurrence survival rate (free) [15, 16]. A loss of balance between more expression of GATA3 in tissues of bladder cancer and suppressing role of GATA3 in cells of bladder cancer may interpreted with capability of GATA3 to make changes in bladder cancer basal cells to luminal cells [15, 16]. These days, GATA3 was documented to occupy an important function in controlling an immune response (anti-cancer function) in tumor microenvironment (TME) [17, 18]. During embryogenesis, GATA-3 is included during maturation of kidney and urothelium collecting system [19]. Immunohistochemistry of GATA3 is employed in the comparison between carcinomas of urothelium from other cancer types in surgical pathology [20, 21]. GATA3 is advised as a powerful tumor suppressor protein in breast cancer; its loss is connected with many tumor charectestics, in addition to poor prognosis [22]. The correlation of GATA3 knockdown and cell migration, cell invasion, epithelial to mesenchymal transformation has seen during in vitro studies [23, 24]. GATA3 expression in urothelial carcinomas was joined with molecular subgroup of the luminal cells [25].

AIM

The aim of this research is to analyze expression levels of GATA-3 in bladder tumor tissues and to prove a relation between expression of GATA-3 and clinicopathological characteristics of bladder tumors, including patient age, sex, tumor grade, and muscle invasion.

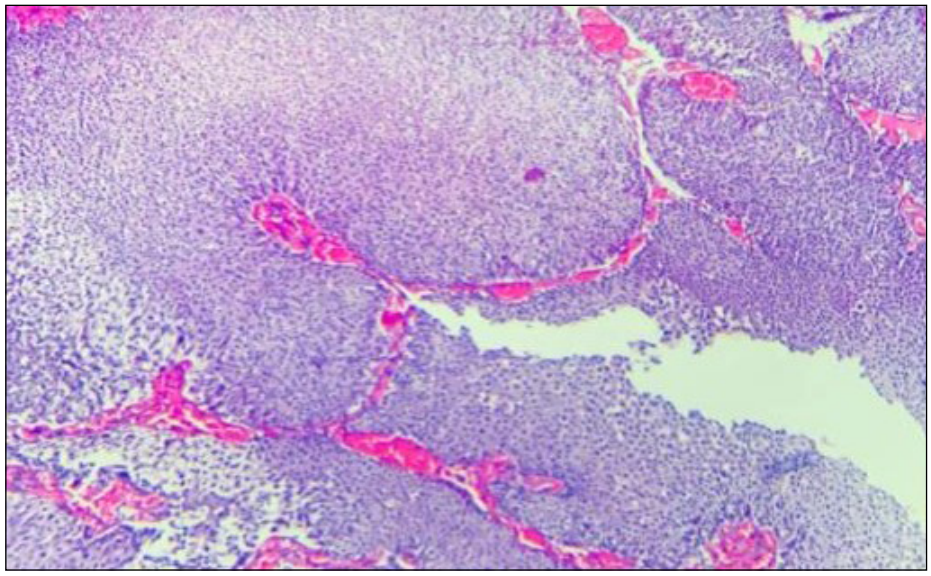

Fig. 1. Transurethral specimen resection shows low grade urothelial carcinoma; nuclei are smaller in size without invasion into lamina propria (H&E, Magnification power X100).

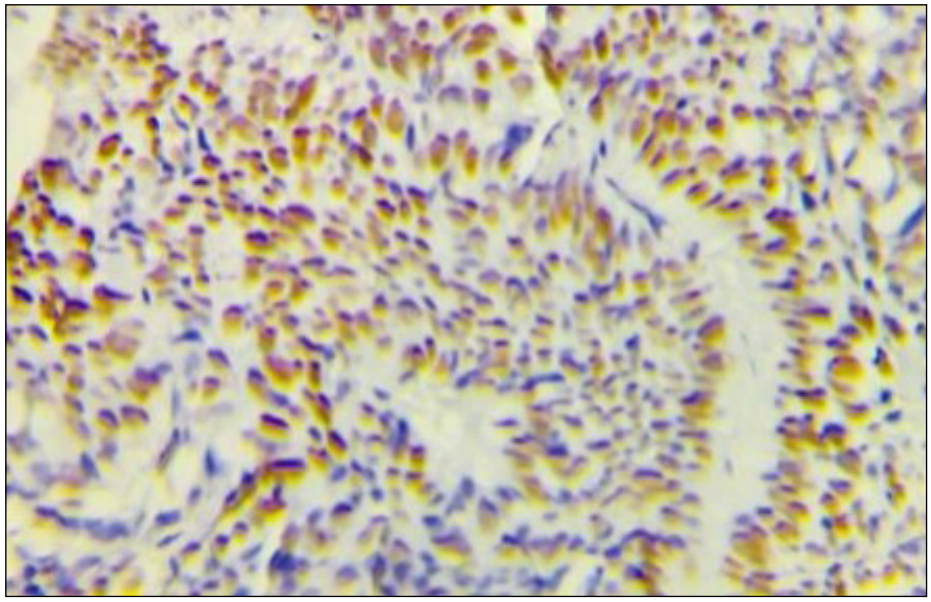

Fig. 2. Transurethral specimen resection of low grade urothelial carcinoma shows patchy nuclear staining for GATA-3 (immunohistochemistry) (Magnification power X400).

MATERIALS AND METHODS

A cross sectional study of 40 samples of Iraqi patients with urothelial carcinoma was completed at faculty of medicine- university of Kufa (middle Euphrates unit for cancer research). Formalin fixed paraffin embedded (FFPE) tissue blocks gathered by transurethral resection of bladder tumor are collected from teaching hospitals at Al-Najaf governorate, the diagnosis of urothelial carcinoma performed by histopathologist. The processing of immunohistochemistry (IHC) was performed by using positive charge slides. IHC staining protocol by labeled streptavidin biotin (LSAB) method was performed after de-paraffinization, heat induced antigen retrieval for 20 minutes, then blocking with peroxidase enzyme for 5 minutes, followed by primary antibody GATA-3 (Bio SB, clone: EP368). After incubation with primary antibody, the secondary antibody was added for 30 minutes followed by horse reddish peroxidase (HRP) for 30 minutes, and chromogen for 15 minutes. Each step washed twice with buffered solution. Finally, counter staining and mounting.

SCORING

Depending on the intensity of staining and the positive percentage, immunohistochemical evaluation of slides stained with GATA3 was scored. The score of intensity was determined as 0 (without stain), score one (simple stain), score two (moderate stain), score three (strong stain) divided by percentage score. Both scores will be assessed apart between the groups.

STATISTICAL ANALYSIS

To determine the relation between GATA-3 expression and urothelial carcinoma, a chi-square test was used along with

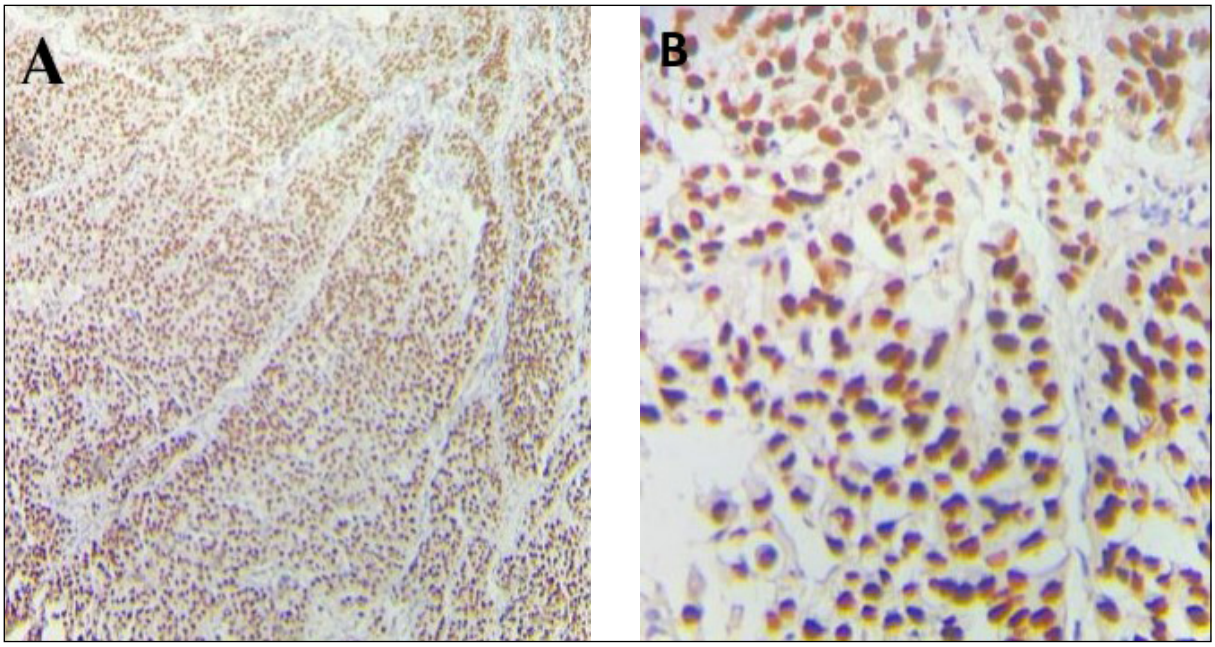

Fig. 3. Transurethral specimen resection of high grade urothelial carcinoma shows muscle invasion with diffuse strong nuclear staining (positive) for GATA-3 (immunohistochemistry) (Magnification power X100 (A), X400 (B)).

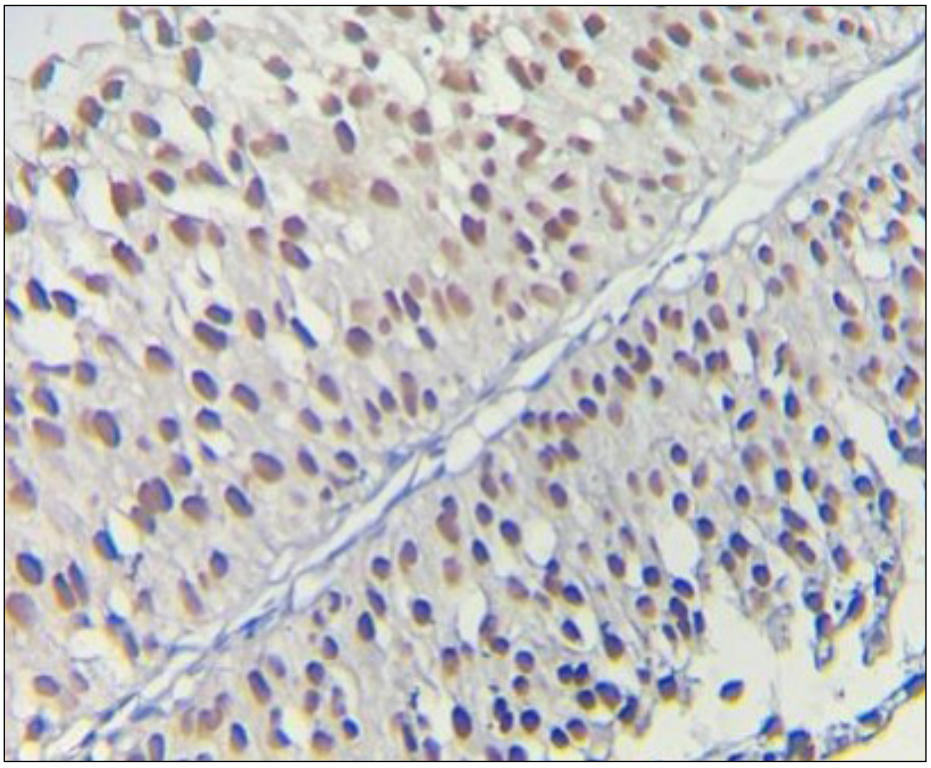

Fig. 4. Transurethral specimen resection of low grade urothelial carcinoma shows no muscle invasion with strongly positive expression for GATA-3 (immunohistochemistry) (Magnification power X100).

the SPSS program version 26, considering several variables: age, sex, histological grade, and muscle invasion. A P-value of 0.05 or less was considered statistically significant.

RESULTS

A forty FFPE tissue blocks of urothelial carcinoma involved in the present study, age categories of patients were less than 67 (50%) years and over 67 (50%) years. There was male predominance of 77. 5%. The microscopical study of these samples was made by using GATA-3 tumor marker test. GATA-3 test was positive in 34 samples of urothelial carcinoma, while GATA-3 test was negative in 21 samples of urothelial carcinoma, details of subject and their numbers are shown in table 1, table 2.

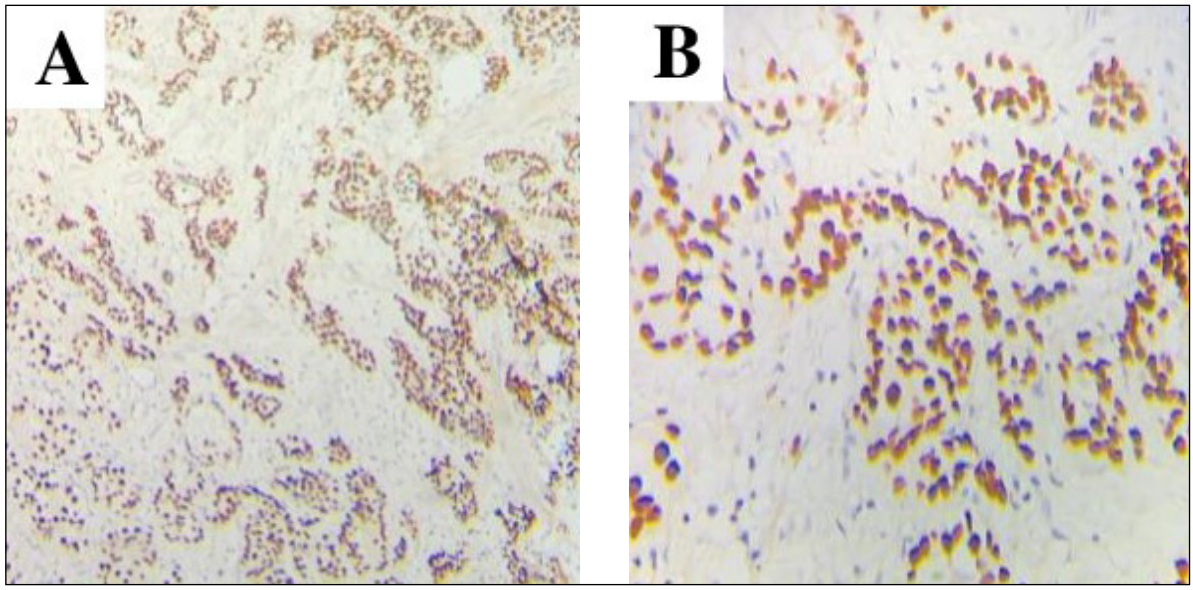

Fig. 5. Transurethral specimen resection of high grade urothelial carcinoma shows strong nuclear staining(positive) for GATA-3 (immunohistochemistry) (Magnification power X100 (A), X400 (B)).

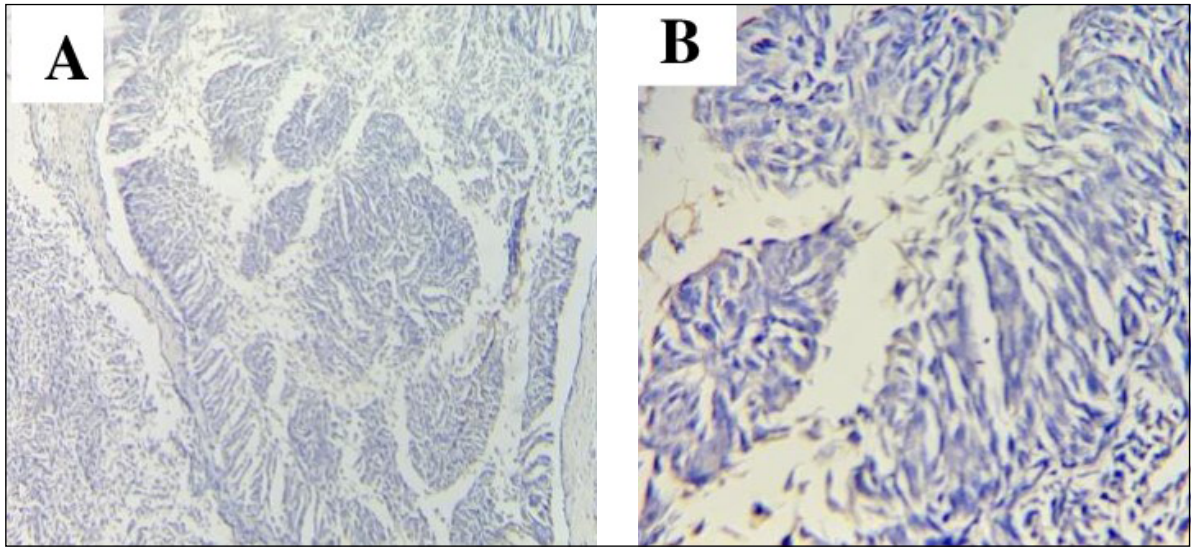

Fig. 6. Transurethral specimen resection of high grade urothelial carcinoma shows negative expression for GATA-3. (immunohistochemistry) (Magnification power X100 (A), X400 (B)).

Table 1 shows that the age category was less than 67 by about 50% and more than 67 by about 50%. The majority of gender group was at the male categories of 77.5% more than females of 22.5%.

Table 2 shows that most cases were positive for GATA-3 among patients suffering from urothelial carcinoma. Regarding to age, sex, grade, muscle invasion categories, GATA-3 was positive in age group less than 67 by about 90% (P-value=0.7), positive among males by about 87.1% more than females (P-value=0.6), positive in in high grade group by about 88.9% (P-value=0.8), and positive in the group where was absence of muscle invasion by about 85.2% (P-value= 0.9).

DISCUSSION

The present study was a fundamental step completed at the Faculty of Medicine, University of Kufa, Iraq, in the Middle Euphrates Unit for Cancer Research, to establish the relationship between GATA-3 and urothelial carcinoma. In the current study, the higher positivity of GATA-3 was at age categories less than 67 years of 90%, with male was more than female – 87.1% to 77.8% respectively (with no significant difference), and this variation of GATA-3 expression in gender category may reflect the characteristics of molecular and biology of bladder tumors, which was comparable with the observation made by Gupta et al [26] in the Indian subcontinent.

We also found clustering of patients over 60 years, like many other studies and four patients less than 40 years, however, no

significant relation of GATA-3 expression with demographic factors, including age, gender. Similar GATA-3 positivity (90%) was seen in approximation with other studies of Liu et al. [27], who found 86% of GATA-3 positivity and Leivo et al. [28] with 99% of positive GATA-3 expression. Regarding to grade of tumor, low grade urothelial carcinoma (Fig.1, Fig.2) showed high GATA-3 positivity of 81.8% in comparison with high grade tumor (Fig.3-5.) of 88,7% without significant difference.

This suggests that GATA-3 has an important role in maintenance and differentiation of normal tissue of urothelium. On the other hand, the same results were achieved by Taber et al. [29] and Kollberg et al. [30], who noted that the most of low grade tumors have moderate positivity. Relating to muscle invasion, GATA-3 expression rely on muscle invasion presence or absence. In our study, the difference between invasive urothelial carcinoma (84,6%) and non-invasive urothelial carcinoma (Fig.6.) (85.2%) was non-significant. Our results were agreed with study by Daeseon Yoo who proved that the relation between muscle invasion and non-muscle invasion urothelial carcinoma was non-significant [31, 32]. Lin et al. [33] analyzed GATA-3 expression changes in high and low grade urothelial carcinoma. They detected that GATA-3 expression downregulation in high grade (77.2%) in comparison with low grade (87.5%), which agreed with our results, GATA-3 downregulated in high grade (11.1%) compared to low grade (18.2%).

CONCLUSIONS

GATA-3 is an immunohistochemical sensitive marker to diagnose urothelial carcinoma. GATA-3 expression showed non-significant relation with age, gender and histopathological parameters and its expression has been observed to be lost or reduced in substantial proportion in relation to urothelial carcinoma. This alteration or down regulation of GATA-3 is correlated with higher tumor grade and stage.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Randa Saad Hameed
University of Kufa
299G+HPX, Kufa Street, Kufa, Najaf Governorate, Iraq
e-mail: randas.albattawi@uokufa.edu.iq

ORCID AND CONTRIBUTIONSHIP

Randa Saad Hameed: 0009-0000-5281-8857 B C D
Rihab Hameed Almudhafar: 0000-0003-4997-5549 C D E
Liwaa Hussein Mahdi: 0000-0002-2310-2419 A E F

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

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ORIGINAL ARTICLE

CONTENTS

Small common bile duct – the risk factor for post-ERCP pancreatitis in patients with choledocholithiasis

Ivan Mamontov[1], Tamara Tamm[1], Kostiantyn Kramarenko[1] , Dmytro Ryabushchenko[1], Dmytro Sytnik[2], Samer Dghaili[3]

[1]KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE
[2]POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE
[3]SALISBURY NHS FOUNDATION TRUST, SALISBURY, UNITED KINGDOM

ABSTRACT

Aim: To investigate the risk factors for PEP in patients with choledocholithiasis

Materials and Methods: We have retrospectively analyzed 253 cases with choledocholithiasis that underwent ERCP. The primary endpoint was the occurrence of PEP. A number of potential risk factors for PEP were taken into account: gender, age (10 mm); type of choledocholithiasis – microcholedocholithiasis, choledocholithiasis (1-2 stones), multiple choledocholithiasis (≥ 3 stones) and choledocholithiasis due to Mirizzi syndrome; periampullary diverticulum; papilla size (≤5 or >6 mm); ERCP success; selective biliary cannulation; pancreatic cannulation/injection; precut; papillotomy.

Results: PEP was in 8 (3,2 %) cases. Univariate analysis identified two factors associated with PEP – common bile duct ≤10 mm (P=0.045) and papilla ≤5 mm (P=0.036). In multivariate analysis, among all variables only the common bile size ≤10 mm appeared to be significant (P=0.018).

Conclusions: In patients with choledocholithiasis the occurrence of PEP is related to common bile duct size less than 10 mm.

KEY WORDS: risk factor, ERCP, choledocholithiasis, post-ERCP pancreatitis

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an invaluable procedure in the diagnosis and management of pancreaticobiliary disorders. Most often ERCP treatment modalities are used in biliary diseases such as common bile duct stones or malignant biliary obstruction. In case of common bile duct stone ERCP is a routine and primary method to be used. The stone removal rate and ranges from 74% to 98% and usually is higher than 90 % [1]. Among patients who undergone ERCP common bile duct stone is the indication for it in majority of cases – 50-70 % [2-5].

Nevertheless, the incidence of adverse events reported after ERCP is between 4 and 20% [2 ,4,5,]. Post-ERCP pancreatitis (PEP) is the most common and serious complication after ERCP and related endoscopic procedures [2, 4-7]. The incidence of PEP was reported to be 1% to 19,6% [2, 3, 8]. Being a serious complication PEP extends the hospital stay and increases hospital costs, and in severe cases may even lead to fatal outcome [6, 7].

In general PEP risk factors have been well investigated [2-17], identification of these factors is essential to the recognition high-risk cases in which ERCP should be avoided if possible, or in which protective measures should be done [6-8, 10, 14]. Factors are generally divided into two groups: patient-related factors and procedure-related factors.

Despite the plenty of works discovering the PEP risk factors, these factors vary from work to work. The reason for this may be in differences of patients' groups and indications for ERCP, operator preference and experience and other factors.

AIM

The aim of this study was to investigate the risk factors for PEP in patients with choledocholithiasis as the most common indication for ERCP.

MATERIALS AND METHODS

PATIENTS

We retrospectively analyzed the records of patients (form № 003/o) of all consecutive cases with undergo-

ing ERCP between January 2013 and December 2020. Indications for ERCP were determined on the basis of clinical and radiologic finding. There were 355 patients with choledocholithiasis (Fig.. 1). Exclusion criteria were: papillotomy in history, complications (biliary pancreatitis and/or cholangitis), ampulla impacted sone, Billroth II gastrectomy and incomplete medical data (lack of laboratory and visualisation data after ERCP).

ERCP

ERCP was performed by two experienced operators (K.O. Kramarenko, I.M. Mamontov). Before the procedure all patients received diclofenac (100 mg) per rectum for PEP prevention [18]. Premedicated with an injection of scopolamine butylbromide (10–20 mg) and local anesthesia of the pharynx with 8 % lidocaine were done.

Procedure usually was started with a guided sphincterotom or canula. Priority was given to obtain selective biliary cannulation which is defined as deep canulation of common bile duct through naïve papilla followed by cholangiography without canulation of pancreatic duct or wirsungography. Precut papillotomy was used to achieve biliary access in case of failure of selective biliary cannulation after 5-10 attempts or approximately 5 min of trying. After cholangiography and estimating quantity and size of the common bile duct stone sphincterotomy and lithoextraction with basket were done. In case of need mechanical lithotripcy was used. Ballon dilatation was used only after sphincterotomy in case of distal common bile duct and/or its orifice was much smaller than the stone. Maximum balloon size was 12 mm. If complete removal was not achieved, nasobiliary drainage or biliary stenting was considered.

After the procedure, the patient fasted until the next morning, received an intravenous infusion and ceftriaxone (2 g). Blood tests – hemoglobin, bilirubin and amylase levels were measured at baseline, 4-8 hours after the procedure, and next morning. Biliary decompression was confirmed by decreasing bilirubin level and common bile duct size which was measured by ultrasound. ERCP-related adverse events and incidents were recorded. PEP was defined as upper abdominal pain with amylase levels more than three times the normal rate [18]. The severity of PEP was defined as mild (no organ failure, no local or systemic complications); moderate (transient organ failure, local or systemic complications without persistent organ failure); severe (persistent organ failure) [18].

The primary endpoint of this study was the occurrence of PEP in patients with choledocholithiasis. Although some of the studied patients, who had more than 1 ERCP procedure performed, PEP incidence was analysed only after the first session. A number of potential risk factors for PEP were analysed. All variables were made as categorical and included: gender, age (< 60 or ≥ 60 years); blood total bilirubin level (normal or increased); common bile duct size (≤10 or >10 mm); type of choledocholithiasis – microcholedocholithiasis, choledocholithiasis (1-2 stones), multiple choledocholithiasis (≥ 3 stones) and choledocholithiasis due to Mirizzi syndrome; periampullary diverticulum; papilla size (≤5 or >6 mm); ERCP success; selective biliary cannulation; pancreatic cannulation/injection; precut; papillotomy.

STATISTICS

To detect the association between PEP and any categorical variable univariate analyse was performed by Chi-square test (χ^2). Also, all variables were taken for entry into multivariate analyses by multinominal regression. A P-value less than 0.05 was regarded as significant. Variables with P<0,05 both for univariate and for multivariate models considered as a PEP risk factor.

Statistical analysis was done with SPSS® version 19 (IBM, USA).

RESULTS

Characteristics and medical data of the patients are presented in Table 1

Two-thirds of the patients were female (66%) and 17,8% of patients had cholecystectomy in history. The main clinical sign was jaundice. Initial ERCP was achieved in 98 % cases and complete stone extraction in 90,5 %.

Among 8 patients with PEP mild pancreatitis was in 6 cases, moderate – in 1 and severe in 1 patient. There was no lethal outcome. In case of more than 1 ERCP procedure/session needed there were no cases of PEP after the 2nd or 3d session.

Table 2 shows the results of univariable and multivariable analyses with the endpoint of PEP.

Univariate analysis (Table 2) identified two factors associated with PEP – common bile duct ≤10 mm (P=0.045) and papilla ≤5 mm (P=0.036).

In multivariate analysis (Table 2), among all variables only the common bile size ≤10 mm appeared to be significant (P=0.018). Other variables including the papilla size were not significant (P>0,05).

DISCUSSION

ERCP is a well-known preferred procedure for treating choledocholithiasis with a highly successful rate and relative safety [1, 6, 7]. Common bile duct stones are

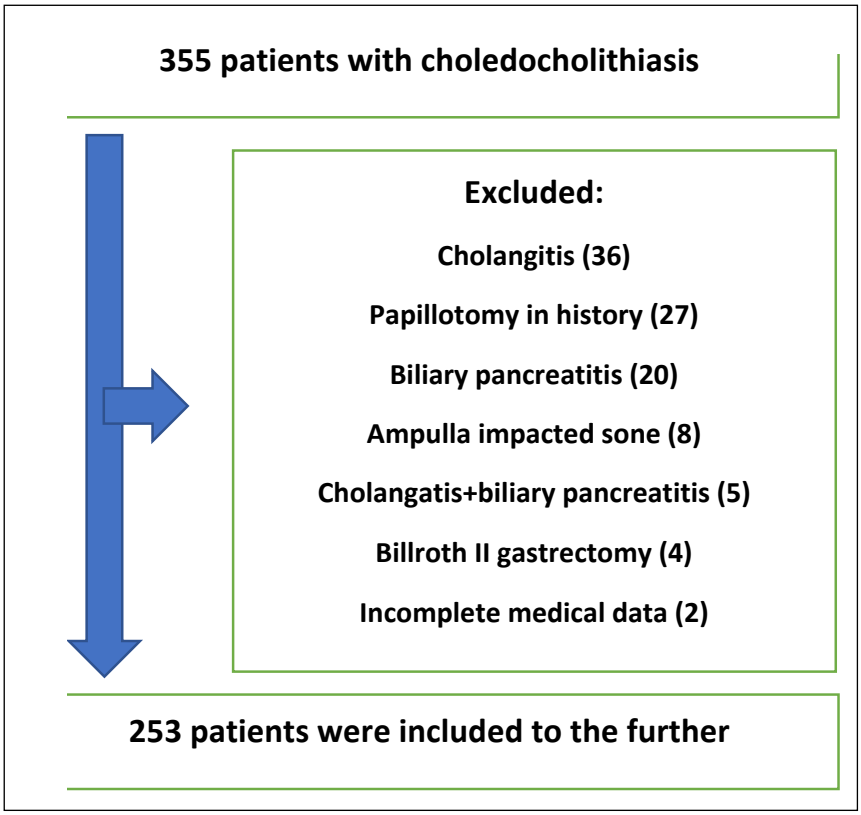

Fig. 1. Inclusion flowchart of the study.

Table 1. Baseline and Clinical Characteristics of the Patients with Choledocholithiasis (n=253)

Measure	Value
Age (range), yrs	64±14,6 (20-91)
Male/Female	86/167
History of cholecystectomy	45 (17,8 %)
Total bilirubin level (range), mmoll/l	71±61,2 (10-426)
Common bile duct (range), mm	12±3,8 (4-28)
Type of common bile duct stones	
Microcholedocholithiasis	38 (15 %)
Choledocholithiasis (1-2 stones)	166 (65,1 %)
Multiple common bile duct stones (≥3)	35 (13,8 %)
Common bile duct stone(s) due to syndrome Mirizzi	14 (5,5 %)
Periampullary diverticulum	44 (17,4 %)
Initial ERCP success	248 (98 %)
Selective biliary cannulation	190 (75,1%)
Pancreatic cannulation/injection	33 (13%)
EPST	231 (91,3 %)
Precut	73 (28,9 %)
Balloon dilatation of common bile duct	2 (0,8 %)
Complete stone extraction	229 (90,5 %)
> 1 endoscopic session required	52 (20,6 %)
PEP	8 (3,2 %)

the most common indication for ERCP [2-5]. However, despite improvement of the equipment for ERCP and implemented options for PEP-preventing in recent years, the incidence of PEP has not decreased significantly [4, 10]. In case when ERCP is considered to be used, identifying high risk patients for PEP is crucial for choosing treatment strategy and prevention measures [10, 12-14].

Table 2. Univariate and multivariate analysis of risk factors for PEP

Variables	PEP	Non -PEP	Analysis					
			Univariate		Multivariate			
			χ^2	P	B	P	Exp (B)	CI (95%)
Gender								
Male	5	81	2.992	0.084	0.580	0.509	1.787	0.320 - 9.990
Female	3	164						
Age, years								
< 60	3	64	0.515	0.473	1.344	0.189	3.835	0.515 - 28.559
≥ 60	5	181						
Blood bilirubin level								
Normal	0	48	1.934	0.164	-*	-*	-*	-*
Increased	8	197						
Common bile duct, mm								
≤10	6	97	4.024	0.045	2.539	0.018	12.665	1.539 - 104.196
>10	2	148						
Type of choledocholithiasis								
Microcholedocholithiasis	1	37						
Choledocholithiasis (1-2 stones)	6	159	2.016	0.570	-*	0.694	-*	-*
multiple choledocholithiasis (≥ 3 stones)	0	35						
Mirizzi syndrome	1	13						
Periampullary diverticulum								
Yes	3	41	2.325	0.127	2.044	0.056	7.718	0.952 - 62.542
No	5	204						
Papilla size, mm								
≤5	2	15	4.405	0.036	2.928	0.124	7.601	0.572 - 101.072
>6	6	230						
ERCP success								
Yes	8	240	0.167	0.683	-*	-*	-*	-*
No	0	5						
Selective biliary cannulation								
Yes	6	184	0.000	0.995	1.617	0.309	5.036	0.223 - 113.569
No	2	61						
Pancreatic cannulation/injection								
Yes	2	31	1.041	0.308	0.627	0.658	1.872	0.117 - 30.014
No	6	214						
Pre-cut								
Yes	1	72	1.076	0.300	-3.848	0.055	0.021	0.000 - 1.086
No	7	173						
Papillotomy								
Yes	7	224	0.151	0.698	-0.646	0.640	0.524	0.035 - 7.837
No	1	21						

* Calculation is unfeasible because one of the comparable groups contains 0 cases.

In variety of prospective and retrospective studies, there were some differences in risk factors for PEP, which may be connected with definitions, technique, patients' inclusion criteria and especially the indication for ERCP. It is well known that in case of sphincter of Oddi dysfunction PEP incidence is significantly higher [3, 10, 12]. Besides, the sphincter of Oddi dysfunction, an example may be malignant biliary obstruction when some special factors, such as level of obstruction [19] and pancreatic duct obstruction, [2, 19] may play a role in PEP incidence.

That is why we have been focused on PEP in a particular group of patients – with choledocholithiasis. It seemed to us reasonable to investigate the homogeneous group of patients with a certain most common pathology for ERCP – choledocholithiasis to clarify PEP risk factors without impact connected with other diseases.

To obtain pure results we have analysed only the cases with naïve papilla and excluded patients with Billroth II gastrectomy, which have some features of endoscope intubation and biliary canulation. We also have not included patients with complications, such as biliary

pancreatitis and/or cholangitis and with an ampulla impacted stone.

We have carefully chosen the variables to be studied and intentionally have not taken such factors as smoking, drinking and comorbidities, which appear in other studies [4, 9]. We consider them irrelevant to PEP, though, this decision might be quite subjective. Unfortunately, we have not had data about history of pancreatitis, so we have not been able to take into account this important factor like in other works [4, 9-12], though results on this factor are controversial. We also have not considered the factor of difficult canulation as in our technique manner pre-cut papillotomy was done in case of it.

We have taken all the variables into multivariate regression as there is an opinion that such a model may give more reliable results [5, 20].

In our study the incidence of PEP is in line with those reported in other series, but comparison may be difficult, because we have investigated only the cases of choledocholithiasis and other works mainly represent variety of different conditions when ERCP was used [13-17]. In spite of not very huge number of patients and quite a few cases with PEP, we have managed to obtain statistically reliable data. The limitation in PEP cases did not allow us to make a multivariate analysis for blood bilirubin level, type of choledocholithiasis and ERCP success. However, by Chi-square test these factors turned out to be insignificant.

Some works show that young age [3, 11, 14, 17] or female gender [15, 16] or both of them [2, 5] may be independent factors for PEP. Our data show no influence of gender and age on PEP incidence. Such results were obtained in other studies as well [4, 9, 13].

No significant connection (P>0,05) has been found also for such factors as periampullary diverticulum, selective biliary cannulation, pancreatic cannulation/injection, pre-cut of papillotomy. Some of these factors turned out to be risk factors for PEP according several studies [3, 4, 5, 11, 12, 14].

By univariate analysis among all factors two have had significant connection with PEP – common bile duct ≤10 mm and papilla ≤5 mm (P=0.045, P=0.036 respectively).

But the only one appeared an independent risk factor – common bile duct ≤10 mm (P=0.018). This factor corresponds to other studies [13, 16]. But in these works, borderline value of CDB were 9 and 12 mm respectively.

The reason why common bile duct size has influence on PEP is not clear. We may suppose that higher biliary pressure in case of larger common bile duct (>10 mm) prevents PEP. On the contrary, subnormal pressure with common bile duct ≤10 mm is associated with increased incidence of PEP. The pathophysiology of that effect is to be investigated in the future.

Apart from the common bile duct size, according to the multivariate analysis there are factors with modulus of B-coefficient value ≥1,0 (table 2). That means that these factors (age, periampullary diverticulum, papilla size, selective biliary cannulation, Pre-cut) may have influence on the development of PEP. So further investigations with lager number of cases are needed to clear it up.

CONCLUSIONS

Our data shows that in patients with choledocholithiasis the occurrence of PEP is related to common bile duct size less than 10 mm. So small common bile duct was the only risk factor for PEP in patients with choledocholithiasis.

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CONFLICT OF INTEREST

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CORRESPONDING AUTHOR

Ivan Mamontov
Kharkiv National Medical University
4 Nauky Avenue, 61000 Kharkiv, Ukraine
e-mail: ivan.n.mamontov@gmail.com

ORCID AND CONTRIBUTIONSHIP

Ivan Mamontov: 0000-0003-0059-2715 A B C D E F
Tamara Tamm: 0000-0001-6372-2092 B E
Kostiantyn Kramarenko: 0000-0002-1997-8928 B
Dmytro Ryabushchenko: 0000-0002-0655-1466 C D
Dmytro Sytnik: 0000-0002-4885-334X C D
Samer Dghaili: 0009-0005-7816-4843 B D

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

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ORIGINAL ARTICLE

CONTENTS

Woman's self-realization in the system and structure of family relations

Olena Vysotska[1], Olena Falova[2], Liubov Rysovana[3], Oksana Platyniuk[3], Oleksandr Bazhenov[2]
[1]NATIONAL AEROSPACE UNIVERSITY H.E. ZHUKOVSKY «KHARKIV AVIATION INSTITUTE», KHARKIV, UKRAINE
[2]UKRAINIAN ENGINEERING PEDAGOGICS ACADEMY, KHARKIV, UKRAINE
[3]KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

Aim: To study the peculiarities of self-realization of women with different states of family interaction, to build a mathematical model that allows to identify the probability of self-realization of women, depending on their psycho-emotional, individual-psychological, behavioral and partnership patterns, to consider the family as a whole system, to define the phenomenon of family interaction as a leading the construct of the process of family functioning, to distinguish levels of family crisis and states of family interaction.

Materials and Methods: Women of different social status and level of self-realization participated in this study.

Results: In the given sample, it was displayed what percentages of divorced women compared to those living in families are self-actualized in their lives.

Conclusions: A mathematical model was developed to explore the probability/lack of self-realization in women, which allowed the studying of the main indicators that affect the determination of the probability of self-realization in women depending on their psycho-emotional state and individual psychological or behavioral patterns.

KEY WORDS: social stress, self-realization of woman, psychological equilibrium, woman's self-realization in the context of marriage

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INTRODUCTION

In modern society, the role of women has changed significantly. She actively participates in various spheres of life, holds managerial positions, and engages in scientific and creative activities. At the same time, a woman remains the center of family life, performing the roles of mother, wife and daughter. Self-realization of women is a key factor in their psychological well-being and affects the quality of life of both the woman herself and her family members [1].

The relevance of this study is due to the fact that in today's world, where divorce, conflicts and instability have become more frequent, it is important to understand how psycho-emotional, individual-psychological, behavioral and partnership patterns can affect women's self-realization [2].

Psycho-emotional, individual-psychological, behavioral and partner patterns are important factors that significantly affect the process of self-realization of women. Psycho-emotional patterns include emotional stability, stress resistance, ability to self-regulate and manage emotions. Women who have high emotional stability more easily overcome life's difficulties and better adapt to new challenges, which contributes to their successful self-realization. On the other hand, high emotional lability or a tendency to depression and anxiety can create barriers to self-realization, reducing the level of motivation and self-confidence [3].

Individual psychological patterns include personal characteristics such as self-esteem, level of self-esteem, achievement motivation, value orientations, and personal attitudes. Women with high self-esteem and motivation to achieve usually show greater persistence and purposefulness in the process of self-realization [3,4]. Qualities such as self-confidence, autonomy and a focus on personal development can contribute to success in various areas of life, including professional and personal.

Associated with specific models of behavior that a woman uses to achieve her aims [1,5]. For example, the ability to self-control, effective time management and communication skills can contribute to successful self-actualization. Behavioral patterns that include

traits of passivity, dependence or avoidance of difficult situations, on the contrary, can hold back the process of self-realization, since such behavioral strategies often lead to the postponement of important decisions and actions [4].

Partnership patterns include the quality of relationships with partners, the level of support and mutual understanding in these relationships. Lack of support from a partner or conflictual relationships can negatively affect a woman's self-realization, causing emotional stress and limiting her opportunities for development. On the other hand, partner support, shared values and willingness to cooperate can create a favorable environment for self-realization, increasing a woman's self-confidence and her ability to achieve her goals [3,4]. Women who have support from their partners and families can more successfully realize themselves in the professional sphere, personal growth and creativity.

The combination of these patterns plays a key role in determining how successful a woman's self-realization will be in various areas of life. Taking into account these aspects in the study of self-realization of women will help to develop effective strategies of psychological support and interventions aimed at improving their psycho-emotional state and achieving success in life. On the other hand, women facing conflicts and lack of support may have difficulties in self-actualization, which may lead to a decrease in their psychological well-being [1].

The research is also relevant in the context of modern socio-cultural changes. It becomes important to understand how these changes affect a woman's self-realization. Gender roles and expectations are changing, and women are facing new challenges and opportunities. Social networks and mass culture create new standards of success and self-realization [6,7], and most research focuses on individual aspects, such as professional self-realization, psychological well-being, sexual problems, and the distribution of roles in the family [8].

The phenomenon of family interaction is becoming more and more significant in the context of modern social and cultural changes, since the family is the key environment where the formation and development of the individual takes place. Understanding family interaction as a leading construct of family functioning, which affects personal changes of family members, is important for identifying factors that contribute to or hinder the self-actualization of an individual. Highlighting the levels of family crisis and states of family interaction allows for a more in-depth assessment of the impact of family dynamics on personal development and relationships in the family [7,9].

The study of a woman's self-realization in the context of marriage and divorce is important for understanding her psychological state, social needs and development in modern society [10, 11]. That is, without a doubt, there is an urgent need to clarify the concept of self-realization of a woman, to introduce it into scientific circulation in a correct form, but there are not enough empirical studies devoted to the peculiarities of women's self-realization in the system and structure of family relations. This study is relevant for the development of family support strategies, especially in crisis situations, which ultimately can contribute to increasing the level of self-actualization and general well-being of family members.

One of the most acute problems faced by modern psychology is insufficient attention to the complex approach to the study of families and the problem of self-realization of women, therefore we consider it timely and appropriate to consider the family as a system that has a certain structure and takes into account the influence of family functioning, family interactions and family crises on a woman's self-realization. Studying these aspects in a complex will allow getting a more complete picture and developing effective support strategies that will help women improve their health and achieve success in life.

AIM

To study the peculiarities of self-realization of women with different states of family interaction, to build a mathematical model that allows to identify the probability of self-realization of women, depending on their psycho-emotional, individual-psychological, behavioral and partnership patterns, to consider the family as a whole system, to define the phenomenon of family interaction as a leading the construct of the process of family functioning, to distinguish levels of family crisis and states of family interaction.

MATERIALS AND METHODS

To study the peculiarities of self-realization of women with different states of family interaction, a sample was formed, which included 86 divorced and 144 married women, of whom 73 live in crisis families, 71 in normative ones. The total number of subjects was 230 people. At the time of the anamnesis collection, the age of the subjects was in the range from 29 to 56 years. All women had children. Women who had been married for less than 7 years did not participate in the study.

An initial interview and anamnesis collection were conducted beforehand, which consisted of four sections: the main part (age, marital status, number of children, place and position of work); complaints

(psychological, somatic); anamnesis of the problem; life history

To conduct the experimental part of the research, a set of methods adequate to the purpose of the work was compiled. The inclusion of specific tests in the methodological apparatus of research was carried out on the basis of the following criteria: conceptual validity of the method, high validity, compliance with the set goal.

A socio-psychological examination was conducted with women from three conditionally selected blocks: current psycho-emotional state, family crisis and personal block.

The current psycho-emotional state was assessed using the Derogatis Psychopathological Symptom Severity Questionnaire (SCL-90), L. Reeder's psychosocial stress scale, and the Hospital Anxiety and Depression Scale (HADS).

The personality of women was studied using a 16-factor questionnaire by R.B. Cattell (form C), self-actualization test (SAT); test of the level of subjective control (SC); the test of getting out of difficult life situations (R.S. Nemov), the "Index of Life Style" questionnaire (diagnosis of the frequency of use and severity of psychological protection mechanisms).

The presence and level of family crisis was assessed by the marriage satisfaction test (V.V. Stolin), questionnaires: – possible styles of personality behavior in conflict situations (K. Thomas), – attitudes towards sex (H. Eysenck), – "Love and sympathy scale"; – REA (understanding, emotional attraction, authority).

With the help of correlation factor analysis, 4 components of family interaction were identified: psycho-emotional, individual-psychological, behavioral and partnership. The analysis of the research results made it possible to identify diagnostic markers that allow us to identify the etiology of family, personal, emotional disorders and disorders of self-realization, to predict further destruction or positive development [2].

To study the specifics of the psychology of self-realization, scientists often use such methods of mathematical data processing as correlation analysis (using the Pearson or Spearman correlation coefficient), comparative analysis (Student's test, Wilcoxon's signed test, rank test, Mann-Whitney U-test criteria) [12 -14].

The method of binary logistic regression is actively used in various fields of medicine and psychology, but the application of this method to determine the probability of self-realization of women has not been found. The reason for this can obviously be considered to be the presence of real problems related to the construction of a mathematical model for determining the self-realization of women with different states of family interaction. First of all, we are talking about the problem of multidimensionality of signs and the need to select from it the most significant indicators from the point of view of correction [15,16].

In addition, it is interesting and important to find a way to predict mental and psychological disorders in women with different states of family interaction who cannot realize themselves in life. The authors used binary logistic regression [15] to determine the probability of self-realization of such women.

In order to develop a mathematical model for assessing the probability of self-realization in women with different states of family interaction, the necessary sample size was determined to obtain the best result during a sample survey, according to the formula:

$$n_\omega = \frac{z^2 \cdot \omega \cdot (1-\omega)}{\Delta_\omega^2},$$

where z is a standardized value at a given level of reliability γ = 0.95; ω – the number of women with the studied signs of family interaction, %; – marginal sampling error (5-6)%.

To determine the probability of falling into one of the two groups (high or low level of self-realization), the method of binary logistic regression was used, which allows identifying indicators that affect the lack of self-realization of women.

Processing of the received data was carried out using the SPSS statistical data processing program package, version 23 and Microsoft Office Excel 2016.

RESULTS

Analysis of the results of the study revealed significant differences in the above-mentioned three blocks in divorced, women from crisis and normative families. A quantitative analysis of the total volume of relationships of self-actualization with the components of the current psycho-emotional state, personal (individual-psychological features) and family crisis blocks was carried out. Significant correlations between the investigated indicators were also determined.

Analysis of the results of the study of women from crisis families revealed problems related to interpersonal sensitivity, depression (clinical and subclinical), anxiety, somatization, hostility, paranoid symptoms, psychosocial stress, value orientations, flexibility of behavior, self-esteem, self-acceptance, acceptance of one's own aggression, creativity, ways of getting out of difficult life situations, level of subjective control, level of satisfaction with marriage. The analysis of the results of the study of the attitudes towards sex of women from crisis families showed that a high level prevails only on the scale of sexual satisfaction. Predominantly low levels

Table 1. The value of the Wald criterion

Indicator	Wald criteria	Significance (p)
X_1	18,558	≤0,001
X_2	15,580	
X_3	16,512	
X_4	16,202	
X_5	21,823	

Table 2. Characteristics of the mathematical model to determine the probability of lack of self-realization in women with different states of family interaction

Results of the final step of the analysis	-2 Log-likelihood (G)	Cox and Schell's R-squared	Nigelkirk's R-square
	107,013	0,637	0,873

were noted on the scales of sexual shyness, chastity, and aggressive sex. According to all other scales, the highest number of percentages was scored by women with an average level.

Divorced women showed a high level on the following scales: interpersonal sensitivity, depression (clinical and subclinical), anxiety, somatization, psychopathy, flexibility of behavior, acceptance of one's own aggression, creativity, a way out of difficult life situations, and subjective control.

Women from normative families are characterized by a high level of interpersonal sensitivity, psychosocial stress, and a low level of creativity and subjective control. The analysis of the results of the study of attitudes towards sex showed that the high level prevails on the scale of sexual satisfaction, and the low level prevails on the indicators of impersonal sex, sexual shyness, chastity and aggressive sex.

To obtain additional information, we used the method of binary logistic regression to determine the probability of self-realization of the studied women.

According to the results of the research, the women were divided into two groups. The first group included women with a high level of self-realization (104 women), the second – with a low level (126 women).

At each step of the research, it was necessary to choose the optimal option from a given set of options.

In order to select the most informative signs for discrimination, the selection was carried out by the method of stepwise selection. In each version of the equation, the algorithm step by step selected predictors that indicated the percentage of correct predictions – the value and magnitude of the correlation coefficient. At this stage of the research, 5 significant indicators for classification were selected: X1 – self-esteem, X2 – creativity, X3 – physical sexuality, X4 – flexibility of behavior and X5 – depression, which make it possible to determine the probability of lack of self-realization in women with different states of family interaction.

$$P = \frac{\exp(12{,}371 - 0{,}790 \cdot X_1 - 0{,}749 \cdot X_2 - 0{,}693 \cdot X_3 - 0{,}486 \cdot X_4 + 0{,}736 \cdot X_5)}{1 + \exp(12{,}371 - 0{,}790 \cdot X_1 - 0{,}749 \cdot X_2 - 0{,}693 \cdot X_3 - 0{,}486 \cdot X_4 + 0{,}736 \cdot X_5)}$$

where P is the probability of lack of self-realization in women, X is the indicator of the results of psychological assessments; β is the sensitivity coefficient for variables.

The results of the constructed mathematical model for determining the probability of self-realization in women with different states of family interaction shows below (table 1). This result reflects statistically significant variables tested for significance using Wald tests. All variables are significant ($p<0.001$) and correctly selected.

A set Xi is obtained, where i=1,…, N (N=5).

The Wald test statistic as a criterion of extreme pessimism refers to the decision-making strategy under conditions of uncertainty. That is, according to this criterion, a strategy is adopted that ensures making the right decision in the worst conditions.

Quality control of the regression model was carried out using the likelihood function (table 2). The measure of plausibility was the negative doubled value of the logarithm of this function. The determination of the part of the explained variance was carried out using the Cox, Schell, and Nigelkirk indices, which are measures of certainty and indicate the part of the variance that is explained by the regression.

As can be seen from the table, the value of G = 107.013 obtained in the study, which means that, in general, the independent variables make a significant contribution to the forecast of the dependent variable. The other two measures are measures of certainty, suggesting that the portion of variance explained by logistic regression is 87.3%.

The obtained results show that the indicators of self-esteem and creativity have the greatest influence on the self-realization of women, regardless of whether they are married or divorced. Physical sexuality and behavioral flexibility also had a significant positive effect, but at about the same level. Depression negatively affects self-realization.

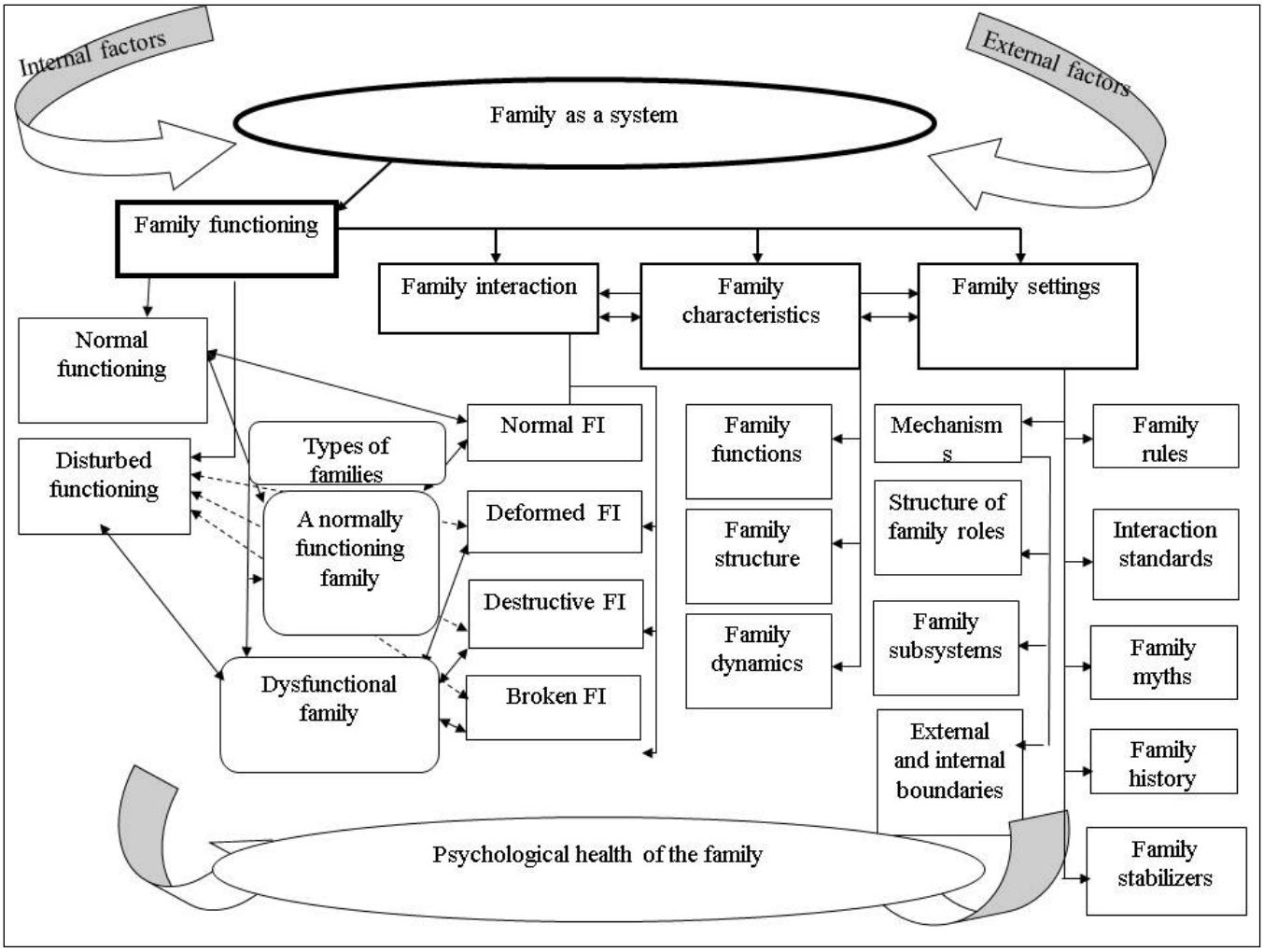

Fig. 1. Scheme of the family as a system.

The decision to assess the probability of self-realization in both married and divorced women depending on their psycho-emotional, individual-psychological, behavioral and partner patterns was made according to the 0.5 criterion. With an interval of 0.5 and more, the probability of self-realization is low, and with an interval of less than 0.5, the probability of self-realization is high. In the studied sample, among divorced women, 78% are satisfied with self-realization, among women from crisis families, only 54% are satisfied with their own self-realization.

The research carried out, the construction of a mathematical model for determining the probability of self-realization of women depending on their psycho-emotional, individual-psychological, behavioral and partnership patterns and the results obtained with its help made it possible to clarify the content of the blocks of research that we have conditionally selected and to start compiling and substantiating the structure of family interaction, because precisely the normal or destructive functioning of the family in general and its members, determining the levels of family crises and prognostic factors (predictors and preventers) of women's self-realization depends on her condition.

A system is a set of elements with one common connection, and a structure is the same set of elements, but with the addition of private relations between them, not only connections, but also other relations. The family itself is a complex and systemic object, a special structural aspect of which is family functioning (FF) – a universal way of family existence and life, a way of life that affects all aspects of its manifestation. Subsystems of the FF system are family interaction (FI), family characteristics and parameters, which, in turn, have their own substructures.

The central element of the majority of family crises, conflict situations, and destructive reactions of family members are problems related to the violation of family interaction, that is, deformed and destructive social interaction congruent with the concept of "family crisis" (FC).

Its manifestations occupy their niche in a number of socio-psychological and mental phenomena. They exist alongside such phenomena as mental illnesses,

pathological conditions, neuroses, psychosomatic disorders, deviant behavior, and sometimes lead to them. However, medical phenomena are considered from the point of view of the medical norm on the axis "health – pre-disease – disease", deviant behavior expresses the socio-psychological status of the individual on the axis "socialization – maladaptation – isolation".

The state of family interaction reflects the personal contacts of family members, as a result of which there is a mutual change in their personality, behavior, activities, and relationships, so we consider it on the axis "norm – deformation – destruction – destruction" (Fig. 1) and distinguish 4 states FI and 4 levels of family crisis: – normal FI (level 1 of FC), – deformed FI (level 2 of FC), – destructive FI (level 3 of FC), – destroyed FI (level 4 of FC).

In the context of our study of a woman's self-realization and her psychological health, it looks as follows: – women from normative families – normal FI, – women from crisis families (whose husbands recognize the presence of problems and are ready to cooperate) – deformed FI, – women with crisis families (whose husbands do not recognize the existence of problems and refused to cooperate) – destructive FI, divorced women – destroyed FI.

Fig. 1. shows our proposed scheme of the family as a system, on which the following are highlighted: external and internal factors affecting the functioning of the family, components of the functioning of the family, levels of family interaction, characteristics and parameters of the family.

All these components that make up the family as a system affect the psychological health of the family and the self-realization of its members.

Normal family interaction implies the absence of a clearly identified family crisis (level 1). In the event of family difficulties, disagreements, internal mobilization occurs in families, they find adequate methods of solving problems, increase their cohesion, efforts to overcome internal and external problems, take responsibility for what happens to them, are ready to develop, show flexibility in behavior, choose adequate styles of behavior in conflict situations, try to understand each other and thus preserve the family and move to a new level of development and personal self-realization.

The second level of family crisis indicates a deformed family interaction. There is a concept of latent family disorder [8]. That is, it is such a violation that does not have a significant negative impact on family life under normal conditions; however, it can play a significant role in difficult life situations, determining the family's inability to resist them. During a crisis of this level, a married couple communicates, feels certain feelings for each other, distributes rights and responsibilities, performs various family functions. Under normal conditions, certain violations are acceptable (not significant complications of mutual understanding, communication, responsibility, violations of sexual disharmony of spouses, moderate conflict, hostility, anxiety, interpersonal sensitivity, tension, etc.).

However, in difficult situations, the degree of mutual understanding, affection, sympathy, love and resistance to stress and other feelings, personal qualities, which are characteristic of this family, are not enough. This is how the prerequisites for the occurrence of family-induced psycho-traumatic conditions are formed: family and personal dissatisfaction, states of anxiety, depression, and feelings of guilt, hostility, conflict, mental and somatic disorders. At the same time, we can talk about two forces that cause such violations: peculiarities of intra-family relations (violation of ideas about the family and each other's personality, communications, integration mechanisms, structural and role aspects of life) and individual and psychological characteristics of family members (psychological, spiritual, cultural, sexual incompatibility). Psychological correction and support can contribute to internal mobilization, getting out of the situation of deformed self-esteem and reaching the level of development and personal self-realization.

Negative dynamics can lead to the third-level FC – destructive FI and the strengthening of psycho-traumatic states: the emergence of psycho-emotional disorders, an increase in the level of psychosocial stress, worsening of family and personal dissatisfaction, states of anxiety, depression, self-esteem, self-perception, hostility, conflict, the level of responsibility, conflict, somatic disorders.

Further deterioration of the situation, the destruction of family interaction leads to the 4th level of FC, completely destroyed FI and divorce.

DISCUSSION

The family is the basic social unit that forms a person's personality from childhood. Not only a woman's emotional state depends on how family relationships develop, but also her ability to achieve her goals, develop her talents, and realize her potential. Support from the partner, level of trust, emotional closeness and ability to resolve conflicts are important factors that determine the state of family interaction. In turn, these factors can either promote or hinder women's self-realization [2,3].

Foreign concepts of personality (A. Adler, A. Maslow, G. Allport, K. Rogers, Z. Freud, E. Fromm, V. Stern, E. Erikson, K. Jung, etc.) had a certain influence on the study of the female personality , issues and problems of the formation of a woman's personality. Considering the problems of family and marriage, M. James emphasized the inequality in the relationship between a man and a woman through-

out the history of mankind. The same applies to the issue of self-realization.

Modern studies show that women who have high support from their partner and harmonious family relationships are more successful in their self-realization. They more often achieve high results in the professional sphere, engage in self-development and have a high level of psychological well-being [7,8]. On the other hand, women who face family conflicts, lack of support, and emotional distance have a lower level of self-realization and may experience greater stress and dissatisfaction with life [7].

In the context of socio-cultural changes, it is also important to consider how gender roles and expectations for women are changing. Modern women face double pressure: on the one hand, they have to meet traditional expectations regarding the role of mother and wife, and on the other hand, to achieve success in the professional sphere [4]. This can create additional difficulties in self-realization and require women to have greater psychological stability and support from others.

Lack of self-realization in women can have a significant negative impact on their physical and mental health. This influence becomes even more pronounced when women live in crisis families, where there is a high level of stress, conflict and instability. Women who do not have the opportunity to realize their potential often face feelings of helplessness and dissatisfaction with life, this can lead to the development of depressive states, increased anxiety, and the development of psychosomatic disorders. For example, depression can lower immunity and increase the risk of developing chronic diseases. Physical problems, such as chronic pain or sleep disorders, can exacerbate a woman's mental state, creating a vicious circle [11].

In crisis families, these feelings can be exacerbated by constant conflicts and lack of support. Women who do not have the opportunity to realize their interests and talents may feel isolated from society, this feeling may increase in crisis families, where there is emotional distance and insufficient support from family members [8,9,12]. A crisis that occurs at any level of family functioning will inevitably affect all other levels, causing a disruption in their functioning [2,8].

Increased attention to the phenomenon of women's self-realization is explained, in our opinion, by a growing understanding of her defining role in society. The study of self-realization of a woman at the stage of maturity is connected, first of all, with the fact that this age period is a period of higher development of all (intellectual, physical, spiritual) abilities of a person. Knowledge and understanding of laws, mechanisms, conditions, factors that contribute to the formation of a woman's mature personality, her personal and professional achievements, will allow to provide significant assistance to a woman in reaching her state of acme, peaks in personal, physical, professional, spiritual and moral development [2] .

CONCLUSIONS

The theoretical analysis and generalization of scientific sources showed that modern society needs a review of the role of women and a deeper understanding of gender equality, as the current state of the problem limits opportunities for their self-realization. In addition, disruptions in family functioning and interaction, which are accompanied by a family crisis, have a multi-vector effect on a woman's personal development and self-realization.

The most important indicators for determining the probability of self-realization in women with different states of family interaction were found, which allow reducing the time for diagnosing a woman's condition and correcting her attitude towards herself. Using the obtained model, the probability of self-realization of women was determined depending on their psycho-emotional, individual-psychological and behavioral patterns, and these indicators are the same for divorced and married women. The given indicators indicate that a divorced woman and a woman from a normative family can realize themselves more than a married woman who is in a crisis relationship with a partner.

The built mathematical model for determining the probability of self-realization of women with different degrees of family interaction allows for a more accurate assessment of the influence of key psychological and behavioral factors on the process of self-realization. The inclusion of indicators such as self-esteem, creativity, physical sexuality, behavioral flexibility, and depression provides a comprehensive understanding of the conditions that facilitate or hinder women's self-actualization in different family contexts. In general, these indicators together form a coherent picture of factors that determine the success or difficulty of self-realization of women in various spheres of life. Taking them into account in the model makes it possible to more accurately predict the probability of successful self-realization or its lack, which is important for the development of individualized approaches to support women in their personal development.

This model provides an opportunity to predict the probability of lack of self-realization depending on the state of family interaction, which is important for the development of effective psychological support strategies. The use of this model can help increase the level of self-realization of women, which will positively affect their psychological well-being, personality development, and overall quality of life. Knowledge and application of these results is important not only for specialists in the field of psychology and social work, but also for society as

a whole, as it contributes to the formation of conditions that support the harmonious development and self-realization of women in the modern world.

4 levels of family crisis and 4 states of family interaction are distinguished: normal, deformed, destructive and destroyed, which defines the phenomenon of family interaction as a leading construct of the process of family functioning.

The components of family interaction are determined: psycho-emotional, individual-psychological, behavioral and partnership, which are substantiated as targets of psychological correction aimed at the growth of a woman's self-realization.

Psychological correction can contribute to internal mobilization, getting out of the situation of disturbed family functioning, deformed family interaction and reaching the level of positive development of self-realization. Negative dynamics can lead to a family crisis of the third level – destructive family interaction, strengthening of psycho-traumatic conditions and reaching the level of destroyed family interaction.

The results obtained during the research can be used in the work of psychologists-consultants when drawing up an individual plan for the correction of psychological and family problems that arise in women who have not been able to realize themselves in any field.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Liubov Rysovana
Kharkiv National Medical University
4 Nauky Avenue, 61000 Kharkiv, Ukraine
e-mail: lm.rysovana@knmu.edu.ua

ORCID AND CONTRIBUTIONSHIP
Olena Vysotska: 0000-0003-3723-9771 B D F
Olena Falova: 0000-0001-5983-0090 A B D
Liubov Rysovana: 0000-0001-7937-4176 A C D
Oksana Platyniuk: 0000-0002-7279-7368 B E F
Oleksandr Bazhenov: 0000-0003-2941-9078 C E

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

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ORIGINAL ARTICLE

CONTENTS

Evaluation of the clinical effectiveness of conservative (pre-surgical) treatment schemes for generalized periodontitis in patients with various somatic pathologies

Maryana M. Shevchuk, Andriana P. Skalat, Khristina B. Burda, Nataliya S. Magera, Olesia I. Martovlos
DANYLO HALYTSKYI LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Aim: Optimization of conservative treatment schemes for generalized periodontitis (GP) against the background of somatic pathology, depending on the indicators of the Community Periodontal Index of Treatment Needs (CPITN).

Materials and Methods: CPITN was performed in 134 patients with GP against the background of various somatic pathologies and divided into main and comparison subgroups. Treatment scheme No. 1 was developed, including means for local and supportive therapy, and was used in the main subgroup 1 (CPITN ≤ 2). Scheme No. 2, developed for the main subgroup 2 (CPITN > 2), included drugs of local and general action. Clinical dynamics were assessed by the values of PMA and OHI-S indices before GP treatment, and 3, 6, and 12 months after treatment.

Results: After 12 months, «stabilization» of the pathological process in the periodontal tissues was observed, with CPITN index values ≤ 2, in 82.76% of the main subgroup patients, which was 2 times higher than the indicators of the comparison subgroup – 40.74%, $p<0.01$. With CPITN index values > 2, «stabilization» of the pathological process in the periodontal tissues was noted in 68.18% of patients of the main subgroup, which was 4.6 times higher than the indicators of the comparison subgroup – 14.71%, $p<0.01$.

Conclusions: GP treatment with CPITN index values ≤ 2 and > 2 points against the background of somatic pathology using the developed schemes contributed to the elimination of inflammation and improvement of oral hygiene, which was confirmed by the positive dynamics of index scores in the immediate and long-term follow-up.

KEY WORDS: periodontal disease, generalized periodontitis, general somatic diseases, conservative treatment, index assessment of periodontal status.

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INTRODUCTION

Generalized periodontitis (GP) as a progressive disease of periodontal tissues, which leads to a weakening of the function of the dentofacial apparatus and can provoke irreversible disorders of digestion and metabolic processes in the human body, represents an urgent problem of modern periodontology. Against the background of the aggressive effect of periodontal pathogenic infection, the processes of sensitization of the body may deepen [1], there is a threat of the development of chronic sepsis, complex organ pathology, and neuropsychiatric disorders, which negatively affect the quality of life of such patients [2-5]. The loss of alveolar bone during the progression of periodontal infection is caused by dysregulation of the inflammatory process and/or immunopathological conditions that are close to the pathogenic mechanisms that form the basis of various severe systemic diseases [6, 7].

Over the decades, numerous studies have shown the relationship between periodontal pathology and a wide range of concomitant diseases, including cardiovascular disease, hypertension, diabetes, rheumatoid arthritis, osteoporosis, Parkinson's disease, Alzheimer's disease, respiratory infections, psoriasis, etc. [8-12]. It has also been established that individuals with periodontal tissue diseases of various forms, stages, and degrees have a higher susceptibility to systemic concomitant diseases [13]. The development of GP is the result of the action of various factors, both exogenous and endogenous, and is caused by a combination of hereditary and environmental factors [14-18].

However, today the provision of periodontal care is insufficiently developed, in particular in the first initial phase of complex treatment for patients with GP and organ pathology. One of the possible reasons for the imperfection of periodontal treatment is insufficient

consideration of the influence of systemic diseases on the course of generalized periodontitis. Therefore, the main working hypothesis of this study was to implement effective therapeutic and preventive algorithms for various stages of GP against the background of systemic diseases and conditions affecting its course, which, in turn, is relevant for the establishment of close cooperation between periodontists and general practitioners.

AIM

Optimization and substantiation of the clinical effectiveness of pre-surgical (conservative) treatment schemes for generalized periodontitis of various stages against the background of somatic pathology, depending on the indicators of the community periodontal index of treatment needs (CPITN) for the treatment of periodontal diseases.

MATERIALS AND METHODS

The design of the research was as follows. The prospective study included an examination of 134 periodontal patients (aged 25-65 years), who were diagnosed with concomitant cardiovascular, neurological, gastroenterological and rheumatological pathologies, and were in the inpatient conditions of the Lviv Regional Clinical Hospital, Lviv.

General outpatient records of all patients were analyzed taking into account their somatic pathology. Therefore, a dental card (form No. 043/o) was created for each patient, which included a dental and periodontal examination protocol. Inclusion criteria: generalized periodontitis in patients with cardiovascular, neurological, rheumatological and gastroenterological diseases, written consent of the patient for the study. Exclusion criteria: generalized periodontitis in patients with other somatic pathologies (for example, tumor diseases, blood diseases), pregnancy and breastfeeding.

To diagnose GP, we used the classification of diseases and conditions of periodontal and peri-implant tissues (EFP & AAP World Workshop, Chicago – 2017), (World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions) [19]. Probing of periodontal pockets was carried out with a periodontal probe (Hu-Friedy, USA). X-ray examination of the jaw bones was performed using intra-oral and panoramic radiography (Orthophos XG 3, Germany).

All patients were assessed for the Community Periodontal Index of Treatment Needs (CPITN) [20]. Treatment was guided by the following CPITN results: CPITN value ≤ 2 – the need for only conservative treatment of GP stage I and II (treatment scheme No. 1 developed by us), and CPITN value > 2 – as an indicator of the additional need for surgical periodontal treatment of GP stage III (developed treatment scheme No. 2 for conservative preparation of patients for surgical treatment).

Based on the results of the CPITN index values, 134 study participants were divided into two groups. Group 1 – 56 (41,78 %) patients with CPITN values ≤ 2, who, in turn, were divided into the main subgroup 1 (29 people – CPITN – 39,73 %) and the comparison subgroup 1 (27 people – CPITN – 44,26 %)). Group 2 with CPITN values > 2 – 78 (58,20 %) patients, who were also divided into main subgroup 2 (44 individuals – CPITN – 60,27 %) and comparison subgroup 2 (34 individuals – CPITN – 55,74 %)), (Table 1).

Treatment schemes No. 1 and No. 2 of conservative periodontal therapy developed for the main subgroups (73 people) (main subgroup 1, n=29; main subgroup 2, n=44) jointly included: teaching patients individual hygiene measures (brushing teeth with «Prodental toothpaste»(«TianDe», China); toothbrushes «Colgate®Total» («Colgate®», USA); rinse aid «Octenidol MouthWash» (Schulke & Mayr/Oral care, Germany); interdental ridges «TePe» («TePe», Sweden), «Oral-B» floss («Procter & Gamble Ireland Limited», Ireland). Oral hygiene began with a professional hygienic teeth cleaning: air-abrasive treatment with the «ProphyFlex» device (KAVO) and the use of an ultrasonic scaler «Woodpecker UDS-A» (China) to remove supra- and subgingival soft and mineralized deposits as part of the SRP (Scaling & Root Planing) protocol. Teeth were coated with fluoride-containing varnish «Admira Protect» (Voco, Germany). Selective polishing and rational prosthetics were performed according to the indications.

The peculiarities of the treatment scheme No. 1, developed by us, (for the main subgroup 1 with the CPITN index values ≤ 2) consisted in the fact that for local and supportive therapy it was recommended to use the following means: in the form of applications – «NBF Gingival Gel» (Korea) and «Ratanhia Mouthwash» (Weleda, Switzerland) (Fig. 1).

Features of the developed conservative treatment scheme No. 2 (for the main subgroup 2 with the CPITN index values > 2 points, additionally requiring surgical periodontal interventions): as preoperative preparation for local conservative treatment and in the subsequent stages of maintenance therapy, «Actovegin-gel» (Nikomed, Austria, GmbH) as part of a protective hardening bandage («Septopack») was used after the SRP protocol («Local therapy» – Fig. 2). With the consultative help of general practitioners, pa-

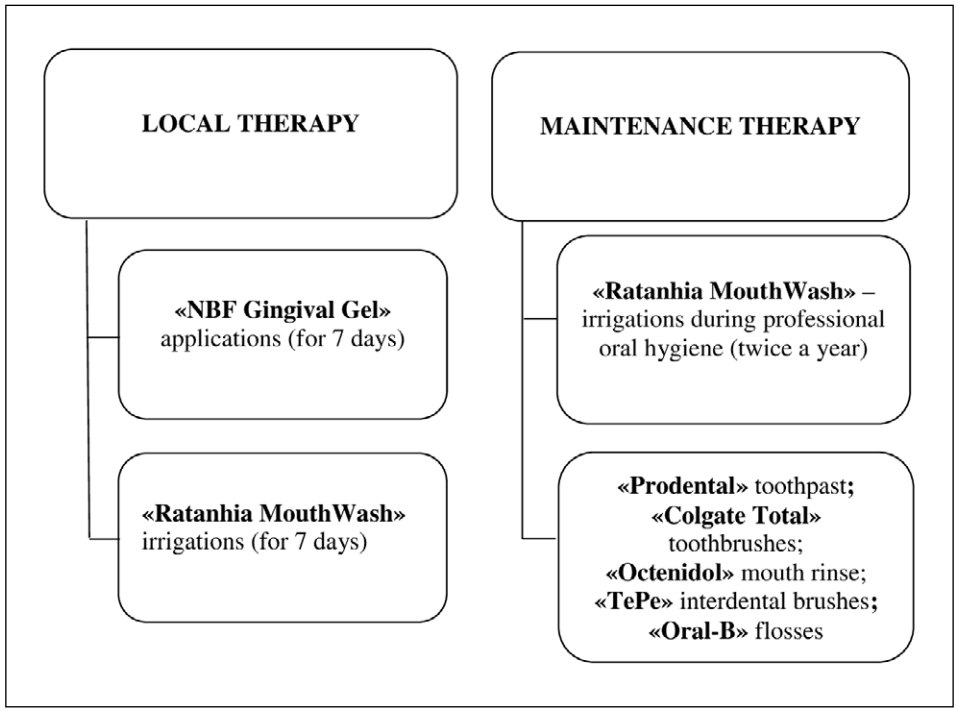

Fig. 1. Scheme No. 1 of GP I, II stages of conservative treatment against the background of various somatic pathologies, with the CPITN index values ≤ 2 points (main subgroup 1).

tients with GP III stage (main subgroup 2), depending on the somatic pathology diagnosed in them, were prescribed a number of drugs of general direction («General therapy» – Fig. 2).

At the same time, all patients of the main subgroup 2, regardless of concomitant somatic disease, were prescribed the drug of general direction «Koenzym Q10» (Now Foods, USA) (Fig. 2).

Patients of both comparison subgroups (n=61) – comparison subgroup 1 (GP I-II stages, n=27) and comparison subgroup 2 (GP III stage, n=34) received a traditional scheme of GP conservative treatment according to the "Protocols of medical care of Ministry of health of Ukraine in the specialty «Therapeutic dentistry» [21]. The traditional scheme included teaching individual hygiene with the appointment of Parodontax paste; irrigation of the oral cavity with the antimicrobial agent chlorhexidine bigluconate 0,05% and «Metrodent» gel in the form of applications on the gums after removing supra- and subgingival dental deposits. The course of treatment took 7 days.

All patients who participated in this study were constantly under the supervision of internists and received the general therapy prescribed by them according to the general somatic diseases diagnosed in them.

In all subgroups, the dynamics of the values of the papillary-marginal-alveolar index (PMA, Papillary-Marginal-Alveolar Index, Parma (1960)), and the simplified index of oral hygiene according to Green-Vermillion (OHI-S, Oral Hygiene Index-Simplified, Green-Vermillion, (1964)) [20], was assessed before treatment and 3, 6 and 12 months after treatment.

The obtained results were statistically processed using the standard software package of «STATISTICA 6.0». The validity of the test data was determined using Student's t-test [11].

BIOETHICS

The study was performed taking into account the main provisions of the GCP ICH and the Declaration of Helsinki on biomedical research where a person is the object, and the subsequent revisions (Seoul, 2008); the Council of European Convention on Human Rights and Biomedicine (2007) and the recommendations of the Bioethics Committee at the Presidium of the National Academy of Medical Sciences of Ukraine (2002), as well as a positive opinion of the commission on ethics of Danylo Halytsky Lviv National Medical University (extract from protocol No. 10 of December 20, 2021). No violations of moral and ethical norms were identified during the research.

RESULTS

Before treatment, in patients with GP I stage of the main subgroup 1 (value of the CPITN index ≤ 2), the PMA index indicators averaged 28,28±1,50 %, which was close to such indicators in the comparison subgroup 1 (28,81±1,25 %), which corresponded to an inflammatory process in periodontal tissues of moderate severity, p1>0,05 (Table 2).

Three months after the application of scheme No. 1 in the main subgroup 1, the PMA index values

Table 1. Distribution of patients with GP of I, II III stages against the background of somatic pathology depending on the CPITN index values, (%)

Total (n=134)	Group 1 CPITN ≤ 2 (n=56)		Group 2 CPITN > 2 (n=78)	
	Main subgroup 1 (n=29)	Comparison subgroup 1 (n=27)	Main subgroup 2 (n=44)	Comparison subgroup 2 (n=34)
Cardiovascular diseases (n=29)	4	4	12	9
	13,79	14,81	27,27	26,47
Neurological diseases (n=33)	7	6	10	10
	24,14	22,22	22,73	29,41
Gastroenterological diseases (n=36)	10	9	10	7
	34,48	33,33	22,73	20,59
Rheumatic diseases (n=36)	8	8	12	8
	27,59	29,63	27,27	23,53

Table 2. The dynamics of the PMA, OHI-S index values in patients with GP I stage at the CPITN index values ≤ 2 after performing conservative treatment measures in different observation periods (M±m)

Observation periods	Observation groups	Indicators	
		PMA (%)	OHI-S (points)
Before treatment	Main subgroup (n=29)	28.28±1.50	0.91±0.86
	Comparison subgroup (n=27)	28.81±1.25	0.96±0.08
Three months after treatment	Main subgroup (n=29)	5.16±1.60°,***	0.58±0.03
	Comparison subgroup (n=27)	12.40±2.64°	0.80±0.80
Six months after treatment	Main subgroup (n=29)	5.28±1.66°,*	0.69±0.06
	Comparison subgroup (n=27)	17.59±2.80°	0.92±0.08
12 months after treatment	Main subgroup (n=29)	6.46±2.01°,*	0.75±0.07
	Comparison subgroup (n=27)	19.14±3.04°°	0.96±0.09

Notes:

1. °p<0,001, °°p<0,01 – reliability of the difference in values between indicators before and after treatment.
2. *p1<0,001, ***p1<0,05 – reliability of the difference in values between the indicators in persons of the main subgroup 1 and comparative subgroup 1.

decreased to 5,16±1,60 %, which indicated the elimination of distinct signs of the inflammatory process. In contrast to the indicators of the main subgroup 1, in the comparison subgroup 1, the PMA value was 12,40±2,64 %, which indicated the presence of a mild inflammatory process in the periodontal tissues, p<0,001. The values of the analyzed parameter of the PMA index were 2,4 times lower in the treated patients of the main subgroup 1 than in the comparison subgroup 1, p1<0,05.

If the OHI-S index indicators before treatment in both subgroups averaged 0,93 points, then already three months after the treatment, an improvement in the hygienic state of the oral cavity was detected in patients of both observation subgroups (main subgroup 1 and comparison subgroup 1). However, a decrease in the OHI-S index data to a digital value of 0,58±0,03 points («good» level of oral hygiene) was noted in patients of the main subgroup 1, treated with scheme No. 1. While in patients of comparison subgroup 1 (traditional conservative treatment scheme), the following indicator was observed – 0,80±0,80 points («satisfactory» level of oral hygiene), p>0,05; p1>0,05.

After 12 months of observation, the quantitative values of the PMA index values remained significantly lower compared to the indicators before treatment: 6,46±2,01 %, p<0,001 in persons of the main subgroup 1, and 19,14±3,04 %, p<0,01 in patients of comparison subgroup 1. Moreover, this indicator was 2,9 times lower in the patients of main subgroup 1, compared to the comparison subgroup 1, p1<0,001.

The state of oral hygiene (OHI-S index) both after 6 and 12 months of observation remained satisfactory in patients of the main subgroup 1 (0,69±0,06 points and 0,75±0,07 points, respectively). In patients of the comparison subgroup 1 – 0,92±0,08 points and 0,96±0,09 points, which indicated an unsatisfactory level of hygiene, p>0,05; p1>0,05.

The dynamics of periodontal tissue condition of group 2 (with GP II-III stage – the CPITN index values > 2, Table 1) – in patients of the main subgroup 2 (use of scheme No. 2 of GP conservative preoperative therapy,

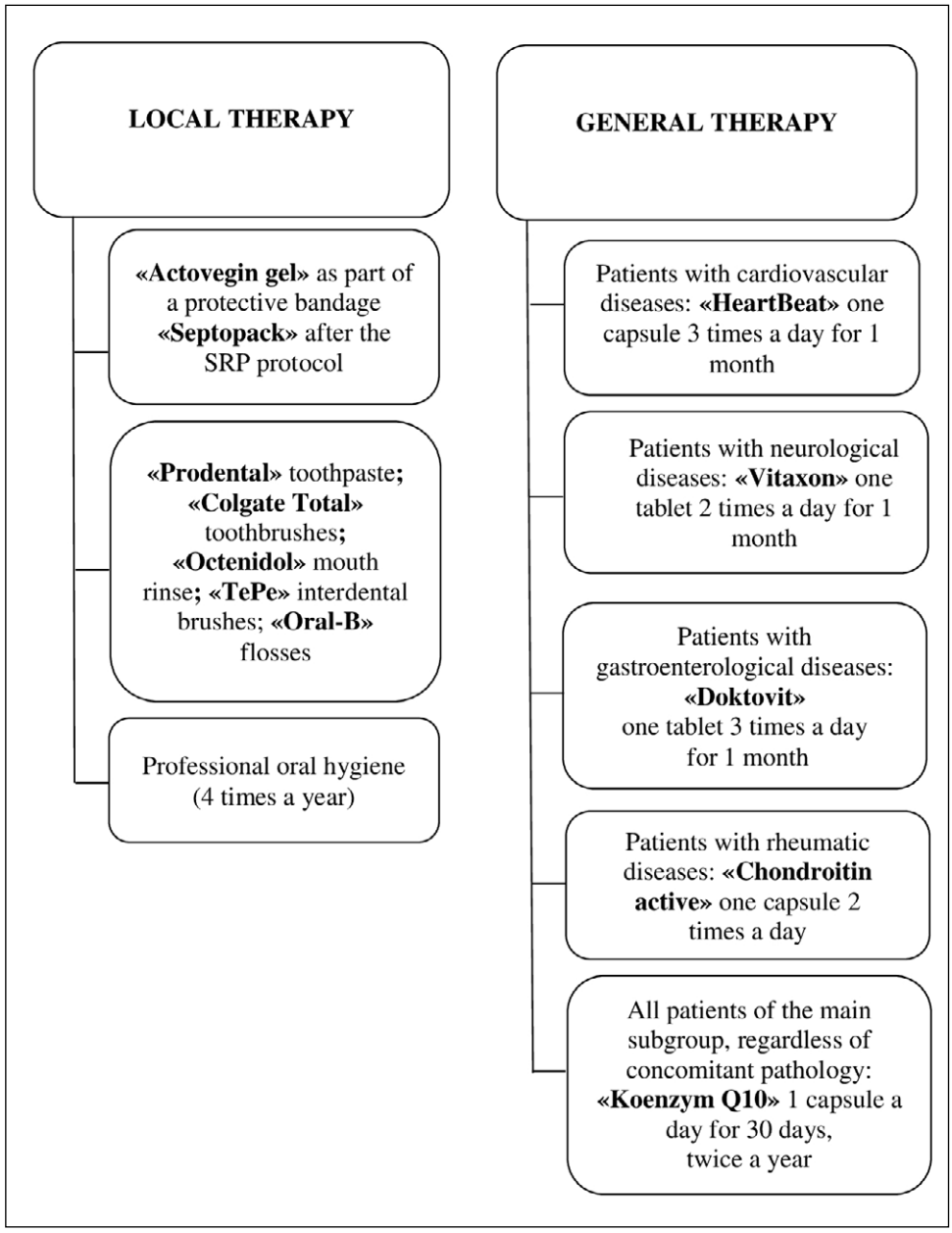

Fig. 2. Scheme No. 2 conservative pre-operative therapy of GP III stage treatment against the background of various somatic pathologies, with the CPITN index values > 2 points (main subgroup 2).

Fig. 2) and comparison subgroup 2 (the use of a traditional scheme of GP conservative treatment), before treatment and after 3, 6 and 12 months of observation, were convincingly emphasized by the PMA and OHI-S index data (Table 3).

Before treatment in patients with GP II-III stages against the background of somatic pathology (with the CPITN index > 2), the PMA index values were equal to – 49,09±2,59 % in the main subgroup 2, and 49,74±2,96 % – in the comparison subgroup 2, which corresponded to the severe degree of the inflammatory process course in the periodontal tissues, p1>0,05.

Three months after conservative preoperative therapy according to scheme No. 2 (Fig. 2), the PMA index values decreased to 23,40±3,89 % (mild severity of inflammation) in the main subgroup 2 and to 28,10±4,64 % (average severity of inflammation) in comparison subgroup 2 (traditional treatment regimen), p<0,001.

If before treatment the OHI-S index in both subgroups averaged 2,15±0,07 points, then after the treatment, an improvement in the hygienic condition of the oral cavity was found in patients of both observation subgroups, which was accompanied by a decrease in the data of this index to 0,99±0,08 points in patients of the main subgroup 2 and up to 1,18±0,09 points in patients of the comparison subgroup 2, which corresponded to a satisfactory level of oral hygiene, p<0,001.

Six months after treatment, patients of the main subgroup 2 showed a decrease in the average PMA index value to 22,49±3,66 %, which corresponded to a mild degree of severity of the inflammatory process and was

Table 3. Dynamics of PMA, OHI-S index values in patients with GP II-III stages with the CPITN index values > 2 after conservative preoperative treatment measures in different observation periods (M±m)

Observation periods	Observation groups	Indicators	
		PMA (%)	OHI-S (points)
Before treatment	Main subgroup (n=44)	49.09±2.59	2.16±0.07
	Comparison subgroup (n=34)	49.74±2.96	2.14±0.07
Three months after treatment	Main subgroup (n=44)	23.40±3.89°	0.99±0.08°
	Comparison subgroup (n=34)	28.10±4.64°	1.18±0.09°
Six months after treatment	Main subgroup (n=44)	22.49±3.66°,*	1.29±0.13°,***
	Comparison subgroup (n=34)	43.83±4.35	1.74±0.13°°
12 months after treatment	Main subgroup (n=44)	16.53±3.66°,*	1.30±0.13°,*
	Comparison subgroup (n=34)	44.16±4.28	1.95±0.14

Notes:

1. °p<0,001, °°p<0,01 – reliability of the difference in values in relation to indicators before treatment.
2. *p1<0,001, ***p1<0,05 – reliability of the difference in values between the indicators in persons of the main subgroup 2 and comparative subgroup 2.

significantly lower in relation to the data in the comparison subgroup 2 – 43,83±4,35 % (average degree of severity of the inflammatory process), as well as in relation to these indicators before treatment (49,09±2,59 % – in the main subgroup 2 and 49,74±2,96% – in the comparison subgroup 2), p<0,001; p1<0,001.

The average OHI-S oral hygiene index values 6 months after the treatment indicated a satisfactory level of oral hygiene in patients of the main subgroup 2 – 1,29±0,13 points, p<0,001, and unsatisfactory in the patients of the comparison subgroup 2 – 1,74±0,13 points, p<0,01; p1>0,05.

It was found that after 12 months of observation, the quantitative values of the PMA index value in the treated patients of the main subgroup 2 decreased to 16,53±3,66 % and corresponded to a mild degree of severity of the inflammatory process, p<0,001. In patients of the comparison subgroup 2, the value of this indicator almost returned to the initial level – 44,16± ±4,28% and was 2,7 times higher than in the patients of the main subgroup 2, p>0,05; p1<0,001.

The state of oral hygiene, after 12 months of observation, in the patients of the main subgroup 2 remained satisfactory – 1,30±0,13 points, p<0,001, and was unsatisfactory in the patients of the comparison subgroup 2 – 1,95±0,14 points, p>0,05; p1<0,001.

Thus, treatment schemes No. 1 and No. 2, developed for both main subgroups, revealed good clinical effectiveness and can be recommended for widespread use in periodontal practice for the conservative treatment of GP I, II, and III stages against the background of somatic pathology.

DISCUSSION

Summarizing the data of clinical studies in patients of the main subgroups (1 and 2) with the CPITN index values ≤ 2 (GP I stage) and > 2 points (GP II and III stages) against the background of cardiovascular, neurological, gastroenterological and rheumatological pathologies, the use of the developed schemes contributed to the elimination of inflammation and improvement of oral hygiene, which was confirmed by the positive dynamics of periodontal indices (PMA, OHI-S) in the immediate and long-term follow-up observation periods. After the entire observation period (12 months), «stabilization» of the pathological process in the periodontal tissues was observed, with the CPITN index values ≤ 2 in 82,76% of the treated patients of the main subgroup 1, where the scheme No. 1 proposed by us was used for the GP I stage treatment. The result was 2 times higher than the indicators of patients of comparison subgroup 1 – 40,74%, p<0,01, where the treatment was carried out according to the traditional method.

With the CPITN index values > 2 (GP II and III stages), «stabilization» of the pathological process in the periodontal tissues was noted in 68,18 % of patients of the main subgroup 2, which was 4,6 times higher than the data of patients of the comparison subgroup 2 – 14,71 %, p<0,01.

It was found that the «increase» of the pathological process in the periodontal tissues with the CPITN index values ≤ 2 was diagnosed in 44,44 % of patients in comparison subgroup 1. While in the main subgroup 1, such an «increase» was not observed in any patient. Accordingly, with the CPITN index values > 2, the «increase» of the pathological process in the periodontal tissues was observed in 64,70 % of the treated patients of the comparison subgroup 2, which was 3,56 times more than in the patients of the main subgroup 2 – 18,18 %, p <0,01. This indicated the insufficiency of measures of traditional treatment for GP in this category of patients.

The novelty of the study was to supplement and clarify scientific data on the periodontal status of patients with some general somatic diseases, taking into account the data of the papillary-marginal-alveolar index (PMA), the oral hygiene index (Green-Vermilion–OHI–S) and the community periodontal index of treatment needs (CPITN). Fundamentally new in the conducted research is the development of schemes for the conservative phase of treatment of generalized periodontitis stages I, II, and III, including not only pathogenetically directed local gel compositions, but also general remedies, which were chosen together with internists for the supervision of the patients diagnosed with somatic diseases. We have clinically proven and substantiated the effectiveness of the proposed treatment schemes.

It should be noted that the treatment of GP patients against the background of cardiovascular, neurological, gastroenterological, and rheumatological pathologies was carried out in hospital conditions and required the mandatory supervision of such patients by general specialists. These diseases were taken into account as factors in the development and burden of the GP clinical course [5].

The data from modern literature indicate that there are a number of diseases that are combined with absolute regularity with the damage of periodontal tissues: diabetes, arterial hypertension, coronary heart disease, chronic diseases of the gastrointestinal tract, chronic obstructive pulmonary disease, rheumatoid arthritis, stressful conditions [2-7]. However, we have not found specific data in the world literature indicating the periodontists' use of general remedies approved by internists regarding the general somatic pathological conditions indicated in this study against the background of GP of different stages.

It can be assumed that the reason for obtaining better results in the main subgroups was the adequately selected components of the developed treatment schemes. Thus, «NBF Gingival Gel» (NanoCureTech, Inc, Korea), included in scheme No. 1, realizes its therapeutic potential due to vitamins C and E as natural antioxidants, which play an important role in maintaining the integrity of the cell membrane and restoring the epithelium of the gum mucosa. In turn, propolis has an antibacterial, antifungal, anti-inflammatory, and analgesic effect and stimulates local immunity. «Ratanhia Mouthwash» (Weleda, Switzerland) is a highly effective oral care product containing exclusively plant components (ratanhia root, tannins) that strengthen gum tissues and eliminate irritation and inflammation.

The effectiveness of the treatment scheme No. 2 was provided by two local drugs. The first one is «Actovegin-gel» (Nicomed, Austria, GmbH), which contains a deproteinized hemoderivative from the blood of calves and promotes the acceleration of healing processes and the utilization of oxygen (increases resistance to hypoxia) and glucose, increasing the energy metabolism of gum tissues by strengthening the energy state of cells. The second drug is the antiseptic preparation «Octenidol MouthWash» (Schülke & Mayr, Germany), the main active substance of which is octenidine dihydrochloride with affinity to teichoic acid, located in the outer membranes of microorganisms and involved in the processes of oxidative phosphorylation. The drug has a high bactericidal, antifungal, and anti-inflammatory effect.

The joint pathogenetic effect of these local drugs in periodontal patients of the main subgroup 2, burdened with general somatic diseases, was in a synergistic balance with the general purpose drugs recommended by internists, which were additionally included in scheme No. 2.

For patients of the main subgroup 2 with cardiovascular pathology against the background of GP II and III stages, cardiologists approved the appointment of the vitamin complex «Heart Beat» (Natures Plus, USA) with a high level of resveratrol, which has a proven effect on blood cholesterol level. The drug also contains B vitamins, calcium, magnesium, potassium, and selenium, which are antioxidants and promote healthy heart function.

For neurological diseases, neuropathologists recommended the vitamin drug «Vitaxon» (PJSC «Farmak», Ukraine), which belongs to vitamin B_1 preparations and, in combination with vitamins B_6 and B_{12}, has a beneficial effect on the course of inflammatory and degenerative diseases of the nerves and the motor apparatus. The drug has analgesic properties, improves blood circulation, as well as normalizes the function of the nervous system and the hematopoietic process.

For gastroenterological disorders, gastroenterologists added the vitamin drug «Doktovit» (OmniPharma, Ukraine) to the scheme No. 2, which is recommended as a dietary supplement to the diet as a source of vitamins B_5 and U for cytoprotection of the gastric and duodenal mucosa. The drug accelerates the healing of ulcerative and erosive damages, as well as normalizes digestive processes.

For rheumatological diseases, rheumatologists recommended the drug «Chondroitin Active» (Switzerland), the main active component of which is chondroitin, which eliminates inflammatory processes in tissues, stops the destruction of joint tissues and cartilage, and promotes the active production of intra-articular fluid. Another active component of this product is glucosamine, which eliminates pain and swelling, improves blood circulation,

strengthens capillaries, and prevents their fragility. The additional component Alpha-arthroferol is a source of essential oils and amino acids that stimulate blood circulation, strengthen the capillary network, reduce the sensitivity of nerve endings and pain receptors, and also contribute to the accelerated recovery of tissue structure. This drug also strengthens the overall immune system, helps the body neutralize dangerous microorganisms and toxins that can negatively affect the structure of connective tissues and bones, starts systemic processes of connective tissue regeneration, participates in the neutralization of cellular markers of inflammation, as well as eliminates swelling of soft tissues.

The drug «Coenzyme Q10» (Now Foods, USA), included in scheme No. 2, was approved and recommended by all doctors of related specialties for patients of the main subgroup 2. Regardless of the type of concomitant pathology, the drug is a vitamin compound that plays a major role in the production of cellular energy.

Thus, the originally developed two schemes of conservative treatment for GP I, II, and III stages in patients with various somatic diseases can be considered as adapted in the conditions of inpatient treatment of a general profile.

CONCLUSIONS

Conservative treatment for GP I, II, and III stages with the CPITN index values ≤ 2 and > 2 points against the background of somatic pathology, using developed treatment schemes in the main subgroups, contributed to the elimination of inflammation and improvement of oral hygiene and clinical indicators, which was confirmed by the positive dynamics of index assessments in the nearest and long-term follow-up periods.

After 12 months of observation, «stabilization» of the pathological process in the periodontal tissues with the CPITN index values ≤ 2 was noted in 82,76 % of treated patients, and with the CPITN index values > 2 – in 68,18 % of patients, which significantly exceeded these indicators when using traditional conservative treatment schemes for GP against the background of various somatic pathologies, $p<0,01$.

Consequently, the developed treatment schemes No. 1 and No. 2 have revealed good clinical effectiveness and can be recommended for widespread use in periodontal practice for conservative preoperative treatment of GP of different stages against the background of somatic pathology.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Maryana M. Shevchuk
Danylo Halytskyi Lviv National Medical University
69 Pekarska St., 79010 Lviv, Ukraine
e-mail: maryanashevchuk4@gmail.com

ORCID AND CONTRIBUTIONSHIP

Maryana M. Shevchuk: 0000-0003-0370-0101 A B C D F
Andriana P. Skalat: 0000-0002-3688-4907 B C D E
Khristina B. Burda: 0000-0002-1454-3079 B C D
Nataliya S. Magera: 0000-0003-3814-255X B C D
Olesia I. Martovlos: 0000-0003-4833-8935 A D E F

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

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ORIGINAL ARTICLE

CONTENTS

Biomarkers of inflomation in the blood of patients with the degenerative lumbar spine disease and complications after transpedicular fixation

Vladyslav Tuliakov, Oleksander Barkov
SYTENKO INSTITUTE OF SPINE AND JOINT PATHOLOGY UKRAINIAN NATIONAL ACADEMY OF MEDICAL SCIENCES, KHARKIV, UKRAINE

ABSTRACT

Aim: To investigate the peculiarities of deviations of preoperative values of biochemical markers of inflammation in the blood serum of patients with degenerative diseases of the lumbar spine after transpedicular fixation, with a complicated postoperative course to predict the development of various postoperative complications.

Materials and Methods: The content of glycoproteins (GP), sialic acids (SA), C-reactive protein (CRP), seroglicoids (SG), haptoglobin (HG), Veltman`s test (VT) were investigated. The results are comparable by the Student-Fisher method.

Results: When compared to data of the control group, patients without complications showed 37.21% higher content of SA, by 67.36% – HG, by 56.70% – CRP, by 22.22% – VT; in patients with soft tissue inflammation – an increase of 136.84% of HG content, 86.00% – SA, 160.00% – CRP and a decrease in 51.11% of VT; in patients with hypercoagulation, the content of GP, SA, HG, CRP is higher by 109.30%, 82.00%, 131.57% and 133.33%, and VT – less by 48.48%; in patients with screw instability, the level of GP is higher by 48.83%, HG – by 78.94%, the SA – by 19.00%, the CRP – by 53.53% and lower VT – by 15.56%; with several complications GP more than 93.02%, SA – by 69.00%, HG – by 123.16%, CRP – by 111.33% of VT – lower by 40.00%.

Conclusions: According to our data, the indicators that are more suitable for predicting the development of complications are CRP, GH, and CA. However, none of the studied indicators is universal, and their prediction requires the use of diagnostic complexes.

KEY WORDS: complications, biochemistry, transpedicular fixation, prediction, degenerative diseases of the spine

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INTRODUCTION

Lumbar discectomy with transpedicular fixation of adjacent vertebrae is most often performed by a surgical procedure for the treatment of patients with a disk protrusion into the spinal canal [1]. The standard procedure is open discectomy (OD), which produces good results [2], which range from 75 % to 100 % [3]. However, transpedicular vertebral fixation is highly likely to develop complications that significantly worsen the patient's condition and quality of life. In particular, the OD can cause muscle damage and other complications [4]. In addition, the operation causes destabilization due to the required resection of the vertebral structures [5, 6]. The prevalence of infectious and specific complications is from 0.44 to 1.81 % [7].

Complications of decompression-stabilizing operations may be instability or fracture of one of the elements of the structure, the formation of pathology at adjacent levels, neurological disorders associated with a violation of the technique of installation of the transpedicular system [8].

Improper handling of transpedicular screws can lead to the development of a delayed infection [9, 10]. In this case, infection can lead to screwing and pain, which leads to the need to remove the screw [11].

A frequent complication in orthopedic interventions is the thrombosis of the deep veins of the lower extremities [12], which can lead to the development of pulmonary thromboembolism [13].

There is an interaction between inflammation and coagulation systems, in which inflammation leads to the activation of the coagulation system, and coagulation in turn increases inflammatory activity [14].

Due to the widespread spread of complications in transpedicular fixation of vertebrae in degenerative diseases of the lumbar spine, the development of a system of forecasting the development of various types of complications in the postoperative period is relevant on the basis of the results of preoperative biochemical examination. This may give a new opportunity to improve the quality of treatment by timely taking measures to prevent the complicated course of

the postoperative period and to improve the quality of treatment of patients with this pathology.

AIM

To investigate the peculiarities of deviations of preoperative values of biochemical markers of inflammation in the blood serum of patients with degenerative diseases of the lumbar spine after transpedicular fixation, with a complicated postoperative course to predict the development of various postoperative complications.

MATERIALS AND METHODS

The studies were conducted on the basis of the clinic of the Sytenko Institute of Spine and Joint Pathology Ukrainian National Academy of Medical Sciences (Accreditation Certificate (Higher Category) dated 19.04.2021 to 18.04.2024 M3 No 015211) in the department of laboratory diagnostics and immunology of the Institute (certificate of compliance with the system of measurement with the requirements of DSTU ISO 10012:2005 dated 14.03.2023 to 14.03.2026 No 01-0017/2023).

The research plan was considered and approved at a meeting of the Committee on Bioethics of the Institute of 19.04.2021, protocol No. 215.

The basis for the preparation of work was the data transferred from medical cards of inpatient patients (f. 003/o) department of pathology of the spine of the Institute, which are stored in the archive of the Institute.

Research design. The work is based on the results of retrospective analysis of the data of biochemical examination of 46 patients with degenerative diseases of the lumbar spine, which performed discectomy with transpedicular fixation of the vertebrae in the department of spine pathology in the period 2015-2023.

Observation groups. The biochemical parameters in patients of four groups were investigated, in which complications were observed in the postoperative period: I – inflammation of soft tissues around the instrument zone (10 patients); II – development of hypercoagulation conditions (6 patients); III – instability of transpedicular fixation (5 patients), IV – several complications at the same time (5 patients). The comparison group was the results of the preoperative examination of 20 people with uncomplicated postoperative period, and data of the control group, which included 20 donors (almost healthy people).

Criteria for patients in study or exclusion from the study – the presence of other lesions of the skeleton (injuries, osteporosis), as well as serious diseases that could affect the course of the disease (cancer, cardiac, liver and renal insufficiency of high degree, thrombotic diseases, autoimmune diseases (rheumatoid arthritis, lupus erythematosus, etc.; rheumatism, chronic infectious diseases (chlamydia, trichomonados, etc.; a severe course of Covid-19 in history, mental illness, including alcoholism, drug addiction), disruption Adding appropriate diseases in the process of diagnosis and treatment of the underlying disease.

Before surgery, inflammatory markers were determined in the blood serum of all patients: blood content of sialic acids (SA), C-reactive protein (CRP), seroglicoids (SG), haptoglobin (HG) according to the instructions to the sets [15]. The content of total glycoproteins (GP) in serum was determined by the modified method of O.P. Shtenberg and Ya.N. Dotsenko, the content of C-reactive protein (CRP) – a semi-quantitative latex test with fixed values of 6, 12, 24 and 48 mg/l, Weltman`s test (WT) – by modified method [16]. The results were processed using MS Windows software, № licensing package 439108-251. The normality of distribution was checked by Kolmogorov – Smirnova. The results are presented as the average square ± standard deviation (M±m). For comparison, the Fisher-Student Fisher method was used. The difference was considered statistically significant at $p<0.05$ [17].

To evaluate the diagnostic significance of these parameters in various types of complications, we calculated their diagnostic sensitivity (DS), which is the probability that the patient will have a positive test result. DS was evaluated by the chance (%) of positive analysis results in patients with appropriate disease by formula:

$$DS = \frac{RP}{RP + FN} \text{ x } 100\ \%,$$

where RP is really positive test results;
FN – false-negative test results [18].

RESULTS

Patients with uncomplicated post–operative period were shown by 37.21 % higher than 67.35 % – HG, as well as WT results by 22.22 % with respect to such in persons in the control group (Table 1).

The CRP concentration in serum <6 mg/l (an average of 3 mg/l) was recorded in 8 people, 6-12 mg/ml (an average of 9 mg/l) in two patients, 12-24 mg/l (an average of 18 mg/l) – in 1 patient of 20 in the group (as a whole in the group 7.05 ± 1.09 g/l), in that time, as in the control group of 30 people, the value of 6-12 mg/kg (an average of 9 mg/l) was determined in 7 people 12-24 mg/l (an average of 18 mg/l) – in one patient, the

Table 1. Biochemical markers of inflammation of patients with postoperative complications after transpedicular fixation of vertebrae

№ p/n	Indexes	Control group (n=20)	Patients without postoperative complications (n=20)	Patients followed by soft tissue inflammation (n=10)	Patients with the subsequent development of hypercoagulation (n=6)	Patients with subsequent instability of structures (n=5)	Patients with multiple complications at the same time (n=5)
1	2	3	4	5	6	7	8
1	the content of common glycoproteins, mmol/l	0,43±0,01	0,59±0,04 +37,21 %[1, 5)]	0,84±0,05 +95,57 %[1, 7)] +42,37 %[2, 6)]	0,90±0,06 +109,30 %[1, 7)] +52,54 %[2, 6)] +7,14 % [3, 4)]	0,64±0,04 +48,83 %[1, 7)] +8,47 %[2, 4)] -23,81 %[3, 5)]	0,83±0,09 +93,02 %[1, 7)] +40,68 %[2, 5)] -1,19 %[3, 4)]
2	the content of sialic acids, mmol/l	2,00±0,03	2,19±0,25 +9,50 %[1, 4)]	3,72±0,19 +86,00%[1, 7)] +69,86 %[1, 7)]	3,64±0,35 +82,00%[1, 7)] +66,20 %[1, 7)] -2,15 % [3, 4)]	2,38±0,45 +19,00 %[1, 5)] +8,68 %[1, 4)] -49,58 %[1, 6)]	3,38±0,45 +69,00 %[1, 7)] +54,34 %[1, 6)] -9,14 %[1, 4)]
3	gaptoglobin content of g/l	0,95±0,04	1,59±0,07 +67,36 %[1, 5)]	2,25±0,12 +136,84 %[1, 5)] +41,51%[2, 5)]	2,20±0,11 +131,57 %[1, 5)] +38,36%[2, 5)] -2,22 % [3, 4)]	1,70±0,10 +78,94%[1, 7)] +6,92 %[2, 4)] -24,44 %[2, 5)]	2,12±0,15 +123,16 %[1, 7)] +33,33 %[2, 5)] -5,78 %[2, 4)]
4	Weltman's test results, ml	0,45±0,01	0,35±0,02 -22,22 %[1, 5)]	0,22±0,02 -51,11 %[1, 7)] -37,14 %[2, 5)]	0,23±0,02 -48,48 %[1, 6)] -34,29 %[2, 5)] +4,55 % [3, 4)]	0,38±0,02 -15,56 %[1, 5)] +8,57 %[2, 4)] +72,72 %[3, 6)]	0,27±0,02 -40,06 %[1, 5)] -22,85 %[2, 5)] +22,73 %[3, 5)]
5	content of C-reactive proteins, mg/l	4,50±0,62	7,05±1,09 +56,70 % [1, 7)]	11,70±0,95 +160,00 %[1, 7)] +66,00 %[2, 7)]	10,50±1,01 +133,33 % [1, 7)] +48,94 % [2, 5)] -10,25 % [3, 4)]	6,90±0,66 +53,33 % [1, 7)] -2,13 % [2, 4)] -41,03 % [3, 5)]	9,60±2,40 +111,33 % [1, 7)] +36,17 % [2, 5)] -17,95 % [3, 4)]

[1)] in relation to the indicators of the control group (almost healthy people);
[2)] in relation to patients without postoperative complications;
[3)] with respect to patients with subsequent soft tissue inflammation;
[4)] $p > 0,05$;
[5)] $p < 0,05$;
[6)] $p < 0,01$;
[7)] $p < 0,001$.

other 22 people had a serum of CRP <6 mg/l, we took it as an average of 3 mg/l (as a whole in the group 4.50 ± 0.62). Based on the data, patients without postoperative complications, 56.70 % exceeded the data of the control group (table 1).

Analysis of the results of the examination of patients with postoperative inflammation of the soft tissue showed an increase of 136.84 % of HG content, by 86.00 % of the content of the SA and a decrease in 51.11 % of the results of WT. When measuring the CRP content in serum with latex test in the analyzed group of patients found out that of serum of 20 persons were 12-24 mg/l (an average of 18 mg/l) – in 6 patients and 6-12 mg/l (average 9 mg/l) – in 14 patients (as a whole in the group 11.70 ± 0.95 g/l). The comparison with such persons in the control group showed an exceeding by 160.00 % (table 1).

When comparing with the results of examination of patients without postoperative complications, it is stated that in patients who have been inflammation of the soft tissues in the postoperative period in serum were higher than in the comparison group by 41.51 %, SA – by 69.86 %, for 37.14 % lower WT results (table 1).

Serum CRP content was significantly higher by 66.00 % in a given group of patients than in patients who have been having complications (table 1).

In patients with postoperative development of hypercoagulation conditions, the content of GP, SA and HG were higher than those in the control group, respectively by 109.30 %, 82.00 %, 131.57 %. According to the results of WT, the analyzed group of patients was inferior to the persons of the control group by 48.48 %.

When measuring CRP concentrations in the blood of patients with the development of hypercoagulation conditions, it was recorded that 10 patients were CRP, 6-12 mg/l (an average of 9 mg/l), and in two patients was observed in the range of 12-24 mg/l (an average of 18 mg/l). After statistical treatment, the result in the group was 10.50 ± 1.01 mg/l, which exceeded 133.33 % of the level of indicator in persons of the control group.

Compared to patients without postoperative complications, higher values of 109.30 % were indicated by 82.00 %, HG by 131.57 % at 48.48 % lower results of WT.

Table 2. diagnostic sensitivity of the studied laboratory parameters of patients with degenerative spinal diseases and subsequent surgical treatment depending on the type of postoperative complications

№ n/p	Indexes	Diagnostic sensitivity, %			
		patients with the subsequent development of soft tissue inflammation	patients with the subsequent development of hypercoagulation	patients with subsequent development of instability of constructions	patients with subsequent development of several complications at the same time
1	the content of total glycoproteins	80	65	70	100
2	the content of gaptoglobin	90	70	60	75
3	results of Weltman`s tests	75	70	55	80
4	the content of C-reactive proteins	100	68	60	90
5	the content of sialic acids	90	65	40	80

The level of CRP in patients of the analyzed group was 48.94 % higher in relation to patients without complications, but 10.25 % less than in patients with postoperative inflammation of soft tissues.

In patients with the development of instability of metal structures compared to such persons of the control group, the level of 48.83 %was found in persons, HG – by 78.94 %, SA – by 19.00 % and lower results of WT – by 15.56 %.

Of the 20 patients with the development of instability of metal structures, the CRP concentration was in the range of 6-12 mg/ml (an average of 9 mg/l) in 13 patients, the value is less than 6 mg/l (an average of 3 mg /l) – in 7 patients. The average value in the group of 6.90 ± 0.66 mg/l, exceeding such in persons of the control group by 53.33 % (table 1).

Indicators of the analyzed group of patients did not have reliable differences with such patients without postoperative complications.

Comparison of inflammation markers of patients analyzed with patients with postoperative development of soft tissue inflammation showed that in patients with instability of metal structures in serum was 23.81 % less than GP, 24.44 % HG and 49,58 % SA. The result of WT and CRP in the group under consideration was 72.72 % and by 41.03 %, respectively, more than in patients with soft tissue inflammation (table 1).

Patients with simultaneous development of several complications were characterized by more significant abnormalities, since they developed several types of postoperative conditions at the same time. At the same time, they found at 93.02 % higher concentration of GP, by 69.00 % – SA, by 123.16 % – HG with at the same time by 40.00 % lower result of WT.

The serum content of the CRP in one patient of the analyzed group of 5 occurred in the range of 6-12 mg/l (an average of 9 mg/l), and in the one patient the concentration of CRP was within 12-24 mg/l (an average of 18 mg/l), that the group averaged 9.60 ± 2.40 mg/l, by 111.33 % exceeding such in persons in the control group (table 1).

When comparing the indicators of a group of patients with multiple complications with such patients with uncomplicated post-operative period, it was recorded that the exceeding of the serum of GP, SA, HG, respectively by 40.68 %, 54.34 % and 33.33 %. At the same time, lower of 22.85 % results of WT were observed (table 1).

The concentration of CRP in the analyzed group of patients was 36.17 % higher than in patients with uncomplicated postoperative period (table 1).

When comparing the indicators of a group of patients with the development of multiple complications with such in patients with the development of inflammatory complications of soft tissues, the results of WT exceeded the data of the comparison group by 22.73 % at 17.95 % of the CRP concentration (table 1).

The requirements of evidence-based medicine require the formalization of evaluative systems of diagnostic significance of the parameters under study.

Diagnostic sensitivity means the ability of the test to properly identify patients who really have this condition [18].

Based on the results obtained in this study, the DS of used tests were calculated. The results are given in table 2.

In patients who have postoperative inflammation of soft tissues around metal structures, the most informative are (in order of reduction of DS): CRP content (100 %), HG content (90 %), SA (90 %), total GP content (80 %), WT (70 %).

In patients with subsequent development of hypercoagulation in the study before the intervention, the largest DS in the content of HG (70 %), WT (70 %), CRP (68 %), content of total GP and SA (65 %) were required in the intervention.

In patients who have observed postoperative instability of metal structures, the most informative are (in

order of reduction DS): total GP content (70 %), CRP content (60 %) and HG (60 %).

In patients with several complications at the same time, the highest DS was observed in the content of total GP (100 %), the content of CRP (100 %), the results of the WT (80 %), and the content of SA (80 %), the content of HG (75 %) (table *2)*.

DISCUSSION

All patients before surgical treatment were characterized by moderate activation of inflammatory processes, which was reflected in the excess of the studied inflammatory markers. In the group with an uncomplicated postoperative period, the above may indicate the presence of chronic inflammatory processes in patients that accompanied the development of the underlying disease. This corresponds to the modern idea of the pathogenesis of osteochondrosis as a disease with degenerative and inflammatory bases of development [19].

In patients with postoperative soft tissue inflammation, there were greater differences with those in the control group than in patients without postoperative complications, indicating a higher baseline inflammatory activity. In degenerative diseases of the musculoskeletal system, but of a different localization – large joints – congenital activation of populations of systemic immune cells, especially macrophages, was recorded, which may lead to the conclusion that some people have a hereditary predisposition to these diseases of the musculoskeletal system [20].

In patients with postoperative development of hypercoagulable states, as in the previous group, biochemical signs of a higher inflammatory background were noted compared with those of both control subjects and patients without postoperative complications. The level of inflammatory markers in the analyzed group of patients generally corresponded to that in patients with postoperative soft tissue inflammation, which, in our opinion, can be explained by the pathogenetic relationship between inflammation and hypercoagulability [21].

When comparing the results of the examination of patients with the development of instability of metal structures with those of the control group, it was found that the markers of the inflammatory process in patients of the analyzed group were only slightly increased and corresponded to those of patients with an uncomplicated course of the postoperative period. Patients of the analyzed group were characterized by a lower level of baseline inflammation than patients with the development of soft tissue inflammation in the postoperative period, which was reflected in the lower values of the studied inflammatory markers. In general, patients with osteochondrosis have more frequent disorders of anatomical structures than healthy individuals [22]. In particular, deviations in the morphology of the upper articular process of the 5th sacral vertebra are quite common [23]. The angle of the sacrum and the type of pelvis are important, and under combined loading, the pelvis with a neutral type of tilt demonstrated the highest flexibility of the lumbar spine, on average by 2.46o, compared with that with a pelvis tilted forward or backward [24]. Probably, the presence of such features contributes to the development of instability of metal structures. In this case, the use of intraoperative navigation systems is highly advisable [25]. Perhaps greater deviations in preoperative laboratory parameters in this group of patients could be found among the parameters characterizing the processes of bone metabolism and mineralization [26]. In particular, deviations in visual indicators are reported by R. L. Witkam et al. (2022) [27]. This may be the rationale for the expediency of including the latter in the examination of patients before surgical treatment of spinal osteochondrosis.

Patients with the simultaneous development of several complications predictably exceeded the content of the studied inflammatory markers in the control group, as well as the group of patients with an uncomplicated course of the postoperative period by most indicators. Nevertheless, judging by the intensity of the manifestation of inflammatory markers, these patients did not have a simple summation of the intensity of inflammatory processes, but rather an expansion of the nomenclature of pathology with their mutual relationship and parallel course.

CONCLUSIONS

1. A comparative analysis of the results of preoperative laboratory examination of patients with transpedicular fixation of the vertebrae and the complicated course of the postoperative period showed that the development of complications in the postoperative period is preceded by changes in preoperative laboratory parameters.
2. In patients with uncomplicated course of the postoperative period before surgery, a moderate increase in serum content of total glycoproteins (<0.60 mmol/l), haptoglobin (<1.6 g/l), C-reactive protein (<12 mg/l).
3. In patients with soft tissue inflammation and with the development of hypercoagulation conditions, similar changes in preoperative markers of serum inflammation have been recorded: a significant increase in serum of total glycoproteins (<90 mmol/l), sialic acids (>3.5 mmol/l), haptoglobin (up to 2.1 g/l), C-reactive protein (>6-12 mg/l).

4. The development of instability of transpedicular structures was preceded by an increase in the serum of haptoglobin (<1.8 g/l) with a slight increase in the content of total glycoproteins (<0.70 mmol/l) and sialic acids (up to 2.5 mmol/l).
5. Before the development of multiple complications after transpedicular fixation of the vertebrae, there was a significant increase in serum haptoglobin (>2.0 g/l) and a moderate increase in the content of sialic acids (3.0-3,5 mmol/l), C-reactive protein (> 6-12 mg/l).
6. According to our data, indicators that are more suitable for predicting the development of complications, as well as its focus are the content of C-reactive protein, haptoglobin and sialic acids.
7. None of the studied indicators is universal for the differential diagnosis of possible complications, and to predict the latter, it is necessary to use diagnostic sets of indicators.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Oleksander Barkov
Sytenko Institute of Spine and Joint Pathology
Ukrainian National Academy of Medical Sciences
80 Hryhoriy Skovorody St, 61000 Kharkiv, Ukraine
e-mail: a.barkov.79@gmail.com

ORCID AND CONTRIBUTIONSHIP

Vladyslav Tuliakov: 0000-0002-3187-1592 B C D E
Oleksander Barkov: 0000-0003-2161-416X A C D E F

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

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ORIGINAL ARTICLE

CONTENTS

Assessment of prescribing practice of anti-hypertensive medications in a sample of Iraqi patients with diabetes

Amina Jabri, Zaid Fakhrulddin, Evan Hameed
DEPARTMENT OF CLINICAL PHARMACY AND THERAPEUTICS, FACULTY OF PHARMACY, UNIVERSITY OF KUFA, KUFA, IRAQ

ABSTRACT

Aim: This research aims to comprehensively assess the prescribing practices of anti-hypertensive medications in a sample of Iraqi patients with diabetes. Specifically, exploring medication types and classes, adherence to clinical guidelines for managing hypertension in the context of diabetes, and factors influencing prescribing decisions.

Materials and Methods: This descriptive cross-sectional retrospective study investigates medication usage in an outpatient clinic in Najaf, Iraq, utilizing systematic sampling. A total of 157 prescriptions from hypertensive outpatients aged 18 and above with comorbid diabetes were randomly selected.

Results: In our study, diabetic hypertensive patients were found to be administered antihypertensive medicines. The usage patterns revealed that a substantial proportion relied on CCBs (48.4%), followed by ARBs (34.4%), ACEIs (32.5%) and Diuretics (32.5%). Notably, single-drug therapy with CCB was more common than multiple-drug therapy among diabetic hypertensive patients in this investigation.

Conclusions: This study reveals that CCBs are the most commonly prescribed antihypertensive class among diabetic patients in Iraq, followed by ARBs, diuretics, and ACEIs. While this pattern shows partial alignment with guidelines recommending ACEIs and ARBs as first-line treatments, the preference for CCBs suggests a need for further studies exploring the reasons behind these prescribing patterns.

KEY WORDS: anti-hypertensive, diabetic patients, medications, drug combinations, pattern of prescription, calcium channel blocker

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INTRODUCTION

The clinical and pharmacological management of diabetes and hypertension is of utmost importance, as they are prevalent, life-threatening disorders [1, 2]. Non-communicable diseases (NCDs) are the leading cause of death and morbidity in Iraq, with 55% of Iraqi deaths attributed to NCDs in 2019 [3]. Diabetes and hypertension affect each other. It has been demonstrated that people with uncontrolled blood pressure, despite hypotensive medication, have a higher chance of developing diabetes [4]. Diabetes and hypertension are components of metabolic syndrome, they coexist and influence one another's courses [5]. People with diabetes are twice as likely to develop hypertension as non-diabetics of equivalent age [6].

In recent decades, diabetes mellitus and hypertension have increased globally. Several risk factors for these chronic diseases, such as population ageing and rapid shifts in lifestyles toward westernization, have grown more prevalent [7]. Behavioral alterations for hypertension management in diabetic patients are shown in table 1. Over the past decade, blood pressure standards globally have revised their recommended blood pressure objectives due to a better understanding of hypertension management in diabetics [8]. Hypertension treatment in diabetes mellitus avoids problems. People with diabetes who manage to control their blood pressure effectively can significantly benefit, as this helps prevent both microvascular and macrovascular complications associated with diabetes and hypertension [9]. Hypertension is a significant NCDs and the third-leading global disability-adjusted life year cause. In 2000, there were 972 million hypertensive individuals worldwide; this number is projected to increase by 60 percent to 1.56 billion by 2025 [10]. Diabetes is often accompanied by hypertension, which can be prevented by controlling BP. People with diabetes should aim for BP under 130/80 mmHg [8, 11] and angiotensin receptor II blockers (ARB) and angiotensin converting enzyme inhibitors (ACEI) are recognized treatments for reducing cardiovascular events and slowing the progression of diabetic kidney disease (DKD). They slow the progression of renal failure and mortality from cardiovascular disease [11-13]. Controlling blood pressure in diabetics may be facili-

tated by calcium channel blockers (CCB), especially in combination therapy [14]. Beta-blockers and CCB have favorable benefits in the managing hypertension in diabetic individuals. Beta-blockers prevent cardiovascular events and are useful in a multidrug regimen [11]. Numerous diabetic patients necessitate combination therapy with multiple antihypertensive medications [4]. The majority of diabetes individuals have a BP that is greater than 140/90 mmHg, as evidenced by numerous studies [15-16]. ACEIs or ARBs are good first-line treatments for high-risk CV events. According to the Lipid-Lowering and Antihypertensive medication for Prevention of Heart Attack trials (ALLHAT) diabetic subgroup results, for diabetics with normal urine albumin excretion (<30 mg/day), calcium channel blockers (CCB) are currently the first-line drugs [17-18]. If target BP levels are not achieved with monotherapy at the standard dose, further antihypertensive medication should be administered. A di-hydro pyridine CCB is superior to a thiazide/thiazide-like diuretic for patients being evaluated for combination therapy with an ACE inhibitor. Based on the Avoiding Cardiovascular Events via Combination Treatment in Patients Living with high systolic blood pressure (ACCOMPLISH) trial, ACE/CCB combination medication is recommended for type 2 diabetes patients [17, 19]. Combining medications from different classes with diverse mechanisms of action helps achieve successful blood pressure control with minimal adverse effects [20].

SELECTION OF THERAPY FOR HYPERTENSION

All guidelines recommend lifestyle adjustments before or alongside BP-lowering medications for hypertension management. Important lifestyle changes include dietary modifications, weight loss, and regular exercise [20]. If blood pressure is significantly raised, more than 160/100 mmHg, a pharmaceutical prescription with at least two medicines should be initiated. Any therapy, including ACEI, ARBs, diuretics, and CCB, may be employed [21, 22]. ACEIs or ARBs should be used first in individuals with significant albuminuria to prevent renal disease development, reduced estimated glomerular filtration rate, edema, or other strong cardiovascular signals, such as heart failure with arrhythmias and reduced ejection fraction [23, 24]. Combination Therapy Prevents Cardiovascular Events in Individuals Living with Systolic Hypertension (ACCOMPLISH) study gives the strongest data that an ACEI-CCB is better than an ACEI-thiazide diuretic for reducing adverse CV events in diabetic and non-diabetic patients DM [19].

AIM

The present research aims to comprehensively assess the prescribing practices of anti-hypertensive medications in a sample of Iraqi patients with diabetes. Specifically, exploring medication types and classes, adherence to clinical guidelines for managing hypertension in the context of diabetes, and factors influencing prescribing decisions.

MATERIALS AND METHODS

A descriptive, cross-sectional, retrospective study of medication use in an outpatient clinic in Najaf, Iraq, where we randomly selected 157 prescriptions from outpatients with hypertension and diabetes over 18 years of age using systematic sampling. Diabetic hypertensive medication histories were obtained, and anti-hypertensive drug classes and combinations were administered to hypertensive diabetes patients by general practitioners and pharmacological treatments variety. Patients with incomplete medical records were excluded from the study.

DATA ANALYSIS

Microsoft Excel was used to do the data analysis. Variables are continuous; the data was depicted as the mean (standard deviation) and the frequency for categorical variables.

RESULTS

For the study, 157 prescriptions were taken from 65 (41.4%) men with a mean age of 55.2±5 years and 92 (58.6%) women with a mean age of 61.1±6.2 years. Table 2 summarizes the data on the use of antihypertensive agents in patients with diabetes. Among those with both diabetes and hypertension, CCBs are the most frequently prescribed, with a utilization rate of 48.4%, mostly amlodipine. Following CCBs, ARBs are the second most commonly used antihypertensive class at 34.4%, while 32.5% of diabetic patients are treated with ACEIs. Diuretics are also used by 32.5% of patients with diabetes and hypertension, although indapamide is the least prescribed one. β-blockers are rarely prescribed for this patient group. The prescription patterns for each class of antihypertensive medication in males and females are illustrated in Fig. 1 and Fig. 2, respectively.

Table 3 compares males and female's antihypertensive drugs usage and whether there are gender differences between the two groups of diabetic patients. Women use CCB, ARB, and diuretics more than men, who use ACE inhibitors, CCB, and diuretics. Fig. 3 reveals the different

Table 1. Behavioral alterations for hypertension medication in diabetic patients

Alteration	Suggestion
Diet	Follow the dietary approaches to stop hypertension DASH diet
Physical activity	Small modifications in exercise can improve cardiovascular health
Smoking cessation	To improve cardiovascular health, quit smoking.
Sodium restriction	Limit sodium consumption to 2.0 g/day
Weight loss	If required, lose weight to maintain a healthy weight.

Table 2. Use of medications for hypertension in patients with diabetes

Class	Drug	Prescriptions Quantity	Percentage
ACEIs	Perindopril	45	28.7%
	Captopril	6	3.8%
	Total	51	32.5%
CCBs	Nifedipine	11	7.0%
	Amlodipine	65	41.4%
	Total	76	48.4%
β-blockers	Bisoprolol	7	4.45%
	Carvedilol	4	2.57%
	Atenolol	11	7.0%
	Total	22	14.0%
Diuretics	Indapamide	9	5.73%
	Hydrochlorothiazide	17	10.83%
	Furosemide	25	15.9%
	Total	51	32.5%
ARBs	Telmisartan	3	1.9%
	Losartan	1	0.64%
	Candesartan	22	14%
	Valsartan	28	17.83%
	Total	54	34.4%

Table 3. Comparison of antihypertensive drug use in men and women

Class	Males, n (%)	Females, n (%)
ACEI	36 (55.38)	15 (16.3)
CCB	27 (33.8)	49 (53.3)
β-Blockers	4 (6.15)	18 (19.57)
Diuretics	22 (33.85)	29 (31.5)
ARB	17 (26.2)	37 (40.2)

antihypertensive medications along with the number of patients who received them as monotherapy. Among the 71 patients who received monotherapy for hypertension, 26 (36.6%) received CCBs, followed by 18 (25.4%) who received ACEIs, 15 (21.1%) who received ARBs, 6 (8.5%) who received diuretics, and 6(8.5%) who received β-blockers. As it shown in table 4, among the 73 patients prescribed two antihypertensive medications, 19 received a combination of a CCB and ARB, while 15 were given a combination of diuretics and an ACEI. Additionally, 12 (16.4%) patients were treated with a combination of diuretics and an ARB, and another 12 (16.4%) patients received an ACEI and CCB. Further, 5 (6.85%) patients were prescribed a combination of a CCB and β-blockers, 4 (5.48%) patients were given CCBs and diuretics, 3 (4.1%) patients received an ARB and β-blockers, and another 3 patients (4.1%) were prescribed diuretics and β-blockers. In the same table 4, out of 13 patients prescribed three anti-hypertensives, 3 (23.08%) received a combination of diuretics, CCB and ACEI, and another 3 (23.08%) were given a combination of diuretics, ARB, and CCB. In addition, 2 (16.7%) of patients were treated with ACEI, CCB and β-blockers, while 2 (16.7%) patients were prescribed ARB, β-blockers, and diuretics. Another 2 (16.7%) patients received diuretics, CCB, and β-blockers, and one patient was given a combination of diuretics, β-blockers, and ACEI.

DISCUSSION

To assess compliance with evidence-based guidelines, we examined diabetes and hypertension patients' an-

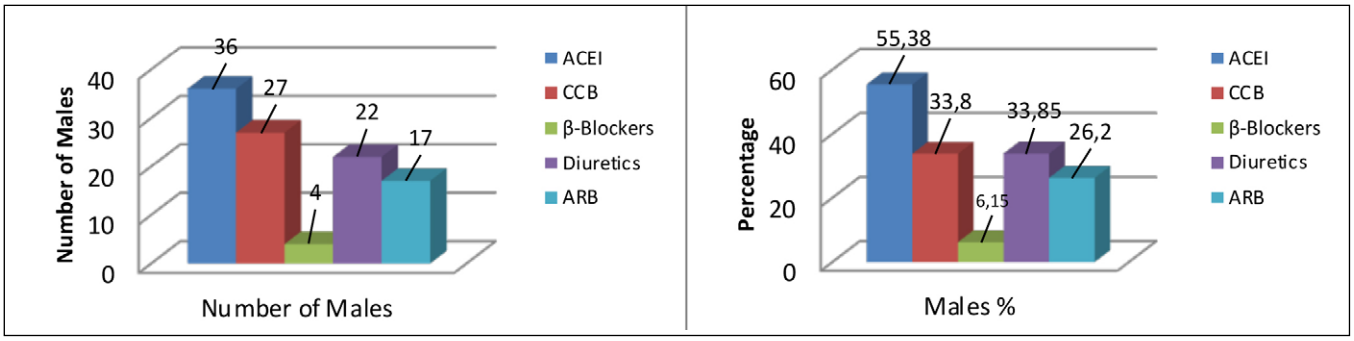

Fig. 1. Anti-hypertensive Class vs (a) No. of Males, (b) Males %.

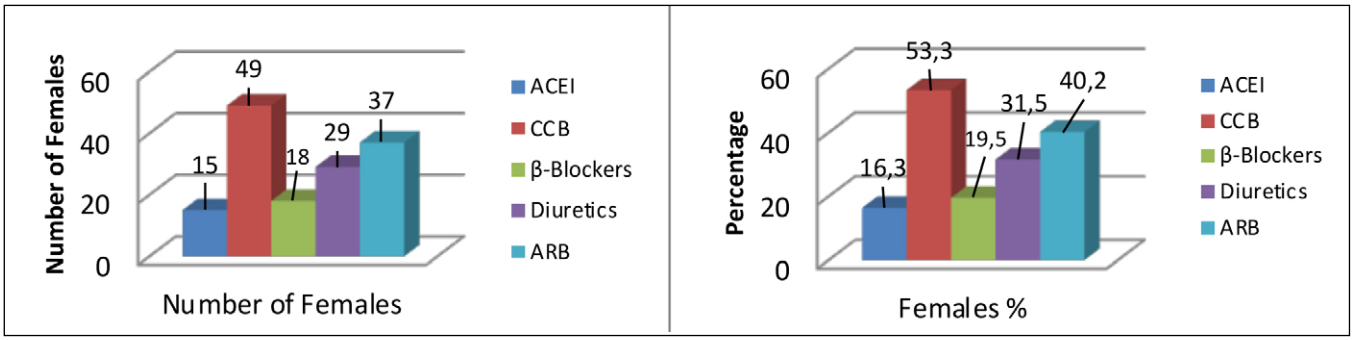

Fig. 2. Anti-hypertensive Class vs (a) No. of Females, (b) Females %.

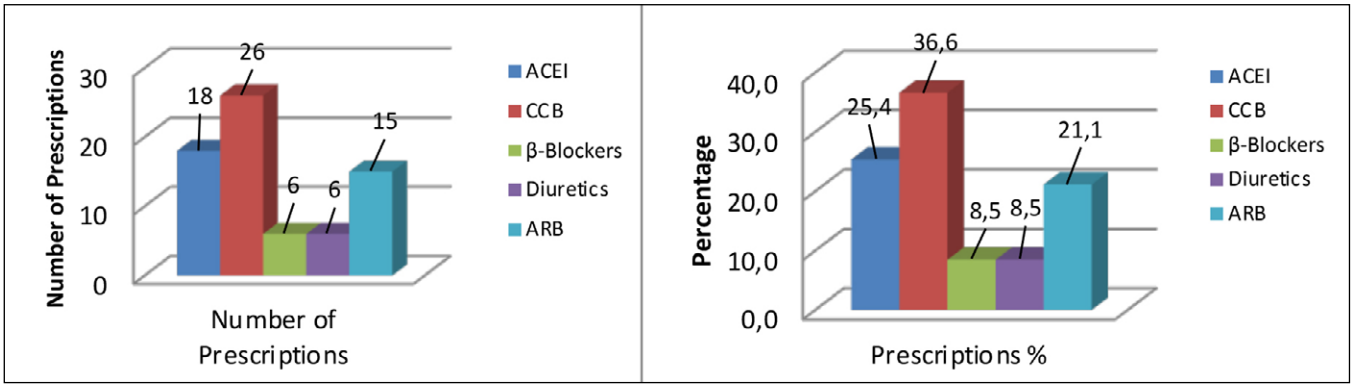

Fig. 3. Antihypertensive Monotherapy Prescribing Patterns (n=71): Analysis by (a) No. of Prescriptions, (b) Prescription Percentage. w

tihypertensive use. The analyzed prescriptions showed that the most commonly prescribed classes, in order, were CCBs, ARBs, diuretics, and ACEIs, followed by β-blockers, regardless of whether mono or polytherapy was used. Consistent with the findings of a Saudi study, CCBs were the most frequently used group of medicines among diabetic hypertensive patients [25]. This result partially aligns with that found by an Indian study, where CCBs were the second most prescribed antihypertensive medications [26]. One probable justification for this prescription pattern could be the effectiveness of CCBs in minimizing cardiovascular events in diabetic hypertensive patients. According to the current investigation results, a CCB was usually prescribed as a single-drug therapy in 48.4% of the cases, rather than as part of a combination treatment. These findings lend credence to previous studies, which demonstrated that a monotherapy might effectively manage hypertension [27, 28]. Also, this study compared patients on multiple therapy to those on a single BP-lowering medicine. The present findings match Marinier et al. who reported that the usage of several antihypertensive medications significantly improved BP control in the treated hypertension population [29]. The combination of CCBs and ARBs was the most prescribed two drug regimen with a prescription rate of 26.03%. This finding is in accordance with Elenchezhiyan V. et al., who revealed that the combination of CCBs and ARBs was given to 44 % of patients [26]. The prescription of CCBs and ARBs may indicate that practitioners are better aware of the long-term cardiovascular and renovascular benefits. Approximately

Table 4. The use of combined antihypertensive drugs

Drug combinations (DC)	Prescriptions quantity	Percentage
2 DC		
ARB + diuretics	12	16.4
ARB + CCB	19	26.03
ARB + β-Blockers	3	4.1
Diuretics + CCB	4	5.48
β-blockers + Diuretics	3	4.1
CCBs + β-blockers	5	6.85
ACEI + diuretics	15	20.55
ACEI + CCB	12	16.4
Total	n = 73	46.5
3 DC		
β-blockers + ACEI + CCB	2	16.7
β-blockers +ACEI + diuretics	1	7.69
Diuretics +ACEI + CCB	3	23.08
ARB + Diuretics + β-blockers	2	15.38
Diuretics + ARB + CCB	3	23.08
β-blockers + CCB +diuretics	2	15.38
Total	n =13	8.3

46.5% of medicines in this study were for combinations of two medications, with third-drug varieties coming in at 8.3% (Table 4). These findings are comparable to two earlier studies which illustrated that nearly half of patients were given multiple medications [25, 30]. However, this outcome does not go well with Dahal et al., where combination antihypertensive medications were prescribed to only 6.6% [31]. This research is not without limitations. One significant limitation is the cross-sectional setting, which hinders the ability to establish whether the observed patient characteristics and prescription patterns are causally linked. Additionally, relying on patient reports and medical records may introduce biases due to recall errors and potential mis-categorization. Moreover, the data was gathered from a limited number of outpatient clinics, which may limit the generalizability of the findings to all hypertensive diabetic patients in Iraq.

CONCLUSIONS

This study provides a detailed assessment of antihypertensive prescribing patterns among diabetic patients in Iraq. The results show that CCBs were the most commonly prescribed antihypertensive class, followed by ARBs, diuretics, and ACEIs. While the high use of CCBs, particularly as monotherapy, suggests a preference for these medications, the findings reveal a partial alignment with evidence-based guidelines, which generally recommend ACEIs and ARBs as the first-line treatment for diabetic patients due to their renoprotective and cardiovascular benefits. The significant use of ARBs, often in combination with CCBs, does reflect some adherence to these guidelines, particularly in the context of combination therapy. However, the predominance of CCBs as monotherapy may indicate a deviation from the recommended first-line use of ACEIs and ARBs, potentially due to local prescribing practices or patient-specific factors. Overall, while the study's findings partially align with current guidelines, they also highlight the need for further education and alignment with best practices in antihypertensive management for diabetic patients. Future research with larger and more diverse populations is recommended to explore the reasons behind these prescribing patterns and assess their impact on long-term patient outcomes.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Amina Jabri
University of Kufa
299G+HPX, Kufa Street, Kufa, Najaf Governorate, Iraq
e-mail: aminam.jabri@uokufa.edu.iq

ORCID AND CONTRIBUTIONSHIP

Amina Jabri: 0009-0007-2207-1335 A B C
Zaid Fakhrulddin: 0009-0002-2030-1073 C D E
Evan Hameed: 0000-0002-8216-6893 E F

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

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ORIGINAL ARTICLE

CONTENTS

Heart rate and blood pressure in soccer players differing in sports qualification

Yevhen Mykhaliuk[1], Yehor Horokhovskyi[2], Anatolii Bosenko[3], Oleg Bazylchuk[4], Mykhailo Khoroshukha[5], Nadiia Orlyk[3], Mariia Topchii[3]

[1]ZAPORIZHZHIA STATE MEDICAL AND PHARMACEUTICAL UNIVERSITY, ZAPORIZHZHIA, UKRAINE
[2]ZAPORIZHZHIA NATIONAL UNIVERSITY, ZAPORIZHZHIA, UKRAINE
[3]SOUTH UKRAINIAN NATIONAL PEDAGOGICAL UNIVERSITY NAMED AFTER K. D. USHYNSKY, ODESA, UKRAINE
[4]KHMELNYTSKYI NATIONAL UNIVERSITY, KHMELNYTSKYI, UKRAINE
[5]BORYS GRINCHENKO KYIV METROPOLITAN UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: To investigate the effects of exercise training on heart rate and blood pressure in soccer players of different skill levels.

Materials and Methods: 693 soccer players with different sports qualifications were studied. Heart rate (HR) and blood pressure (BP) were measured at rest at the beginning of the preparatory phase of the training cycle.

Results: HR in elite soccer players is 64.4±0.83 bpm, bradycardia occurs in 47.4%, tachycardia in 5.3%, hypotonic state of systolic (SBP) and diastolic (DBP) blood pressure in 9.0% and 8.3%, hypertensive state of SBP and DBP in 41.4% and 17.3%, respectively. HR in advanced soccer players is 67.5±0.5 bpm, bradycardia occurs in 36.0%, tachycardia in 8.6%, hypotonic state of SBP and DBP occurs in 11.1% and 32.9%, hypotonic state of DBP in 9.1%, and hypertensive state of DBP in 13.7%. The HR in intermediate soccer players is 71.3±0.73 bpm. Players with bradycardia in this group were found 21.3%, and with tachycardia 17.8%. Hypotonic state of SBP was found in 17.2% of players, and hypertonic state in 19.0%. Hypotonic state of DBP was found in 19.5% and hypertensive state in 8.6% of players. Bradycardia and hypertensive state of SBP are significantly more frequent in elite players than in intermediate players.

Conclusions: Considering the presence of 12.9% of athletes with BP ≥ 140/90 mmHg among advanced soccer players, it is recommended to perform additional examinations, including daily BP monitoring, as well as to make adjustments in the training and rehabilitation process.

KEY WORDS: soccer players, sports qualification, bradycardia, tachycardia, hypotonic and hypertensive states

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INTRODUCTION

As physical culture and sports developed in Western Europe, medical control over the health of those involved in physical culture and sports began to develop. This task was carried out by doctors and paramedical staff. Their duties included, first and foremost, the medical examination of persons for the purpose of their admission to a particular type of sport or recreational physical training. At that time, in order to evaluate functional tests of the cardiovascular system, medical control specialists (sports physicians) used simple instrumental methods of heart rate (HR) and blood pressure (BP) measurement not only at rest, but also after dosed physical exertion in the form of the Martinet-Kushelevsky test (20 knee bends for 30 s).

At the time, the scientific interest was in comparing indicators of people involved in physical training and sport with healthy people not involved in such activities to determine the effects of physical activity on the human body and to develop medical recommendations.

Nowadays, sports physicians and trainers are no longer satisfied with such comparisons. They need the results of an examination of an athlete of a particular sport, taking into account his qualification, age, gender, training experience, period of the training cycle, as well as the specifics of the influence of training and competitive loads on the functional state of the body systems, and first of all on the cardiovascular system [1].

The development of sports science allows the introduction of new research methods into the practice of sports medicine, expanding the practitioner's ability to assess the health and functional status of athletes. At the same time, the provision of complex portable instrumental research methods to the practicing sports

physician is still inadequate. This motivates the continuation of the use of relatively simple, easily accessible research methods in medical control.

It is well known that various organs and systems of the athlete's body undergo functional and morphological changes as a result of sporting activity. Most of the changes in cardiovascular activity are related to the state of training. They are related to sympathoinhibitory and cholinergic mechanisms. In the first place, this refers to the reduction in the heart rate and the blood pressure. It is the decrease in heart rate and blood pressure that forms the concept of the so-called phenomenon of "economisation" of cardiac activity or training of a highly skilled athlete.

Regarding the heart rate, it is known that the average resting HR of healthy men who don't exercise varies between 60 and 80 beats min^{-1}(bps) and is somewhat dependent on age, gender and body size. During regular exercise, the heart rate of athletes decreases due to the development of strong cholinergic responses at rest, one of the consequences of which are negative chronotropic effects and consequently a slowing of the heart rate. At the same time, there is a certain correlation between the intensity of negative chronotropic influences and the type and direction of the training process [2].

The results of almost all authors who have studied BP in athletes show that under the influence of systematic training BP decreases and corresponds to 100-110/60-70 mmHg [3]. These are average values obtained from a study of BP in a large number of athletes, without taking into account gender, age, sport specialization, years of experience and qualification, as all these factors influence BP in athletes.

Relatively reduced values of systolic (below 100 mmHg) and diastolic (below 60 mmHg) blood pressure are often observed in trained athletes, representing physiological hypotension, which is not always a sign of good training [4]. Sometimes hypotension is associated with circulatory dysregulation, in which case it is a syndrome of overtraining or an independent disease [5].

Based on the findings of Dembo [5], it has been observed that hypotension is more common in young athletes, with an incidence rate of 21.0% in masters and 2.6% in beginners. In addition, the incidence of hypotension in athletes tends to increase with more athletic experience. Specifically, up to 15-16 years of experience, the percentage of athletes with hypotension continues to increase. Beyond this point, however, the percentage begins to decrease due to the influence of the age factor. The prevalence of hypertension in athletes is reported to be between 9% and 13% [4]. It is noteworthy that an increase in blood pressure is observed from 3-4% to 10-15%, often reaching the upper threshold of the generally accepted range or entering the realm of potential danger. The improvement in cardiovascular regulatory mechanisms resulting from increased physical fitness contributes to the return of blood pressure to a normal range. Conversely, impaired fitness, characterized by conditions such as overfatigue, overtraining, or overexertion, often manifests as both an increase and a decrease in blood pressure levels [6].

There is evidence that exercise and sports training are inversely related to the level of blood pressure and the prevalence of arterial hypertension, and this decrease can occur both in individuals with normal blood pressure numbers and in patients with arterial hypertension. There are studies in which the authors consider arterial hypertension in athletes as one of the forms of manifestation of overstrain of the cardiovascular system, which leads to pathological remodeling of the athlete's heart. According to the development of arterial hypertension, athletes whose training is dominated by static loads (weightlifting, athletic throwing, etc.) are at risk, since isometric loads are characterized by an increase in peripheral vascular resistance, causing transitional conditions with a potential risk of hypertension and an increase in overload with normal or slightly increased cardiac output. Significant influence on the increase in blood pressure also has the degree of emotional tension, gender, age. Thus, in men, increased blood pressure occurs 3 times more often than in women, and with increasing age of the athlete, the frequency of arterial hypertension increases. It should be taken into account that among athletes with hypertension there can be people with hereditary predisposition to hypertension [7].

The frequency of increase in blood pressure to some extent depends on the type of sports activity. Increased blood pressure in some athletes indicates the first manifestations of hypertension or is a symptom of other diseases. In some athletes the increase in blood pressure can be associated with improperly organized individual training process, as well as with the phenomena of fatigue, overstrain and mental overload [8, 9].

The importance of the issue of correct clinical assessment of changes in heart rate and blood pressure in athletes is not in doubt. It is not only about the possibility of doing sports for people with altered heart rate and blood pressure, but also about the frequency of detection and clinical evaluation of bradycardia and tachycardia, hypotensive and hypertensive conditions in athletes of different age and sports qualification.

AIM

The aim of this study is to investigate the effects of exercise training on heart rate and blood pressure in soccer players of varying skill levels.

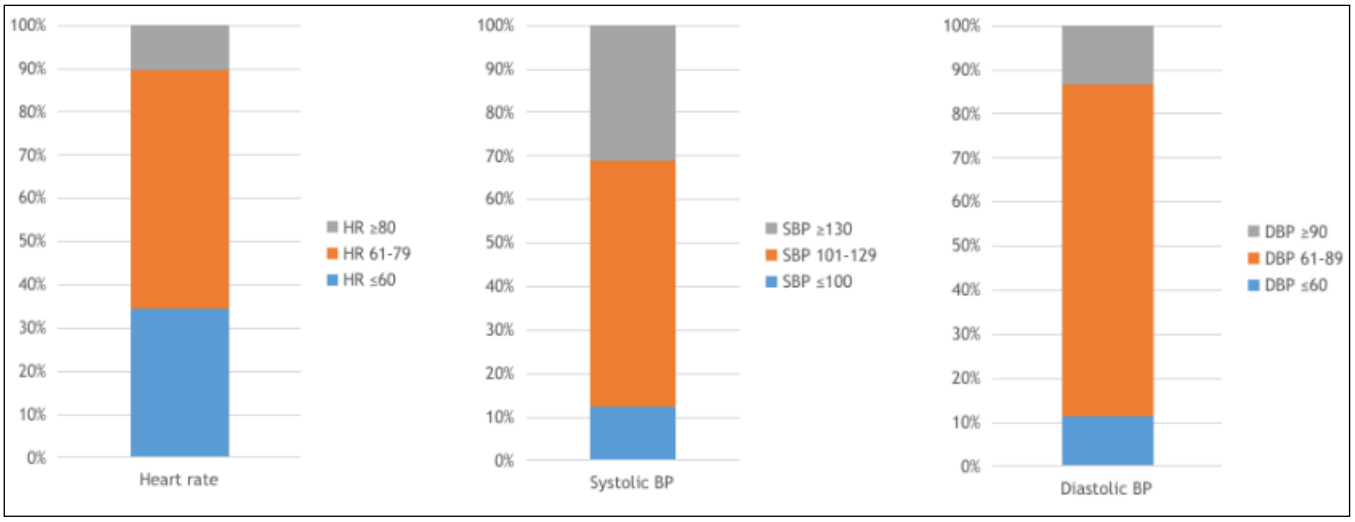

Fig. 1. Heart rate, systolic and diastolic blood pressure of the soccer players studied.

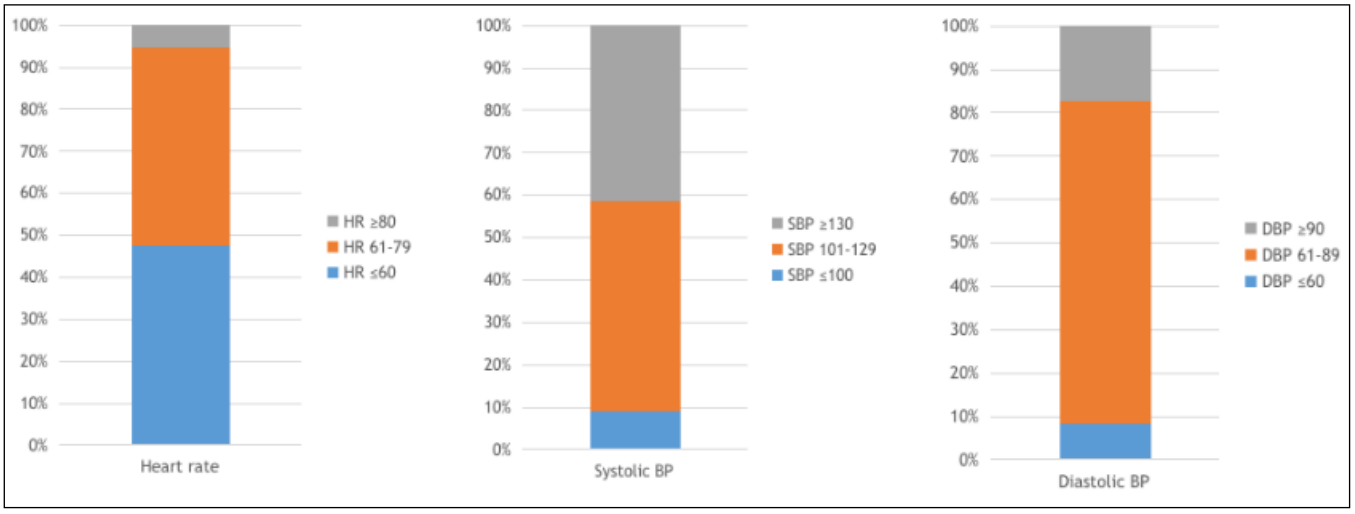

Fig. 2. Heart rate, systolic and diastolic blood pressure of elite soccer player.

MATERIALS AND METHODS

PARTICIPANTS

The study included 693 soccer players between the ages of 11 and 36 years (mean age 19.9±0.18 years), with a sports qualification from 3rd class athlete to Master of Sports of International Class. Included were 133 athletes with sports qualifications of Master of Sports and Master of Sports of International Class (elite soccer players), 386 athletes with sports qualifications of 1st class athlete and Candidate for Master of Sports (advanced soccer players), and 174 athletes with sports qualifications of 2nd or 3rd class athlete (Table 1).

The research was conducted in accordance with the main provisions of the Convention of the Council of Europe on Human Rights and Biomedicine (04.04.1997), Declaration of Helsinki of the World Medical Association on ethical principles of scientific medical research with human participation (2008-2013), Regulations of the Ministry of Health of Ukraine №690 from 23.09.2009, № 944 from 14.12.2009, № 616 from 03.08.2012. All participants were informed about their rights and the possibility to leave the study at any time without explanation.

PROCEDURE

The study was conducted during the preparatory phase of the training process. Heart rate was measured by an auscultatory method at rest in sitting position. Systolic and diastolic blood pressure were measured according to Korotkoff using the aneroid sphygmomanometer Romed (Netherlands) on the right hand. Measurements were performed in the sitting position, three times with an interval of 5 minutes, taking into account the minimum result [10].

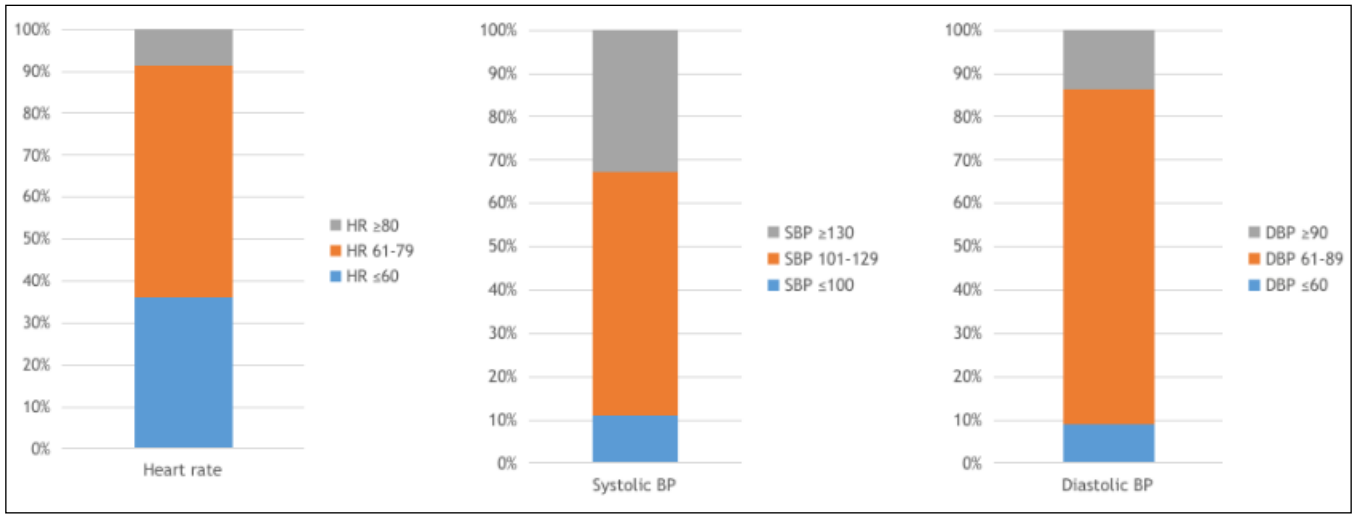

Fig. 3. Heart rate, systolic and diastolic blood pressure of advanced soccer player.

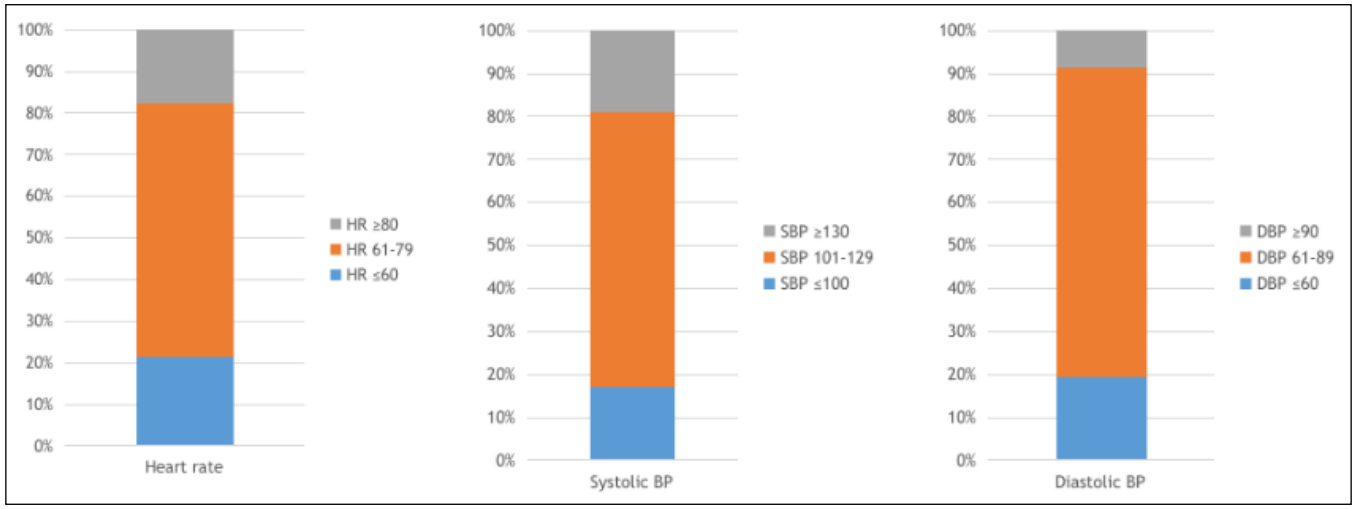

Fig. 4. Heart rate, systolic and diastolic blood pressure of intermediate soccer player.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistica 13.0 software (StatSoft, USA)). Data are presented as mean (M)±standard error of the mean (SE). A two-tailed t-test was used to analyze independent samples. To determine a statistically significant association between two categorical variables, two-tailed Fisher's exact test was used**.** Differences between two subsets of data were considered statistically significant at $p<0.05$.

RESULTS

Out of 693 players, 383 (55.3%) had a HR in the range of 61–79 bpm, which is considered normal. HR in the range of 60 bpm or less, i.e. bradycardia, was found in 239 (34.5%, $p<0.001$), and 80 bpm or more, i.e. tachycardia, occurred in 71 (10.2%, $p<0.001$). Systolic blood pressure (SBP) in the range of 101–129 mm Hg, considered as normal, was found in 393 (56.7%) soccer players, with a value of 100 mm Hg or less, i.e. with a hypotensive state, in 85 (12.3%, $p<0.001$), and with systolic blood pressure 130 mm Hg or more, i.e. with a hypertensive state — in 215 (31.0%, $p<0.001$). Diastolic blood pressure (DBP) within normal values — 61–89 mm Hg was in 522 (75.3%) soccer players, diastolic blood pressure 60 mm Hg or less, i.e. with a hypotensive state — in 80 (11.5%, $p<0.001$) soccer players, and with a value of 90 mm Hg and more, i.e. with a hypertensive state — in 91 (13.1%, $p<0.001$) soccer players (Fig. 1).

Thus, in soccer players, who do not differ in sport qualification and age, HR, SBP and DBP are more often within normal values.

In order to obtain reliable information about the heart rate and the systolic and diastolic blood pressure, we have formed 3 groups of soccer players (elite,

Table 1. General characteristics of the examined soccer players

Group	n	Age, years	Height, cm	Weight, cm
Elite soccer players (Master of Sports, International Class, Master of Sports)	133	25.6 ±0.37	182,9 ±0,52	77,4± 0,66
Advanced soccer players (Candidate for Masters of Sports, 1st class athlete)	386	19,8± 0,17	180,8± 0,31	73,0± 0,35
Intermediate soccer players (2nd-3rd class athlete)	174	15,8± 0,15	174,8± 0,68	64,2± 0,85

Table 2. Heart rate, systolic blood pressure and diastolic blood pressure of soccer players with different levels of athletic ability

Group	HR, bpm	SBP, mm Hg	DBP, mm Hg
Elite players	64,4±0,83 *‡	122,4±1,08 ‡	76,9±0,9 ‡
Advanced players	67,5±0,5	121,2±0,66 †	76,5±0,47 †
Intermediate players	71,3±0,73	116,3±0,97	72,1±0,68

Note: * — elite vs advanced, p≤0.001; † — advanced vs intermediate, p≤0.001; ‡ — elite vs intermediate, p≤0.001

advanced, intermediate) according to their sport qualification and their age. The results of heart rate, systolic and diastolic blood pressure measurements are shown in Table 2.

Comparison of the studied indicators between groups showed that elite soccer players were older than advanced (25.6±0.37 vs 19.8±0.17 years, p<0.001) and intermediate players (25.6±0.37 vs 15.8±0.15 years, p<0.001). HR was lower in the elite group than in the advanced (p=0.001) and intermediate (p<0.001) groups. At the same time, elite players did not differ from advanced players in SBP and DBP. Statistically significant differences between SBP (p<0.001) and DBP (p<0.001) were found when comparing elite and intermediate soccer players, and between advanced and intermediate soccer players.

In the group of elite soccer players, HR in the normal range was found in 47.4%, bradycardia in 47.4%, tachycardia in 5.2% of athletes. Normal values of SBP and DBP were found in 49.6% and 74.4% of athletes, respectively. Hypotensive state of SBP and DBP was found in 9.0% and 8.3%, hypertensive state of SBP and DBP was found in 41.4% and 17.3%, respectively (Fig. 2).

In the group of advanced soccer players, HR in the normal range was found in 55.4% of the athletes studied, bradycardia in 36.0% and tachycardia in 8.6% of the athletes. SBP within reference values was found in 56.0% of athletes, with hypotensive state in 11.1% and with hypertensive state in 32.9%. DBP within normal limits was registered in 77.2% of athletes, with hypotension – in 9.1%, and with hypertension – in 13.7% of soccer players (Fig. 3).

In the group of intermediate soccer players, HR within normal limits was found in 60.9% of athletes. 21.3% and 17.8% of athletes had bradycardia and tachycardia, respectively. SBP within normal limits was found in 63.8% of soccer players, athletes with hypotensive state was found 17.2% and hypertensive state – 19.0%. DBP was within normal limits in 71.8% of athletes, hypotensive – in 19.5% and hypertensive – in 8.6% of athletes (Fig. 4).

The next stage of our work was to determine the relationship between HR and BP in soccer players according to sport qualification. Thus, in a group of elite soccer players, compared to a group of intermediate soccer players, bradycardia is more common – 47.4% vs 21.6% (p=0.009) and a hypertensive state of SBP – 41.35% vs 19.0% (p=0.030).

At the trend level, intermediate athletes had a higher prevalence of: normal HR – 60.9% vs 55.4% (p=0.351) in advanced athletes and 47.37% (p=0.086) in elite athletes; tachycardia – in 17.8% vs 8.6% (p=0.271) in advanced and 5.3% (p=0.407) in elite athletes; normal SBP – in 63.8% vs 56.0% (p=0.173) in advanced and 49.6% (p=0.064) in elite players; hypotonic state of SBP – in 17.2% vs 11.1% (p=0.455) in advanced and 9.0% (p=0.499) in elite players; hypotonic state of DBP – in 19.5% vs 9.1% (p=0.213) in advanced and 8.3% (p=0.384) in elite players. Hypertensive DBP was more common in the elite athletes group, 17.3% compared to the advanced group 13.7% (p=0.688) and intermediate athletes 8.6% (p=0.449). In terms of normal DBP values, advanced soccer players were 77.2% compared to elite (74.4%, p=0.574) and intermediate (71.8%, p=0.241) soccer players. Thus, the differences between the soccer player groups among HR and BP parameters were at the trend level except for bradycardia and hypertension, which were prevalent in elite athletes compared to younger intermediate soccer players.

DISCUSSION

According to the classification of major sports according to Dembo et al. soccer is characterized by acyclic training and competitive work of variable power, developing qualities of agility, speed and strength [11]. Thus, it will be correct to compare the results of the study of heart rate and blood pressure obtained from soccer players or athletes in the training and competitive process of which such physical qualities prevail. In addition, it should be noted that this is a team sport where players have different roles [1].

It is known that as a result of systematic training the heart rate of athletes decreases. A certain value is the effect of increased tone of the vagus nerve on the automatism of the heart. In most trained athletes the HR is in the range of 44–66 bpm [3]. Deshin et al. [12] believed that the reduction of resting pulse in athletes is very favorable, and in well-trained athletes it can be reduced to 32–36 bpm. We assume that the authors of most studies use the term "trained" athletes to mean athletes who are in a high level of training during a competition period. "Untrained" athletes are those who do not participate in sports [1].

Among the studies can be given the results of medical examination of professional soccer players. First of all, sixty-three players from the 1st and 2nd divisions of the Spanish football championship, examined in the preparatory period, whose HR was 61.3±10.4 bpm [13], seven players of the Brazilian soccer club, examined in the competitive period (age 23±5 years, HR – 55±3 bpm) [14], twenty professional players of the Croatian team "Hajduk Split" (average age 22.0±2.9 years, and HR 59.6±5.9 bpm) [15], twenty-five elite players of the Italian soccer club "Fiorentino" (age 26±3.5 years, HR – 60±2 bpm) [16], as well as players of the Indian national soccer team (average age 27.1±1.5 years, HR – 57.8±0.6 bpm) [17] and seventeen professional soccer players from Brazil (average age 24±3 years, HR 57±3 bpm) [18].

Comparison of the average heart rate of elite soccer players of foreign teams, which amounted to 59.1 bpm, and the heart rate of elite Ukrainian soccer players showed that the latter had a slightly higher HR and amounted to 64.4±0.83 bpm.

We also present HR data obtained from soccer players of lower sports qualifications or younger age. These are mainly the data of 101 Ethiopian soccer players (mean age 24.06±3.46 years) without specifying the period of the survey whose HR was 62.45±13.31 bpm [19], 20 players under the age of 18 with a HR of 68.9±12.0 bpm [20], 35 Indian players aged 14-16 years with a HR of 71.5±6.4 bpm [21] and 30 Indian football players (mean age 21±3 years) with a HR of 69±4 bpm [22]. The average HR of the less skilled players was 67.9 bpm, which is almost identical to our data obtained from advanced soccer players, which was 67.5±0.5 bpm.

We have already reported that, without taking into account sport qualifications, soccer players have normal HR values in 55.3% of cases. As far as the HR is concerned, there is a tendency to reduce the number of such players with increasing sport qualification, i.e. from 60.9% for intermediate players to 47.4% for elite players (p=0.086). Bradycardia without sport qualification occurred in 34.5% of cases and tachycardia in 10.3% of cases. At the same time, there was a significant increase in the number of players with bradycardia from the intermediate (21.3%) to the elite level – 47.4% (p=0.009), while the number of players with tachycardia tended to increase from 5.3% in elite athletes to 17.8% (p=0.407) in intermediate athletes.

Graevskaya and Shafeeva [23], having examined 500 soccer players in a state of good physical condition, obtained an average HR equal to 50.3±7.5 bpm (in the range from 39 to 68 bpm). Athletes with bradycardia were 96%, and in the range of 47–54 bpm there were 59.9% of athletes, and 55–60 bpm – 16.5% of athletes. The resulting low HR can be explained by the state of good training, which is possible for soccer players during the competition period. Our data obtained at the beginning of the preparation period differ significantly from the above results. HR in the range of 47–54 bpm was found in 79 (11.4%) athletes and in the range of 55–60 bpm in 235 (33.91%) athletes, which can also be explained by the training period in which the studies were conducted and the level of skill of the athletes.

According to our results, normal values of SBP were found in 56.7% of soccer players. Among them 12.3% were diagnosed with hypotensive state, and 31.0% with hypertensive state. According to Graevskaya and Shafeeva [23] 85.5% of soccer players in a good training condition had normal SBP, 11.7% had a hypotensive state and 2.8% had a hypertensive state, while SBP was in the range from 95 to 140 mm Hg. Volnov [24] found increased systolic blood pressure in soccer players in 16.6% of cases, and according to Levin – in 7.5% of cases [25].

As for normal values of DBP, they were found in 75.3%, hypotonic state in 11.5% and hypertension in 13.1% of soccer players. Graevskaya and Shafeeva [23] reported normal values of DBP in 69.6%, hypotension in 30% and hypertension in 0.4% of soccer players (in the range of 55-82 mm Hg). We believe that the existing discrepancies in the values of HR and blood pressure in soccer players can be associated with the

training periods in which the studies were conducted, as well as with the contingent of athletes studied, since Graevskaya and Shafeeva obtained these values from elite soccer players of the national team level. It should not be forgotten that football is a team sport, in which there are athletes who have a role from goalkeeper to striker, with training of different physical qualities, which naturally affects the average values of heart rate and blood pressure.

Studies conducted among foreign professional soccer players showed a significant variation in the average values of blood pressure. In 63 Spanish players, the values of SBP and DBP were 127.8±10.5 and 71.2±8.4 mm Hg [13], in 7 Brazilian players – 108.0±4,0 and 65.0±6.0 mm Hg [14], in 20 Croatian players – 129.8±8.8 and 73.0±6.7 mm Hg [15], in 18 Indian players – 108.3±5.1 and 70.6±5.9 mm Hg [17], and in 17 professional Brazilian soccer players – 112.0±2.0 and 71.0±2.0 mm Hg [18]. That is, the SBP of foreign elite soccer players averaged 119.5 mm Hg, and the diastolic blood pressure – 71.45 mm Hg, which was slightly different from the values obtained by us from elite players – 122.4±1.08 and 76.9±0.9 mm Hg. In this case, the relatively low values of SBP (108±4 mm Hg) and diastolic blood pressure (65±6 mm Hg) in Brazilian football players can be explained by the fact that the pressure was measured during the competition period.

The SBP and DBP values of young or less skilled soccer players are presented in the results of the survey of 101 soccer players from Ethiopia and amounted to 120.3±10.15 / 75.3±10.10 mm Hg [19], 20 players under the age of 18 – 118.0±11.0 and 69.5±8.2 mm Hg [20], 95 Indian soccer players aged 14–16 years with blood pressure 113.0±8.0 and 63.0±6.5 mm Hg [21], as well as 30 football players of the Indian college with blood pressure – 120±3 and 78±3 mm Hg [22]. The average value of blood pressure in low-skilled football players was 117.8/71.4 mm Hg, and compared to the advanced football players we studied showed slightly lower values – 121.2±0.66 per 76.5±0.47 mm Hg, which does not exceed age norm.

The type of physical exercises used in training in certain sports has some influence on the percentage of athletes with hypertension, although the range is quite wide. Our results, obtained from football players without taking into account qualifications and age, indicate 215 (31.0%) individuals with increased systolic blood pressure and 91 (13.1%) with increased diastolic blood pressure.

Of interest is increased SBP in soccer players of different skill levels. Among 693 soccer players, 78 (11.3%) had systolic blood pressure ≥140/90 mm Hg. Among elite athletes, increased systolic pressure was found in 20 (25.6%) individuals, among advanced athletes in 48 (61.5%), and among intermediate athletes in 10 (12.8%). Thus, the number of athletes with stage I hypertension was significantly higher in advanced soccer players compared to elite (p=0.007) and intermediate soccer players (p=0.005). We came across a study of 594 soccer players (mean age 25 years) from two Norwegian elite divisions who recorded blood pressure 1 hour after exercise as the arithmetic mean of two measurements taken after 5 minutes in a sitting position. Hypertension was defined as ≥140/90 mm Hg. 38 (6.4%) soccer players were diagnosed with stage I hypertension [26]. Our results, obtained among 529 players from intermediate to elite level, without previous physical activity, showed the presence of 68 (12.85%) athletes blood pressure ≥140/90 mm Hg. This is 2 times more than indicated above, and considering that most of them were advanced soccer players, whose age was 19.8±0.17 years, attention should be paid to preventive measures against the development of hypertension and to adequate physical activity according to their functional state.

CONCLUSIONS

1. Elite soccer players have a heart rate of 64.4±0.8 bpm. Among them, 47.4% had bradycardia and 5.3% had tachycardia. The hypotensive state of the systolic and diastolic blood pressure was found in 9.0% and 8.3% of the studied athletes, respectively. The hypertensive state of the systolic and diastolic blood pressure was found in 41.3 % and 17.3 % of elite soccer players.
2. Advanced players have a heart rate of 67.5±0.5 bpm. Bradycardia occurs in 36.0%, tachycardia in 8.6% of players in this group. Persons with hypotonic state of systolic blood pressure were found in 11.1%, with hypertensive state – in 32.9%, with hypotonic state of diastolic blood pressure – in 9.1%, with hypertensive state – in 13.7%.
3. The heart rate of the intermediate soccer players was 71.3±0.7 bpm. Athletes with bradycardia were found in 21.3% and tachycardia in 17.8%. Hypotonic state of systolic blood pressure was found in 17.2%, hypertensive in 19.0%, hypotonic state of diastolic blood pressure in 19.5%, hypertensive in 8.6% of soccer players.
4. The main difference in sports qualification among the indicators studied is the frequency of bradycardia and hypertension, which are statistically more frequent in elite soccer players compared to intermediate soccer players.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Yehor Horokhovskyi
Zaporizhzhia National University
66 Zhukovsky St, 69600 Zaporizhzhia, Ukraine
e-mail: yehor.horokhovskyi@gmail.com

ORCID AND CONTRIBUTIONSHIP
Yevhen Mykhaliuk: 0000-0003-3607-7619 A E F
Yehor Horokhovskyi: 0000-0002-4555-9110 B C
Anatolii Bosenko: 0000-0003-3472-0412 B D
Oleg Bazylchuk: 0000-0002-8137-9950 D E
Mykhailo Khoroshukha: 0000-0001-5024-5792 D E
Nadiia Orlyk: 0000-0003-0144-6576 C
Mariia Topchii: 0000-0002-7470-1032 C

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ORIGINAL ARTICLE

CONTENTS

Change of the anterior talus-fibular ligament length of asymptomatic patients during inversion stress test

Yurii O. Hrubar[1], Iryna Ya. Hrubar[2], Nadiia M. Hrabyk[2], Markiian Yu. Grubar[3] , Yuliana Yu. Hrubar[3]

[1]TERNOPIL I. IA. HORBACHAVSKYI NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

[2]TERNOPIL VOLODYMYR HNATIUK NATIONAL PEDAGOGICAL UNIVERSITY, TERNOPIL, UKRAINE

[3]MUNICIPAL NONPROFIT ENTERPRISE «TERNOPIL REGIONAL CLINICAL HOSPITAL», TERNOPIL REGIONAL RADA, TERNOPIL, UKRAINE

ABSTRACT

Aim: To study the ATFL length among asymptomatic population of young patients on both joints by using the method of ultrasound examination of the ankle joint and applying the inversion stress test.

Materials and Methods: the length of the ATFL was measured among 60 boys and 60 girls during the research. Sonography was performed on both joints, in each of the two studied positions, three times per position in order to obtain the average ligament length. A total of 720 examinations were conducted.

Results: According to the results of sonographic research, the average length of the ATFL of the right ankle joint of young men in a neutral position was 19,08±0,3 mm, of the left one – 19,08±0,31 mm. During the inversion stress test, the length of the ligament increased on the right up to 19,65±0,3 mm, on the left – up to 19,63±0,3 mm. The average length of the ATFL of the right ankle joint of girls in neutral position was 16,92±0,2 mm, of the left one – 16,9±0,19 mm. During the inversion stress test, the length of the ligament increased on the right up to 17,37±0,2 mm, on the left – up to 17,36±0,20 mm. Statistical difference of the length of the ATFL of both joints between the neutral position and the stress test was at the level p<0,001 among boys and girls.

Conclusions: Comparison of the length of the anterior talus-fibular ligament of boys and girls in different positions during testing of both joints indicates a statistically significant difference at the level (P <0,001).

KEY WORDS: ankle joint, anterior talus-fibular ligament, inversion stress test, stress sonography

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INTRODUCTION

Trauma of ligaments of the ankle joint belongs to the most common injuries, both in everyday life and in sports. It is the reason for requests for urgent medical help in 20% of cases, however, total number of these injuries is much higher, since less than half of all people with ligament damage of this specified localization seek qualified medical assistance [1].

Patients with ligament damage are usually young and physically active people between 14 and 24 years old. [2]. More than 65% of cases are isolated injuries of the anterior talus-fibular ligament (ATFL). Interest in this ligament is due to the fact that it is considered the main means of protection against injuries, associated with ankle joint inversion combined with plantar flexion [3].

The consequences of ligament damage can lead to a number of chronic residual symptoms, which are diagnosed among from 40% to 50% of patients and include injury recurrence, chronic pain, chronic instability, osteoarthritis, adverse psychological effects [4].

The diagnosis of ligament damage is established on the basis of the patient's complaints, the mechanism of trauma occurrence, study of the local status, conducting of diagnostic tests and use of additional diagnostic methods. It is well known that there is limited evidence of the use of many specific orthopedic tests, which are widely used at injuries of ankle joint ligaments [5].

Among the non-invasive instrumental methods of diagnosis, they most often use stress radiography and magnetic resonance tomography. Stress radiography is often not informative enough to establish a final diagnosis [6]. Magnetic resonance imaging is the most accurate diagnostic method for assessing ligament damage, considering its high resolution and accuracy, however, its use in case of an acute injury of the specified location is not considered appropriate [7].

In order to improve the results of diagnostics, sophisticated devices and structures are introduced, but they are unlikely to be widely used in everyday practice during study of the state of the ATFL [8, 9].

Today, sonography is becoming increasingly important for the assessment of the ligamentous system of the ankle joint because of low cost, speed, availability and absence of ionizing radiation [10]. Unlike MR- images, it allows to perform dynamic maneuvers, which increses the level of visualization of intact ligaments and improves localization of their injuries [11-13].

Dynamic sonography has a high potential for detecting ankle joint ligament instability, but the parameters of the normative values of change of the length of the anterior talus-fibular ligament during stress tests in different age groups have not been fully determined.

AIM

To study changes of the anterior talus-fibular ligament length among asymptomatic population of young patients by using the device and the method of ultrasound examination of the ankle joint during applying the inversion stress test on both ankle joints.

MATERIALS AND METHODS

The research was conducted using an ultrasound console Acuson Antares (Siemens) applying a high-frequency broadband linear sensor with the operating frequency 7–12 MHz and using a standard acoustic gel.

The researcher visualized and measured the length of the anterior talus-fibular ligament of all examined persons in two positions, three times per position, in order to obtain the average length of the ligament. The examined persons relaxed the lower limb in the intervals between measurements, in order to avoid possible distortions of motion range due to the development of muscle contracture.

In the first position (position A), the examined persons were lying on the couch, the examined lower limb was placed on the device for ultrasound examination of the ankle joint in the position of bending in the knee joint at an angle 45°, and the area of the ankle joint hung freely in the position of plantar flexion at the angle 20° (Fig. 1. A.). This position was defined as the neutral resting position and as the baseline value for each subsequent measurement of the ATFL length.

The sonographic sensor was placed in accordance with the anatomical localization of the ATFL almost parallel to the sole of the foot (Fig. 1. B.)

A. Neutral position of the examined lower limb, the lower leg is placed on the ultrasound device. B. Location of the sonographic sensor for sonography of the anterior talus-fibular ligament in a neutral position.

During the sonographic examination, the distance from the anterolateral edge of the lateral bone was measured, which corresponds to the beginning of the ATFL, to the anterolateral corner of the lateral surface of the talus, which corresponds to the anatomical location of ligament fixation. The length of the anterior talus-fibular ligament was determined as a straight line between these two bony reference points, and was measured on a longitudinal ultrasound image made along the course of its fibers (Fig. 2. A, B).

In the second position (position B, of maximum inversion): examined persons were lying on the examination table, in the standard starting position. The researcher performed maximum inversion in the ankle joint till tissue resistance began.

The length of the anterior talus-fibular ligament in the position of the inversion stress test was defined as a straight line between the bone reference points described above, and measured on a longitudinal ultrasound image, which was performed along the course of its fibers (Fig. 3. A, B).

STATISTICAL ANALYSIS

Statistical analysis was performed using the software Statistica 8.0. Results were presented as average values with 95% confidence intervals. The Shapiro-Wilk test was used to confirm whether the data were normally distributed. Student's criterion was used to compare the continuous data. A Wilcoxon signed-rank test was performed to compare ultrasound results for the right and the left ankle.

RESULTS

The research was conducted in 2022-2023. The students of Ternopil National Medical University voluntarily participated in it. We examined the ankle joints of both limbs of 60 boys and 60 girls. The sample did not include persons with a medical history including injury of ligament of the ankle joint, operative interventions of the specified area, positive tests for joint hypermobility syndrome. All enrolled subjects signed a consent form prior to participating in the study.

Sonography was performed three times in a neutral position and during the inversion stress test. The average length of the anterior talus-fibular ligament of the right and the left ankle joint in each position was included in the protocol. In total 720 tests were carried out.

The morphometric characteristics of the examined persons is given in the Table 1.

According to the results of sonographic research, average length of the anterior talus-fibular ligament

Fig. 1. Neutral position for examining the length of the anterior talus-fibular ligament.

Table 1. Morphometric characteristics of the examined persons

Parameters	Boys	Girls
Age, years	22,63±0,11	22,54±0,12
Height, cm	181,42±0,74	168,68±0,69
Foot length, size cm	42,87±0,15	37,97±0,16
Body weight, kg	76,38±1,22	59,63±0,92
Body weight index, conventional unit	21,14±0,28	18,05±0,25

Table 2. The length of the anterior talus-fibular ligament of the ankle joint of the examined persons in different test positions

Group	Test state	The length of the anterior talus-fibular ligament, the right ankle joint	The length of the anterior talus-fibular ligament, the left ankle joint	Statistical difference between the ligaments of the right and the left joint, P	Statistical difference of ligament length in different positions, the right joint, P	Statistical difference of ligament length in different positions, the left joint, P
Boys	Neutral position, mm	19,08±0,3	19,08±0,31	>0,05	<0,001	<0,001
	Stress test, mm	19,65±0,3	19,63±0,3	>0,05		
	Difference of ligament length, mm	0,57	0,56	>0,05		
Girls	Neutral position, mm	16,92±0,2	16,9±0,19	>0,05	<0,001	<0,001
	Stress test, mm	17,37±0,2	17,36±0,2	>0,05		
	Difference of ligament length, mm	0,45	0,45	>0,05		

of the right ankle joint of young men in a neutral position was 19,08±0,3 mm (Table II). The length of the ligament increased up to 19,65±0,3 mm during maximum inversion stress test. The difference of

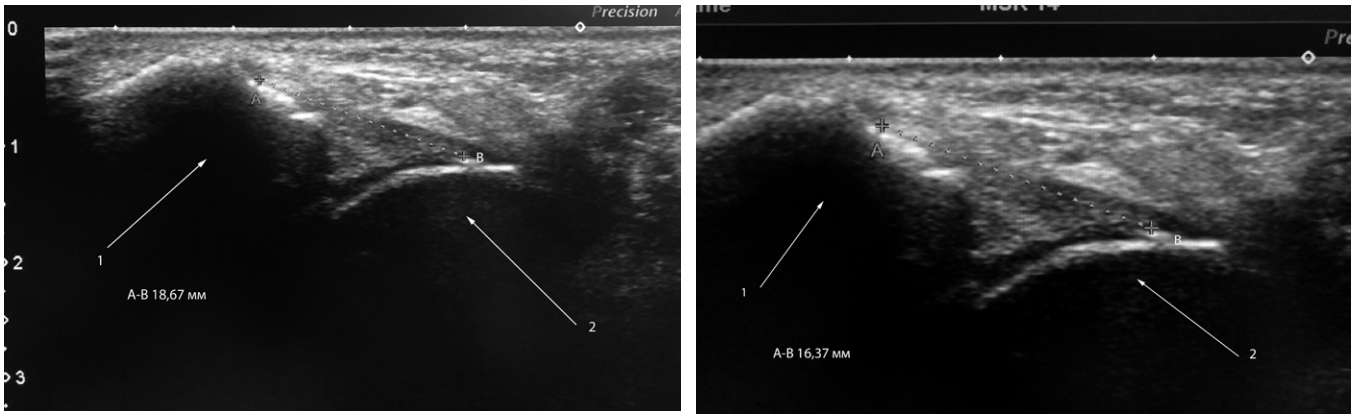

Fig. 2. Length measurement of the anterior talus-fibular ligament (ATFL) in a neutral position during sonography.
A. Dimensions of the anterior talus-fibular ligament in a neutral position of the examined person, male (A-B measurement points of the anterior talus-fibular ligament in a neutral position, 1 – splintbone; 2 – talus).
B. Dimensions of the anterior talus-fibular ligament in a neutral position of the examined person, female (A-B measurement points of the anterior talus-fibular ligament in a neutral position, 1 – splintbone; 2 – talus).

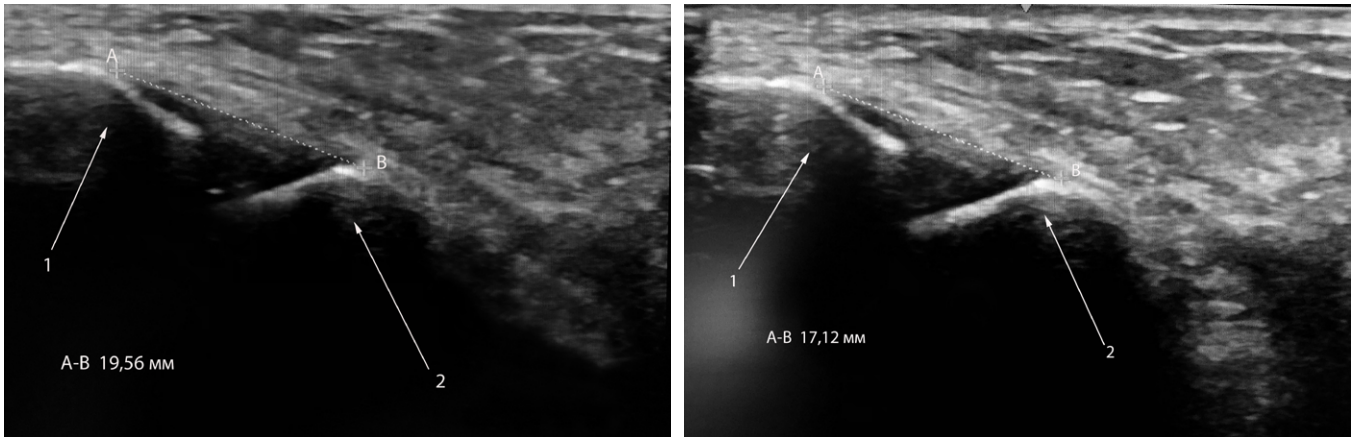

Fig. 3. Length measurement of the anterior talus-fibular ligament in the position of the inversion stress test during sonography.
A. Dimensions of the anterior talus-fibular ligament in a maximum position of the inversion stress test of the examined person, male (A-B measurement points of the anterior talus-fibular ligament, 1 – splintbone; 2 – talus).
B. Dimensions of the anterior talus-fibular ligament in a maximum position of the inversion stress test of the examined person, female (A-B measurement points of the anterior talus-fibular ligament, 1 – splintbone; 2 – talus).

the ligament length between neutral position and maximum inversion was 0,57 mm. 95% DI in the neutral position was 0,078 mm (19,01-19,16 mm), and during the inversion stress test – 0,078 mm (19,58-19,73 mm). ATFL extension in percentage terms was 2,99%. Statistical difference of the length of the anterior talus-fibular ligament of the right ankle joint between the neutral position and the stress test was at the level of $p<0,001$.

As for girls, average length of the anterior talus-fibular ligament of the right ankle joint in a neutral position was 16,92±0,2 mm (Table 2). At maximum inversion it increased up to 17,37±0,2 мм. 95% DI amounts 0,05 mm in both positions: in a neutral position within 16,87-16,97 mm, and during the stress test – 17,32-17,42 mm. The difference of the ligament length between neutral position and maximum inversion was 0,45 mm. In percentage terms it was 2,67%. As for girls, statistical difference of the length of the anterior talus-fibular ligament of the right ankle joint between the neutral position and the stress test was at the level of $p<0,001$.

Sonographic research of the ATFL the left ankle joint of girls showed that in the neutral position its length was 16,9±0,19 mm, and during the inversion stress test – 17,36±0,20 mm. 95% DI (confidence interval) in both positions was 0.05 mm: in neutral position it was within the limits 16,85-16,95 mm, and during the inversion stress test – 17,31-17,42 mm. The difference of the ligament length between neutral position and maximum inversion was 0,45 mm, and in percentage terms it was 2,66%. As for girls, statistical difference of the length of the anterior talus-fibular ligament of the left ankle joint between the neutral position and the stress test was at the level of $p<0,001$.

Our research shows that statistically significant difference between the parameters of the ATFL ligament of the right and the left ankle joint is absent in the group of boys and girls, both in the neutral position and during the inversion stress test (P>0,05).

Length comparison of the ATFL of boys and girls in different positions during testing of both joints indicates a statistically significant difference between the parameters of boys and girls at the level of p<0,001

Difference of the ligament length of the right ankle joint of boys is 0,57 mm, and of girls – 0,45 mm. A similar situation is observed with the length of the anterior talus-fibular ligament of the left ankle joint in different positions: 0,56 and 0,45 mm.

DISCUSSION

With increasing the evidence of efficiency and accuracy of sonography of the musculoskeletal system, more and more attention is paid to ultrasound methods of diagnosing injuries of the anterior talus-fibular ligament (ATFL). So, Oae K. et. al. Informed about the high accuracy of using longitudinal ultrasound examination of ATFL at identification of morphological changes indicating its damage [14]. Study of ligament dimensions was carried out both on cadaveric material and by instrumental methods. Inchai C.et al., while studying fresh-frozen cadavers with ages at death ranging from 25 to 90 years old [15] established, that average dimensions of the anterior talus-fibular ligament were 19,54±2,96 mm. During MRI studies, the average length of ATFL was from 21,5±0,5 mm to 24,5±3,3 mm and significant differences in size between its one- and two-bundle structure were not found [16].

Longitudinal sonographic measurement between bony attachment ATFL showed that its visible length varies in the neutral position from 16,1±3,63 mm to 21,73±2,67 mm [17]. With inversion load, it can increase up to 23,14±2,49 mm [18].

The results of our research show that the average length of the right of the ATFL of boys in the neutral position was 19,08±0,3 mm. Average length values increased to 19,65±0,3 mm during the maximum inversion stress test. Average length of the left anterior talus-fibular ligament of boys in the neutral position was 19,08±0,31 mm. It increased to 19,63±0,3 mm during maximum inversion. Average values of the length of both the right and the left left anterior talus-fibular ligament of girls in the neutral position were 16,92±0,2 mm for the right ankle joint and 16,9±0,19 mm for the left ankle joint. It increases to 17,37±0,2 mm та 17,36±0,2 mm accordingly during the inversion stress test. Thus, the average length of the ATFL of both boys and girls according to the results of our research corresponds with the data obtained by Mizrahi D.J et. al. [19]. Extension of the ATFL of boys in percentage terms it was 2,99% for the right ankle joint and 2,88% for the left ankle joint. Extension of the ligament of girls accordingly was 2,67% and 2,66%. These results correspond with the data obtained by Jeys L. et al. [20], which indicate that change of the ATFL length during movement is less than 5%.

The results of our research regarding the definition of the average length of ATFL of boys and girls in neutral position and during inversion are within the limits reported by Croy et al. for neutral position and inversion, 18,6±1,5 mm and 19,9±2,3 mm respectively [21]. The length of the anterior talus-fibular ligament both in the neutral position and during maximum inversion stress test of boys compared to girls was longer (P <0,001).

Potential limitation of this research was that the exact force applied during manual loading wasn't measured, however, maximal loading in plantar flexion and talar bone inversion can be reproduced in clinical conditions.

CONCLUSIONS

Our research shows that statistically significant difference between the parameters of the ATFL ligament of the right and the left ankle joint is absent in the group of boys and girls, both in the neutral position and during the inversion stress test (P>0,05).

Length comparison of the ATFL of boys and girls in different positions during testing of both joints indicates a statistically significant difference between the parameters of boys and girls at the level of P<0,001

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Yurij O. Hrubar
Ternopil National Medical University
1 Maidan Voli, 46001 Ternopil, Ukraine
e-mail: Yuhrubar@gmail. com

ORCID AND CONTRIBUTIONSHIP
Yurii O. Hrubar: 0000-0002-4221-2250 B C D
Iryna Ya. Hrubar: 0000-0002-0809-1299 A D E
Nadiia M. Hrabyk: 0000-0002-8882-9782 C D F
Markiian Yu. Grubar: 0000-0002-4696-0213 B D E
Yuliana Yu. Hrubar: 0000-0003-0951-9485 A D F

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ORIGINAL ARTICLE

CONTENTS

Phytochemical analysis of ethanolic leaf extract of Cordia myxa and its anti-Inflammatory and cytotoxic activities

Lubna Sami Ali[1], Ali M. Janabi[2]

[1]DEPARTMENT OF PHARMACOGNOSY, FACULTY OF PHARMACY, UNIVERSITY OF KUFA, KUFA, IRAQ

[2]DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY, FACULTY OF PHARMACY, UNIVERSITY OF KUFA, KUFA, IRAQ

ABSTRACT

Aim: Testing Cordia myxa extract on colon cancer cell line and caspase-3 gene and COX-2 protein expression.

Materials and Methods: This study used Cordia myxa ethanolic extract at various dosages on SW480 cells. Cell proliferation was measured using MTT, also examined effect of Cordia myxa extract on caspase-3 gene expression using quantitative real-time polymerase chain reaction. The Elisa technique measured cox2 protein.

Results: Cell proliferation tests showed the dose-dependent anticancer effects of Cordia myxa ethanolic extract. Cordia myxa extract also upregulates caspase-3 gene expression and decreases COX-2 protein levels.

Conclusions: Cordia myxa may be a good choice for colon cancer research and anticancer drug development. This plant may cure cancer because of its antioxidant, anti-inflammatory, and anticancer properties.

KEY WORDS: colorectal cancer, apoptosis, inflammation, Cordia myxa

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INTRODUCTION

The glandular epithelial cells of the large intestine often give rise to colorectal (CRC) cancer, a complex solid tumor. Cancer is caused by genetic or epigenetic alterations that favor specific epithelial cells [1]. Colorectal cancer (CRC) is the second leading cause of death and the third most prevalent malignancy globally, with 1.9 million cases and 0.9 deaths in 2020 [2]. Several factors can cause colorectal cancer. If they or their family have cancer, colon polyps, inflammatory bowel diseases, diabetes, or cholecystectomy, colorectal cancer risk increases, according to research. Lifestyle factors are major causes of colorectal cancer [3]. Genetic alteration, including the inactivation of tumor-suppressor genes like adenomatous polyposis coli (APC), which may transform the normal colonic epithelium, and DNA-repair gene inactivation lead to a hyperproliferative stage that activates K-RAS oncogenes in the early adenoma stage, and epigenetic alterations through aberrant chromosomes. Later, the tumor suppressor gene p53 is inactivated, which may be associated with the adenoma-to-carcinoma transition [4]. Plant or drug repurposing is an emerging concept that involves using old drugs or exploring medicinal plants for new treatment indications. Several studies and clinical trials have been conducted on drug repurposing, showing that Dipyridamole, a platelet inhibitor with antithrombotic properties, and Nebivolol, a beta blocker used for high blood pressure and heart failure, have a significant heart-protective effect against doxorubicin-induced cardiotoxicity in rats [5-6]. Among the medicinal herbs, *Cordia myxa* is a medicinal plant used to cure several ailments. Several studies have shown that *C. myxa* is anti-inflammatory, anti-diabetic, antiparasitic, antibacterial, and immunomodulatory [7]. *Cordia myxa*, a Boraginaceae plant, is known as the "Indian cherry and Assyrian plum" for its tasty fruits [8]. The relaxing properties helped minimize coughing and treat respiratory infections and sore throats. The pulp was also an anthelminthic, abscess emollient, and rheumatism pain reliever. A leaf macerate lotion was used for tick bites to treat trypanosomiasis [9]. In health and illness, apoptosis is well-planned and controlled. An understanding of apoptosis is vital to the genesis of many diseases. Cancer is a result of inadequate apoptosis. Multiple paths make apoptosis challenging. Any error in any of these channels might produce malignant cells, tumor spread, and anticancer drug resistance [10].The extrinsic

death receptor and intrinsic mitochondrial pathways are the primary apoptotic pathways [11]. Caspase-3, a cysteine-aspartic acid protease, is encoded by CASP3 [12]. Caspase-3 is crucial to the apoptotic pathway which is activated by extrinsic stimulation [13]. Linked to cancer chronic inflammation contributes to tumor growth, making it a hallmark of cancer [14]. Chronic, unresolved, dysregulated inflammation increases cancer risk and spreads most tumors [15]. Human COX-2, also known as prostaglandin-endoperoxide synthase 2, is encoded by PTGS2. A homodimer comprising 581 amino acids, it weighs 70 kDa. COX-2 converts arachidonic acid to prostaglandins, which are then converted to PGH2. PGH2 is metabolized by tissue-specific synthases into five prostaglandins (PGD2, PGE2, PGF2α), prostacyclin (PGI2), and thromboxane A2 (TXA2) [16]. COX-2 is known to cause inflammation and cancer. Numerous studies showed that Inflammation causes cells to produce COX-2, which they don't ordinarily express. COX-2 aids tumor invasion, angiogenesis, metastasis, and apoptosis [17]. Overexpressing COX-2 is associated to gastrointestinal malignancies, particularly colorectal cancer [18].

MATERIALS AND METHODS

CELL LINE CULTURE

Colon cancer cell line SW480 was supplied by the Iran Center of Cancer and Medical Genetics Research (ICCMGR). It was derived from the colorectal adenocarcinoma epithelial cells of 50 years 50-year-old Caucasian male. Cells were grown in RPMI-1640 media supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin, and were kept at 37°C with 5% CO2 in a fully humidified environment.

PREPARATION OF PLANT EXTRACTS

Collected leaves of cordia myxa were cleaned, shade-dried, and powdered. The dried coarse powder was subjected to Soxhlet extraction with ethanol to get the crude extract. The appearance of colorless solvent in the siphon tube was taken as the termination of extraction. The extract was filtered and then concentrated to dryness in a rotary evaporator under reduced pressure and controlled temperature. The extract was then kept in a sterile bottle, under refrigerated conditions, until further use [19]. The stock solution of the extract was prepared by dissolving 50 mg of each extract in 10 ml of serum-based medium (5 mg/ml), then filtered through a 0.2 µm- Millipore filter. From this stock, serial dilutions were made resulting in six concentrations (1000, 500, 250, 125,6.5, and 3.25 µg/ml).

PHYTOCHEMICAL SCREENING OF PLANT EXTRACTS

DETERMINATION OF TOTAL ALKALOIDS CONTENT

A fraction of both extracts was mixed with 2 N HCl and subsequently filtered. A separatory funnel was used to transfer 1 ml of each solution, which was then rinsed with 10 ml of chloroform. The pH of every solution was modified to a neutral state using 0.1 N NaOH. Next, each solution was supplemented with 5 ml of BCG solution and 5 ml of phosphate buffer. After shaking the mixtures, the resulting complexes were extracted using chloroform through vigorous shaking. The samples were gathered and placed into a 10-milliliter flask. Afterward, they were combined with chloroform until the volume was reached. The measurement of complex absorbance in chloroform was conducted at a wavelength of 470 nm [20].

DETERMINATION OF TOTAL PHENOLIC CONTENT

The Folin-Ciocalteu procedure was used to determine the quantity of total phenolics present in the extracts. Samples of 2 ml volume were placed inside test tubes, following which 1.0 mL of Folin-Ciocalteu's reagent and 0.8 mL of sodium carbonate 7.5% were included. The tubes were combined and left undisturbed for 30 minutes. The measurement of absorption at 765 nm was conducted using a UV-visible spectrophotometer. The overall amount of phenolic compounds was measured in milligrams of Gallic acid equivalents (GAE) per gram of dry substance [21].

DETERMINATION OF TOTAL TANNINS CONTENT

To determine the tannin content or Proanthocyanidin levels, 400µL of the extract was mixed with 3 mL of a vanillin in methanol solution and 1.5 mL of concentrated hydrochloric acid. A 500 nm wavelength was used to measure the absorbance after it had been incubated for 15 minutes. The produced color can be measured quantitatively and represented as tannic acid equivalents [22].

DETERMINATION OF TOTAL FLAVONOIDS CONTENT

The colorimetric technique using aluminum chloride was employed to determine the flavonoids. The extracts (0.5 ml) were combined individually with 2.8 ml of distilled water, 0.1 ml of 10% aluminum chloride, 1.5

Table 1. HPLC system components

	Component	Model or version	Company and origin
1	Binary high-pressure gradient pump	P6.1L	Knuaer, Germany
2	Diode array detector	DAD 2.1L	Knuaer, Germany
3	Sample loop (20 µl) and injector	D1357	Knuaer, Germany
4	Analyses and system control software	Claritychrom, V 7.4.2.107	Dataapex, Czech Republic

ml of methanol, and 0.1 ml of 1 M potassium acetate. After 30 minutes at room temperature, the reaction mixture's absorbance was calculated using a UV/Visible spectrophotometer at 415 nm. Quercetin was used as the standard in the calibration curve [23].

DETERMINATION OF TOTAL GLYCOSIDE CONTENT

10 mL of newly made Baljet's reagent (95 mL of 1% picric acid + 5 mL of 10% NaOH) was combined with 10% of each plant's extracts. Once the mixture had been mixed for one hour, 20 milliliters of distilled water were added, and a UV/VIS spectrophotometer was used to detect the absorbance at 495 wavelengths. Milligrams of securidaside per gram of dried extracts were the standard of measurement for total glycosides [24].

DETERMINATION OF VITAMIN C CONTENT

A small amount of bromine water was added to the filtrated sample solution until the solution took on color, signifying that the conversion of ascorbic acid to dehydroascorbic acid had been completed. The clear solution was then obtained by adding a few drops of thiourea solution to eliminate the excess bromine. Next, the oxidized ascorbic acid and 2,4-ditrophenyl hydrazine solution were thoroughly added to all standards. Total vitamin C is measured by spectrophotometric means using a coupling reaction between vitamin C and 2,4-ditrophenyl hydrazine dye [25].

DETERMINATION OF VITAMIN E CONTENT

To span the range of the calibration curve (0.5 – 28 µg/ml vitamin E), a serial dilution was prepared in a 10 mL calibrated flask starting with a concentration of 100 µg/mL of vitamin E solutions. Subsequently, 2 mL (100 µg/mL) of [FeNH4(SO_4)2. 12H_2O] and 4 mL (100 µg/mL) of K3Fe(CN)6 were added. The solutions were then adjusted to pH = 4 and diluted with methanol to the appropriate level. Measure the absorbance at 743 nm against the reagent blank after 10 minutes [26].

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY ANALYSIS OF PLANT EXTRACTS

PRINCIPLE

According to the HPLC concept, a liquid phase (mobile phase) is pushed through a porous material (stationary phase) at a greater pressure in a column where the sample solution injected into it. The solute adsorbs on the stationary phase according to its affinity for the stationary phase, which is the separation principle that is used. The separation process can occur in four distinct ways, depending on the characteristics of the stationary phase (Table 1) [27].

PROCEDURE

The sample was separated using a C18 column from Knauer, Germany, with dimensions of 250 x 4.6 mm, a particle size of 5 µm, and a pore size of 80 Å The mobile phase consists of a 1% aqueous acetic acid solution (Solvent A) and acetonitrile (Solvent B). The flow rate was set to 1 ml/min, the column temperature was maintained at 28°C, and the injection volume was 20 µl. Gradient elution was conducted by altering the ratio of solvent B to solvent A (Table 2). HPLC chromatograms were detected using a photodiode array UV detector at wavelengths (210 nm) .

The detection of compounds was performed by matching the retention time and absorbance spectrum of each standard. The concentration was calculated by serial concentrations of external standard materials (ten standards are used) to build a calibration curve between concentration and its equivalent peak area.

PREPARATIONS OF SAMPLES FOR MTT ASSAY

When cell growth in the flask became monolayer before it reached the exponential time, monolayer cells were harvested and re-suspended with a serum-free medium in a concentration of $5*10^5$ cells/ml and seeded in a 96-well cell culture plate. Since the cell growth reached 80%, the wells were treated with six concentrations (1000, 500, 250, 125, 62.5, and 31.25 µg/ml) of *Cordia myxa* extract to evaluate its cytotoxic effects on the SW480 cell line during a 24-hour incubation period. Three wells were used for each concentration.

Table 2. The gradient program

Time (min)	Mobile A (%)	Mobile B (%)	Flow rate ml/min
0	90	10	1ml/min
28	60	40	1ml/min
39	40	60	1ml/min
60	10	90	1ml/min

MOLECULAR STUDY BY REAL-TIME PCR

SAMPLE PREPARATION

To create a monolayer with 80% confluence, 12.5 ml cell culture flasks are seeded with Sw480 cells and cultured for 24 hours. Following that, 6 ml of the experimental drug-containing media was added to the flask, and the old medium was discarded. In addition, a flask treated with media alone was used as the control group. Every flask underwent a 24-hour incubation period. Trypsinization was used to separate the cells in each flask after the incubation time. Next, two milliliters of media were added to the centrifuge tube containing the cells. To get a pellet of cells, centrifugation was performed for five minutes at 13,000 rpm.

RNA EXTRACTION

TransZol Up Plus RNA Kit was used for the isolation of total RNA from cells according to the manufacturer's protocol**.**

PRIMER PREPARATION

The lyophilized version of the primers was provided. Each primer was dissolved in 300 µl of nuclease-free water following the "Macrogen Company instructions" to produce a final stock concentration of "100 pmol/µl." This inventory was kept at -20 °C. The working primer solution (10 pmol/µl) was created by mixing 10µl of primer stock solution with 90 µl of nuclease-free water.

COMPLEMENTARY DNA SYNTHESIS

EasyScript® One-Step gDNA Removal and cDNA Synthesis SuperMix kit was used to produce complementary DNA (cDNA) by reverse transcription using mRNA as a template, reverse transcriptase enzyme, and a thermostable primer, complementary to the 3' end of the RNA template for quantifying gene expression analysis using real-time PCR according to the manufacturer's protocol.

EVALUATION OF GENE EXPRESSION BY RT-PCR

Quantify CASP3 gene expression in untreated cells (control group) and cells treated with 500 and 1000 µg/ml of *Cordia myxa* extract.

PREPARATION OF SAMPLES FOR ELISA ASSAY

48-culture plates were seeded with Sw480 cells. The plate was then placed in an incubator for 24 hours at 37°C and 5% CO_2. Following the medium's removal, tested compounds were applied to the wells. Three wells were treated for each concentration. In addition, eight wells served as controls by receiving no treatment at all from any experimental medicine. The plate was then left to incubate for a full day. Following the completion of the exposure time, each well's supernatant was pipetted into a sterile 5-milliliter sterile tube, which was then kept at -20°C. The COX2 content was determined in untreated cells (control group) and cells treated with *Cordia myxa* extract at concentrations of 100, 500, and 1000 µg/ml.

STATISTICAL ANALYSIS

The program GraphPad Prism version 8.4.3 (GraphPad program, La Jolla, CA, USA) was used to analyze the data in this study. Unless otherwise noted, all data were expressed as mean ± Standard Error Mean (SEM). The data was analyzed using One-Way Analysis of Variance (ANOVA) and the Bonferroni multiple comparison test. For all tests, statistical significance was determined at a significance level of $P < 0.05$.

RESULTS

PHYTOCHEMICAL SCREENING

The *Cordia myxa* extracts underwent quantitative phytochemical screening, which revealed the presence of many classes of chemicals, including tannins, flavonoids, alkaloids, polyphenols, glycosides, vitamin C, and vitamin E. The screening was conducted using established techniques (Table 3).

PHENOLIC PROFILE OF CORDIA MYXA EXTRACTS BY HPLC

The chemical composition of *Cordia myxa* extract was analyzed using high-performance liquid chromatography (Table 4).

Table 3. Phytochemical screening results of Cordia myxa crude plant

Chemical compound	*Cordia myxa*	
Alkaloids	3.5904	atropine mg/g
Polyphenol	18.072	Gallic acid mg/g
Tannins	3.8103	tannic acid mg/g
Flavonoids	11.808	Rutin mg/g
C	10.932	ascorbic acid mg/g
E	1.656	vitamin E mg/g
Glycosides	4.6	Securidaside mg/g

Table 4. The main composition of Cordia Myxa extracts

Phenolic compounds	Concentration (µg/mg)
Caffeic acid	728
Chlorogenic acid	214
Silybin	81
Naringin	126
Rutin	9932
Gallic acid	114

CYTOTOXIC EFFECT OF CORDIA MYXA EXTRACT ON SW480 CELL LINE

The data from the study showed that there was a significant decrease in the viability for all concentrations except with the lower two concentrations (62.5 µg/ml and 31.25 µg/ml) which caused an insignificant variation in the viability in comparison with the control (Table 5, Fig. 1). Also, the present study found an IC_{50} of 500 µg/ml of the extract inhibits 50% of SW480 cells.

Serum-starved cells were incubated at concentrations of 31.25 62.5, 125,250, 500, and 1000 µg /ml of cordia myxa extract for 24 hours. Cell viability was measured using an MTT assay. One-way ANOVA followed by the Bonferroni multiple comparison test was used for analysis. Data are presented as mean ± SEM.

EFFECT OF CORDIA MYXA EXTRACT ON CASP3 GENE EXPRESSION IN SW480 CELL LINE

The real-time PCR data analysis reveals a significant variation in CASP3 level between the control group and treated SW480 cells with *Cordia myxa* extract at concentrations of 1000 µg /ml. However, there was no significant increase at 500 µg /ml concentration (Table 6, Fig. 2).

Serum-starved cells were incubated at concentrations of 500, and 1000 µg /ml of cordia myxa extract for 24 hours. Gene expression of CASP3 was measured using the RT-PCR technique. One-way ANOVA followed by

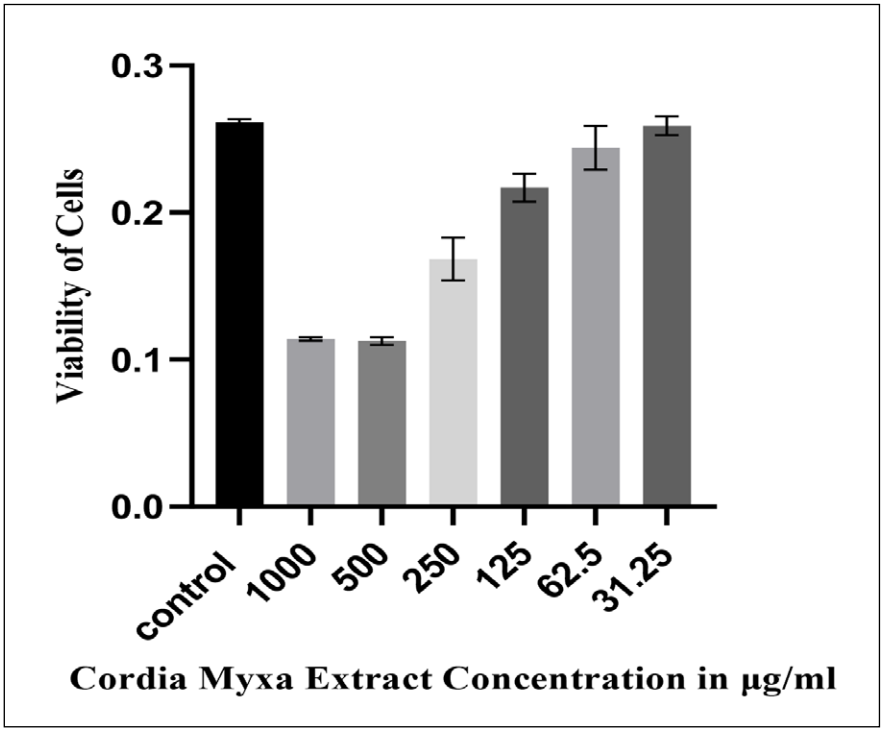

Fig. 1. Effect of Cordia myxa extract on the viability of SW480 cells.

Table 5. Effect of Cordia myxa extract on the viability of SW480 cells

Concentration (µg/ml)	Mean ± SEM	P Value
1000	0.1475 ± 0.01023	<0.0001 ****
500	0.1488 ± 0.01023	<0.0001 ****
250	0.09317 ± 0.01023	<0.0001 ****
125	0.04450 ± 0.01023	0.0026 **
62.5	0.01750 ± 0.01023	0.6316 ns
31.25	0.00250 ± 0.01023	>0.9999 ns

ns: non-significant, **P<0.01 vs. control , ****P<0.0001 vs. control

Table 6. Effect of Cordia Myxa Extract on CASP3 Gene Expression

Concentration (µg/ml)	Mean ± SEM	P Value
500	-0.4977 ± 0.2573	0.1885 ns
1000	-2.578 ± 0.2573	<0.0001 ****

ns: non-significant, ****P<0.0001 vs. control

Table 7. Effect of Cordia myxa extract on the COX-2 level

Concentration (µg/ml)	Mean ± SEM	P Value
100	-1.521 ± 0.7961	0.2405 ns
500	6.368 ± 0.7961	<0.0001 ****
1000	11.91 ± 0.7961	<0.0001 ****

ns: non-significant, ****P<0.001 vs. control

the Bonferroni multiple comparison test was used for analysis. Data are presented as mean ± SEM.

IMPACT OF CORDIA MYXA EXTRACT ON COX-2 LEVELS FOR SW480 CELL LINE

The study's data demonstrated that the COX-2 level decreased significantly for the two concentrations (1000 and 500 µg/ml), However, in comparison to the control, the COX-2 level decreased somewhat at the 100 µg/ml concentration (Table 7, Fig. 3).

Serum-starved cells were incubated at concentrations of 100, 500, and 1000 µg /ml of *Cordia myxa* extract for 24 hours. COX-2 level was measured using a human COX2 ELISA kit. One-way ANOVA followed by the Bonferroni multiple comparison test was used for analysis. Data are presented as mean ± SEM.

DISCUSSION

Cancer is a significant worldwide health concern that is projected to overtake heart disease in terms of impact. Chemotherapy has been a prominent therapeutic intervention since World War I, but it induces several detrimental side effects. In the last two decades, there has been a rise in the development of treatments derived from plants, herbs, and vegetables that have the potential to prevent or decrease the occurrence of cancer. Scientists suggest prioritizing the use of botanicals for secure and efficient anticancer therapies, as opposed to synthetic alternatives [28]. The study demonstrates that *Cordia myxa* leaves extract contains a variety of phytochemical substances, including alkaloids, polyphenols, tannins, flavonoids, vitamin C, vitamin E, and glycosides in different quantities. These components may contribute to the anti-proliferative action of the extract. The study demonstrates that *Cordia myxa* extract effectively suppresses the proliferation of SW480 cells, and the cytotoxicity of the extract escalates proportionally with the dosage. The findings align with the study conducted by [29], which showed a clear cytotoxic effect on human colon cancer HCT116 and SW480 cell lines in a dose-dependent manner. Furthermore, other studies discovered that the application of *Cordia myxa* ethanolic extract to MCF7 human breast cancer cell line and A549 lung carcinoma epithelial cells resulted in a substantial reduction in cell viability, with the extent of this effect depending on the dosage [30]. One approach to treating cancer is to exert control over or perhaps halt the unregulated proliferation of cancer cells. Utilizing the cell's intrinsic apoptotic pathway is an exceedingly efficient approach. Furthermore, focusing on apoptosis is the most effective non-invasive therapy [31]. Caspases are enzymes responsible for carrying out apoptosis, a process of programmed cell death. Among these enzymes, caspase-3 is a commonly activated protease that is crucial for initiating, transmitting, and enhancing intracellular signals that lead to apoptosis [32]. The real-time PCR data analysis reveals a significant increase (P <0.0001) in casp3 level between the control group and treated SW480 cells with *Cordia myxa* extract at high concentrations. This finding supports [33] conclusion that the Cordia species extract triggers apoptosis in the MCF-7 breast cancer cell line by upregulating casp8 expression and downregulating bcl2 expression. Another study has shown that following treatment of a human cervical cancer cell line with *Cordia* species extract, a rise in apoptotic cells displaying typical features and noticeable DNA fragmentations, key indicators of apoptosis, was detected. So the extract of *Cordia myxa* leaves demonstrates anticancer properties by causing cell death in sw480 cells by the activation of apoptosis, which is facilitated by an increase in casp3 levels. The extract's polyphenolic components may contribute to these effects because of its combined antioxidant and pro-oxidant characteristics. The relationship between inflammation and the formation of tumors is widely recognized and has been extensively supported by genetic, pharmacological, and epidemiological research in the past

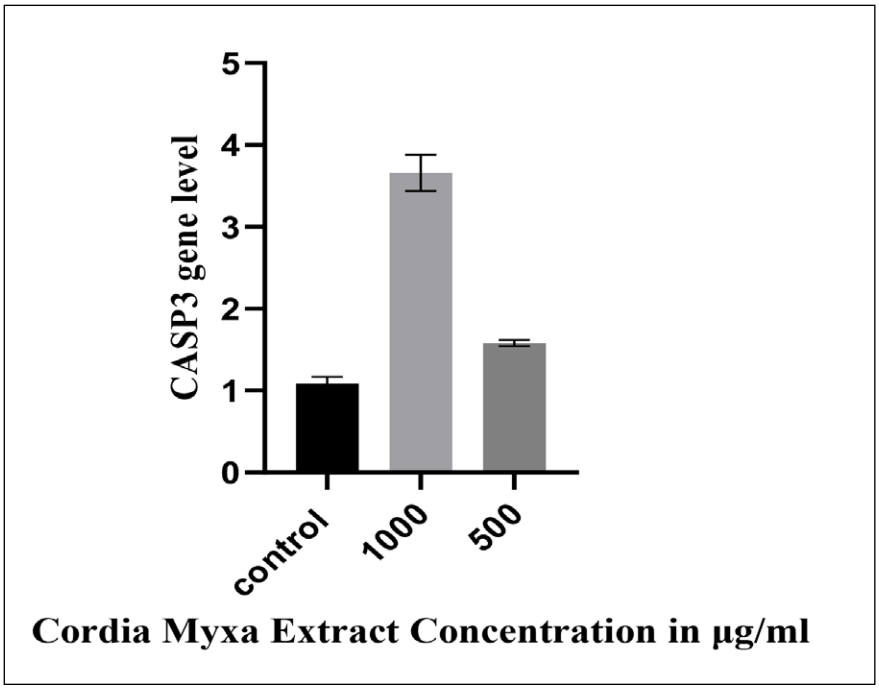

Fig. 2. Effect of Cordia myxa extract on CASP3 gene expression for SW480 cells.

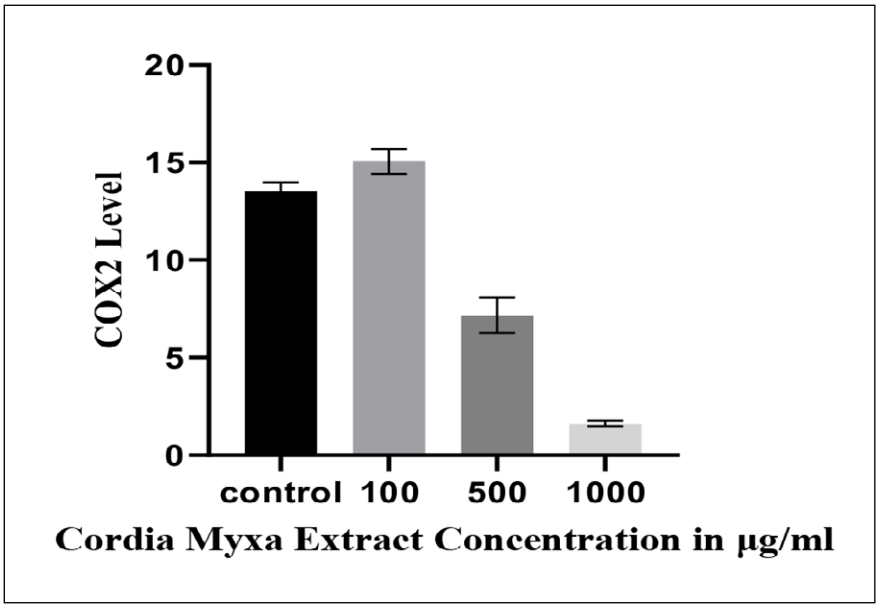

Fig. 3. Effect of Cordia myxa extract on COX-2 level for SW480 cells.

decade. Inflammatory bowel disease significantly increases the risk of developing colon cancer [34]. In the present study, the data demonstrated that the COX-2 level decreased significantly for the two concentrations (1000 and 500 µg/ml) in comparison to the control. As a result, Cordia myxa extract can act as a COX-2 inhibitor with anti-inflammatory properties. This finding aligns with the research conducted by [35] which showed that cordia myxa extracts may act as analgesic and anti-inflammatory agents via COX-2 mechanisms in experimental mice models. The ethanolic leaf extract of Cordia myxa was found to include alkaloids, glycosides, flavonoids, phenols, vitamin C, vitamin E, and tannins, as determined by the phytochemical analysis. Hence, it may be inferred that the extract's anti-inflammatory properties may be attributed to its bioactive components, particularly flavonoids. The anti-inflammatory and anti-cancer action of leaves may be influenced by the polyphenols and flavonoids present in them.

CONCLUSIONS

Cordia myxa shows promise as a suitable option for developing anticancer medications and warrants more research as a prospective candidate for studying colon cancer. This plant may have potential uses in cancer treatment due to its activities as an antioxidant, anti-inflammatory, and anticancer.

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CONFLICT OF INTEREST

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CORRESPONDING AUTHOR

Lubna Sami Ali
Department of Pharmacognosy, Faculty of Pharmacy,
University of Kufa, Iraq
e-mail: lubnas.altohafi@uokufa.edu.iq

ORCID AND CONTRIBUTIONSHIP

Lubna Sami Ali: 0000-0002-6820-8399 B C D E
Ali Janabi: 0000-0002-8569-7964 A E F

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

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ORIGINAL ARTICLE

CONTENTS

Radial shock wave therapy with "Intelect PRW Lite" for calcifying tendinopathy of the shoulder, comparative effectiveness with conventional physical therapy and follow up data

Radostina Hristova Simeonova[1], Ignat Ignatov[2], Zlatin Ivanov[3], Georgi Nanov[4]

[1]PRIVATE MEDICAL PRACTICE PLOVDIV, PLOVDIV, BULGARIA

[2]SCIENTIFIC RESEARCH CENTER OF MEDICAL BIOPHYSICS (SRCMB), SOFIA, BULGARIA

[3]MEDICAL CENTER MEDICUS, PLOVDIV, BULGARIA

[4]SPECIALISED REHABILITATION HOSPITAL, BANYA, BULGARIA

ABSTRACT

Aim: To reveal the criteria for effective treatment of this pathology and to compare it with the conventional physical factors.

Materials and Methods: The research has been taken on 60 people, A control group (CG), including 30 people, treated with basic therapy and experimental group (EG). including 30 people, treated with the same basic therapy and RSWT once per week for seven consecutive weeks. The effect of the treatment was shown by: sonographic examination before and after treatment, physical tests for motor skills in shoulder region, scale of pain and the range of motion (ROM).

Results: The results have high statistical significance ($p<0,001$) for both groups. The comparision between EG and CG ($p<0,001$) proves that usage of RSWT reduces the pain quicker and restores mobility in the shoulder region in a shorter period than conventional physical therapy and only in the EG there is reduction in the parameters of the calcifications and total disappearance in the follow up.

Conclusions: The results have high statistical significance ($p<0,001$) for both groups. The statistical difference between EG and CG ($p<0,001$) proves that usage of RSWT reduces the pain quicker and restores mobility in the shoulder region in a shorter period than conventional physical therapy and only the patients in the EG have reduction in the parameters of the calcifications and total disappearance in the follow up.

KEY WORDS: physical therapy, shoulder, tendinopathy, shockwave

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INTRODUCTION

Radial shock wave therapy (RSWT) is a well-known modality for treatment of different musculoskeletal conditions [1]. However, in the treatment context of chronic calcifying tendinopathy of the shoulder, its effectiveness is still controversial [2-5]. The lack of control groups and follow-up data are the main weakness of most of these studies.

Calcifying tendinopathy, also known as calcific tendonitis, is a condition characterized by the formation of calcium crystal deposits in one or several tendons, most often in the shoulder. The exact cause of calcific tendinopathy remains unknown. Here are some key points about its etiology [6,7].

- It is not typically caused by trauma or overuse, and it is rarely part of a systemic disease
- It may be associated with certain conditions such as diabetes, thyroid disorders, or kidney stones
- Some reports suggest a genetic predisposition for the development of intratendinous calcific deposits
- Tissue tears and natural tissue breakdown (degenerative changes) increase the chance of these deposits occurring
- The calcium deposits result from the deposition of calcium hydroxyapatite within the substance of a tendon. This is thought to be due to decreased oxygen tension, leading to fibrocartilaginous metaplasia and secondary mineralization

The inflammation around the deposits and increased intratendinous pressure are thought to contribute to the pain associated with this condition. However, the exact mechanisms are still not fully understood and research is ongoing.

AIM

The purpose of this clinical study is to evaluate the additive value of radial shock wave therapy as adjunctive

modality in treatment of chronic calcifying tendinopathy of the shoulder in comparison with the conventional modalities alone and to present follow up data for the long-term efficacy of this treatment combination.

MATERIALS AND METHODS

The clinical study involved 60 patients diagnosed with calcifying tendinopathy due to different etiological factors (chronic micro traumatic damage to the tendons, acute trauma and metabolic syndrome) [2]. Informed consent was received by each patient included in the study. Only adult patients were enrolled (18-58 years, 13 men and 17 women). The Ethics Committee of the MBAL St. Sofia Hospital (Sofia, Bulgaria) has reviewed and approved this study.

For the aim of the study the patients were divided into 2 groups and we used the model of autocontrol.

1. Control group (CG) consisting of 30 patients who were treated with basic physiotherapy (TENS, kinesiotherapy and BIC) during a course of 7days.
2. Experimental group (EG) of the same 30 patients who were treated with basic physiotherapy (TENS, kinesiotherapy and BIC) in combination with RSWT during a course of 7 weeks (once per week) after the first week of basic physiotherapy.

The efficacy of the treatment was evaluated by: sonographic examination [7,8] before and after treatment (after 1 month and after 3 months), physical tests for motor skills of the shoulder region (SPADI), scale of pain (VAS) and the range of motion (ROM).

The two groups were treated in two different medical centers in order to eliminate the subjective factors. The basic physiotherapy was funded by the National Health Insurance Fund, whereas the shockwave therapy was covered by the patients.

Objective criteria for including and comparing the two groups:

1. History and duration of the illness
2. Number of affected ligaments and size of the calcifications according to the sonographic examination
3. Range of motion – ROM
4. Pain scale – VAS (visual analogue scale)
5. SPADI (Shoulder Pain and Disability Index)

THERAPEUTIC PROCEDURES

RSWT was done once per week for 7 weeks. Prior to the procedure, a sonographic examination was performed in order to measure and mark the calcifications. The dosage for each individual patient was based on the following:

- The total hit counts depend on the number of affected muscles but does not exceed 6000 per day.
- The subjective level of discomfort for the patient – the aim was to reach the maximum tolerance threshold while not causing pain.

The patients were instructed not to take any nonsteroid anti-inflammatory drugs (NSAIDS) for the next 4 hours after the therapy as well not to carry out any other physical therapy in the same day.

INCLUSION CRITERIA

1. Age over 18 and under 70 years
2. Informed consent
3. History of pain no more than a year

EXCLUSION CRITERIA

1. Pregnancy
2. Ade under 18 and over 70 years
3. Cancer
4. Not signed informed content

SONOGRAPHIC DATA

In order to measure the density of the calcifying tendinopathy, we used a 3-grade scale proposed by the Cohen M. et al [9]. It describes the possible findings as follows:

Type 1 – full thickness shadow

Type 2 – echogenic with non-full thickness shadow

Type 3 – without shadow on the underlying bone

The obtained data together with the medical history were collected in a personal patient's file.

RADIOLOGIC DATA

We have used the Radiological classification of Calcifying Tendinitis by Gartner and Heyer, which describes the possible findings as follows:

Type 1 – clearly circumscribed and dense, formative

Type 2 – clearly circumscribed, translucent, cloudy and dense

Type 3 – cloudy and translucent, resorptive.

RSWT TREATMENT PROTOCOL

During the procedure the patient is positioned comfortably, and the posture is modified for every treated tendon. The calcifications are measured sonographically and then marked. The transmitter is situated over the marked places and is moved circularly for 2000 hits on certain area. Communication with the patient is carried out during the procedure in order not to reach the pain threshold. Each target zone received 2000 hits but no more than 6000 in one day.

STATISTICS

The collected data was statistically analyzed by means of descriptive statistics, t-test, chi-square and one-way

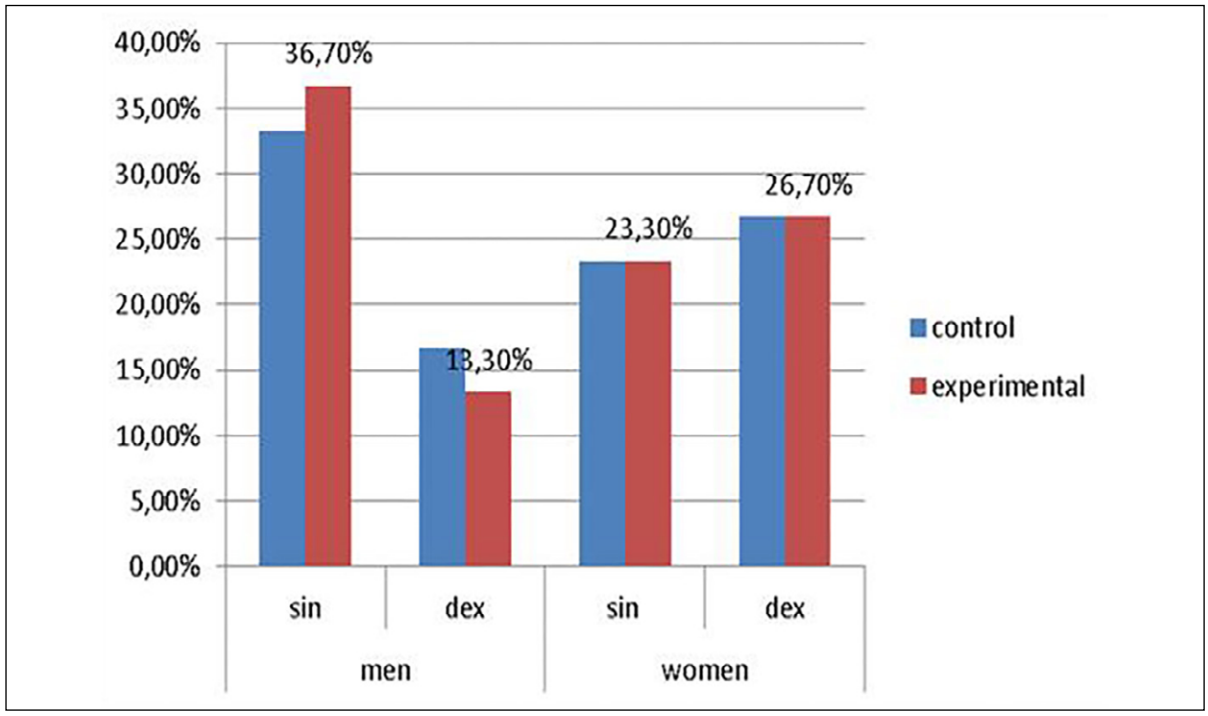

Fig. 1. Sex distribution (1) and distribution of the affected shoulder – left (sin) or right (dex), (p=0,067).

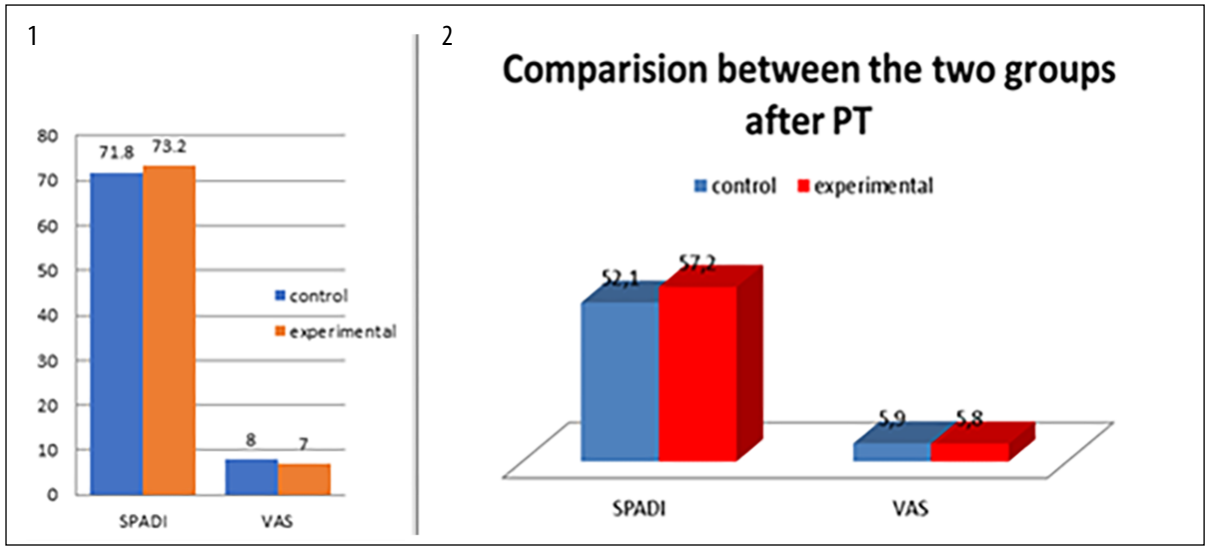

Fig. 2. Comparison of SPADI and VAS before start of PT (1) and after PT (2).

ANOVA. Statistical significance was set at p <0.05. All statistical analyses were performed using SPSS v. 20.

RESULTS

The initial data are favorable for further comparison of the provided treatment modalities.

The statistical analyses revealed that there are no statistically significant differences between the two groups in terms of their sex distribution (Fig.1), p=0,069. The left shoulder joint in men is statistically more affected than in women (Fig. 2) (p=0.011). The mean age of the patients and the history of pain duration are without statistical difference for both groups.

The comparison of SPADI and VAS scores before starting of PT (Fig. 2(1)) and after PT (Fig.2(2)) for both groups revealed equivalent decrease in the measured parameters without statistical significance for the outcome, p=0.004.

Similar treatment outcomes in both groups after PT revealed positive effects of the basic physiotherapy which confirmed the homogeneous distribution of the patients in the study groups. The additional application of RSWT however led to different results.

The statistical analyses of the size of calcifications in the experimental group (EG) before starting of PT (Fig.3(1)) and the size of calcification in EG after RSWT (Fig.3(2)) revealed statistically significant difference by T-TEST of pairs(p < 0.05).

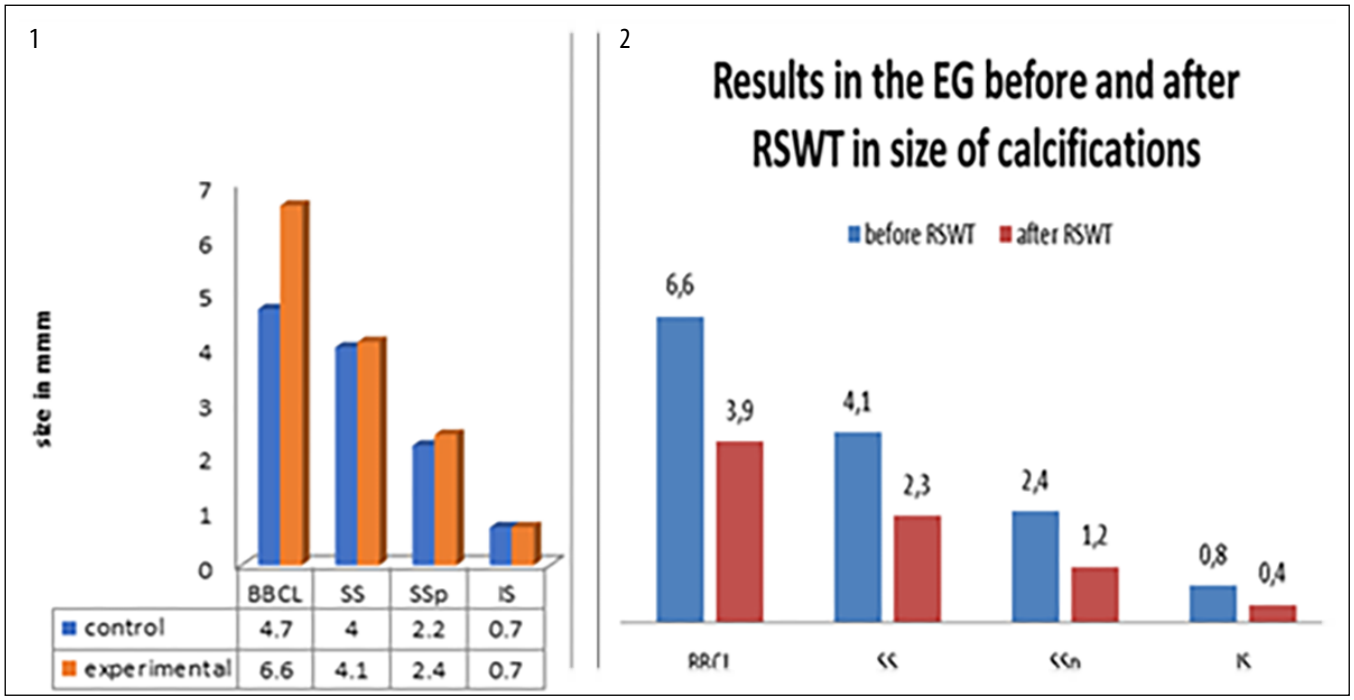

Fig. 3. Comparison of the size of calcifications before starting of PT (1) and the size of calcification in EG after RSWT (2), p=0.001.

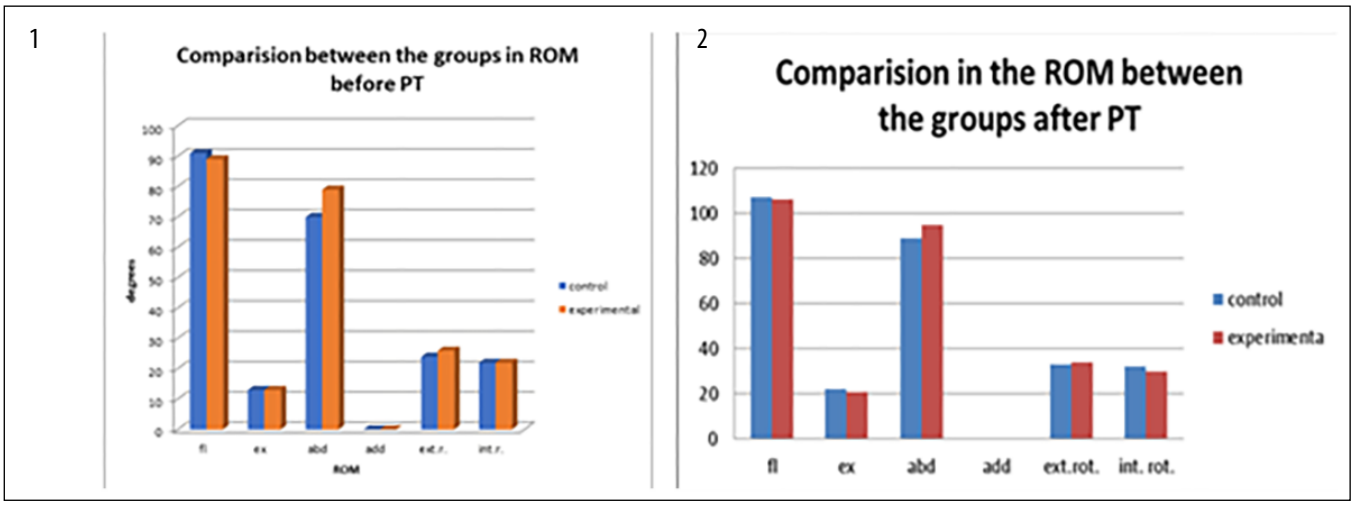

Fig. 4. Comparison of the ROM before start of PT (1) and after PT (2) in both CG and EG., (p>0.05).

A similar tendency was observed when comparing the ROM before start of PT (Fig.4(1)) and after PT (Fig.4(2)) for both CG and EG. It confirms again the homogeneity of the patients and the positive effect of basic physiotherapy.

The additional application of RSWT resulted in statistical differences in SPADI and VAS scores in the EG by Levene's Test, (p<0.05) (Fig. 5).

Short-axis view of the SSP tendon with intratendinous bursal side migration pattern of a softly hydrated fragment (white void arrow) of calcific deposits with sub-bursal space involvement (C,). Del: deltoid, Cor: coracoid, HH: humeral head, blue lines: subacromial bursa, white dotted lines: cartilage, white lines: outer surface of the rotator cuff tendons.

DISCUSSION

The exact causes and mechanisms of the chronic calcifying tendinopathy of the shoulder are still not fully understood [6]. Despite the etiological factor and the variety of clinical symptoms, the main attribute of this pathological condition is the presence of calcified tissue [8]. In patients with chronic micro traumatic damage, the calcifications are usually smaller but are presented in all the tendons of the rotator cuff [10]. In patients with

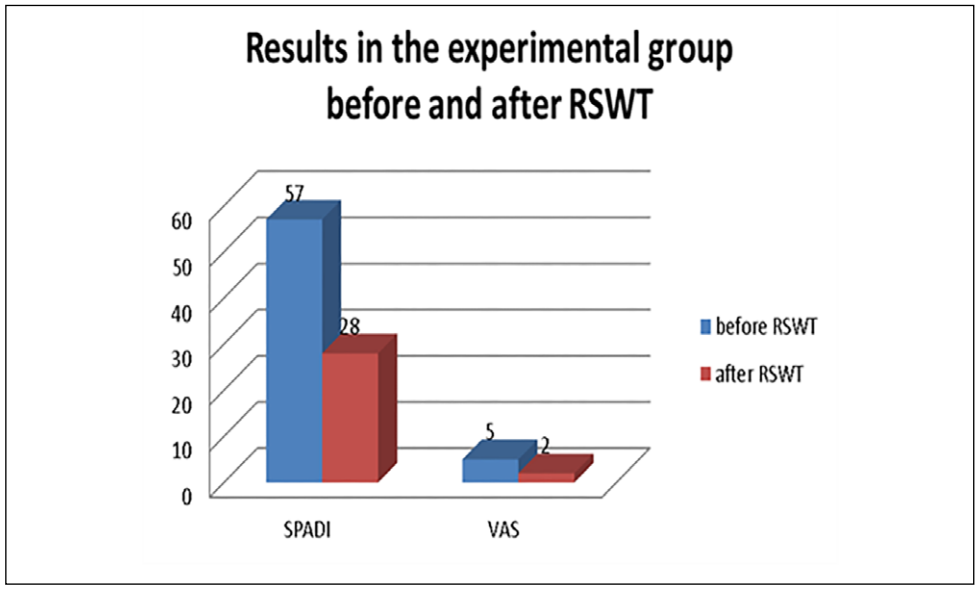

Fig. 5. Comparison of SPADI and VAS values before start of RSWT and after RSWT, p<0,05

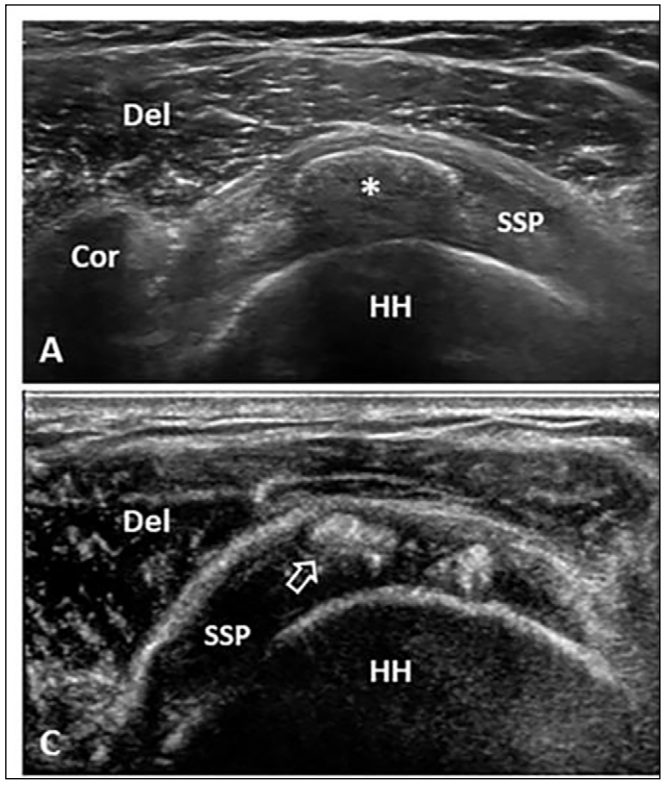

Fig. 6. Demonstration of the change in the calcification before (A) and a month after therapy (C). Short-axis view of the supraspinatus (SSP) tendon with elliptical calcification (asterisk) in resting phase – i.e., type 1 Gartner and Heyer (A).

acute traumatic injuries, the calcifications are larger, and thus needed more therapy sessions to fully resorb. In patients with metabolic syndrome, the calcifications are multiple and could be found in almost all the tendons of the rotator cuff. They are managed quickly but the recurrence is also often depending on the control of systemic condition [11,12].

The presence of calcified tissue requires careful selection of physiotherapeutic modalities to prepare the local site for faster disintegration and further resorption of the calcificates. We could not find other articles comparing the effect of the two modalities – PT and RSWT that have similar to our materials and methods.

The mechanism of action of TENS and IFC involves both peripheral and central mechanisms.

- Peripheral Mechanisms: TENS and IFC stimulate the nerves in the area where the pain is felt. This stimulation helps to block the transmission of pain signals along the nerves to the brain, a theory known as the Gate Control Theory. Additionally, these modalities can stimulate the body to produce its own pain-relieving substances, called endorphins [13].
- Central Mechanisms: TENS and IFC may also exert their effects centrally in the brain, where they may influence the perception of pain [13].

CONCLUSIONS

Combining RSWT with other physical factors and kinesiotherapy statistically shortened the length of the therapeutic process. Follow-up appointments on the first month showed further reduction in the size of the calcifications, and that tendency was present in the third month as well.

The results of our study revealed that the combination of basic physiotherapy (TENS, kinesiotherapy and BIC) and RSWT plays in coherence amplifying their effects. The results in their integrity revealed that there is a significant improvement in the SPADI and VAS scores, ROM and reduction in the size of calcifications after additional application of RSWT in the treatment plan of the experimental group (p<0.001). None of the patients reported side effects or discontinued the treatment.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Radostina Hristova Simeonova
Private Medical practice Plovdiv
Trakia, bl181, D, 4023 Plovdiv, Bulgaria
e-mail: simeonova750509@gmail.com

ORCID AND CONTRIBUTIONSHIP

Radostina Hristova Simeonova: 0000-0001-6864-8493 A B C D E F
Ignat Ignatov: 0000-0002-4761-2982 A
Zlatin Ivanov: 0009-0000-0266-6162 C D
Georgi Nanov: 0000-0001-9072-1343 A D

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

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ORIGINAL ARTICLE

CONTENTS

Treatment of chronic wounds of the lower limb with the use of VAC-therapy. Impact on immunity and bacterial films

Igor V. Korpusenko[1], Nadiia N. Nor[1], Valery P. Kryshen[1], Valentina E. Kudryavtseva[2], Olena I. Korpusenco[1], Olexander M. Makarenko[3], Vasyl V. Koshtura[1]

[1]DNIPRO STATE MEDICAL UNIVERSITY, DNIPRO, UKRAINE

[2]PRYDNIPROVSKA STATE ACADEMY OF PHYSICAL CULTURE AND SPORT, DNIPRO, UKRAINE

[3]INTERREGIONAL ACADEMY OF PERSONNEL MANAGEMENT, KYIV, UKRAINE

ABSTRACT

Aim: To improve the results of treatment of patients with chronic wounds of the lower extremities by using complex treatment, including surgical interventions, VAC- therapy, as well as studying the effect of negative pressure on bacterial films of wounds, based on microbiological examination and immune-histochemical data.

Materials and Methods: During the period from 2019 to 2023 at the department's clinic, 68 patients with chronic wounds of the lower extremities were examined and treated. These are mainly women (n=63) aged from 35 to 80 years.

Results: Complete wound healing was achieved in all patients. In 79% of patients, the transplanted skin graft took root completely. Partial lysis was observed in 17%, requiring repeated operations. In 4%, the wounds healed without surgery. The VAC- therapy we used prevented the restoration of the biofilm and prevented further infection of the wound. After complex treatment, we observed positive dynamics of clinical and immunological parameters. Indicators of T-cell immunity (CD3+, CD4+, CD19+) were restored, the level of CIC significantly decreased and the level of IgM increased. The level of interleukins on day 21 showed a tendency towards normalization.

Conclusions: A modern integrated approach gives the chance to radically solve the problems of healing chronic wounds. VAC- therapy in combination with surgical treatment and antibacterial therapy prevented the restoration of biofilm and further infection of wounds, which led to the wound healing in 100% cases.

KEY WORDS: Chronic wounds, negative pressure treatment, biofilms, immunity

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INTRODUCTION

Bacterial films often complicate the course of inflammatory processes, causing antibiotic resistance, relapses, and chronicity [1]. According to modern literature, the incidence of infections caused by biofilm is about 80% of all infectious and inflammatory diseases [2]. An important reason for the complicated course of biofilm infections is the increased resistance of biofilm bacteria to immune effectors. Today, the statement that bacteria in biofilms are inaccessible to various parts of the immune system is very relevant. Some authors argue that biofilms can block the initial stages of inflammation, leading to "stupor and inactivity of the innate immune system" [3,4]. Research over the past two decades has established the pervasive role of biofilm in the formation of chronic wounds [5]. Analysis of published data indicates a prevalence of biofilms of 78.2% in chronic wounds, which poses a significant threat to their healing [6]. Our knowledge of biofilm and its impact on wound healing, especially non-healing wounds, is still evolving. In patients with chronic wounds, a long-lasting inflammatory phase, inflammatory mediators and proteases delay the onset of proliferation and disrupt the normal epithelialization process. The inability of the host immune system to suppress hyperinflammation induces the conversion of the innate immune response into an adaptive immune response, which leads to arrest of wound healing in the inflammatory phase and inhibition of the proliferative phase and epithelialization [7]. One of the promising methods for treating wounds of various etiologies is the vacuum method, which is used to improve the course of the wound process [8-11]. In recent years, significant progress has been made in the study and use of VAC- therapy, however, the mechanisms of influence of this method on various parts of the wound process require further research.

AIM

To improve the results of treatment of patients with chronic wounds of the lower extremities by using complex treatment, including surgical interventions, VAC- therapy, as well as studying the effect of negative pressure on bacterial films of wounds, based on microbiological examination and immune-histochemical data.

MATERIALS AND METHODS

STUDY DESIGN, SETTING, AND POPULATION

During the period from 2020 to 2024 at the department's clinic, 68 patients with chronic wounds of the lower extremities were examined and treated. These are mainly women (n=63) aged from 35 to 80 years. The effectiveness of treatment was assessed based on the study of clinical indicators of wound healing and microbiological examination and immunohistochemical data. The studies were carried out when patients were admitted to the hospital on the 14th and 21st days after the start of treatment. Identification of microorganisms was carried out using MALDI-TOF spectrometry (Bruker, Germany). Quantitative assessment of the ability of microorganisms to form biofilms was carried out using the photometric method in 96-well plates for enzyme immunoassay [12]. To study the ability to form biofilms, one-day cultures of Staphylococcus aureus and Escherichia coli isolated from patients were used. The quantitative expression of the degree of biofilm formation was the optical density values measured on a StatFax2100 photometer. We studied various components of the immune system, in particular its cellular immunity (total number of T- and B-lymphocytes, subpopulations of T-lymphocytes: CD3, CD19, CD4, CD8, CD16) using flow cytometry, the humoral link of immunity – changes in the content of immunoglobulins of classes: IgA, IgM, IgG in blood serum were determined by the radial immunodiffusion method according to Mancini (1965) [13]. Mononuclear cells were isolated from the peripheral venous blood of patients in a density gradient of 1.077 g/cm. The functional activity of granulocytes was assessed in the NBT test using the nitroblue tetrazolium reduction reaction. Circulating immune complexes were determined by the method of V. Haskova (1977).

The C-300 TS VAC- system was used to treat wounds with negative pressure. During the first installation of the system, the device was set to a constant aspiration mode with a negative pressure in the wound cavity of 80-110 mm Hg. Art. Vacuum dressings were used (hydrophilic polyurethane sponges with a pore size of 400–2000 μm with a transparent adhesive coating, connected by a drainage tube to a vacuum source apparatus). The first period of system operation lasted from 24 to 48 hours, the second up to 3 days, the subsequent ones – on average up to 5 days. The system was remounted for the purpose of wound revision and during surgical treatment in the operating room.

ETHICS

Ethical approval for this study was obtained from the ethical authority committee of the Dnipro State Medical University, Dnipro, Ukraine. This study was conducted in accordance with the principles Declaration of Helsinki. Written informed consent for participation in this study was not required in accordance with national legislation and institutional requirements.

STATISTICAL ANALYSIS

Statistical processing of the data was carried out by determining the arithmetic mean (M) and its error (m). The significance of the difference in mean values was determined using the Student's t test. Statistical data processing was carried out using a personal computer using STATISTICA 6.1 software (StatSoftInc., serial AGAR909E415822FA) and Microsoft Excel (Microsoft Office 2016 Professional Plus, Open License 67528927) using descriptive and analytical biostatistics methods and multivariate statistical analysis methods.

RESULTS

Treatment of the patient has begun with VAC – therapy, which was used both as an independent method and to prepare wounds for surgery. VAC- therapy was also used after skin graft surgery (Fig. 1).

The use of VAC- therapy contributed to the rapid cleansing of wounds, reducing their area and depth, accelerated formation of granulations and epithelization of edges, and reduced costs for wound care products. This is confirmed by positive changes in the local status on days 4–5 of treatment: a decrease in hyperemia, tissue edema, as well as the amount of wound exudate, a change in its nature from purulent to serous. Signs of epithelization of the wound edges appeared, the tissue defect was gradually filled with granulations and decreased in size (Fig.2).

Complete wound healing was achieved in all patients. In 79% of patients, the transplanted skin graft took root completely. Partial lysis was observed in 15%, requiring repeated operations. In 4%, the wounds healed without surgery. In 2%, severe pain was observed during exposure to negative pressure, which forced the abandonment of VAC- therapy and plastic surgery using a

Fig.1. The C-300TS VAC system was used to treat wounds with negative pressure.

perforator propeller flap. Relapses were observed in 3 patients after 1 year and in 4 patients 2 years after treatment.

Before starting antimicrobial therapy and during the course of antibiotic treatment, microbiological monitoring was carried out. As a result of the study, 58 strains of pathogens were isolated (Fig. 3). The main representatives among the isolated microorganisms were Staphylococcus aureus (18 strains), coagulase-negative staphylococci Staphylococcus haemolyticus (6 strains). Enterobacter cloaceae (5 strains) and Escherichia coli (9 strains) were found among enterobacteria; P.aeruginosa (16 strains), and Acinetobacter spp. (4 strains). The contamination of the wound in the examined patients at the time of the initial examination averaged 2.8±0.03x104 CFU/ml.

To examine the ability of isolated microorganisms to participate in the formation of biofilm conglomerates consisting of bacteria and extracellular matrix, a photometric method was used. The intensity of biofilm formation was assessed 24 hours after introducing microbes into plastic plates with Mueller-Hinton broth. Biofilm formation was studied before the start of antimicrobial therapy and 10-14 days after the start of treatment. Targeted antibacterial therapy was carried out against the background of VAC- therapy and complex surgical treatment. The course of treatment was carried out in accordance with the results of bacteriological cultures and the choice of drugs to which the greatest sensitivity was identified.

A slight predominance of P. aeruginosa activity in the formation of biofilms was noted at 1,8 – 2,1 cu of optical

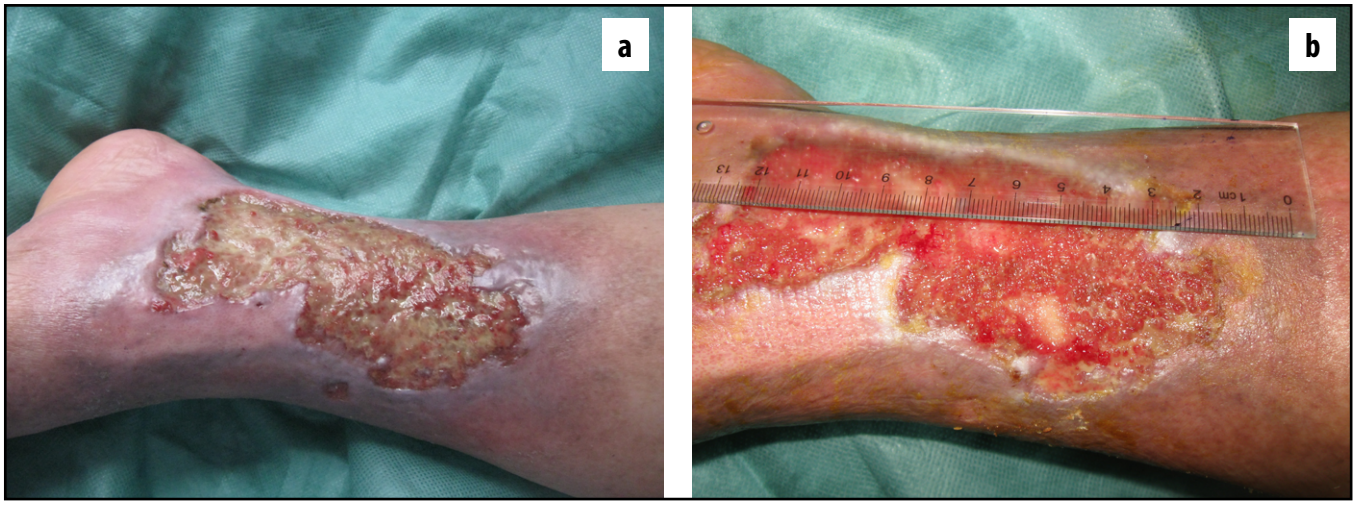

Fig. 2. a) Chronic wound of the left leg. b) On the 10th day after VAC- therapy.

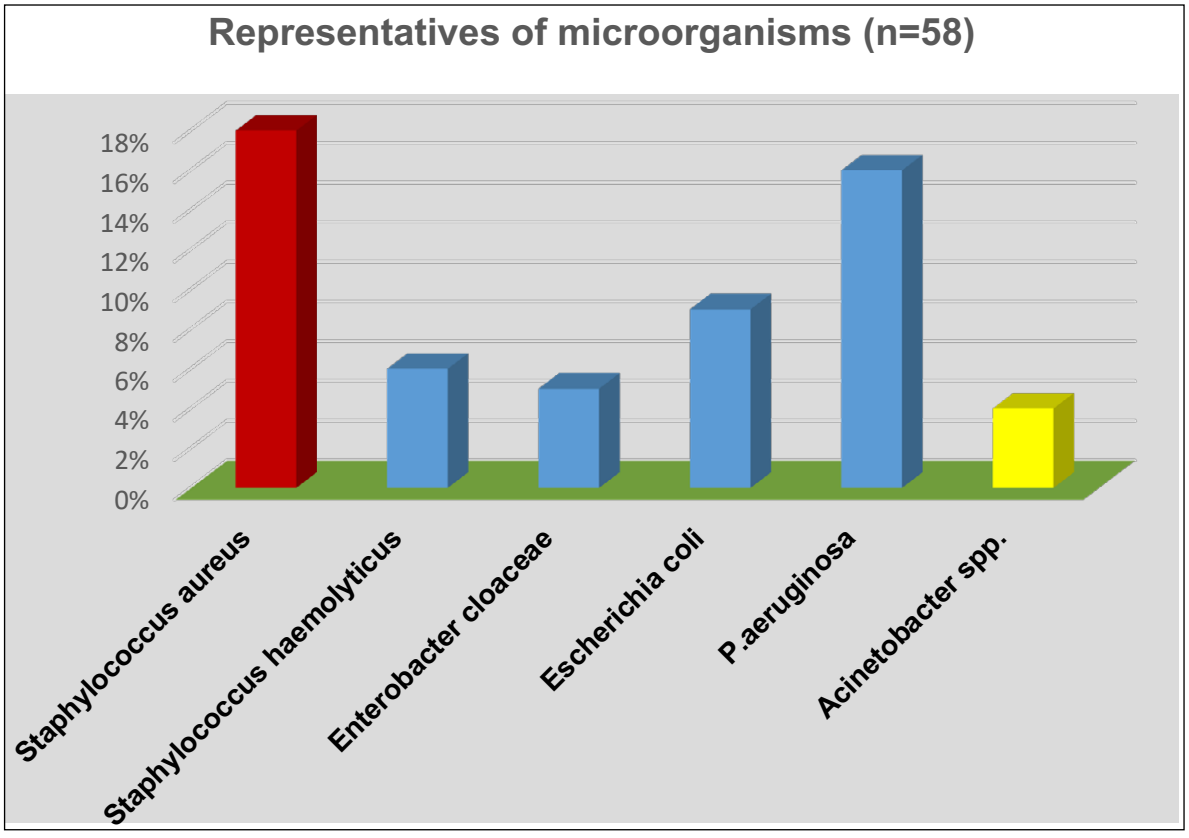

Fig. 3. Representatives of microorganisms in chronic wounds of the lower extremities.

plane compared to S. aureus – 1,5-1,9 cu of optical plane and with E. coli – 1,2-1,4 cu of optical plane before the start of treatment. After a certain period of time after the start of the use of antimicrobial agents, a tendency to a decrease in the intensity of biofilm formation was found: in P. aeruginosa – 1,3 -1,6 cu of optical plane for S. aureus – 0,8-0,9 cu of optical plane and in E. coli – 0.7-0.9 cu of optical plane respectively.

Studies have shown that all patients before treatment had deep disturbances in the T- and B-cell components of immunity. An analysis of the results of studies of the T-cell and humoral immunity in patients with chronic wounds of the lower extremities is given in Table 1.

In the patients studied, the number of phagocytic cells and their functional activity drops sharply. The number of B- cells increases, an inversion of immune-regulatory subpopulations is observed, and the balance between the T- and B – cell components of immunity is disrupted. The data we obtained indicate significantly pronounced immune disorders and we did not observe a full-fledged immune response.

Table 1. The state of cellular and humoral immunity in the examined patients before and after treatment

Indicators	Tests values (n=25)	Before treatment (n=68)	After treatment (n=68)
Leukocytes	5,35±0,21	7,92±0,76*	5,4±0,73
Lymphocytes % a.n.	28,71±0,81 1,61±0,07	19,72±1,56* 1,31±0,19	29,61±2,54 1,52±0,17
T- lymphocytes % CDZ+ a.n. x10^9 cel/l	50,88±0,68 0,76±0,04	32,12±2,68* 0,43±0,15*	50,37±2,58** 0,69±0,05
T- helpers % CD4+ a.n. x10^9 cel/l	38,71±0,52 0,53±0,03	21,42±1,58* 0,24±0,08*	33,4±2,24 ** 0,45±0,03
T- suppressors % CD8+ a.n. x10^9 cel/l	18,39±0,57 0,30±0,02	26,17±2,1 0,38±0,04	19,35±3,89 0,29±0,06
B- lymphocytes % CD19+a.n x10^9 cel/l	14,78±0,48 0,25±0,01	25,16±2,13* 0,42±0,08	14,26±1,39** 0,32±0,07
Th/Ts	1,97±0,07	1,13±0,13*	1,63±0,21
CIC cu	3,42±0,23	9,89±1,35*,	3,69±1,68**
Ig A g/l	2,25±0,26	2,85±0,36	2,2±1,93
IgM g/l	1,53±0,1	1,07±0,18	2,14±0,36**
IgG g/l	12,72±0,42	18,07±1,33	13,81±0,87

Notes:
1. * – p<0.05 compared to control
2. ** – p<0.05 between indicators before and after treatment.

Table 2. Level of interleukins in examined patients before and after treatment

Indicators	Control values (n=15)	Before treatment (n=68)	After treatment for 21 days (n=68)
IL –8 pg/ml	26,0±2,62	219,63±15,87*	127,42±17,98*
IL- 4 pg/ml	18,5±1,67	82,62±12,49*	65,43±10,74*
IL1Ra pg/ml	750±186	1596,93±582,88*	1053,74±497,68*
IL – 2 pg/ml	14,50±0,93	658,39±48,49 *	455,54±47,38 *

Note: * – p<0.001 compared to control.

The range of immune disorders includes a deficiency of T- cells, T- helper cells in all patients. The suppressor effect is due to insufficient production of T- cells and is accompanied by leukocytosis, lymphopenia, and suppression of the phagocytic system. Changes in the subpopulation ratios of T-lymphocytes in patients lead to a statistically probable inversion of immunoregulatory indices. A decrease in T-helper cells with an increase in the CIC leads to a decrease in the immunoregulatory index, which indicates an immunological imbalance and an important pathogenetic role. The response characteristics of the immune system indicate the possible specificity of changes in the immune system in patients with chronic wounds of the lower extremities. We found an increase in the level of the studied interleukins in all patients Table 2.

A significant increase in IL-2 concentration occurred in all patients. Influencing T- and B- cells, IL-2 is a central regulator of the immune response. Long-term stimulation by bacterial antigens leads to chronicity of the inflammatory process and indicates an insufficient voltage of the immune response in the studied patients.

Indicators of T-cell immunity (CD3+, CD4+, CD19+) were restored, the level of CIC significantly decreased and the level of IgM increased. The level of the studied interleukins on day 21, despite the short period of time, showed a tendency towards normalization, which indicates the positive dynamics of treatment using VAC – therapy.

DISCUSSION

Clinically, a wound with red, loose granulation tissue covered with a mucous layer of exudate that returns after debridement, with increased production of discharge, and signs of recession of the epithelial edge, most likely has a biofilm [14]. Features of the immune system response indicate the specificity of changes in immunity in patients with chronic wounds. Long-term stimulation with bacterial antigens modified by altered autologous

tissue cells leads to chronicity of the inflammatory process and indicates an insufficient tension of the immune response. The profile of the T-cell response to the Th2 type changes, probably ensuring the persistence of bacteria, the pathological process turns out to be chronic. IL-4 acts as a growth factor for Staphylococcus aureus, leading to systemic infection. It inhibits the synthesis of the pro-inflammatory cytokine IL-8 by macrophages and promotes the formation of highly active oxygen and nitrogen metabolites. It was found that in the studied patients, an increase in the blood level of anti-inflammatory cytokines leads to an increase in wound processes. Also, the increase in the pro-inflammatory cytokine IL-8 is maximally expressed. The increase in IL-8 in the blood serum is associated with the activity of the inflammatory process, since it, by activating neutrophils, leads to their degranulation, the release of lysosomal enzymes and reactive oxygen metabolites, which have a damaging effect on the mucous membranes, increasing the damaging effect on the wound surface. Increased production macrophages of soluble mediators IL-2, IL-8, oxygen radicals and other biologically active substances leads to tissue damage, impaired penetration and the formation of a chronic focus of inflammation. Inflammatory reactions are accompanied by a complex systemic response, mediated through IL-1. It should be noted that for the progression of the inflammatory process, the imbalance in the production of IL-1 antagonists by phagocytes: the antagonist of its receptors IL-1Ra, which we observed in patients with chronic wounds of the lower extremities, is of great importance. All this indicates that the formation of a biofilm is associated with an immunodeficiency state which ultimately leads to the formation of long-term non-healing chronic wounds.

CONCLUSIONS

1. A modern integrated approach gives the chance to radically solve the problems of healing chronic wounds. VAC- therapy in combination with surgical treatment and antibacterial therapy prevented the restoration of biofilm and further infection of wounds, which led to the wound healing in 100% cases.
2. Microbial biofilms were found in 72% of patients with chronic wounds. The causative agents of chronic infection were representatives of gram-positive and gram-negative flora with a tendency to predominance of representatives of the genus Staphylococcus.
3. Imbalance of immune-regulatory mechanisms plays an important role in the wound process in patients with chronic wounds of the lower extremities, as evidenced by a decrease in B-cell component of immunity against an adequate increase in T-helper cells and the restoration of the balance between the T- and B-cell links with the normalization of the CIC index on 21th days after treatment.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Nadiia N. Nor
Dnipro State Medical University
9 Vernadskogo st, 49044 Dnipro, Ukraine
e-mail: norsurgery@gmail.com

ORCID AND CONTRIBUTIONSHIP

Igor V. Korpusenko: 0000-0001-7929-7350 A E F
Nadiia N. Nor: 0000-0002-6468-6297 B C D
Valery P. Kryshen: 0000-0002-8318-6239 B C D
Valentina E. Kudryavtseva: 0000-0003-0643-5884 B C E
Olena I. Korpusenco: 0000-0002-4018-951X B C
Olexander M. Makarenko: 0000-0002-6892-2314 B C D
Vasyl V. Koshtura: 0009-0007-9253-6097 B C

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

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CREATIVE COMMONS 4.0

ORIGINAL ARTICLE

CONTENTS

Anatomic-biomechanical substantiation of stabilization of the sacroiliac joint in cases of unstable pelvic injuries with a countersink-compression screw

Yuriy Sobolevskiy, Oleksandr Burianov, Volodymyr Kvasha, Volodymyr Domin
BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: Study the mechanism of interaction between the 'sacroiliac joint – screw' system and determine the optimal parameters of the stabilizing structure, the strength of the system connection through computer modeling, and anatomical-biomechanical experiment

Materials and Methods: The optimal parameters of the stabilizing structure for the sacroiliac joint were calculated using software package MathCAD. To validate the results of the numerical modeling, corresponding investigations of mechanical characteristics and determination of stiffness of the studied systems were conducted by an upgraded testing stand, TIRAtest-2151

Results: Optimal dimensions of the stabilizing structure were calculated as follows: a thread length with a diameter of 9 mm ranges from 20 mm to 25 mm, and a thread length with a diameter of 7 mm ranges from 30 mm to 80 mm. The screw body, with a length from 15 mm to 70 mm and a diameter of 4.5 mm, is positioned between two thread portions. Under standard screw connection loading, a region of plastic deformation is observed under low force (≈40 N). Subsequently, elastic deformations are observed up to 900 N, after which the connection fails, and deformation of the stabilizing structure occurs

Conclusions: Resulting from the study the authors revealed that the stiffness of the fixed system with countersink-compression screws increases with the applied load, reaching 67-68% of the stiffness of an undamaged joint.

At all load levels, residual deformations in systems with C1Cc screws are significantly lower than the residual deformations in systems with C2Ct screws, indicating an enhanced deformation reliability of fixation with counter-compressive screws.

KEY WORDS: sacroiliac joint, stabilization, pelvic injuries, compression screw, combined pelvic fractures, operative treatment methods

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INTRODUCTION

Injuries to the pelvic bones constitute 5% to 12% of the total number of traumas. Isolated injuries occur in 7-8.5% of cases, multiple pelvic injuries account for up to 18%, and combined injuries reach up to 36% [1].

Injuries to the pelvic ring result from the high-energy mechanical factor which causes combined damage in various anatomical areas. In 62-87% of cases, such injuries are characterized as "polytrauma" [2].

The injuries of the pelvis combined with internal organs' trauma are observed in 48-80% of cases; with cranial-cerebral traumas – in 25-55%; with closed chest traumas – in 25-44%; with closed abdominal traumas – in 16-55%; with urinary tract injuries – up to 20%; with spinal injuries – up to 14%; with fractures of limb bones – 20-69%; with damage to major vessels and nerves – up to 10% [3].

The mortality rate, depending on the severity of the trauma, reaches 30% and does not tend to decrease. Disability manifests in 22-66% of afflicted individuals, while suboptimal outcomes are documented within the range of 20-74% [4].

The universally recognized classification of pelvic injuries is the Tile-AO/ASIF classification, which is grounded in the concept of pelvic ring stability/instability. It encompasses three types of fractures: Type A, characterized by minimal displacement without disruption of the integrity of the dorsal aspect of the pelvic ring, with an intact pelvic diaphragm capable of withstanding routine physiological loads; Type B, distinguished by rotational instability and vertical stability; and Type C, characterized by both rotational and vertical instability, accompanied by complete disruption of the pelvic ring, encompassing the posterior sacroiliac complex, including the ligaments sacrospinosum and sacrotuberosum [5].

The treatment strategy for these patients is founded upon the principles of "damage control surgery – DCS" [6] and "damage control orthopedics – DCO" [7].

According to the AO/ASIF guidelines, Type A fractures are considered stable injuries and generally do

not require surgical intervention. For Type B injuries, characterized by anterior, rotational, and partial posterior instability, stabilization of the anterior segment is typically sufficient, utilizing external fixation devices as customary, taking into account the patient's overall condition. Type C injuries, characterized by both anterior and posterior instability, necessitate stabilization of both the anterior and posterior semirings [8].

The stabilization of the posterior semiring is objectively necessitated; however, the overall condition of patients, particularly in the early stages of hospitalization, and the anatomical peculiarities of the affected area, require minimally invasive technologies and appropriate fixation methods. This forms the basis for further research in this field.

AIM

To investigate the interaction mechanism of the "sacroiliac joint – screw" system and determine the optimal parameters of the fixation construct, as well as assess the strength of the connection system through computer modeling and anatomic-biomechanical experiment.

MATERIALS AND METHODS

A comprehensive analysis of literature on the treatment of unstable pelvic fractures from 2010 to 2023 was conducted using three databases (PubMed, Scopus, and Web of Science). The search focused on keywords such as pelvic fractures, combined pelvic fractures, operative treatment, methods, and means of fixation.

Titles and abstracts were reviewed during the selection process, and potentially relevant articles were assessed for inclusion.

Inclusion criteria: Full-text articles encompassing clinical/anatomic-biomechanical studies.

Exclusion criteria: Case reports, pilot studies, and preliminary investigations were excluded.

Through computer modeling employing formulas to assess the load-bearing capacity of threaded connections, the interaction mechanism of the sacroiliac joint-screw system was investigated. Furthermore, the correlation between the axial force of the threads of small and large diameters in the countersink-compression screw was studied. Optimal areas of load-bearing thread surfaces, the optimal number of turns, and the magnitude of their pitch were determined. Additionally, the necessary lengths of the larger and smaller threads, as well as the entire countersink-compression screw, were identified to create compression and prevent the thread of small diameter from breaking with a larger pitch during the screw insertion into the bone.

In addition, the reserve strength of the sacroiliac joint-screw system connection was determined under static dosed loading. The time spent to create axial force from the total tightening moment of the countersink-compressing screw was also calculated, which allowed the authors to determine the direction and magnitude of compression. All calculations were performed using the MathCAD software package.

The screw interaction with the bone is based on the spatial curve mechanism, where the screw line, is formed by the hypotenuse of a right-angled triangle when projected onto the lateral surface of a cylinder (Fig. 1).

For testing the fixator-bone systems, the authors utilized a universal testing machine TIRAtest-2151. This machine was used to determine the strength and deformation characteristics of materials and objects under tension, compression, and bending.

RESULTS

Based on the anatomical and functional characteristics of the sacroiliac joint, the design of the screw corresponded to the initial parameters: compression force – 1.5-2 kN; joint gap 3 mm; the material strength limit of the bone in cross section – 5 MPa.

CALCULATION OF THREAD STRENGTH

Since the bone has a significantly lower strength limit than the material of the screw, calculations were performed for the strength of the bone thread, as well as plastic deformations in the bone body, known as slipping, specifically in the section of the screw with a smaller diameter. The actual distribution of the load on the threads depends on many factors, most of which are random. Therefore, in practice, the strength calculation of the thread is made considering not actual stresses, but conditional stresses, which are compared with permissible ones. The scheme for calculating the strength of the thread is presented in Fig. 2.

The conditions for thread strength based on crushing stress were determined by the formula:

$$\sigma_{cr} = \frac{F}{z \cdot \pi \cdot d_2 \cdot h} \leq [\sigma_{cr}],$$

where z=H/S – the number of threads with a height H. Substituting the given parameters for the smaller diameter thread, we get:

$$\sigma_{cr} = \frac{6064}{3 \cdot \pi \cdot 0{,}0058 \cdot 0{,}0012} = 92444020Pa.$$

The screwing length H was determined by the inequality:

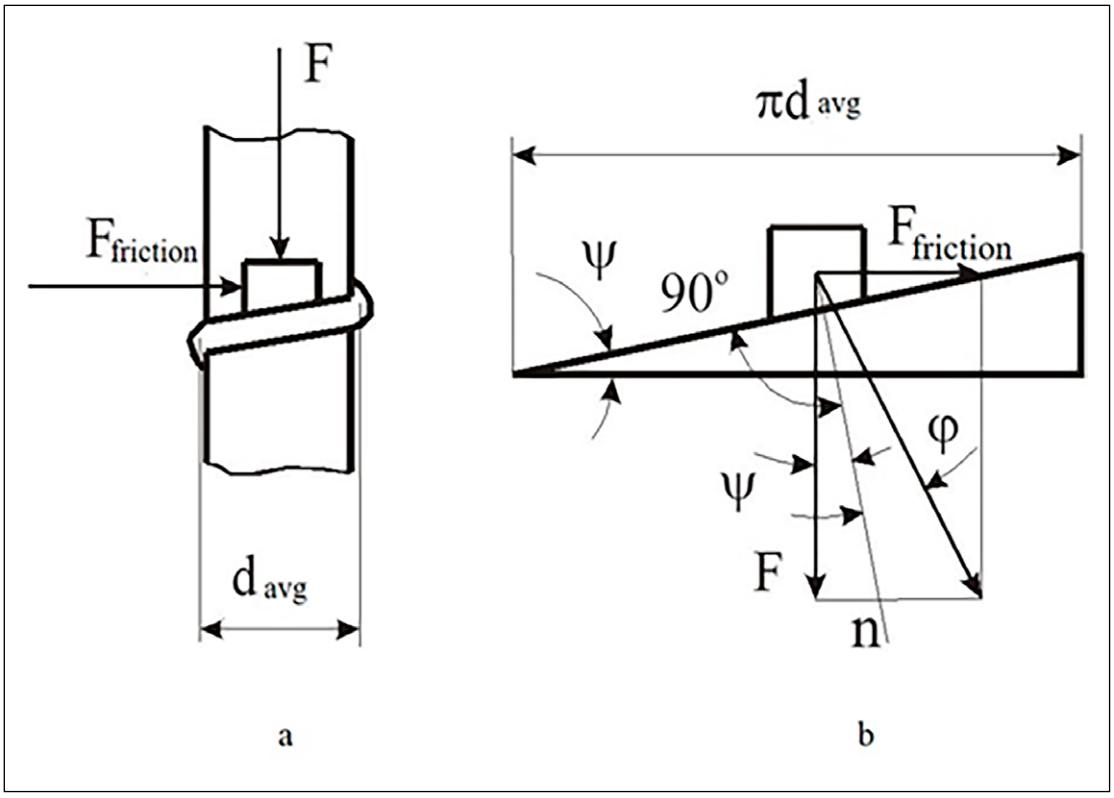

Fig. 1. Mechanism of screw interaction with bone. a) – spatial curve of screw-bone interaction; b) – unwinding of one turn along the average thread diameter; F – compression force; d_avg – average thread diameter, ψ – thread pitch angle, n – radius perpendicular to the direction of the screw, F_friction – friction force component, φ – angle of friction.

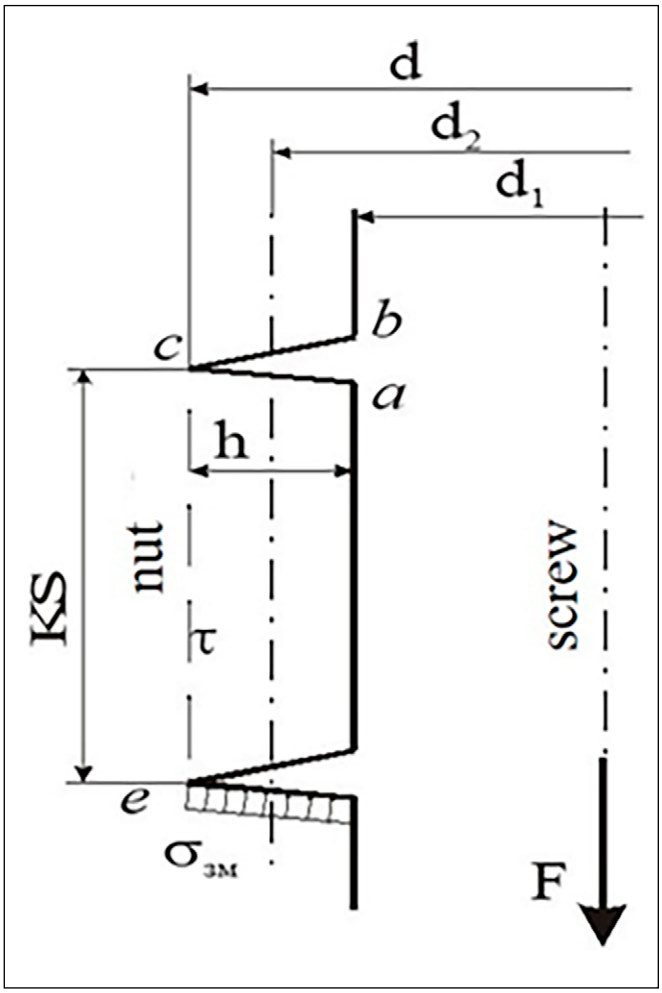

Fig. 2. Scheme for calculating thread strength.

$$H \geq \frac{F}{\pi \cdot d \cdot [\tau_{crosssection}]}.$$

Substituting the values of the parameters for the smaller diameter thread, we obtain

$$H \geq \frac{1819}{\pi \cdot 0{,}007 \cdot 5\ (10^6} = 0{,}02m.$$

The strength limit for the cancellous bone layer under compression is taken to be one-tenth of the modulus of elasticity of the first kind. Since $E=7{,}8\times10^9$ Pa, $s_{cr}=7{,}8\times10^8$ Pa, and the strength limit of the cancellous bone layer varies within the range $[t_{cross\ section}]=(4{,}32\text{-}12{,}26)\times10^6$ Pa.

The strength calculations based on the above formulas show that under the compression condition, even a thread with three turns withstands the maximum calculated force of 6064 N. The calculated crushing stress is 92,444,020 Pa.

Thread cross section calculations showed that with the minimum accepted cross section limit $[t_{cross\ section}]$ = 5 x 10^6 Pa and the minimum axial force F = 1819 N, the thread length should be at least 20 mm, which corresponds to 8 turns.

PLASTIC DEFORMATIONS IN THE THREADED PART OF THE BONE

The plastic deformations in the nut significantly affect the strength limit of the threaded connection (Fig. 3).

Due to deformations, the nut increases in transverse dimensions and may "slide" off the bolt with partial cutting of the thread crests. This is particularly character-

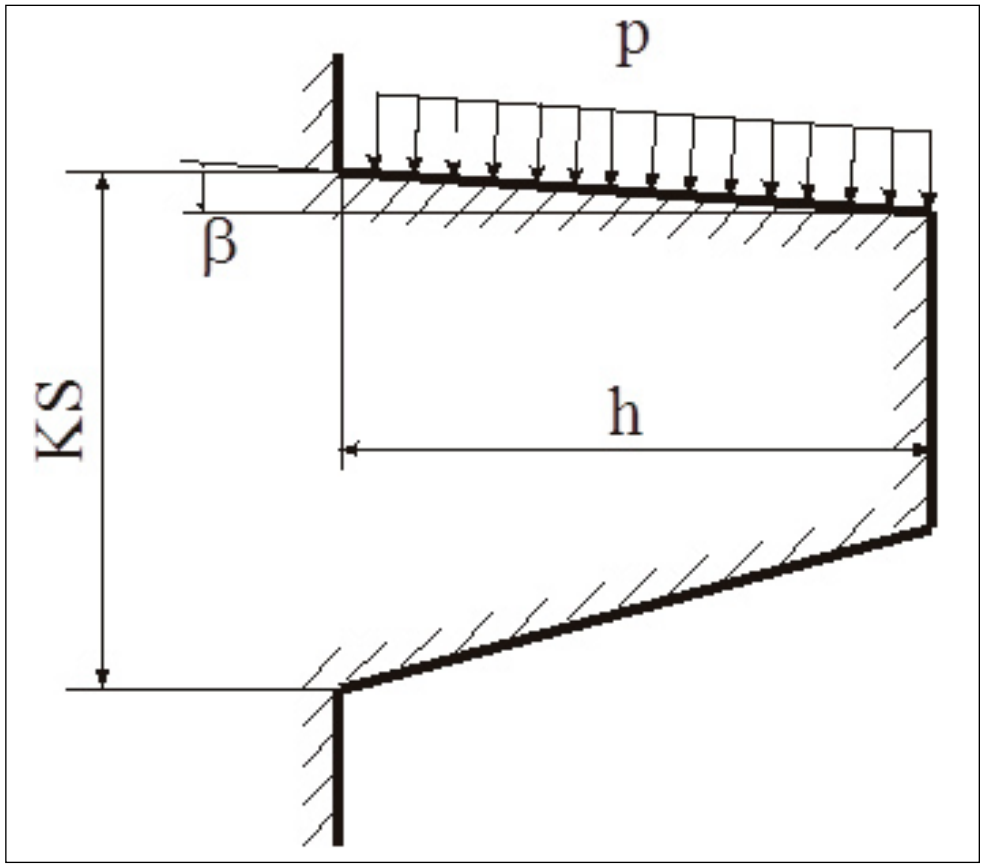

Fig. 3. Load on a thread of an asymmetric profile.

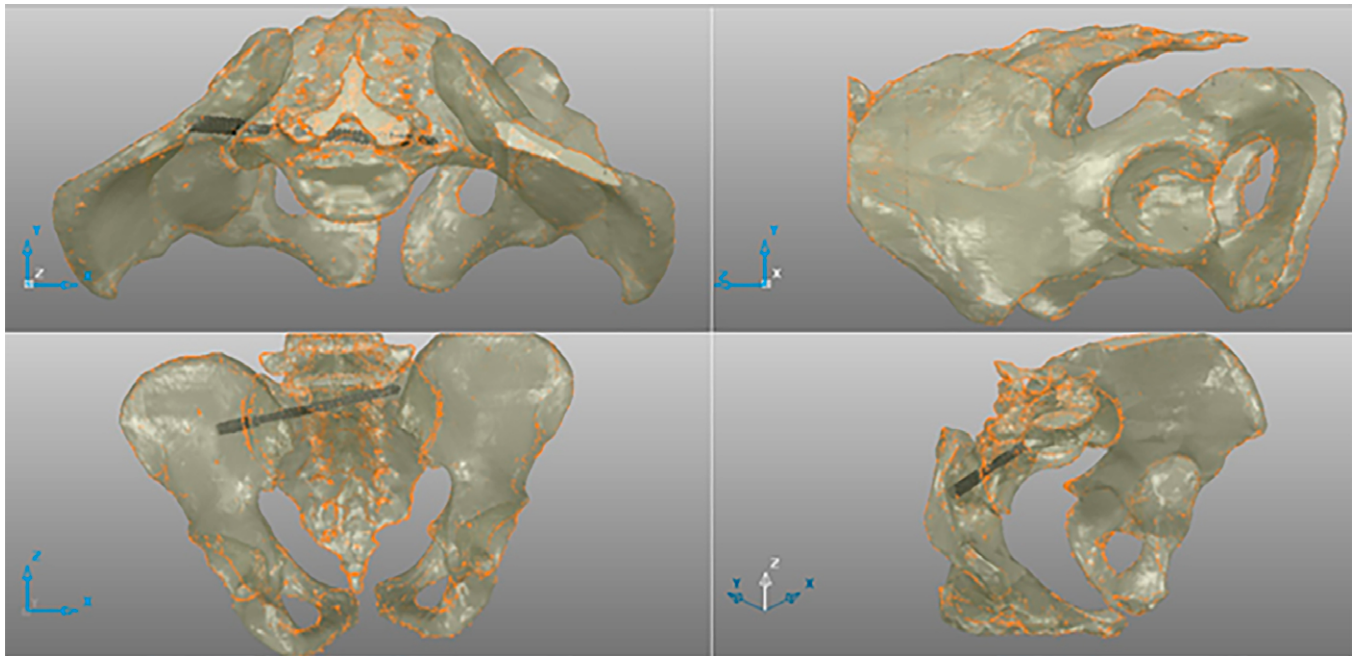

Fig. 4. General view of the stabilization of the sacroiliac joint with a newly designed screw.

istic for thin nuts and for structural components made of lightweight materials. It is evident that such a type of thread disruption will be present in the screw-bone connection as well. Therefore, let's consider under what loads the condition for bone strength against "sliding" will be satisfied.

For a thread of asymmetric profile (Fig. 3), the average radial stress in the nut wall is determined by the formula:

$$\sigma_{av} = p \cdot \frac{h}{S} \cdot tg\beta \quad ,$$

where: p – pressure on the working side of the thread profile, h – height of the thread profile, S – pitch of the

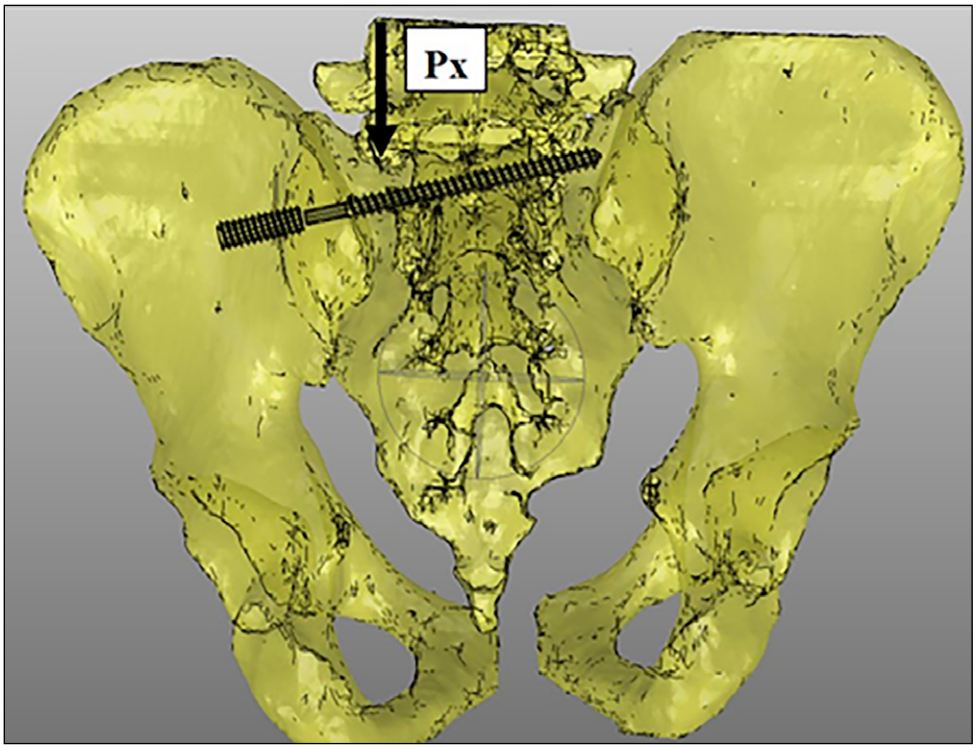

Fig. 5. Load scheme for the connection of the sacral and iliac bones.

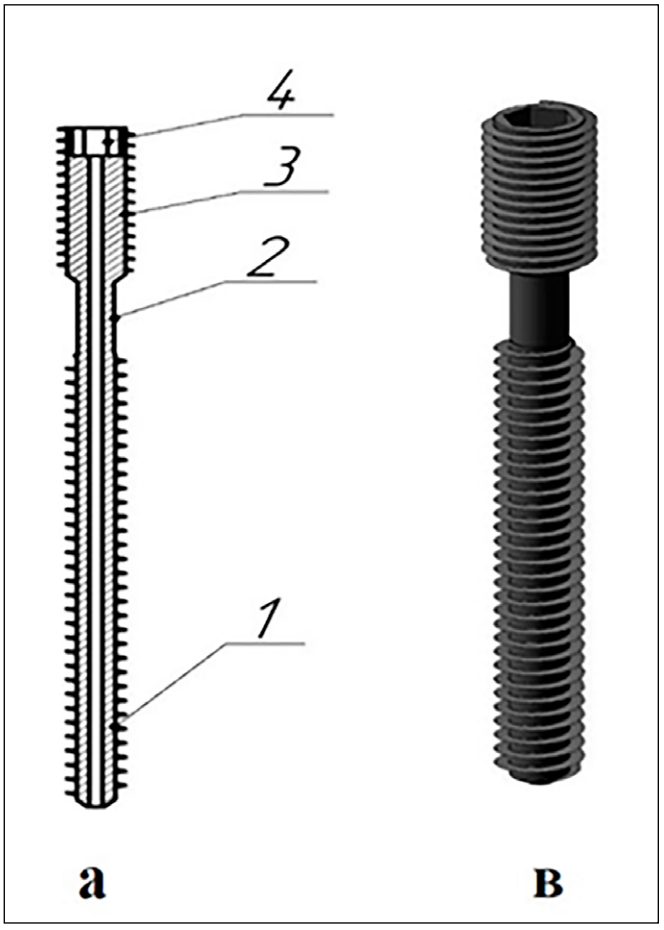

Fig. 6. Schematic representation of the counter-compressing screw, where: a) screw drawing (1 – thread with a diameter of 7 mm; 2 – screw body; 3 – thread with a diameter of 9 mm; 4 – hexagonal hole for the key.), b) overall view of the screw (3D model).

thread, β – angle of inclination of the working side of the thread profile.

Taking the load distribution between the threads as uniform, we find the pressure p on the lateral surface of the thread:

$$p = \frac{\sigma_0 \cdot A_0}{a \cdot z}$$, where

A_0 – is the cross-sectional area of the screw, $a=\pi d_2 h$— s the area of the ring of the thread, z – is the number of turns. Substituting $s_0 \times A_0$ with the force F, we get:

$$\sigma_{av} = \frac{F}{\pi \cdot d_2 \cdot H} \cdot tg\beta,$$

H= where z×S is the height of the nut.

Considering the nut as a ring with a thickness d and an average diameter D_{aver}, we obtain the formula for determining the stress in the ring:

$$\sigma_\theta = \sigma_{aver} \cdot \frac{D_{aver}}{2 \cdot \delta} = \frac{F}{2 \cdot \delta \cdot H} \cdot \frac{D_{aver} \cdot tg\beta}{\pi \cdot d_2}.$$

The strength condition against "sliding" will be expressed by the inequality:

$$\frac{F}{2 \cdot \delta \cdot H} \cdot \frac{D_{aver} \cdot tg\beta}{\pi \cdot d_2} \leq \frac{\sigma_{cross\ section}}{n_{cross\ section}}$$, where:

$s_{cross\ section}$ – is the cross section strength of the nut material, and $n_{cross\ section}$ – is the safety factor for cross section strength.

Hence, the strength of the nut against 'sliding' depends on the angle of inclination of the working surface of the

Table 1. The main design parameters of the screw

Parameters	Measurement unit	Thread of small diameter	Thread of large diameter
External thread diameter	mm	d=7	d¢=9
Internal thread diameter	mm	d_1=4,6	$d¢_1$=7
Mean thread diameter	mm	D_{aver}=5,8	$d¢_{aver}$=8
Thread pitch	mm	S=2,5	S¢=2
Thread height	mm	h=1,2	h¢=1
The angle of the screw line ascent	°	y= 8,6804°	y = 5,0554°

Table 2. Deformation characteristics of the undamaged (H1, H2) and damaged sacroiliac joint with stabilization by the countersink compression (C1Cc) and standard (C2Ct) screws.

Joint type	Δ_{AG}/ mm	P_{AG}/ H	δ-10³, mm/H	C, H/mm
H1	1	1845	0,542	1845
H2	1	1840	0,543	1840
C1Cc	1	1238	0,8	1238
C2Ct	0,85	885	0,96	1041

Note: Δag – specified compression deformation, mm; V – deformation rate, mm/min; δ – specific deformations, mm/N; Pag – compression forces in the joint at specified deformations Δag, H; C – stiffness of the sacroiliac joint, defined as the ratio of the change in load to the change in deformation within the linear region of the deformation diagram, N/mm.

Table 3. Mean test data for objects under compression

Joint type	Δ_{AG}/ mm	P_{AG}/ H	C, H/mm	ψк
H1	1	1845	1845	1
H2	1	1840	1840	1
C1Cc	1	1238	1238	0,67
C2Ct	0,85	885	1041	0,56

thread. Therefore, the use of a self-tapping thread with a working angle β≈0 is entirely justified for thin nuts and nuts made of material with a significantly lower strength limit than the screw material under large static loads.

Substituting the values of the parameters for the smaller diameter thread, we obtain

$$\frac{6064}{2 \cdot 0{,}02 \cdot 0{,}02} \cdot \frac{0{,}007 \cdot tg3^{\circ}}{\pi \cdot 0{,}0058} = 152611 \leq \frac{5 \cdot 10^{6}}{2} = 2\,500\,000 Pa$$

The calculations for bone thread sliding showed that the bone with a thickness of the hypothetical ring of 20 mm and a thread height of 20 mm has a significant safety margin against sliding at the maximum calculated axial force.

Thus, through strength calculations, the conclusion can be drawn that the critical factor when using countersink-compression screws is the strength limit of the cancellous bone layer in cross section.

THE CALCULATION OF THE CONNECTION IN CROSS SECTION

The general view of the stabilization system for the sacroiliac joint using a newly designed screw is presented in Fig. 4.

Since the weight force is practically directed transverse to the screw, only one component of force will act in the connection (Fig. 5). The component PX acts in the direction of cross sectioning the screws and crushing the bone, so the critical factors will be the cross section strength of the screw and the compressive strength of the bone due to the action of component PX

Let's assume that the weight of a person is 80 kg. Therefore, we can assume that the PX component is 800 N. Since the screw is screwed into the sacral and iliac bones, we have a connection of the sacrum-screw and screw-iliac bone without clearances. Therefore, in further calculations, friction between the sacral and iliac bones is not taken into account.

The strength condition of the screw based on cross section stress is determined by the formula:

$$\tau = \frac{4 \cdot P_X}{\pi \cdot {d_C}^2} \leq [\tau],$$

where *dc* – is the diameter of the shank (4.6 mm), [t] – is the allowable cross section stress in the material.

Substituting the given values into the formula, we get:

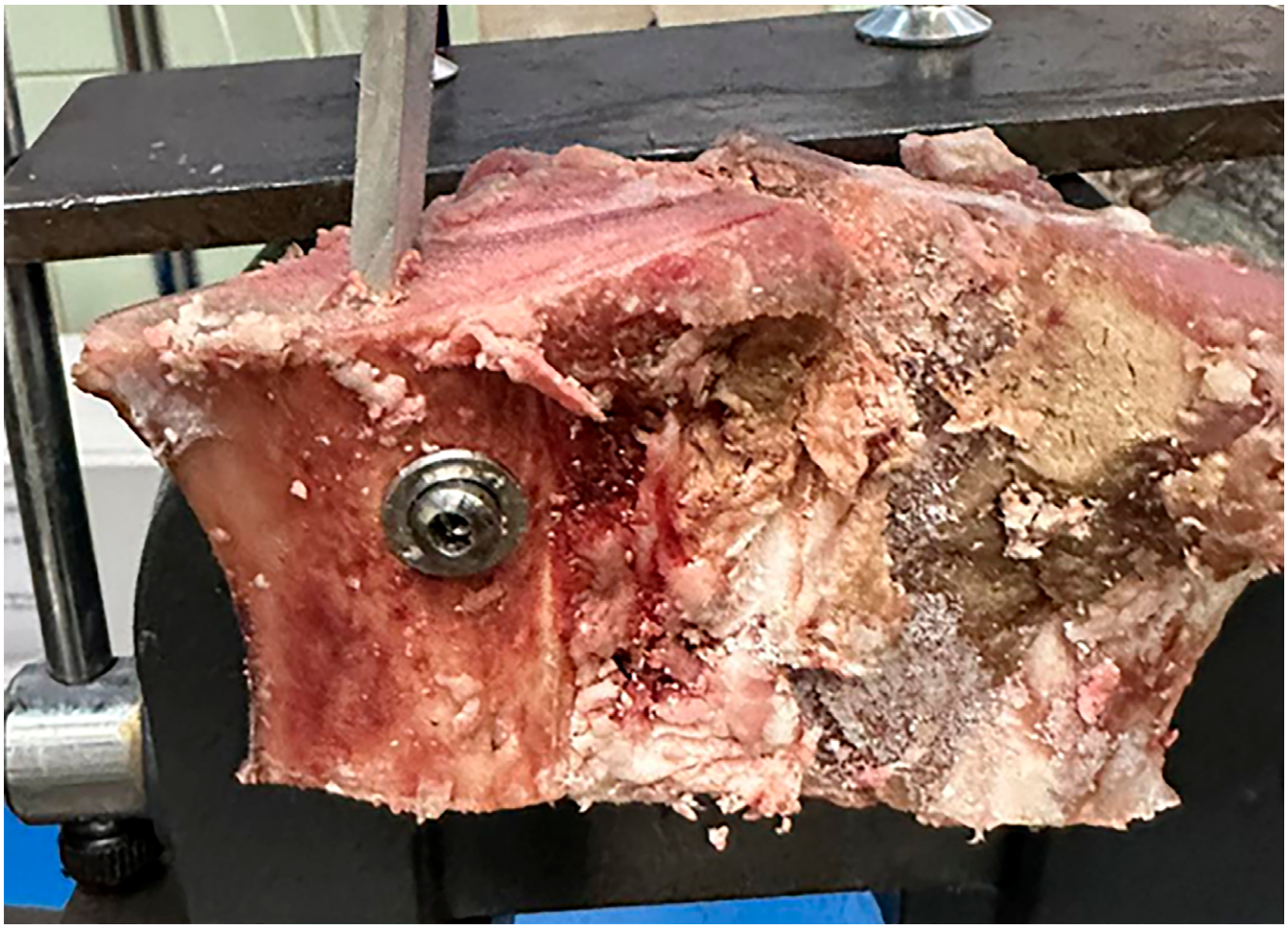

Fig. 7. Secured native specimen of the sacroiliac joint in the research machine.

$$\tau = \frac{4 \cdot 800}{\pi \cdot 0.0046^2} = 48{,}1376\text{MPa}.$$

In this case, the cross section strength limit for hardened steel 95X18 is 770 MPa.

The compression stress, taking into account the assumed uniform distribution through the thickness of the connected parts, is determined by the relation:

$$\sigma_{crush} = \frac{P_X}{d_C \cdot \delta} [\sigma_{crush}], w$$

where d – is the thickness of the connected elements.

Calculations are performed for the fracture, as the diameters of the screw in the fracture zone and the bone differ insignificantly, and the thickness of the bone is significantly larger than that of the fracture. In this case, the thickness of the iliac bone is approximately 20 mm, and the diameter of the screw shank is 4.6 mm.

Substituting these values into the formula, we get:

$$\sigma_{crush} = \frac{800}{0{,}007 \cdot 0{,}02} = 5{,}7mPa$$

which is within the allowable limits, ranging from 4,32-2,26×10^6 Pa.

The proposed design of the counter-compressing screw and technical characteristics are presented in Fig, 6 and Table 1.

The screw differs from known designs in that it has a central hole with a diameter of 2mm or 1.6mm, depending on the diameter of the leading spike. The pitch of the thread of the smaller diameter is 2.5mm, and the pitch of the thread of the larger diameter is 2mm. The threads of the larger and smaller diameters have a profile known in the technology of a supporting thread. In this case, the rectangular segments of the thread profiles of the larger and smaller diameters are directed towards each other. This type of thread is used in cases where significant unidirectional axial loads are transmitted. Due to the small angle of inclination of the working surfaces of the threads, this thread provides increased efficiency even compared to a trapezoidal thread, while retaining all its advantages.

The length of the thread with a diameter of 9 mm varies from 20 mm to 25 mm, and the length of the thread with a diameter of 7 mm ranges from 30 mm to 80 mm. The body of the screw, with a length from 15 mm to 70 mm and a diameter of 4.5 mm, located between the two threads, does not have a thread.

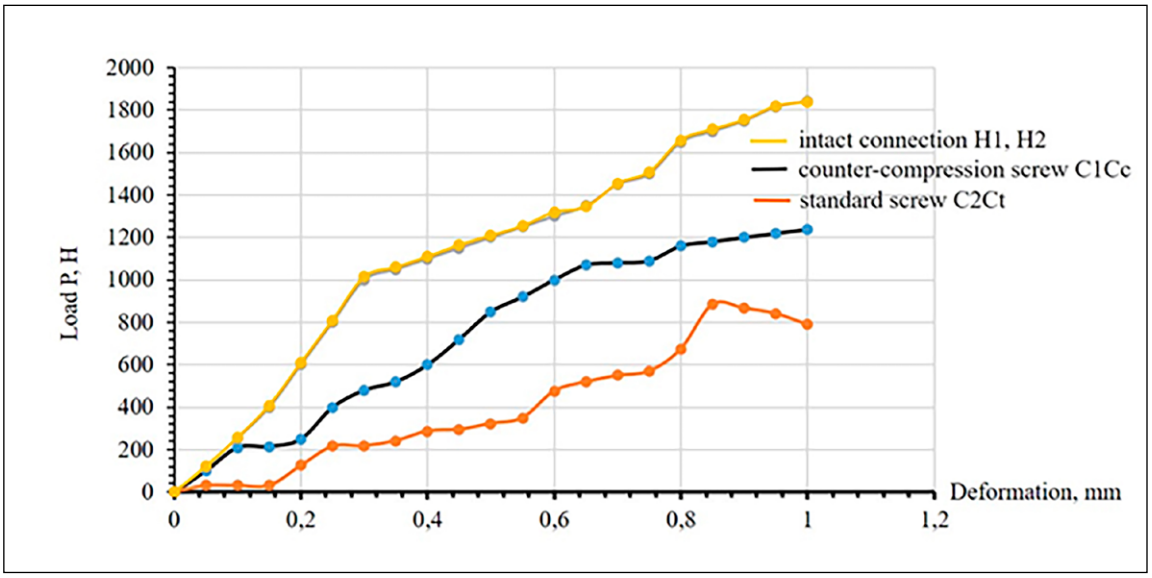

Fig. 8. Deformation diagram for cross section deformation of an undamaged sacroiliac joint (H1, H2), damaged joint stabilized with a countersink screw (C1Cc), and damaged joint stabilized with a standard screw (C2Ct).

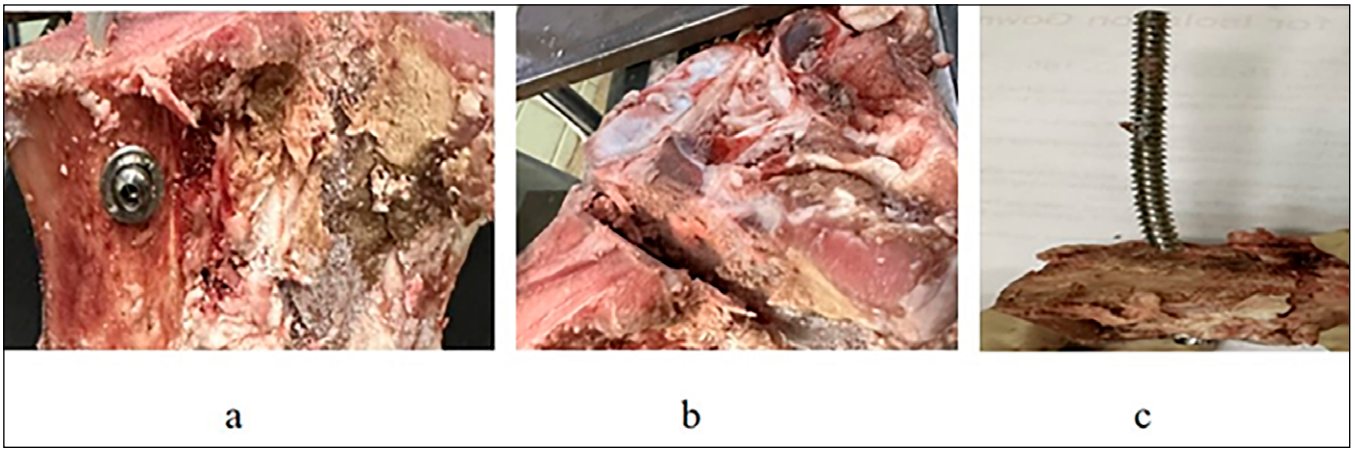

Fig. 9. Destruction of the connection, where: a – damaged sacroiliac joint, connected with a standard screw (C2Ct); b – visualized loss of stability under a load exceeding 900N; c – visible deformation of the screw.

To verify mathematical calculations and for a comparative characterization of the cancellous and countersink screws of our own design for stabilizing the sacroiliac joint, an anatomical-biomechanical experiment was conducted using native preparations of the sacroiliac joint. The anatomical-biomechanical study was carried out at the laboratory of the Department of Normal Anatomy of the Bogomolets National Medical University and the Research Center "Reliability" of the National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute" (Fig. 7).

CHARACTERISTICS OF JOINTS UNDER SHORT-TERM SINGLE LOADS

Based on the obtained data, deformation diagrams were constructed for cross section deformation of samples in the vertical direction N1 and N2 (undamaged joints), sample C1Cc (damaged sacroiliac joint, stabilized with countersink screw), and sample C2Ct (damaged sacroiliac joint, stabilized with a standard screw) (Fig. 8).

The loading automatically stopped when the maximum load decreased by the value of Δ2 (100N) or when the displacement/cross section h reached 1mm.

The analysis of the diagrams shows that the deformation of undamaged samples has an elastic character throughout the entire experiment interval. When loading the connection with the countersink screw, there is an initial short elastic deformation segment up to 200N over a length till a cross section of 1mm. A

When loading the connection with the standard screw, a plastic deformation segment is observed almost from the beginning at a small force (≈40N). Subsequently, elastic deformations are observed up to 900N, after which the connection fails, and the stabilizing structure deforms (Fig. 9).

Deformation diagrams in load ranges are not linear. Therefore, the elastic properties of both undamaged joints and joints with compromised integrity but stabilized by both types of screws in the specified force ranges can be characterized by stiffness coefficients C, N/mm (the ratio of the applied load Pmax to the deformation increase Δr) C = Pmax / Δr, where: Pmax – maximum load (N), measured from the deformation diagram; Δr – deformation (mm) corresponding to Pmax.

Quantities inversely proportional to stiffness characterize the flexibility of a system (its ability to deform under applied loads). The flexibility of the specimens was determined based on the calculated stiffness values (specific deformations, mm/N) as quantities inverse to stiffness, denoted as δ = 1/C. This parameter reflects the displacement magnitude resulting from loading the specimen with a force of 1 N. Elastic characteristics of the specimens were determined based on the constructed deformation diagrams (Table 2).

Table 3 presents summarized results of tests on undamaged objects and samples with modeled damage, stabilized by two types of screws. The table also includes data on the change in stiffness due to damage and stabilization by screws compared to undamaged preparations, calculated using the formula: $\psi_к = C^C/C^H$, where $C^c=1/\Delta^c$, $C^H=1/\Delta^H$, with indices "N" representing characteristics of undamaged preparations and indices "C" representing characteristics of preparations with damaged objects fixed by screws.

DISCUSSION

Despite a significant increase in the number of operative interventions for pelvic injuries, especially in combined trauma, the conservative method is used much more often (conservative in 70.4-89.2%; operative in 10.8-29.6%) [9]. However, the conservative method is only possible in patients with stable pelvic injuries. When applying the conservative treatment method for unstable pelvic injuries, unsatisfactory results are observed in 35-66.7%, and mortality is 2.5 times higher than with operative treatment – 21.8% and 8.3%, respectively [10].

The main factor contributing to lethal cases is massive bleeding, which occurs in 80-90% of cases with unstable fractures due to damage to presacral, retrosacral, and paravesical venous plexuses. Unstable pelvic injuries are also accompanied by damage to retroperitoneal muscles (iliopsoas, sciatic, and their fascia), leading to the so-called "chimney effect" – an increase in intrapelvic bleeding, which extends cranially and leads to the development of pelvic and abdominal compartment syndrome [11].

Experimental studies have shown that for every centimeter of diastasis in the symphysis pubis area, the pelvic volume increases by almost 5%, and in the sacroiliac joint area, it increases by 3%. A 5 cm diastasis increases the pelvic volume by up to 20%. All these data suggest the need for the fastest possible reduction of this volume mechanically to reduce blood loss and provide a tamponade effect [12].

The modern concept of treating individuals with unstable pelvic injuries in combined trauma within the first 48 hours requires urgent stabilization, mainly extrafocally, using external fixation devices, C-clamps, or a Hanzc frame, and if possible, performing percutaneous osteosynthesis. The latter type of surgical intervention is recommended when there are urgent indications related to pelvic or intraperitoneal organ injuries (bladder rupture, urethral injury), where bone fragments protrude into the wound, and fixation itself will not be traumatic and prolonged [13]

Stabilization of the pelvic ring in the initial emergency care stage using external fixation devices is the most commonly used method due to its relatively simple application technique [14]. However, in type "C" pelvic injuries involving a complete rupture of the sacroiliac ligaments, fractures of the posterior parts of the iliac bone, transforaminal sacral fractures with vertical displacement of the pelvic bones, fixation of only the ventral part of the pelvic ring does not provide stability to its dorsal part [15]. For the stabilization of the posterior pelvic complex, pelvic C-clamps or a Hanzc frame have become widely used in the early intensive care period [16].

Internal osteosynthesis for fractures of the pelvic bones in patients with combined trauma is implemented as a final stage in cases where life-saving surgeries are performed within or near the pelvis (using a single laparotomy approach). This approach is applied in open and closed multifragmentary fractures with significant displacement, dislocations, and disruption of pelvic organs [17].

Open surgical methods provide good results due to direct visualization and the ability to anatomically align the fractures. However, considering the specificity of this area, the complication rate reaches up to 27%. In addition to iatrogenic trauma to neurovascular plexuses, open osteosynthesis often leads to infectious complications, pelvic hematomas, and secondary hemorrhages. It is essential to consider the traumatic nature of these surgical interventions, which, against the backdrop of a patient's unstable condition, can lead to the so-called "second kick" [18].

Therefore, a large number of studies and implementations are currently being conducted regarding the stabilization of the sacroiliac joint, based on the principles of minimal invasiveness [19,20].

At the moment, there are several methods of internal fixation of the sacroiliac joint: transcutaneous sacroiliac screw, anterior plate, posterior sheath, minimally invasive adjustable plate, and other fixation systems. These methods have a number of advantages and disadvantages, but none of them practically differs in terms of fixation degree [21].

Transcutaneous screws have advantages and are widely

used due to minimal additional trauma, making them a promising direction in the treatment of patients with integrity issues in the sacroiliac joint area [22].

Based on their own research, Osterhoff et al. argue that pelvic stabilization using sacroilial screws is sufficient. However, the implementation of this method requires significant expertise and is associated with a high incidence of iatrogenic vascular and nerve injuries. Additionally, both patients and surgeons are exposed to substantial radiation during the performance of such surgical interventions [23].

To minimize complications, a variety of instrumental methods and navigation techniques have been proposed, ensuring visualization during the placement of the fixation screw [24].

Based on the analysis of the effectiveness of percutaneous fixation with sacroiliac screws for stabilizing the sacroiliac joint, it is considered that two screws represent the optimal method of fixation for this location, provided they traverse three cortical layers, and this is regarded as the technique of "central fixation" [25].

However, the frequency of sacral dysmorphism in adults is approximately 30-40%, and in this patient category, the "safe zone" for conducting fixation constructs is 36% smaller than usual [26]. Based on this, Griffin D.R. et al. believe that in such cases, it is challenging to place two sacral screws into the body of the first sacral vertebra. However, according to these same authors, the routine placement of a single screw is considered safe and sufficient for stabilizing the posterior pelvic half-ring [27].

Despite certain controversies in the options for minimally invasive synthesis of the sacroiliac joint, research results indicate their higher effectiveness (around 80%) compared to open synthesis [28]

CONCLUSIONS

1. Percutaneous stabilization of the sacroiliac joint is a minimally invasive fixation method widely used in patients with an unstable overall condition, characteristic of polysystemic and polyorgan injuries. Achieving a sufficient level of stabilization is crucial, making the development and implementation of constructions with optimal characteristics a relevant issue.
2. The results of anatomical-biomechanical research, comparing deformations of intact joints and joints with modeled damage, showed that the rigidity of the system fixed with a countersink-compression screw increases with the load and constitutes 67-68% of the rigidity of the undamaged joint. At all load levels, residual deformations in systems with C1Cc screws are significantly less than residual deformations in the system with C2Ct screws, indicating enhanced deformational reliability of fixation with countersink-compression screws.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Yuriy Sobolevskiy
Bogomolets National Medical University
13 blvd Tarasa Shevchenko, 01601 Kyiv, Ukraine
e-mail: soburik@icloud.com

ORCID AND CONTRIBUTIONSHIP

Yuriy Sobolevskiy: 0000-0002-8690-8620 B C E
Oleksandr Burianov: 0000-0002-2174-1882 A E F
Volodymyr Kvasha: 0000-0002-7444-6289 A D
Volodymyr Domin: 0000-0001-9036-0680 B C

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

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ORIGINAL ARTICLE

CONTENTS

The effect of succinic acid in liposomal emulsion on the humoral component of the immune system of rats

Yaroslav S. Stravskyy[1], Mariia I. Kulitska[1], Yaroslav O. Bilyk[1], Oksana M. Matolinets[2], Natalia V. Porokhovska[2], Oksana V. Sadlyak[2], Larisa Ya. Fedoniuk[1]

[1]I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

[2]LVIV NATIONAL MEDICAL UNIVERSITY NAMED AFTER DANYLO HALYTSKYI, LVIV, UKRAINE

ABSTRACT

Aim: To investigate the effect of succinic acid on the humoral component of the immune system in rats.

Materials and Methods: The study was conducted on two groups of mature non-linear white rats (males) of similar weight (200-270 g, aged 6-8 months), with 5 animals in each group. The control group was fed a standard diet with free access to water throughout the experiment. Rats in the experimental group were subcutaneously injected with a 0,1% solution of succinic acid in a liposomal emulsion at a dose of 20 cm^3 for five days. The state of the humoral component of the immune system was assessed by measuring serum immunoglobulins A, M, and G using solid-phase enzyme-linked immunosorbent assay. Circulating immune complexes were determined in a 40% solution of polyethylene glycol.

Results: Under the influence of succinic acid in liposomal emulsion the content of class A immunoglobulins increased by 44,0% ($p<0.01$) compared to rats in the control group. The activation of class A immunoglobulin synthesis points to the provision of local immunity of the mucous membranes in the rat's body. The content of class M immunoglobulins increased by 61,0% ($p<0.001$) compared to the control group rats. This high activity of class M immunoglobulins indicates their rapid activation in the body of rats in response to primary contact with succinic acid in liposomal emulsion. The content of class G immunoglobulins increased by 36,0% ($p<0.05$) compared to the control group rats. No clinical deviations from physiological norms were observed in the rats after the use of succinic acid in liposomal emulsion. After the use of succinic acid in liposomal emulsion in the experimental group of rats, the concentration of CICs increased by 15,0% ($p<0.05$) compared to the control group rats. In our case, the increase in CIC levels is not correlated with clinical manifestations but is a consequence of increased levels of class M and G immunoglobulins.

Conclusions: The succinic acid in liposomal emulsion activates the production of class A, M, G immunoglobulins, circulating immune complexes, it prevents the development of secondary immunodeficiency and has a positive impact on the humoral branch of the immune system in rats.

KEY WORDS: succinic acid, immune system, humoral immunity, rats, liposomal emulsion, immunoglobulins

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INTRODUCTION

The immune system serves to protect the body from various genetically foreign factors [1]. Humoral factors (interferons, interleukins, chemokines), as well as components of the immune system such as the complement system, lysozyme, and immunoglobulins, play a significant role in the immune response [2, 3].

Disruption of the innate or adaptive immunity components can lead to the development of immunodeficiency conditions [4, 5]. Primary immunodeficiencies are caused by congenital dysfunctions of the immune system, typically of genetic etiology, while secondary immunodeficiencies result from other factors, often of exogenous origin, leading to immune system exhaustion [6, 7].

Currently, there has been limited progress in the use of immunotropic drugs [8].

A significant portion of the pharmaceutical market is occupied by synthetic immunotropic drugs, which are often associated with numerous adverse side effects. An alternative to these is herbal-based medicines [9, 10].

In immunotherapy, herbal drugs and medications are used to stimulate the synthesis of interferons (e.g., Aloe arborescens, Kalanchoe pinnata), influence the complement system (e.g., basil, mountain arnica) [11], and increase lysozyme levels in the body (e.g., anise, eucalyptus) [12].

According to the State Register of Medicines in Ukraine, as of 2024, approximately 1,020 immunomodulatory drugs are registered under the L category according to the ATC classification, with 10% being domestic products and the remaining 90% being of foreign origin.

Succinic acid and its salts, or succinates, are important intermediates in metabolism, possessing protective properties for the body. Succinic acid is present in all living organisms in certain quantities as it is produced in the mitochondria [13].

Research data [14] indicates that succinic acid is harmless to the body and has several beneficial properties: it positively influences oxygen absorption by cells, exhibits anti-stress and adaptogenic effects, and more. It is known that succinic acid not only has detoxifying properties but also stimulates cellular respiration, enhances the body's resistance, and improves the absorption of nutrients due to its chelating properties [15].

Another important property of succinic acid is its ability to influence immune defense processes in infectious diseases [16, 17]. The immunostimulating properties of succinic acid form the basis of some medications. It should be noted that succinic acid is non-toxic to the body, does not accumulate, and can therefore be used over prolonged periods [18].

Medications based on succinic acid activate aerobic oxidation processes, have antioxidant and antihypoxic effects, and can reduce free radicals and restore cellular immunity [19]. Succinic acid-based medications have also been shown to be effective in the treatment and prevention of influenza, forming a stable immunity [20].

One of the modern approaches in medicine and pharmacy is the development of drug delivery systems that enhance the bioavailability and efficacy of therapeutic substances. One such approach is the creation of liposomal drugs [21].

There are few studies on the effect of succinic acid on the humoral component of the immune system in rats, making the development and search for effective prevention schemes of immunodeficiency conditions relevant.

AIM

To investigate the effect of succinic acid on the humoral component of the immune system in rats.

MATERIALS AND METHODS

In the first stage of the study, a liposomal emulsion with succinic acid was prepared using an ultrasonic disperser УЗДН-А at a working frequency of 22 kHz at the Ternopil Research Station of the National Academy of Agrarian Sciences of Ukraine. To enhance the strength of the liposomal emulsion membranes, up to 40% cholesterol was added to the initial lipid mixture. The internal aqueous volume of the liposomes contained a 0.1% solution of succinic acid [22].

In the second stage, the effect of succinic acid in the liposomal emulsion on the humoral component of the immune system in rats was studied.

The study was conducted on two groups of mature non-linear white rats (males) of similar weight (200-270 g, aged 6-8 months), with 5 animals in each group. The rats were kept under identical conditions at the vivarium of I. Horbachevsky Ternopil National Medical University. The control group (Group I) was fed a standard diet with free access to water throughout the experiment. Rats in the experimental group (Group II) were subcutaneously injected with a 0,

1% solution of succinic acid in a liposomal emulsion at a dose of 20 cm^3 for five days.

Clinical research was conducted using a typical parallel group model. Rats were randomly selected for the groups to achieve statistically significant results.

On the fourth day after the last injection of succinic acid in the liposomal emulsion, the rats were decapitated under thiopental anesthesia. Blood was collected aseptically into two test tubes: one with heparin for morphological studies and another without heparin for biochemical studies.

The state of the humoral component of the immune system was assessed by measuring serum immunoglobulins A, M, and G using solid-phase enzyme-linked immunosorbent assay (ELISA) with an "eBioscience Inc." reagent kit and a "StatFax" analyzer [23]. Circulating immune complexes were determined in a 40% solution of polyethylene glycol [24].

The care of rats and all experiments involving animals were conducted in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 2005) and the Law of Ukraine "On the Protection of Animals from Cruelty".

Statistical processing of the study results was performed using Microsoft Excel 2003. The significance was assessed using Student's t-test, and the results were considered statistically significant at $p \leq 0.05$, $p \leq 0.01$, and $p \leq 0.001$.

RESULTS

To determine the effect of succinic acid in liposomal emulsion on the state of the humoral link of the immune system of rats, the content of immunoglobulins A, M, G, and CIC in the blood of rats before and after the use of the drug was investigated.

The obtained data indicate that under the influence of succinic acid in liposomal emulsion the content of class A immunoglobulins increased by 44,0% ($p<0.01$) compared to rats in the control group (Table 1). The obtained data

Table 1. The content of immunoglobulins A, M, G and CICs in the blood of rats after the use of succinic acid in a liposomal emulsion (M±m, n = 5)

Groups	Indicators			
	Immunoglobulins, A, g/l	Immunoglobulins, M, g/l	Immunoglobulins, G, g/l	Circulating immune complexes, con. un.
Control	0,36 ±0,02	0,90 ± 0,06	2,24 ± 0,07	32,50 ± 1,45
Experiment	0,52 ± 0,06**	1,45 ± 0,09***	3,04 ± 0,05*	37,52 ± 1,53*

Note. * – $p < 0,05$; ** – $p < 0,01$; *** – $p < 0,001$ compare with control group.

give grounds for asserting that under the influence of succinic acid in liposomal emulsion there is activation of plasma cells located under the mucous membranes, which facilitated the production of class A immunoglobulins. The activation of class A immunoglobulin synthesis under the influence of succinic acid points to the provision of local immunity of the mucous membranes in the rat's body, as serum immunoglobulin class A protects the respiratory, urinary tracts, and gastrointestinal tract from various infections. These antibodies prevent bacteria from attaching to epithelial cells, thus inhibiting their adhesion and preventing bacterial damage to cells. Consequently, succinic acid in liposomal emulsion, along with nonspecific immune factors, ensures the protection of mucous membranes from viruses and microorganisms. Thus, succinic acid in liposomal emulsion has a positive effect on the formation of immunity in mucosa in rats.

From the data presented in Table 1, it can be seen that after the application of succinic acid in liposomal emulsion in the experimental group of rats, the content of class M immunoglobulins increased by 61,0% ($p<0.001$) compared to the control group rats. This high activity of class M immunoglobulins indicates their rapid activation in the body of rats in response to primary contact with succinic acid in liposomal emulsion.

Given that class M immunoglobulin is part of the antigen-specific receptor of B-lymphocytes, and IgM is found in monomer form on the cell membrane with an additional hydrophobic domain, succinic acid in liposomal emulsion promoted the activation of B-lymphocytes that secrete pentameric IgM, later switching to IgG or other immunoglobulin classes. IgM is the first barrier against infection. Although it has low specificity (affinity) for antigens, its pentameric structure allows it to bind five antigen molecules simultaneously, resulting in high avidity binding. Furthermore, due to its oligomeric nature, IgM easily causes the agglutination of microbial cells, aiding their destruction by macrophages.

Therefore, it can be assumed that succinic acid in liposomal emulsion activates the production of class M immunoglobulins, prevents the development of secondary (acquired) immunodeficiency, and has a positive impact on the humoral branch of the immune system in rats.

The data in Table 1 also show that after the application of succinic acid in liposomal emulsion in the experimental group of rats, the content of class G immunoglobulins increased by 36,0% ($p<0.05$) compared to the control group rats. No clinical deviations from physiological norms were observed in the rats after the use of succinic acid in liposomal emulsion. Therefore, the increase in the content of class G immunoglobulins in the rats' bodies after using succinic acid in liposomal emulsion indicates the induction of antibody-dependent cell-mediated cytotoxicity and the formation of long-term humoral immunity.

Circulating immune complexes (CICs) form as a result of the immune response to foreign antigens. The immune system reacts to antigens that enter from outside (during viral, bacterial, parasitic infections, etc.), as well as to autoantigens formed during physiological or pathological processes in the body. These complexes are usually quickly removed by the phagocytic system. The mechanisms of their elimination are linked to a complex of cellular, biochemical, and enzymatic mechanisms, including the activation of the complement system.

After the use of succinic acid in liposomal emulsion in the experimental group of rats, the concentration of CICs increased by 15,0% ($p<0.05$) compared to the control group rats. In our case, the increase in CIC levels is not correlated with clinical manifestations but is a consequence of increased levels of class M and G immunoglobulins.

DISCUSSION

Blood tests are an important diagnostic method, a way to control treatment effectiveness, and a marker of recovery. Biochemical blood analysis allows for an assessment of the functioning of internal organs and systems. Some biochemical blood parameters are markers that determine the magnitude of the inflammatory process.

Immunity is one of the elements of homeostasis in the body. The immune system ensures immune responses that contribute to the preservation of genetic homeostasis.

After the application of succinic acid in liposomal emulsion in the experimental group of rats, the con-

tent of class A immunoglobulins increased by 44,0% ($p<0.01$) compared to the control group rats. The obtained data allow us to state that under the influence of succinic acid in liposomal emulsion, there was an activation of plasma cells in the rats' bodies aimed at producing class A immunoglobulins, which ensure the local protection of mucous membranes.

Thus, succinic acid in liposomal emulsion positively affects the formation of immunity in the mucous membranes of rats. Our data supplement research [6], which reports that succinic acid prevents the loss of IgA neutralizing activity during the massive entry of antigens, including superantigens, through the mucous membranes, and reports [15] regarding increased resistance of the body due to succinic acid exposure.

Up to 10,0% of the total amount of immunoglobulins is accounted for by class M immunoglobulins. These immunoglobulins are effective in agglutination and opsonization reactions and bind complement well. After the application of succinic acid in liposomal emulsion in the experimental group of rats, the content of class M immunoglobulins increased by 61,0% ($p<0.001$) compared to the control group rats.

This high activity of class M immunoglobulins indicates their rapid activation in the rats' bodies in response to the primary contact with succinic acid in liposomal emulsion. Therefore, it can be assumed that succinic acid in liposomal emulsion activates the production of class M immunoglobulins, prevents the development of secondary (acquired) immunodeficiency, and has a positive effect on the humoral branch of the immune system in rats. This expands upon reports [6] that reduced immune insufficiency underlies immunodeficiency and that the use of succinic acid in liposomal emulsion positively affects the body's metabolic processes, complementing reports [16] on its use as a regulator of metabolic processes.

From 70,0 % to 85,0 % of the total amount of immunoglobulins is accounted for by class G immunoglobulins. It should be noted that these immunoglobulins are found in the body's tissue fluids, and during the immune response, they appear in the serum following class M immunoglobulins.

After the application of succinic acid in liposomal emulsion in the experimental group of rats, the content of class G immunoglobulins increased by 36,0% ($p<0.05$) compared to the control group rats. No clinical deviations from physiological norms were observed in the rats after using succinic acid in liposomal emulsion. Therefore, the increase in the content of class G immunoglobulins in the rats' bodies after using succinic acid in liposomal emulsion indicates the formation of long-term humoral immunity. Our data expand on reports [8] about the immunomodulatory properties of succinic acid.

Circulating immune complexes form in response to foreign antigens. The immune system reacts to antigens that come from outside (during viral, bacterial, parasitic infections, etc.), as well as to autoantigens formed during physiological or pathological processes.

After the application of succinic acid in liposomal emulsion in the experimental group of rats, the concentration of circulating immune complexes increased by 15,0% ($p<0.05$) compared to the control group rats.

The increase in CIC concentration by 15,0% is a result of decreased tolerance to autoantigens and impaired elimination processes. Succinic acid in liposomal emulsion dissolves and circulates in the rats' bloodstream, leading to its slight accumulation on the membranes of small vessels and tissues, which subsequently causes an increase in the concentration of circulating immune complexes. The elevated CIC level is not specific to any particular disease and does not indicate immune complex pathology or tissue damage.

CONCLUSIONS

Succinic acid in liposomal emulsion positively influences the humoral branch of the immune system in rats, as evidenced by the increase in immunoglobulin class A by 44,0% ($p<0.01$), immunoglobulin class M by 61,0% ($p<0.001$), immunoglobulin class G by 36,0% ($p<0.05$), and circulating immune complexes by 15,0% ($p<0.05$).

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Larisa Ya. Fedoniuk
I. Horbachevsky Ternopil National Medical University
9 Valova St., 46000 Ternopil, Ukraine
e-mail: Fedonyuk22Larisa@gmail.com

ORCID AND CONTRIBUTIONSHIP
Yaroslav S. Stravskyy: 0000-0001-6541-9097 A E F
Mariia I. Kulitska: 0000-0001-7116-6655 B C
Yaroslav O. Bilyk: 0000-0001-8971-1420 B C
Oksana M. Matolinets: 0009-0008-6521-8867 B C
Natalia V. Porokhovska: 0000-0001-5221-8544 C D
Oksana V. Sadlyak: 0000-0002-2654-2217 C D
Larisa Ya. Fedoniuk: 0000-0003-4910-6888 A B E F

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

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ORIGINAL ARTICLE

CONTENTS

Immunohistochemical evaluation of SOX-10 in patients with urinary bladder cancer

Randa Saad Hameed[1], Ghufran Salman Abd Alhussain[1], Rihab Hameed Almudhafar[2], Liwaa Hussein Mahdi[2]
[1]DEPARTMENT OF BASIC SCIENCES, COLLEGE OF DENTISTRY, UNIVERSITY OF KUFA, KUFA, IRAQ
[2]DEPARTMENT OF GENERAL PATHOLOGY AND FORENSIC MEDICINE, COLLEGE OF MEDICINE, UNIVERSITY OF KUFA, KUFA, IRAQ

ABSTRACT

Aim: To evaluate the expression levels of SOX-10 in tissues of bladder tumor and to prove the correlation between SOX-10 expression and clinicopathological characteristics of bladder tumors, including patient age, sex, tumor grade, and muscle invasion.

Materials and Methods: Forty formalin fixed paraffin embedded FFPE tissue blocks gathered by transurethral resection of bladder tumor are collected from teaching hospitals at Al-Najaf governorate. Those blocks were stained by hematoxylin and eosin. The histopathological characteristics were examined and immunostained by SOX10.

Results: An assessment of the expression of SOX-10 in urothelial carcinoma showed that the SOX-10 test was positive in five samples of urothelial carcinoma, while the SOX-10 test was negative in thirty-five samples. The correlation of SOX-10 with other variables (age, sex, and grade) was statistically non-significant.

Conclusions: SOX-10 is an immunohistochemical sensitive marker for the diagnosis of urothelial carcinoma. SOX-10 expression appeared to be non-significant relation with age, gender and histopathological parameters and its expression has been showed to be lost or decreased in substantial proportion in relation to urothelial carcinoma. This variation or down regulation of SOX-10 is correlated with higher tumor grade and stage.

KEY WORDS: urothelial carcinoma, SOX-10, immunohistochemistry

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INTRODUCTION

Bladder carcinoma (BC) is the most frequently malignant tumor of urological field in world [1]. Transitional cell carcinoma (TCC) is the commonest kind and reports about 90% of cancers bladder [2]. Despite aggravating factors like smoking and obesity was determined for long time, the underlying causes of bladder cancer formation and development still unknown [3, 4]. Although an advancement of techniques of surgical and chemotherapy in the treatment of bladder cancer, the end results of therapy (for invasive and superficial bladder cancer) still substandard. Proof demonstrates that the formation bladder cancer is multistep mechanism which involves initiation, promotion and progression [5]. In spite of carcinoma of urothelium (UC) may be affect many areas of the urinary tract, more frequently occurs in the urinary bladder. Bladder cancer is sometimes determined in older age patients (more than 50) [6]. Hematuria (blood in urine) is the commonest symptom [7]. Nearly ninety percent of cancers of bladder are carcinomas of urothelium originated from the tissue of urothelium [8]. Urothelial carcinomas (non–invasive) occupy the most of primary bladder tumors and are divided depend on their structure as flat and papillary lesions [9]. On the other hand, seventy-five percent of carcinomas (invasive) are non-muscle invasive of bladder cancers and twenty-five percent of carcinomas are muscle invasive of bladder cancers [10]. Superficial type of bladder cancers may found in the mucosal layer, invaded to the lamina propria layer, or carcinoma in situ (noninvasive). The muscularis propria was recorded like a progressed cancer [11-13]. During the time of treatment of urothelial carcinoma, the tumor grade and stage are very important step. Meanwhile low grade tumors progression is uncommon, on other hand, progression and recurrence of high grade tumors are more frequent [14]. Bladder cancers grading and staging must be properly determined for the type of treatment to be used. It is critical for deciding the follow-up of the disease [15]. SOX-10 sex determining region is a type of SOX family, that is a group of translation factors coding a high-mobility group (HMG) domain that are joined to the factor of determination of testis [15]. Firstly, SOX-10 is known depend on its important

function in crest cells differentiation of neuron [16, 17]. Mutations in SOX-10 gene of human are joined with the appearance of neurocristo pathies of Warrensburg Shah Syndrome and patients show hypopigmentation, cochlear neurosensory deafness and enteric aganglionosis [18, 19]. Newly, SOX-10 was proved to be included in the genesis and development of many cancers [20, 21]. However, in digestive cancers SOX10 act a tumor suppressor and work against the signaling pathway of WNT/β-catenin [22]. We are well aware that SOX-10 is more appeared in bladder cancer tissues and cells, and its appearance is connected to the clinical and pathological features of bladder cancer patients. Besides, SOX-10 was played an important role in the bladder cancer cells growth, migration and invasion that connects with tumor genesis, infiltration and metastasis of bladder cancer [23]. SOX-10 is joined with salivary gland tumors, breast, nasopharyngeal, ovarian and prostate cancers growth and progression. SOX-10 high expression represents an oncogene for stimulating the signal pathway of WNT/β-catenin in hepatocellular carcinoma, and represents a tumor suppressor for suppressing the signal pathway of WNT/β-catenin in cancers digestive system [24-26].

AIM

To evaluate the expression levels of SOX-10 in tissues of bladder tumor and to prove the correlation between SOX-10 expression and clinic-pathological characteristics of bladder tumors, including patient age, sex, tumor grade, and muscle invasion.

MATERIALS AND METHODS

The cross-sectional study of 40 samples of Iraqi patients with urothelial carcinoma was performed at faculty of medicine of University of Kufa (middle Euphrates unit for cancer research). Formalin fixed paraffin embedded tissue blocks (FFPE) gathered by transurethral resection of bladder tumor are collected from teaching hospitals at Al-Najaf governorate, and the diagnosis of urothelial carcinoma performed by histopathologist. Those blocks were stained by hematoxylin and eosin (Fig.1). The processing of immunohistochemistry (IHC) was done using positive charge coated slides. IHC staining protocol by labeled streptavidin biotin (LSAB) method was performed after de-paraffinization, heat induced antigen retrieval for 20 minutes, then blocking with peroxidase enzyme for 5 minutes, followed by primary antibody SOX-10 (Bio SB, clone: EP268). After incubation with primary antibody, the secondary antibody was added for 30 minutes followed by horse reddish peroxidase (HRP) for 30 minutes, and chromogen for 15 minutes. Each step washed twice with buffered solution. Finally, counter staining and mounting. The reactivity of SOX-10 was considered as positive when there was nuclear staining.

SCORING

Depending on the intensity of staining and the percentage of positivity, immunohistochemical evaluation of slides stained with SOX-10 was scored. An intensity score was assessed as 0 (no stain), score 1 (light stain), score 2 (moderate stain) score 3 (strong stain) divided by score percentage, both scores will be recorded apart between the groups.

STATISTICAL ANALYSIS

Statistical methods employed to assess the correlation between SOX-10 expression and clinicopathological features of urothelial carcinoma, like age, sex, histological grade, and muscle invasion was chi-square test. SPSS version 26 was used for the calculation. P-value equal to 0.05 or less was regarded as statistically significant.

RESULTS

Samples of urothelial carcinoma in this study were forty FFPE tissue blocks. The age categories of patients were over 67 (50%) and less than 67 (50%). The microscopic study of these samples was made by using SOX-10 tumor marker test. SOX-10 test was positive in five samples of urothelial carcinoma (Fig.2), while SOX-10 test was negative in thirty-five samples of urothelial carcinoma (Fig.3-5). There was male predominance 77.5%; details of subject and their numbers were shown in the following (Table 1, Table 2).

Table 1 shows that the age category was less than 67 by about 50% and more than 67 by about 50%. The majority of sex group was at the male categories by about 77.5% more than females 22.5%.

Table 2 shows that most cases were positive for SOX-10 among patients suffering from urothelial carcinoma. Regarding to age, sex, grade, muscle invasion categories, SOX-10 was positive in age less than 67 by about 15%% (p value=0.9), positive in male by about 16.1% more than female (p value=0.6), positive in low grade by about 18.2% more than in high grade by about 5.6% (p value=0.4), and positive in the absence of muscle invasion by about 14.8% (p value=0.9).

DISCUSSION

Our study was completed at University of Kufa, faculty of medicine (Iraq, middle Euphrates unit for cancer research) to prove the relation between SOX-10 and urothelial carcinoma. In the present study, there was a high negativity of SOX-10 at age categories less than 67 years about 90 %, with

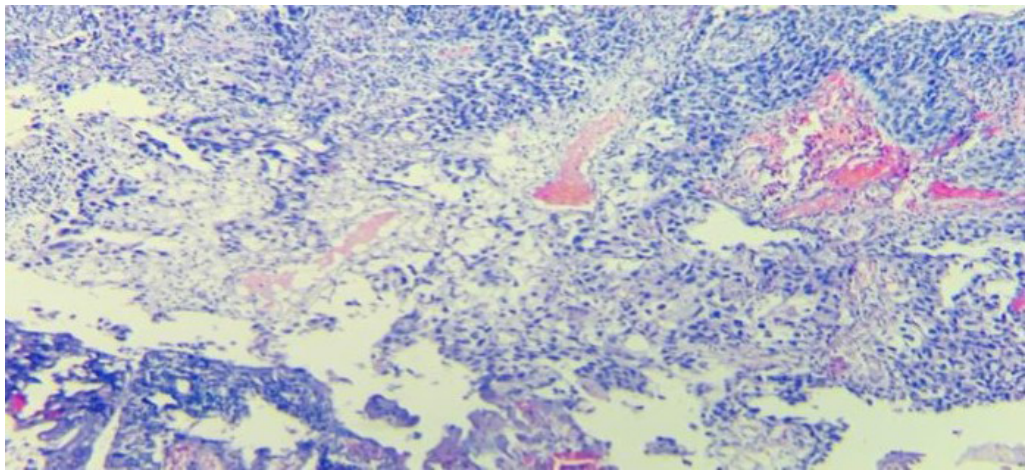

Fig. 1. Transurethral resection, high grade urothelial carcinoma, H&E. Magnification power X100.

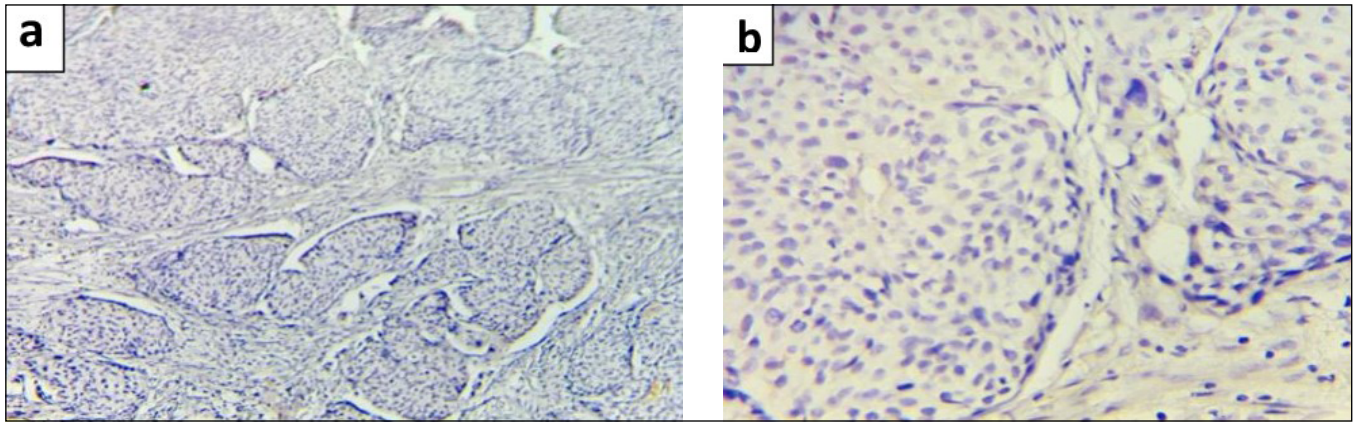

Fig. 2. Transurethral resection, low grade urothelial carcinoma, immunohistochemical positive for SOX-10. Magnification power (a) X100, (b) X400.

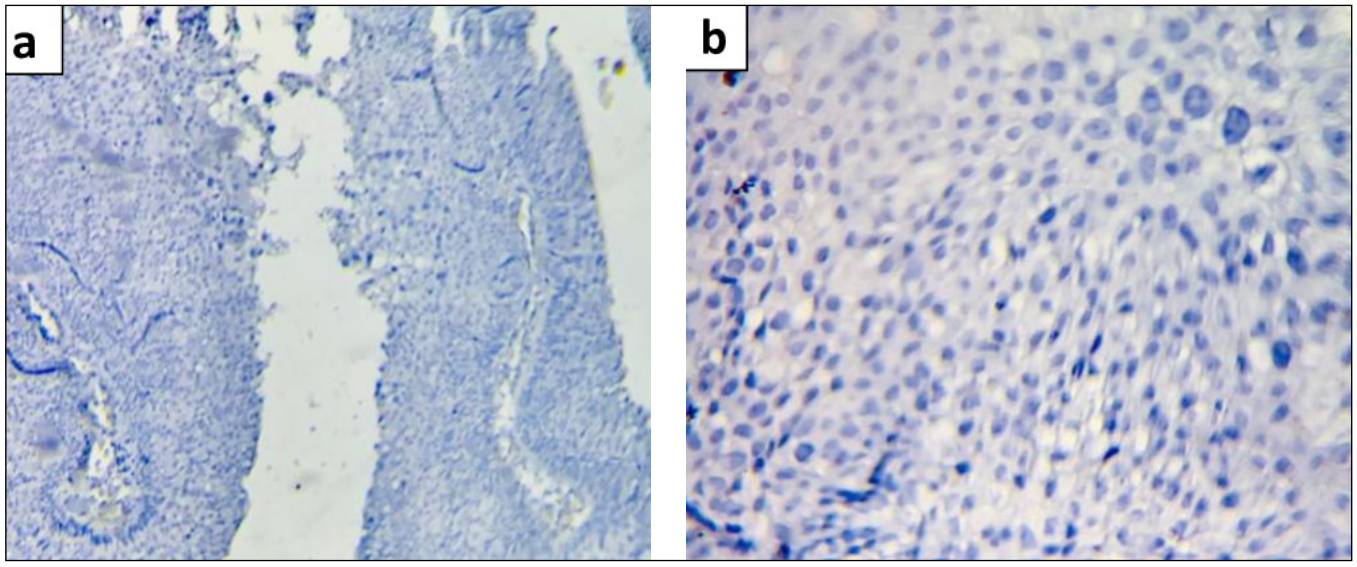

Fig. 3. Transurethral resection, high grade invasive urothelial carcinoma, immunohistochemical negative for SOX-10. Magnification power (a) X100, (b) X400.

male was less than female – 83.9 % to 100% and positive in low grade urothelial tumor 4/22 cases, 18.2% in comparison with high grade expression 1/22 case, 5.6% with no significant difference, which comparable with study made by *Selcen I et al.* [24], who proved low expression of SOX-10 (19 out of 50; 38%) of bladder tumor. According to grade and muscle invasion, there was no statistically significant relation of SOX-10 expression with grade of urothelial tumor (p-value equal to 0.4), muscle invasion (p-value equal to 0.9), and those results disagree with other study performed by

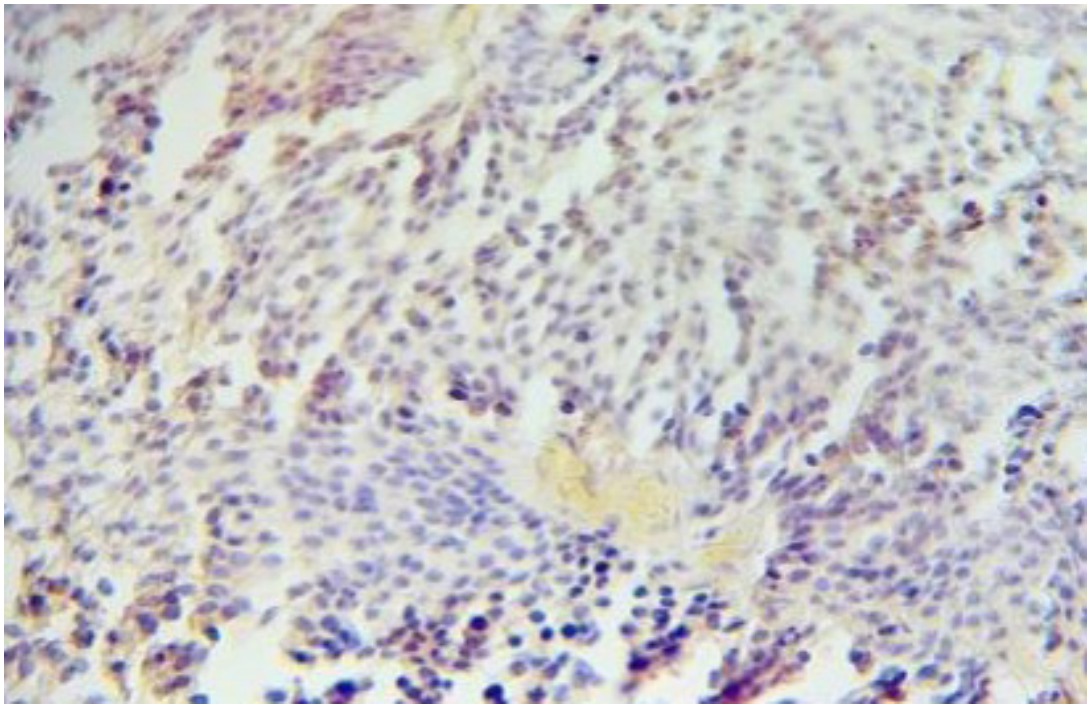

Fig. 4. Transurethral resection, low grade urothelial carcinoma, immunohistochemical negative for SOX-10. Magnification power (a) X100, (b) X400.

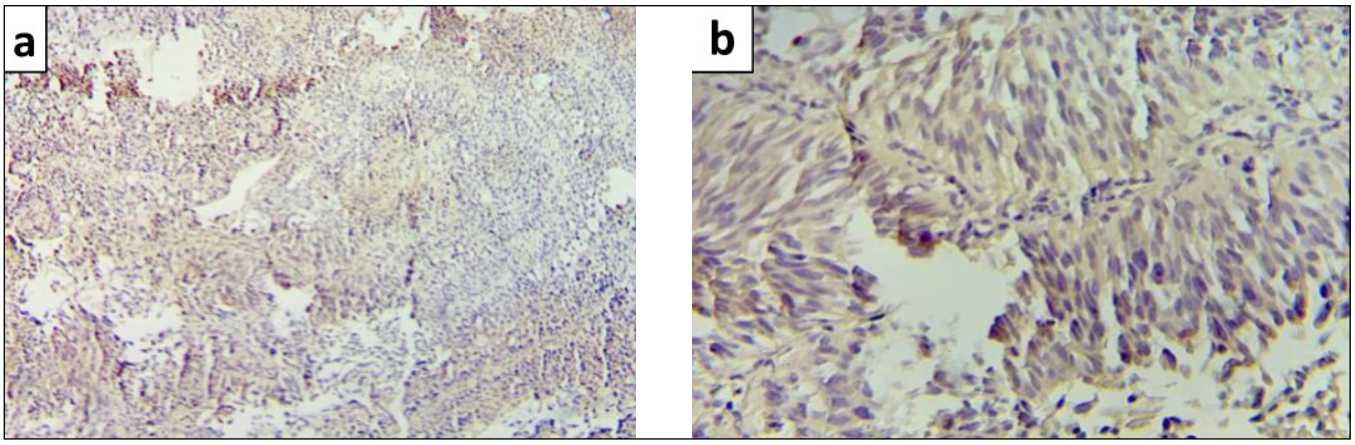

Fig. 5. Transurethral resection, low grade urothelial carcinoma, immunohistochemical negative for SOX-10. Magnification power (a) X100, (b) X400.

Table 1. Clinical and demographic features of studied groups

Variable	Subgroup	No.	%
Age group	less than 67	20	50
	67+	20	50
Sex	Male	31	77.5
	Female	9	22.5
Grade	Low	22	55
	High	18	45
Muscle invasion	Present	13	32.5
	Absent	27	67.5

Yin H et al. [25] who proved a statistic significant relation between SOX-10 appearance and the tumor grade with SOX-10 expression in low grade cases was 33.3% and in high grade cases was 64.2%. Although *Li C et al.*[26] detected that there was no SOX-10 staining in tumor bladder groups, our study showed positive SOX-10 expression in 15% of cases. In addition, our study showed disapproval with that performed by Yin et al [27] who showed over-expression of SOX-10 in high grade cases (40/45) and in low grade cases (27/45) with level of p-value = 0.002.

Table 2. Relationship among studied groups according to immunohistochemistry of SOX-10

		SOX 10		Total	P
		Positive (n=5) No.(%)	Negative (n=35) No.(%)		
Age group	< 67	3(15%)	17(85%)	20(100%)	0.9
	67+	2(10%)	18(90%)	20(100%)	
Sex	Male	5(16.1%)	26(83.9%)	31(100%)	0.6
	Female	0(0%)	9(100%)	9(100%)	
Grade	Low	4(18.2%)18	(81.8%)	22(100%)	0.4
	High	1(5.6%)	17(94.4%)	18(100%)	
Muscle invasion	Present	1(7.7%)	12(92.3%)	13(100%)	0.9
	Absent	4(14.8%)	23(85.2%)	27(100%)	

CONCLUSIONS

SOX-10 is an immunohistochemically sensitive marker for the diagnosis of urothelial carcinoma. SOX-10 expression appears to have a non-significant relationship with age, gender, and histopathological parameters, and its expression has been shown to be lost or decreased in a substantial proportion of cases in relation to urothelial carcinoma. This variation or downregulation of SOX-10 correlates with higher tumor grade and stage. Our study confirmed a reduced SOX-10 expression in urothelial carcinoma. In addition, low SOX-10 levels in bladder cancer can inhibit cells proliferation, migration and invasion while over expression of SOX-10 promotes the progression of bladder cancer. This explained the role of SOX-10 as transcription factor in the nuclei that suppress or activate the target genes.

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The study was approved by medical committee of ethics at University of Kufa, faculty of medicine (MEC-93). Verbal consent was taken from all patients.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Randa Saad Hameed
University of Kufa
299G+HPX, Kufa Street, Kufa, Najaf Governorate, Iraq
e-mail: randas.albattawi@uokufa.edu.iq

ORCID AND CONTRIBUTIONSHIP

Randa Saad Hameed: 0009-0000-5281-8857 B C D
Ghufran Salman Abd Alhussain: 0000-0002-2310-2419 C D E
Rihab Hameed Almudhafar: A0000-0003-4997-5549 C
Liwaa Hussein Mahdi: 0000-0001-8161-5354 A F

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

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ORIGINAL ARTICLE

CONTENTS

Comprehensive assessment of caries resistance in 6 -7 year-old children residing in Poltava and internally displaced children

Olha Sheshukova, Anna S. Mosiienko, Tetiana V. Polishchuk, Alina I. Maksymenko, Alla V. Marchenko, Sofia S. Bauman, Nataliia M. Lokhmatova
POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

Aim: The aim of this study is to assess caries resistance in children from Poltava and internally displaced children from frontline regions by analyzing caries indicators and oral fluid properties. This will help evaluate the impact of war and displacement on their dental health.

Materials and Methods: This study was conducted at the City Children Dental Clinic in Poltava and included 330 children aged 6-7 years, of whom 56.7% were boys and 43.3% were girls. Among them, 230 children were internally displaced persons (Group I), and 100 were permanent residents of Poltava (Group II).

Results: The analysis of caries prevalence and intensity showed a significant difference between the groups. In Group I, the prevalence of caries was 77.8%, and the intensity of the dmft+DMFT index was 3.31±0.2, which is significantly higher than in Group II (66% and 1.91±0.2; $p<0.05$). Indicators of oral fluid homeostasis were also worse in internally displaced children; pH was 13% lower, and the salivary flow rate was 1.3 times lower than in Group II children ($p<0.05$).

Conclusions: The study revealed a higher prevalence of caries among internally displaced children (77.8%) compared to children from Poltava (66%). Internally displaced children showed higher caries rates and lower caries resistance. These findings highlight the urgent need for preventive programs to improve the dental health of internally displaced children.

KEY WORDS: children, dental caries, oral fluid, enamel resistance, microcrystallization, war time

Wiad Lek. 2024;77(12):2487-2492. doi: 10.36740/WLek/197114 DOI

INTRODUCTION

In the context of the ongoing armed conflict in Ukraine, which began in 2014, the number of internally displaced persons (IDPs), including children, has significantly increased. According to the Ministry of Social Policy, as of 2024, there are over 4.9 million IDPs in Ukraine. Of these, nearly 21% (approximately 997,000) are children under the age of 18. This poses an urgent need for society to thoroughly study the dental health of this vulnerable group [1, 2, 3].

The conflict in Ukraine also has serious global environmental consequences, which negatively impact health and food security. The chaos and fear resulting from hostilities are accompanied by intimidation, leading to increased violence and depression among the civilian population. These actions of the aggressor country aim at weakening the will of the people and diminishing their resistance, particularly among vulnerable groups such as women, children, and the elderly people, who endure both physical and psychological suffering [4, 5].

War and forced displacement significantly affect children's health, particularly due to limited access to healthcare and worsening living conditions. Concerns are growing regarding the dental health of children from frontline regions and those who are internally displaced [6]. Epidemiological studies have shown an increased prevalence of dental caries among children who have experienced stressful situations, including those related to warfare [7].

Oral fluid is known to play a crucial role in preserving the integrity of dental hard tissues, maintaining enamel homeostasis and microcrystallization processes under the influence of external factors [8]. Preliminary studies suggest a deterioration in the properties of oral fluid among these children, potentially leading to impaired tooth mineralization due to constant stress and environmental changes. Investigating the properties of oral fluid and its mineralizing potential remains an important tool for assessing the dental health of children in crisis situations.

AIM

The aim of this study was to assess dental enamel resistance to caries through a comprehensive analysis of

caries indicators and oral fluid properties in children from Poltava, including both local children and internally displaced children (IDC) from frontline regions.

The study hypothesizes that internally displaced children (IDC) from frontline zones demonstrate poorer dental health indicators compared to local children residing in Poltava.

MATERIALS AND METHODS

This cohort study was conducted at the City Children Dental Clinic in Poltava. The study included 330 children aged 6–7 years who visited the clinic for dental care or preventive examinations. Inclusion criteria were: age 6–7 years, absence of chronic somatic pathologies, and specified place of residence. Two groups were formed: Group I (IDC) consisted of 230 internally displaced children who had been residing in Poltava for six months at the time of examination (from February 2022 to August 2022), and Group II included 100 children who were permanent residents of Poltava. Among the participants, 56.7% were boys and 43.3% were girls.

Dental status was assessed by evaluating the intensity of caries using the dmft, dmft+DMFT, and DMFT indices; the prevalence of caries was determined by the percentage of children having at least one decayed, missing or filled tooth; oral hygiene was assessed using the Fedorov-Volodkina Index (1971); the degree of gingivitis was evaluated with the papillary-marginal index (PMI) in Parma modification (1960). Enamel resistance was assessed using the TER test (V.R. Okushko, L.I. Kosareva, 1983); the crystal-forming function of mixed saliva was measured using P.A. Leus's method (1977). The rate of unstimulated saliva flow was calculated using the formula Rs = V/T (ml/min), where V represents the volume of saliva (ml), and T is the collection time (min). The hydrogen ion concentration (pH) of the oral fluid was determined using standard test strips (SPOFA, Czech Republic).

The normality of the data distribution was assessed using the Shapiro Wilkinson test. Statistical analysis of the findings obtained was performed using SPSS software, applying parametric methods. The arithmetic mean (M) and standard error of the mean (m) were calculated, and Student's t-test was used to compare the variables.

The study adhered to the key provisions of GSP (1996), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (2013-2014), and the Ethical Code of Scientists of Ukraine (2009). These ethical standards were confirmed by the protocol of the Bioethics Committee of Poltava State Medical University (No. 231) for data collection and processing of information about children.

RESULTS

The survey was conducted on a sample of children divided into two groups based on their place of residence: Group I involved 230 internally displaced children who previously lived in frontline areas, with an average age of 6.47±0.03 years; Group II included 100 children permanently residing in Poltava, with an average age of 6.53±0.05 years (Table 1). According to the analysis, the majority of children were previously residents of the Kharkiv (59.6%), Donetsk (30%), Luhansk (7.4%), and Zaporizhzhia (3%) regions.

The analysis of caries prevalence and intensity revealed a significant difference between the groups (Table 2). In children of Group I, the average caries prevalence was 77.8%, representing 179 children with carious lesions. In Group II, the prevalence was slightly lower and approached to 66%. Correspondingly, a higher caries intensity, measured by the dmft+DMFT index, was observed in Group I, with a value of 3.31±0.2, which is more than 1.5 times higher than in Group II (1.91±0.2; $p<0.05$). A similar trend was noted for the intensity of caries in primary teeth: in Group I, the value was 3.12±0.19, while in Group II, it was 1.72±0.18 ($p<0.05$).

Regarding permanent teeth, the prevalence and intensity of caries were similar in both groups. The prevalence of caries according to the DMFT index was 10% in Group I and 11% in Group II. The intensity of caries in permanent teeth did not show significant differences between the two groups ($p>0.05$).

The state of oral hygiene in internally displaced children (Group I) was 1.52±0.03, while in children living in Poltava (Group II), this indicator was 1.42±0.02, and both were assessed as good.

We observed reduced enamel resistance in internally displaced children, with the enamel resistance test in Group I exceeding that of Group II by 1.6 times (4.23±0.18 and 2.64±0.12, $p<0.05$) (Table 3).

When analyzing the indicators of oral fluid homeostasis, a decline was found in the IDP children (Table IV). The hydrogen index (pH) of oral fluid was lower than normal in both groups, but Group I children had the lowest value, at 5.6±0.04. The salivary flow rate in Group I was 0.29±0.004 ml/min, which is 1.3 times lower than in Group II (0.4±0.01 ml/min, $p<0.05$).

The analysis of crystal-forming characteristics of oral fluid showed that the mean value of microcrystallisation types in the Group I was higher and amounted to 2.5±0.04 compared to 2.02±0.07 in children of Group II ($p<0.05$).

In the distribution of oral fluid microcrystallization (MCS) types, it was found that type I MCS was most prevalent among children in Group II, observed in 25% of the subjects, while in Group I, this type was less frequent, at 12.2% (Fig. 1). Type II MCS was detected in 51%

Table I. Age characteristics of the examined children (age, M±m)

Groups	N	Age	Sex			
			Boys		Girls	
			N	%	n	%
I	230	6,47±0,03	137	59,6	93	40,4
II	100	6,53±0,05	50	50	50	50

Table II. Caries indicators in the examined children

Groups	Prevalence, absolute number/(%)			Intensity, (M±m)		
	dmft	dmft+DMFT	DMFT	dmft	dmft+DMFT	DMFT
I	179/77,8	179/77,8	23/10	3,12±0,19	3,31±0,21	0,19±0,04
II	66/66	66/66	11/11	1,72±0,18	1,91±0,21	0,19±0,06
				p<0,05	p<0,05	p>0,05

Table III. State of oral hygiene (points), periodontal inflammation (%), and enamel resistance (points), M±m

Groups	Gingival index, points	PMA,%	Enamel resistance test, points
I	1,52±0,03	0,17±0,08	4,23±0,18
II	1,42±0,02	0,45±0,33	2,64±0,12
	p<0,05	p<0,05	p<0,05

Table IV. Indices of oral fluid, M±m

Groups	Ph, (units)	Microcrystallization of oral fluid (points)	Rate of oral fluid unstimulated secretion (ml/min.)
I	5,6±0,04	2,5±0,04	0,29±0,004
II	6,45±0,07	2,02±0,07	0,4±0,01
	p<0,005	p<0,05	p<0,00

of children in Group II, almost double the occurrence in Group I, where it was 23.5%. The worst MCS index, type III, which indicates low caries resistance and serves as a marker of stress, was recorded in 64.3% of children in Group I. This is significantly higher than in Group II, where this index was found in only 24% of the subjects.

DISCUSSION

The war in Ukraine, one of the largest humanitarian crises of this century, has caused millions of Ukrainians to become internally displaced [9]. The conflict has severely impacted life in towns and villages on the frontline, forcing people to seek refuge in remote locations. With constant fighting, local residents cannot lead normal lives, facing daily threats to their safety. The destruction of infrastructure, social services, and the healthcare system, along with economic hardships caused by the war, has left many without access to essential psychological and medical care, including dental care. Many children have suffered from both physical and emotional trauma and require support to recover and adapt to their new circumstances.

Our study aimed to evaluate caries resistance of the teeth by conducting a comprehensive analysis of caries prevalence and assessing oral fluid parameters in two groups: children from Poltava and internally displaced children from frontline regions. The study sought to examine the impact of the armed conflict and displacement on the dental health of this group of children compared to those living in a city farther from the frontline, who had not been displaced.

Most districts in Poltava Oblast, an agricultural region, have normal or elevated fluoride concentration in drinking water, and the regional dental disease prevention program considers this factor. According to the literature, the regions from which children were primarily resettled to Poltava—namely Kharkiv, Donetsk, Luhansk, and Zaporizhzhia—are industrially polluted and have higher than normal fluoride levels in drinking water, which influences caries rates [10]. To evaluate the impact of resettlement on caries rates in children, we compared literature data on caries prevalence in children from these regions [11, 12] with our survey data from children in Poltava. This comparison indicates that children from Poltava [13, 14] have a lower

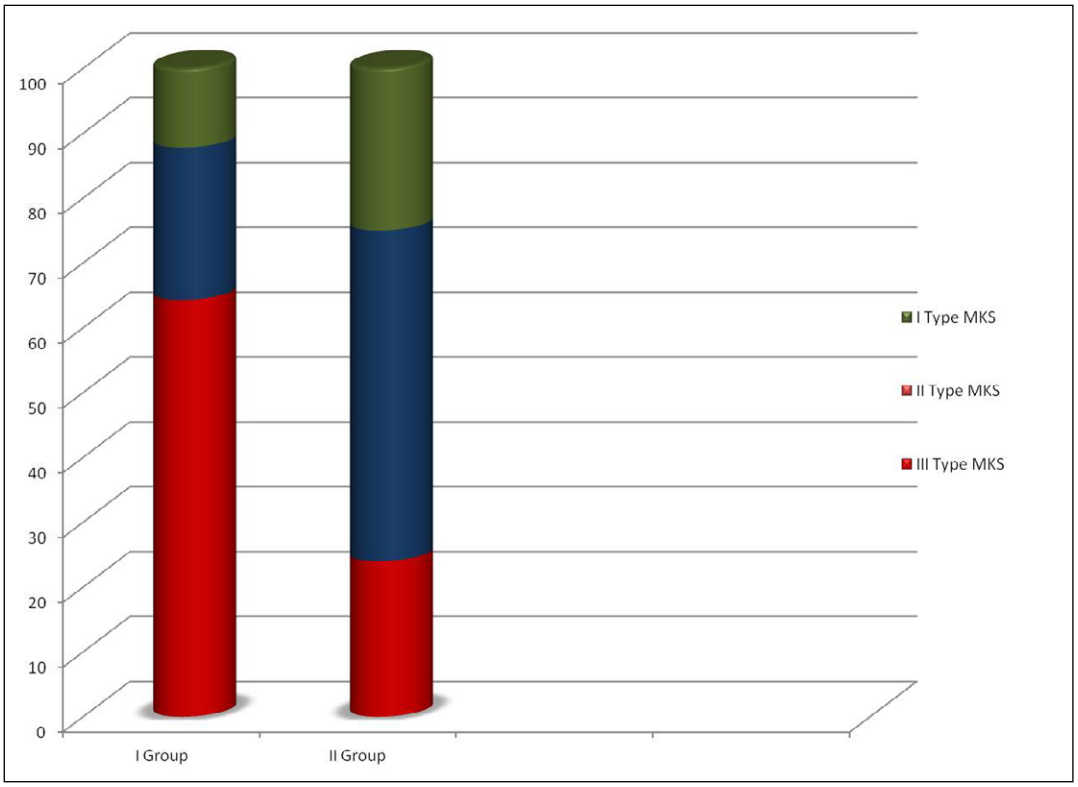

Fig. 1. Characteristics of microcrystallisation of mixed saliva in the examined children depending on the distribution by groups, (%).

prevalence and intensity of caries, as reflected by the dmft and DMFT indices.

When assessing the level of oral hygiene in children from both groups, it was found that the indicators did not differ significantly: the average oral hygiene index for internally displaced children was 1.52±0.025, and for children living in Poltava, it was 1.42±0.02. Both values are considered to indicate good oral hygiene status. This suggests that, despite the different living conditions and stressful situations faced by the internally displaced children, their level of oral hygiene remains acceptable.

In contrast to the findings on oral hygiene, the analysis of caries prevalence showed significant differences between the two groups. The average prevalence of caries among internally displaced children was 77.8%, an alarming indicator of the high level of caries in this vulnerable population. In comparison, the prevalence of caries among children living in Poltava was 66%, which, although lower, still represents a significant dental health concern for these children. Given the acceptable oral hygiene levels, it can be assumed that other factors—such as nutrition, access to healthcare services, and psycho-emotional stress—may have a significant impact on the oral health of the studied children [15].

The negative impact of armed conflicts on the psychological state of the population has been widely discussed in numerous scientific studies. The link between the dental health of internally displaced children and the consequences of living under constant stress has also been explored. A study conducted in Syria by Wail Habal et al. examined the effects of the Syrian crisis, assessing the mental and oral health of 99 Syrian internally displaced adolescents. The results demonstrated a significant relationship between mental health and oral health: participants diagnosed with psychological changes were more likely to rate the condition of their teeth and gums as average or poor [16].

According to our data, internally displaced children were found out to have decreased oral fluid parameters, such as lower pH levels, reduced salivary flow rates, and diminished mineralizing potential, all indicating low caries resistance. This may be attributed to stress factors and limited access to dental care, which contribute to higher rates of caries. It is well known that saliva maintains oral homeostasis through various functions, including lubrication, buffering, enamel mineralization, and antimicrobial activity. Salivary gland innervation and secretion are regulated by the central nervous system, and chronic stress can influence the concentration of salivary proteins and reduce salivary flow rates. This increases the risk of caries affects the concentration of salivary proteins and salivary flow rate [17, 18, 19, 20, 21].

Numerous studies have reported changes in the saliva composition and properties under the influence of stress caused by traumatic events [22, 23, 24, 25]. Research conducted by N. Yu. Yemelyanov in 2023 confirms that prolonged chronic stress significantly affects both the qualitative and quantitative parameters of oral fluid, highlighting the importance of non-invasive diagnostic methods, such as saliva microcrystallization analysis, for detecting stress [26].

In our study, the microcrystallization properties of oral fluid in internally displaced children showed significant changes that negatively impacted their dental health. The differences identified in the prevalence of microcrystallization (MCS) types suggest varying levels of stress and, consequently, potential health risks. In children who were exposed to considerable stress, Type I MCS, the most favorable for caries resistance, was observed twice as rarely as in children from Poltava (12.2% versus 25%). Similarly, Type II MCS was detected in 51% of children in Group II, nearly double the occurrence compared to Group I (23.5%).

The most alarming finding is the high rate of Type III MCT, recorded in 64.3% of children in Group I. This value is significantly higher than in Group II (24%), further confirming that stress factors related to the living conditions of internally displaced children have a substantial impact on their health.

CONCLUSIONS

This study revealed an increased susceptibility to caries in internally displaced children. The prevalence of caries among them was 77.8%, significantly higher than the 66% observed in children from Poltava. Although the level of oral hygiene in both groups was good (1.52 in internally displaced children and 1.42 in Poltava children), the morphological characteristics of the oral fluid indicated a high cariesogenic potential reflected in the lower pH (5.6 ± 0.04), reduced salivary flow rate (0.29 ml/min), low mineralizing potential (2.5 ± 0.04), and enamel resistance in internally displaced children, which was 1.6 times lower than in children from Poltava. These findings highlight the urgent need for targeted preventive programs to protect the dental health of this vulnerable group of children. These findings underscore the need for targeted prevention programs to support the dental health of this group of children and to adapt the regional prevention program accordingly.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Olha Sheshukova
Poltava State Medical University
23 Shevchenka St., 36000 Poltava, Ukraine
email: oldista@gmail.com

ORCID AND CONTRIBUTIONSHIP

Olha Sheshukova: 0000-0002-4739-4890 A B F
Anna S. Mosiienko: 0000-0003-2129-8304 A B D
Tetiana V. Polishchuk: 0000-0003-1114-5830 A D
Alina I. Maksymenko: 0000-0002-9791-0873 C
Alla V. Marchenko: 0000-0003-2178-6383 B
Sofia S. Bauman: 0000-0002-9029-8968 E
Nataliia M. Lokhmatova: 0000-0002-7800-0516 E

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

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ORIGINAL ARTICLE

CONTENTS

Causes of stress and its impact on women's mental and physical health

Grygoriy P. Griban[1], Valentyna P. Trufanova[2], Mykola I. Lyukianchenko[3], Nadiya Yu. Dovhan[4], Zoia M. Dikhtiarenko[5], Olena V. Otravenko[6], Tetiana V. Nadimyanova[3]

[1]ZHYTOMYR IVAN FRANKO STATE UNIVERSITY, ZHYTOMYR, UKRAINE
[2]POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE
[3]DROHOBYCH IVAN FRANKO STATE PEDAGOGICAL UNIVERSITY, DROHOBYCH, UKRAINE
[4]PETRO MOHYLA BLACK SEA NATIONAL UNIVERSITY, MYKOLAIV, UKRAINE
[5]STATE TAX UNIVERSITY, IRPIN, UKRAINE
[6]LUHANSK TARAS SHEVCHENKO NATIONAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

Aim: The aim is to investigate the causes of stress and its impact on women's mental and physical health indicators.

Materials and Methods: The research was conducted from 2022 to 2024 and involved 157 women from Zhytomyr oblast (Ukraine) of different ages, education, professions, and geographic residence. The research methods included analysis of literary sources, medical and sociological (survey), statistical method.

Results: It has been established that during the war, the vast majority of women surveyed experienced very high and high levels of stress (45.2 % and 35.0 %, respectively). The main causes of stress for women include: "full-scale war" – 41.2 %, "financial difficulties" – 12.4 %, and "job loss" – 11.9 %. At the same time, only a fifth of the respondents (21.7 %) said they were able to overcome stress and neutralize the state of anxiety. It was found that stress in women led to insomnia (31.8 %), gastrointestinal disorders (40.1 %), exacerbation of chronic diseases (20.6 %), decreased immunity (8.4 %), and menstrual irregularities (7.2 %).

Conclusions: It has been found that the war had a significant impact on women's mental and physical health: the frequency of anxiety and depression, psychosomatic disorders, uncontrollable fear, and the desire to withdraw from people increased. Given this, public health professionals need to intensify awareness-raising activities in this area.

KEY WORDS: stress, women, psychosomatic disorders, health

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INTRODUCTION

Maintaining and improving the health of the population, including mental health, is an important task of Ukraine's state policy. However, since the beginning of the full-scale invasion of Ukraine by the russian aggressor, the number of various diseases and mental disorders has increased due to the negative impact of stressors. Stress and various stress reactions are an integral part of the existence of living organisms, which ensures the body's adaptation to the effects of adverse factors [1]. Therefore, the relevance of studying and disclosing the essence of the phenomenon of stress, its nature, causes, and prevention of possible consequences still encourages scientists and specialists to study it further.

As scientists note [2], stresses are very similar and diverse simultaneously. Stresses of different natures can be repetitive and unique but identical. It should be noted that the vast majority of stressors are similar, primarily in terms of the body's reactions to them, behavior, and experiences. For most people, stress causes unpleasant feelings and negative emotions, irritating memories, and unpleasant associations [3]. Stress has long been a part of almost every person's life and accompanies them constantly. Due to their emotional nature, women are the most exposed to daily stresses. Various stimuli affect their bodies on a daily basis [4].

Different functional systems of women's bodies can undergo significant changes due to stress. The intensity and frequency of changes and disorders in the body can range from minor disturbances in the emotional state or just mood to serious illnesses such as myocardial infarction or, stomach ulcers, etc. [5]. Scientists distinguish several types of classification

of stress reactions, but the most optimal is the division of stress signs into the following manifestations: emotional, behavioral, intellectual, and physiological. The latter also includes biochemical and hormonal reactions [6]. According to experts [7], women and men do not react to stress similarly. Men are ready to "fight or flight" when exposed to stressors. Women, on the other hand, are capable of negotiating in stressful situations. This ability of women's physiology to have a high level of stress resistance has developed historically. It is ensured by the hormonal support of women and is directed by the need to save their children. Therefore, women can simultaneously perform several tasks [8]. Physiologists point out that due to a woman's constant stressful conditions, certain processes associated with changes in hormonal levels occur in her body. Elevated levels of stress hormones lead to a decrease in immunity and disruptions in hormone production, which in turn leads to accelerated aging and a reduction in the body's ability to recover, and changes in hormone levels result in a decrease in reproductive functions [9]. In a woman experiencing constant emotional discomfort, the symptoms of nervous reactions and strain become more pronounced, somatic reactions appear, and hormonal levels change, provoking the development of diseases and imbalances in the whole body [10].

AIM

The aim is to investigate the causes of stress and its impact on women's mental and physical health indicators.

MATERIALS AND METHODS

The research was conducted in 2022-2024 at Zhytomyr Ivan Franko State University. The research involved 157 women of different ages, with various education, professions, and residences in various geographic areas. The age of the respondents ranged from 18 to 70 years and more: 18-29 years old – 45 women (28.6 %), 30-39 years old – 53 women (33.7 %), 40-49 years old – 31 women (19.7 %), 50-59 years old – 19 women (12.1 %), 60-69 years old – 7 women (4.4 %), over 70 years old – 2 women (1.2 %). The largest percentage of the women were aged 30 to 39 (33.7 %). The vast majority of the respondents are residents of Zhytomyr and other cities in the Zhytomyr oblast (Ukraine) – 144 women (91.7 %); a small percentage of the respondents are residents of villages and towns in the Zhytomyr oblast – 13 women (8.2 %). The research involved only women who, during the russian-Ukrainian war in 2022-2024, were forced to be relocated from the temporarily occupied territories (Kharkiv, Zaporizhzhya, Luhansk, and Donetsk regions) to Zhytomyr region, regardless of their age, profession, education, marital status.

Research methods: analysis of literary sources on the topic of the research (18 literary sources from various world scientometric databases for the period from 2000 to 2024 were processed); medical and sociological (survey) – to determine the causes of stress in women and its impact on the mental and physical health indicators of women during the war; statistical – to process and analyze the results of the research. The survey was conducted using the author's questionnaire, which contains 4 blocks. Block I. Factors that cause stress in women during the war (studying the most important stress factors, including war and its consequences – death of loved ones, loss of housing, work and property, relocation to other territories, etc.). Block II. The impact of stress on women's mental health (studying the levels of anxiety, irritability, aggressiveness, emotional exhaustion, restructuring of the emotional sphere, the level of interaction with the immediate environment, etc.). Block III. The impact of stress on women's physical health (studying the impact of stress on sleep quality, eating behavior, psychosomatic disorders, immunity, menstrual cycle disorders, the possibility of pregnancy). Block IV. Ways to overcome stress in women during the war (studying of appropriate methods effective for women of Ukraine). The questionnaire was anonymous without any references to the authors of the article in the answers. The results were used for scientific purposes only. Questionnaire was assessed by the experts in this field (2 professors and 4 associate professors) and was approved by the Academic Council of Zhytomyr Ivan Franko State University (Protocol No. 7 dated 21.11.2022).

Data collection, processing, and analysis of the research results were performed on a personal computer using MS Excel, a software package that allows statistical data processing methods. Consent to voluntary participation in the survey was obtained from all the respondents involved in the study. This research followed the regulations of the World Medical Association Declaration of Helsinki – ethical principles for medical research involving human subjects.

RESULTS

The analysis of answers to the question "How would you rate your general health?" showed that the largest number of the respondents – 64 women (40.7 %) – have a satisfactory state of health. There are fewer respondents with good health – 45 women (28.7 %).

Almost a quarter of the respondents assess their health as "poor" – 30 women (19.1 %), and "very poor" – 18 women (11.5 %). The analysis of the next two questions assessing the presence of bad habits of the respondents before the war and during the war shows that the war provoked an increase in bad habits. During the war, women resorted to excessive consumption of salt and spices (29.3 % to 36.3 %), fatty smoked, and fried foods (26.1 % to 33.1 %). Thus, women began to comfort eat. However, the level of alcohol consumption and smoking decreased from 8.9 % and 36.3 % to 7.0 % and 24.2 %, respectively.

The respondents' assessment of the level of financial security of the family before the war shows the following distribution of answers: "very low level" – 24 women (15.3 %), "low level" – 39 women (24.9 %), "average level" – 77 women (49.0 %), "high level" – 17 women (10.8 %). After two years of war, the respondents assessed their financial situation differently: "very low level" – 48 women (30.6 %), "low level" – 67 women (42.7 %), "average level" – 36 women (22.9 %), "high level" – 6 women (3.8 %). We can see that the "high" and "average" categories have significantly decreased – by 7.0 % and 26.0 %, respectively. The "low" and "very low" categories increased by 18.0 % and 15.0 %, respectively. The change in the family's financial situation for the worse could not but cause stress among women.

The comparison of answers to the question about assessing the level of stress in interaction with the immediate environment before the war and during the 2 years of war shows that the largest share of answers was "low" when the respondents were mostly in a state of psycho-emotional balance – 43.9 %, the rest of the answers had the following distribution: "very high (state of constant stress)" – 7.6 %, "high (I get into episodic stressful situations)" – 9.5 %, "sufficient (I feel mostly psycho-emotional stress)" – 15.9 %, "average (sometimes I feel anxious)" – 22.9 %. The distribution of responses to the assessment of the level of psychological stress in the war shows that the "very high" level of stress was 45.2 %, "high" – 35.0 %, "sufficient" – 14.0 %, "average" – 3.8 %, "low" – 1.9 %. It should be noted that the "very high" stress level increased by 37.5 %, and the "high" level increased by 25.4 %. Thus, psychological equilibrium during the 2 years of war remained inherent in only a small part of the surveyed women.

Next, let's consider the analysis results of the respondents' answers regarding assessing their physiological changes, changes in behavior, feelings, environment, etc. Sleep disturbance is one of the signs of stress. 72.6 % of the women surveyed said they had had problems sleeping over the past year. When asked about changes in sleep quality, the vast majority said they had problems falling asleep and sleep duration. The main reason for sleep disturbances among women is anxiety, which prevents them from falling asleep. Sleep and its quality are very important in the body's recovery processes, as well as in its emotional and physical states. It should be noted that half of the respondents feel tired after sleep – 49.9 %. Doctors note that prolonged insomnia leads to changes in emotional and physical state, which ultimately causes the onset and development of various diseases.

Stress can often be caused by certain situations in which people find themselves. As a result, a person feels irritable and angry. Thus, 77.7 % of women have experienced an outbreak of anger and irritability over the past year. More than a third of the respondents (37.5 %) reported manifestations of self-destructive reckless behavior over the past year.

Impaired ability to memorize or reproduce information and concentrate on the task at hand, and problems with vocabulary and communication, especially during the war, are manifestations of prolonged stress. It was found that 69.4 % of the women surveyed had experienced such problems over the past year. The feeling of "being on the alert" and "excessive anxiety" was experienced by the majority of the respondents over the past year – 63.1 % and 68.2 %, respectively. Such an assessment of the respondents' feelings indicates that women are in a state of prolonged stress provoked by the events of the war.

The distribution of answers to the question "Have you experienced excessive anxiety over the past year" is as follows: "very often" – 54.7 %, "often" – 21.6 %, "sometimes" – 14.6 %, "rarely" – 5.7 %, "never" – 3.2 %. To the question "Have you experienced anxiety that is not rational for the situation, but it was beyond your control," the respondents gave the following answers: "very often" – 57.9 %, "often" – 20.3 %, "sometimes" – 18.4 %, "rarely" – 2.5 %, "never" – 0.6 %. The results suggest that more than half of the respondents suffer from excessive anxiety, which is often irrational and uncontrollable. The following distribution of answers to the question about the causes of anxiety confirms the irrationality and uncontrollability of such anxiety states. The largest proportion of the respondents (61.8 %) confirm that they very often do not understand the causes of anxiety, "often" – 20.4 %, "sometimes" – 13.4 %, "rarely" – 3.8 %, "never" – 0.6 %. The largest share of responses was for difficulty concentrating in everyday life or work and decreased working capability (52.2 %).

Table 1. Causes of stress experienced by women before the war (n = 157)

Causes of stress	Number of responses	Share of responses
Work, work issues	41	15,2%
The COVID-19 pandemic	39	14,5%
Personal health status	31	11,5%
Health status of loved ones	29	10,7%
Financial difficulties	27	10,0%
Social and political situation in the country	25	9,2%
Romantic relationships	19	7,0%
High inflation in the country	17	6,3%
Unemployment	16	5,9%
Family affairs and relationships in the family	14	5,2%
Communication with friends and acquaintances	11	4,0%

Table 2. Causes of stress experienced by women during the war (n = 157)

Causes of stress	Number of responses	Share of responses
Full-scale war	156	41,2%
Financial difficulties	47	12,4%
Job loss	45	11,9%
Social and political situation in the country	31	8,2%
Problems at work	27	7,1%
High inflation in the country	19	5,0%
Personal health status	13	3,4%
Family affairs and relationships in the family	13	3,4%
Health status of loved ones	11	2,9%
Communication with friends and acquaintances	9	2,3%
Romantic relationships	7	1,8%

Table 3. Indicators of health deterioration in women as a result of stress during the war (n = 157)

Health indicators	Number of responses	Share of responses
Insomnia	57	31,8%
Chronic diseases exacerbation	37	20,6%
Inability to get pregnant	29	16,2%
Decreased immunity (diseases worsened)	15	8,4%
Menstrual cycle disorder	13	7,2%
Eating disorder (binge eating)	12	6,7%
Diffuse toxic goiter	7	3,9%
Complicated labor and delivery	5	2,7%
Breast cancer	2	1,1%
Immunodeficiency	1	0,5%
Miscarriages	1	0,5%
Fetal pathology	0	0,0%

Psychosomatic manifestations such as nervousness, unusual tension, chest pain, heart palpitations, or shortness of breath are signs of a nervous and often depressive state. More than half of the women surveyed have experienced these symptoms. When asked the question, "Have you felt too nervous or unusually tense lately?" the following distribution of answers was obtained: "very often" – 54.8 %, "often" – 32.5 %, "sometimes" – 8.3 %, "rarely" – 3.2 %, "never" – 1.3 %. Such manifestations of stress as chest tightness, shortness of breath, and heart

palpitations were recorded by the respondents: 49.7 % of women experienced them "very often," 27.4 % – "often," 15.3 % – "sometimes," 5.7 % – "rarely," and 1.9 % – "never."

In addition to the above-mentioned psychosomatic manifestations, the respondents noted the following: a feeling of muscle tension, muscle pain in the absence of physical activity, cramps, and digestive problems without significant dietary changes. The analysis of answers to the question "Have you recently experienced persistent muscle tension or muscle pain without excessive physical activity?" showed the following distribution: 36.3 % answered "very often," 26.7 % answered "often," 18.4 % answered "sometimes," 13.3 % answered "rarely," and 5.1 % answered "never." The largest share of the responses regarding gastrointestinal disorders was "often" – 40.1 %. The survey results give grounds to conclude that most respondents are in a state of stress, in response to which the nervous system reacts to changes in the functioning of the digestive system. Tingling sensations and partial or complete numbness of the body are also psychosomatic manifestations of stressful conditions. Such symptoms were experienced "very often" by 18.5 % of women, "often" by 16.6 %, "sometimes" by 21.7 %, "rarely" by 19.8 %, and "never" by 23.6 %.

When studying the range of causes that could have triggered stress before the war, we found that the most common causes were work and work-related issues (15.2 %), the COVID-19 pandemic (14.5 %), personal health (11.5 %), the health of loved ones (10.8 %), and financial difficulties (10.0 %) (Table 1).

When we asked the respondents about the causes of stress during the two years of war, we got the following results (Table 2): "a full-scale war with russia" – 41.3 %, "financial difficulties" – 12.4 %, "job loss" – 11.9 %, "social and political situation in the country" – 8.2 %. The smallest percentage is "romantic relationships" – 1.9 %.

The analysis of answers to the question "How did stress affect your health status?" showed the following: "insomnia" – 31.8 %, "chronic diseases exacerbation" – 20.6 %, "inability to get pregnant" – 16.2 %, "decreased immunity (acute diseases worsened)" – 8.4 %, "menstrual cycle disorder" – 7.2 % (Table 3).

Thus, it has been found that the war had a significant impact on women's mental and physical health: the frequency of anxiety and depression, digestive system disorders, headaches, sleep disorders and chronic insomnia, uncontrollable anxiety, and the desire to withdraw from people increased.

DISCUSSION

People understand the concept of stress in different ways. For some people, stress is situations with unbearable bosses or unfriendly neighbors, while for others, it is certain physiological reactions, such as chest pressure or other pains, that are the consequences of stressful situations [11]. According to scientists [12], stress is the greatest threat to human mental health. Experts [13] interpret stress as a trigger that leads to pathological abnormalities in the functioning of all human body systems. Stress causes serious illnesses, such as heart attacks or stomach ulcers, resulting from prolonged stress or repeated stressful incidents.

According to Canadian researcher G. Selye, many diseases begin in the same way for most people, manifested by weakness, loss of appetite, headaches, etc. All this becomes the beginning of various chronic diseases. Continuing his research, G. Selye became convinced that harmful factors affecting people or laboratory animals lead to the same physiological reactions that eventually cause pathologies. The researcher called such a general or universal reaction of the body to external factors a general adaptation syndrome, a nonspecific response of the body to the effects of stimuli or stress [14].

According to experts [15], a person in a stressful situation and trying to adapt to the effects of stress goes through three phases: 1. Anxiety phase. As a result of the stimulus, a person's respiratory rate increases, blood pressure rises, and tachycardia occurs – physiological manifestations of this stress phase. Psychological manifestations include increased concentration of attention on the influencing factor and increased personal control of the situation. All reactions of the body contribute to the mobilization of the body's defenses, provoking the body's self-regulatory mechanisms to protect itself from stress. When the human body is mobilized, stress ends. The person becomes capable of "fight or flight." 2. The phase of resistance (resilience, adaptation). If the factor continues to act, the body turns on a "reserve" supply of strength. All body systems begin to work at maximum capacity. If the threat to a person continues and cannot be avoided, the body tries to resist the danger or overcome it. Over time, the body adapts to stress, and physiological processes return to normal. As the body's systems reach a certain stress level, the body adapts to new conditions better and faster. 3. The phase of exhaustion. In the case of long-term exposure to a stressor, the body's ability to cope with stress is significantly reduced. Stress "takes over" the body, which can lead to illness. The exhaustion phase is characterized by vulnerability to physical and emotional fatigue, the so-called "burnout." Physical problems lead to disease and even death. Physiological reactions that occur during short-term stresses and contribute to the mobilization

of the human body (increased blood pressure, lack of pain, significant muscle tension, and suspension of digestion) begin to harm the body. This reveals the failure of the body's defense and recovery mechanisms, ultimately violating vital functions.

According to scientists [5, 6], a woman's constant psychological stress or the experience of stressful events leads to changes in the endocrine and immune systems, which provokes exacerbation of chronic diseases and the development of new ones, which in turn causes additional nervous stress and the further development of new stresses. Doctors and physiologists often note changes in a woman's body due to the negative impact of various stresses. Such changes include menstrual irregularities, which occur due to changes in hormonal levels on nervous grounds. The cycle disorder can cause anovulation and scanty, short, or light menstruation. Menstruation can disappear altogether due to severe long-term stress, the so-called "wartime amenorrhea" develops [7, 8]. Under the influence of prolonged stress, the body shuts down its reproductive function, concentrating its efforts on overcoming the effects of stress. Such reactions of the body often cause such diseases as stress infertility. Scientists say that one in three women cannot get pregnant due to chronic stress [10].

Women are five times more likely to suffer from diffuse toxic goiter than men. Among the factors that provoke the development of the disease, doctors single out mental trauma and prolonged nervous tension [16]. Breast oncopathology ranks first among all types of cancer not only in Ukraine but also worldwide. More than half of the cases of this type of oncology arise and develop under the influence of constant nervous exhaustion. The main reason for this is, again, changes in a woman's hormonal background and the increased sensitivity of the mammary gland to hormones. Excessive synthesis affects the mammary gland's condition, provoking the development of benign changes. However, under the influence of various negative factors, benign changes are transformed into malignant ones, causing oncology development [16].

With constant prolonged nervous stress and exhaustion of the nervous system, ARVI, various candidiasis, cystitis in acute phases, or exacerbation of chronic forms occur more often than normal. This, in turn, provokes the development of immunodeficiency. Doctors state that most often, exacerbation of chronic diseases and their complicated course in women occurs under the influence of constant stress factors and prolonged nervous tension [17]. Women are more likely than men to suffer from eating disorders. Experiencing stress ten times more often than men, they comfort eat. Again, the reasons for these phenomena are the influence of female hormones, namely, under stress, estrogen production decreases, the level of the "happiness hormone" serotonin drops, and the amount of the "stress hormone" cortisol increases rapidly. Such physiological processes cause a strong feeling of hunger, resulting in uncontrolled consumption of unhealthy foods high in fat and carbohydrates [18].

CONCLUSIONS

Based on the analysis of scientific literature, it has been found that stress is an emotional, behavioral, intellectual, and physiological response of the body to the action of stressors, which, to some extent, affects the effectiveness of human activity. The nature of the reaction to stressors is not identical for women and men. Various stressors in women's lives, combined with traumatic events related to the war, can provoke the development of stress, which in turn causes disorders in the body and contributes to the development of chronic diseases.

It has been found that during the war, the vast majority of the women surveyed experienced very high and high levels of stress (45.2 % and 35.0 %, respectively). Among the causes of stress that arose during the last two years of the war, the respondents mentioned "full-scale war" – 41.3 %, "financial difficulties" – 12.4 %, "job loss" – 11.9 %, "social and political situation in the country" – 8.2 %, "problems at work" – 7.1 %. At the same time, only a fifth of the respondents (21.7 %) said they were able to overcome stress and neutralize anxiety.

Women's prolonged exposure to stress has had a significant impact not only on their mental but also on their physical health. The respondents have insomnia (31.8 %), gastrointestinal disorders (40.1 %), exacerbation of chronic diseases (20.6 %), decreased immunity (8.4 %), and menstrual irregularities (7.3 %). It has been found that the war had a significant impact on women's mental and physical health: the frequency of anxiety and depression, psychosomatic disorders, uncontrollable fear, and the desire to withdraw from people increased. Given this, public health professionals need to intensify awareness-raising activities in this area.

PROSPECTS FOR FURTHER RESEARCH

It is planned to investigate the impact of wartime stress on psychosomatic disorders in the male population of Ukraine.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Valentyna P. Trufanova
Poltava State Medical University, Poltava, Ukraine
23 Shevczenka St., 36000 Poltava, Ukraine
e-mail: trufanovav4@gmail.com

ORCID AND CONTRIBUTIONSHIP

Grygoriy P. Griban: 0000-0002-9049-1485 B
Valentyna P. Trufanova: 0000-0002-7819-0188 A
Mykola I. Lyukianchenko: 0000-0002-0253-858X D
Nadiya Yu. Dovhan: 0000-0002-4715-028X C
Zoia M. Dikhtiarenko: 0000-0003-1869-7494 D

Olena V. Otravenko: 0000-0001-8308-5895 E
Tetiana V. Nadimyanova: 0000-0002-4330-304X F

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

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ORIGINAL ARTICLE

CONTENTS

Treatment of delusional ideas: Analyzing the effectiveness of pharmacotherapy and psychotherapeutic methods

Olha Zahariichuk
SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: To investigate the etiology, pathogenesis, and effectiveness of pharmacotherapy and psychotherapeutic modalities of delusions in Schizophrenia spectrum and other Psychotic Disorders.

Materials and Methods: In our study, we included English-language studies from online databases such as Web of Science, Scopus, Google Scholar, PubMed, and the Cochrane Library conducted until January 2024 using the following keywords "delusions", "Schizophrenia spectrum and other Psychotic Disorders", "pharmacotherapy", "psychotherapy", and "antipsychotics".

Scientific novelty: There is already published evidence that has studied Schizophrenia spectrum disorders from definition to treatment. However, a lack of studies has identified a comprehensive analysis of the available therapies for managing this condition. In our article, we studied Schizophrenia spectrum disorders and evaluated the role of both pharmacotherapy and psychotherapy in managing this condition.

Conclusions: The management of delusions requires combined pharmacotherapy and psychotherapy. Cognitive therapy combined with antipsychotics has a significant beneficial role in improving delusions. Further randomized trials are required to properly estimate the efficacy of the available therapies and determine the first-choice therapy in patients with different categories of Schizophrenia spectrum disorders.

KEY WORDS: delusions, antipsychotics, pharmacotherapy, psychotherapy, Schizophrenia spectrum disorders

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INTRODUCTION

Delusion is a persistently incorrect belief that is based on a faulty perception of the outside world in spite of evidence to the contrary. This false belief often contradicts the patient's culture and subculture, and almost everyone else is aware that it is untrue [1]. Delusion is the hallmark of schizophrenia disorder, and it is among the primary diagnostic criteria for this disease. It can appear in patients with stroke, neurodegenerative illnesses, nervous system abnormalities, brain trauma, and other psychological diseases [2]. Delusions may negatively affect functioning and independent living and have been associated with higher carer load, lower medication compliance, and an overall deteriorating prognosis across conditions [3,4]. A person is diagnosed with Schizophrenia spectrum Disorder if one or more non-bizarre (possible, albeit unlikely real-world events) delusional thoughts are present for a month or longer. They cannot be explained by any other physiological, drug-induced, medical, or mental health condition, in addition to the cultural beliefs of each patient, which aid in the delusions diagnosis [5].

Delusions can be classified into various categories and types, but the most frequent types are grandiosity, jealousy, erotomania, religious, delusion of reference, bizarre, persecutory, somatic, thought insertion, thought broadcasting, and mixed type with no single dominant type [6]. More specific types of delusions have also been seen throughout diseases, such as Othello's syndrome (delusional jealousy concerning family members) and Capgras delusion (thinking family members have been switched with a look-alike) [7]. Delusions are involved in various psychotic disorders. However, there is usually a dominant type of delusion in each disorder. Patients with bipolar disorder typically have delusions of grandiosity, while those with depression suffer from delusions of guilt. In contrast, persecutory delusions are dominant in schizophrenia. Chronic psychotic disorders are often associated with delusions of thought broadcasting, insertion, or withdrawal [8,9]. Unfortunately, patients with delusions do not seek medical advice because of their ego-syntonic delusions, which are defined as a lack of insight [10]. Patients often notice social and occupational disruption and are urged to seek therapy by anxious family members.

Treatment depends mainly on combining antipsychotic medications and psychotherapy with a good and trusted doctor-patient relationship. An assessment of the antipsychotic's efficacy should be conducted after a six-week trial period and trial use [11]. Once you reach the desired level, titrate up. If, after six weeks, no improvement is shown with the first course of therapy, a different medication from a different class might be attempted [12]. In this review, we aim to study the molecular and neurophysiological mechanisms of delusions and analyze the effectiveness of pharmacotherapy and psychotherapeutic methods.

AIM

The study is conducted to investigate the aetiology, pathogenesis, and effectiveness of pharmacotherapy and psychotherapeutic modalities for Schizophrenia spectrum disorders, with a focus on delusions.

RESEARCH FOCUS

Our review focused on studying delusions in terms of the definition, etiology, pathogenesis, and treatment modalities.

RESEARCH PROBLEM

Although combined pharmacotherapy and psychotherapy showed many benefits in patients with Schizophrenia spectrum disorders, there are still no clear guidelines for managing this condition. The accuracy of delusion incidence is compromised, as it can manifest both as an isolated disorder and as part of other mental illnesses.

RESEARCH QUESTIONS

1. What are delusions?
2. What is the pathogenesis of Schizophrenia spectrum disorders?
3. What are the etiology and theories that explain delusions?
4. What are the most effective pharmacotherapy and psychotherapy that can improve delusions?

MATERIALS AND METHODS

Delusion is defined as a fixed false belief rooted in an inaccurate understanding of the external world, persisting despite contradicting evidence. This belief often diverges from the patient's cultural or subcultural norms, with most individuals recognizing its inaccuracy. Delusions are categorized into several types, including grandiosity, jealousy, erotomania, religion, the delusion of reference, bizarre delusions, persecutory, somatic, thought insertion, thought broadcasting, and mixed types without a dominant category. Patients experiencing delusions often avoid seeking medical help due to their ego-syntonic nature, characterized by a lack of insight. Treatment approaches primarily involve a combination of antipsychotic medication, psychotherapy, and the establishment of a strong therapeutic alliance.

INCLUSION CRITERIA

1. Studies of all designs, including case series, randomized clinical trials, case-control studies, and systematic reviews, are included.
2. Articles evaluating Schizophrenia spectrum disorders concerning definitions, aetiology, and treatment modalities are selected.
3. Priority is given to studies published between 2018 and 2023.

EXCLUSION CRITERIA

1. Articles not subjected to peer review, including proposals, procedures, letters, and opinion pieces, are excluded.
2. Studies conducted prior to 2010 are not considered.
3. Studies unrelated to the topic or with aims misaligned with the research objective are omitted.
4. Research involving organic disorders, psychoactive substance users, individuals with mental retardation, elderly populations, and children is excluded. The analysis is limited to adult patients aged 18 to 60 years with Schizophrenia spectrum disorders to narrow the focus.

DATABASES AND SEARCH STRATEGY

The following online databases were utilized: Web of Science, Scopus, Google Scholar, PubMed, and the Cochrane Library. The search employed keyword combinations such as "delusions," "antipsychotics," "pharmacotherapy," "psychotherapy," and "Schizophrenia spectrum disorders." Studies conducted until January 2024 were collected to ensure an unbiased selection of publications. References were selected based on their relevance to the research topic.

STUDY SCREENING AND REVIEW PROCESS

The review process was conducted in three stages. Initially, EndNote Software was used to import search results from electronic databases into a Microsoft Excel sheet. Titles and abstracts of the entries were screened

during the second stage. The full texts of citations from the previous stage were examined in the third stage. Additionally, references from the included publications were manually reviewed to identify potentially overlooked studies.

DATA ANALYSIS

A qualitative review of previously published studies was conducted. Quantitative analysis was not performed due to the research being a narrative review. The requirements for quantitative analysis, including specifying measurable outcomes and locating and comparing data from at least two relevant studies, were not met. Despite attempts at quantitative analysis, relevant and comparable data were not identified. Instead, qualitative analysis was performed to present and compare findings from relevant papers, ensuring strong evidence and updated conclusions.

REVIEW AND DISCUSSION

Delusion is a significant mental condition marked by the existence of a persistent, preoccupying, irrational belief. It is a psychotic condition that is part of the schizophrenia spectrum diseases [13]. It is believed that it is among the most severe manifestations of mental disorders in clinical practice [14]. Delusional ideas cannot be eradicated by education or persuasion since they depend on a misperception of external reality. Perception disorders or affective symptoms might occasionally accompany delusions, although they are not the main focus of the condition [15]. There are two categories of delusions: organic and functional. The organic delusion usually could be explained by brain injury (such as lesions to the right cerebral hemisphere), whereas a functional delusion could be explained by psychodynamic or motivational causes. However, nowadays, most forms of delusions are caused by certain biological and psychological variables, while further research may be needed to determine these components precisely and identify how they interact [14].

Due to the fact that delusions may manifest as an isolated disorder or as a component of psychological disease, obtaining the accurate and appropriate incidence data is challenging. However, it is estimated that the overall morbidity due to Schizophrenia spectrum disorders is 0.05-0.1%. According to the DSM-V, about 0.02% of people will have Schizophrenia spectrum disorders at some point in their lives. Compared to other conditions such as bipolar disorder, schizophrenia, and other mood disorders, isolated Schizophrenia spectrum disorders are far less common. This may be attributed to the underreporting of the disorder because individuals suffering from Schizophrenia spectrum disorders may not seek mental health treatment unless forced to do so by friends or family. Delusions may present at any age from 18 to 90 years, with an average age of 40 years. Studies showed that males are more likely to suffer from paranoid delusions, persecutory, and jealous types of delusions. In contrast, women usually have delusions of erotomania [16]. While the global prevalence of schizophrenia exhibits variations, it is generally estimated that around 1% of adults are affected by the disorder. In the United States, the prevalence ranges from 0.6% to 1.9% [17]. Men tend to receive diagnoses more frequently and experience an earlier onset compared to women. Additionally, there is a higher incidence of schizophrenia among African-Caribbean migrants and their descendants [18]. Despite the increased interest in delusion and numerous attempts to understand this phenomenon properly, a clear cause explaining its occurrence remains elusive. Patients with Schizophrenia spectrum disorders were found to have impaired limbic system and basal ganglia with intact and functioning cortex [16]. Delusions may be brought on by a variety of biological situations, including drug abuse, illnesses, and neurological disorders [19,20]. Psychodynamic theories about delusional disease include hypersensitive individuals and ego defense strategies such as projection, denial, and response formation. A person who experiences social isolation, jealousy, mistrust, suspicion, and poor self-esteem may develop a delusion as a coping mechanism when these things become untenable. Furthermore, Delusions are prevalent among some demographics, such as elderly people, deaf and visually impaired people, as well as immigrants with language difficulties [21]. Different theories may explain the occurrence of delusions as follows: it is supposed that in the brain network, 'signal to noise' disparities may rise due to enhanced dopaminergic transmission; as a result, this excessive dopamine status emerges as a propensity to give personal relevance to unconnected external events [22]. This disrupted dopaminergic activity may affect motivation, focus, attitude, and social relationships. Certain areas of the brain may be incorporated into delusion thoughts, such as the ventral striatum, ventromedial prefrontal cortex, dorsolateral prefrontal cortex, substantia nigra, hippocampus, and mesolimbic pathways [23]. Previous research demonstrated the significant role of dopamine antagonists in decreasing the severity of delusions, which proved the evidence of the involvement of excess dopamine in the neurobiology of delusion [24].

Delusional ideas represent a significant facet of several psychiatric disorders, with their prominence notably observed in conditions such as schizophrenia,

Table 1. Shows a general data about delusional ideas

Characteristics	Schizophrenia	Schizoaffective Disorder	Acute Polymorphic Psychotic Disorder with Schizophrenia Symptoms	Delusional disorder
Prevalence	Approximately 1% of the global population	Estimated to be less common than schizophrenia	Limited prevalence data, often considered rare	is about 0.02%
Types of Delusional Ideas	Paranoid delusions	Paranoid delusions	Polymorphic delusions (varying themes)	Persecutory delusion. Delusion of grandeur
	Grandiose delusions	Grandiose delusions	Persecutory delusions	Delusional jealousy Erotomania or delusion of love
	Persecutory delusions	Persecutory delusions	Grandiose delusions	Somatic delusional disorder Induced delusional disorder
	Referential delusions	Referential delusions	Referential delusions	Bizarre delusion – Refers to delusion that is implausible or bizarre such as alien invasion.
Onset of Disease	Usually, in late adolescence or early adulthood	Can occur at any age, but often in late adolescence	Sudden onset, typically acute and brief, Symptoms may emerge following severe stressors, Criteria include hallucinations, disorganized speech, and grossly disorganized or catatonic behavior	has a later age of onset
Hypotheses of Occurrence	Neurodevelopmental factors	Genetic and neurobiological factors	Stress-related factors may contribute to onset	substance use
	Genetic predisposition	Dysregulation in neurotransmitter systems	Genetic vulnerability, environmental stressors, and	medical conditions
	Neurochemical imbalances	Environmental stressors and trauma	alterations in neurotransmitter systems may play a role	neurological conditions
Pharmacotherapeutic Approaches	Antipsychotic medications	Antipsychotic medications	Antipsychotic medications (short-term)	Antipsychotic drugs,
	Atypical antipsychotics are often preferred	Mood stabilizers (for mood component)	Short-term use of antipsychotics to manage symptoms	mood-stabilizing medications
	May include combination therapy	Antidepressants (for depressive component)	Medications may be tapered as symptoms resolve	antidepressants medications
			Supportive care and monitoring for potential recurrence	
Psychotherapeutic Approaches	Cognitive-behavioral therapy (CBT)	Individual and group therapy	Supportive psychotherapy during acute phase	Supportive psychotherapy
	Family therapy	Cognitive-behavioral therapy (CBT)	Psychoeducation to enhance coping skills and resilience	cognitive behavioral therapy (CBT)
	Supportive psychotherapy	Supportive psychotherapy	Family involvement in understanding and supporting the individual's recovery process	

Source: author's development.

delusional disorder, schizoaffective disorder, and acute polymorphic psychotic disorder with schizophrenia symptoms. These disorders are characterized by disruptions in thought processes, emotions, and perceptions, leading to a distorted understanding of reality.

Schizophrenia, a severe and chronic psychiatric disorder, is marked by a diverse range of symptoms, among which delusions are key diagnostic criteria. Individuals with schizophrenia often experience profound disruptions in their thought processes, leading to the development of delusional ideas that may manifest as paranoid, grandiose, or persecutory in nature. Schizoaffective disorder, a condition exhibiting features of both schizophrenia and mood disorders, similarly incorporates delusions into its clinical presentation, further complicating the landscape of cognitive and affective disturbances [25].

Acute polymorphic psychotic disorder with schizophrenia symptoms represents a transient but intense manifestation of psychotic symptoms, including delusions, resembling those seen in schizophrenia. This disorder is characterized by its sudden onset and polymorphic nature, with symptoms varying across different psychotic features. Understanding the nuances of delusional ideas within these psychiatric conditions is crucial for both clinicians and researchers seeking effective interventions and a deeper comprehension of the complex interplay between cognition, perception, and emotional regulation in these disorders [26].

This exploration of delusional ideas in schizophrenia, delusional disorder, schizoaffective disorder, and acute polymorphic psychotic disorder with schizophrenia symptoms aims to shed light on the intricacies of these psychiatric phenomena. By delving into the unique manifestations and implications of delusions in each disorder, we hope to contribute to a comprehensive understanding of these mental health conditions, facilitating improved diagnostic accuracy and targeted treatment strategies for individuals grappling with the challenges posed by delusional thinking (Table 1) [27].

In this theory, it is supposed that delusions represent the outward expression of unresolved conflicts between the superego, ego, and id, the person's psychological agencies. In 1992, Roberts provided a model of three phases. The pre-psychotic is the first stage in which stress exposure acts as the antecedent in an individual who has an underlying susceptibility or tendency to a psychotic type of disorder. Then, the patient proceeds to the second stage, in which delusions develop when the individual starts to have different or unusual feelings, and these concepts and feelings are given a personal significance. Eventually, delusions are established and expanded, thus involving their relevant thoughts and ideas in the patient's thinking [28].

This includes the salience hypothesis, which claims that delusions arise from an unbalanced attention pattern, whereby particular aspects of a situation get more attention than relevant data, yielding distorted decision-making as a result. The two-factor hypothesis elaborates on this concept, claiming that delusions must be supported by both salience and flawed cognition [29,30]. These poor perceptual-cognitive processes may be related to a 'jumping to conclusions' propensity. People with this tendency to analyze information quickly before making judgments are more prone to ignore or misunderstand facts with more assurance of their choices. As a result, the false fixed belief is established, and the false logic impairs the perception which maintains the distinctive significance given to individuals, locations, and circumstances. Because of this, the patient's overall perceptions and conclusions become less accurate, which affects information integration and processing and raises the possibility of incorrect stimulus interpretations. According to brain network theory, problems integrating perception, cognition, and emotion result from disconnections between key components of the default mode and semantic networks, which prevents cognitive resources from being used effectively.

Trauma, especially that which involves interpersonal violence, has been associated with an increased chance of developing psychosis and delusions. The growing brain is altered by early childhood trauma. These changes include the hippocampus shrinking, the amygdala becoming hyperarousal, changes in neurotransmitters such as dopamine, GABA, and glutamate, and an increase in diathesis towards delusional symptoms.

When compared to other conditions, global functionality is often maintained to some extent. Impairment may have a major impact on a patient's lifestyle. Social isolation might exist. Persecutory type is among the most prevalent delusion categories in which the patient becomes aggressive, anxious, and irritable. In contrast, in the jealous type, men are more affected, and they usually have homicidal and suicidal thoughts, which require meticulous care and management. The erotomanic type involves the belief that a person is in love with the patient. These individuals often exhibit poor social and career functioning, sexual inhibition, dependency, and social withdrawal. Males with this type often become more aggressive. The somatic type is the most deteriorating type, with a major negative impact on the patient's lifestyle. The patient believes that he has severe symptoms without any evidence of real disease. Delusion parasitosis is the most prevalent type of somatic delusion in which the patient believes

Table 2. Comparative Overview of Pharmacological and Psychotherapeutic Treatments across Psychotic Disorders

Treatment Approach	Schizophrenia	Schizoaffective Disorder	Acute Polymorphic Psychotic Disorder with Schizophrenia Symptoms	Delusional disorder
Antipsychotic Medications	- Risperidone: 2-6 mg/day	- Aripiprazole: 10-30 mg/day	- Olanzapine: 10-20 mg/day	- Clozapine: 300-900 mg/day
	- Olanzapine: 10-20 mg/ day	- Quetiapine: 150-300 mg/day	- Quetiapine: 150-300 mg/day	- Aripiprazole: 10-30 mg/day
	- Quetiapine: 300-800 mg/ day	- Olanzapine: 10-20 mg/day	- Risperidone: 2-4 mg/day	- Olanzapine: 10-20 mg/day
	- Clozapine: 300-900 mg/ day	- Lithium: Blood levels maintained at 0.6-1.2 mEq/L	- Aripiprazole: 10-30 mg/day	- Quetiapine: 300-800 mg/day
	- cariprazine: 1.5 mg	- Clozapine: 300-900 mg/day		- Risperidone: 2-4 mg/day
		- Antipsychotic medications adjusted based on symptomatology		
Psychotherapeutic Approaches	- Cognitive-behavioral therapy (CBT)	- Individual and group therapy	- Supportive psychotherapy during acute phase	Cognitive behavioral therapy (CBT)
	- Family therapy	- Cognitive-behavioral therapy (CBT)	- Psychoeducation to enhance coping skills and resilience	- Individual and group therapy
	- Supportive psychotherapy	- Supportive psychotherapy	- Family involvement in understanding and supporting the individual's recovery process	Family-focused therapy
	- Positive psychotherapy in the period of remission for more than a year		- Eye Movement Desensitization and Reprocessing (EMDR) for trauma-related symptoms	
	- Gestalt psychotherapy to explore current experiences and promote self-awareness		- Gestalt psychotherapy to explore current experiences and promote self-awareness	

Source : author's development.

he has an infection with a worm, parasite, fungus, bacteria, mites, or other living organisms. Patients with the grandiose type have increased self-importance, while those with mixed type have two or more dominant categories. The unspecified type is considered when there is no dominant delusional theme [5].

Like most other psychological diseases, there are no specific labs or tests that can diagnose or identify Schizophrenia spectrum disorders. However, all reported laboratory tests and imaging modalities aim mainly to exclude any organic etiology. Proper genetic and family history taking may help detect susceptible patients. History of recent head trauma may be associated with the subsequent development of delusions. A urine drug screen may be conducted to rule out substance-induced delusions. Complete mental examination should be considered after excluding organic causes of delusions [5,31].

The lack of insight is the main challenge in the management of patients with delusions. It is doubtful that direct efforts to address delusions would be helpful and might yield considerable distress to the patient [32]. Due to the integrated neuropsychiatric framework of delusion, the proper treatment requires an integrated management of both the psychological and biological aspects simultaneously. The biological element is remitted by using antipsychotic medicine to reduce mesolimbic dopamine release. Since there is less dopamine released into the brain, stimuli in the environment are given less weight and are given a more individualized interpretation. Reevaluating the stimuli and allocating attention more precisely allows the individual to minimize the intensity of salience. This lowers the degree of over-personalized meaning and promotes a more realistic assessment of the circumstances. The psychological aspect is also important in those patients. Antipsychotic drugs showed great benefits in those patients. The efficacy of these medications may be investigated after a six-week trial period and trial use. Once the patient reaches the desired level with no improvement after six weeks, a different medication from a different class might be attempted. Other medications, such as carbamazepine, valproic

acid, and lithium, may be utilized as adjuvant therapy to the primary antipsychotic drugs if the monotherapy fails to control the condition (Table 2) [12].

To the best of our knowledge, there are no established guidelines or licensed medications for Schizophrenia spectrum disorders and schizophrenia. Antipsychotic medications showed a considerable benefit in managing patients with various psychotic disorders such as Schizophrenia spectrum disorders, schizophrenia, mania, major depressive disorder with psychotic features, agitation, Tourette, dementia, and delirium. First-generation antipsychotics (FGAs), also known as typical antipsychotics, act by antagonizing the dopamine receptors. They include various medications such as butyrophenones (haloperidol), phenothiazines (mesoridazine, trifluoperazine, acetophenazine, prochlorperazine, triflupromazine, perphenazine), dihydroindoles (molindone), dibenzoxazepines (loxapine), thioxanthenes (thiothixene, chlorprothixene), and diphenylbutylpiperidines (pimozide) [33–34]. In contrast, second-generation antipsychotics (SGAs), also known as atypical antipsychotics, act as serotonin-dopamine antagonists. Twelve atypical antipsychotic medications were approved by The Food and Drug Administration (FDA). They include ziprasidone, quetiapine, olanzapine, asenapine, lurasidone, aripiprazole, risperidone, iloperidone, clozapine, cariprazine, paliperidone, and brexpiprazole [35]. Great efforts have been made to reach out to the drug of choice among antipsychotic drugs that can manage delusional disorders. A previous study showed that FGAs, particularly pimozide, were associated with a considerable treatment response compared with other antipsychotic medications [36]. In contrast, another more recent systematic review concluded that the overall favourable response among treated patients was 33.6%, with a statistically significant superiority of FGAs compared to SGAs. Additionally, they showed no advantage of pimozide in managing delusional disorder compared to other antipsychotics [37]. Most published studies estimate the response to treatment via collecting medical records rather than using rating scales, which have high accuracy results in evaluating this response [38]. In 2020, a systematic review of studies that utilized clinical-rated scales was conducted to evaluate the accurate response and efficacy of antipsychotics in managing patients with delusions. They reported that FGAs were associated with a significantly better treatment response than SGAs. Although pimozide was found to be superior to other antipsychotics, $P \leq 0.03$ in most delusional disorder subtypes, it showed comparable results when compared with other FGAs. However, this study was limited by the high degree of heterogeneity and insufficient safety profile data of the investigated drugs [39]. A previous national cohort analyzed 9076 patients with the delusional disorder who received various pharmacotherapies to prevent work disability and reduce the incidence of hospitalization due to psychosis. They reported that most antipsychotics were effective in managing delusions. However, clozapine and long-acting injectables should be given greater consideration since they were associated with the lowest risk of hospitalization because of psychosis and work disability [39]. Adherence to drugs has an impact on the overall treatment response. Cognitive behavior therapy (CBT) has been found to be beneficial in both schizophrenia and delusions. Treatment with CBT results in a statistically significant decrease in the degree of delusional belief, the degree of affective symptoms of delusion, and the frequency of behaviors driven by the delusions [15]. Freeman et al. conducted a randomized controlled trial to evaluate the role of psychotherapy in the form of CBT to relieve the level of worry in patients with persecutory delusions and improve the delusions themselves.

LIMITATIONS

There is a lack of randomized clinical trials and high-quality evidence research that assesses both pharmacotherapy and psychotherapy in the management of delusions. The other main limitation of our study is that it is a narrative review, including mainly observational studies. The included research results are presented in written paragraphs without any pooled analysis using the data from the summarized studies. Real objectivity and pooled analysis are therefore precluded. A narrative review serves as a comprehensive source of the latest published evidence. This may be useful to understand a body of evidence fully. As it does not thoroughly consider the alternative hypothesis, it does not guarantee that the prevailing ideas are true.

CONCLUSIONS

Schizophrenia spectrum disorders can be presented as an isolated disorder or as a sign of psychological diseases such as schizophrenia and bipolar disorders. Delusions have negative impacts on the patient's life and can significantly cause work disability and social isolation. Delusions have no specific or proven etiology. However, there are many theories which may explain its occurrence. The treatment of delusions usually requires combined pharmacotherapy and psychotherapy. CBT and antipsychotics, either FGAS or SGAS, have a significant beneficial role in improving delusions. Further high-quality evidence randomized trials are required to properly estimate the efficacy of the available therapies and determine the first-choice therapy in patients with different categories of Schizophrenia spectrum disorders.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Olha Zahariichuk
Shupyk National Healthcare University of Ukraine
9 Dorohozhytska St, 04112 Kyiv, Ukraine
e-mail: inna.articles.ama@gmail.com

ORCID AND CONTRIBUTIONSHIP

Olha Zahariichuk: 0000-0003-4301-6611 A B D E F

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

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CREATIVE COMMONS 4.0

REVIEW ARTICLE

CONTENTS

Practical Uses of Fruits in Ancient Medicine (based on the treatise of Quintus Gargilius Martialis *Medicinae ex oleribus et pomis*)

Marta J. Petryshyn[1], Halina M. Zahaiska[2], Oxana V. Liubimova[2]
[1]VASYL STEFANYK PRECARPATHIAN NATIONAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE
[2]YURIY FEDKOVYCH CHERNIVTSI NATIONAL UNIVERSITY, CHERNIVTSI, UKRAINE

ABSTRACT

Aim: The aim of the article is to study the therapeutic effect and pharmacological characteristics of using fruits, berries, and nuts in ancient medicine, expanding and deepening knowledge in the history of medicine.

Materials and Methods: The study material was *Medicinae ex oleribus et pomis*, the work of Quintus Gargilius Martialis, a third-century Roman writer, a systematizer of rules for cultivating and medical application of over 60 types of vegetables and fruits.

The methodological basis of the research is a set of general scientific and special research methods, including analysis and synthesis, induction and deduction, historical, interdisciplinary, descriptive methods, and the method of contextual analysis.

Conclusions: Gargilius' treatise *Medicinae ex oleribus et pomis* is a valuable source of knowledge about the use of vegetables, herbs, fruits, and nuts for the treatment and prevention of various diseases in antiquity. Roman physicians sought remedies in nature, considered fruit crops as a miniature pharmacy, learned to use bark, stems, flower petals, seeds, fruits, and other parts of plants to strengthen immunity, prevent and treat diseases of therapeutic and surgical profile, laying the foundations of modern phytotherapy. Ancient medicine highly valued the therapeutic and prophylactic properties of pomegranates, plums, apples, pears, quinces, figs, almonds, and other plants. Studying the experience of ancient physicians in historical retrospective, analyzing the healing properties of fruits and nuts used in their practice by ancient doctors, provides an idea of the development of the healing art, understanding the functions of the human body, means of prevention, and treatment of diseases in ancient times.

KEY WORDS: history of medicine, Quintus Gargilius Martialis, fruits, nuts, treatment, complementary alternative medicine

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INTRODUCTION

Fruits in human diet are a source not only of vitamins, organic acids, mineral salts, but also of fiber, tannins, and pectin substances, which beneficially affect digestion and metabolism processes, play an important role in immune system formation, health preservation, reduce the risk of gastrointestinal, cardiovascular, nervous, and circulatory system diseases, and have a beneficial effect on the human body. Ancient physicians sought remedies in nature, learned to use bark, stems, flower petals, seeds, fruits, and other parts of plants for medicinal purposes, laying the foundations of modern phytotherapy. In view of this, it is important to study the experience of ancient writers and physicians in historical retrospective, analyze the healing properties of fruits and nuts used by ancient physicians in their practice, adapt their achievements to the history of the development of modern phytotherapy.

AIM

The aim of the article is to study the therapeutic effects and pharmacological characteristics of using fruits, berries, and nuts in ancient medicine, as well as to expand and deepen knowledge in the history of medicine. This research is a continuation of the series of publications by the authors' group dedicated to the issues of prevention and treatment of surgical and therapeutic profile diseases with the gifts of fields, meadows, forests, and gardens in ancient times.

MATERIALS AND METHODS

The research material was *Medicinae ex oleribus et pomis,* the work of Quintus Gargilius Martialis, a third-century Roman writer, known in the history of medicine as Book IV of the *Medicina Plinii* [1]. The manual consists of 60 chapters and contains instructions for growing fruit

trees and vegetables, as well as information about their medicinal properties and medical applications.

The methodological basis for studying the healing properties of fruits in ancient medicine includes a series of general and special scientific methods. The method of analysis and synthesis allows for the systematization of scientific developments on the mentioned issues; the inductive-deductive method enables the comprehension of theoretical and practical material; the method of contextual analysis contributes to the identification of features in the use of garden gifts in the therapeutic practices of ancient Romans; the historical method provides an opportunity for retrospective consideration; the interdisciplinary method traces the connection between the history of medicine and pharmacology, and the descriptive method is used for the description and interpretation of research material.

REVIEW AND DISCUSSION

Over the past decades, medical professionals and biologists have conducted a series of significant studies dedicated to the issues of treatment, health prevention, formation of a healthy lifestyle ideology, and proper nutrition with the gifts of fields and forests. The scientific-popular research by Artemenko M. and Latanska L. is devoted to legends about fruit trees, characteristics of the taste and healing properties of fruits and berries [2]. The scope of scientific interests of Mamchur F. is associated with studying the influence of biologically active substances of vegetables, garden greens, fruits, berries, and mushrooms on the human body, their application in disease prevention, treatment, and rational nutrition [3]. The phytotherapeutic guide edited by Orach A. and Orach O. contains information not only about the effectiveness of plant-based preparations in the treatment of pulmonological, gastroenterological, gynecological, endocrine, and surgical diseases but also about the analogs of using vegetables, greens, fruits, and berries in a particular phyto mix based on the pharmacologic properties of their bioactive components [4]. A thorough analysis of the biologically active substances of apples and their therapeutic value for human health (prevention of cardiovascular diseases, diabetes, inflammations, oncology) is presented in the article by Patocka J. et al. [5]. The subject of scientific interests of Hong S. is the research of the therapeutic properties of pears *in vitro, in vivo*, and in humans based on the evidence from ancient literature and modern protocols [6]. Scientific investigations by Jurenka Ju. [7], as well as Fahmy H. and Farag M. [8], are devoted to studying the antioxidant, anticarcinogenic, antimicrobial, antihypertensive, antidiabetic, hepatoprotective, neuroprotective, and immunomodulatory effects of pomegranates. The dietary properties and medical application of peaches in ancient medicine based on the treatises of the 1st-7th centuries CE were studied by Jagusiak K. and Kokoszko M. [9]. The sphere of scientific interests of Barolo M., Ruiz Mostacero N., and López S. is related to the study of the biological and medicinal properties, nutritional value, and ethno-pharmacological use of figs [10]. In the context of research on the creative legacy of Gargilius in recent publications, we can highlight the investigation by Brodersen K., dedicated to illuminating the use of various herbs, vegetables, fruits, and nuts for the prevention and treatment of various diseases [11]. An overview of Gargilius' treatise as a source of knowledge in ancient pharmacology and dietetics is presented in the translation of fragments of the work into English by Riddle J. [12]. The problem of researching the origins and sources of medical knowledge of Gargilius is highlighted in the article *L'esprit ou la lettre: les sources des Medicinae de Gargilius Martialis* by Maire B. [13]. The description of the healing properties of cultivated plants based on Gargilius' work can also be found in the monograph by the researcher *'Greek' and 'Roman' in Latin Medical Texts. Studies in Cultural Change and Exchange in Ancient Medicine* [14]. Valuable thoughts and generalizations regarding Gargilius' contribution to the development and popularization of medical knowledge in Roman society are also presented in the review of the Polish translation of the botanical-pharmacological work *Medicinae ex oleribus et pomis* by Stuligrosz M. [15]. Research on the use of citrus crops in the Western Mediterranean based on ancient Greek and Latin texts, including Gargilius' work, is encountered in the article by Pagnoux C. [16]. Mention of Gargilius' contribution to the systematization and popularization of knowledge about the use of fruits for medicinal purposes in the ancient period is found in the popular scientific exploration by Kovalenko O. [17]. The subject of interest for Kelbecheva V. is the nature, therapeutic effect, and healing properties of individual plants, including radishes, savory, and mallows, based on the material of Gargilius' medical treatise [18]. The experience of using vegetable crops in the practice of ancient Roman physicians for the prevention and treatment of diseases of therapeutic and surgical profile based on the material of the medical-pharmacological treatise *Medicinae ex oleribus et pomis* is outlined in the exploration by Petryshyn M., Zahaiska H., et al. [19] The issue of the medical application of thyme as a repellent against snake bites based on Gargilius' treatise is addressed in the article by Rodriguez A. [20]. However, Gargilius' creative legacy has attracted the attention of scholars not only from the perspective of pharmacology and the history of medicine but also from philology. For example, the research by Maire B. [21] and Mantzilas D.

[22] is dedicated to the analysis of the lexical composition and stylistic devices and figures in *Medicinae ex oleribus et pomis*. Researcher T. Krynytska not only translated Gargilius' work into Polish, but also thoroughly analyzed the author's life and work, as well as the sources of his medical knowledge, and presented a bibliographic study of Gargilius' scientific legacy [23]. However, the question of the practical application of fruits, berries, and nuts in the medical practice of ancient Romans from the perspective of medical history requires further elucidation, as the medical knowledge of Ancient Greece and Rome laid the foundations for the further development of European medicine, and the introduction of numerous plant-based preparations into medical practice owes much to Roman scholars and physicians who, based on the works of ancient Greek physicians, created their own concept of disease prevention and treatment using gifts of nature.

In the early stages of societal development, plants were the primary source of human nutrition. By consuming the gifts of fields, orchards, and forests, people learned not only to satisfy hunger but also noticed the therapeutic effect of consuming various plants. Vegetables, fruits, and berries have become not only food products but also a means of treating many diseases, a source of health, strength, and vitality. Ancient writers and physicians synthesized accumulated experience and knowledge, devoting entire treatises to the healing properties of plant-based products. Therefore, we can objectively assert that even Roman physicians understood that nature was the source of remedies, and consuming an adequate amount of fruits and vegetables postponed the need for a visit to the doctor.

Our analysis focuses on the second part of the medical treatise by Quintus Gargilius Martialis, dedicated to describing the healing properties of fruits and nuts (chapters XL-LX). Gargilius creatively synthesized the experience and medical knowledge of his predecessors: Pliny the Elder, Dioscorides, Galen, Columella, and others.

The research indicate that Roman physicians successfully treated gastrointestinal, blood, pulmonary, and skin diseases with fruits and nuts which were accessible to all strata of the population of Rome, namely: apples, pears, plums, pomegranates, cherries, peaches, quinces, etc. Roman physicians most often prescribed the use of fruits for medicinal purposes in cases of gastrointestinal infections, which can be explained by the disruption of the digestive system due to the consumption of poor-quality food, contaminated drinking water, and poor hygiene practices. For diarrhea, it was recommended to drink a decoction of dried pears or leaves: *Aqua in qua pira sicca decocta sunt mirifice valet fluxum ventris inhibere* (XL, 10)[1], quince soaked in vinegar or wine: *Infudi quoque in aceto sive in vino solent quod stomachicis et intestinorum fluore vexatis* (XLIII, 9), resin from the peach tree: *fluenti alvo medetur* (XLIV, 11), sour cherries: *austera ... ventrem constrigat, stomachum vero confirment* (LII, 8), wine with burnt pomegranate powder: *Alvum fluentem miro modo sistit* (XLI, 12), medlar fruits: *fluctus ventris fortissime detinet* (XLVII, 5). The astringent and disinfectant effects of dried pears [3, 141; 24, 129], medlar [24, 287], and quince [3, 129; 24, 30] are still successfully used in folk medicine today. Roman physicians noticed and widely used the laxative effect of fruit pectin substances, which activate peristalsis, to treat constipation. Regular consumption of plums boiled in wine with honey: ... *ventris operaci maximeque proficere* (XLVI, 5) or fresh cherries with pits intact: ... *alvum copiose fluere* (LII, 4) improved intestinal motility, softened stool masses, and increased the frequency of defecation. Fresh or dried plums and cherries are also recommended by modern medicine as natural remedies for constipation and intestinal atony [24, 401]. In addition, as a prokinetic agent, walnut with fish sauce garum was recommended to be consumed: *Potest … ventrem cum garo sumpta mollire* (LVII, 2). To stabilize the stomach mucosa and alleviate symptoms of gastric ulcer disease, as well as to stop gastric bleeding, ancient physicians prescribed a drink made from pomegranates soaked in rainwater for three days: *coeliacis sanguinemque iactantibus salutaris est* (XLI, 11), or dried ripe elderberries: *matura siccata sublevant stomachum* (L, 2). Roman physicians recommended to alleviate intestinal colic caused by a disorder of motor, secretory, and absorptive functions of the digestive system by drinking a decoction of pine bark with wine: ... *contra ventris tormina subministrat* (LVIII, 8), and normalized hyperacidity by regular consumption of pine cone nuts: *ex nucleis cibus … stomachi acrimoniam temperat* (LVIII, 1). Reduction of stomach receptor stimulation and suppression of nausea and vomiting were achieved by the intake of cherry tree resin dissolved in aged wine: ... *fastidium stomachi nausiantis avertit* (LII, 12-13), cedar nuts: *stomachum a nausia vindicat* (XLV, 2), apples baked with flour: *putat stomachi nausiantis offerri*" (XLII, 6). For liver pain, Romans consumed crushed pear seeds with honey: ... *dolorem iecoris submovere* (XL, 16), crushed lemon with wine: *tritum et in potionem datum lieni ... querelis iecoris occurit* (XLV, 3), or juice of jojoba roots and bark with wine: *radicis et corticis … succus ... cum mero mixtus iecori medetur* (XLVIII, 6-7).

In Gargilius' treatise, we also find recipes for using fruits in cases of kidney dysfunction. The consumption of sour pomegranate fruits: ... *urinam movent* (XLI, 4), and unripe

[1] The Roman numeral stands for the number of the chapter, the Arabic numeral – for the number of the verse line.

cherry fruits: ... *urinam movere* (LII, 4) contributed to the removal of excess fluid and the restoration of the body's water-salt balance. The high potassium and sodium content provide diuretic properties to cherries. Therefore, a decoction of cherry stems is successfully used today as an adjunctive treatment for dropsy, edema, and urinary stone disease. Ancient therapy accumulated significant experience in treating *urolithiasis* with garden gifts. A lithotriptic effect was observed with the intake of cherry tree resin with honey: *calculos vesicae in harenae pulverem solvit* (LII, 14), peach tree resin with wine: ... *mixta cum vino etiam in vesica lapillos frangit*" (XLIV, 11-12), and enemas with almond decoction with resin of the turpentine tree: *pro ecligmate data calculos frangunt* (LIII, 11).

In Gargilius' treatise, we find numerous recipes for treating diseases of the nose, throat, ear, and lungs with garden remedies. For instance, in cases of rhinitis, it was recommended to burn dry hazelnuts in clay vessels: ... *distillationibus mitigandis utilissime offeruntur* (LIV, 2). Inflammation of the tonsils was successfully treated with crushed pomegranate flowers mixed with honey: ... *itemque toxillis et uvae medetur cum melle contritus* (XLI, 20). The therapeutic properties of cherry tree resin with aged wine were highly valued in ancient times. This remedy was used to treat tracheitis: *Gummi, quod truncus inlacrimat, … si in vino vetere detur in sorbitione resolutum* (LII, 12). Dried cherry tree sap (gum) is considered one of the effective demulcents in folk medicine for coughs [24, 86]. To alleviate symptoms of throat dryness and irritation in pharyngitis, as well as throat swellings, it was recommended to consume a decoction of peach tree resin with saffron: ... *thoracis obstrictos sinus reserat* (XLIV, 12). The symptoms of cough were treated by ancient physicians with remedies made from nuts and fruits. For instance, to soothe coughing, it was recommended to consume balls the size of nuts made from crushed almonds and honey: *tussi … prosunt cum elelisfaco ac melle contrita* (LIII, 12), chestnuts roasted with honey in a dry clay pot: *tussientibus prosunt* (LVI, 2), juice of the jujube tree with honey: ... *tussim mitigat* (XLVIII, 7), which is used in alternative medicine as an anti-inflammatory and soothing agent for upper respiratory tract infections [24, 173]. Honey water with crushed forest hazelnuts, which ancient botanists referred to as "abellean," was considered an effective remedy for treating chronic cough: ... *vetustissimae tussis molestiam sedant* (LIV, 3). The disinfecting and expectorant effect of pine cones was used for hemoptysis: ... *excreantibus sanguinem salutare est* (LVIII, 7); The disinfecting and expectorant effect of pine cones was used for hemoptysis: ...*excreantibus sanguinem salutare est* (LVIII, 7); a decoction of pine buds is still recommended by doctors for inflammation of the upper respiratory tract [24, 413]. Over the years, for the prevention and treatment of lung diseases and coughs, a powder made from rowan berries with barley groats and wine was also used, whose anti-inflammatory effect relieved disease symptoms, while its bactericidal properties destroyed pathogenic microflora: *pulmonis molestiam sentientibus obtulerunt* (L, 3), the decoction of peach tree trunk resin with saffron: *decocta cum croco … vitia pulmonis expurgat* (XLIV, 12), the decoction of figs with hyssop: ... *pectus expurgat* (XLIX, 5).

In ophthalmology, Roman preparations from fruits were rarely used. From the analysis of the treatise text, only a recipe for eye pain relief based on pomegranate flower calyces: *ab oculorum dolore praestare* (XLI, 13), and an ointment made from powdered Assyrian plum seeds with oil and honey: ... *non abiecti vigoris xerocollyrium praestant* (LIX, 4) were found.

In general therapy practice, Roman physicians recommended baked quince for chronic fever: ... *aegris quorum diuturna iam febris est sine periculo dantur* (XLIII, 5), and for headaches, they applied an ointment made from peach pits, olive oil, and vinegar: *capitis dolori ... inlinitur* (XLIV, 10).

When the body was infected with helminths, Gargilius recommended applying compresses to the abdomen made from crushed peach tree leaves: ... *animalia perimunt et expellunt* (XLIV, 8).

The history of infectious diseases also goes back to ancient times as well. From the descriptions of ancient physicians, it can be concluded that infectious diarrhea and dysentery were endemic problems in the ancient world. In the treatise *Medicinae ex oleribus et pomis*, a number of recipes are dedicated to treating dysentery. For example, in cases of dysentery, Gargilius recommends consuming ripe or unripe quince: *dysentericis, sanguinem reiectantibus prosunt* (XLIII, 3), dried wild plums: ... *siccum etiam veteres dysentericos certum est adiuvare* (XLVI, 9), infusion of rowan berries: ... *dysentericis iniecta medicatur* (L, 4), or chestnuts: ... *dysentericis propinatur* (LVI, 3).

Ancient Romans also learned to prepare antidotes from fruits. Dried and crushed rowan leaves and bark with wine were considered a universal remedy against various poisons: ... *veneficis potionibus repugnare* (XLVII, 9), and one of the best remedies for alcohol intoxication was almond nuts: *Sicca etiam ebrietatem valent* (LIII, 4).

Preparations made from tree fruits were successfully used by ancient physicians in dermatology to treat baldness, lichen, and warts. An effective remedy for combating alopecia, according to Gargilius, is an ointment made from bear fat and crushed hazelnuts: ... *alopeciis inlitae capillorum damna restituunt* (LIV, 6). The author provides a precise recipe for treating baldness based on nuts, including grinding and placing 100 young

nuts with skins in a clay pot, adding three pounds of crushed alum, three libras of good-quality olive oil, and infusing the mixture for 90 days (LVII, 5-8). In addition to medicinal treatments for alopecia, modern medicine recommends incorporating nuts rich in B vitamins, zinc, and essential fatty acids into the daily diet, which improve hair growth and volume [24, 119]. Lichen, known to physicians since ancient times, was treated with a mixture of plum tree resin and vinegar: ... *lichenas optime purgat* (XLVI, 10). For the treatment of papillomas and warts, ancient physicians used external remedies aimed at eliminating skin defects. Positive results were observed with the use of ointment made from apples, saffron, wine with raisins, fresh bread pulp, or sulfur: ... *in ceroti lentorem mollescant* (XLII, 14).

Surgery and traumatology were integral parts of ancient medicine. Ancient Roman physicians were skilled in treating various injuries, boils, ulcers, abscesses, fistulas, frostbite, bites, and more. In ancient times, people were not immune to dog bites, snakebites, scorpion stings, and infections by pathogens causing deadly diseases. For dog bites and cancerous ulcers, it was recommended to apply crushed almonds with honey: *Ulceribus canceratis et caninis morsibus trita cum melle subveniunt* (LIII, 9); for snakebites, crushed pistachios with wine were deemed effective : … *morsum serpentium prosunt* (LV, 4). Applications of crushed figs with salt were used to treat scorpion stings: … *scorpionum plagis medetur* (LIX, 11). Additionally, compresses made from figs boiled in wine were successfully employed in surgical practice to treat acute purulent-necrotic inflammation of the hair follicle and surrounding connective tissue: *Ipse panno inlitae et impositae … furunculos rumpunt* (XLIX, 7). Similarly, figs mixed with copper oxide were applied to wounds of the tibia bone: … *tibiarum vulneribus imponuntur* (XLIX, 10), compresses made from crushed figs were also utilized to treat various ulcers: *Canceratis quanto pinguinores fuerint tritae et impositae tanto efficacius subveniunt* (XLIX, 12). In traditional medicine, figs are applied to abscesses to hasten their maturation and to remove calluses [24, 404]. The wound-healing properties of powder of peach tree leaf: ... *plagas cruentorum vulnerum claudunt* (XLIV, 9) and of pomegranate flowers… *exedit carnem quaecumque vulneribus* (XLI, 16) were widely used in surgical practice. Fresh pear pulp not only stopped bleeding but also promoted wound healing: *Recentibus certe admota vulneribus sistere sanguinem profluentem, perducere vulnus ad cicatrem* (XL, 2), and boiled and crushed tart and sour apples, when applied with lard, were used to alleviate swelling and hematomas: *Tumores atque livores ex aqua cocta et cum axungia trita compescunt* (XLII, 10). Compresses made from Assyrian plums with finely ground flour treated festering wounds effectively: *Trita et cum polline imposita collectiones suppurare non patiuntur* (LIX, 3).

In gynecological practice, compresses made from quince soaked in rainwater were applied to uterine tumors: ... *et matricibus feminarum in tumore succurit* (XLIII, 8). Warm compresses made from figs and fenugreek were used for uterine diseases): … *fomentum faciunt quod extinguit vitia matricum* (XLIX, 8). Roman physicians also recommended pregnant women suffering from morning sickness to consume sour cedar seeds: *praegnantibus fastidio laborantibus esui datum stomachum a nausia vindicat* (XL, 2).

Ancient Romans paid close attention to oral hygiene since halitosis was a common symptom of dental diseases. Dentists recommended rinsing the oral cavity with a decoction of plum leaves for gum diseases: *gingivas … ab omni querela ore conluendo defendi"* (XLVI, 11). For toothaches, chewing medlar fruits was advised: ... *dentibus … subvenire, si in dolore mandatur* (XLVII, 5). Stomatitis was treated with pomegranate flowers crushed with honey: *Ulceribus oris itemque toxillis et uvae medetur* (XLI, 20). Additionally, remedies for oral diseases were prepared based on the juice of sour pomegranates, saffron, myrrh, alum, and honey, known as "stomatice" among the Greeks: *Hoc medicamento oris vitia sanantur* (XLI, 24-27).

CONCLUSIONS

For thousands of years, indigenous and sometimes original medicine has accumulated a rich experience in treating various pathologies. Ancient physicians sought remedies in nature, learning to utilize the bark, stems, petals of flowers, seeds, fruits, and other parts of plants for medicinal purposes, laying the foundations of modern phytotherapy. They left descendants many works that are a valuable source of information about therapeutic agents made on a plant basis. One such work is Quintus Gargilius Martialis' treatise *Medicinae ex oleribus et pomis*, dedicated to the application of vegetables, herbs, fruits, and nuts in the medical practice of ancient Romans. Roman physicians successfully used the fruits of fruit trees and nuts to strengthen the immune system, prevent and treat diseases of therapeutic and surgical profiles. The advantage of plant-based remedies is the possibility of prolonged use of natural medicines without side effects. In antiquity, the healing and preventive properties of pomegranates, plums, apples, pears, quinces, figs, almonds, and other plants were highly valued.

Studying the past of medicine provides important information about the development of the art of healing, means of disease prevention and treatment, and understanding the functions of the human body in ancient times.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Oxana V. Liubimova
Yuriy Fedkovych Chernivtsi National University
2 Kotsyubynsky St., 58012 Chernivtsi, Ukraine
e-mail: o.liubimova@chnu.edu.ua

ORCID AND CONTRIBUTIONSHIP
Marta J. Petryshyn: 0000-0003-4060-7440 A B D E
Halina M. Zahaiska: 0000-0003-1449-0269 A B D
Oxana V. Liubimova: 0000-0003-0413-309X A E F

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

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CREATIVE COMMONS 4.0

REVIEW ARTICLE

CONTENTS

The influence of heredity and environment on human cognitive ability

Valentyn Pomohaibo, Natalia Karapuzova, Yuliia Pavlenko, Vasyl Fazan
POLTAVA V. G. KOROLENKO NATIONAL PEDAGOGICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

Aim: The aim of the study is to consists in the theoretical analysis of the results of modern genetic studies of human cognitive abilities as a key to successful education and upbringing.

Materials and Methods: To solve the tasks and achieve the goal of the article, we used general scientific methods of the theoretical level (analysis, synthesis, comparison, systematization, generalization of scientific and theoretical data), regarding the influence of heredity and environment on human cognitive ability.

Conclusions: Human cognitive abilities develop under the influence of both genetic and environmental factors. In addition, there is also an active interaction between a person's genotype and his environment, the result of which also affects his cognitive abilities. Different specific cognitive abilities are influenced differently by genes and environment. The regularities of these processes should be known by education leaders, teachers and parents in order to use them in a timely and qualified manner to ensure the most successful education and upbringing of school-aged children.

KEY WORDS: heritability, heredity, school performance, common and individual environment, general cognitive ability, specific cognitive ability.

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INTRODUCTION

The main postulate of genetics is that all characteristics of a living organism are determined by its genes, and are formed under the influence of environmental factors. However, there is another important aspect of an organism's development – the interaction between its genotype and the environment [1]. It is a phenomenon where environmental factors affect different people differently, depending on their gene set, and genetic factors have different effects on a person's characteristics, depending on the characteristics of the environment. These three key principles of genetics carry out the implementation of each characteristic, including the cognitive abilities of a person, which are the determining conditions for education and upbringing. Politicians, teachers, and parents need to know the features of these phenomena to use them in a timely and qualified manner for the successful education of children, especially in primary school, where the foundations of further compulsory school and professional education are laid to ensure achievements in life.

AIM

The study aims to theoretically analyze the results of modern genetic studies of human cognitive abilities as a key to successful education and upbringing.

MATERIALS AND METHODS

To solve the tasks and achieve the article's goal, we used general scientific methods of the theoretical level (analysis, synthesis, comparison, systematization, and generalization of scientific and theoretical data), regarding the influence of heredity and environment on human cognitive ability.

The leading role in the work was also played by the interdisciplinary approach, which, within the framework of historical-philosophical research, involves the synthesis of not only the norms of scientific research of primary sources but also theoretical ideas and principles that determine the directions of object research. Also, the interdisciplinary approach played a leading role in the work, which within the scope of the study involves the synthesis of not only the norms of scientific

research of primary sources but also theoretical ideas and principles that determine the directions of the object's research.

REVIEW AND DISCUSSION

Cognitive abilities, that is, individual differences in properties such as thinking and memory, are one of the oldest and best-studied areas of psychogenetics, or behavioral genetics [2]. Attention to cognitive abilities is partly due to their growing importance in modern human society, where «intellectual capital» is key. In addition, measures of cognitive ability predict major social achievements, such as academic and occupational success, far better than any other [3, 4]. They also predict good health and longevity [5].

Genetic studies of cognitive abilities are based on a hierarchical model of their relationships in which a large number of individual test results on various cognitive abilities are grouped into specific cognitive abilities, which, in turn, make up general cognitive ability [6]. The index of general cognitive ability (g) was proposed by the British psychologist and author of factor analysis Charles Spearman more than a century ago [7]. The term «general cognitive ability» better reflects the essence of the phenomenon than the word «intelligence», since the latter has a large number of different interpretations in psychology and general usage [8].

Intelligence tests, often called IQ (intelligence quotient) tests, are well known. They tend to assess several cognitive abilities together, such as vocabulary, picture completion (pointing out what is missing in a picture), similarity and block building (using colored blocks to create the structure shown in the picture), etc., and give an indicator of general intelligence, or general cognitive ability, or intelligence. In research, general cognitive ability (g) is usually calculated using factor analysis, which takes into account the tests, depending on their contribution to this measure. The contribution of a particular test to g depends on the complexity of the cognitive operations it assesses.

It should also be borne in mind that the existing methods of determining g do not take into account all components of cognitive ability. Thus, the real cognitive ability is greater than the calculated one. As a result, it is better to examine individual cognitive abilities and cognitive skills acquired in the learning process. In addition, cognitive skills play a greater role in achievement than cognitive abilities themselves.

GENERAL COGNITIVE ABILITY

Early studies of human genetics found that parent-child IQ correlations in normal families were greater than in foster families [9, 10]. A later study of families with adopted children showed that the same pattern was observed when comparing adopted children with their biological parents [11]. This proved unequivocally that IQ is genetically influenced. The next major step in the study of the nature of IQ was the so-called Louisville Twin Study, initiated in the early 1960s, which was the first large longitudinal study of IQ [12]. It determined further ways of studying the role of genetic and environmental factors in human intellectual development. At the same time, the special attention of scientists was directed to increasing the volume of experimental samples, increasing the accuracy of measurements and the duration of research.

At the end of the 20th century, it has been conclusively shown that not only IQ but also general cognitive ability g is influenced by genes [1, 13–15]. According to the results of these studies, first-degree relatives who live together are moderately correlated in g (about 0.45). This can be due to both genetic and environmental factors since such relatives are simultaneously affected by both. In families with adopted children, both genetic and environmental factors are shared. The g correlation between adopted children and their biological parents, and between genetically related siblings raised separately, was only. 24. Since relatives of the first degree of consanguinity are only 50% genetically similar, the level of heritability of the indicator g is 0.48 (0.24 x 2), or 48%. This suggests that only about half of the differences between people in g can be accounted for by genes.

A similar pattern is repeated in studies of twins. The average correlation g for monozygotic twins is 0.86 because they are genetically almost identical, and for dizygotic twins, it is 0.60 [8]. The level of heritability g is 0.52, or 52%. Of interest to researchers is the situation when monozygotic twins are raised in different families [1, 15]. Correlation by trait between such twins directly testifies to the level of heritability. According to the results of these studies, the correlation and heritability of g were 0.72 and 0.78, respectively (an average of 0.75, or 75%). This rate of heritability is significantly higher than under other conditions of the experiment.

In the case of an analysis of the combined results of studying all studied situations (within normal families, adopted children, and twin pairs), the heritability g was about 50% [14, 16]. It is noteworthy that the genetic component in this case determines half of the variability of such a complex trait as general cognitive ability. In addition, measurement errors are not taken into account in these studies. If this were done, then the level of heritability would be higher. But, despite this, the genetic influence on g is not only statistically significant but also substantial.

These patterns of inheritance of the g index are observed not only in the population of the countries of Western Europe and North America, where most of the research was conducted. And among the population of Asian countries – Japan and India [8].

Recently, the heritability of traits has been determined using hundreds of thousands of single-nucleotide polymorphisms (SNPs) in the DNA molecules of the entire genome. At the same time, the heritability of g and other behavioral traits is approximately two times lower than in twin studies [17, 18].

If one part of the variability of g can be explained by heredity, then the other part can be explained by the influence of the environment. For example, members of the same family are influenced by common factors of the family environment, as a result of which they partially become similar to each other. Indicators of the influence of the shared environment can be determined based on correlations in the trait between parents and adopted children, as well as between native and adopted children. The g correlation of 0.32 between native and adopted children is particularly impressive. Since they are not genetically related to each other, what makes them similar is nothing more than the shared conditions of existence – the same parents, the same food, studying in the same school, etc. Thus, about a third of the total variability of the trait can be explained by the influence of the common environment. The g correlation between parents and own children turned out to be smaller – 0.19 than between biological and adopted children. This indicates that the shared environment is not perceived the same by parents and their children, in contrast to the perception of it by their own and adopted children [13, 14].

Twin studies also support the presence of shared environmental effects on g. In addition, a shared environment appears to contribute more to the similarity of twins than normal siblings, as the correlation for g even in dizygotic twins (0.60) exceeds that of normal siblings (0.47) [1, 15]. These twins can be more similar to each other than ordinary siblings because their embryos developed in the same conditions and they are the same age. Since they are of the same age, they are most likely to study in the same school, or even in the same class, and be surrounded by the same peers [19].

Calculations have shown that the share of shared environmental influence on g is about 20% for parents and their children, about 25% for siblings, and about 40% for twins [16]. The remaining non-genetic influence is caused by the individual's environment and the presence of possible measurement errors.

SPECIFIC COGNITIVE ABILITIES

Specific cognitive abilities have been less studied than general, but genetic patterns are similar to those of general cognitive ability [20]. The largest study of specific cognitive abilities was the so-called Hawaii Study of the Process of Cognition, which included more than a thousand families [21]. As in other similar studies, it used the method of factor analysis to identify groups of the most interconnected tests. At the same time, 15 tests were divided into four-factor groups: verbal abilities (including vocabulary and fluency), spatial abilities (visual representation of objects and their rotation in two and three-dimensional space), perception speed (simple calculations and comparison of numbers) and visual memory (recognition of pictures after a short and long period). Parents and their children were significantly similar in all groups of factors, although family similarity was greater in verbal and spatial abilities than in perceptual speed and visual memory.

The generalized results of dozens of early studies of cognitive abilities in twins (Table 1) showed that the heritability of specific cognitive abilities is much smaller than the heritability of general cognitive ability [22]. Word comprehension and perceptual speed were inherited by 40%–50%, and the rest (spatial representations, thinking, fluency, and memory) – on average, by 30% (from 26% in spatial representations to 35% in memory).

The rest of the influence on specific cognitive abilities is provided by the environment – shared and individual. In the above-mentioned studies of twins (table), on specific cognitive abilities, as well as on general, the common environment exerted a moderate influence on different levels – from 14%–18% (memory and speed of perception) to 36%–44% (spatial representations, fluency of speech, understanding of words and thinking). The individual environment also moderately affects specific cognitive abilities, but the levels of influence do not coincide with the levels of influence of the common environment. It mostly affects spatial representations and memory (38% and 51%, respectively). The rest of the abilities are influenced by the individual environment by an average of 30%. The shared environment affects specific cognitive abilities somewhat less on average than general cognitive ability. However, the level of influence of the individual environment on specific cognitive abilities is more than 4 times higher than on general cognitive ability. Such discrepancies regarding the influence of genes and the environment on general and specific cognitive abilities can be explained mainly by the fact that there are still a large number of specific cognitive abilities that have

Table 1. The ratio of the influence of heredity and the environment on specific (SCA) and general (GCA) cognitive abilities according to the generalized results of a study of twins (in %)

Specific cognitive abilities	Heredity	Environment		Together
		common	individual	
Understanding words	38	38	24	100
Freedom of speech	29	36	35	
Thinking	28	44	28	
Spatial representations	26	36	38	
Perception speed	50	18	32	
Memory	35	14	51	
Average specific cognitive abilities	34	31	35	
General cognitive ability	52	40	8	

not been identified or have not been taken into account in the research.

Since the content of the individual environment largely depends on a person's choice and personal perception of the common environment, that is, on its hereditary characteristics, it can be assumed that the influence of the individual environment is partially determined by the genes of a specific person.

SCHOOL PERFORMANCE

At first glance, school tests of students' academic performance differ significantly from tests of specific cognitive abilities. School performance tests focus on program performance in specific academic subjects such as literacy (reading and writing), numeracy (mathematics) and science. Although some subjects, such as history, may seem to be largely about memorizing events and dates, successful study of such subjects requires cognitive skills such as thinking and extracting the essentials from large amounts of information. Other subjects, such as reading and writing, mathematics and science, appear to be more like cognitive abilities because, regardless of content, they are based on general cognitive processes. When it comes to reading, most children in early school age move quickly from learning to read to reading for learning. The difference between literacy numeracy and cognitive abilities is that the first two are subjects that are taught in school, while the general and specific cognitive abilities discussed earlier are not directly taught anywhere, ever. Nevertheless, as will be shown below, multivariate genetic studies reveal significant genetic overlap between academic achievement and cognitive ability.

It is widely believed that success in school is achieved with the help of certain efforts, which are considered components of the environment, while abilities are formed under the influence of genetic factors. As a result, over the past half-century, educational research has focused on environmental factors, such as characteristics of schools, neighborhoods, and parents. At the same time, the possibility of the influence of heredity on children's learning abilities was practically ignored [23).

By far the best studied is reading ability [24]. The results of a long-term study of more than 4,000 twins indicate that processes related to literacy, such as word recognition and reading comprehension, have average heritability rates in a narrow range of 57% to 67%, that is, they are subject to significant genetic influence [25]. Interestingly, the level of heritability of literacy components in the first grades of Australia, Scandinavian countries and the USA is similar and varies around 64% [26]. Similar results were obtained with twins in China, despite the specific orthography of the Chinese language [27].

At first glance, it may seem that the ability to learn to read (recognize words) may be less heritable than reading comprehension, but both processes are highly heritable [28; 29]. Even skills that precede reading (sounding letters and their rapid naming, verbal memory) are significantly influenced by genetics [30, 31]. Studies of the interaction between genotype and environment in twins have shown a decrease in the heritability of reading ability in children from low-income families [32] and an increase in it in children who study with better teachers [33].

As for abilities in other academic subjects of elementary school, even early studies of twins showed their significant heritability and a moderate influence on them in the common environment [34, 35]. Similar results were obtained later in the Netherlands [36], Australia [37] and Great Britain [38]. For example, the results of a study of the performance of British twins of different age groups in English, mathematics and science showed that the heritability of the ability to learn in these subjects varies at the level of 60%, and the influence of the shared

environment at the level of only 20%, even though twins grew up in the same family, attended the same school, and were often taught by the same teachers in the same classroom [38]. Similar results were also obtained in the study of educational achievements at the end of compulsory education at the age of 16 [39].

CONCLUSIONS

Human cognitive abilities develop under the influence of both genetic and environmental factors. In addition, there is also an active interaction between a person's genotype and his environment, the result of which also affects his cognitive abilities. Different specific cognitive abilities are influenced differently by genes and environment. The regularities of these processes should be known by education leaders, teachers and parents to use them in a timely and qualified manner to ensure the most successful education and upbringing of school-aged children. This is extremely relevant in terms of the modernization of Ukrainian education and bringing it closer to the level of international standards.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Vasyl Fazan
Poltava V. G. Korolenko National Pedagogical University
2 Ostrohradskoho St., 36000 Poltava, Ukraine
e-mail: Fazanvv@gmail.com

ORCID AND CONTRIBUTIONSHIP

Valentyn Pomohaibo: 0000-0002-9828-2565 B D F
Natalia Karapuzova: 0000-0003-1430-0648 B E F
Yuliia Pavlenko: 0000-0001-7430-9869 A E F
Vasyl Fazan: 0000-0002-9823-3704 A E F

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

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REVIEW ARTICLE

CONTENTS

Criminal law ensuring the information security of persons living with the immunodeficiency virus

Vyacheslav I. Borisov, Olexander O. Pashchenko, Kateryna A. Novikova
ACADEMICIAN STASHIS SCIENTIFIC RESEARCH INSTITUTE FOR THE STUDY OF CRIME PROBLEMS NATIONAL ACADEMY OF LAW SCIENCES OF UKRAINE, KHARKIV, UKRAINE

ABSTRACT

Aim: To determine the specifics of criminal liability for disclosing information about a medical examination for detection of infection with the human immunodeficiency virus or another incurable infectious disease under the criminal legislation of Poland and Ukraine in order to improve the legal protection of the interests of people living with HIV.

Materials and Methods: The authors used the decisions of national courts in the field of ensuring the information security of a person living with the immunodeficiency virus, international and national legal acts of Ukraine and Poland. The study was carried out on the basis of a systematic approach using the methods of dialectical and formal logic, general scientific and special legal research methods.

Conclusions: It was determined the need to use the means of criminal liability only in extreme cases to ensure proper legal protection of the interests of people living with HIV, healthcare professionals, other related entities, and the public interest.

KEY WORDS: information security, HIV infection, criminal law, offences, liability

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INTRODUCTION

By the end of 2022, about 39 million people worldwide were living with human immunodeficiency virus (hereinafter referred to as HIV). At the same time, 25.6 million people live in the African region, about 3.8 million are residents of North and South America, 3.9 million are residents of Southeast Asia, 3 million are residents of the European region, 490,000 are in the Eastern Mediterranean and 2.2 million are in the Western Pacific [1]. As of 01.04.2024, 157,139 people living with HIV were under medical supervision in health care facilities in Ukraine, which are 383.3 per 100,000 people [2]. In Poland, at the beginning of 2024, 19,496 patients were being treated for HIV infection [3]. It should be noted that these are only official data. We currently do not know the actual number of people who are carriers of the infection or suffer from this disease. However, even these figures confirm the fact that HIV infection is a serious social problem for Ukraine, and obviously a certain problem for Poland.

At the same time, HIV/AIDS is not only a social problem, but also an individual tragedy. People living with HIV often face discrimination due to the disease, which leads to low attendance at counseling and HIV testing, identity crisis, social isolation, loneliness, low self-esteem and lack of interest in overcoming the disease [4]. People living with HIV/AIDS often experience violence related to the disease. A study conducted among people living with HIV/AIDS in South Africa found that out of 500 survey participants, 16.1% reported experiencing physical violence, with 57.7% of them being perpetrated by intimate partners such as husbands and wives [5].

Discrimination and stigmatization of HIV/AIDS-infected people make it necessary to properly ensure the confidentiality of information about a person's illness. An important role in ensuring compliance with such information security of a person belongs to the means of criminal legislation. In contrast to the Criminal Code of the Republic of Poland, the Criminal Code of Ukraine contains a special provision regarding responsibility for disclosing information on conducting a medical examination to detect infection with the human immunodeficiency virus or another incurable infectious disease (Article 132 of the Criminal Code of Ukraine).

AIM

To determine the peculiarities of criminal liability for disclosure of information about a medical examination to detect infection with the human immunodeficiency

virus or other incurable infectious disease under the criminal laws of Poland and Ukraine in order to improve legal protection of the interests of a sick person, to draw public attention to the existing problem and the need to solve it.

MATERIALS AND METHODS

To achieve the objectives of the study, the authors analyzed statistical data from the World Health Organization, the Public Health Centre of the Ministry of Health of Ukraine, and the National Centre for AIDS Prevention and Control in Poland on the number of HIV-infected people in this country and other regions of the world. The study also uses statistical data from criminal cases in Ukraine and Poland concerning offences in the field of information security of a person living with the immunodeficiency virus. The author analyses the provisions of the Criminal Code of the Republic of Poland of 06 June 1997 and the Criminal Code of Ukraine of 05 April 2001 in this area. An exhaustive list of court decisions in Poland (51 verdicts), which mention HIV, was studied.

The methods of theoretical analysis and synthesis were used in the study of the content of legislative norms and provisions contained in international and national legal acts on combating the spread of HIV and protecting the rights of people living with it. Certain issues required the use of the systematic analysis method, in particular, during the study of legal acts in the medical field and comparing its provisions with criminal law.

The formal and legal analysis of international and national legislation was used to study the differences in their application in Poland and Ukraine for various criminal offences, and to formulate proposals for improving liability for such offences in accordance with their social danger and harmfulness.

In solving the research tasks, the historical method was also used, which allowed the authors to trace the attitude of modern medicine to HIV infection, its transmission methods and the possibilities of influencing it through antiretroviral therapy, starting from the first cases of its detection to the present.

REVIEW AND DISCUSSION

Unlike in Ukraine, the criminal law of Poland does not specifically address the issue of ensuring the information security of a person living with an immunodeficiency virus. However, this is not to say that this problem is not given any attention at all. The Polish Criminal Code provides for liability for disclosure of information in connection with the performance of official duties. Thus, according to § 1 of Article 266 of this Code, liability is established for the person's actions who, contrary to the law provisions or his/her obligations, discloses or uses information that he/she has become aware of in connection with the performance of official duties, work, public, social, economic or scientific activities. These actions include disclosure of information about a patient regarding HIV infection or AIDS [6]. At the same time, Polish law contains provisions that should be taken into account when disclosing information about a patient without his or his/her consent when:

1) it is provided for by law;

2) the medical examination was conducted at the request of a person entitled to do so, in accordance with certain acts, bodies and institutions; when the physician is obliged to report the patient's health status only to these bodies and institutions;

3) keeping the secret may endanger the life or health of the patient or other persons;

4) the patient or his/her legal representative agrees to disclosure of the secret, having previously informed the patient of the adverse consequences for him/her;

5) there is a need to transfer the necessary information about the patient related to the provision of medical services to another physician or authorized persons involved in the provision of these services;

6) it is necessary for practical training of the medical profession;

7) it is necessary for scientific purposes;

8) it is necessary to provide the necessary information about the patient to the healthcare professional, while the disclosure of secrecy may be disclosed only to the extent necessary [7]. Thus, we can see that in Poland there is a sufficient range of statutory exceptions related to information leakage, which allow not applying criminal liability to healthcare professionals without justified necessity.

In contrast, the Criminal Code of Ukraine contains a special provision establishing liability for disclosure of information about a medical examination to detect infection with human immunodeficiency virus or other incurable infectious disease (Article 132). According to Ukrainian scholars, the social danger of this act lies in the fact that informing at least one unauthorized person that a person is HIV-positive or has AIDS causes the latter to suffer, humiliates his or her honor and dignity, and causes significant damage to the good name of not only this person, but also those close to him or her [8]. Only the following individuals shall be liable for this criminal offence 1) officials of a healthcare facility, 2) auxiliary workers who have unauthorizedly obtained the relevant information, and 3) medical professionals if they have become aware of the relevant information

in connection with the performance of their official or professional duties.

Ukrainian lawyers note that in addition to medical personnel, the subjects of this criminal offence may also be employees of law enforcement agencies, prisons, etc. [8]. At the same time, Ukrainian scholars also cite certain restrictions on the interpretation of the subject of this offence: it can only be persons who have reported information about positive data on HIV infection or AIDS or other incurable infectious disease found during the examination, while the notification of an examination that gave negative results is not covered by Article 132 of the Criminal Code of Ukraine [9]. Unfortunately, it was not possible to identify the real position of the law enforcement agencies of Ukraine on this issue, since since the entry into force of the Criminal Code of Ukraine in 2001, we found only one sentence for this criminal offence in the Unified State Register of Court Decisions of Ukraine, and that one was with limited access [10]. According to the information provided by the Office of the Prosecutor General from 2013 till 2023, 7 criminal offences under this article were registered, of which only one criminal offence was reported, where the proceedings were sent to court with an indictment [11].

It is worth noting that along with the special legislative prescription contained in Article 132 of the Criminal Code, the legislator of Ukraine has also provided for a general rule in Article 145 of the Criminal Code – illegal disclosure of medical secrets. According to the Prosecutor General's Office, 55 criminal offences were registered under this article [11]. However, if we look at the court statistics, there is no data on the verdicts passed by the courts under Article 145 of the Criminal Code over the past ten years [12]. That is, the effectiveness of the general rule specified in Article 145 of the Criminal Code of Ukraine is actually zero, and some of the advantages that law enforcement practice gives to the special rule specified in Article 132 of the Criminal Code are insignificant.

The following conclusions can be drawn from the data obtained. First of all, there are very few criminal proceedings in these cases due to the fact that there are a lot of latent carriers of HIV infection in Ukraine (those who do not know that they are HIV-infected). This is, in particular, due to the rather long period of time between HIV infection and its detection. In addition, there is still a significant fear that outsiders will find out that a person is ill. In this regard, there is also a fear of being registered, as well as failure to take other actions necessary for timely treatment. It seems that a small number of registered offences are related to this.

Regarding the implementation of criminal proceedings in relation to medical secrecy and its disclosure, it should also be borne in mind that today they are quite difficult to prove, and therefore, on more or less appropriate pretexts, criminal proceedings are closed (for example, because there is insufficient evidence to prove the person's guilt in court and the possibilities of obtaining it have been exhausted) or the person is released from criminal liability (for example, due to effective remorse). In addition, the victim may not be aware that information about him/her has been disclosed, inter alia, due to the lack of a proper mechanism for informing him/her of this fact (for example, due to hacking of the Health system or the introduction of new methods of obtaining such information via the Internet).

Finally, we can also conclude that the legislative norms that provide for liability for these criminal offenses are imperfect, as well as the general perception of the fact of such disclosure as not being a significant violation of civil rights.

In the context of ensuring human information security, Polish researchers raise the question of the expediency of criminalization and social justification if a person knows that he/she is infected with HIV and directly exposes another person to the virus. For example, what is the significance of the analyzed crime in the public perception and what role does it play in the justice practice? [13]

The fact is that the criminalization of actions in this area has its origins in the situation that developed in the world after the first case of HIV was recorded in the United States in 1981 and the subsequent rapid increase in morbidity and mortality from diseases caused by this virus impact on the human body. At that time, medical science had a very rough understanding of the infection and its transmission, and there was no effective antiretroviral therapy. Therefore, public concern about the consequences of AIDS began to become critical.

In Ukraine, back in Soviet times, in November 1987, the Criminal Code of 1960 was amended with a provision (Article 108^2) that established liability not only for "infection of another person with AIDS by a person who knew that he/she had the disease" (Part 2), but also for "knowingly putting another person in danger of contracting AIDS" (Part 1) [14]. A little later, in December 1991, the Criminal Code in force at that time was supplemented with two more articles related to HIV infection and AIDS: Article 108^3 "Infection with the human immunodeficiency virus by medical, pharmaceutical and other workers", i.e. a provision that became special to Article 108^2 of the Criminal Code, Article 108^4 "Disclosure of information on medical examination for human immunodeficiency virus infection and its results" [15], i.e. a norm analogous to Article 132 of the current Criminal Code.

At the time, in the context of the spread of the AIDS epidemic worldwide, which was called the "plague of the twentieth century," such legislative decisions seemed justified. Therefore, in the original version of the Criminal Code (2001) there were three norms that corresponded to the above: Article 130 " Infection with HIV or any other incurable contagious disease", Article 131 "Professional misconduct causing infection of a person with HIV or any other incurable contagious disease", Article 132 "Disclosure of information on medical examination for HIV or any other incurable contagious disease" [16].

However, over time, the situation regarding the disease in question has begun to change dramatically as a result of medical science advances. Thanks to modern antiretroviral therapy, people living with HIV have the opportunity to live a full life without putting their sexual partners at risk of infection, and to give birth to healthy children without transmitting HIV infection to them [17]. These circumstances are also reflected in the investigative and judicial practice of Ukraine in recent years regarding the application of the Criminal Code provisions for acts that were the HIV infection subject. In addition to the indicators of application of Article 132 of the Criminal Code of Ukraine, we consider it appropriate to provide official information on the application of Articles 130 and 131 of the Criminal Code of Ukraine. In the period from 2013 to 2023, law enforcement agencies of Ukraine registered 83 criminal offenses classified under Article 130 of the Criminal Code [11]; 8 people were convicted under this article [12], while no one has been convicted of this criminal offense in the last 5 years.

As for the criminal offenses under Article 131 of the Criminal Code, 18 cases were registered during the specified period [11], but no one was convicted under this article [12]. In this regard, current research rightly notes that one of the negative aspects of the criminalization of HIV transmission is that it has slowed down the detection and timely treatment of new cases of HIV infection [17]. Therefore, it is no coincidence that one of the international legal documents emphasizes that criminalization is deadly; it fuels the HIV pandemic. Abuse of criminal law also massively violates human rights around the world. The evidence of such harm is compelling and undeniable [18].

In this regard, criminal liability should be *ultra ratio*, when other means of special preventive and legal influence are no longer able to work. In most cases, preference should be given to the use of other means: timely detection of HIV, the use of antiretroviral therapy, which helps to transform the virus in such a way that it can no longer be transmitted. Therefore, the position of the drafters of the new Criminal Code of Ukraine seems quite consistent, where, on the one hand, there are no longer any special provisions related to HIV and AIDS, and on the other hand, the circumstance associated with dangerous contagious diseases (including AIDS [19]) is included in the list of signs that define health damage caused to a person as grave, namely infection of a person with a particularly dangerous contagious disease or its causative agent (subpara. e, clause 3, part 1, Article 1.4.3) [20].

CONCLUSIONS

The study demonstrates the need for a systematic approach to the regulation and application of liability for violation of information security of a person living with an immunodeficiency virus.

During the resolution of the issue regarding the criminalization of certain offenses that may be committed in this area, it is appropriate to take into account their public danger. Thus, at present, criminal liability for any violation of the information security of a person living with an immunodeficiency virus seems inappropriate.

In the criminal legislation of Poland, the issue related to ensuring the information security of a person living with the immunodeficiency virus is not specifically identified, but the responsibility for disclosing information in connection with the performance of official duties is established. Such actions also include possible cases of gossiping about a patient about HIV infection or AIDS. In contrast to this, the Criminal Code of Ukraine contains a special rule that establishes responsibility for disclosing information on conducting a medical examination to detect infection with the human immunodeficiency virus or another incurable contagious disease, the practice of which has not become widespread. The draft of the new Criminal Code of Ukraine no longer contains such a norm, as well as other special norms related to HIV infection and AIDS.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Vyacheslav I. Borisov
Academician Stashis Scientific Research Institute
for the Study of Crime Problems
National Academy of Law Sciences of Ukraine
49 Pushkinska St., 61002 Kharkiv Ukraine
e-mail: borisov_v.i@ukr.net

ORCID AND CONTRIBUTIONSHIP
Vyacheslav I. Borisov: 0000-0003-0291-9347 D E F
Olexander O. Pashchenko: 0000-0001-9640-0137 A D E
Kateryna A. Novikova: 0000-0001-8646-3441 A B D

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

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REVIEW ARTICLE

CONTENTS

Mechanism for Implementing the State Guarantee Program for Medical Services at the Primary Level

Igor V. Hushchuk[1], Vladyslav A. Smiianov[2], Natalya P. Topishko[1], Halina V. Kraichynska[1], Oleksandr N. Stratyuk[3], Volodymyr I. Potseluiev[2], Oleksandr Pryimenko[2]

[1]NATIONAL UNIVERSITY OF OSTROH ACADEMY, OSTROH, UKRAINE

[2]SUMY STATE UNIVERSITY, SUMY, UKRAINE

[3]OSTROH DISTRICT PRIMARY HEALTH CARE CENTRE OSTROH CITY COUNCIL OF RIVNE DISTRICT, OSTROH, UKRAINE

ABSTRACT

Aim: The goal of this work is to investigate the effectiveness of state regulatory tools influencing the HCS reform process and the institutional support for the implementation of SGPMS at the primary level.

Materials and Methods: To evaluate the effectiveness of SGPMS implementation at the primary level, methods of observation, analysis and synthesis, grouping, and generalization were applied

Results: In the implementation of SGPMS, PMC is prioritized. It ensures the accessibility, timeliness, safety, and effectiveness of medical services. Achieving a balance between the quantity and quality of provided medical services, as well as equality and fairness in access to them, is crucial.

Conclusions: The ways to improve the implementation of SGPMS at both the state and PMC facility levels may include: adjusting the global budget and contracts based on healthcare needs assessment at the regional level; enhancing comprehensive contract strategy and procurement tools; improving financial incentives for PMC; increasing the efficiency of healthcare expenditures; and improving the functioning of mental health services.

The improvement of SGPMS implementation at the primary level is determined by the medical enterprise, specifically: activating preventive activities in primary care; enhancing strategic planning to achieve specific goals; investing in the development and renewal of infrastructure; accelerating the implementation of digital solutions and integrated data systems for remote consultations; seeking effective financial incentives for healthcare facility staff; and developing monitoring of effectiveness and management of primary healthcare activities.

KEY WORDS: health care system reform, medical guarantee program, primary medical care

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Healthcare System (HCS)
Ukraine's Healthcare System (UHS)
Primary Medical Care (PMC)
Medical Care (MC)
State Guarantee Program for Medical Services (SGPMS)
Primary Healthcare (PHC)
The level of available economic resources (GDP)
Municipal Healthcare Institutions (MHIs)
Ostroh Primary Health Care Centre (OPHCC)
Public Utility Company (PUC)
Territorial Community (TC)
Regional Emergency Medical Care Centre (REMCS)

INTRODUCTION

HCS is a way of financing, organizing and delivering health care to the population. The goal is to maintain the health of the population in the most efficient way possible in relation to the available resources of society and competing needs. The HCS model defines the specifics of access to healthcare services (for whom and to what services), costs and resources. In the Beveridge model, the government provides funding for the HCS. In the Bismark model, medical services are provided privately and paid for by individual contributions to an insurance company. In the national HCS model, funding is provided by the state and medical institutions are autonomous. All models have private insurance and private practice of medical care. All models have problems with financing the HCS. Even in developed countries (where 8-15% of GDP is spent on HCS), this is due to the high frequency of health care visits, their urgency, and the high cost of instrumental and medicinal components [1].

Since 2018, Ukraine has been using the Beveridge system [2]. The HCS is divided into primary, secondary and tertiary levels of health care. The list of services to be provided at each level is defined. The source of funding for primary care is the state budget. The state pays for a contract with

a doctor chosen by the patient. Payments for patient treatment are not tied to the level of individual contributions. The SGPMS is the only national insurer and purchaser of medical services. Healthcare providers are autonomous. The e-Health system and the Affordable Medicines program are in place. The mechanism for implementing the PMC at the primary care level remains a relevant topic for research.

AIM

To study the effectiveness of state instruments of regulatory influence on the process of reforming the SGPMS and institutional support for the implementation of the PMC at the primary level.

MATERIALS AND METHODS

The assessment of the state of implementation of the HCS at the primary level was carried out using the methods of observation, analysis and synthesis, grouping and generalization.

REVIEW AND DISCUSSION

The PMC is a program guaranteed at the legislative level, according to which the scope and list of medical services and medicines are formed, which are paid for by the state budget through the SGPMS at tariffs for the prevention, diagnosis, treatment and rehabilitation of diseases, injuries, poisoning and pathological conditions, as well as pregnancy and childbirth. State guarantees for the provision of medical services determine the degree of coverage of the population, namely: what services are included in the guaranteed package; who can use them; and what share of costs is covered by public funds. The package of PMC includes the main types of medical care: primary, emergency, specialized care, palliative care and rehabilitation in the healthcare sector. It includes a list and scope of medical services and medicines paid for from the state budget at unified national tariffs.

Every year, the Parliament approves the PMC package in the Law of Ukraine "On the State Budget". The level of available economic resources (GDP) determines the structure of the HCS, the amount and means of financial support, and the structure of the PMC. The means of financing the HCS reflect the values and priorities of society. The principle of centralized management helps to curb the growth of HCS expenditures. The amount of funding also depends on the amount of funding for other items of state budget expenditures and competes with them [3].

Access, costs and quality of healthcare are affected by the level and means of remuneration of healthcare providers. In connection with COVID-2019 and the Russian invasion, the provision of the Law of Ukraine "On State Financial Guarantees of Medical Care for the Population" has been suspended, which stipulates that the amount of state budget funds allocated for the implementation of the PMC should be at least 5% of Ukraine's GDP [4]. In today's difficult conditions, the HCS budget reaches 2-3% of GDP.

In 2021, expenditures from the state budget of Ukraine for HCS amounted to UAH 173.6 billion (including UAH 123.6 billion for fuel and lubricants). In 2022, respectively, 215.3 billion UAH and 146.3 billion UAH. [5]. In 2023, respectively, 206.8 billion UAH and 142.7 billion UAH. In 2024 – 203.4 billion UAH and 158.8 billion UAH. [6,7]. In the context of the Russian aggression, the attraction of international financial assistance contributed to the stable financing of the PMC and allowed timely payment of salaries to more than 500 thousand employees of medical institutions [5].

The development and implementation of the PMC changed the principles of financing the HCS. To implement the changes, a new central executive body (the NHSU) was created, which is controlled by the CMU through the Minister of Health of Ukraine. The NHSU implements the policy of state guarantees of medical care for the population in the HCS; develops a draft PMC based on the analysis and forecasting of the population's needs; identifies reference healthcare facilities and analyses the costs of these facilities for medical services; informs the authorised state bodies of the information on violations of the terms of the PMC contracts; applies measures defined by the regulations to ensure efficient, targeted use of funds under the PMC; concludes, amends and terminates contracts for healthcare services and reimbursement agreements; analyses reports of pharmacies on the dispensed medicines and their reimbursable cost; ensures the maintenance of registers that are part of e-Health; provides proposals and advice on the formation, structure, operation and improvement of the efficiency of the network of state and municipal HCS institutions; ensures the functioning of e-Health, etc [8].

There are 7 registers in the central database of the EHCS, namely: The Patient Register, the Register of Declarations of Choice of Primary Care Physician, the Register of Healthcare Business Entities, the Register of Medical Specialists, the Register of Healthcare Professionals, the Register of Medical Records, Referral Records and Prescriptions, and the Register of Medical Conclusions [9]. To ensure the reliability, relevance and accuracy of the data in these registers, the NHSU carries out their verification.

It is believed that 70-80% of a person's lifetime healthcare needs are met at the primary care level [1]. Primary care includes patient consultations, diagnosis, and treatment of common diseases, poisonings, injuries, physiological and pathological conditions. Primary care is provided by healthcare facilities and individual entrepreneurs who operate in accordance with the current legislation and have obtained a license. The requirements for healthcare providers are de-

Table 1. Adjustment factors for the base capital rate

Patients age group	Coefficients
From 0 to 5 years of age	2,465
From 6 to 17 years of age	1,356
From 18 to 39 years of age	0,616
From 40 to 64 years of age	0,739
Over 65 years	1,232
Mountain factor	1,2

Source: [12].

Table 2. Coefficients depending on the level of exceeding the limit for the provision of primary care

Level of limit exceedance	Coefficient
From 100 per cent of the limit + one declaration up to and including 110 per cent of the limit	0, 616
From 110 per cent of the limit + one declaration up to and including 120 per cent of the limit	0, 493
From 120 per cent of the limit + one declaration up to and including 130 per cent of the limit	0, 37
From 130 per cent of the limit + one declaration up to and including 140 per cent of the limit	0, 246
From 140 per cent of the limit + one declaration up to and including 150 per cent of the limit	0, 123

Source: [12].

fined by the Resolution of the Cabinet of Ministers of Ukraine "On Approval of Requirements for the Provider of Healthcare Services to the Population, with whom the Main Spending Units of Budget Funds Conclude Contracts for Healthcare Services to the Population" of 28.03.2018 No. 391 [10].

The main funding for primary care medical centres is provided on the basis of the PMG. The mechanism for implementing the PMC is structured as follows: the legislator defines the PMC for each year in the Law of Ukraine "On the State Budget of Ukraine"; a healthcare facility must enter into an agreement with the NHSU; a person signs a declaration with a doctor (whom he or she chooses); after providing medical services, the provider reports to the NHSU through the eHealth system and receives payment for the services provided.

At the primary level of the HCS, the list of primary healthcare services includes medical services of a family doctor, general practitioner, and paediatrician. They provide effective prevention and treatment of a wide range of diseases. Procedure for the provision of primary care [11]. The permissible scope of primary healthcare practice is established: for one general practitioner (family doctor) – 1800 persons; for one therapist – 2000 persons; for one paediatrician – 900 persons. The basic capitalisation rate is UAH 786.65 per year [12]. Adjustment coefficients are applied to the basic capital rate (Table 1).

Coefficients are applied to the tariff for primary care services provided to patients who submitted declarations in excess of the limit, depending on the excess (Table 2).

The actual cost per month of primary care services provided under each contract is calculated as the sum of the products of 1/12 of the base capital rate and the number of declarations active as of the first day of the reporting period. Adjustment factors are taken into account. Payment for services rendered is made by the tenth business day after the end of the relevant reporting period in accordance with the applicable tariffs and adjustment coefficients based on reports submitted to the NHSU through the eHealth system.

According to the NHSU report, as of 31.12.2022 [13], the number of declarations submitted to primary care doctors by the forms of ownership of service providers was a total of 32440321, including: municipal institutions – 29659749; state institutions – 2323; private (without sole proprietorship) 1404616; individual entrepreneur (IE) – 1373633. Patients who chose their own doctor accounted for 78.8% of the population of Ukraine. The distribution of declarations was as follows: by doctor's speciality – 74.7%, general practitioner – 14.8%, paediatrician – 10.5%; by patients' gender: 54.5% women; 45.5% men; by age group of patients: 0-5 years – 5.1%; 6-17 years – 15.2%; 18-39 years – 26.9%; 40-64 years – 35.1%; over 65 years – 17.8%.

In 2022, the number of cases treated by priority service groups was as follows: the number of providers – 910; total services provided – 921414; the amount of payment for services provided was UAH 10172.8 million. The number of services provided and the amount of payment in 2022 is shown in Table 3.

The number of patients who received services in 2022 was 22615950 people. Payment to healthcare providers amounted to UAH 33913 million, including the breakdown by ownership type as shown in Table 4. Most declarations were signed with MHIs. They received the largest amount of funds for primary care.

Once every three months, the NHSU evaluates the achieve-

Table 3. The number of medical services provided in Ukraine by the Ministry of Health and the amount of payment in 2022

Service group	Providers	Services provided	Payment amounts (UAH)
Outpatient services	834	588488	578273260
In-patient services	494	332926	9594524138

Table 4. Payment to healthcare providers

Ownership type	Payment amounts (UAH)	Number of providers
state	22670805	3
communal	142419477178	2454
private (without IE)	2204701864	354
IE	1009542492	688
Total, including by type of assistance	145656392340	
primary	24685328795	
emergency	11361076676	
specialised	92510757993	

Source: [13].

Table 5. Receipt and use of funds of the PUC "REMCS" in 2020-2022

Indicators	2020 рік	2021 рік	2022 рік
Primary medical care, UAH	18671528,70	19579608,02	24817600,33
State budget (including centralised procurement), UAH	715844,87	10158997,83	1685707,56
Regional, district and local government budgets, UAH.	869401,69	858716,06	717266,31
Charitable assistance	63416,46	0	962350,25
% of the bank	261370,85	138581,15	282100,56
Total income	20581562,57	30735903,06	26948025,01
Usage	19970226,40	19074028,72	24280594,28

Source: financial report of REMCS

ment by healthcare providers of the indicators of fulfilment of the contractual terms in terms of vaccination. Based on the results of the assessment, the amount of the surcharge is calculated for the level of vaccination of children under six years of age (inclusive) in accordance with the "Calendar of preventive vaccinations in Ukraine" approved by the Ministry of Health. The amount of the additional payment is calculated as the product of the sum of the cost of medical services for the two months preceding the evaluation period and the month in which such evaluation is carried out, and the adjustment coefficient for achieving the indicators of fulfilment of the contractual terms in terms of vaccination for the relevant period, which is 0.025 for the duration of the contract.

Once a year, the NHSU evaluates the achievement by healthcare providers of the indicators of contractual performance in terms of the level of coverage of people aged 40-64 and 65 and older with hypertension, cardiovascular disease, and diabetes [14].

The mechanism for implementing PMG at the primary level can be seen on the example of the OPHCC of the Ostroh City Council of the Rivne Region of the Rivne District. The founder and owner of the PUC is the Ostroh City TC represented by the Ostroh City Council. The PUC "Ostroh Primary Health Care Centre" serves almost 30,000 citizens of Ostroh Territorial Community. Patients are served by 29 doctors, 39 nurses and 8 paramedics. The agreement with the NHSU was signed in 2018. Service packages concluded by the institution with the NHSU: No. 1 "Primary health care"; No. 41 "Support and treatment of adults and children with tuberculosis at the primary level of health care"; No. 24 "Mobile palliative care for adults and children"; No. 36 "Vaccination against acute respiratory disease COVID-19 caused by coronavirus SARS-CoV-2"; No. 50 "Ensuring the human resources potential of the health care system by organising medical care with the involvement of interns". The REMCS uses the Medical Information System "MEDIX". There is a hospital cash desk. The hospital participates in the "Affordable Medicines" programme. The revenues of the PUC by sources of funding are shown in Table 5.

The largest amount of funding was received under the PUC "REMCS". The volume of revenues increased due to the increase in medical services provided to the population, especially during the COVID-19 epidemic and the war. Under martial law, in order to ensure the continuity of funding for

hospitals and patients' access to medical care in an emergency, the government introduced certain changes to the PMG Procedure. From March 2022 to July 2022, most payment methods were temporarily replaced by a global monthly budget. Later, they returned to payment for the services actually provided. The NHSU launched an additional funding package that was in effect until the end of 2022 [15].

Due to the full-scale Russian invasion in 2022, new services were introduced in the state primary healthcare system. In particular, support and treatment of adults and children with mental disorders at the primary level and comprehensive rehabilitation care for adults and children in inpatient settings.

More than 15200 primary care physicians (60% of the total number of physicians) were trained in the course "Management of common mental disorders in primary care using the mhGAP guidelines". As of 05.12.2023, almost 850 healthcare facilities were involved in this PMG package. More than 85.5 thousand patients used the service [16].

For 2024, despite the emergency conditions and limited resources, 44 service packages are provided for in the PMG. Starting from 1 April 2024, the NHSU does not pay for excess services if the healthcare provider exceeds the rehabilitation capacity of the institution when providing services under the contract for healthcare services under the package "Rehabilitation care for adults and children in inpatient settings" [17]. As of 08.02.24, the NHSU has paid under the contracts: Primary health care – UAH 1.95 billion; emergency medical care – UAH 1.74 billion; specialised medical care – UAH 3.3 billion. [18].

Internal monitoring of the use of funds from the state budget for PMG is carried out by the Ministry of Health of Ukraine and the NHSU. State external financial control (audit) is provided by the Accounting Chamber of Ukraine through financial audit, performance audit, expertise, analysis and other control measures [19]. It assesses the state of affairs and control over the quality of healthcare services provided by their providers; the degree of systematic analysis of the results and effectiveness of healthcare services; emphasises the need to improve the algorithm for collecting information for further analysis and the mechanism for ensuring the continuity of FMH provision (outside of the hours of reception of patients by doctors, as well as for providing such care on weekends, holidays and non-working days). The degree of interaction of the ESHC with other information systems and state information resources is determined to help ensure the reliability, completeness and accuracy of the data in it [19, 6].

To support the total funding of the PMG in 2022-2023, the US government allocated USD 1.7 billion (UAH 49.7 billion) and UAH 4.2 billion from the state budget of Ukraine to ensure the payment of salaries to healthcare providers. These are almost 560 thousand employees who provided emergency, primary, and specialised medical care and were deployed to the territories controlled by Ukraine [9, 5].

From August to December 2023 the Accounting Chamber conducted an audit in accordance with the International Standards of Supreme Audit Institutions (ISSAI) to assess compliance with the conditions for the use of US direct budget support (DBS) for the SHCU, timeliness and completeness of management decisions, the state of the NHSU internal control system, and analysis of the reports of the Cabinet of Ministers (Ministry of Finance) on "US Direct Budget Support at the Beginning of Russia's Military Invasion of Ukraine: Preventing Collapse and Maintaining the Stress Resilience of the Ukrainian Healthcare System" on 21 December 2023 [20].

The NHSU paid funds to medical institutions on the basis of reports on medical services provided or NHSU registers for the transfer of funds. The audit confirmed that the NHSU's internal control system complies with the requirements of Ukrainian legislation, namely the "Basic Principles of Internal Control by Budgetary Fund Managers" [21].

Before the war, the NHSU used a unified approach to procuring healthcare services across Ukraine. The current conditions, significant displacement of the population and healthcare workers have raised the issue of adjusting the budget, calculated as 1/12 of the planned budget under the contract. Practice has shown the problematic nature of applying the capital rate. According to O. Tulai and S. Nytka, it does not encourage family doctors to provide the maximum possible amount of medical care to patients, but shifts responsibility to narrow-profile specialists [1].

In 2024, in order to ensure the functioning of the HCS facilities network and provide medical care to citizens in the combat zone under the package "Preparedness and provision of medical care to the population located in the territory where hostilities are taking place", the tariff is defined as a global rate per month equal to the actual cost of medical services for December under the contract that was in force until 31 December 2022 for packages of medical services for inpatient care with surgical operations and/or "Mental health care for adults and children in inpatient settings", and/or "Prevention, diagnosis, monitoring and treatment in outpatient settings", and/or 1/12 "Diagnosis and treatment of adults and children with tuberculosis in inpatient and outpatient settings" of the relevant health care provider) [22].

Contracts can be adjusted to take into account specific regional needs and the use of different approaches to financing healthcare services in different regions. It is important to improve the interaction of the EHCS with other information systems and government information resources to help ensure the reliability, completeness and accuracy of data. In 2023, the Ministry of Health approved a roadmap for the introduction of complementary health insurance to expand the sources of financial resources for the HCS and the choice of healthcare providers, insurers and insurance packages, and to support the development and modernisation of HCS facilities and infrastructure.

CONCLUSIONS

Ways to improve the implementation of PMG at the state level and at the level of primary care facilities include: adjusting the global budget and contracts based on the study of the needs for HCS at the regional level; improving the comprehensive contracting strategy and procurement tools; improving financial incentives for primary care; increasing the efficiency of HCS spending; and improving mental health services.

Ways to improve the implementation of primary care in the primary link are identified by the healthcare enterprise, namely: intensification of preventive primary care activities; improvement of strategic planning to achieve specific goals; investment in infrastructure development and renewal; acceleration of the introduction of digital solutions and convenient integrated data systems for remote consultations; search for effective financial incentives for healthcare staff; development of performance monitoring and management of primary healthcare activities. It is incredibly difficult to ensure this in the context of large-scale Russian aggression.

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CONFLICT OF INTEREST

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CORRESPONDING AUTHOR

Igor V. Hushchuk

Department of Public Health and Physical Education
National University of Ostroh Academy, Ostroh, Ukraine
e-mail: igorgus2014@gmail.com

ORCID AND CONTRIBUTIONSHIP

Igor V. Hushchuk: 0000-0002-8075-9388 A D E F
Vladyslav A. Smiianov: 0000-0002-4240-5968 A B E F
Natalya P. Topishko: 0000-0001-9823-0805 D F
Halina V. Kraichynska: 0000-0002-7355-3779 D F
Oleksandr N. Stratyuk: B E
Volodymyr I. Potseluiev: 0000-0003-2140-4058 B E
Oleksandr Pryimenko: 0009-0007-9672-6648 B F

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REVIEW ARTICLE

CONTENTS

Effectiveness of non-operative methods of treatment of carpal tunnel syndrome: a narrative review

Andrzej Żyluk[1], Alicja Żyluk[2]

[1]DEPATRMENT OF GENERAL AND HAND SURGERY, POMERANIAN MEDICAL UNIVERSITY, SZCZECIN, POLAND

[2]DEPARTAMENT OF GENERAL NAD HAND SURGERY, STUDENT'S SCIENTIFIC CIRCLE, POMERANIAN MEDICAL UNIVERSITY, SZCZECIN, POLAND

ABSTRACT

Carpal tunnel syndrome (CTS) can be treated with several methods, including surgical and non-surgical techniques. Non-surgical methods include wrist splinting, systemic pharmacotherapy, intracarpal injections of steroids hydrodissection, acupuncture, nerve and tendon mobilization, osteopathy, taping, topical application of ointments, laser, ultrasound and shock-wave therapies. These treatments are generally less effective than surgery, and provide only short-lived effect, but it may be quite sufficient for a certain category of patients, particularly those suffering from mild symptoms. Over the last years, these techniques have attracted increasing popularity, because they offer non-invasive option for surgical treatment what can be attractive for some patients. However, although these methods were shown in the literature, their actual effectiveness has not been scientifically verified. The objective of this study was a review of the effectiveness of non-operative methods of treatment of CTS. A review of the published literature from PubMed and Medline databases on the effectiveness of CTS non-operative treatments of was done. The review indicates that each of the presented methods is effective in reduction of symptoms and improvement of hand function in CTS patients, but their effect is only short-lived. None of these treatments provides a permanent cure, like does surgical treatment. In spite of numerous non-operative treatments of CTS, surgery is the only method that provides permanent recovery.

KEY WORDS: carpal tunnel syndrome, non-operative treatment, outcomes of the treatment, literature review

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INTRODUCTION

Carpal tunnel syndrome (CTS) is caused by compression of the median nerve in the carpal tunnel. It is the most common compression neuropathy, affecting 1-1.5% of the total population and about 6% of women over 40 years of age. Middle-aged and elderly women are the largest group affected by this condition. The age of onset varies: in the clinic managed by the author, the average age of women admitted for carpal tunnel release was 57 years. Although several predisposing factors are known (diabetes, hypothyroidism, rheumatoid arthritis), in about 80% of cases the cause of the syndrome cannot be determined (an idiopathic syndrome) [1-8].

Carpal tunnel syndrome can be treated with several methods [1, 2, 6, 7]. Although surgical treatment (cutting of flexor retinaculum) is most often used, other, non-surgical methods have their place in the CTS management. These include immobilization of the wrist joint in a splint or orthosis, various methods of physiotherapy, systemic pharmacotherapy and local injections of steroids. Conservative treatment is generally considered to be less effective than surgery and only temporary effective, but it may be quite sufficient for a certain category of patients, particularly those suffering from mild symptoms. Over the last years, non-operative methods of treating carpal tunnel syndrome have to be offered, such as: hydrodissection, acupuncture, nerve and tendon mobilization, osteopathy, taping, topical application of ointments, as well as laser, ultrasound and shock-wave therapies. These techniques have attracted increasing popularity, because they offer non-invasive option for surgical treatment what can be attractive for some patients. However, although these methods were shown in the literature, their actual effectiveness has not been scientifically verified.

AIM

The objective of this study was to review an effectiveness of non-operative methods of the treatment of carpal tunnel syndrome.

MATERIAL AND METHODS

This article presents a review of the published literature from PubMed and Medline databases on the effec-

tiveness of non-operative treatments of carpal tunnel syndrome. A randomized clinical trials, systematic reviews and meta-analyses reporting on use of these methods were reviewed. Keywords used at searching articles were: carpal tunnel syndrome, non-operative treatment, clinical outcomes, treatment effectiveness, systematic review, meta-analysis and treatment complications.

REVIEW AND DISCUSSION

The results of the literature review will be presented separately for each non-standard treatment. First three paragraphs will end with the author's comment on the results presented.

HYDRODISSECTION

USG-guided injection (also named as hydrodissection or perineural injection) delivering a range of injectates, i.e. normal saline, corticosteroids, dextrose and platelet-rich plasma attracts growing popularity in the treatment of CTS [9-13]. In assumption, this procedure, provides a mechanical effect to release and decompress the entrapped nerves and adds a pharmacological effect of delivered drug relieving pain and promoting recovery. During hydrodissection, ultrasound guidance is used to identify the nerve and guide the needle to the nerve. After this, an adequate volume of an injectate is placed around the nerve to separate it from surrounding tissue, fascia, or adjacent structures that may be compressing the nerve. The volume of fluid injected into carpal tunnel varies from 4 to 10 ml. Depending on the patient, only one treatment may be needed, but this procedure typically needs to be repeated 2-3 times to achieve the expected result.

Several publications presenting effectiveness of this procedure using various injectates were published [9-13]. Most studies compared different ultrasound-guided interventions to different comparison injectate or other conservative treatments such as wrist splinting or physical therapy, but none compared a matched intervention and comparison groups. Various injectates were used such as 0,9% saline solution, 5% dextrose solution, corticosteroids, local anaesthetics, hyaluronic acid, platelet-rich plasma and ozone. Outcome measures after intervention included pain intensity in the Numeric Rank Scale (NRS, range 0-10, higher means stronger pain), Boston Carpal Tunnel Questionnaire (BCTQ; range 1-5, higher means worse symptoms and greater disability) and Disability of Arm, Shoulder and Hand questionnaire (DASH; range 0-100, higher means greater disability) as well as the electrodiagnostic studies. Results reported in these studies show generally good results after hydrodissection procedure using various injectates, in terms of cessation of pain, clinical improvement (decreasing of BCTQ and DASH scores) and improvement of electrodiagnostic parameters. All considered variables were statistically significantly better after treatment, comparing to baseline [10, 11].

Yang et al. reported results of investigations of efficacy of various injectates used in hydrodissection procedures in the treatment of carpal tunnel syndrome through a network meta-analysis of randomized control trials. Platelet-rich plasma was identified to be the most effective injectant for short-term functional improvement and pain relief. Platelet-rich plasma is the processed liquid fraction of autologous peripheral blood with a platelet concentration. The authors conclude that results of their network meta-analysis show that platelet-rich plasma can be used as first-line treatment for carpal tunnel syndrome, and other injectates such as 5% dextrose and steroids may serve as alternative treatments [13].

Interestingly, favourable outcomes after hydrodissection procedure were observed also in a control groups using injections with plain saline or local anaesthetics; unfortunately there were no clear placebo-controlled trials. However considering normal saline injection as placebo, these results may suggest that hydrodissection itself results in clinical improvement, regardless the injectate used [9, 11, 12]. No serious adverse events were reported after hydrodissection. Results of the analysis of literature on use of this procedure show that USG-guided hydrodissection is a safe but only temporary effective treatment for mild to moderate CTS. A major rationale for using this technique is to reduce the risk of iatrogenic nerve injury during blind intracarpal injection of various substances.

CRITICAL COMMENT

Current evidence supporting use of hydrodissection for carpal tunnel syndrome has a significant drawback: a short follow-up. Almost all studies presented results up to 6 months! There may be concern that after a longer time the symptoms may return in most patients. In essence, hydrodissection does not differ much from ordinary steroid or hyaluronic acid injections. Although it is ultrasound-guided and more fluid is injected into the carpal tunnel, but the procedure does not change anatomical relations in the carpal tunnel. The only procedure that changes the anatomical relations in the carpal tunnel is surgical cutting the flexor retinaculum. When all structures in the carpal tunnel remain unchanged, it is difficult to assume that the pressure on the me-

Fig. 1. Application of shock wave in carpal tunnel syndrome.

dian nerve, which was reduced after the intervention, will not return after a shorter or longer period of time. Therefore beneficial effect of hydrodissection reported in many studies should be treated with caution as potentially short-lived. The reviewed literature also did not provide any evidence that patients with CTS who underwent hydrodissection will avoid surgery in the future.Therefore the assurances of some doctors that hydrodissection is as effective treatment as surgery and without unpleasant adverse effects are unfair.

STEROID INJECTION

Intracarpal steroid injection is one of the most commonly accepted treatment among the various conservative managements for CTS. There are several supposed mechanisms of action of local steroids in carpal tunnel syndrome, including:

- Anti- inflammatory effect by inhibiting the production of inflammatory cytokines by lymphocytes and macrophages in the tenosynovium.
- Antifibrotic effect via the suppression of collagen expression.
- Anti-oedematous effects through reduced vascular permeability.

Activation of all these mechanisms results in a beneficial effect in the form of cessation of symptoms and improvement of hand function [13-17]. In some studies an improvement in electrophysiological parameters in the median nerve has also been observed [15, 17]. Basically 3 substances are used for injections: triamcinolone, methylprednisolone and betamethasone. Effectiveness all these injectates is similar and their use depends mainly on the individual surgeon's preference. Steroids are injected into carpal tunnel with landmark-guided technique or with USG guidance; the former technique is much more common, but it carries some risk of intraneural injection, even with correct needle insertion and localization. Therefore, ultrasound-guided injection is gradually applied for accurate localization of intracarpal structures. However, landmark-guided injection still seems to be one of the most available management procedures, attributed to good effectiveness, more convenience, and lower cost [17].

In general 1-3 injections at 2-4 week intervals are needed to achieve permanent improvement, but some patients respond excellently to one injection. Steroid injections provide a very quick relief of symptoms, usually within 24 hours after the injection, which is why patients often ask for such treatment. This applies especially to patients with severe symptoms who are referred for surgical treatment, but their waiting time is long, i.e. several weeks or months.

There is abundant literature on steroid injections for carpal tunnel syndrome. We provide reviews of only several studies.

Marshall et al., presented results of systematic review of on the efficacy of local steroid injections in carpal tunnel syndrome [14]. They included 12 studies involving altogether 671 participants. Results of this analysis show

that in most studies steroid injection provides greater symptom relief one month after injection, compared to placebo, however this effect was short-living and was not demonstrated beyond one month. Other findings from this study are as follows: steroid injection provides significantly greater clinical improvement than oral corticosteroid for up to three months; steroid injection does not significantly improve clinical outcome compared to either anti-inflammatory treatment and splinting after two months or laser treatment after 6 months; two local corticosteroid injections do not provide significant added clinical benefit compared to one injection [14].

In a more recent study, Ashworth et al. presented results of Cochrane database systematic review of placebo-controlled studies investigating the efficacy of local steroid injections for CTS [15]. The authors found 14 trials with 994 participants. The main conclusion from this analysis is that intracarpal steroid injections are effective for the treatment of mild and moderate CTS with benefits lasting up to six months. Another finding is that this therapy reduces need for surgical treatment of the syndrome up to 12 months. All studies reported a very low risk of serious adverse events [15].

Similar conclusions were presented in study by Yang et al., (2024), who presented results of a systematic review and network meta-analysis of randomized controlled trials on the effectiveness of injection therapy using various injectables for CTS. In the part relating to the use of steroids these authors state that steroid injections are effective in terms of symptom and pain relief as well as functional improvement in the short term (up to 6 months) but not in the long term [13].

Kaile et al., reported results of the study investigating safety of landmark-guided steroid injections with 40 mg triamcinolone for CTS. These authors have encountered only 4 serious complications in 9515 injections. At routine follow-up, 6 weeks after injection 33% patients reported some side effects, the most commonly it was short-lived local pain (13%) which resolved in all cases within 3 weeks. No cases of intraneural injection or tendon rupture occurred. Most adverse effects were transient, only 13 hands exhibited persistent skin depigmentation or subcutaneous atrophy. The authors conclude that landmark-guided intracarpal steroid injection is safe procedure, burdened with a very low risk of complications [16].

CRITICAL COMMENT

Intracarpal steroid injections are commonly used in the treatment of CTS. Although it is well known that it does not provide a permanent cure, many patients are very satisfied with such therapy. It is safe and cheap, unlike other, non-operative treatments, which are usually much more expensive and similarly (or less) effective. The method is safe, both when given with landmark-guided method or with USG guidance. Steroid injection also has diagnostic value: in doubtful cases, significant improvement after steroid injection confirms diagnosis of carpal tunnel syndrome and that surgical treatment should be effective.

SPLINTING

Among the non-operative treatment modalities splinting has emerged as a first-line treatment in mild to moderate CTS [18-23]. Splints are typically recommended for use at night, but may also be worn during daytime hours depending on patient work and activity demands. By maintaining the wrist in a neutral position, splints prevent the extremes of wrist flexion and extension, which have been shown to increase pressure within the carpal tunnel, irritate the median nerve and causes symptoms. Most of splints only immobilize the wrist, but some extend distally and keep the metacarpophalangeal joints extended. This (theoretically) prevents the lumbrical muscles from proximal migration and entering the carpal tunnel. There are many studies in the literature supporting the use of splints in mild to moderate CTS. Older studies reported significant beneficial effect of splinting. Manente et al. (2001) reported significant reduction of nocturnal symptoms (pain and numbness) and functional improvement, after use of a soft hand splint at night for 4 weeks, when compared with a control group [18]. Other studies reported similar benefits from splinting [19-22].

However, an updated meta-analysis of the literature by Karjalainen et al. showed different picture. Results of recent studies showed that night splinting provides little or no benefits in reduction of symptoms in the short term (< 3 months) and does not improve hand function in the short and long term (> 6 months). In the short and long term, the mean BCTQ was 0,24 points better after splinting compared with no active treatment. The Minimal Clinically Important Difference (MCID) for BCTQ is 0,7 points, what means that this improvement was not clinically meaningful. Nevertheless, these variables were better after splinting compared to before treatment [23].

An assessment of efficacy of splinting as an additional treatment to steroid injection, rehabilitation, kinesiology taping, rigid taping or extracorporeal shock wave treatment (ESWT) showed that splinting does not provide additional benefits in reduction of symptoms or improvement of hand function when given together

with these measures. Results of some studies showed that splinting for 12 weeks was not better than 6 weeks, but 6 months of splinting was more beneficial than 6 weeks of splinting in cessation of symptoms and improving of hand function [23].

The evidence whether splinting benefits patients with carpal tunnel syndrome is not clearly convincing. This means possibility of small improvements in symptoms and hand function, but they may not be clinically meaningful. Results of some studies suggest that patients may experience overall improvement with night-time splints comparing to no treatment. As splinting is simple, cheap and safe, even small effects could justify its use, particularly when patients are afraid of more invasive treatments. It is unclear if a splint is optimally worn full time or at night-time only and whether long-term use is better than short-term use, but some evidence suggests that the benefits may manifest in the long term [19, 22].

CRITICAL COMMENT

Splinting is now considered an effective treatment for mild CTS, devoid of adverse effects, although somewhat inconvenient for patients. However, it should be stated that it is a good method only for patients with mild symptoms who do not feel discomfort during the day and without impaired hand function. Such a clinical presentation concerns only about 5% of patients, which is a significant minority. The author's experience shows that night splinting never results in full recovery and almost all patients treated with this method are eventually operated on. Night splinting is also recommended for the waiting time for surgery, which can take up to several months. This allows patients survive the waiting time in greater comfort. An intracarpal steroid injection is similarly effective procedure used in patients who are waiting for surgery and suffer from severe pain.

OHER NON-INVASIVE TREATMENTS.

Other, less commonly used non-invasive treatments will be presented in short paragraphs, below.

LOW-LEVEL LASER THERAPY

The beneficial effect of the low-level laser in CTS is (in theory) achieved through several mechanisms, such as increasing myelin production, anti-inflammatory effects, selective inhibition of nociceptive activation at peripheral nerves, increased ATP production and improvement of blood circulation in the median nerve [24-26]. These mechanisms are also mentioned in other disorders in which the laser is used. The most common treatment protocol involved 5 laser sessions a week for a total of 2-3 weeks. Three or 5 application points over the course of the median nerve at the wrist was the most commonly used action position. Different laser irradiation energy doses were used, from 2,7 to 11 J (Joule) for each point or as total energy from 81 to 300 J for the entire treatment [24, 26].

Results of older studies showed reduction of pain and improvement of hand function in patients who received 2-3 weeks laser therapy, however all these studies were uncontrolled [24, 25]. Li et al., (2016) reported results of a meta-analysis of placebo-controlled studies published in recent years. Results of these studies have shown a short-term (3 months in average) beneficial effects of laser therapy on clinical and electrophysiological parameters in the CTS. These findings, however, were not consistent because of different laser intervention protocols used in these studies. Moreover, the functional mechanism of low-level lasers is not clear, and some studies suggested that laser irradiation did not change the functional properties of peripheral nerves [26]. The fundamental disadvantage of these studies is very short follow-up period. Therefore beneficial effect of laser therapy reported in these studies should be treated with caution as potentially short-lived. The reviewed literature also did not provide any evidence that patients with CTS who underwent laser therapy will avoid surgery in the future.

ULTRASOUND THERAPY

Ultrasound (US) treatment within an intensity range of 0,5 – 2,0 W/cm^2 may have the potential to induce various biophysical effects within tissue. The rationale of using US therapy in carpal tunnel syndrome is based on results of some studies which showed its beneficial effects such as an anti-inflammatory effect, stimulation of nerve regeneration via enhanced blood flow, and membrane permeability, as well as improvement of conduction properties in the nerve. Activation of these mechanisms by US treatment might (in assumption) facilitate recovery from nerve compression [27, 28]. Results of study by Ebenbichler et al., (1998) showed that pulsed ultrasound at frequency of 1MHz, and energy of 1,0 W/cm^2 applied to the palmar side of the wrist over 15 min for ten consecutive days, followed by twice weekly treatments for five additional weeks resulted in cessation of pain and nocturnal paresthesiae, improved sensation in the fingers innervated by the median nerve, increased grip and pinch strength and improved electrophysiological parameters. Treatment effects were observed up to 6 months [27]. However,

no additional placebo-controlled studies were available to support the actual effect of US, with certain studies calling its utility into question [21, 28]. Finally, Page et al., (2013) presented results of Cochrane review of studies presenting results of treatment of carpal tunnel syndrome with ultrasound therapy and concluded that there is only poor quality evidence from very limited data to suggest that therapeutic ultrasound may be more effective than placebo for either short- or long-term symptom improvement in CTS patients. They also stated that is insufficient evidence to support the use of therapeutic ultrasound as a treatment with greater efficacy compared to other conservative treatments, such as splinting, physiotherapy, steroid injections and oral drugs [28].

ACUPUNCTURE

Acupuncture aims to stimulate trigger points along the meridian, a proposed pathway of energy through the body. Meridian is a concept from traditional Chinese medicine. According to this concept, meridians form a system of channels wrapping around the human body. They connect to the organs of the body that play a key role in the production, processing, and transmission of energy called Qi. Optimizing this energy pathway is believed to have beneficial effect in CTS without altering mechanical pressures within the carpal tunnel [21]. The mechanism of action of acupuncture remains unknown, proposed theories include a neuromodulatory effect on pain perception by promoting endogenous central nervous system analgesic production and activating anti-inflammatory pathways [21, 29, 30].

In a recent Cochrane review compiling 12 studies and 869 patients, Choi et al. concluded that acupuncture may have little or no short-term effect on CTS symptoms in comparison with placebo or sham procedures [31]. This was largely attributed to heterogeneity of the studies and the risk of bias. The authors also stated that the adverse effects of acupuncture, such as skin bruising and local pain after needle insertion, are inconsistently reported among trials and must be documented to comprehensively assess risks and benefits prior to recommending treatment [31].

EXTRACORPOREAL SHOCK WAVE THERAPY

Extracorporeal shock wave therapy (ESWT) has been used for the treatment of CTS as a novel and non-invasive method (Fig. 1) [32-35]. The mechanism of action of ESWT in carpal tunnel syndrome is not fully understood; the proposed theories include the anti-inflammatory and neuronal regeneration effects as potential mode of action. The anti-inflammatory effect is similar to observed in other musculoskeletal disorders treated with ESWT. This effect on intracarpal structures can modulate the perineural pressure and promote cessation of CTS symptoms. Second proposed mechanism is induction of peripheral nerve regeneration by accelerating the elimination of the injured axon, increasing Schwann cell proliferation, and increasing axonal regeneration. These mechanisms can have effect on improvement of clinical symptoms and electrophysiologic parameters [32, 33].

Xu et al., reported results of randomised study comparing the effect of ESWT vs steroid injection in mild and moderate carpal tunnel syndrome. At the 3 months follow-up, a statistically significantly greater effect on reduction of symptoms and improvement of function was noted for the ESWT group than for the steroid injection group. For the nerve conduction study, there was a significant improvement in the median nerve sensory nerve action potential distal latency at the 3 months follow-ups for the ESWT group. The authors conclude that ESWT is a useful non-invasive short-term treatment for mild to moderate carpal tunnel syndrome and elicits a better recovery than local steroid injection [33].

Kim et al., presented results of a systematic review and meta-analysis of randomized controlled trials on the effect of ESWT in carpal tunnel syndrome. These authors found 6 studies meeting the requirements for analysis, involving a total of 261 patients. Based on results of this analysis they noted that ESWT treatment improves symptoms, functional outcomes, and electrophysiologic parameters in patients with CTS, however, there was no obvious difference between the efficacies of ESWT and local corticosteroid injection. No serious side effects were reported in all included studies [34].

In contrast, results of recent meta-analysis by Chen et al., (2022) which involved 7 randomized controlled trials with a total of 376 participants showed that at the 3 months follow-up, the ESWT did not demonstrate superior efficacy compared to treatment with night wrist splinting alone. The authors conclude that the therapeutic effect of ESWT is transient and mostly nonsignificant [35].

SHORTVAWE AND ELECTROMAGNETIC DIATHERMY

Diathermy is a therapeutic technique that produces deep heating under the skin, muscles, and joints for therapeutic purposes. It is classified into two types: shortwave and microwave diathermy Recently, an electromagnetic diathermy has been introduced alongside these categories. It is known as capacitive resistive electric transfer and it can be considered as longwave

diathermy, as the wave frequency used is relatively lower than those of shortwave and microwave. The physiological effects of diathermy include an increase in blood perfusion which facilitates tissue healing, a local increase of oxygen and nutrients, improved muscle contraction capacity, and a possible positive change in pain sensation [36, 37]. Beneficial effects of diathermy could also be mediated at a central nervous system. Results of functional MRI studies showed central effects of skin warming, with increased activation of the posterior insula and thalamus of the brain which promoted pain relief in the peripheral body parts [37].

Several studies are available investigating an effect of diathermy in carpal tunnel syndrome.

Incebiyik et al., reported results of a randomized clinical trial involving 31 CTS patients who were assigned randomly to 2 treatment groups: first received a hot pack, shortwave diathermy, nerve and tendon gliding exercises (treatment group) and second which received a hot pack, placebo diathermy, nerve and tendon gliding exercises (control group). The treatment was applied five times weekly for a total of 15 sessions. At the one-month follow-up, improvement (cessation of symptoms, better hand function) was observed in both groups, however only in the treatment group it was statistically significantly better than at baseline [36].

Pollet et a., presented results of a systematic review with meta-analysis on efficacy of electromagnetic diathermy for the treatment of musculoskeletal disorders, including CTS, based on 68 studies included in the analysis. Many pathologies were treated with diathermy against placebo. The analysed studies showed controversial results and most of them did not show significant improvements in the primary outcomes. The authors conclude that results of current evidence does not confirm that diathermy or electromagnetic diathermy can be considered an effective therapy in musculoskeletal disorders, including CTS [37].

NEURAL MOBILIZATION

This method generally consists of techniques termed neural glides, neural flossing or neural stretching.

The main objectives of neural mobilisation is to facilitate the gliding of tendons and nerves within the carpal tunnel in order to maximize nerve and tendon excursion to improve axonal transport and nerve conduction [38-40]. Some joint mobilizations described as transverse and ventral glide on dorsal side of the first carpal row were designed to release carpal tunnel syndrome by increasing cross-sectional area of the carpal tunnel. In addition, soft tissue mobilization aims to reduce pressure on the carpal tunnel syndrome by improving the mobility of the myofascial tissues adjacent to the nerve. For CTS, the nerve gliding exercises are done by alternately flexion and extension of fingers with different wrist positions and forearm in pronation and supination [38, 39]. Tendon gliding exercises are done by alternately flexion and extension of all fingers and thumb in metacarpophalangeal and interphalangeal joints, making hook fist, all finger joints in full flexion and full fist [38, 39].

However, variability of manual techniques, lack of terminology consensus and standardization in the techniques whose aim is to mobilize the nervous system raises doubts the actual effectiveness of these techniques. Moreover, parameters such as the mobilization dosages, the number of joints to be mobilized and the consideration to stabilize or not the wrist joint while performing the gliding mobilization techniques are not uniform throughout the studies. These doubts were highlighted in the study by Page et al. (2012) who conducted a systematic review of studies presenting results of neural mobilization for carpal tunnel syndrome. These authors concluded that there was limited and very low quality evidence of benefit for all of a diverse collection of exercise and mobilisation interventions for carpal tunnel syndrome. In most of reviewed studies nerve mobilization techniques provided short-live improvement and only in mild CTS [40]. Therefore patients who indicate a preference for exercise or mobilisation interventions should be aware of the limited effectiveness of this therapy.

KINESIOTAPING

Kinesiotaping is a therapeutic technique that pulls up the skin and provides a space under the skin, directing connective tissue to the expected area. Application of this measure can control the pulling force to a certain tendon or ligament to avoid further injury, so that spontaneous tissue repair can be facilitated. It has been hypothesized that kinesiotaping application, through neural technique and space correction may be beneficial for patients with mild and moderate carpal tunnel syndrome. Geler Kulcu et al. (2016) reported good outcomes after use of kinesiotaping in 45 patients (65 wrists). The tape was applied at beginning of the week, to stay on for 5 days, with a 2-day rest, for a total of four times. At a final follow-up, pain and paresthesiae significantly reduced and hand function significantly improved as assessed by Numeric Rank Scale and the Boston Carpal Tunnel Questionnaire. The problem with this study is that the authors did not provide the follow-up period, therefore actual effect of this therapy cannot be credibly evaluated [41]. In an another study, a

beneficial effect of kinesiotaping combined with splinting was shown [42]. However, it should be stated that this method, although simple and safe, is not popular as a basic treatment and does not constitute a significant alternative to the previously discussed, much better known techniques.

CONCLUSIONS

The review of non-operative treatments of CTS presented in this paper indicates that each of the presented methods provide only short-live improvement and none of them provides a permanent cure. The multitude of these methods is only a confirmation of this fact. Current scientific evidence on the effectiveness of various CTS treatments indicates that only operative treatment by cutting the flexor retinaculum changes the anatomical relations in the carpal tunnel and ensures a permanent cure. It is obvious that surgery is burdened with a certain risk of complications, but this risk is disproportionately small in relation to the benefits achieved. Therefore, without denying the legitimacy of non-surgical therapies in some patients and in some situations, it must be clearly stated that scientific evidence from reliable scientific publications clearly indicates surgical treatment as ensuring permanent recovery from the disease. Therefore, the statements sometimes found in advertisements of some private clinics that one of the new methods of non-surgical treatment is the same effective as surgery, but without unpleasant adverse effects are unjustified and unfair.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Andrzej Żyluk
Klinika Chirurgii Ogólnej i Chirurgii Ręki
Pomorski Uniwersytet Medyczny,
ul. Unii Lubelskiej 1, 71-252, Szczecin, Poland
email: azyluk@hotmail.com

ORCID AND CONTRIBUTIONSHIP
Andrzej Żyluk: 0000-0002-8299-4525 A B D E F
Żyluk Alicja: 0009-0006-0309-0568 B C D

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

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REVIEW ARTICLE

CONTENTS

Legal regulation of the circulation of dietary food and dietary supplements in eu countries: the experience of Germany

Vitalii M. Pashkov[1], Oleksii S. Soloviov[2], Olga A. Khmelnytska[3]

[1]ACADEMICIAN STASHIS SCIENTIFIC RESEARCH INSTITUTE FOR THE STUDY OF CRIME PROBLEMS; YAROSLAV MUDRIY NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE

[2]INTERNATIONAL ACADEMY OF PERSONAL MANAGEMENT, KYIV, UKRAINE

[3]PROFESSIONAL COLLEGE OF MEDICINE AND PHARMACY OF POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

Despite the EU legislation regulating the circulation of dietary and food supplements within the internal market, the system of state control requires improvement. For instance, due to existing regulatory gaps, certain pharmaceutical entities commit violations of regulatory requirements, such as failing to register medicinal products and selling them under the guise of dietary and/or food supplements. Conversely, physicians may recommend ordinary dietary and food supplements to patients as if they were medicinal products.

Additionally, violations posing health risks may include the presence of active pharmaceutical ingredients, including prescription-only substances that should be used exclusively for production of medical product ; the absence of declared nutrients (proteins, fats, carbohydrates, vitamins, minerals) or other substances with nutritional or physiological effects; and labeling that fails to meet established requirements, such as claims of therapeutic effects.

In other words, there is a lack of clear mechanisms in legislation for introducing dietary and/or food supplements to the market and defining requirements for substances used in their production, such as vitamins, minerals, and other substances with nutritional or physiological effects.

KEY WORDS: dietary food for special medical purposes, dietary supplements, food supplements, food products for specific consumer groups, legal regulation

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INTRODUCTION

Over the past few decades, there has been a rapid increase in knowledge about the biochemical and physiological cellular functions of human nutrients. Moreover, recommendations for the consumption of macroelements, microelements, and essential nutrients for maintaining health have grown. Additionally, the social perception of dietary habits and physical activity, along with their impact on current and future health, has evolved rapidly [1]. Clinical trials have not demonstrated the efficacy of certain dietary and food supplements in disease prevention. However, concerns about the safety of increased daily doses of such products necessitate legislative regulation of new aspects of their circulation. This issue is common across all countries, as the dietary and/or food supplement market is becoming increasingly global. Nutrition is one of the factors linking humans to the external environment and significantly influences national health. Modern humans require fewer calories and smaller food quantities than in the past. However, the need for essential nutrients and biologically active substances remains unchanged, resulting in a deficit. Insufficient quantities of these substances lower the body's resistance to adverse environmental impacts, contribute to immune deficiency and chronic diseases, or increase the risk of developing illnesses. Consequently, this leads to reduced quality of life and effectiveness of medical treatments.

In response to these regulatory challenges, the following three-tier regulatory framework has been established at the international level:

1. Diet modification**:** Promoting healthy and balanced nutrition through state policies in the field of healthy eating.
2. Fortification of staple foods**:** Enriching foods like salt (with iodine), flour (with vitamins and minerals), vegetable oils, and margarine (with vitamins A and D). The mandatory fortification of foods is typically stipulated by regulatory acts.
3. Use of food supplements**:** Addressing the problem of high-quality and balanced nutrition as a basis for optimal human health.

This mechanism has led to the emergence of one of the most pressing global healthcare issues today: the quality, efficacy, and safety of medicinal products and food for special medical purposes.

AIM

The purpose of this article is to determine the legal status of food products for special medical purposes, dietary and food supplements, and food products intended for specific consumer groups, including herbal and fruit teas for infants or young children. For instance, Directive 2002/46 (Article 2) and Regulation No. 609/2013 (Article 2) should be interpreted to mean that the terms "food supplements" and "food products for special medical purposes," as defined in these provisions, are mutually exclusive. Each case requires individual analysis based on the characteristics and conditions of use to determine whether a product falls under one category or the other.

MATERIALS AND METHODS

This study primarily relies on the analysis of EU Directives and Regulations, using Germany's legal framework as an example, including content analysis and case law. It also employs the dialectical method and incorporates perspectives from scientific literature.

REVIEW AND DISCUSSION

For example, the German Dietary Supplement Regulation (NemV) of May 24, 2004, as amended [2], regulates the circulation of dietary supplements, which, under this Regulation, are classified as food products (§ 1). These products:

1. Are intended to complement the general diet;
2. Consist of concentrates of nutrients or other substances with nutritional or physiological effects, either individually or in combination;
3. Are marketed in dosed forms, such as capsules, lozenges, tablets, pills, and similar pharmaceutical forms, as well as powder sachets, liquid ampoules, dropper bottles, and similar forms for consumption in small measured quantities.

Nutrients, under this Regulation, include vitamins and minerals, including trace elements.

Thus, the term "dietary supplement" (§ 4 NemV) refers to food products as defined by Regulation (EU) No. 1169/2011. A dietary supplement (§ 2 NemV), intended for consumer supply, may only be sold as a pre-packaged food product under Article 2(2)(e) of Regulation (EU) No. 1169/2011 of the European Parliament and Council, dated October 25, 2011, regarding the provision of food information to consumers, amending Regulations (EU) No. 1924/2006 and (EU) No. 1925/2006, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, European Parliament and Council Directive 2000/13/EC, Commission Directive 2002/67/EC, Commission Directive 2008/5/EC, and Regulation (EU) No. 608/2004 [3].

The production of dietary supplements is limited to substances (§ 3 NemV) listed in Annex I of Directive 2002/46/EC of the European Parliament and Council, dated June 10, 2002, concerning the approximation of member states' laws regarding dietary supplements (OJ L 183, July 12, 2002, p. 51). The nutrients listed under § 1, paragraph 2, are used in forms outlined in Annex II of Directive 2002/46/EC. Annexes I and II to Directive 2002/46/EC are applied in the version of December 5, 2011 (OJ L 296, November 15, 2011, p. 29).

Food products are defined as "specific substances suitable for human consumption." They consist of basic food items (e.g., meat, fish, eggs, dairy products, fruits, vegetables, and grains containing proteins, carbohydrates, fats, vitamins, and minerals) and additives (herbs and spices, sweeteners, colorants, preservatives, antioxidants, emulsifiers, thickeners, stabilizers, and solvent carriers) [4].

Substances listed in Annex II of Directive 2002/46/EC, as amended on December 5, 2011 (OJ L 296, November 15, 2011, p. 29), must conform to the specifications set forth in Regulation (EU) No. 231/2012 of the Commission, dated March 9, 2012, which establishes specifications for food additives listed in Annexes II and III to Regulation (EU) No. 1333/2008 of the European Parliament and Council (OJ L 83, March 22, 2012, p. 1), in its current version, and meet the prescribed purity requirements. Simultaneously, substances listed in Annex II of Directive 2002/46/EC, as amended on December 5, 2011, (OJ L 296, November 15, 2011, p. 29), but not listed in Regulation (EU) No. 231/2012, must meet purity requirements achievable under generally recognized standards.

According to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, and Article 2 of Regulation (EU) No. 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control, repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC, and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council, and Regulations (EC) No. 41/2009 and (EC) No. 953/2009 of the Council and the Commission, it should

be interpreted that, to distinguish between the terms "medicinal products" and "food for special medical purposes" as defined in these provisions, it is necessary to assess whether the product is a food in light of the nature and characteristics of the relevant product designed to meet specific dietary needs, or whether it is a product intended to prevent or treat human disease, restore, correct, or influence human physiological functions through pharmacological, immunological, or metabolic action, or to establish a medical diagnosis.

Regulation No. 609/2013 should be interpreted, firstly, that the term "dietary compliance" encompasses the need caused by a disease, disorder, or health complaint, and the satisfaction of such a need is critically important for the patient in terms of nutrition. Secondly, the qualification as a "food for special medical purposes" cannot depend on the success of "dietary management" caused by a disease, disorder, or complaint and, thus, the product's effect that necessarily arises due to or as a result of digestion. Thirdly, the phrase "diet modification for the patient only" includes situations where diet modification is impossible or dangerous for the patient, as well as situations where it is very difficult for the patient to meet their nutritional needs using regular food.

In Article 2 of Regulation No. 609/2013, this sentence should be interpreted, firstly, that the product must be used under medical supervision if a recommendation and subsequent evaluation by a medical professional regarding a disease caused by a specific condition or dietary needs related to a disorder or specific complaints is necessary due to the impact of the product on the patient's nutritional requirements. On the other hand, the requirement that food for special medical purposes "must be used under medical supervision" does not exist as a mandatory condition for classifying the product as food for special medical purposes.

Directive 2002/46 (Article 2) and Regulation No. 609/2013 (Article 2) should be interpreted to mean that the concepts of "food supplements" and "food for special medical purposes," as defined in these provisions, are mutually exclusive. In each case, it is necessary to decide based on the characteristics and conditions of use whether the product falls under one or the other of these definitions.

Thus, among regular food and/or dietary supplements and food products, it is essential to distinguish food for specific consumer groups, including herbal and fruit teas for infants or young children.

According to the Regulation on Food for Specific Consumer Groups (LMBVV) of 26 April 2023 [5], herbal and fruit teas for infants or young children are defined as: 1) herbal or fruit tea, extracts of herbal or fruit tea, or food products containing extracts of herbal or fruit tea, which must be prepared with water to be suitable for consumption, and which, according to their name, other information, or symbols on the packaging or label attached to the packaging, based on their presentation, appearance, or advertising claims, are exclusively or partly intended for consumption by infants and young children; and 2) beverages prepared from herbal or fruit tea extracts and intended for immediate consumption, their extracts, or preparations, as determined by the name, other information, or symbols on the packaging or label attached to the packaging, product appearance, or advertising claims, which are exclusively or partly intended for consumption by infants and young children.

When preparing these specific types of food for infants and young children, certain groups of ingredients listed in § 4 LMBVV must not be used. Herbal and fruit teas for infants and young children may only be sold in retail stores as pre-packaged food products, provided that the labeling on the packaging or a label attached to it contains information:

1. indicating that sugar and other sweeteners should be avoided when preparing and serving the tea;
2. specifying the age from which infants or young children can consume the tea.

This information must be clearly visible, legible, and understandable on the packaging and must not be hidden or obscured by other information, symbols, or inserted materials.

The marketing of infant formula or follow-up formula with statements that may mislead consumers is prohibited pursuant to § 7 LMBVV, such as "contains only lactose" or "lactose-free," "very low-calorie diet," or "low-calorie diet."

Advertising for infant formula or follow-up formula is not allowed. Specifically, promotional activities in retail settings are prohibited, including distributing samples or using other promotional materials like special displays, discount coupons, bonuses, special offers, incentives, etc., as part of marketing agreements.

It shall be prohibited for manufacturers and distributors to engage in the distribution of products at no cost or at reduced prices, including but not limited to promotional samples to the general public, pregnant women, mothers, or their families, either directly or indirectly through healthcare services or medical professionals.

The use of phrases such as "for special medical purposes" is prohibited if it may mislead specific categories of consumers. Often even professionals fail to distinguish between foods for special medical purposes, dietary supplements, and medicinal products.

The Court of Justice of the European Union has issued a preliminary ruling on this matter [6] in response to a request for a preliminary ruling concerning the

interpretation of Article 2(2)(g) of Regulation (EU) No 609/2013 of the European Parliament and Council of June 12, 2013, on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control, repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC, and 2006/141/EC, Directive 2009/39/EC of the European Parliament and Council, and Regulations (EC) No 41/2009 and (EC) No 953/2009 of the Council and Commission (OJ 2013, L 181, p. 35), and the interpretation of Directive 2002/46/EC of the European Parliament and Council of June 10, 2002, on the approximation of laws of the Member States relating to food supplements (OJ 2002, L 183, p. 51).

The European Court emphasizes that the characteristics and functions of foods for special medical purposes differ from those of medicinal products. Foods for special medical purposes are intended to support the dietary management of patients and are not meant to prevent or treat human diseases that affect physiological functions through pharmacological, immunological, or metabolic processes, nor to restore or correct physical conditions or provide medical diagnoses.

Therefore, foods for special medical purposes do not inherently combat diseases or bodily disorders. The patient benefits from consuming the product insofar as its ingredients contribute to preventing, alleviating, or treating the disease. However, the product is not intended to provide nutritional benefits to the patient but rather to address, prevent, or restore human physiological functions through pharmacological, immunological, or metabolic effects. This suggests that the product should be classified as something other than "food for special medical purposes".

Foods for special medical purposes are designed for patients with specific nutritional needs that cannot be met by modifying a regular diet as defined in Article 2 of Regulation No 609/2013. These needs cannot be satisfied by consuming ordinary foods alone.

The requirement of 'under medical supervision' as set forth in Article 2 of Regulation No 609/2013 shall be interpreted to mean that qualified medical oversight must be established prior to the product's placement on the market.

Thus, the use of foods for special medical purposes, which are tailored to the patient's nutritional needs, should be recommended by a healthcare professional based on the patient's dietary requirements, without necessarily requiring a prescription. In this context, "medical supervision" necessitates that a healthcare professional, as defined in Regulation 2016/128, ensures that the use of foods for special medical purposes aligns with the patient's specific nutritional needs.

Additionally, the legislator, based on Article 9 of Regulation No 609/2013, allows for the provision of useful information or recommendations exclusively for medical, dietary, or pharmaceutical professionals or other healthcare workers responsible for maternal and child care, recognizing their unique responsibilities when dealing with foods for special medical purposes.

Moreover, a healthcare professional's recommendation for foods for specific medical purposes is even more critical, as indicated in the fourth preamble of Regulation No 2016/128. The composition of these foods may significantly differ depending on the disease, disorder, or condition they are intended to manage, as well as the patient's age, the location of medical care, and the intended use of the product.

Such a recommendation ensures that food products for special medical purposes, as specified in Article 2 of the Regulation, can be used effectively in accordance with the manufacturer's instructions and fulfill the specific dietary needs of the individuals for whom they are intended. Specifically, since food products for special medical purposes are designed to address nutritional needs arising from specific diseases, disorders, or medical conditions, using an unsuitable product may not only fail to meet the patient's needs but could also lead to negative consequences.

This risk must also be communicated to the patient, and according to Article 5 of Regulation 2016/128, it must be indicated on the packaging of foods for special medical purposes. In view of this, Article 2 of Regulation No. 609/2013 should be interpreted to mean, on the one hand, that a product must be used under medical supervision if special dietary management is required due to a disorder or specific complaints affecting the patient's nutritional needs. On the other hand, the requirement that a food product for special medical purposes "must be used under medical supervision" is not an absolute condition for classifying a product as food for special medical purposes.

There is also a question about the criteria for distinguishing the terms "food for special medical purposes" under Regulation No. 609/2013 and "dietary supplements" as defined in Article 2 of Directive 2002/46, and whether these terms are mutually exclusive.

In this regard, it should be noted that considering the respective characteristics of foods for special medical purposes and dietary supplements, their uses may overlap. However, the two terms and the legal classifications they imply are necessarily mutually exclusive. Thus, in each specific case, it must be determined whether the product should be classified as "food for special medical purposes" or as a "dietary supplement".

Although dietary supplements under Article 2 of Directive 2002/46 merely supplement a "normal diet,"

Article 2 of Regulation No. 609/2013 and Article 2 of Regulation 2016/128 establish the concept of "foods for special medical purposes." For purposes that wholly or partially replace regular nutrition, dietary supplements are concentrates of nutrients or other substances with specific nutritional or physiological effects that, like certain foods, may meet some nutritional needs for specific medical purposes. However, foods for special medical purposes are characterized by their medical intent, which dictates that they are intended for patients and must be used under medical supervision.

For these reasons, the Court (Second Chamber) has ruled that the requirements of Directive 2001/83/EC of the European Parliament and Council of November 6, 2001, on the Community code relating to medicinal products for human use, as amended by Directive 2004/27/EC of March 31, 2004, and Article 2 of Regulation (EU) No. 609/2013 on foodstuffs intended for infants and young children, foods for special medical purposes, and total diet replacement for weight control must be interpreted as follows: "To distinguish between the terms 'medicinal products' and 'foods for special medical purposes,' as defined in these provisions, it is necessary to assess, based on the nature and characteristics of the relevant product, whether it is a food intended to meet specific dietary needs or a product designed for the prevention, treatment, restoration, correction, or modification of human physiological functions through pharmacological, immunological, or metabolic action, or for making a medical diagnosis".

Article 2 of Regulation No. 609/2013 should be interpreted as follows: firstly, the term "dietary management" includes needs caused by disease, disorder, or condition that are nutritionally significant for the patient. Secondly, the classification as "food for special medical purposes" should not depend on the success of "dietary management" resulting from disease, disorder, or condition or necessarily depend on digestion as the product's mode of effect. Thirdly, the subcategory "modification of the patient's diet alone" includes situations where dietary change is impossible, dangerous, or very challenging to meet nutritional needs with regular food consumption.

In this context, it should be noted that food for special medical purposes and dietary supplements are foodstuffs intended for different target groups. Specifically, Article 3 of Directive 2002/46 does not imply that dietary supplements, like foods for special medical purposes, are intended only for patients.

It is important to emphasize that, according to Article 2 of Regulation No. 609/2013, foods for special medical purposes must meet specific dietary requirements. This classification depends on the fact that modifications to the normal diet are insufficient to meet these needs, while dietary supplements are intended to complement a regular diet as an integral part of it.

The rules regarding the composition of these two categories of food products reflect these differences and particularities. For example, Directive 2002/46 establishes maximum levels for vitamins and minerals in dietary supplements, taking into account safe upper levels based on risk assessments from scientific data, consumer sensitivity variations, dietary intake from other sources, and reference population levels for vitamins and minerals.

However, such reference values are established for the general population pursuant to the provisions of Directive 2002/46/EC, not patients with dietary needs arising from diseases, disorders, or medical conditions.

Dietary supplements may only be marketed if, in addition to the information required by Regulation (EU) No. 1169/2011, the packaging indicates: (1) the names of categories of nutrients or substances characterizing the product or their characteristics, (2) the recommended daily portion, (3) a warning not to exceed the recommended daily intake, (4) a statement that supplements should not substitute a balanced diet, and (5) a directive to store the product out of children's reach.

Dietary supplements may not be marketed under names, claims, or presentations, nor advertised in a way that implies a balanced and varied diet does not generally provide sufficient nutrients.

Products that contain, exclusively as an addition to vitamins or minerals, other substances with nutritional or physiological effects may also be labeled as "food supplements" provided this does not mislead consumers. This is because food supplements are not defined solely by their nutrient content. Instead, what determines the product's classification as a food supplement is the presence of ingredients intended to complement the general diet and the fact that the product is marketed in a dosed form. In such cases, other specific labeling elements in accordance with NemV [8] must be taken into account. In this context, misleading consumers is prevented by the obligation to specify the category of the characteristic substance, meaning the necessary trade name is supplemented with descriptive elements. If a product is suitable both as a standard food supplement and for dietary purposes, the manufacturer must decide and develop the product according to its designation. A product either serves as a supplement to the general diet, thereby qualifying as a "food supplement," or it is intended for a special diet and, depending on the product type, is given a trade name.

Moreover, according to the Regulation implementing Union law provisions related to consumer information

about food products, dated July 5, 2017 [9], if the country or place of origin of the food product does not match the country or place of origin of its primary ingredient, the food product must also indicate the origin of the main ingredient or specify that the primary ingredient comes from a different country or place of origin than the food product itself.

Regarding the incorrect labeling of dietary supplements in terms of health benefits or effects on health, there is relevant case law in Germany. For instance, the Higher Regional Court of Munich considered a case of misleading labeling of a dietary supplement for weight loss. The product was labeled in a way that gave the impression it was a medicinal product. The Court issued an injunction prohibiting the distribution and sale of said product pursuant to the applicable provisions of pharmaceutical law [10].

Given the closely related functions of medicinal products and dietary supplements, as well as the complex interplay of European and national standards in pharmaceutical and food law, numerous issues traditionally arise in distinguishing between these two product categories. This has been one of the most interesting areas of administrative and competition law over the past 30 years. "The issue of differentiation is further complicated by the external appearance of dietary supplements, the economic significance of the differentiation outcome for sales, and the rapid Europeanization of the market", says German expert Marc Dilewski [11]. First and foremost, the researcher notes, the relevant terms for differentiating medicinal products from food/food supplements have fundamentally changed in recent years.

With the entry into force of Directive 2002/46/EC of the European Parliament and Council of June 10, 2002, on the approximation of the laws of the Member States relating to food supplements as of July 12, 2002 [12], and its implementation at the national level through the Dietary Supplement Ordinance (NemV) of May 24, 2004 [13], the term "dietary supplement" was legally defined at the Community level for the first time. It was also clearly stated that dietary supplements are not medicinal products within the meaning of Directive 2001/83/EC of the European Parliament and Council of November 6, 2001, on the Community Code for Medicinal Products for Human Use [14]. Furthermore, existing case law has shown that the legal definition of dietary supplements is becoming increasingly important for distinguishing them from medicines [15]. By the decision of the First Civil Senate of the Federal Court dated May 6, 2004 [16], specific distinctions between medicines and food supplements were clarified.

The matter had previously been subject to judicial review by the Fifth Civil Senate of the Supreme Court, specifically, the decision of the Fifth Civil Senate of the Supreme Court dated May 11, 2001, which was overturned upon appeal by the defendant, and the case was returned to the appellate court for rehearing and decision, including appeal costs.

For example, The defendant, a legal entity established under the laws of the Netherlands, engaged in the distribution within the territory of the Federal Republic of Germany of products not registered there as medicinal products but claimed to help build larger or stronger muscles. These products, including "Creatine Monohydrate,""HCA+," and "Liquid L-Carnitine," were positioned as aids for fat reduction and products for boosting the body's resistance.

CONCLUSIONS

For the purposes of this Regulation, food supplements shall be defined as food products that:

1. Are intended to complement the general diet;
2. Contain a concentrated source of nutrients or other substances with nutritional or physiological effects, individually or in combination;
3. Are marketed in a dosed form, such as capsules, lozenges, tablets, pills, and other similar pharmaceutical forms, sachets of powder, liquid ampoules, dropper bottles, and similar liquid and powdered forms for intake in measured doses.

Among regular food and/or dietary supplements and food products, food for specific consumer groups should be distinguished, such as herbal and fruit teas for infants or young children.

Food products for special medical purposes are those intended for the dietary management of patients and are not designed to prevent or treat human diseases, nor to restore, correct, or affect physiological functions through pharmacological, immunological, or metabolic processes, nor to make medical diagnoses.

Thus, food products for special medical purposes do not allow them to counteract diseases or disorders as such.

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CONFLICT OF INTEREST

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CORRESPONDING AUTHOR

Vitalii M. Pashkov
Academician Stashis Scientific Research Institute
for the Study of Crime Problems of the
National Academy of the Law Sciences of Ukraine,
Yaroslav Mudriy National Law University , Kharkiv, Ukraine
e-mail: v.pashkov26.06@ukr.net

ORCID AND CONTRIBUTIONSHIP
Vitalii M. Pashkov: 0000-0001-9489-7768 A B D E F
Oleksii S. Soloviov: 0000-0002-6615-4868 A B D E F
Olga A. Khmelnytska: 0009-0009-1489-8062 A B D E F

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CASE STUDY

CONTENTS

Laparoscopic treatment of perineal hernia after previous abdominal perineal rectal resection due to cancer. Case report

Mariusz Uryszek, Wiesław Tarnowski, Pavel Wileński
DEPARTMENT OF GENERAL, ONCOLOGICAL AND DIGESTIVE TRACT SURGERY, MEDICAL CENTRE OF POSTGRADUATE EDUCATION, ORŁOWSKI HOSPITAL, MEDICAL CENTRE OF POSTGRADUATE EDUCATION, WARSAW, POLAND

ABSTRACT
The aim of this study is to present a case of laparoscopic treatment of perineal hernia in a patient after abdominoperineal resection od the rectum. We present the case of a 63-year-old woman who was operated on laparoscopically with a mesh sewn in at the level of the sacrum, iliac vessels and pubic symphysis. and covered with a peritoneal flap above the urinary bladder. A 63-year-old woman 4 years earlier underwent neoadjuvant treatment and laparoscopic abdominoperineal resection. The postoperative period was uncomplicated. Histological examination after operation was: adenocarcinoma ypT3N1aM0. The perineal wound healed without complication. 2 years after the above-mentioned surgery, the patient began to experience abdominal pain, especially when sitting down, and symptoms related to „sitting on a pillow". Physical examination revealed a palpable bulge in the perineal wound. The tomographic examination revealed intestinal loops in the perineum and the presence of fatty tissue without any signs of cancer recurrence. 10 cm in diameter mash was sewn at the level of the sacrum, iliac vessels and pubic symphysis. The abdominal symptoms disappeared completely, the so-called perineum cushion was entirely reduced. Laparoscopic treatment of perineal hernia may be a beneficial method for patients, but a demanding method for surgeons mainly due to the proximity of the iliac vessels.

KEY WORDS: perineal hernia, laparoscopy, abdominoperineal resection

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ABBREVIATIONS
APR: abdominoperineal resection of the rectum
PK: perineal hernia

INTRODUCTION
A perineal hernia is defined as the result of damage to the pelvic diaphragm resulting in the contents of the abdominal cavity bulging through the perineum. Yeoman described perineal hernia for the first time in 1939 [1]. One of the reasons for the formation of such a hernia is APR surgery due to diagnosed rectal cancer. Most often, loops of the small intestine move into the smaller pelvis, causing recurrent difficulties with the proper passage of food content, including full-blown obstruction, but also perineal pain, urination disorders and cosmetic defects. In rare cases, the hernia is completely asymptomatic. Predisposing factors include: previous APR surgery, pelvic exenteration surgery, perineal wound infection, previous hysterectomy, female gender, smoking, immunosuppression and previous radiochemotherapy [2, 3] The incidence of hernias is estimated at less than 1 percent after standard APR surgeries, while after ELAPE (extra-levator abdominal perineal resection) it is 2.6-26% [4]. Perhaps this is due to the greater tissue loss of the levator ani muscles compared to standard APR and higher frequency of perineal wound healing disorders. The hernia appears 0.5 to 5 years after the primary surgery. The most frequently used diagnostic method is a physical examination confirmed by computed tomography or a contrast examination such as gastrointestinal passage.

It seems that surgical treatment is absolutely justified, especially in cases complicated by intestinal transit disorders. The number of treated cases in the world remains a problem [5]. There are so few of them that there are currently no established treatment priorities. Both the most commonly used perineal approach and the recently used laparoscopic approach have no prospective studies and, as in the case of surgical treatment of parastomal hernias after APR, there are no uniform guidelines.

AIM
The aim of this study is to present a case of laparoscopic treatment of perineal hernia in a patient after abdominoperineal resection od the rectum.

CASE REPORT
A 63-year-old woman was admitted to our Department for surgical treatment of perineal hernia 4 years

after laparoscopic APR performed by author who now performed perineal hernia repair. She underwent neoadjuvant treatment in Oncology Center. Laparoscopic APR surgery was performed in a standard manner. The postoperative period was uncomplicated. Histological examination was: adenocarcinoma ypT3N1aM0. The perineal wound healed by root growth. 2 years after the above-mentioned surgery, the patient began to experience abdominal pain, especially when sitting down, and symptoms related to "sitting on a pillow". Physical examination revealed a palpable bulge in the perineal wound. The patient did not present any symptoms of intestinal transit disorders. The tomographic examination revealed intestinal loops in the perineum and the presence of fatty tissue without any signs of cancer recurrence. Possibility of cancer metastasis in the left lung is now during observation at the Oncology Center. She has been through in the past hysterectomy due to cervical cancer. The operation began with the insertion of three trocars, including a camera and two working tools. The surgeon stood on the patient's right side, and the assistant held the camera from the patient's head. The abdominal cavity was inflated using a Hasson trocar. Two 5 mm working trocars were inserted in the right iliac fossa and right midabdomen. The intra-abdominal pressure was set at 12 mmHg. After placing the patient in the Trendelenburg position and rotating to the right side, the following items were found in the abdominal cavity: a few adhesions after surgery, including one of the loops of the small intestine and the greater omentum attached (diving) to the area of the perineal scar. There was no local recurrence of the cancer. The place after the removed uterus also showed no signs of cancer recurrence. Both adhesions were released with ligasure. In this way, the entire perineal wound was visualized from the abdominal cavity and the levator muscles, which were very distant from each other (approx. 9 cm). It was considered that suturing the pelvic muscles and sewing the mesh to the perineal scar would be extremely difficult due to the distance (depth) of the operating field. It was decided to close the entrance to the small pelvis using a macroporous mesh (decisions were made because macropore meshes only cause small seromas). A circle with a diameter of approximately 10 cm (Fig. 1) was cut out and sewn with several layers of sutures from the front to the scar of the removed uterus, to the side in the immediate vicinity of the iliac arteries and backward to the sacrum below the promontorium. The mesh was attached with 10 single non-absorbable sutures, then with a continuous non-absorbable V-lock zero suture (a barbed suture is a type of knotless surgical suture that has barbs on its surface) and was additionally attached to the uterine scar with single tackers. Then, due to the fact that it was a single-layer mesh, i.e. adhesive, a peritoneal flap was removed from the supravesical area and covered with the mesh, securing it with single absorbable sutures. During the dissection of the peritoneal flap in the place after hysterectomy, the bladder wall was damaged. The lesion was treated with absorbable V-lock 2 zero suture. A Redon drain was left in the abdominal cavity and its end was placed over the mesh. It was removed on the 3rd day after surgery. A physical examination of the perineum revealed a small seroma. It was not punctured. It was left to resorb spontaneously. The patient was left in the hospital for 10 days. After 14 days, the catheter was removed from the urinary bladder. During the stay, an X-ray of the gastrointestinal tract with contrast was performed, which revealed the lowest loops of the small intestine, slightly below the promontorium. The patient returned home without any symptoms. 5 weeks later, the patient was called for a check-up and a contrast examination was performed, as before (Fig. 2). The intestines remained at the same level (pubic bone). The abdominal symptoms disappeared completely, the so-called perineum cushion was entirely reduced (the seroma was also absorbed).

DISCUSSION

Perineal hernias after abdomen perineal resection are very rare, but they constitute a serious challenge for surgeons, especially when treatment standards have not been developed. It seems that decisions about the type of surgery should be made based on one's own experience in general and laparoscopic surgery. Methods from the perineum are much more difficult because the muscles should be approached without tension, which seems to be the most important stage of the operation, and only then should the mesh be sewn on. Failure to follow this rule increases the possibility of hernia recurrence. In addition, there is a very weakened blood supply to the perineal area due to neoadjuvant radiotherapy [6]. Moreover, laparoscopic or open methods make it possible to release interloop adhesions, and this element of the operation is an advantage over the perineal approach especially in patients with symptoms of transit disorders.

Each of the currently used methods, whether open (laparotomy), from the perineum, or laparoscopically from the abdominal cavity, are currently recognized treatment methods [6-9]. The frequency of using lap *vs* perineal methods is comparable [10]. Various types of meshes are used for perineal hernia repair. The frequency of using meshes made of artificial material to biomeshes is similar [10]. Unfortunately, postoperative recurrence is quite high. The recurrence rate was high-

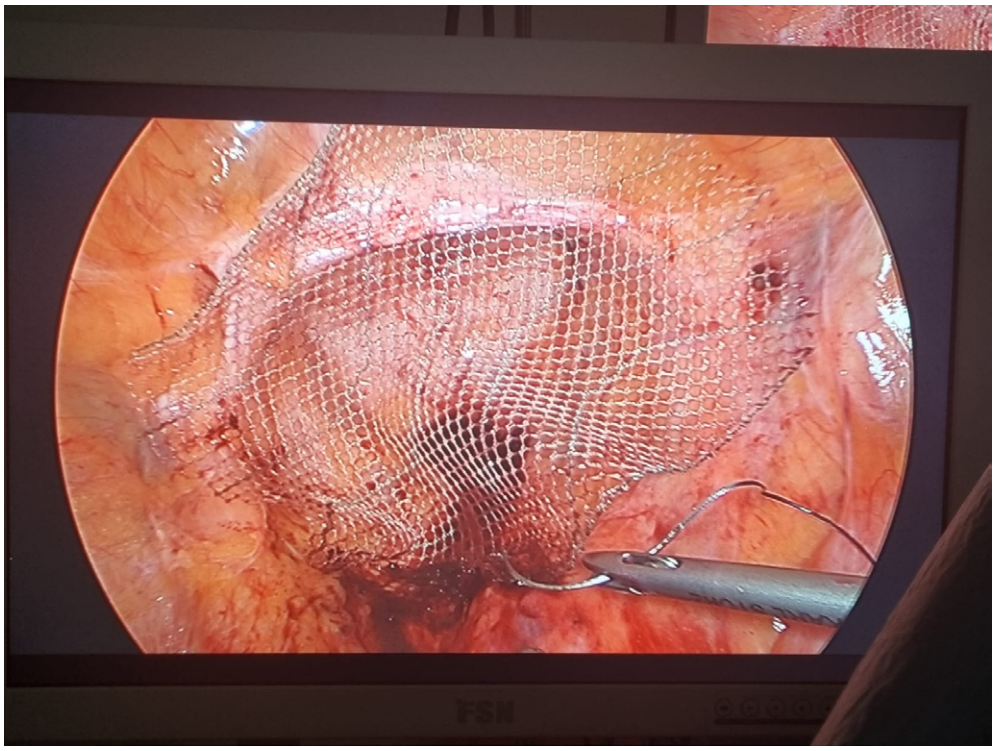

Fig. 1. Mesh in small pelvis.

Fig. 2. Contrast examination after 5 weeks

est with the use of biological mesh (40.4%) and the perineal approach (35.6%). The recurrence rate was lowest in the combined abdominal & perineal approach (0%), followed by the abdominal approach (8.8%) and the laparoscopic approach (11.8%) [10]. Surgeons place the mesh either directly in the perineal scar, or use the IPOM (double layer mesh) at the level of the coccyx and pubic bone, or, as in my patient's case, at the level of the sacrum and pubic bone. There are no statistical studies in the literature comparing treatment results in terms of both the use of single- and double-layer meshes and their position in the small pelvis. This is probably due to the too small number of operated cases [11]. A similar situation occurs with the use of a peritoneal flap from the supravesical area covering a unilateral mesh. Some centers use this method, others do not. Centers that do not use the bladder flap in the case of single-layer (adhesive) meshes claim that they

do not observe complications such as mesh infection and/or intestinal fistulas [12]. Surgeons who operated using the flap did not observe any recurrences [13]. If the surgical field is infected, some surgeons use only a flap over the bladder without a mesh [14].

Laparoscopic methods as mini-invasive methods provide better vizualization, less surgical trauma, faster recovery, less postoperative pain and lower risk of infections, especially if we have to remove a part of the intestine. In mini-invasive procedures, the robot certainly has an advantage due to the difficult conditions of attaching the mesh with sutures [8]. This significantly speeds up and facilitates the operation, especially in the immediate vicinity of large arteries and veins. Access from the perineum if it is impossible to pull the muscle edges together would require assistance from a plastic surgeon and vazcularized muscle grafts.

This is probably the first description of laparoscopic treatment of perineal hernia in our country.

CONCLUSIONS

APR is a commonly used treatment for colorectal cancer. Unfortunately, perineal trauma caused first by radiochemotherapy and then by extensive surgery may result in the development of a perineal hernia. The only form of treatment is surgery. It depends only on our experience which method we will use. Laparoscopic treatment of perineal hernia may be a beneficial method for patients, but a demanding method for surgeons.

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CONFLICT OF INTEREST

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CORRESPONDING AUTHOR

Mariusz Uryszek
Department of General, Oncological and Digestive Tract Surgery
Medical Centre of Postgraduate Education, Orłowski Hospital
Czerniakowska 231, 00-416, Warsaw, Poland
e-mail: mariusz_ury@mac.com

ORCID AND CONTRIBUTIONSHIP
Mariusz Uryszek: 0000-0003-1728-3994 A B D E F
Wiesław Tarnowski: 0000-0003-2638-8595 B
Pavel Wileński: 0009-0008-6849-9000 B

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CASE STUDY

CONTENTS

"Billiary-cast" syndrome in a patient with acute biliary pancreatitis and pulmonary embolism

Olexii Dronov, Dmytro Vlasenko, Vladyslav Makarov
0.0. BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

"Biliary-cast syndrome" ("BCS") is most often encountered in clinical practice as a complication after liver transplantation, there are also described cases of biliary-cast syndrome in patients who did not undergo liver transplantation, isolated cases of "BCS" developing in patients with acute pancreatitis, choledocholithiasis are described in literature. Ischemic damage to bile duct epithelium with development of cholestasis and retrograde biliary tract infection are considered as the main etiological factors. This work presents a clinical case of "Biliary-cast syndrome" in a patient with acute biliary pancreatitis and pulmonary embolism.

KEY WORDS: biliary cast syndrome, BCS, acute pancreatitis

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INTRODUCTION

«Biliary-cast» syndrome is a pathological condition in which there is an obstruction of the biliary tract by formations, which are repeating the shape of the bile ducts, unlike gallstones, in the histological structure of the "casts" there is an luminal epithelium of the biliary tracts. Pathophysiologically, gallstone disease develops as a consequence of impaired metabolism of bile pigments and, or cholesterol. «BCS» – develops as a consequence of a violation of microcirculation in the arterial blood supply of the biliary system, at different levels, which leads to desquamatization of the luminal duct epithelium, cholestasis, the formation of a cast of the lumen of the duct with subsequent obstruction of the latter, the development of cholangitis and cholangiogenic abscesses. «Biliary-cast Syndrome" mostly described as a complication after liver transplantation (2.5 – 4%) [1-3]. The main mechanism of development is ischemic damage to the biliary tract, desquamatization of the integumentary epithelium and cholestasis lead to the formation of «casts» of the bile ducts [6]. The clinical picture corresponds to mechanical jaundice, cholangitis. The most sensitive diagnostic method is MR – cholangiopancreatography. Ultrasound can be useful for confirmation of biliary hypertension, but it is not always possible to visualize the «cast» on sonography. Endoscopic retrograde cholangiopancreatography combines both diagnostic and therapeutic techniques, with the help of endoscopic papillosphincterotomy, it is possible to clear lumens of bile ducts. Treatment, in most cases, is surgical, removal of the "cast" in order to restore the passage of the biliary tract.

In our case, there was a total necrosis of the epithelium of the internal bile ducts. With necrosis of the extrahepatic bile ducts.

CASE REPORT

Patient D., born in 1973, was delivered by ambulance. On admission, the patient complains of epigastric pain which is spreading to the right hypochondrium, dry mouth. He has a history of right hip fracture complicated by pulmonary embolism in 2021. Total bilirubin on admission 102 mmol/l. blood amylase 605 U. On abdominal ultrasound: gallbladder is not enlarged, gallblader`s wall is 3 mm. Contains calculi up to 5.0 mm. in diameter; The common bile duct s is dilated to 9 mm.

Patient was diagnosed with Acute biliary pancreatitis. Endoscopic retrograde cholangiopancreatography was performed: biliary sludge and stones up to 2 mm. were identified in the lumen of the CBD. Papillosphincterotomy was performed, stones and debree were removed.

On the second day of the postoperative period, patient's condition deteriorated sharply, complaints of weakness, shortness of breath developed. On examination, cyanosis of the nasolabial triangle is noted, respiration rate up to 22 per minute. Laboratory: D-dimer – 1.08 mg/l. Pulmonary embolism was diagnosed. The patient was transferred to

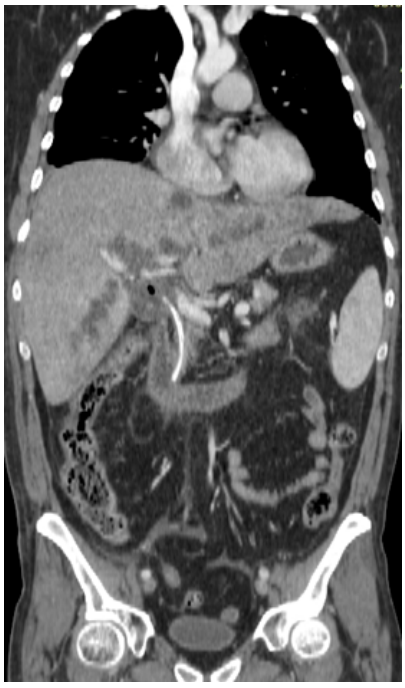

Fig. 1. liver parenchyma, along the course of the biliary tract, multiple confluent hypodense foci surrounded by a zone of perifocal edema are determined. Aerobilia. Internal and extrahepatic bile ducts are diffusely dilated with signs of aerobilia.

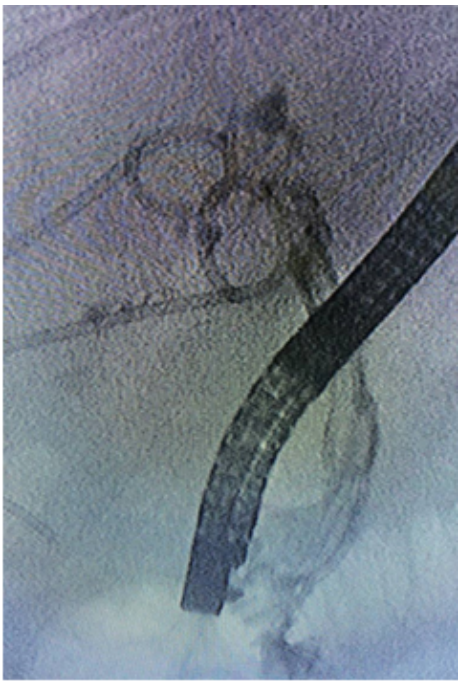

Fig. 2. ERCP: diffuse ductal dilation, proximal choledochal stenosis.

Fig. 3. "Casts" removed from segmental, lobar bile ducts. Necrotic common hepatic and common bile ducts.

the intensive care unit, where cardiac arrest was recorded within 5 minutes, resuscitative measures were carried out, after the restoration of cardiac activity, artificial lung ventilation was started, on which, patient remained for 12 hours. After extubation, patients hemodynamics remained unstable, inotropic support continued up to 3 days. The patient's condition stabilized. Blood pressure 110/70 mmHg, pulse 74/min, Sp02-97%. Leukocytes – 17.5 x 10^9. Hemoglobin – 111 g/l., Bilirubin – 68.1 mmol/l., urea – 9.3 mmol/l., creatinine – 163 mmol/l. On abdominal ultrasound: the liver is enlarged, the echogenicity of the parenchyma is increased. The echostructure is heterogeneous due to multiple anechoic formations localized in the right lobe, ranging in size from 16 to 23 mm. Intrahepatic bile ducts are dilated to 2-3 mm. Common bile duct is dilated up to 10 mm. Contains sludge.

Despite the biliary decompression, the patient retains jaundice and fever. A control ultrasound of the abdominal organs revealed numerous anechoic formations in the right lobe of the liver. Dilated intrahepatic bile ducts. Expanded to 1 cm. common bile duct, filled with echo-positive content. Total bilirubin – 91.2 mmol/L. A decision was made to repeat endoscopic retrograde intervention with stenting of the common bile duct: an endobiliary stent diameter of 8.5 Fr was installed, the outflow of bile into the lumen of the duodenum was observed. On the 26th day from the onset of the disease, computed tomography of the abdominal cavity was performed (Fig. 1).

Under ultrasound guidance, drainage of intrahepatic abscesses was performed. Obtained pus was sent for microbiological evaluation. Result: E.coli 5 x 10^7 CFU, Kl. Pneumoniae 5 x10^7 CFU, St. epidermiditis 5 x 10^5 CFU, sensitive to cefopyrazone. Despite the conservative treatment, the patient's condition remains severe, the patient has hyperthermia up to 38.5^{0}C, white blood cell count up to 15 x 10^9, severe anemia – hemoglobin 70 g/l. On the 37th day of the disease, CT control of the abdominal cavity was performed, on which a positive dynamic was determined – a moderate decrease the size and number of liver abscesses, much less pronounced dilatation of the biliary tract.

On the 58th day of the disease, endoscopic retrograde cholangiopancreatography was repeated: the left and right lobar ducts were dilated, diffusely, unevenly. The zone of stenosis of the proximal part of the CBD was determined (Fig. 2).

Given the lack of a positive response to conservative treatment, septic condition of the patient. A decision was made on surgical intervention in the scope of debridement and drainage of intrahepatic abscesses. Intraoperatively, the liver is enlarged, the right lobe is

violet – blue in color, jelly-like consistency. In the 4b segment, there is an abscess up to 3 cm. in diameter. The gallbladder is wrapped in omentum, contents: a single calculus up to 1 cm. in diameter. The hepatoduodenal ligament is infiltrated, edematous. After division of hepatoduodenal ligament, a necrotized common bile duct was identified, with a defect along the posterior wall up to 1 cm. Necrotic changes extended up to the confluence, left and right lobe ducts. During the removal of necrotized walls of the common hepatic duct, cast like formations of the segmental bile ducts were removed from the liver parenchyma, mucous pus with bile removed from the wound canals. (Fig. 3). External drainage of the intrahepatic bile ducts was performed.

In the postoperative period, patient remained jaundiced, bilirubin 187.2, direct fraction – 147 mmol/l. White blood cell count – 14.0 x 10^9, ALT – 196, AST – 233. The debit of bile through drains, installed in the intrahepatic ducts, was up to 100 ml of bile with purulent material, per day. Patient stayed in intensive care unit, antibiotic therapy was performed: Tigecycline, Amikacin. For 37 days from the moment of surgical treatment, the patient's condition remained severe, without significant dynamics. On the 38th day of the postoperative period, the patient's condition deteriorated sharply. Complaints of weakness, shortness of breath, tachycardia were noted. Hemoglobin – 65 g/l. Intra-abdominal hemorrhage was diagnosed. The patient was taken to the operating room, a relaparotomy was performed, the source of bleeding was identified – a defect in common hepatic artery up to 1 centimeter in diameter. Hemostasis was accomplished by suturing common hepatic artery. The patient was transferred to the intensive care unit in critical condition, in which he remained for 2 days. On the 105th day from the onset of the disease, patient died of cardiac arrest.

"Biliary-cast" syndrome is a rare phenomenon. In clinical practice, often described as a complication in patients after liver transplantation [1-3], cases of this syndrome have also been described in patients with biliary pancreatitis [4] and choledocholithiasis [5]. The main mechanism of development is ischemia of the bile ducts, desquamatization of intraluminal epithelium and cholestasis lead to the formation of "cast-like" formations inside bile ducts. By their structure and chemical composition are similar to that of gallstones [6]. These "casts" may form intrahepaticaly and extrahepatically, cause mechanical obstruction of the bile ducts, followed by an infection and development of cholangitis, necrosis of the biliary tract, and the formation of cholangiogenic abscesses. Lemmers et al. in their paper, where 14 cases of BCS in patients after liver transplantation were prospectively evaluated, propose the hypothesis that "Biliary-cast" syndrome is not a variant of prolonged ischemic damage to the bile ducts, but is an independent disease. In favor of this hypothesis, the authors note the specific nature of secondary strictures of the biliary tract. Absence of time correlation from the moment of liver transplantation prior to the onset of BCS or other non-anastomotic complications[3]. Voigtländer et al. In their retrospective study in liver transplant patients, ischemic injury is preferred in determining the etiology of BCS. Mainly, microcirculation disorders as a consequence of renal failure in patients after liver transplantation[7]. Currently, there is no concensus on management of biliary cast syndrome. This is due to the occurrence of BCS in liver transplant patients of 2.5%[1]. And even fewer patients with BCS who do not have a history of liver transplantation.

The clinical picture is similar to cholangitis, patients complain of jaundice, pain in the right hypochondrium, chills. Ultrasound diagnostics makes it possible to confirm the mechanical etiology of jaundice, the presence of dilated bile ducts and to detect hyperechoic "casts" in the lumen of the ducts. Magnetic resonance cholangiopancreatography has diagnostic sensitivity and specificity of 0.95 and 0.92, respectively. On MRCP, the "casts" appear as hypointense filling defects inside the bile ducts, surrounded by a ring of hyperintense bile. On computed tomography with contrast, it is possible not to identify "casts", especially in the early stages of the disease, due to the fact that the latter can be of the same density as the liver parenchyma. Severe cases of "Biliary-cast" syndrome have manifestations of severe biliary hypertension, with intraluminal hypodense formations, with increased contrast and thickening of the walls of the bile ducts.

The main direction in treatment of «Biliary-cast» syndrome is the elimination of the mechanical block of the bile ducts, with restoration of bile passage. Endoscopic papillosphincterotomy with endoscopic debridement and extraction is used as a therapeutic method with success in 25% to 60% of cases[9,10]. If endoscopic retrograde papillosphincterotomy is ineffective, percutaneous transhepatic biliary decompression techniques under ultrasound and radiological control are used.

CONCLUSIONS

The problem of "Biliary-cast" syndrome remains insufficiently studied, now this syndrome occurs less and less often as a complication after liver transplantation due to the evolution of surgical technique. The occurrence of "Biliary-cast" syndrome without liver transplantation is represented by isolated cases in the world literature, often in severe, comorbid patients.

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CORRESPONDING AUTHOR

Vladyslav Makarov
O.O. Bogomolets National Medical University
13 T. Shevchenko boulevard, 01601Kyiv, Ukraine
e-mail: vlad111776@gmail.com

ORCID AND CONTRIBUTIONSHIP

Olexii Dronov: 0000-0003-4033-3195 A E F
Dmytro Vlasenko: 0000-0002-8218-2703 B
Vladyslav Makarov: 0009-0009-7778-7079 B D

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

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CASE STUDY

CONTENTS

Fertility before and after treatment of the patient with Leydig cell tumor – case report

Paweł Miklis[1], Monika Rudzińska[2], Michał Sulewski[3]

[1]CLINIC OF GASTROENTEROLOGY, CHILD NUTRITION AND PEDIATRICS, UNIVERSITY CLINICAL CENTER OF THE MEDICAL UNIVERSITY OF WARSAW, WARSAW, POLAND

[2]CLINICAL DEPARTMENT OF INTERNAL DISEASES AND ENDOCRINOLOGY, WOLSKI HOSPITAL DR. ANNA GOSTYŃSKA, WARSAW, POLAND

[3]DEPARTMENT OF UROLOGY AND ONCOLOGICAL UROLOGY NATIONAL MEDICAL INSTITUTE OF THE MINISTRY OF THE INTERIOR AND ADMINISTRATION, POLAND

ABSTRACT

Even though Leydig cell tumor (LCT) represents the most common neoplasia among testicular sex cord–stromal tumors (SCSTs), it is a rare condition, comprising 1-2% of all testicular tumors, with a 10% risk of malignancy most commonly located in retroperitoneal lymph nodes. LCTs may demonstrate various clinical manifestations – from asymptomatic intratesticular swelling through nonspecific symptoms such as loss of libido, impotence or infertility, up to feminizing or virilizing syndromes due to hormonal activity of the tumor. This article presents a case of Leydig cell tumor that was associated with azoospermia what have rarely been reported worldwide. A 27-year-old male presented to the urologist with one-month history of palpable testicular mass. Imaging tests revealed a well demarcated solid focal lesion in the upper pole of the left testicle and semen analysis indicated azoospermia. Due to small testicular lesion, negative serum markers and negative reports for malignancy in MRI imaging, testis-sparing surgery (TSS) was performed. The final histopathological examination revealed a Leydig cells tumor positive for inhibin, calretinin and MelanA. Six months after the surgery spermatogenic function was partially restored what have rarely been reported in scientific papers. This case indicates that TSS may provide an effective way of semen quality improvement, although further research is required.

KEY WORDS: Leydig cell tumor, sex cord–stromal tumors, azoospermia, testis-sparing surgery, fertility

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INTRODUCTION

Although testicular cancer is a relatively rare tumor, accounting for 1-2% of all oncological diagnoses in men generally, it remains the most common neoplasm and most frequent malignancy in young men (aged 15-40) [1, 2]. Even though Leydig cell tumor (LCT) represents the most common neoplasia in the testicular sex cord–stromal tumor (SCSTs) category, it continues to be an unusual diagnosis due to the fact that SCSTs represent only about 5% of all testicular neoplasms [3]. Leydig cell tumors are hormonally active with excessive steroid secretion which may lead to variable endocrinological findings [4]. While children typically present with feminizing or virilizing syndromes, most adults remain asymptomatic due to infrequent noticeable effects of the excess androgen in this group of patients [4]. Some may demonstrate nonspecific symptoms such as loss of libido, impotence or infertility [4]. The most frequent manifestation is a palpable intratesticular mass [5] but due to poor knowledge about the importance of testicular self-examination, patients rarely present with this sign [6].

AIM

This article presents a case of a Leydig cell tumor that was associated with azoospermia which has rarely been reported worldwide.

CASE REPORT

In December 2022, a 27-year-old male from Eastern Europe presented to the private clinic with a 1-month history of left testicular swelling. The clinical examination was negative for any other symptoms. Patient did not suffer from any chronic illnesses and family history was negative for testicular tumours. An ultrasound of the scrotum and testes revealed a well demarcated solid focal lesion with homogeneously reduced echogenicity in the upper pole of the left testis measuring 12x11x11 mm. The dimensions of the left testis was approximately 26x24x42 mm. The left epididymis was normal and the amount of fluid between the testicular sheaths was within the normal limits. The diameter of left spermatic vein did not exceed 2 mm. The right testis appeared homogenic and normoechoic measuring approximately 25x21x42

Table 1. Results of semen analysis before and after treatment.

	Before treatment	After treatment	Reference value
Duration of abstinence [days]	7	5	2-7
Liquefaction time [min]	30	< 60	< 60
Color	clear	grey-white – milky	grey-white – milky
Semen volume [ml]	4.50	5.00	> 1.40
Total sperm number [mln/probe]	0	28	>39
Sperm concentration [mln/ml]	0	5.6	>15
pH	8.5	8.3	> 7.2
Number of round cells [mln/ml]	0.20	single	< 5.00
Total motility [%]	0%	37.82%	>42%
Progressive motility [%]	0%	9.33%	>30%
Normal forms [%]	0%	1.33%	>4%
Comments on the preparation:	Lack of spermatozoa neither in the direct nor in the sediment preparation		

mm. The right epididymis was normal and the diameter of right spermatic vein did not exceed 1,5 mm. A primary testicular neoplasm was suspected and the patient was referred to the hospital for further diagnostics. Blood tests including tumor markers and semen analysis were also recommended.

The patient's blood test results were within normal limits: beta-HCG (performed twice within 2 weeks): <0.200 mIU/ml (0.0-2.0), AFP 1.020 ng/ml (0.000-7.000), LDH 171 U/l (135-225), Syphilis antibodies: negative, HIV Ab/Ag Elecsys HIV Duo: negative.

Semen analysis indicated azoospermia (total absence of spermatozoa in the ejaculate) (Table 1).

In January 2023 MRI of the scrotum was performed and revealed a contrast-enhancing lesion in the upper pole of the left testicle located near the border of epididymis with the dimension of 11x15x15 mm.

Due to relatively small size of the lesion, negative serum markers and negative reports for malignancy in MRI imaging the patient was offered a testis-sparing surgery (TSS) proceeded by sperm cryopreservation, however, two consecutive tests failed to obtain sperm for freezing.

About two weeks later, removal of the left testicular tumor with preservation of healthy testicular tissue was performed. Intraoperative frozen section evaluation indicated tumor with low malignant potential and negative margins. The final histopathological examination revealed a Leydig cells tumor positive for inhibin, calretinin and MelanA. The analysis of unaffected testicular parenchyma adjacent to tumor cells indicated preserved spermatogenesis with the formation of mature sperm cells.

Three months after the surgery, the follow-up CT-scan of the chest, abdomen and pelvis revealed numerous borderline enlarged mesenteric lymph nodes. Despite mesenteric lymph nodes remain infrequent localization of Leydig cell tumor metastases, this finding required further investigation. The PET-CT scan with 18F-FDG revealed neither pathological 18F-FDG accumulation in the mesenteric lymph nodes nor hypermetabolic features of testicular tumor recurrence.

Postoperative levels of serous markers were within normal limits: LDH 191 U/l (135-225), beta-HCG <0.2 mIU/ml (<2.6), AFP <0.9 ng/ml (<7.0).

The spermiogram performed 6 months after the surgery showed improvement of semen parameters (Table 1).

DISCUSSION

The Leydig cell tumor is a rare condition, comprising 1%-2% of all testicular tumors, with a 10% risk of malignancy most commonly located in retroperitoneal lymph nodes [7]. LCTs belong to the steroid hormone-synthesizing neoplasms what may lead to infertility due to impaired spermatogenesis. It is mostly explained by long-term inhibition of the hypothalamic-pituitary axis and direct effects on the testes [8]. Although the neoplastic process affected only one gonad, impaired spermatogenesis was present in both testes leading to azoospermia. After TSS, the spermatogenic function was partially restored what supports the conclusion that azoospermia was due to the neoplastic process. Moreover, the histopathological analysis of unaffected testicular parenchyma adjacent to tumor cells indicated preserved spermatogenesis with the formation of mature sperm cells. This finding indicates that testicular activity preserved at the cellular and tissue level was efficiently suppressed by tumor cells. Due to patient failure to follow-up we do not have an information about subsequent semen analyses. The literature review indicates that isolated cases have been reported so far [9, 10]. In described cases the authors hypothesized that impaired spermatogenesis could result from endocrine disruption such as androgen-induced decrease in gonadotropin secretion. A limitation of our study, given the context of the potential sources of patient's azoospermia, is lack

of information on his hormone levels. Nevertheless, we decided to publish this case because of infrequently described finding such as restoration of spermatogenic function following TSS.

CONCLUSIONS

Leydig cell tumors are very rare, accounting for 1% of testicular tumors. Its clinical features may vary from asymptomatic intratesticular swelling to the symptoms resulting from hormonal disbalance. In this case, the patient who primarily presented with a history of intratesticular mass, was diagnosed with azoospermia. After the testis-sparing surgery was performed, spermatogenic function was partially restored. In patients with Leydig cell tumor who are eligible for TSS, this type of treatment may provide an effective way of semen quality improvement, although further research is required.

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CORRESPONDING AUTHOR

Paweł Miklis
Klinika Gastroenterologii i Żywienia Dzieci i Pediatrii
Uniwersyteckie Centrum Kliniczne
Warszawskiego Uniwersytetu Medycznego,
ul. Stefana Banacha, 02-097, Warsaw, Poland
e-mail: pawelmiklis3@wp.pl

ORCID AND CONTRIBUTIONSHIP

Paweł Miklis: 0009-0008-4578-233X A B D E F
Monika Rudzińska: 0009-0000-7890-2686 B D E F
Michał Sulewski: 0009-0002-5233-5446 B D E F

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VARIA

CONTENTS

Effectiveness of the program for developing leadership skills among managers of police organizations as a guarantee of their mental health

Ivan M. Okhrimenko[1], Olena O. Yevdokimova[2], Natalia E. Miloradova[2], Valentyna O. Tyurina[2], Hryhorii V. Dzhahupov[2], Liliia O. Bondarenko[2], Olena M. Mokhorieva[2]

[1]NATIONAL ACADEMY OF INTERNAL AFFAIRS, KYIV, UKRAINE

[2]KHARKIV NATIONAL UNIVERSITY OF INTERNAL AFFAIRS, KHARKIV, UKRAINE

ABSTRACT

Aim: The aim is to substantiate the program for developing leadership skills among managers of police organizations and to test its effectiveness.

Materials and Methods: The research, which was conducted in 2022-2024, involved 64 mid-level managers of police organizations and 462 officers from police units (departments, divisions) directly subordinated to these managers. To achieve the aim, a set of methods was used: bibliosemantic, diagnostic, analysis and generalization, statistical.

Results: The program for developing leadership skills among managers of police organizations has been worked out and substantiated. It has been found that well-organized and targeted psychological work with police unit managers allows for changing the indicators of the staff management style towards improving efficiency. An increase in the indicator of a high level of efficiency of the service activities of police unit managers (formation of the category "successful manager") has been revealed. The positive dynamics convincingly indicate the appropriate mobilization of leadership qualities, even for those managers who do not meet the requirements of management activities and cannot be useful to subordinate staff

Conclusions: The authors' program outlines the organizational and psychological conditions for the effective development of leadership qualities in police managers, namely: creating a personality-oriented developmental environment in training and real interaction with staff; taking measures to identify their advantages and disadvantages, showing respect and care for all members of the team, etc. Moreover, a high level of leadership qualities of managers of police organizations will contribute to strengthening their mental health and improving the efficiency of their professional activity.

KEY WORDS: leadership skills, psychological qualities, managers of police organizations, mental health

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INTRODUCTION

The implementation of leadership in a police organization is based on the relevant socio-psychological prerequisites, which provide for the presence of stable individual psychological qualities of the leader (purposefulness, perseverance, self-confidence, responsibility, initiative, etc.), their developed social and psychological skills (ability to organize a favorable atmosphere in the team, put oneself in the place of other people, mediate a conflict between officers, show respect for team members, demonstrate a high communication culture in relations with other people). Organizational skills and abilities of leaders are also important, which include the ability to set up productive activities of the organization's officers, set clear tasks for the team, monitor the progress of the execution of assignments and orders, be responsible together with everyone for the final result of work, etc. [1-3].

It should be noted that leadership standpoints in police organizations often depend on the manager's position and are determined by his or her authority, ability to lead, inspire, take care of the team, form a team, organize and maintain effective interpersonal interaction with officers; be able to make decisions in conditions of uncertainty; solve problems; apply a creative approach to solving management problems [4-6].

According to some researchers [7-10], leadership is the result of both objective factors (goals and objectives of a social (labor) group in a particular situation) and subjective factors (interests, needs, individual and typological characteristics of group members), as well as the actions of the leader as an initiator and organizer of professional activity. In addition, scholars often argue that the problem of leadership among police managers is currently quite urgent [11-13], as quite frequently in this area, some specialists do not have suf-

ficient professional competence, organizational skills, leader motivation, etc. Instead, realizing the manager's leadership standpoints directly determines the staff's effectiveness and the organization's success. That is why the problem of leadership realization among managers of police organizations requires scientific and applied research and the search for effective ways to develop the leadership qualities of managers.

AIM

The aim is to substantiate the program for developing leadership skills among managers of police organizations and to test its effectiveness.

MATERIALS AND METHODS

The research involved 64 mid-level managers of police organizations in Kyiv, Kyiv and Kharkiv regions (Ukraine) and 462 officers from police units (departments, divisions) directly subordinated to these managers. Special ranks of managers ranged from captain to colonel of police. The selection of police officers for the respondents' category was voluntary. The respondents' intellectual level, performance indicators of their service activities, and psycho-emotional state did not differ.

The research was conducted in 2022-2024 at the National Academy of Internal Affairs (Kyiv, Ukraine), Kharkiv National University of Internal Affairs (Kharkiv, Ukraine), and included several stages. The first stage involved an analytical review of the literature on the problem of leadership implementation among managers of police organizations and the determination of the diagnostic and methodological tools for the research. At the second stage the author's program for developing leadership skills among managers of mid-level police organizations was designed and implemented. In the third stage, the managers were diagnosed, and their subordinate staff was interviewed. The dynamics were determined, the data were interpreted logically and semantically, and the research conclusions were formed.

To achieve the aim, a set of methods was used: bibliosemantic, diagnostic, analysis and generalization, statistical. The main block of diagnostics included a psychological examination and a social survey of the respondents using valid methods, namely: 1) the methodology referred to as "Diagnostics of Leadership Abilities"; 2) the methodology referred to as "Leadership Effectiveness"; 3) the methodology referred to as "Expert Assessment of the Manager's Activities Effectiveness" [14].

The methodology referred to as "Diagnostics of Leadership Qualities" is designed to determine a person's level of leadership potential and the ability of a person to be a leader in a team-spirited workforce. The respondents were offered a methodology form containing 50 questions, to which they had to choose an affirmative or negative answer (in those questions with "yes" and "no" options) or choose among the proposed ones (with two other answer options). Processing occurs according to the methodology's key, where 1 point is awarded for each match and 0 points for a non-match. The total amount of points determines the level of expressiveness of the respondent's leadership qualities: 0-25 points – weakly expressed leadership qualities, low level; 26-35 points – leadership is manifested in a mediocre way, average level; 36-40 points – leadership qualities are expressed sufficiently for effective work; more than 40 points – excessive level of leadership qualities, the respondent's tendency to total domination and control.

The methodology referred to as "Leadership Effectiveness" is designed primarily to determine the potential effectiveness of the manager's practical activities as a leader. The methodology includes 42 questions that must be answered unequivocally: "yes" or "no". For each positive answer to the proposed questions ("yes"), the respondent receives 1 point, and for each negative answer ("no") – 0 points. The sum of points determines the effectiveness of the leadership of the management team of a particular organization: from 30 to 40 points – the leadership style of the leader is considered highly effective; from 11 to 29 points – the leadership style is supposed to be medium effective; 10 points or less – the leadership style of the leader is considered to be ineffective, and they are not recommended to be the team leader.

The methodology referred to as "Expert Assessment of the Manager's Activities Effectiveness" is aimed at determining the levels of effectiveness of the management activities of managers-leaders. The methodology makes it possible to assess several factors that form the basis for an opinion on the effectiveness of a particular manager. First, this methodology is suitable for evaluating mid-level managers of police departments. The respondents were given a methodology form and instructions on evaluating 30 factors that characterize a particular manager on a 7-point scale. The processing process involves determining the total result. This makes it possible to visualize the degree of expressiveness of each leader-manager. The levels of effectiveness of a leader-manager's management activity are defined as follows: 30-48 points – the manager does not meet the requirements of the management activity (very low level); 49-60 points – the manager has few reasons to be useful for the organization (low level); 61-90 points – the

manager's performance is too low (reduced level); 91-120 points – the manager is not effective enough, the effectiveness of the leader-manager's style is below average; 121-150 points – it is advisable to reconsider the leadership style (average level); 151-179 points – there are all opportunities to increase one's effectiveness (above-average level); 180-210 points – an effective manager (high level).

The author's program for developing leadership skills and optimizing the leadership style of mid-level managers consisted of 6 training sessions totaling 2 hours each on the following topics: "Who is a Leader, What is Leadership?" "An Authoritative Leader", "Traits of a True Leader", "Ethics and Charisma in the Life of a Leader", "Influence of Leadership Styles on the Success of a Leader in a Team", "Stimulation of Self-Development of Leadership Potential". The program's main objectives are to familiarize oneself with the techniques and recommendations for gaining authority in the team of subordinates, to practice the acquired knowledge and skills; to stimulate managers to achieve important professional goals, to intensify the desire for self-development and self-improvement, etc.

The data processing involved qualitative data analysis, calculation of percentage values, and their generalization. The research results made it possible to form conclusions about the peculiarities of the manifestation of leadership implementation by managers of police organizations. The statistical method was used to process the experimental data obtained. The reliability of the difference between the indicators was determined using Pearson's Chi-square (χ^2) criterion. The significance of the difference was set at $p<0.05$. This this research followed the regulations of the World Medical Association Declaration of Helsinki and ethical principles for medical research involving human subjects. Informed consent was received from all respondents who took part in this research.

RESULTS

Based on the literature analysis, we consider it advisable to conduct specially organized psychological work with mid-level managers to develop their leadership skills and optimize the leadership style in the team. For this purpose, the author's program for developing leadership qualities and optimizing leadership style in mid-level managers has been created. The program aims to promote the development of leadership qualities in managers, to develop activity and initiative, responsibility in making management decisions, to form an individual leadership style, and to stimulate self-development and self-improvement. The developed program was implemented during training work with mid-level managers. During the training sessions with mid-level managers, a lot of attention was paid to developing leadership skills in the team, planning their work on self-development, and improving organizational qualities and abilities. During the practical exercises, the training sessions participants were able to practice their skills in applying different leadership styles, using criticism in communication with subordinates, discussing the specifics of creating a favorable climate in the team, and receiving recommendations on business ethics in dealing with officers. At the end of each session, mid-level managers summarized the knowledge and skills they had gained, and each time, they found something useful for their practice. Another positive result of the program implementation was the development of group and individual plans for improving leadership skills and developing leadership potential, which were drawn up by mid-level managers while participating in various brainstorming sessions, practical exercises, discussions, art therapy exercises, etc.

To verify the effectiveness of the author's program and the psychological work done, mid-level managers (n=64) and their subordinates in police units (n=462) were re-diagnosed for changes in the manifestations of leadership skills and the effectiveness of the leadership style in the team. Here are the results of the survey of managers and their subordinates. First, we noted a positive trend in the manifestations of leadership qualities of mid-level police managers (Table 1).

Thus, as can be seen from the results, the author's program developed by us contributed to significant changes ($p<0.001$) in the level of leadership qualities development, namely: the number of successful leaders increased (46.3 % of managers and 35.5 % of subordinate officers indicated a sufficient level) (dynamics: +11.9 % and +9.1 %, respectively). At the same time, there is a drop in the indicator of management's lack of aptitude for leadership – it has decreased by more than 10 % in two groups of respondents. This indicates that unsuccessful leaders focused on self-improvement practices, including working with staff and self-presentation.

At the same time, the redefinition of leadership style among police unit leaders also showed a significant improvement (Table 2).

The results show that the indicators of the leadership style of police unit managers have significantly changed in the direction of improving efficiency. In particular, 50.0 % of managers and 41.4 % of subordinate officers state it as highly effective (dynamics: +15.6 and +19.1, respectively). At the same time, there is a decline in the indicators of an ineffective style of unit management (dynamics: -6.2 and -13.2, respectively). This indicates

Table 1. Levels of leadership qualities manifestations among mid-level police managers

Levels of leadership qualities manifestations among police managers	Categories of respondents				Reliability of the difference	
	Mid-level police managers (n = 64)		Police units officers (n = 462)			
	%	Dynamics	%	Dynamics	χ^2	p
Very high level, tendency to dictatorship	0	0	0	0	4.41	<0.001
Sufficient level of leadership qualities development, successful leader	46.3	+11.9	35.5	+9.1		
Average level of leadership qualities and skills	48.6	−1.4	52.4	+1.3		
Low level, not aptitude for leadership	5.1	−10.5	12.1	−10.4		

Table 2. Leadership styles of mid-level managers of police units

Leadership style of the leader	Categories of respondents				Reliability of the difference	
	Mid-level police managers (n = 64)		Police units officers (n = 462)			
	%	Dynamics	%	Dynamics	χ^2	p
Highly effective leadership style of the leader	50.0	+15.6	41.4	+19.1	2.72	<0.05
Medium effective leadership style	43.7	−9.4	46.5	−5.9		
Ineffective leadership style of the leader	6.3	−6.2	12.1	−13.2		

Table 3. Levels of management activities effectiveness of mid-level police manager

Levels of management activities effectiveness of police manager	Categories of respondents				Reliability of the difference	
	Mid-level police managers (n = 64)		Police units officers (n = 462)			
	%	Dynamics	%	Dynamics	χ^2	p
High level, effective manager	35.9	+10.9	28.6	+11.9	3.95	<0.001
Above-average level, performance can be improved	40.7	+4.8	36.1	+2.8		
Average level, it is advisable to review the management style (management methods)	20.3	−6.3	27.5	+2.6		
Effectiveness of the manager-leader's style is below average	3.1	−4.7	5.2	−6.5		
Reduced level, the effectiveness of the manager's work is too low	0	−4.7	2.6	−7.1		
Low level, the manager cannot be useful to the organization	0	0	0	−3.7		
Very low level, the manager does not meet the requirements of management activities	0	0	0	0		

that managers are rethinking the approaches to their management activities, revising the priority incentives for self-development and self-improvement, which is felt even from the perspective of subordinate officers of police organizations.

Later, using the methodology referred to as "Expert Assessment of the Manager's Activities Effectiveness" again, we obtained changed results of the diagnosis of the respondents of both groups (Table 3).

Hence, we can see a certain difference in the effectiveness of management activities that managers and subordinate officers assess. However, despite this, there is a clear trend toward improving the level of management activities and effectiveness of police managers. This is evidenced by an increase in the indicator of the high level of management activities effectiveness (among respondents from among managers, there is a +10.9 % increase, and among subordinate staff, +11.9 %). The data on the effectiveness of above-average management activities also increased to some extent (+4.8 % and 2.8 %, respectively). At the same time, we also paid attention to the effectiveness of the below-average levels of management activities. Here, we noted a negative trend, which convincingly indicates the appropriate mobilization of the leadership and organizational potential of those managers with these levels.

Thus, the psychological work with managers contributed to improving the effectiveness of their team management style and optimized the development of their leadership skills. Such managers not only began to meet the requirements of management activities but also became useful to their organization, which undoubtedly demonstrates the effectiveness of targeted and well-organized psychological work with mid-level managers of the police. Moreover, a high level of leadership qualities of managers of police organizations will contribute to strengthening their mental health and improving the efficiency of their professional activity.

DISCUSSION

It is also worth noting that it is justified for a manager to turn to an organizational psychologist who will not only familiarize them with the list of leadership qualities but will also help to create a self-improvement program for the development of these qualities, offer individual exercises and techniques aimed at awakening leadership potential. In particular, self-hypnosis, relaxation, and auto-training exercises have proven effective, during which the leader increases their faith in their strength, attracts internal energy to find more optimal self-development, and activates the desire to succeed [10]. In addition, participation in psychological training and specially organized exercises and games contributes to the development of leadership qualities of managers [15]. Our observations in the research showed that psychologists, through specially designed training programs, can help managers understand their motives and develop leadership skills, direct the leadership activity of the individual, and help develop leadership skills. However, in our opinion, organizational and psychological conditions for the effective development of leadership qualities of an individual should include:

– taking into account individual psychological characteristics and the development of leadership motivation in an individual;

– development of responsibility (from specific situational to responsibility as a stable personal trait) as the basis of responsible leadership;

– creation of a personality-oriented developmental environment in training and real interaction, which is marked by relevant characteristics (content of activities, group dynamics, problematics, reflection);

– ensuring the targeted development of leadership qualities of individuals through team organization, etc.

According to G. Campbell [16], to ensure favorable conditions for the development of leadership qualities of managers, it is advisable to create a "launching pad" associated with the availability of relevant professionally significant qualities of the personality of managers, as well as instilling in them an interest in corporate changes. Under such conditions, an updated tactic of psychological selection of persons suitable for this type of activity becomes relevant, which, according to our research, currently has certain problems and difficulties.

Due to purposeful and properly organized work with the management of police units, results can be achieved when the level of management activities and effectiveness of police units improves. A new category of specialists is being formed – the successful manager. At the same time, the number of managers who demonstrate an ineffective management style and are relatively useful for their police organization may decrease proportionally. To this end, some scholars rightly recommend developing the motivation of leadership and the desire to lead followers; increasing self-confidence and adequate self-esteem, getting to know yourself, your strengths and weaknesses better, taking them into account when working with the team; learning to show respect and care for all team members; creating a favorable psychological climate in the team [17-19].

In general, our results complement and expand the findings of many scientists on this range of problems [8, 10, 13, 20-23].

CONCLUSIONS

The program for developing leadership skills among managers of police organizations has been worked out and substantiated. With the help of training, special motivational games aimed at developing leadership qualities, role-playing exercises, dialogues, and problem situations, a manager can build leadership skills and form their style of leadership influence on the team. It has been proven that well-organized and targeted psychological work with police unit managers allows for changing the indicators of the staff management style to improve effectiveness. This contributes to managers rethinking their management approaches and revising priority incentives for self-development and self-improvement, which is felt from the standpoint of subordinate officers.

The increase in the indicator of high level and above-average level of police unit managers' effectiveness has been revealed. The positive dynamics convincingly demonstrate the appropriate mobilization of leadership and organizational qualities even for managers who do not meet the requirements of management activities and cannot be useful for their police organization.

Organizational and psychological conditions for the effective development of leadership qualities of modern police managers should include taking into account

individual psychological characteristics of an individual; creating a personality-oriented developmental environment in training and real interaction; conducting activities to increase self-confidence, highlighting one's advantages and disadvantages, taking them into account when working with the team; showing respect and care for all team members; creating a favorable psychological climate in the team, etc. Moreover, a high level of leadership qualities of managers of police organizations will contribute to strengthening their mental health and improving the efficiency of their professional activity.

PROSPECTS FOR FURTHER RESEARCH

It is planned to study the impact of communication skills of police unit managers on the effectiveness of their service activities.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Ivan M. Okhrimenko
National Academy of Internal Affairs, Kyiv, Ukraine
e-mail: ivango-07@ukr.net

ORCID AND CONTRIBUTIONSHIP

Ivan M. Okhrimenko: 0000-0002-8813-5107 A B
Olena O. Yevdokimova: 0000-0003-4211-7277 A D
Natalia E. Miloradova: 0000-0002-0716-9736 B D
Valentyna O. Tyurina: 0000-0003-2308-1977 B
Hryhorii V. Dzhahupov: 0000-0003-4443-9114 E
Liliia O. Bondarenko: 0000-0001-7975-9797 C
Olena M. Mokhorieva: 0000-0002-9420-2847 F

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

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