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ORIGINAL ARTICLE

Experimental and morphological rationale for applying a synthetic bone graft containing Hydroxyapatite and β-tricalcium phosphate in combination with a collagen sponge with polydeoxyribonucleotide in the treatment of mandibular bone defects

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ABSTRACT

Aim: To evaluate the effectiveness of the simultaneous use of a synthetic bone graft containing hydroxyapatite and β-tricalcium phosphate in combination with a collagen sponge impregnated with polydeoxyribonucleotide for the treatment of mandibular bone tissue defects through comprehensive morphological analysis of experimental material.

Materials and Methods: In this study, an experiment was conducted on 96 male rats of the WAG population aged 6 to 8 months. All animals were randomly divided into four groups. Group 1 included 24 rats in which a perforated defect was modeled in the region of the mandibular angle. Group 2 included 24 rats in which a perforated defect similar to that in group 1 was modeled in the region of the mandibular angle. The defect was filled with the synthetic bone graft «Biomin GT» (RAPID, Ukraine), which is composed of hydroxyapatite and β-tricalcium phosphate. Group 3 included 24 rats with a mandibular defect similar to those in groups 1 and 2. The defect was filled with a collagen sponge (DSI Dental Solutions Ltd., Israel) impregnated with polydeoxyribonucleotide (BNC Korea, Korea). Group 4 included 24 rats with a mandibular defect similar to those in the previous groups. The defect was simultaneously filled with the synthetic bone graft «Biomin GT» (RAPID, Ukraine) and a collagen sponge impregnated with polydeoxyribonucleotide. In groups 1 to 4, six rats from each group were sacrificed on days 3, 7, 14, and 28. Fragments of the mandible from the area of the modeled defect were used as material for morphological analysis. Histological, morphometric and statistical research methods were used.

Results: The authors' comprehensive morphological analysis of experimental material demonstrated an activation of reparative osteogenesis in the mandible in cases where the perforated defect was filled either with the synthetic bone graft «Biomin GT», containing hydroxyapatite and β-tricalcium phosphate, or with a collagen sponge containing polydeoxyribonucleotide. The therapeutic effect was more pronounced in the group treated with the collagen sponge impregnated with polydeoxyribonucleotide. However, neither of these treatment strategies led to the formation of fully mature bone regenerate by day 28 of the experiment. In contrast, the simultaneous application of the synthetic bone graft «Biomin GT» and the collagen sponge with polydeoxyribonucleotide resulted in a more active stimulation of reparative osteogenesis and contributed to the formation of a structurally complete bone regenerate by day 28.

Conclusions: Simultaneous filling of a bone defect in the mandible modeled in rats with the synthetic bone graft «Biomin GT», containing hydroxyapatite and β-tricalcium phosphate, and a collagen sponge with polydeoxyribonucleotide stimulates reparative osteogenesis and leads to the formation of a complete bone regenerate by day 28 of the experiment. The therapeutic effect is due to the rapid clearance of the defect cavity from blood fragments and alteratively changed tissues; active production and replacement within the regenerate of granulation, connective, and osteogenic fibroreticular tissues with the formation of lamellar bone tissue characterized by the presence of hematopoietic foci; decrease in the severity of inflammatory infiltration and hemodynamic disturbances in the tissues of the regenerate area.

KEY WORDS: synthetic bone graft, hydroxyapatite, β-tricalcium phosphate, polydeoxyribonucleotide, mandibular bone tissue defect, reparative osteogenesis

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INTRODUCTION

Among the bones of the craniofacial region, the mandible is particularly significant due to its crucial role in supporting dental structures and enabling essential functions such as mastication, speech, and maintaining facial aesthetics [1].

Mandibular bone tissue defects represent one of the key problems in modern dentistry [2]. Mandibular bone defects may arise from a variety of etiological factors. Minor defects are typically associated with tooth extraction or low-impact trauma, whereas larger defects are commonly caused by severe traumatic injuries, degenerative conditions, congenital anomalies, or tumor resections [3]. These defects result in facial deformities, impair mastication and speech functions, and negatively impact both the physical and psychological well-being of patients, thereby significantly reducing their quality of life [4, 5].

The mandible is more difficult to reconstruct than other craniofacial bones due to its complex anatomical curvature,

irregular shape, presence of dentition, and essential role in oral function [5, 6]. The latter fact highlights the need to improve existing methods and develop new approaches for the treatment of patients with mandibular bone defects.

Polydeoxyribonucleotide is a bioactive form of polynucleotides, with molecular weights between 50 and 1,500 kDa, primarily sourced and refined from the sperm cells of trout (*Oncorhynchus mykiss*) or chum salmon (*Oncorhynchus keta*) [7]. Studies have shown that polydeoxyribonucleotide stimulates reparative osteogenesis [8, 9].

Our previous morphological study of experimental material, along with the findings of other researchers, has confirmed the effectiveness of using a synthetic bone graft containing hydroxyapatite and β-tricalcium phosphate in the treatment of mandibular bone tissue defects [10-12].

A promising approach to the treatment of mandibular bone tissue defects may be the simultaneous use of a synthetic bone graft containing hydroxyapatite and β-tricalcium phosphate in combination with a collagen sponge impregnated with polydeoxyribonucleotide. Our literature review revealed no reports of such a combination, which underscores the relevance of this study.

AIM

The aim of this study was to evaluate the effectiveness of the simultaneous use of a synthetic bone graft containing hydroxyapatite and β-tricalcium phosphate in combination with a collagen sponge impregnated with polydeoxyribonucleotide for the treatment of mandibular bone tissue defects through comprehensive morphological analysis of experimental material.

MATERIALS AND METHODS

In this study, an experiment was conducted on 96 male rats of the WAG population aged 6 to 8 months. All animals were randomly divided into four groups.

Group 1 included 24 rats in which a perforated defect was modeled in the region of the mandibular angle. The animals were anesthetized, and an incision was made in the soft tissues of the left submandibular region. A perforated canal-shaped defect with a diameter of 3.0 mm was created in the area of the mandibular angle using a spherical bur with a straight handpiece. After modeling the defect, the wound was closed using 4.0 polyamide sutures (Limited Liability Company «Research and Experimental Production Center «OLIMP», Ukraine).

Group 2 included 24 rats in which a perforated defect similar to that in group 1 was modeled in the region of the mandibular angle. The defect was filled with the synthetic bone graft «Biomin GT» (RAPID, Ukraine), which is composed of hydroxyapatite and β-tricalcium phosphate.

Group 3 included 24 rats with a mandibular defect similar to those in groups 1 and 2. The defect was filled with a collagen sponge (DSI Dental Solutions Ltd., Israel) impregnated with polydeoxyribonucleotide (BNC Korea, Korea).

Group 4 included 24 rats with a mandibular defect similar to those in the previous groups. The defect was simultaneously filled with the synthetic bone graft «Biomin GT» (RAPID, Ukraine) and a collagen sponge impregnated with polydeoxyribonucleotide.

In groups 1 to 4, six rats from each group were sacrificed on days 3, 7, 14, and 28.

Fragments of the mandible from the area of the modeled defect were used as material for morphological analysis. The material was fixed in a 10% solution of neutral formalin (pH 7.4) for 24-48 hours, decalcified and carried out according to the generally accepted method and embedded in paraffin. Serial sections with a thickness of $4\text{-}5\times10^{-6}$ m were prepared from the paraffin blocks and subsequently stained with hematoxylin and eosin, as well as with picrofuchsin according to van Gieson.

The prepared microscope slides were examined using ZEISS Primostar 3 microscope (Carl Zeiss, Germany) equipped with an integrated color digital camera, and BRESSER Science TFM-301 Trino microscope with BRESSER Full HD camera (Bresser GmbH, Germany).

Morphometric analysis was performed using the Labscope software. In each case, five fields of view were examined at ×100 magnification. Within the regenerate, the following parameters were quantified: specific volume (%) of blood and alteratively changed tissues; specific volume (%) of granulation tissue; specific volume (%) of connective tissue; specific volume (%) of osteogenic fibroreticular tissue; specific volume (%) of lamellar bone tissue with connective tissue present in the intertrabecular space; specific volume (%) of lamellar bone tissue with foci of hematopoiesis in the intertrabecular space.

Statistical analysis of the group data was performed using the PAST software (version 4.15, Natural History Museum, University of Oslo, Norway). Mean values between groups were compared using Student's t-test and the Mann-Whitney U-test. Differences were considered statistically significant at $p<0.05$.

RESULTS

On day 3 of the experiment, overview light microscopy of the specimens revealed, in all groups, the presence of blood and alteratively changed epithelial layers, as well as fragments of muscle, connective, and bone tissues within the superficial and middle regions of the mandibular defect. The altered tissues were infiltrated with blood and exhibited diffuse polymorphic cellular infiltration consisting of neutrophilic leukocytes, monocytes, lymphocytes, mast cells, and macrophages. In groups 1 and 2, foci of immature granulation tissue were observed in the deeper regions of the defect cavity. In groups 3 and 4, granulation tissue of varying degrees of maturity and connective tissue were identified in the middle and deep regions. Both granulation and connective tissues showed signs of hemodynamic disturbances and focal-diffuse polymorphic cellular infiltration (Fig. 1). This infiltration included neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, osteoclasts, and fibroblast differon cells. Bone graft granules were identified within the granulation tissue in group 2 and within both granulation and connective tissues in group 4 (Fig. 1).

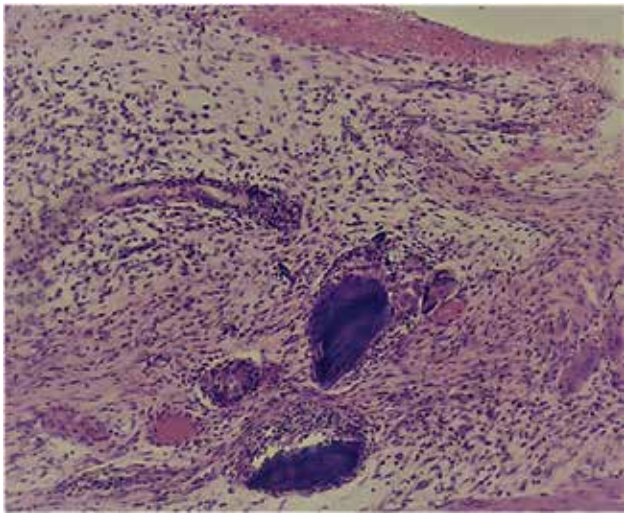

Fig. 1. Day 3. Group 4. Granulation tissue with hemodynamic disturbances, polymorphic cellular infiltration, and bone graft granules. Hematoxylin and eosin staining, ×100.

Picture taken by the authors

Morphometric analysis of the modeled defect cavity revealed a predominance ($p<0.05$) of the specific volume of blood and alteratively changed tissues in groups 1 to 3, whereas in group 4, the specific volume of connective tissue was significantly higher (Fig. 2-5). The specific volume of blood and alteratively changed tissues decreased ($p<0.05$) progressively from group 1 to group 4, indicating gradual clearance of the cavity from these components. The specific volume of granulation tissue increased ($p<0.05$) from group 1 to group 2 and then decreased ($p<0.05$) from group 2 to group 4, which reflected the maturation of granulation tissue and its transformation into connective tissue. The specific volume of connective tissue was significantly higher ($p<0.05$) in group 4 compared to group 3.

By day 7, compared to day 3, the cavity of the perforated mandibular defect in group 4 was completely cleared of blood elements and alteratively changed tissues. The content of these components decreased in groups 1 to 3 as well, which was reflected by a significant reduction ($p<0.05$) in the specific volume of blood and alteratively changed tissues. In group 1, the granulation tissue became more mature, and its amount in the regenerate increased, resulting in a significant increase ($p<0.05$) in its specific volume. In groups 2 to 4, the granulation tissue showed intensive maturation and subsequent transformation into connective tissue, leading to a decrease ($p<0.05$) in its specific volume. In group 2, connective tissue began to appear; in group 3, its specific volume increased significantly ($p<0.05$), while in group 4 it decreased ($p<0.05$). In all groups, predominantly in the middle and deep zones of the regenerate, osteogenic fibroreticular tissue appeared (fig. 6). In groups 2 and 4, this tissue was frequently observed in areas of osteoblast

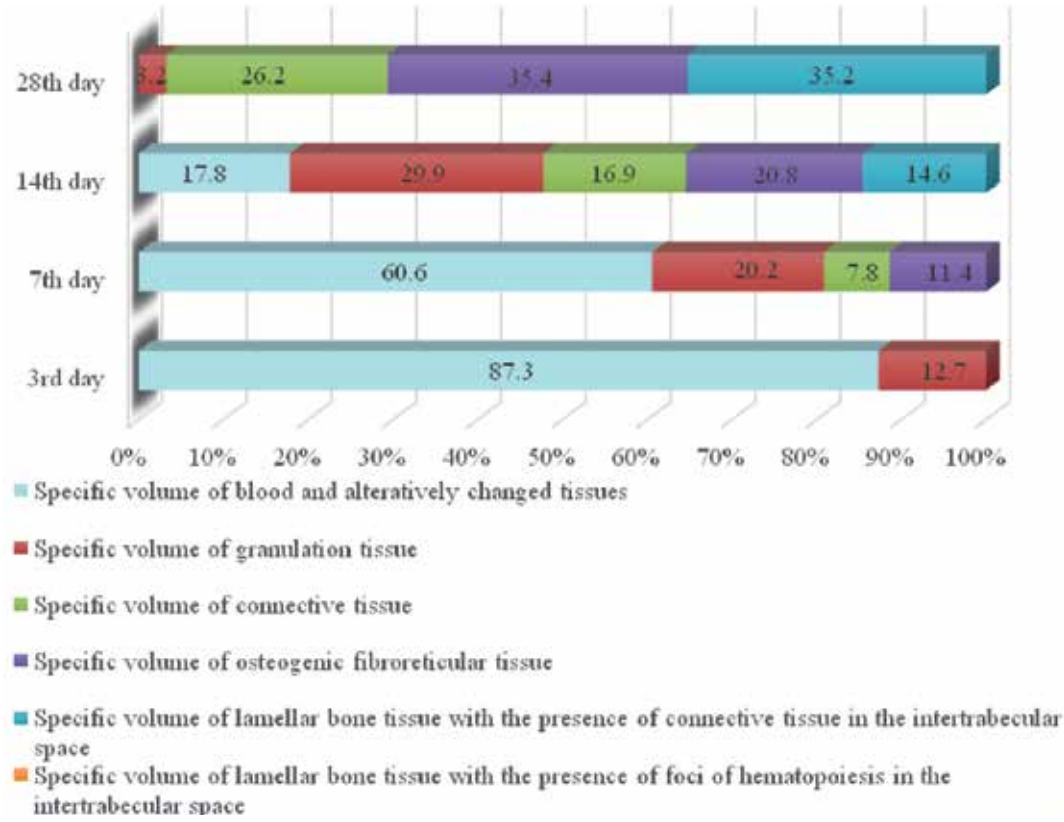

Fig. 2. Morphometric analysis results of the regenerate in group 1

Picture taken by the authors

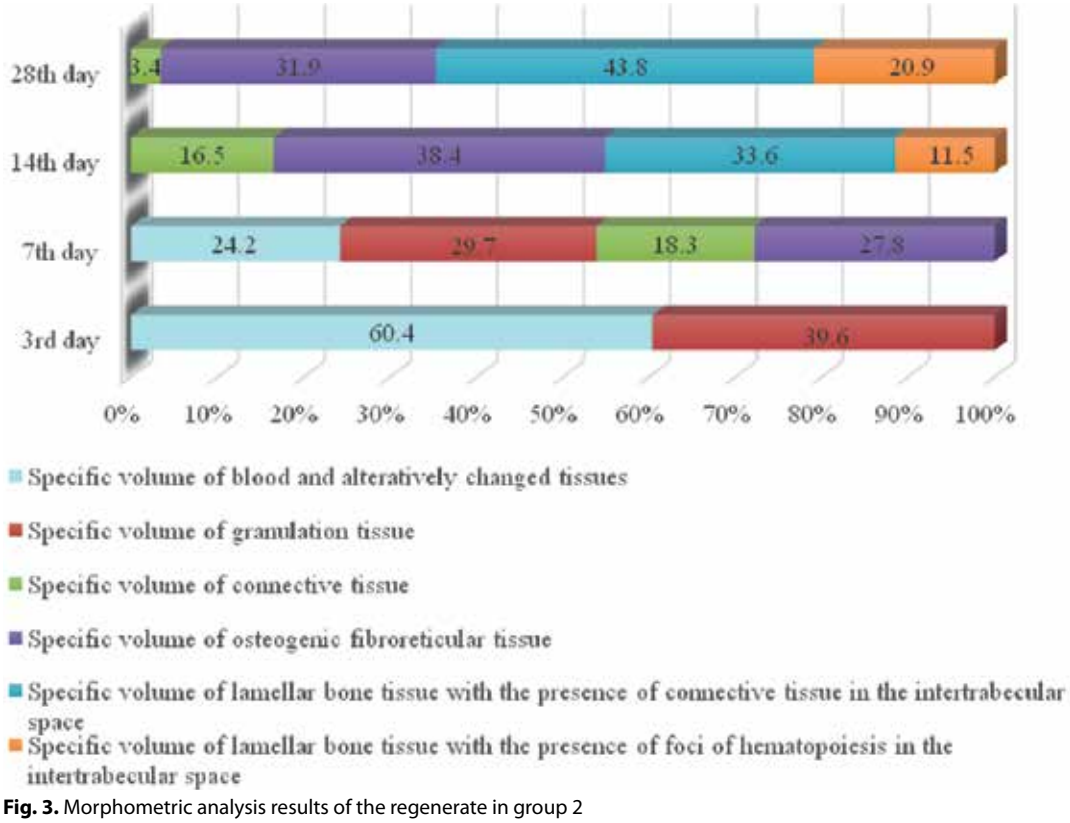

Fig. 3. Morphometric analysis results of the regenerate in group 2

Picture taken by the authors

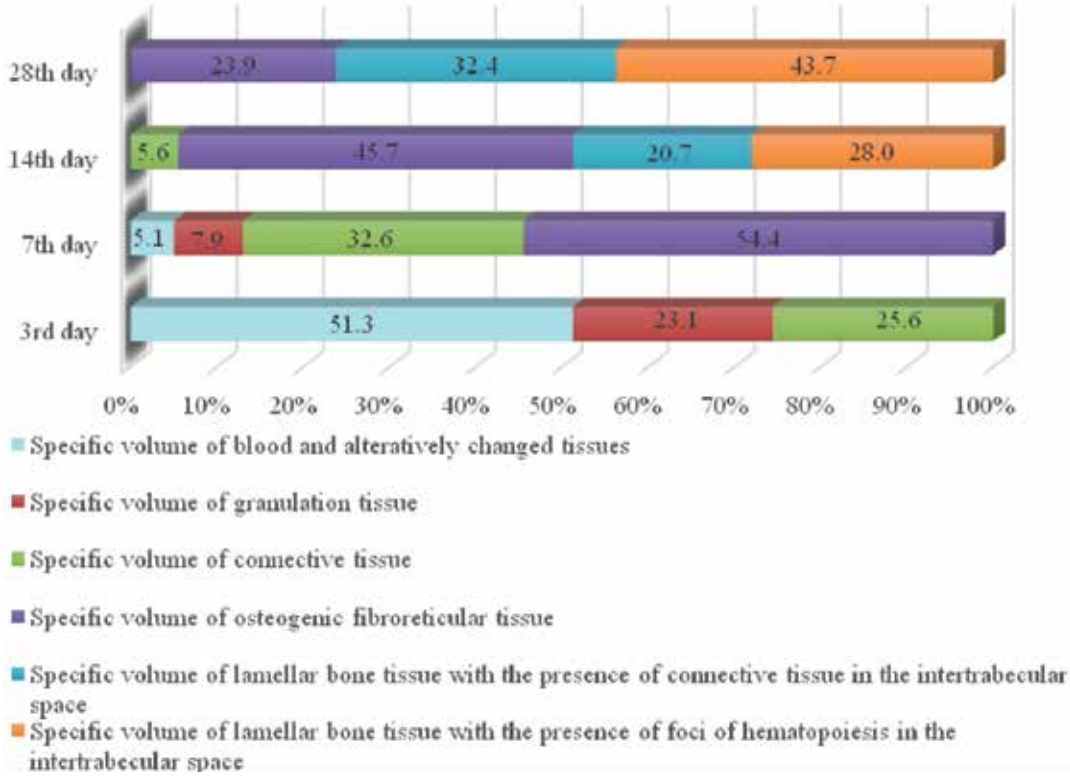

Fig. 4. Morphometric analysis results of the regenerate in group 3

Picture taken by the authors

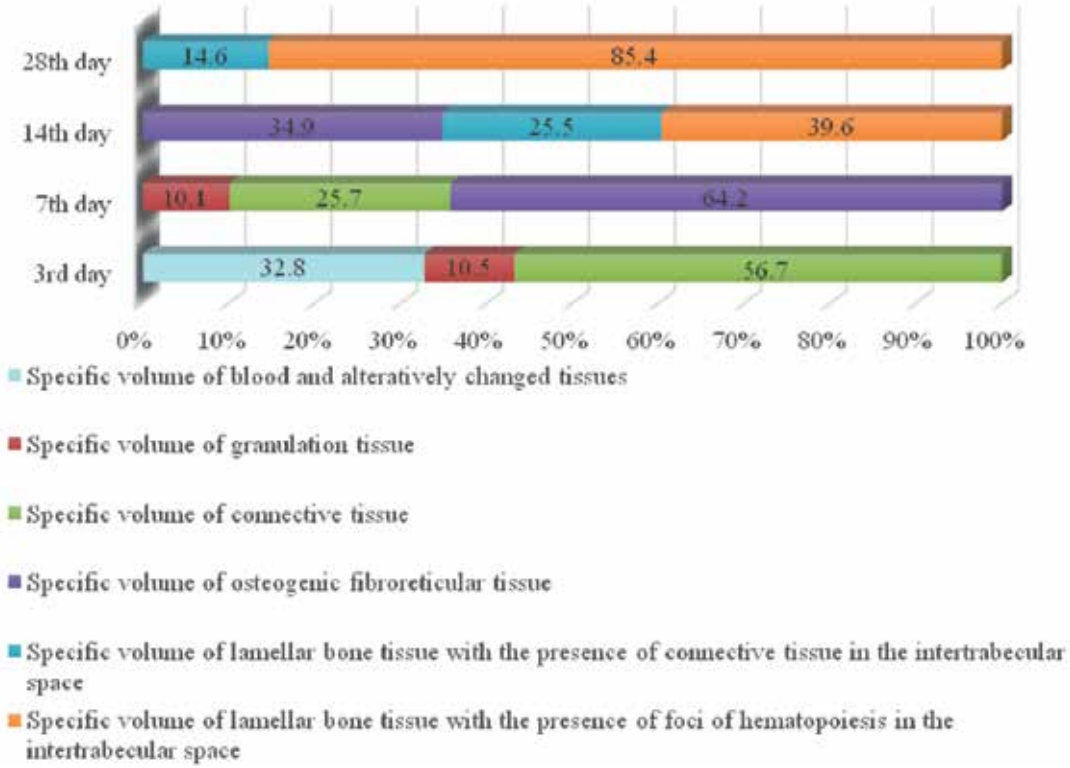

Fig. 5. Morphometric analysis results of the regenerate in group 4

Picture taken by the authors

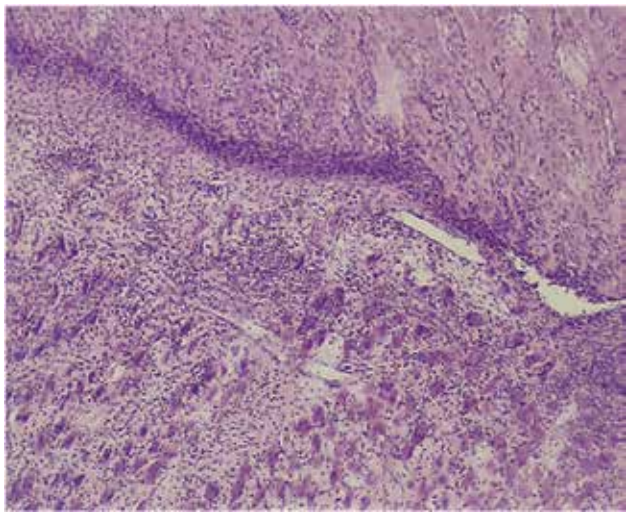

Fig. 6. Day 7. Group 4. Granulation, connective, and osteogenic fibroreticular tissues in the regenerate area. Polymorphic cellular infiltration with numerous osteoclasts observed within the granulation and connective tissues. Hematoxylin and eosin staining, ×100

Picture taken by the authors

accumulation near bone graft granules embedded in the connective tissue. The number of bone graft granules remained unchanged. Hemodynamic disturbances were identified within the granulation, connective, and osteogenic fibroreticular tissues. The severity of these disturbances decreased compared to day 3 and in the direction from group 1 to group 4.

Polymorphic cellular infiltration within the granulation and connective tissues increased. In groups 1 and 2, there was an increase in the number of neutrophilic leukocytes, monocytes, lymphocytes, mast cells, macrophages, osteoclasts, and cells of the fibroblastic lineage; osteoblasts also began to appear. In groups 3 and 4, the number of neutrophilic leukocytes, monocytes, lymphocytes, and mast cells decreased, while the number of macrophages, osteoclasts, and fibroblastic lineage cells increased; osteoblasts also emerged (fig. 6).

Intergroup analysis of the obtained morphometric parameters revealed a significant decrease ($p<0.05$) in the specific volume of blood and alteratively changed tissues from group 1 to group 3. The specific volume of granulation tissue increased significantly ($p<0.05$) in group 2 compared to group 1, decreased ($p<0.05$) in group 3 compared to group 2, and showed no significant change ($p>0.05$) in group 4 compared to group 3. The specific volume of connective tissue increased ($p<0.05$) progressively from group 1 to group 3, but decreased significantly ($p<0.05$) in group 4 compared to group 3. The specific volume of osteogenic fibroreticular tissue increased significantly ($p<0.05$) from group 1 to group 4.

On day 14, compared to day 7, the rate of reparative osteogenesis increased progressively from group 1 to group 4, as evidenced by the results of overview microscopy and morphometric analysis. In group 1, residual blood and tissue debris were still present in the defect cavity, although in lesser amounts, whereas in groups 2 to 4 these elements were no longer detected. In the regenerate of

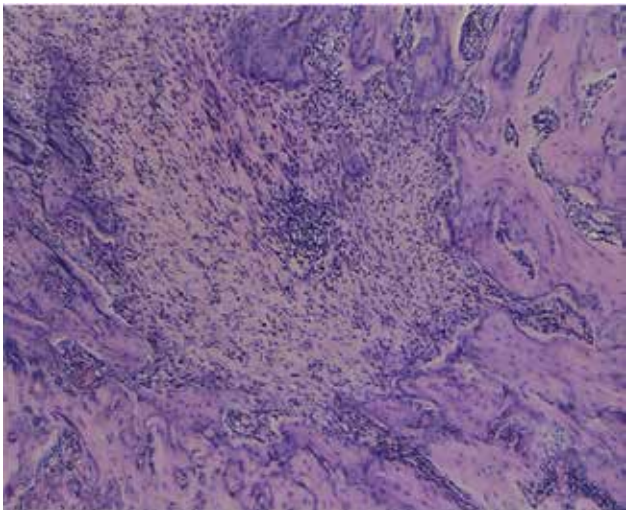

Fig. 7. Day 14. Group 1. Mature granulation tissue and connective tissue. Hematoxylin and eosin staining, ×100

Picture taken by the authors

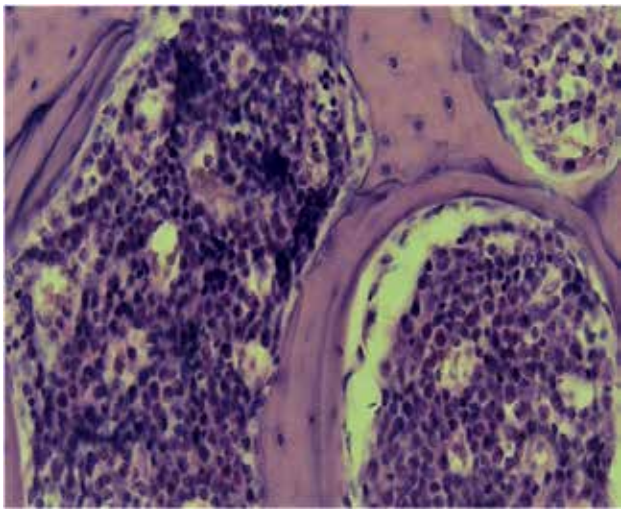

Fig. 8. Day 14. Group 4. Lamellar bone tissue with areas of hematopoiesis. Hematoxylin and eosin staining, ×400

Picture taken by the authors

group 1, the specific volume of mature granulation tissue significantly increased ($p<0.05$) (fig. 7), while this tissue type was not observed in groups 2 to 4. The specific volume of connective tissue increased significantly ($p<0.05$) in group 1, remained unchanged ($p>0.05$) in group 2, and decreased ($p<0.05$) in group 3. In group 4, connective tissue was not identified in the regenerate. The specific volume of osteogenic fibroreticular tissue increased significantly ($p<0.05$) in groups 1 and 2, while it decreased ($p<0.05$) in groups 3 and 4.

In the regenerate of group 1, lamellar bone tissue containing connective tissue in the intertrabecular space was observed, whereas in groups 2 to 4, lamellar bone tissue was present with both connective tissue and foci of hematopoiesis within the intertrabecular space (fig. 8). Notably, in group 2, the specific volume of lamellar bone tissue containing connective tissue in the intertrabecular space predominated ($p<0.05$), while in groups 3 and 4, the specific volume of lamellar bone tissue with hematopoietic foci in the intertrabecular space was significantly higher ($p<0.05$).

Hemodynamic disturbances in the tissues of the regenerate area were observed only in groups 1 and 2, with a decreased severity compared to day 7. The degree of polymorphic cellular infiltration in the regenerate tissue also decreased. In groups 1 and 2, the infiltration showed a reduction in the number of neutrophilic leukocytes, monocytes, lymphocytes, and mast cells, along with an increase in the number of macrophages, osteoclasts, osteoblasts, and cells of the fibroblastic lineage. In groups 3 and 4, inflammatory cells were virtually absent from the cellular infiltration. There was an increase in the number of osteoblasts and fibroblastic lineage cells, while the number of macrophages and osteoclasts decreased.

Intergroup analysis revealed no significant change ($p>0.05$) in the specific volume of connective tissue in group 2 compared to group 1, while a significant decrease ($p<0.05$) was observed in group 3 compared to group 2. The specific volume of osteogenic fibroreticular tissue increased significantly ($p<0.05$) from group 1 to group 3 and decreased ($p<0.05$) in group 4 compared to group 3. The specific volume of lamellar bone tissue containing connective tissue in the intertrabecular space increased significantly ($p<0.05$) in group 2 compared to group 1, decreased ($p<0.05$) in group 3 compared to group 2, and remained unchanged ($p>0.05$) in group 4 compared to group 3. The specific volume of lamellar bone tissue containing foci of hematopoiesis in the intertrabecular space increased significantly ($p<0.05$) from group 2 to group 4.

On day 28 of the experiment, compared to day 14, the specific volume of mature granulation tissue in the regenerate of group 1 decreased significantly ($p<0.05$), while the specific volumes of connective tissue, osteogenic fibroreticular tissue, and lamellar bone tissue without hematopoietic foci increased significantly ($p<0.05$). In group 2, the specific volumes of connective and osteogenic fibroreticular tissues decreased significantly ($p<0.05$), whereas the content of lamellar bone tissue containing both connective tissue and foci of hematopoiesis in the intertrabecular space increased significantly ($p<0.05$). In group 3, the specific volume of osteogenic fibroreticular tissue decreased ($p<0.05$), while the content of lamellar bone tissue with intertrabecular connective tissue and hematopoietic foci increased significantly ($p<0.05$). In group 4, osteogenic fibroreticular tissue was not detected in the formed regenerate. The specific volume of lamellar bone tissue with intertrabecular connective tissue decreased ($p<0.05$), whereas the specific volume of lamellar bone tissue with hematopoietic foci in the intertrabecular space increased significantly ($p<0.05$).

DISCUSSION

The authors' comprehensive morphological analysis of experimental material demonstrated an activation of

reparative osteogenesis in the mandible in cases where the perforated defect was filled either with the synthetic bone graft «Biomin GT», containing hydroxyapatite and β-tricalcium phosphate, or with a collagen sponge containing polydeoxyribonucleotide. The therapeutic effect was more pronounced in the group treated with the collagen sponge impregnated with polydeoxyribonucleotide. However, neither of these treatment strategies led to the formation of fully mature bone regenerate by day 28 of the experiment. In contrast, the simultaneous application of the synthetic bone graft «Biomin GT» and the collagen sponge with polydeoxyribonucleotide resulted in a more active stimulation of reparative osteogenesis and contributed to the formation of a structurally complete bone regenerate by day 28.

Reparative osteogenesis is a complex, multistage process involving the participation of various cell types. Numerous researchers distinguish three phases within this process: the inflammatory phase, the reparative phase, and the remodeling phase [13]. The ultimate outcome of reparative osteogenesis is the complete restoration of bone as a functional organ [14].

In our study, from day 3 to day 28 of the experiment, the cavity of the perforated defect was progressively cleared of blood and alteratively changed tissues with varying intensity depending on the treatment method applied, and became filled with regenerate tissue. Over time, granulation tissue appeared within the regenerate, subsequently maturing and transforming into connective tissue. As the specific volume of the latter decreased, osteogenic fibroreticular tissue emerged and was gradually replaced by lamellar bone tissue containing both connective tissue and foci of hematopoiesis in the intertrabecular space.

In our view, the effectiveness of the synthetic bone graft «Biomin GT», which contains hydroxyapatite and β-tricalcium phosphate, in the treatment of mandibular bone defects is attributable to its osteoconductive properties. Specifically, osteogenic lineage cells were observed to attach to, grow on, and proliferate along the surface of the graft granules, ultimately contributing to the formation of bone tissue. The presence of β-tricalcium phosphate in the composition of the synthetic graft enhances the integration of the polymeric material with native bone tissue, thereby improving its reparative capacity [15].

The stimulation of reparative osteogenesis in cases where the perforated defect was filled with a collagen sponge containing polydeoxyribonucleotide is attributed to both the properties of the collagen scaffold itself and the biological effects of polydeoxyribonucleotide. The collagen sponge acts as a structural framework onto which osteogenic lineage cells adhere. These cells proliferate, ultimately leading to bone formation. Our findings also demonstrated that fibroblastic lineage cells attach to the collagen sponge, and these cells are known to produce the main components of connective tissue [16]. The collagen sponge also enhances the mineralization capacity of osteoblasts [17], inhibits osteoclast differentiation in mineralization formation [18].

Numerous studies have demonstrated the bone regenerative capacity of polydeoxyribonucleotide [7, 19]. Polydeoxyribonucleotide also exhibits anti-apoptotic, anti-osteoporotic, and anti-osteonecrotic effects, suppresses inflammation, enhances the morphofunctional activity of osteoblastic lineage cells, and stimulates angiogenesis [8, 9].

Thus, the aforementioned properties and biological effects of the synthetic bone graft «Biomin GT», containing hydroxyapatite and β-tricalcium phosphate, and the collagen sponge with polydeoxyribonucleotide, when used in combination, effectively stimulated reparative osteogenesis, resulting in the formation of a complete bone regenerate in the mandible of experimental animals by day 28.

CONCLUSIONS

Simultaneous filling of a bone defect in the mandible modeled in rats with the synthetic bone graft «Biomin GT», containing hydroxyapatite and β-tricalcium phosphate, and a collagen sponge with polydeoxyribonucleotide stimulates reparative osteogenesis and leads to the formation of a complete bone regenerate by day 28 of the experiment. The therapeutic effect is due to the rapid clearance of the defect cavity from blood fragments and alteratively changed tissues; active production and replacement within the regenerate of granulation, connective, and osteogenic fibroreticular tissues with the formation of lamellar bone tissue characterized by the presence of hematopoietic foci; decrease in the severity of inflammatory infiltration and hemodynamic disturbances in the tissues of the regenerate area.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Ultrasound assessment of optic nerve sheath diameter during surgery in the Trendelenburg position

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ABSTRACT

Aim: To determine whether the Trendelenburg position during laparoscopic urological surgery changed the ONSD and whether changes correlated with postoperative complications.

Materials and Methods: In this prospective study, we measured ONSD before patients were placed in the Trendelenburg position. Then the Trendelenburg position was established by tilting the operating table to 20-25 degrees. After surgery, the patients were placed in a horizontal position, and the second measurement of ONSD was obtained.

Results: The study included 69 patients. The average preoperative ONSD in the right eye was 5.8±0.7 mm and 5.8±0.8 mm in the left eye. The average postoperative ONSD in the right eye was 6.6±0.8 mm and 6.6±0.7 mm in the left eye. The differences between postoperative and preoperative values in the right and left eyes were statistically significant ($p<0.000001$). ONSD increases above the norm did not correlate with the incidence of postoperative nausea ($p=0.94$), delirium ($p=0.81$), or the time to patient awakening ($p=0.29$).

Conclusions: ONSD increased in patients who underwent surgical procedures performed in the Trendelenburg position, but the increase did not correlate with postoperative complications.

KEY WORDS: optic nerve sheath diameter, point of care ultrasound, Trendelenburg position

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INTRODUCTION

In many clinical contexts, laparoscopy is gradually replacing conventional surgical procedures. Laparoscopy is associated with diminished mortality and less overall and severe morbidity; as well, laparoscopy has curtailed the incidence of surgical site infections, urinary tract infections, bleeding, sepsis, and septic shock [1]. Unfortunately, laparoscopic procedures require peritoneal carbon dioxide insufflation. The gas negatively affects not only the viscera, but also it affects the central nervous system because the resultant pneumoperitoneum leads to increased intracranial pressure (ICP) [2]. Surgeons rarely use computer tomography and magnetic resonance imaging to assess intraoperative ICP. Invasive measurement is the most accurate tool to determine ICP, but it is associated with numerous complications, such as brain damage, bleeding, and infection [3].

The optic nerve is responsive to ICP. The optic nerve can be thought of as an outpouching of intact brain tissue; the intraorbital component is fully encapsulated by dura, arachnoid, and pia matter, enabling the optic nerve sheath to transmit cerebral spinal fluid and fluctuate in size based on intracranial pressure.[4] The meningeal cover of the optic nerve is the continuation of the dural and subarachnoid space.[5] The bulbous portion of the optic nerve, approximately 3 mm posterior to the globe, appears to be the most distensible and sensitive to ICP on the basis of in vivo models of elevated ICP and artificial creation of elevated ICP in cadaveric models [4].

Ultrasonographic measurement of the optic nerve sheath diameter (ONSD) [6, 7] is a favourable noninvasive procedure to assess the ICP of patients who undergo urologic surgery. The procedure is based on the fact that hemodynamic disturbances during laparoscopic surgery lead to increased ICP. Any increase in cerebrospinal fluid pressure increases the diameter of the optic nerve sheath, and the optic nerve sheath directly communicates with the subarachnoid space. Normal ICP values correlate with ONSD values (range of 4.8-6 mm) [8, 9]. Furthermore, ultrasound examination is a simple, reproducible, inexpensive, and widely available modality [10]. Thus, ultrasonographic measurement of the optic nerve sheath diameter is an ideal means to noninvasively assess ICP.

During urological laparoscopic surgery, the patient is placed in the Trendelenburg position, which has a major effect on intra- and postoperative cardiovascular and respiratory function.

AIM

Our goal was to determine whether the Trendelenburg position affects ONSD and whether changes in ONSD correlate with postoperative difficulties. Perioperative and postoperative complications were also recorded. We would like to evaluate the incidence of nausea and vomiting, the impact of perioperative fluid therapy and the length of the procedure on ONSD.

MATERIALS AND METHODS

All study participants provided written consent to participate voluntarily. We excluded persons under 18 years of age who had ophthalmological or neurological conditions and who had undergone prior ophthalmological procedures.

Inclusion Criteria:

- patients undergoing urologic operation in the Trendelenburg position;
- adults 18 to 90 years of age
- American Society of Anesthesiologists Physical grade 1-3;

Exclusion Criteria:

- patients who did not agree to participate in the study;
- patients with ophthalmic diseases;
- patients with previous history of ophthalmic surgery;
- patients with neurological disorders;
- patients with history of head surgery due to neurological disorders;
- patients with history of disease with increased intracranial pressure;
- patients with history of disease with increased intraocular pressure.

Fig. 1. Sonoanatomy of the human eye. The ONSD, as measured with transorbital ultrasonography

Source: Own materials

All consecutive patients operated on at the Department of Urology, Jagiellonian University Medical College, who gave written consent and had a planned procedure in the Trendelenburg position were qualified for the study.

From April 2018 to August 2018, participants underwent urological laparoscopic surgery with general anaesthesia in the Trendelenburg position. Standard monitoring during anaesthesia included arterial oxygen saturation, ECG, and noninvasive arterial blood pressure. Premedication was not used. The standard anaesthesia consisted of propofol (1.5-2 mg/kg body weight iv) and fentanyl (1-2 μg/kg body weight iv) for induction. Cisatracurium (0.2 mg/kg body weight iv) was administered prior to intubation. Anaesthesia was maintained with sevoflurane (MAC 1-1.5) and fentanyl boluses (0.05-1 μg/kg body weight iv). Mechanical ventilation was delivered at the tidal volume of 8 ml/kg body weight. The respiratory rate was tied to the end-expiratory CO_2 ($etCO_2$) concentration with a view to maintaining $etCO_2$ in the 35-45 mm Hg range. The first measurement of ONSD was obtained before patients were placed in the Trendelenburg position. Then the Trendelenburg position was instituted by tilting the operating table to ca. 20-25 degrees. Patients remained in that position during the operation. After surgery, the patients were placed in a horizontal position, and the second measurement of ONSD was obtained. During the procedure, the pressure of the pneumoperitoneum was 10-15 mm Hg.

Before and after surgery, ONSD ultrasound was performed using a 7.5 MHz line head L12-4. Two sonographers (T. S. and E. K.) took three measurements of the same patient before and after the procedure, and the average of these measurements was taken as the final result. The ONSD measurement was standardized by measuring at a depth of 3 mm outside the posterior wall of the eyeball (Fig. 1). Because other investigators [9, 11] showed that ONSD > 5.0 mm correlated with increased intracranial pressure, and the cut-off point of 6.0 mm increases the sensitivity and specificity of the test, we used 6.0 mm as the reference value.

In the postoperative period, we monitored the incidence of nausea, delirium, and the time to patient awakening.

STATISTICAL ANALYSIS

The calculation of the sample size was made using statistical power analysis based on the difference between the average ONSD values in the first 10 patients, for which the statistical power of 80% was considered. The test returned a minimum sample size of 69 patients. The statistical analysis was performed with Statistica 10.0 software. The Wilcoxon was used to determine the statistical significance of the ONSD differences and variables between groups. The Mann-Whitney U test was used to determine the statistical correlation between the ONSD differences and time of surgery, number of fluid during operation. The significance level was set at 0.05.

ETHICS APPROVAL

ClinicalTrials.gov Identifier: NCT03485612.

Bioethics Committee of the Jagiellonian University in Cracow on 23/02/2018 (No. 1072.6120.30.2018).

RESULTS

Seventy-three patients initially qualified for the study. Four patients had poor image quality, and no data were obtained; thus, they were excluded from the study, leaving 69 ASA I and ASA II patients. Sixty-one patients (88%) were men and 8 (12%) were women (Table 1). The urological procedures included 45 prostatectomies, 11 resections of kidney tumours, 4 cystectomies, 4 lymphadenectomies, 3 Anderson-Hynes plasticities, and 2 others. The mean age of the patients was 63±9 years. The average BMI value was 27.7 kg/cm^2. The average duration of the procedures was 174±80 minutes. The average amount of fluids obtained during the procedure was 1469±653 ml. The average preoperative ONSD in the right eye was 5.8±0.7 mm, and the average preoperative ONSD in the left eye was 5.8±0.8 mm. The average postoperative ONSD in the right eye was 6.6±0.8 mm, and the average postoperative ONSD in the left eye was 6.6±0.7 mm. In 33 patients there was a difference in excess of the ONSD norm in one eye before and after operation (Fig. 2-3). All ONSD measurements were statistically significant (p <0.000001; Table 2)

The duration of the procedure did not differ significantly (p=0.96) between patients who had a difference in excess of the ONSD norm in one eye before (182±99 minutes) and after operation and patients who did not have an ONSD greater than the norm (167±57 minutes). The amounts of fluids obtained did not differ significantly (p=0.15) between patients who had a difference in exceeding norm of ONSD in one eye before and after (1574±747 ml) and patients who did not exceed the norm of ONSD (1372±561 ml) (Fig. 4).

One patient who had a difference in exceeding norm of ONSD in one eye before and after had postoperative nausea, and two patients who did not exceed the norm of ONSD had postoperative nausea (p=0.94).

Four patients who had a difference in exceeding norm of ONSD in one eye before and after had postoperative delirium, and four patients who did not exceed the norm of ONSD also had postoperative delirium (p=0.81) (Fig. 5).

We considered that waking more than 10 minutes from the end of the procedure to be a prolonged awakening time. In both groups, 15 patients had prolonged awakening time (p= 0.29)

Table 1. Mean age, gender, mean ASA index and BMI of enrolled patients

Mean age [years]	Gender [m – male f – female]	ASA index	BMI	duration of the procedure [min]
63(±9)	61 m 8 f	I – 2 II – 67	27.7(±4)	174±80

Source: Own materials

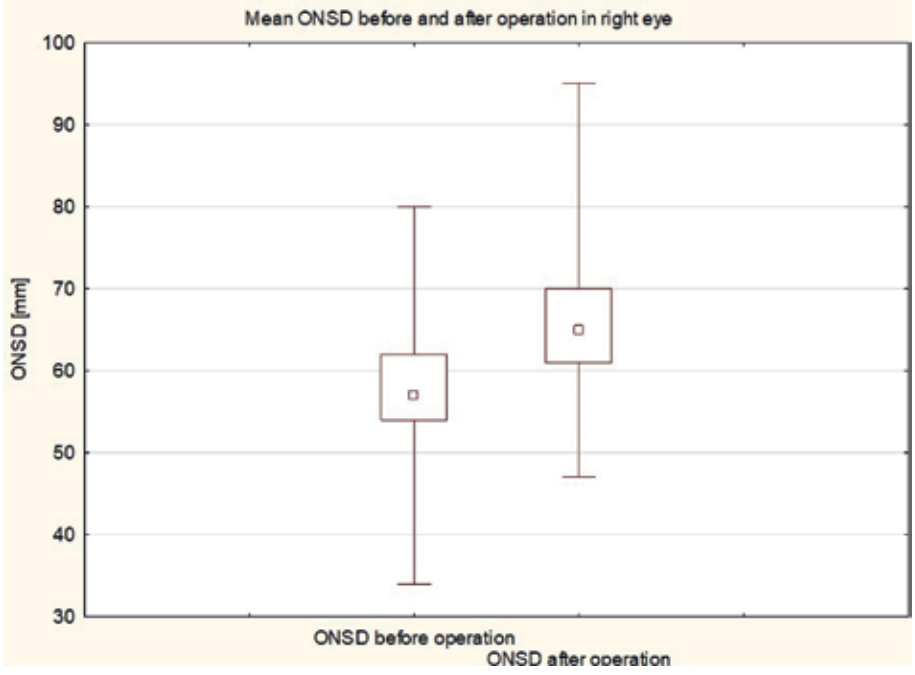

Fig. 2. Mean ONSD before and after operation in right eye

Source: Own materials

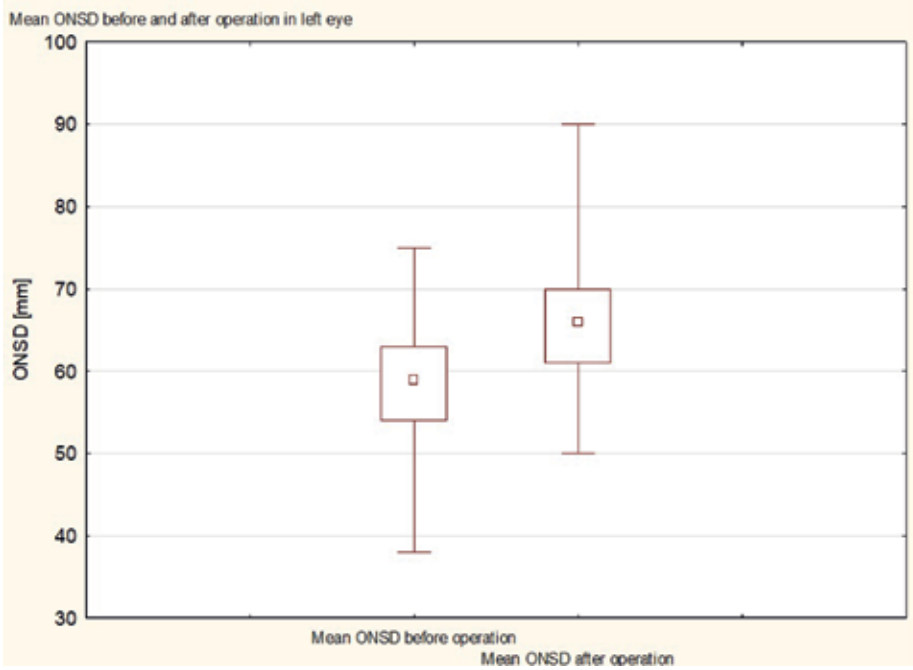

Fig. 3. Mean ONSD before and after operation in left eye

Source: Own materials

Table 2. The average ONSD before and after procedure

	ONSD in the right eye [mm]	ONSD in the left eye [mm]
preoperative	5.8±0.7	5.8±0.8
postoperative	6.6±0.8	6.6±0.7
p-value	p<0.000001	p<0.000001

Source: Own materials

DISCUSSION

We found that ONSD increased in patients who underwent urological procedures performed in the Trendelenburg position. The Trendelenburg position is often used during laparoscopic procedures to improve the visibility of the target organs. In our study, although we proved that this position led to increased ONSD above the norm, the position did not have any significant effect on the incidence of

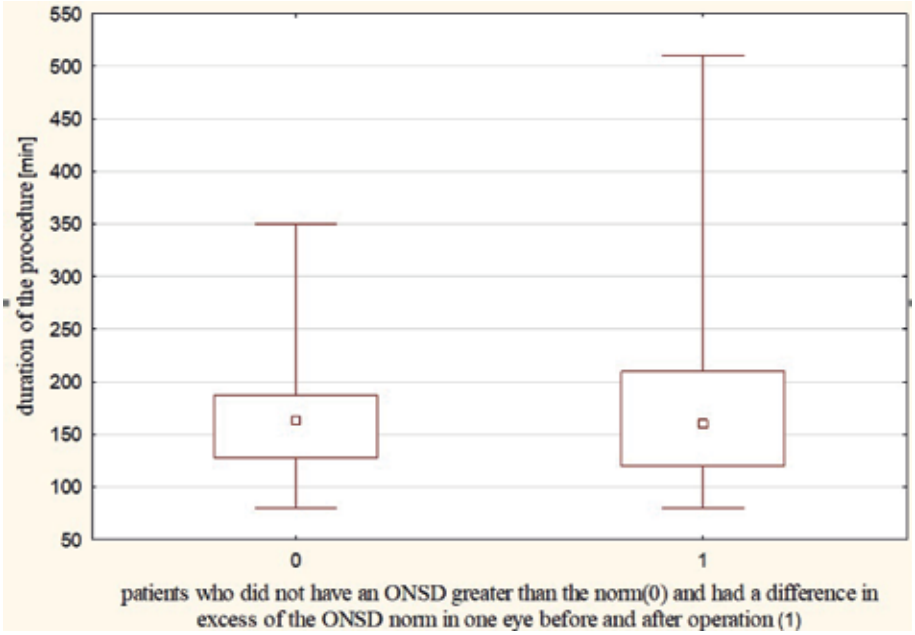

Fig. 4. Averages and measures of central tendency of the duration of the procedure and a difference in excess of the ONSD

Source: Own materials

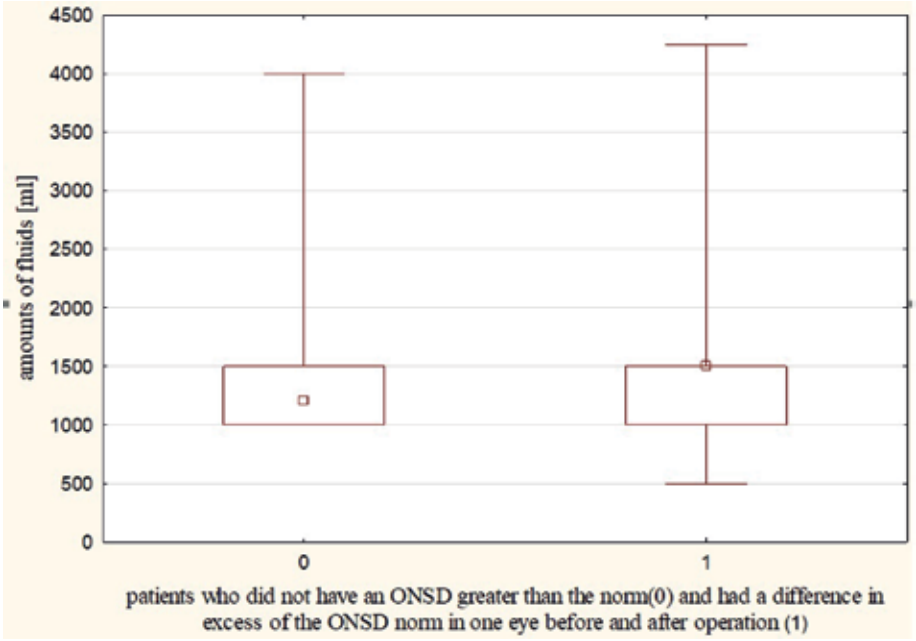

Fig. 5. Correlation between the amounts of fluids and a difference in excess of the ONSD

Source: Own materials

postoperative complications. In a study conducted by Kim et al. [12] with a group of 64 patients, there were no significant differences in ONSD between patients placed in the Trendelenburg position vs. patients placed in the anti-Trendelenburg position within 30 minutes of the establishment of the pneumoperitoneum. Kim et al. [13] also found that the ONSD increased by 12.5% at 10 and 30 minutes after the establishment of the pneumoperitoneum for 20 patients who underwent robotic laparoscopic radical prostatectomy.

Robba et al. performed a systematic review and meta-analysis of seven studies (320 patients) to evaluate the diagnostic accuracy of sonographic ONSD measurements of adults [14]. They found that thresholds in the range of 4.80-6.30 mm demonstrated robust prediction ability (AUC of 0.94) for the assessment of intracranial hypertension (applying a threshold of >20 mmHg or >25 cmH_20).

Verdonck et al. [15] stated that ONSD did not change during robotic laparoscopic radical prostatectomy for 20 patients. Intracranial pressure increased during CO_2 pneumoperitoneum and head-down positioning, but no changes were found in ONSD in the head-down position. This lack of change was due to the compensatory mechanisms that respond to the increase in the intracranial blood volume and the resultant ICP increase.

In animal studies [16-18], investigators found that in peritoneal depression and Trendelenburg position the intracranial pressure increased by 10 mmHg above baseline. According to the Monro-Kellie doctrine, the volume of the intracranial space, composed of brain tissue, blood, and cerebrospinal fluid, is constant. By preserving the balance between these components, clinicians can maintain the correct ICP [14, 19]. Any increase in blood volume (patient placement and pneumoperitoneum) decreases the volume of the cerebrospinal fluid, so the ICP remains constant.

Animal studies by Kalmar et al. [20] showed that an increase in ICP caused intravenous fluid displacement at the rate of 2 ml/min, which was required to maintain normal ICP. Moreover, ICP changes can be monitored in real time by ultrasound assessment of ONSD. Wang et al. confirmed the legitimacy of using ultrasound to assess ICP by examining the intracranial pressure and ONSD in 60 patients [21]; they found a strong correlation between both parameters. Compared with CT and MRI, ultrasound is less expensive, easier to access, less time-consuming, and free from causing patient complications [10, 22]. MRI studies in the paediatric population confirmed the correlation between increased ONSD and increased ICP [23, 24]. Sekhon et al. assessed the relation between ONSD and CT analysis in a group of 57 patients with post-traumatic brain injury [25]; the investigators found a strong correlation between ONSD as measured by CT and ICP. Moreover, with a cut-off at 6.0 mm, the ONSD had a sensitivity of 97%, specificity of 42%, a positive predictive value of 67%, and a negative predictive value of 92%. The meta-analysis performed by Kim et al. [11] with a group of 460 patients revealed that increased ICP during a laparoscopic procedure may result in increased ONSD. The ONSD returned to normal after the pneumoperitoneum was evacuated.

LIMITATION

This study had possible limitations. Inhaled anesthetics may have influenced the ICP. In a dose-dependent manner, sevoflurane increases cerebral blood flow by vasodilation. [26] However, at low concentrations, volatile anesthetics did not dilate the cerebral vasculature, avoiding increases in both cerebral blood flow and ICP [27]. Additionally, we

did not have a control group because we investigated our routine protocol as an observational study. There was no assessment of direct measuring of ICP. Prospective randomized studies are warranted to verify our results.

CONCLUSIONS

Perioperative ultrasound measurement of ONSD may serve as a practical, non-invasive tool to detect potential increases in intracranial pressure (ICP) during laparoscopic procedures involving the Trendelenburg position and pneumoperitoneum. Although we observed statistically significant increases in ONSD, these changes were not associated with clinical complications such as postoperative nausea, delirium, or delayed awakening. Based on our findings, routine ONSD monitoring may not be necessary in all patients undergoing laparoscopic urological surgery in the Trendelenburg position, but may be considered in high-risk individuals or longer procedures as a precautionary measure for intracranial pressure monitoring. Further studies are needed to establish specific clinical thresholds for its use.

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ORIGINAL ARTICLE

Structural features of the endocardium, arteries, prostate and adrenal glands under the conditions of iodine deficiency

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ABSTRACT

Aim: To indicate the morphofunctional changes in the endocardium, wall of the arteries of various types, prostate gland, and adrenal glands in the dynamics of iodine deficiency during postnatal ontogenesis.

Materials and Methods: The experiment involved 50 male Wistar rats (25 immature, aged 3-5 months, and 25 mature, aged 6-8 months). Group 1 (control) included 11 animals of both age groups, while Groups 2 and 3 (with iodine deficiency) consisted of 14 animals each, with material sampling on days 60 and 90 of the experiment, respectively. Morphological (light and electron microscopy), morphometric, biochemical studies, and statistical data processing were conducted.

Results: Key components of thyroid signaling were found in the prostate gland, indicating a possible direct effect of thyroid hormones on this organ. Edematous changes in the epithelium of terminal secretory parts result from ischemia caused by edema in vascular walls and connective tissue elements of the prostate. Structural changes found in endocrine cells of the glomerular, fascicular, and reticular zones of the adrenal glands, along with the dynamic increase in cortical thickness during the experiment, suggest trophic disturbances, as edema was detected in vessel walls and stromal components.

Conclusions: Thus, on both day 60 and day 90 of iodine deficiency, edematous changes occur in all organs in connective tissue components, wall of blood vessels, and epithelial tissues. Altered thyroid status triggers systemic interrelated changes in the organism.

KEY WORDS: endocardium, arteries, prostate gland, adrenal gland, iodine deficiency, structural-metabolic disorders, ontogenesis

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INTRODUCTION

The basis of alimentary hypothyroidism lies in the biogeochemical features of specific regions where iodine levels are reduced [1-5]. Thyroid hormones, which include iodine, regulate energy homeostasis, and even minor reductions in their levels increase the risk of cardiovascular diseases [6-9]. Under iodine deficiency, cardiovascular dysfunction develops asymptomatically [10-13]. Thyroid hormones are essential for the development of reproductive organs. Their deficiency during critical growth periods alters the size and function of the prostate gland in adulthood [14]. Hypothyroidism is known to reduce adrenal gland weight and plasma corticosterone concentration [15]. While a connection between these organs and the thyroid gland is evident, there is no comprehensive study on the impact of iodine deficiency on their morphofunctional state considering age-specific features.

AIM

To trace morphofunctional changes in the endocardium, arterial walls of various types, prostate gland, and adrenal gland during iodine deficiency in postnatal ontogenesis.

MATERIALS AND METHODS

Samples from the endocardium, fragments of the aorta, external carotid, and renal arteries, prostate gland (ventral, dorsal lobes, and coagulating gland), adrenal glands, blood, and urine were analyzed. Iodine deficiency was modeled using a specific methodology [2]. All procedures adhered strictly to humane treatment of animals. The experiment involved 50 male Wistar rats (25 immature, aged 3-5 months, and 25 mature, aged 6-8 months). Group 1 (control) included 11 animals of both age groups, while Groups 2 and 3 (with iodine deficiency) consisted of 14 animals each, with material sampling on days 60 and 90 of the experiment, respectively. Morphological (light and electron microscopy), morphometric, biochemical studies, and statistical data processing were conducted [16].

RESULTS

The thyroid status of immature animals in Group 1 was as follows: TSH 0.10±0.01 μIU/ml ($p<0.01$), T3 3.63±0.12 nmol/l ($p<0.01$), T4 75.44±4.01 nmol/l ($p<0.01$); for mature animals, TSH was 0.08±0.00 μIU/ml ($p<0.01$), T3 2.79±0.15 nmol/l ($p<0.01$), T4 55.18±2.72 nmol/l ($p<0.01$). Cholesterol content under age norm conditions was 1.60±0.05 mmol/l ($p<0.01$) in immature rats and 1.40±0.09 mmol/l ($p<0.01$) in mature rats. Ioduria in immature animals of Group 1 was 97.13±5.40 μg/l, and in mature animals – 101.06±3.44 μg/l ($p<0.01$).

Thyroid status of immature animals in Group 2 showed TSH 0.17±0.02 μIU/ml ($p<0.01$), T3 3.46±0.36 nmol/l ($p<0.01$), T4 75.49±9.60 nmol/l ($p<0.01$); in mature animals, TSH was 0.12±0.01 μIU/ml ($p<0.01$), T3 2.97±0.37 nmol/l ($p<0.01$), T4

67.49±8.25 nmol/l (p<0.01). Cholesterol on day 60 of the experiment was 1.63±0.17 mmol/l (p<0.01) in immature rats and 1.39±0.12 mmol/l (p<0.01) in mature rats. Ioduria in immature animals of Group 2 was 2.73±0.29 μg/l, and in mature animals – 3.77±0.34 μg/l (p<0.01).

On day 60 of iodine deficiency, the endocardium appeared as a thin eosinophilic strip with well-defined oval nuclei; in some loci, nuclei were round. Ultrastructurally, the luminal plasmalemma of endothelial cells formed numerous invaginations. Membrane organelles were swollen. The subendothelial layer contained an amorphous substance of medium electron density. Mitochondria and endoplasmic reticulum were identified in the smooth muscle cells of the muscular-elastic layer (Fig. 1). Endothelin-1 blood levels in immature animals increased by 2.9% (p<0.05), while no change was observed in mature animals.

In the walls of elastic, muscular and muscular-elastic arteries, all layers were identified, but the contour of their lumen was chaned due to uneven twists of the connective tissue framework. The endothelial layer of the intima was light, endothelial nuclei were not visible in all fields of view. The nuclei of smooth muscle cells were oriented in various directions with differing degrees of basophilia. The adventitia was blurred.

Ultrastructurally, endothelial cells showed organelle swelling and multiple luminal plasmalemma invaginations. The internal elastic membrane had loci of luminalization. Sarcoplasm of smooth muscle cells had a granular-fibrillar structure.

Morphometric analysis showed that in immature animals, the thickness of the aortic, external carotid, and renal artery walls increased by 0.9% (p<0.05), 0.9% (p<0.05), and 0.6% (p<0.05), respectively. In mature animals, the thickness increased by 0.2% (p<0.05), 0.7% (p<0.05), and 1.1% (p<0.05), respectively.

At this stage of the experiment, edema was observed in the connective tissue elements of the stroma and wall of blood vessels in all patrs of the prostate gland (ventral, dorsal, and coagulating glands) (Fig. 2). Epithelial cells of terminal secretory parts had apically light cytoplasm and basal basophilia of nuclear poles. Ultrastructurally, nuclei contained euchromatin and a thin band of heterochromatin. Granular endoplasmic reticulum tubules were dilated, and Golgi apparatus cisternae unevenly filled the cytoplasm. Mitochondrial matrix was of low electron density; cristae were disorganized. Secretory granules varied in shape and size. The height of the epithelium in the terminal secretory parts of the ventral, dorsal lobes, and coagulating

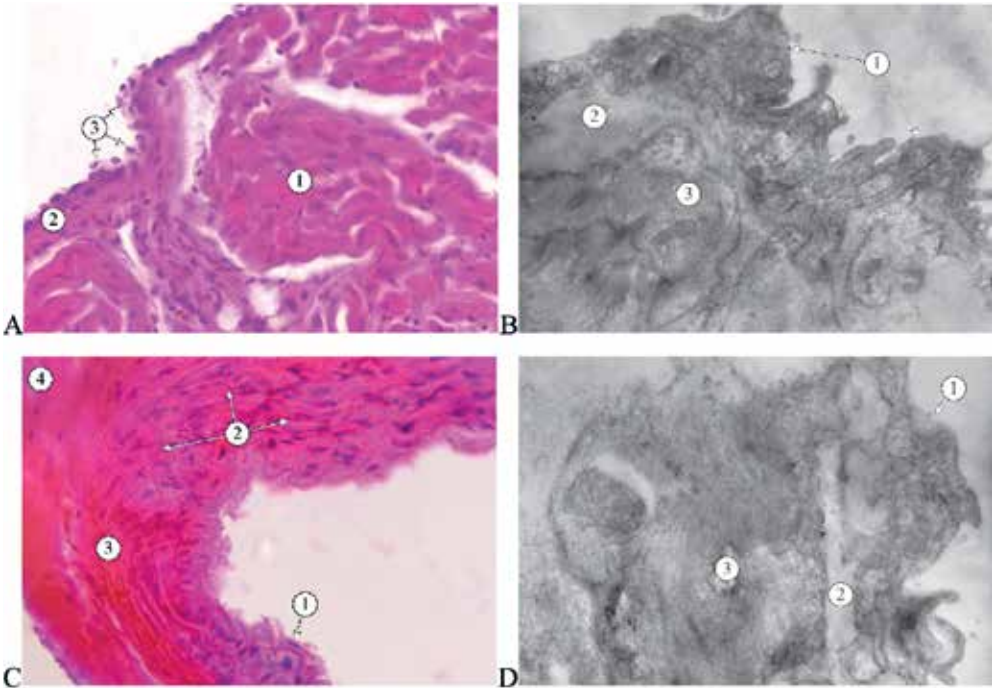

Fig. 1. Structure of the endocardium and arterial walls on day 60 of iodine deficiency.
A. Endocardium of a mature animal: 1 – myocardium, 2 – endocardium, 3 – endothelial cell nuclei;
B. Endocardium of an immature animal: 1 – endothelial cells, 2 – subendothelial layer, 3 – muscular-elastic layer connective tissue;
C. wall of the renal artery of the immature animal. 1 – endothelial cells, 2 – connective tissue fibres of the media, 3 – smooth muscle cells of the media, 4 – adventitia;
D. wall of the carotis externa artery of the mature animal. 1 – endothelial cells, 2 – internal elastic membrane, 3 – smooth muscle cell;
A, C – stained with hematoxylin and eosin, magnification: A, C x 400;
B, D – electron microscopy diagram, magnification: B x 9600, D x 16000

Picture taken by the authors

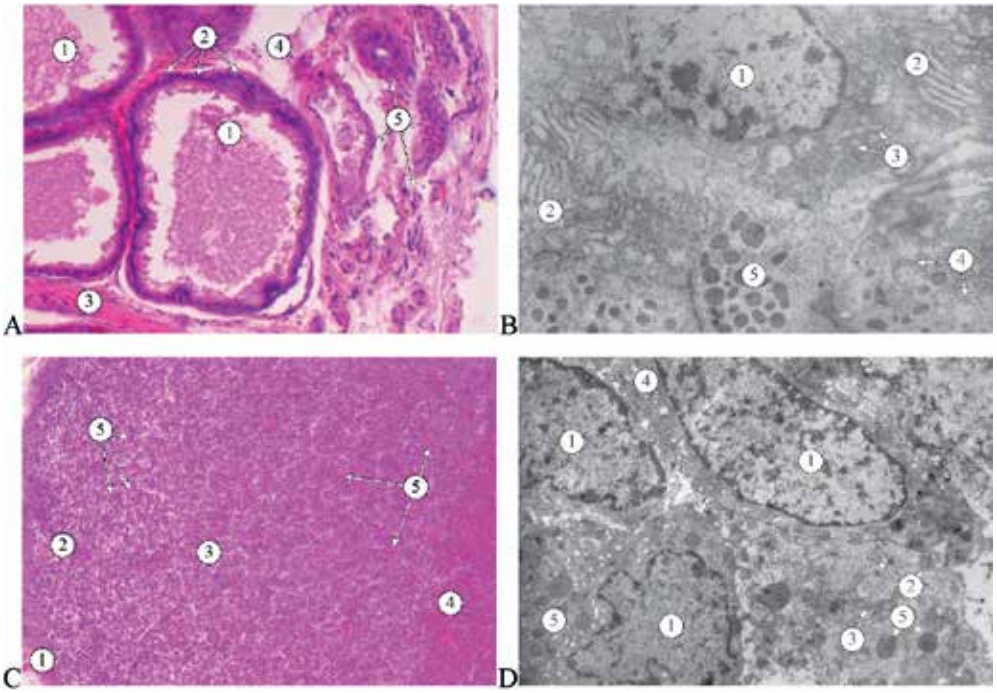

Fig. 2. Structure of the prostate and adrenal glands on day 60 of iodine deficiency.
A. Dorsal lobe of prostate gland in mature animal: 1 – terminal secretory parts, 2 – epithelial nuclei, 3 – smooth muscle cells, 4 – connective tissue fibers, 5 – blood vessels.
B. Ventral lobe of prostate gland in immature animal: 1 – nucleus, 2 – granular endoplasmic reticulum, 3 – Golgi apparatus, 4 – mitochondria, 5 – secretory granules.
C. Adrenal gland of immature animal: 1 – capsule, 2 – zona glomerulosa, 3 – zona fasciculata, 4 – zona reticularis, 5 – blood vessels.
D. Endocrine cells of zona glomerulosa adrenal cortex in mature animal: 1 – nucleus, 2 – mitochondria, 3 – endoplasmic reticulum, 4 – Golgi apparatus, 5 – granules.
A, C – hematoxylin and eosin, magnification: A ×200, C ×100. B, D – electron micrograph, magnification: B, D ×4800

Picture taken by the authors

glands increased by 0.3% ($p<0.05$), 0.7% ($p<0.05$), and 0.9% ($p<0.05$) in immature animals, respectively. In mature animals, epithelium height increased by 0.2% ($p<0.05$), 0.4% ($p<0.05$), and 0.9% ($p<0.05$), respectively.

In the adrenal glands, light microscopy showed edema of the capsule (Fig. 2C). Zona glomerulosa was represented by basophilic-stained endocrine cells; in zona fasciculata, cells were weakly eosinophilic, with more intense eosinophilia in zona reticularis. In all zones of the cortex and in medulla, blood vessel lumens and networks were visible. Submicroscopically, pericellular luminal loci were visible (Fig. 2D). Endocrinocytes showed invagination of the nuclear envelope and marginal chromatin localization. Membrane organelles were swollen. Secretory granules had medium electron density. Cortical thickness of adrenal glands in immature animals increased by 0.4% ($p<0.05$), and in mature animals by 1.5% ($p<0.05$).

Thyroid status of immature animals in Group 3: TSH 0.16±0.02 μIU/ml ($p<0.01$), T3 3.47±0.39 nmol/l ($p<0.01$), T4 51.31±6.53 nmol/l ($p<0.01$); in mature animals: TSH 0.23±0.03 μIU/ml ($p<0.01$), T3 2.43±0.29 nmol/l ($p<0.01$), T4 54.91±7.05 nmol/l ($p<0.01$). Cholesterol content on day 90 of the experiment was 1.66±0.20 mmol/l ($p<0.01$) in immature rats, and 1.44±0.16 mmol/l ($p<0.01$) in mature rats. Ioduria in immature animals of Group 3 was 1.89±0.24 μg/l, and in mature animals 2.29±0.21 μg/l ($p<0.01$).

On day 90 of the experiment, the endocardium appeared as an unevenly swollen strip with a cleared subendothelial layer (Fig. 3). The endothelial cell nuclei showed varying intensities of basophilia and were located at different levels. The cytoplasm had a reticular structure. Ultrastructurally, endothelial cells had medium electron density with poorly differentiated organelles. A swollen subendothelial layer was visible, appearing as a homogeneously deformed strip. In the muscular-elastic layer, swollen, differently oriented collagen fibers were found, surrounded by a cleared amorphous substance. Endothelin-1 levels in the blood of immature animals increased by 4.3% ($p<0.05$), and in mature animals, it increased by 1.2% ($p<0.05$).

When examining arterial walls, frequent adhesion of formed elements obscuring endothelial cells was observed. The collagen-elastic framework was deformed and swollen. Smooth muscle cell nuclei in the media were oriented in different directions. The adventitia consisted of layered fibers in swollen amorphous material. Submicroscopically, endothelial cells rested on a thin basal membrane. Their luminal surface had a blurred contour along the vessel perimeter. The cytoplasm was diffusely granular with alternating optical lighting. The subendothelial layer had

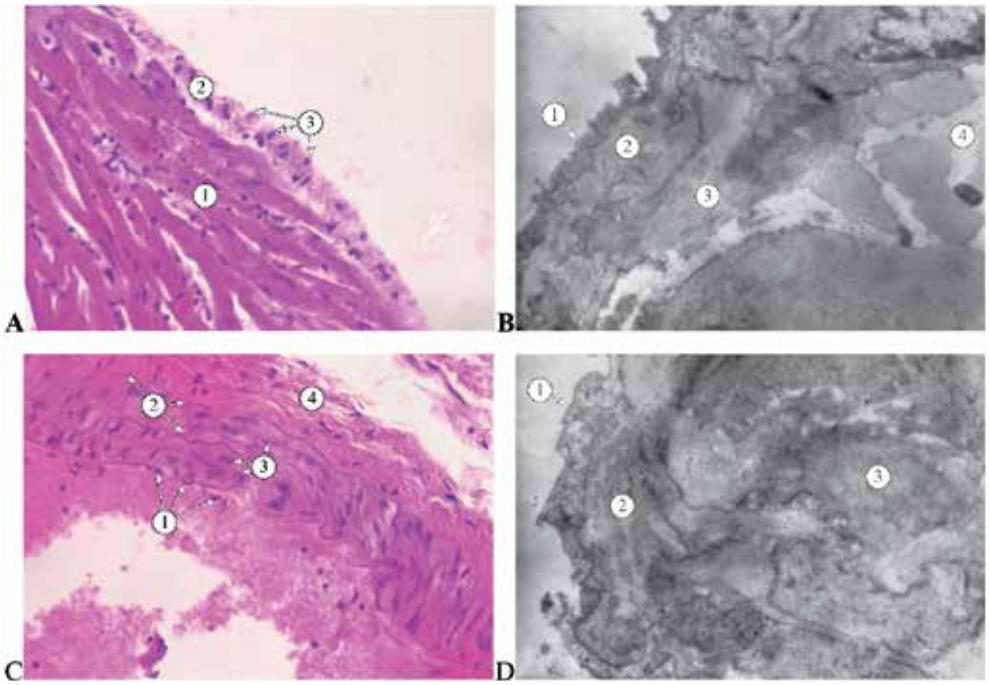

Fig. 3. Structure of the endocardium and wall of the arteries on day 90 of iodine deficiency.
A. Endocardium of a mature animal: 1 – myocardium, 2 – endocardium, 3 – endothelial cell nuclei.
B. Endocardium of an immature animal: 1 – endothelial cells, 2 – subendothelial layer, 3 – connective tissue fibers of the muscular-elastic layer, 4 – substance of the muscular-elastic layer.
C. Wall of renal artery of mature animal: 1 – endothelial cell nuclei, 2 – connective tissue fibers of the media, 3 – smooth muscle cells of the media, 4 – adventitia.
D. Wall of aorta of mature animal: 1 – endothelial cell, 2 – subendothelial layer, 3 – smooth muscle cell.
A, C – hematoxylin and eosin, magnification: A, C ×400. B, D – electron micrograph, magnification: B ×4800, D ×9600
Picture taken by the authors

low electron density. Elastic and collagen fibers of the arterial wall were swollen and fragmented. Sarcoplasm of smooth muscle cells was light. Morphometric analysis showed that in immature animals, the thickness of the aorta, external carotid, and renal artery walls increased by 1.0% ($p<0.05$), 1.2% ($p<0.05$), and 0.8% ($p<0.05$), respectively. In mature animals, these parameters increased by 0.6% ($p<0.05$), 1.3% ($p<0.05$), and 1.7% ($p<0.05$), respectively.

The epithelium of the terminal secretory parts of all prostate lobes was swollen (Fig. 4). Nuclei had blurred contours. The cytoplasm was eosinophilic. Edematous connective tissue fibers, amorphous substances, and smooth muscle cells of the gland stroma were noted. Similar edematous changes were present in the walls of blood vessels. Submicroscopically, cytoplasmic lighting of epithelial cells was observed. Granular endoplasmic reticulum tubules were dilated, and the Golgi apparatus consisted of deformed cisternae and tubules. Mitochondria had disorganized cristae and cleared matrix. The height of the epithelium in the terminal secretory parts of the ventral, dorsal lobes, and coagulating glands increased by 3.6% ($p<0.05$) in immature animals. In mature animals, the height of the epithelium increased by 1.1% ($p<0.05$), 0.9% ($p<0.05$), and 1.4% ($p<0.05$), respectively.

In the adrenal glands, edema was observed in the capsule and parenchyma. Stromal components were layered and deformed, surrounding the swollen walls of blood vessels, whose lumens were changed (Fig. 4C). Prominent pericellular luminalization ligthening was seen in all zones of the adrenal cortex and in the medulla. Edematous processes in adrenal endocrinocytes were confirmed by electron microscopy (Fig. 4D). Mitochondrial matrix was dispersed and of low electron density, with disorganized cristae. Secretory granules were heterogeneous and sparse. Blood vessels showed stasis phenomena. The thickness of the adrenal cortical layer increased by 1.4% ($p<0.05$) in immature animals and by 2.4% ($p<0.05$) in mature animals.

DISCUSSION

Iodine deficiency can significantly impact the structure and function of the endocardium, arteries, prostate, and adrenal glands [6, 19, 25]. In the endocardium, iodine deficiency may contribute to structural changes due to its role in thyroid hormone production, which is crucial for heart development and function [12]. Arteries, particularly their smooth muscle cells, can be affected by iodine deficiency-related hypothyroidism, impacting their structure and function [18]. In the prostate, iodine is essential for normal function, and deficiency can lead to structural abnormalities. Similarly, adrenal glands require iodine for hormone production, and deficiency can disrupt their structure and function [14].

Thyroid hormones influence cellular oxygen metabolism [6, 7, 17]. They maintain vascular homeostasis through positive

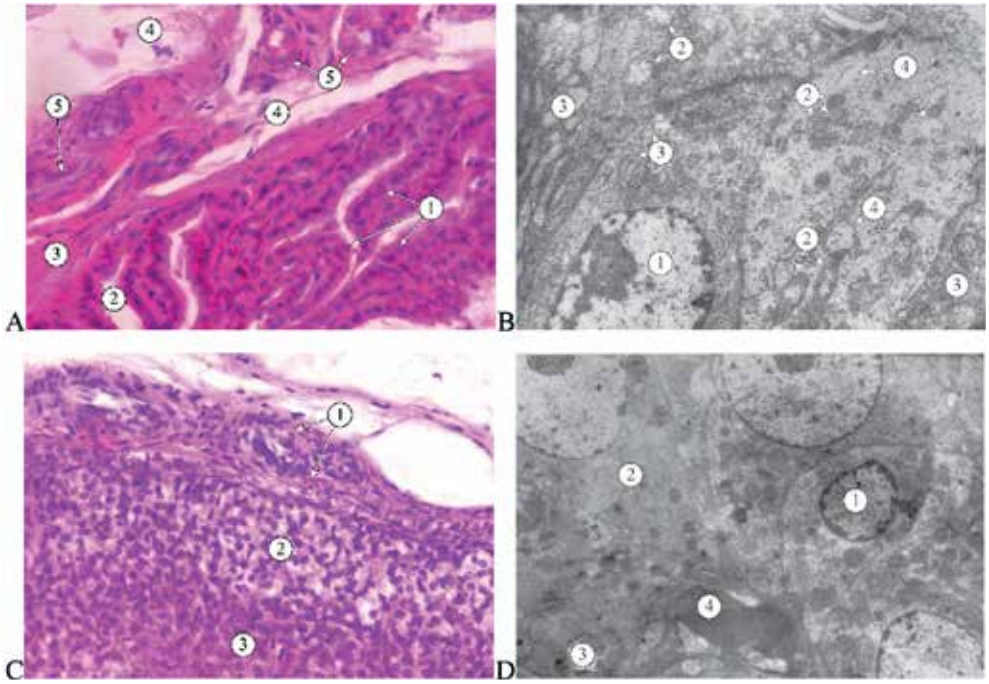

Fig. 4. Structure of prostate and adrenal glands on day 90 of iodine deficiency.
A. Coagulating gland of immature animal prostate: 1 – epithelial cells, 2 – lumen of terminal secretory parts, 3 – smooth muscle cells, 4 – connective tissue fibers, 5 – blood vessels.
B. Dorsal lobe of mature animal prostate: 1 – nucleus, 2 – mitochondria, 3 – granular endoplasmic reticulum, 4 – vacuoles.
C. Adrenal gland of mature animal: 1 – capsule, 2 –zona glomerulosa, 3 – zona fasciculata.
D. Endocrine cells of zona fasciculata adrenal cortex in immature animal: 1 – nucleus, 2 – mitochondria, 3 – lipid inclusions, 4 – erythrocyte sludge.
A, C – hematoxylin and eosin, magnification: A, C ×400. B, D – electron micrograph, magnification: B ×6400, D ×3200

Picture taken by the authors

effects on endothelial cells and smooth muscle cells of blood vessels [18]. Thyroid hormones, influenced by iodine levels, affect the structure and function of smooth muscle cells in arteries. Iodine deficiency can lead to hypothyroidism, which can negatively affect arterial smooth muscle function and structure. Hypothyroidism can cause vasoconstriction (narrowing of blood vessels), potentially leading to increased blood pressure and altered artery structure. According to our data, endothelin-1 levels slightly increased by day 60 of iodine deficiency with further rise by day 90. Endothelin-1 is a potent vasoconstrictor [19, 20]. The observed edematous changes in vascular walls correlate with other authors' findings on decreased elasticity and increased vascular resistance [21-23]. Endothelial dysfunction worsens due to impaired lipid metabolism under iodine deficiency [24, 25].

Iodine is essential for the synthesis of thyroid hormones, which play a crucial role in heart development and function. Iodine deficiency, often leading to hypothyroidism, can disrupt normal heart development and function, potentially affecting the endocardium's structure. According to our data, cholesterol content changes serve as a marker of this. It is known that structural changes in the endocardium are associated with elevated cholesterol levels, indicating the impact of iodine deficiency on thyroid hormones and metabolism, thus increasing the risk of cardiovascular diseases [12, 26].

Key components of thyroid signaling were found in the prostate gland, indicating a possible direct effect of thyroid hormones on this organ [14]. Edematous changes in the epithelium of terminal secretory parts result from ischemia caused by edema in vascular walls and connective tissue elements of the prostate [27, 28].

Iodine deficiency can lead to structural changes in the adrenal glands, particularly in the context of hypothyroidism [4]. These changes can include increased vascularity, alterations in cell size and number, and disruptions in hormone production pathways. In response to iodine deficiency and subsequent hypothyroidism, the adrenal glands may exhibit an increase in the number and size of blood vessels (vascularity). This adaptation may be an attempt to improve hormone delivery or compensate for impaired cellular function. Iodine deficiency can lead to changes in the size and number of cells within the adrenal cortex, which is the outer layer of the gland responsible for producing steroid hormones like cortisol and aldosterone [15]. The hypothalamus and pituitary gland, which regulate the thyroid, also influence the adrenal glands [29]. In turn, hypothyroidism can disrupt the normal hypothalamic-pituitary-adrenal (HPA) axis, affecting adrenal hormone production and potentially leading to adrenal dysfunction. Chronic iodine deficiency can attenuate HPA axis activity. Due to our investigations, which prove the results of other

scientists, structural changes were founded in endocrine cells of the glomerular, fascicular, and reticular zones of the adrenal glands, along with the dynamic increase in cortical thickness during the experiment, suggest trophic disturbances, as edema was detected in vessel walls and stromal components.

CONCLUSIONS

Thus, on both day 60 and day 90 of iodine deficiency, edematous changes occur in all organs in connective tissue components, wall of blood vessels, and epithelial tissues. Altered thyroid status triggers systemic interrelated changes in the organism.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Effect of short duration vitamin E supplementation on some reproductive hormones in infertile women

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ABSTRACT

Aim: To study the effects of short duration vitamin E supplementation (100 mg/day) on reproductive hormones disturbance estrogen, follicle stimulating hormone, luteinizing hormone, and prolactin.

Materials and Methods: The study included 40 women with ages ranged between 18-35 years; they were treated from infertility at Al-Zahraa Teaching Hospital in Al-Najaf City in Iraq between June 2023 and May 2024. Women participated in the study were divided into two groups: Group (A): was given vitamin E supplementation (100 mg/day) starting at the 4th day of menstruation; Group (B): was given vitamin E supplementation (100 mg/day) starting at the mid of menstruation (expected ovulation time). The hormonal measurements for (Follicle Stimulating Hormone, Luteinizing Hormone, estradiol and prolactin) were conducted by immunoassay (Cobas E 411).

Results: The results revealed that there was a significant increase in blood level of E after treatment compared to their levels before treatment. The results also indicated that the levels of estradiol and Luteinizing Hormone have been elevated after intervention as compared to that before intervention.

Conclusions: It was concluded the complementation of vitamin E supplementation (100 mg/day) has a positive impact in the enhancement of female hormonal indicators (especially estradiol and Luteinizing Hormone) which may increase the efficiency of the therapeutic approaches of infertility. Early-cycle supplementation also resulted in higher estradiol (P=0.04) and luteinizing hormone levels (P=0.02) compared with mid-cycle supplementation, indicating increased hormonal activity.

KEY WORDS: vitamin E, FSH, LH, estrogen, prolactin, infertile women

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INTRODUCTION

Infertility is described by the World Health Organization as the failure of pregnancy or the inability of the reproductive system to produce clinical pregnancies after 12 or more months of unprotected sexual intercourse. The WHO epidemiologic definition is „women of reproductive age to getting pregnant who reported failed pregnancy attempts for more than two years." Clinical definitions aim at early spotting and treatment of cases of infertility [1]. Infertility afflicts an estimated 186 million people every year around the globe, most of who are in poorer nations [2]. Infertility may be caused by disorders in the reproductive system of either the male or female. Ovarian causes account 20% Age at conception is considered to be a primary influence on fertility. In addition, lifestyle and environmental variables are considered to be negative prognostic variables, alongside age at conception. One reasons for infertility is decrease or impairment in the functions of reproductive hormones especially follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and prolactin [3-4]. Vitamin E is an essential fat-soluble vitamin that has important roles in the human body. Numerous studies have consistently shown that it can significantly improve hormonal effects, particularly enhancing the activity of reproductive hormones in both men and women. Additionally, this remarkable vitamin may also have the potential to improve several distressing symptoms associated with male sexual dysfunction. These findings highlight the invaluable benefits of incorporating vitamin E into a balanced and healthy lifestyle for overall well-being [5]. Although perhaps a low-definition biocompound, vitamin E has the potential to enhance bodily function in many ways. It has been reported that vitamin E supplementation for 75-150 mg/ day for 3 months improves hormonal levels where hormonal balance is disturbed; this vitamin E supplementation improved serum testosterone concentrations in existing studies that show a reduction in the reproductive hormonal levels. Studies have also indicated that dietary vitamin E supplementation can exert a significant positive influence on reproductive performance, including an increase in testosterone production [6]. Further research on the effects

of vitamin E supplementation on reproductive hormone disturbances, with estrogen, FSH, LH, and prolactin being disturbance subjects, is still essential because abnormalities in reproductive hormones may disrupt fertility in both men and women. Results that show alteration in reproductive hormonal levels may provide insight into additional studies in both experimental and clinical applications. A better understanding of the effects of a certain biocompound on the function of a given hormone can be deciphered. Thus, the purpose of this research is to study the effects of short duration vitamin E supplementation (100 mg/day) in women on their reproductive hormones' including estrogen, follicle stimulating hormone, luteinizing hormone, and prolactin.

MATERIALS AND METHODS

The study included 40 women with ages ranged between (18-35) years (Table 1); they were treated from infertility at Al-Zahraa Teaching Hospital in Al-Najaf City in Iraq between June 2023 and May 2024. A total sample of (5 ml) of blood was collected from the women in order to perform laboratory tests. Women participated in the study were divided into two groups: Group (A): included 20 women that were given vitamin E supplementation (100 mg/day) starting at the 4th day of menstruation; Group (B): included 20 women that were given vitamin E supplementation (100 mg/day) starting at the mid of menstruation (expected ovulation time). The hormonal measurements for (FSH, LH, estradiol and prolactin) were conducted by immunoassay (Cobas E 411). The clinical diagnosis and intervention were done under the supervision of specialized gynecologist. The participation in the study was completely voluntary and previous consent from the patients was taken before conducting the study.

STATISTICAL ANALYSIS

Data were subjected to analysis using SPSS statistics version 25.0 software (SPSS, Chicago). The normality test was used to check the level of parametric data (Shapiro Wilk test). Normally distributed data are presented as mean±standard deviation. Paired t-test was used to investigate the differences in the levels of hormones before and after vitamin E supplementation. A probability value of less than 0.05 was considered statistically significant.

ETHICS APPROVAL

The protocol in this study was approved by the ethical committee of the Medical College in the University of Kufa (No. 122 in 2024).

RESULTS

The current study included 40 infertile women who were treated with vitamin E in order to evaluate its effect on biochemical pregnancy outcome following controlled ovarian stimulation. The results indicated that women participated in this study are young as the majority of them are less than 29 years in age, about two thirds of them have a duration of infertility between 2-4 years, the vast majority undergo primary infertility, and finally, most of them 80% had a menarche at age between 12-14 years.

The effect of vitamin E supplementation on serum levels of vitamin E in both study groups is shown in Table 2. The study has investigated the supplementation of vitamin E and its effects of female infertility, after the end of menstrual cycle duration the study has found that there is a significant increase in serum vitamin E in group A of the patients which have received vitamin E at the 3rd day of the menstruation (4.65±0.77 µg/ml vs. 6.77±1.17 µg/ml respectively), while those who received vitamin E at the mid of the menstruation did not exhibit any significant alteration (5.02±0.94 µg/ml *vs.* 5.02±0.94 µg/ml respectively.

The results of the current study also revealed that the levels of estradiol (E2) in group A were higher than their levels in group B (88.33±77.32 and 47.32±34.7 respectively;

Table 1. Descriptive statistics (frequency and percentage) for patients' characteristics

Patients' Characteristics	Rating	Frequency N=40	Percentage
Age/Years	≤20	5	12.5
	21-24	4	10
	25-28	24	60
	>29	7	17.5
Marriage duration/Years	2-4	25	62.5
	5-7	7	17.5
	≥8	8	20
Type of Infertility	Primary	35	87.5
	Secondary	4	10
Age at menarche/Years	<12	6	15
	12-14	32	80
	≥14	2	5

Source: Own materials

Table 2. Effect of vitamin E supplementation on serum levels of vitamin E in both study groups

Parameter	Vitamin E (µg/ml)		Paired T Test	P value
	Before intervention	After intervention		
	Mean±SD	Mean±SD		
Group A (n=20)	4.65±0.77	6.77±1.17	11.83	0.000 HS
Group B (n=20)	5.02±0.94	5.34±1.18	1.21	0.32 NS

Source: Own materials

Table 3. Differences in serum levels of female reproductive hormones between group A and group B

Parameter	Group A	Group B	Paired T Test	P value
	Mean±SD	Mean±SD		
FSH (mIU/mL)	9.86±2.53	8.12±5.22	1.34	0.18 NS
LH (mIU/mL)	10.89±5.83	6.25±5.99	2.49	0.02 S
E2 (µg/L)	88.33±77.32	47.32±34.70	2.16	0.04 S
Prolactin (µg/L)	14.45±12.34	18.95±11.21	1.21	0.23 NS

NS: Not significant difference at p>0.05; S: significant difference at p≤0.05
Source: Own materials

P value=0.04), the same line that the levels of LH in group A were higher than their levels in group B (10.89±5.83 and 6.25±5.99 respectively; P value= 0.02). The levels of FSH have exhibited a non-significant increase (P value=0.18) in group A in comparison to groups B, and finally the prolactin indicated exhibited a non-significant decrease (P value=0.23) in group A in comparison to groups B, as shown in Table 3.

DISCUSSION

In recent years, vitamin E has gained considerable attention as a potential therapeutic agent in addressing reproductive health disorders and improving fertility. Currently, assisted reproduction techniques such as in vitro fertilization, embryo transfer, and gamete intrafallopian transfer have been employed to treat infertility. However, the overall success rates of these techniques remain low. As a result, there has been a growing interest in investigating natural products, particularly plant-derived medicines, as potential adjunct therapies in the management of reproductive health disorders [7]. Until now, few studies have investigated in depth the effect of vitamin E on female hormones. In the present study, treatment with vitamin E resulted in no significant change in serum hormonal levels regarding FSH but a significant increase in LH. However, it resulted in significant increase in serum estradiol. On the other hand, the levels of both serum estradiol and prolactin remain within acceptable reference ranges at a border lines; therefore, their effect on pregnancy outcome will be minimal. With respect to FSH and LH, these results are similar to the findings of a number of authors [8-9]. However, a conflict results may be present in other studies regarding the effects of vitamin E on the levels of estrogen and LH [10]. Constant feedbacks in the regulation of LH and estrogen are important to guarantee regular follicular oogenesis and ensure that the LH trigger ovulation occurs, and these are the goals of synchronization in reproductive efficiency of sows. The fundamental attributes of follicular oogenesis culminate with the ovulation which is stimulated by the peak of the LH surge that only occurs in the presence of sufficient estrogen and at the end of the luteal functional life. In the intercycle endometrial cavity, estrogen remains at high concentrations for another 10-15 days. The high and long-lasting concentrations of estrogen warrant a negative feedback effect on LH and follicle-stimulating hormone (FSH) from the middle of the follicular phase until the luteal regression, preventing a second ovulation during the gestation and the whole lactation stage, and preventing estrus cascade. At the end of the luteal stage, the expected low estrogen levels promote the positive feedback, sending a Wi-Fi alert for the prolonged-light boar semen collector [11]. Vitamin E is a well-known fat-soluble vitamin that has emerged as a natural nutraceutical option. It exists in two forms, tocopherols and tocotrienols, each having four isoforms. Each isoform possesses distinct biological activities and functions. Vitamin E is regarded as a potential antioxidant and possesses other important biological functions [12]. When supplementation was administered to vitamin E-deficient rats, a significant increase in reproductive hormone levels was observed. Furthermore, additional evidence indicated that vitamin E supplementation could improve reproductive performance and restore estrous cycles in lead nitrate-treated mice. Vitamin E supplementation has been shown to increase the basal ovulatory LH surge, serum estrogen levels, ovarian follicle development, and number of ovulated eggs (i.e., eggs released from the ovaries) [13]. The hypothalamus-pituitary-gonadal (HPG) axis is the most important neuroendocrine reproductive system in vertebrates.

Gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus secrete GnRH that stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in synthesis and secretion of sex hormones, particularly testosterone (in males) and estrogen (in females), from gonads [14]. Aberrant function of the HPG axis is a major factor involved in the onset of reproductive disorders, including, but not limited to, delayed puberty, hypogonadism, and hyposexuality in males or females. Vitamins are essential micronutrients that play key roles in various biological processes and normal physiological functions of the body. In addition to the well-characterized roles of vitamins in preventing avitaminosis, recent studies have rapidly unveiled the beneficial roles of several vitamins in regulating body homeostasis and maintaining health [15].

CONCLUSIONS

Vitamin E supplementation (100 mg/day) on day 3 of the menstrual cycle significantly increased serum vitamin E levels (from 4.65±0.77 μg/ml to 6.77±1.17 μg/ml). Early-cycle supplementation also resulted in higher estradiol (88.33±77.32 *vs.* 47.32±34.7, P=0.04) and luteinizing hormone levels (10.89±5.83 *vs.* 6 .25±5.99, P=0.02) compared with mid-cycle supplementation, indicating increased hormonal activity. These findings highlight that vitamin E supplementation at the beginning of the menstrual cycle can improve hormonal status related to female fertility.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Building a child-centred, multilayered MHPSS eco-system for conflict-affected children (Ukraine)

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ABSTRACT

Aim: This article aims to propose a multilayered, child-centred Mental Health and Psychosocial Support (MHPSS) ecosystem model tailored for conflict-affected children (on example of Ukraine). The model integrates evidence-based interventions, multisectoral collaboration, and cultural adaptation to address acute psychosocial distress and foster long-term resilience, offering a replicable blueprint for humanitarian contexts.

Materials and Methods: The development of the MHPSS ecosystem model was informed by a comprehensive review of theoretical frameworks, peer-reviewed literature, international reports, and successful MHPSS interventions in humanitarian settings. The model synthesizes the Inter-Agency Standing Committee (IASC) pyramid of psychosocial intervention and Bronfenbrenner's ecological systems theory, contextualized through analysis of UNICEF and WHO reports, Ukraine's National the Action Plan for 2024-2026 and Target Model of the MHPSS System, and global best practices. An 11-stage implementation plan was formulated, incorporating adaptation, governance, capacity building, database/certification, supervision, quality assurance, and policy integration, guided by implementation science frameworks.

Results: The proposed model operationalizes a coordinated, scalable MHPSS ecosystem centred on children, layered across family, school, service infrastructure, and policy. Through localization, community-driven delivery, and multisectoral governance, the model enhances cultural fit, professionalizes the MHPSS workforce, and embeds continuous quality improvement. Integration with Community Resilience Centres (CRCs) strengthens local service delivery and sustainability. The staged implementation plan provides a universal roadmap for bridging immediate psychosocial needs and long-term systemic resilience.

Conclusions: The multilayered MHPSS ecosystem represents a paradigm shift in addressing the psychosocial impact of conflict on children. By embedding evidence-based, contextually adapted supports within a sustainable multisectoral framework, the model offers significant potential to mitigate distress and promote resilience, serving as a foundation for future research and global replication.

KEY WORDS: MHPSS eco-system; implementation model; conflict-affected children; Ukraine; psychosocial resilience

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INTRODUCTION

Since the onset of Russia's full-scale invasion of Ukraine in February 2022, Ukrainian children have faced unprecedented psychosocial challenges resulting from exposure to armed conflict, violence, displacement, and loss of family members and communities [1, 2]. According to UNICEF [3], more than two-thirds of Ukrainian children have experienced severe distress, with substantial proportions showing symptoms of post-traumatic stress disorder (PTSD), anxiety, and depression. As humanitarian needs escalate, existing mental health and psychosocial support (MHPSS) infrastructures remain fragmented, overstretched, and inadequately coordinated to effectively address the growing psychological toll [4].

Recognizing these critical gaps, the Government of Ukraine outlined a national Action Plan for 2024-2026 and Target Model of the MHPSS System (https://howareu.com/materials/target-model-of-the-mhpss-system) emphasizing a comprehensive, integrated approach to psychosocial recovery. However, substantial barriers remain at the operational level, including limited capacity, insufficient coordination among sectors, inconsistent adherence to evidence-based interventions, and inadequate monitoring and evaluation mechanisms [5].

To bridge these gaps, this article proposes a structured multilayered MHPSS eco-system model in Ukraine. This approach integrates best practices recommended by the World Health Organization's Mental Health Gap Action Programme (WHO mhGAP) and the IASC Guidelines on Mental Health and Psychosocial Support in Emergency Settings [4]. The aim is to create a coordinated, sustainable response involving humanitarian organizations, educational institutions, healthcare providers, community stakeholders, and government entities. By strengthening local capacities, promoting resilience at multiple levels, and ensuring robust

evaluation mechanisms, the model seeks not only to mitigate the immediate psychosocial impact on children but also to provide a replicable blueprint for broader national and global contexts affected by armed conflict.

This article describes the conceptual framework, methodology, expected outcomes, and practical implications of the proposed MHPSS eco-system. It will also discuss anticipated challenges and facilitators, positioning the model within the wider context of humanitarian mental health intervention science.

CONCEPTUAL FRAMEWORK

The proposed multilayered MHPSS eco-system draws upon established theoretical frameworks, specifically the Inter-Agency Standing Committee (IASC) pyramid model of psychosocial intervention [4] and Bronfenbrenner's ecological systems theory [6]. The IASC pyramid provides a structured, tiered approach emphasizing community-based support, focused non-specialized support, and specialized clinical services, depending on the severity and complexity of mental health needs. Bronfenbrenner's ecological systems theory underscores the interrelated influences of individual, family, community, institutional, and policy-level factors in shaping children's psychosocial well-being [6].

Integrating these frameworks allows the model to holistically address both immediate psychological distress and broader systemic influences. The eco-system approach incorporates multiple sectors education, healthcare, social services, and community-based organizations into a cohesive network that leverages local resources, knowledge, and capacities. By operationalizing these theoretical frameworks, the model promotes both immediate symptom relief and longer-term resilience and recovery [7].

AIM

The aim of this article is to propose a multilayered, child-centered Mental Health and Psychosocial Support (MHPSS) ecosystem model for conflict-affected children in Ukraine, integrating evidence-based interventions, multisectoral collaboration, and cultural localization to mitigate immediate psychosocial distress, foster long-term resilience, and provide a scalable blueprint for humanitarian mental health interventions in global conflict settings.

MATERIALS AND METHODS

The development of the proposed multilayered Mental Health and Psychosocial Support (MHPSS) ecosystem model was informed by a comprehensive review of theoretical frameworks, peer-reviewed publications, international reports, and foreign experiences in humanitarian mental health programming. The following materials were analyzed to construct a robust, evidence-informed model:

THEORETICAL FRAMEWORKS

The Inter-Agency Standing Committee (IASC) Guidelines on Mental Health and Psychosocial Support in Emergency Settings provided a layered intervention structure, while Bronfenbrenner's ecological systems theory [6] offered a lens to address nested influences on child well-being, including individual, family, and community factors.

ACADEMIC PUBLICATIONS

Key studies informed the model's design, including Tol et al. [7] on resilience in conflict-affected children, Betancourt et al. [8] on psychosocial trajectories in war-affected youth, and Bosqui & Marshoud [9] on mechanisms of change in MHPSS interventions. These publications provided evidence on effective psychosocial strategies in low-resource settings.

REPORTS

UNICEF reports [3] on the psychosocial toll of the Ukraine conflict, the Target Model of the MHPSS System (https://howareu.com/materials/target-model-of-the-mhpss-system), and WHO's 2023 report on health financing for mental health services in Ukraine [10] highlighted contextual needs and operational gaps. The IASC Reference Group's 2007 guidelines [4] further shaped the model's multisectoral approach.

INTERNATIONAL EXPERIENCES

The model drew on successful MHPSS programs in other conflict-affected regions, such as the Problem Management Plus (PM+) intervention in Pakistan and Kenya [11], Parenting for Lifelong Health (PLH-Teens) in South Africa [12], and community-based psychosocial programs in Sierra Leone [8]. These examples informed the adaptation of evidence-based interventions to Ukraine's cultural and conflict-specific context.

IMPLEMENTATION RESOURCES

Standardized tools, such as facilitator manuals, Psychological First Aid protocols, and digital referral hub frameworks, were reviewed to support model operationalization. Community Resilience Centres (CRCs) were identified as existing infrastructure for localized service delivery, drawing on Ukraine's national resilience-building framework.

MODEL DESIGN

The MHPSS ecosystem model was developed using five design principles: localization, evidence-informed adaptability, do-no-harm, multisectoral alignment, and continuous learning. These principles guided the integration of child-facing interventions, family supports, school/community environments, service-delivery infrastructure, and policy/governance layers, as outlined in the IASC framework [4].

IMPLEMENTATION PLANNING

An 11-stage implementation plan was formulated, incorporating adaptation of international frameworks, governance establishment, social environment strengthening, stakeholder co-planning, capacity building, database/certification systems, supportive supervision, quality assurance, social impact amplification, sustainability planning, and policy integration. This plan was informed by implementation science frameworks, such as the Exploration, Preparation, Implementation, and Sustainment (EPIS) model.

This methodology leveraged theoretical synthesis, contextual analysis, and practical adaptation of global MHPSS practices to propose a scalable, culturally relevant model.

RESULTS

THE PROPOSED CHILD-CENTRED MULTILAYERED MHPSS ECO-SYSTEM MODEL

THEORETICAL RATIONALE

Model development was guided by two complementary knowledge streams. First, the IASC intervention pyramid provides a normative architecture for organising supports from basic services to specialised care [4]. Second, Bronfenbrenner's ecological systems theory frames children's wellbeing as the sum of nested, interacting social environments [6]. Synthesizing these perspectives yields a multilayered design that addresses both individual symptom relief and the social determinants of mental health [7].

DESIGN PRINCIPLES

Five cross-cutting principles informed every design choice:

- Localization and ownership – at least 80 % of frontline roles are filled by community residents to enhance cultural fit and sustainability.
- Evidence-informed adaptability – only interventions with demonstrated effectiveness in low-resource or conflict settings are included, but all are culturally co-designed before rollout [8].
- Do-no-harm and safeguarding – the model embeds child-protection standards consistent with WHO/UNICEF Guidance on Mental Health & Child Protection (https://www.who.int/publications/i/item/9789240100374).
- Multisectoral alignment – education, health, social protection, and media sectors are formally linked through an oblast-level coordination task-force [13].
- Learning orientation – continuous quality-improvement cycles are built in from inception, using real-time dashboards and quarterly After-Action Reviews [14].

At its core, the model is an eco-system centred on the child and surrounded by four concentric support layers:

- ✓ Child-facing interventions (Layer 2–3) – psychosocial curricula that build emotion-regulation and coping skills [11].
- ✓ Family supports (Layer 2) – e.g., six-session Parenting for Lifelong Health (PLH-Teens) groups to enhance caregiver efficacy and reduce harsh discipline [12].
- ✓ School & community environment (Layer 1–2) – integrated safe-space classrooms, teacher social-emotional learning (SEL) training, and community resilience forums [3].
- ✓ Service-delivery infrastructure (Layers 1-4) – a digital referral hub links primary-health clinics, social-services offices, and regional mental-health centres, ensuring two-way feedback and rapid triage [15].

Policy & governance layer – a region MHPSS coordination task-force, chaired by the Regional Administration, meets quarterly to review dashboards and remove systemic bottlenecks [5].

INTENDED PATHWAYS OF CHANGE

Drawing on realist program theory [16], the model posits that when culturally adapted, layered interventions are delivered with fidelity by trusted local actors, four mechanisms are triggered:

1. Safety and predictability – child-friendly routines counteract toxic stress [17].
2. Self-efficacy and skills – practice-based curricula improve emotion regulation and problem-solving.
3. Social connectedness – peer and caregiver bonding buffers adversity [8].
4. Timely specialist care – digital triage shortens delays for severe presentations [15].

These mechanisms, operating within enabling contexts (e.g., supportive schools, functioning referral pathways), are expected to reduce PTSD, anxiety, and depression symptoms and to strengthen resilience and prosocial behaviour.

MODEL FOR IMPLEMENTING CHILD-CENTRED MHPSS ECO-SYSTEM IN UKRAINE

STRATEGIC AIMS

The implementation model pursues four mutually reinforcing aims:

- ✓ Multisectoral cohesion. To broker durable cooperation among education, health, social-protection, and youth-justice actors at community level, thereby aligning MHPSS investments with locally verified needs [4].
- ✓ Cultural localization. To adapt the internationally validated movement-based psychosocial approach and its underlying child-friendly, health-responsive values to the linguistic and cultural texture of Ukrainian communities.
- ✓ Population-wide mental-health literacy. To equip caregivers, teachers, and adolescents with basic knowledge of stress reactions and help-seeking pathways, consistent with WHO's "whole-of-society" mental-health promotion agenda [10].
- ✓ Sustainable wellbeing gains. To ensure that sessions yield enduring gains in social-emotional competences while catalyzing youth-led micro-initiatives that expand the ecosystem of MHPSS supports [12] .

SEQUENTIAL IMPLEMENTATION STAGES

The model decomposes into eleven inter-locking stages (Fig. 1). Although depicted linearly, feedback loops enable recursive adjustments based on monitoring data and community feedback.

Children in conflict-affected settings face profound psychological challenges, including exposure to violence, displacement, and loss, which elevate risks of post-traumatic stress disorder (PTSD), anxiety, and depression. To address these needs holistically, this implementation plan outlines an 11-stage process for establishing a multilayered MHPSS ecosystem. Grounded in the IASC intervention pyramid and Bronfenbrenner's ecological systems theory, this universal model integrates evidence-based practices with localized strategies to foster resilience and recovery among children aged 6-17 years in any humanitarian crisis. The plan emphasizes multisectoral coordination, cultural adaptability, and sustainability to ensure scalability across diverse contexts [18].

STAGE I: Adaptation of international MHPSS framework

The first stage focuses on tailoring an internationally validated MHPSS framework to the cultural and contextual realities of the target population. A multidisciplinary team, comprising psychologists, linguists, and community representatives, translates program materials such as

Fig. 1. 11-step MHPSS implementation flow

Picture taken by the authors

facilitator manuals and session plans into the local language(s). Rapid prototyping follows, with small-scale pilots conducted in diverse community settings (e.g., schools or community centers) to identify barriers, such as cultural misalignments or trauma-related sensitivities. Feedback from these pilots informs iterative refinements, overseen by a technical advisory group that ensures adaptations preserve the framework's evidence-based core while enhancing its relevance. This process, rooted in human-centered design principles, ensures the program resonates with local values and lived experiences, a critical factor for uptake in conflict-affected communities.

STAGE II: Establishing managerial structure

Effective governance is essential for coordinating a complex MHPSS ecosystem. This stage establishes a centralized coordination body, embedded within a relevant national or regional authority (e.g., health or education ministry), to provide strategic oversight. At the local level, district coordinators are appointed to manage implementation, with clearly defined roles and decision-making authority outlined in formal terms of reference. This hierarchical structure facilitates alignment across sectors health, education, social services, and community-based initiatives while mitigating risks of fragmentation. By fostering accountability and streamlined communication, this stage lays the foundation for a cohesive response, drawing on implementation science principles to enhance operational efficiency.

STAGE III: Strengthening social environment

Creating a supportive social context is pivotal for normalizing mental health support and reducing stigma. This stage launches a multimedia campaign to promote the MHPSS ecosystem's core values, utilizing accessible platforms such as radio, social media, and community posters. Narrative-driven content, developed with the consent of children and families, showcases stories of resilience and recovery to foster community buy-in. Evidence highlights that storytelling outperforms informational approaches in shifting attitudes toward mental health, making this campaign a powerful tool for enhancing help-seeking behavior. By embedding mental health literacy within the social fabric, this stage cultivates an enabling environment for program success.

STAGE IV: Commitment and co-planning with local partners

Collaboration with local stakeholders ensures the ecosystem's operational viability. Community-based organizations, educational institutions, and local authorities formalize their involvement through agreements that outline contributions, such as staff time or venue access. Joint planning teams conduct participatory needs assessments, employing methods like focus groups, key informant interviews, and participatory mapping to align program content with context-specific stressors (e.g., displacement or family separation). This co-design process fosters ownership among partners, enhancing cultural fit and sustainability. By grounding the program in community priorities, this stage strengthens its relevance and feasibility in resource-constrained settings.

STAGE V: Capacity building activities

A skilled workforce is the backbone of effective MHPSS delivery. This stage implements a two-layered training model for facilitators, including frontline workers such as teachers, social workers, or community volunteers. An initial multi-day training introduces core competencies, such as Psychological First Aid and group facilitation techniques, followed by a refresher course after several months of field experience to deepen trauma-informed practices. Regular supervision, delivered through secure virtual platforms or in-person sessions, provides ongoing support, addressing challenges like burnout or complex case management. This structured capacity-building approach, informed by WHO guidelines, equips local actors to deliver interventions with fidelity, bridging workforce gaps common in conflict-affected areas.

STAGE VI: Database and certification system

Standardizing service quality requires robust tracking and accountability mechanisms. This stage establishes a centralized database to register facilitators, logging metrics such as training completion, supervision hours, and session delivery. Certification, valid for a defined period (e.g., 12 months), is granted upon meeting performance thresholds, with renewal tied to continuous professional development. This system professionalizes the workforce while enabling real-time monitoring of program reach and fidelity. By aligning with global standards for competency maintenance, this stage ensures consistent quality across diverse implementation sites, a critical factor for scalability.

STAGE VII: Supportive supervision and mentorship mechanism

Sustained facilitator competence hinges on ongoing mentorship. This stage integrates regular group supervision with on-the-job coaching, where experienced mentors conduct field visits to provide real-time feedback and troubleshoot challenges, such as managing group dynamics or adapting to sudden disruptions. This hands-on support, informed by realist evaluations of MHPSS programs, enhances facilitators' confidence and effectiveness, particularly in volatile settings. By embedding mentorship within routine workflows, this stage safeguards intervention quality while fostering a culture of continuous improvement among frontline workers.

STAGE VIII: Research and quality assurance

A commitment to evidence-based adaptation drives this stage. The ecosystem incorporates a developmental-evaluation framework, collecting routine data to assess outcomes (e.g., changes in children's emotional well-being) through tools like standardized symptom scales. Qualitative methods, such as focus groups or realist interviews, explore context-specific mechanisms of change, illuminating what works and why. These insights feed into iterative program refinements, ensuring responsiveness to emerging needs. By balancing immediate service delivery with long-term learning, this stage aligns with implementation science principles, positioning the ecosystem as a model for rigorous humanitarian intervention.

STAGE IX: Amplifying social impact

Maximizing the ecosystem's influence requires strategic dissemination. This stage produces accessible outputs such as podcasts, infographics, or video testimonials to share success stories with communities, policymakers, and global stakeholders. These materials, developed with participant consent, highlight the program's impact on children, families, and systems, reinforcing social proof and reducing mental health stigma. Annual dissemination events, such as community forums or policy briefings, further amplify reach, encouraging broader adoption. By leveraging diverse communication channels, this stage extends the ecosystem's ripple effects, fostering a culture of psychosocial resilience.

STAGE X: Ensuring sustainability

Long-term viability depends on embedding the ecosystem within local systems. This stage establishes peer-learning networks, such as online forums or in-person communities of practice, where facilitators exchange innovations and solutions. Standardized manuals and offline-accessible training resources (e.g., videos or printed guides) ensure continuity in areas with limited connectivity. Financial sustainability is pursued through blended funding models, combining local government budgets, donor contributions, and community resources. By transitioning responsibilities to local actors and institutionalizing resource-sharing, this stage reduces reliance on external support, ensuring the ecosystem's endurance.

STAGE XI: Integration into policy frameworks

The final stage secures the ecosystem's scalability through policy integration. Advocacy efforts target the inclusion of MHPSS components in national or regional frameworks, such as education or health curricula, unlocking public funding and regulatory support. Regular coordination mechanisms, such as intersectoral task forces, are institutionalized to sustain multisectoral collaboration. This alignment with broader policy priorities such as global mental health agendas or post-conflict recovery plans ensures the ecosystem's relevance and fiscal viability. By embedding MHPSS within governance structures, this stage transforms the program into a permanent feature of the humanitarian landscape.

INTEGRATION OF COMMUNITY RESILIENCE CENTRES (CRCS) INTO THE MHPSS ECOSYSTEM

A pivotal aspect of operationalizing the proposed multilayered Mental Health and Psychosocial Support (MHPSS) ecosystem is the strategic collaboration with local governmental initiatives, particularly the Community Resilience Centres (CRCs). These centres, embedded within Ukraine's national resilience-building framework, offer a pre-existing infrastructure that can be harnessed to deliver child-centered MHPSS services directly within communities. Functioning as localized hubs for psychosocial support, CRCs present a unique opportunity to integrate evidence-based interventions into community settings while fostering multisectoral coordination. This collaboration aligns seamlessly with the ecosystem's core principles of localization, sustainability, and community ownership, ensuring that mental health services are both accessible and culturally relevant.

To illustrate this integration, a structured framework for cooperation with the CRCs has been developed, outlining seven key interventions and their corresponding implementation plans. These interventions are designed to position the CRCs as central nodes within the MHPSS ecosystem, enabling the delivery of tailored, child-centered services while simultaneously enhancing overall community resilience. The framework, presented in the following table, includes critical components such as partnership building, needs assessment, capacity development, resource allocation, dissemination, and sustainability efforts. Each intervention is strategically aligned with the ecosystem's overarching goals, ensuring that CRCs contribute to both immediate psychosocial relief and long-term systemic transformation.

By embedding MHPSS services within the CRCs, the ecosystem enhances service accessibility and promotes a community-driven approach to mental health. Equipped with appropriate resources and training, CRCs can serve as catalysts for broader social impact, fostering a health-responsive society where the mental well-being of children is prioritized. This integration also bolsters the ecosystem's sustainability objectives, leveraging the CRCs' existing ties to local governance structures to reduce dependence on external support and ensure the continuity of services over time.

The Table 1 that follows provides a detailed breakdown of the cooperation model, outlining each key intervention alongside its implementation plan. This framework serves as a practical roadmap for operationalizing the MHPSS ecosystem at the community level, ensuring that child-centered services are delivered effectively, efficiently, and sustainably.

Table 1. Cooperation with Governmental Initiative Community Resilience Centre (CRC) on developing child-centred MHPSS Eco-system in Ukraine (Model)

Key Intervention	Implementation Plan-guidance
Partnership Building activities and elaborating Policies	Establishing Agreements (to establish and ensure multidisciplinary cooperation with local stakeholders)
Review and Assessments	Conducting Needs Assessments and Capacity assessments (to identify concrete needs and capacities of Community, local stakeholders and beneficiaries; to design MHPSS interventions based on these results)
Equipping	To equip CRCs with Kits, materials, etc
	To develop/launch Community MHPSS Centre: e.g., playground for child-centered MHPSS activities
Building Capacities	To organize full cycle of Capacity Building activities on MHPSS Programs (trainings, supportive mentorship) for CRC staff and Community actors
	Widening of child-centered MHPSS services spectrum
Resource for Community Development	MHPSS Fund (to support children initiatives in the Community)
	Recreational/educational Camps for children
	Peer support groups for teachers, caregivers …
Multiplying effect and Dissemination	LL workshops for Regional MHPSS workers (from CRCs)
	Regional Events and Blog on regional Media
	Support of Regional Coordinator' MHPSS activities
Sustainability and Innovations	Continuity of MHPSS Programs
	Research on impact of MHPSS activities on children and society
	Innovation Park on Health-responsive Society and Economy

Source: compiled by the authors of this study

This 11-stage implementation plan provides a comprehensive, evidence-informed roadmap for delivering MHPSS to conflict-affected children in any humanitarian context. By integrating cultural adaptation, robust governance, community engagement, and policy alignment, it addresses immediate psychological needs while strengthening systemic resilience. Its universal design, informed by global best practices and implementation science, ensures adaptability across diverse settings, offering a replicable blueprint for fostering child well-being in the face of adversity.

DISCUSSION

The proposed multilayered MHPSS ecosystem offers a comprehensive, evidence-informed framework to address the psychosocial needs of children affected by conflict. By synthesizing the Inter-Agency Standing Committee (IASC) pyramid model [4] with Bronfenbrenner's ecological systems theory [6], the model transcends traditional siloed interventions, embedding child-centered support within a dynamic network of family, school, service, and policy systems. This holistic approach responds to the complex interplay of conflict-induced stressors displacement, violence, and loss while fostering resilience through culturally adapted, multisectoral strategies. The following discussion critically examines the model's contributions, strengths, limitations, and implications for humanitarian mental health practice, positioning it as a scalable blueprint for global conflict-affected settings [19, 20].

The MHPSS ecosystem advances the field of humanitarian mental health by operationalizing a systems-based approach that bridges immediate psychosocial relief with long-term recovery. Unlike conventional interventions, which often prioritize clinical symptom reduction, this model integrates tiered supports from community-based safe spaces to specialized care within a cohesive infrastructure. This alignment with the IASC pyramid ensures that children with varying needs, from mild distress to severe PTSD, receive appropriate interventions [4]. Furthermore, the incorporation of Bronfenbrenner's ecological systems theory [6] acknowledges the nested influences shaping children's well-being, addressing not only individual trauma but also relational and systemic factors, such as caregiver efficacy and service accessibility.

The model's emphasis on localization evident in its cultural co-design, community-led delivery, and integration into local governance addresses a persistent critique of humanitarian interventions: their reliance on external expertise [8]. By prioritizing local actors, the ecosystem enhances cultural resonance and sustainability, aligning with global calls for decolonized mental health programming [21]. Additionally, the use of digital tools, such as referral hubs and real-time dashboards, introduces technological innovation to resource-constrained settings, improving triage efficiency and data-driven adaptation [15]. These contributions position the model as a testbed for implementation science, offering transferable lessons for other post-conflict contexts.

By incorporating validated components, such as trans-diagnostic coping modules and caregiver skill-building programs [11, 12], the model maximizes therapeutic fidelity while allowing for cultural adaptation. Second, the staged implementation plan, guided by the Exploration, Preparation, Implementation, and Sustainment (EPIS) framework [22], ensures systematic rollout with built-in feedback loops. This iterative approach mitigates risks of operational failure, a common challenge in volatile humanitarian environments.

Third, the model's multisectoral coordination facilitated by intersectoral task forces and blended financing addresses the fragmentation that often undermines MHPSS efforts [4]. By aligning education, health, and social services, the ecosystem optimizes resource allocation and fosters synergy across sectors. Finally, the commitment to continuous learning, through developmental evaluation and real-time monitoring, ensures responsiveness to emerging needs [21]. The integration of qualitative realist methods alongside quantitative outcome measures provides a nuanced understanding of context-mechanism-outcome configurations, enhancing the model's adaptability and external validity [16].

The MHPSS ecosystem carries significant implications for humanitarian practice and policy. For practitioners, the model underscores the value of layered interventions that combine child-focused curricula with family and community supports. Programs like Parenting for Lifelong Health [12] demonstrate that strengthening caregiver-child relationships can amplify clinical gains, creating a buffering milieu that sustains resilience. At the policy level, the model's alignment with global frameworks, such as WHO's Mental Health Gap Action Programme and the European Framework for Action on Mental Health [10], facilitates advocacy for increased MHPSS investment. By demonstrating cost-effectiveness through metrics like disability-adjusted life years (DALYs) averted, the ecosystem provides policymakers with a compelling case for integrating psychosocial support into national health and education systems [23]. The proposed blended financing model, leveraging government budgets and community resources, further enhances fiscal sustainability, addressing the "pilot-and-abandon" cycle that plagues many humanitarian initiatives [14].

Future research and practice should address the model's limitations through three key strands. First, cluster-randomized or hybrid type-1 trials are needed to establish robust effectiveness and cost-utility estimates, particularly in diverse conflict settings [23]. Such studies would strengthen the evidence base for national scale-up and global replication. Second, longitudinal cohorts extending beyond 24 months are essential to assess whether early symptom reductions translate into educational, social, and economic dividends an evidence gap noted in global reviews [7]. Third, adaptive studies exploring digital micro-interventions and disability-inclusive adaptations could expand the model's reach, ensuring equity for marginalized groups [24].

Technological innovation offers additional opportunities. Advances in telepsychiatry and mobile-based MHPSS tools could enhance accessibility in disrupted areas, provided they are paired with offline alternatives to mitigate connectivity challenges [15]. Furthermore, integrating artificial intelligence into monitoring systems could refine predictive analytics, enabling earlier identification of high-risk cases. These innovations, however, must be balanced with ethical considerations, such as data privacy and cultural sensitivity, to uphold the model's do-no-harm principle [4].

CONCLUSIONS

The multilayered MHPSS ecosystem represents a paradigm shift in addressing the psychosocial toll of conflict on children. By weaving together evidence-based interventions, multisectoral collaboration, and continuous learning, it offers a scalable, sustainable response to one of the most pressing challenges in humanitarian mental health. While limitations in causal inference and contextual volatility warrant caution, the model's strengths its ecological design, localization, and policy alignment position it as a transformative framework. With further research and adaptation, this ecosystem has the potential to not only mitigate immediate distress but also foster resilient, health-responsive communities, serving as a beacon for global efforts to support children in crisis.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Effect of winter swimming on the cardiovascular system: adaptive mechanisms and potential hazards

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ABSTRACT

Aim: To investigate the impact of winter swimming on the cardiovascular system.

Material and methods: A group of 30 adult subjects underwent an ECG Holter examination twice (during the winter swimming season and after its end). The following parameters available in the results of the ECG Holter examination were analysed: HR, VE and SVE beats, QT and heart rate variability parameters: SDNN, SDANN, pNN50, RMSSD and Tiangular index.

Results: In subjects over 45 years of age, higher values of the SDNN and SDANN parameters during the winter period may suggest a positive impact of winter swimming on the cardiovascular system. The QTc max parameter showed higher values in males during the winter study, whereas higher values were recorded in females during the summer study. As the frequency of winter swimming episodes increased, higher HR min values and lower SDNN and SDANN values were observed.

Conclusions: In healthy subjects under 45 years of age, winter swimming appears to have no significant impact on the heart rate variability parameters, whereas in individuals over 45 years of age, it shows a statistically significant positive impact. Winter swimming practised more frequently than once a week may reduce the autonomous reserve and increase cardiovascular risk. Further research with a larger sample size is necessary to better understand the effects of winter swimming on the cardiovascular system.

KEY WORDS: heart rate variability, cardiovascular system, autonomic nervous system, ECG Holter, winter swimming

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INTRODUCTION

Winter swimming is becoming an increasingly popular winter activity in Poland. It involves the immersion of the body or a short-term swim in cold water in a lake, sea, river or other water body. The history of winter swimming in Poland dates back to the 16th century, when Józef Struś, the court physician of King Sigismund II Augustus, promoted treatment with cold baths. At the same time, in 1578, in his treatise "Cieplice", doctor Wojciech Oczko included bathing recipes as well as indications and contraindications for their application. There are many reports on the effects of this activity on the human body [1]. Many of them, however, offer weak evidence in the form of observational studies and rely on case reports or subjective opinions [2]. P. Huttunen et al. demonstrated, in a questionnaire survey, that winter swimming improves general well-being, boosts energy and alleviates the symptoms in the course of chronic diseases [3]. The effects of winter swimming on, e.g., morphological and biochemical blood properties [4, 5], oxidative stress indices in healthy males [6], the lipid profile and selected adipokines [7], mental health [8] and the concentrations of ACTH, beta-endorphins, cortisol, catecholamines and cytokines [9] have already been demonstrated in the past. In the field of cardiology, publications have already appeared to suggest that cold water baths lower arterial blood pressure [10, 11] and may contribute to a reduction in the release of cardiac troponins [12]. The main objective of the present study is to expand knowledge on the effects of winter swimming on heart function through an analysis of heart efficiency parameters based on the results of examinations carried out on winter swimmers with a 24-hour ECG Holter examination.

AIM

In response to the rising popularity of winter swimming in Poland - particularly in cities with access to natural bodies of water - our aim is to investigate how this activity affects the cardiovascular system.

MATERIALS AND METHODS

RESEARCH METHODOLOGY

A group of 30 adult subjects underwent an ECG Holter examination twice. Measurements were taken at two time points: during the winter swimming season (approximately two days after a winter swimming episode) and two months after the season had ended. The following parameters available in the results of the ECG Holter examination were analysed: HR min, HR max, average HR, VE beats (ventricular

ectopic beats), SVE beats (supraventricular ectopic beats), SDNN (standard deviation [ms] of all NN intervals), SDANN (standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording [ms]), SDNN index (mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording [ms]), pNN50 (percentage of successive RR intervals that differ by more than 50 ms [%]), RMSSD (square root of the sum of the squares of differences between adjacent NN intervals [ms]), Triangular index (integral of the density of the RR interval histogram divided by its height [ms]), min QT [ms], QT max [ms], average QT [ms], min QTc [ms], max QTc [ms] and average QTc [ms].

In January 2022, the recruitment of a representative study group was initiated by visiting meetings at winter swimmers' clubs in the city of Olsztyn and posting information about the research project on social media. The qualification criteria for the study were as follows:

- at least two full winter swimming seasons completed prior to the study;
- winter swimming practised at least two times a month during the winter swimming period;
- the patient's statement of the absence of any cardiovascular diseases.

Before the commencement of the study, each participant was asked to complete a short questionnaire about their state of health, medication taken, the use of stimulants/drugs, and vaccinations. Of the 30 participants included in the study, three had a diagnosis of hypertension, three had hypothyroidism, and one had depression. All conditions were well controlled with pharmacological treatment. Throughout the entire study period, no participant reported the onset of a new illness or an exacerbation of any pre-existing chronic condition. During the January-March period (study I), 30 individuals practising regular winter baths during the winter swimming season were examined. During the May-June period (study II), the same group of 30 individuals was re-examined after the end of the winter swimming season. In each subject, the ECG Holter examination lasted for 24 hours. During the examination, the echocardiographic recordings from the ECG Holter were entered into the Mortara IT system on an ongoing basis.

STATISTICAL ANALYSIS

The baseline characteristics include the basic results of the ECG Holter examination, along with heart rate variability indices, performed twice: in winter (I) during the winter swimming season, and outside the season, i.e. in the summer (II). The baseline characteristics are presented as medians and interquartile ranges. In order to compare the results of both studies, a non-parametric Wilcoxon matched-pair test was applied.

The study population was then divided into subgroups based on the age, sex and frequency of winter swimming episodes. The statistical differences between the results of the two study rounds (II-I), with the division by age and sex taken into account, are presented using the Mann-Whitney U test with continuity correction, whereas the Kruskal-Wallis test was applied for the frequency of winter swimming episodes.

The two-sided alpha level <0.05 was considered to be statistically significant. All data analyses were carried out using the Statistica software ver. 13.

ETHICS STATEMENT

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Warmia and Mazury in Olsztyn. Each patient provided written informed consent to participate in the study.

RESULTS

A brief description of the study group according to:

- (a) sex: 19 females, 11 males;
- (b) age:
- 21-40 – 7 individuals,
- 41-60 – 16 individuals,
- >61 – 7 individuals;
- (c) frequency of winter swimming:
- >once a week – 7 individuals
- Once a week – 18 individuals
- 2-3 times a month – 5 individuals

Initially, the study results obtained in winter (I) and in summer (II) were compared using a non-parametric Wilcoxon matched-pairs test, which did not show statistically significant differences. The ECG Holter examination, performed twice on a group of 30 adult subjects (during and after the winter swimming season), showed no significant effects of the actual winter swimming activity on any of the heart function parameters measured in this examination. Therefore, when comparing the entire population subjected to the examination twice, it can be concluded that winter swimming does not generally affect cardiac performance.

Additional statistical analyses were then carried out to check whether the differences in the results would be visible if the previously separated specific subgroups of subjects were taken into account. The following tables relating to the subgroups only show the statistically significant ($p<0.05$) parameters.

The first criterion for the division into subgroups was the patient's age. A comparison of the differences between the results obtained in the two studies (I and II), in relation to the subgroups separated based on sex using the Mann-Whitney U test with continuity correction, revealed that the SDNN and SDANN parameters exhibit statistically significant differences. In subjects under 45 years of age, since the difference between SDNN and SDANN medians (II-I) was positive, these parameters had higher values in the summer study (II) than in the winter study (I). In contrast, in subjects over 45 years of age, since the difference between SDNN and SDANN medians was negative, higher values were noted more frequently in the winter study during the winter swimming period (I) than outside of it (II).

Another criterion for the division was the patient's sex. In this case, the Mann-Whitney U test with continuity correction was also used for the analysis. The parameter that differed at the statistical significance level appeared

to be QTc max., which indicated higher values in males during an examination in winter (I), whereas in females during an examination in summer (II).

The final criterion was the frequency of winter swimming in the population under study. Within this criterion, the subjects were divided into three subgroups: those practising winter swimming less frequently than once a week, once a week, and more frequently than once a week. The comparison analysis was carried out between each of the selected subgroups using a Kruskal-Wallis test. A parameter indicating statistical significance was the HR min parameter, which showed that the median difference was lower with a higher frequency of winter swimming episodes reported in the questionnaire survey. In the groups practising winter swimming more frequently than once a week and less frequently than once a week, statistical significance was also demonstrated by the SDNN and SDANN parameters, with difference values being higher in subjects who practised winter swimming less frequently.

DISCUSSION

For many years, there has been an ongoing discussion as to whether winter swimming (voluntary cold water immersion) is beneficial or harmful to health [13]. Many publications have addressed the positive effects of regular winter swimming episodes on the function of various systems. By stimulating the immune system through increased production of leukocytes and anti-inflammatory cytokines, cold baths can reduce susceptibility to upper respiratory tract infections [14, 15]. Winter swimming can also be used to support post-traumatic rehabilitation, as it accelerates muscle regeneration after physical exertion by reducing inflammation and muscle soreness [16].

In addition, exposure to cold increases adiponectin production in the adipose tissue, which contributes to better calorie burning and the regulation of blood glucose levels. This offers the opportunity to help combat both obesity and diabetes mellitus [17-19].

Thanks to the activation of the sympathetic system, winter swimming increases the secretion of noradrenaline, which reduces symptoms of depression and elevates mood [20]. It was also demonstrated that the contribution of cold improves neuroplasticity and reduces the sensation of pain through endogenous opioids and other neuromodulators [21].

Analysis of the effects of winter swimming on the function of various systems in humans revealed that the cardiovascular system appears to be problematic and complex. Assuming that there is reliable scientific evidence to support the aforementioned reports, the quantity and quality of the evidence is mediocre when it comes to the function of the heart. As early as 1980, Zenner et al. reported in the Lancet journal that winter swimming increases arterial blood pressure, mainly through exposure to cold air prior to immersion [22]. These reports have been confirmed by a relatively new study that analysed the regeneration strategy after intensive, intermittent exercises, which involve immersion in cold water. In minutes 6 and 20 after physical exertion, the systolic and diastolic arterial blood pressure was significantly higher in individuals who were recovering by immersing themselves in cold water than in those who were recovering by resting statically. In minutes 6 and 20 of the study, the heart rates of the individuals immersed were also markedly lower, indicating that immersion in cold water lowers the heart rate [23]. There are also reports that contradict the above facts. A study by Srámek et al. demonstrated that immersion in water at a temperature of 14°C lowers the heart rate while increasing, rather than decreasing, the systolic and diastolic arterial blood pressure [24]. These discrepancies may indicate that the mechanisms of cold water's effects on the cardiovascular system are not fully understood. It is the hormonal response of the adrenal glands when immersed in cold water that has a direct impact on the reaction of the cardiovascular system. It was demonstrated that an increase in adrenaline secretion by the adrenal glands shows a certain adaptation to the frequency of winter swimming episodes [25]. Therefore, regular winter swimming episodes result in a lower increase in noradrenaline, as compared with a one-off immersion in cold water, which may suggest that the cardiovascular response differs in winter swimmers depending on the frequency of winter swimming episodes. In a questionnaire survey, Huan-Min Gao et al. demonstrated that the risk of cardiovascular diseases of the heart and brain after 20 years in the group of individuals swimming in cold seawater was higher than in the control group not involved in this activity. This result suggests that swimming in cold seawater may pose a health hazard [26]. Due to the lack of data on the direct effects of winter swimming on the function of the heart, measured by electrocardiographic analysis, the authors decided to conduct the current study using the Holter ECG examination.

The present study, which investigated the effects of winter swimming on heart rate parameters, showed no significant differences across the entire study group. The lack of statistically significant differences between the winter swimming season (I) and the summer period (II) indicates the negligible effect of this activity on cardiac parameters as measured by the Holter method (Table 1).

Analysis of the subgroups according to age revealed statistically significant differences in the SDNN and SDANN parameters, which are heart rate variability (HRV) indices. In subjects over 45 years of age, higher values of the same parameters during the winter period (I) may suggest a positive impact of winter swimming on the cardiovascular system as well as increased activation of the parasympathetic system in this age group. This effect was not observed in individuals under 45 years of age, for whom the SDNN and SDANN values were higher during the summer period (II) (Table 2).

The study noted differences in the QTc results between sexes (Table 3). Higher QTc values were noted for males in the winter period (I), whereas higher values were noted for females in the summer period (II). This diversity in results can be influenced by both hormonal differences and other biological factors affecting the electrical function of the heart.

When considering the relationship between the frequency of winter swimming and cardiac parameters, it was shown that a higher frequency of winter swimming was associated with an increase in minimum heart rate- HR min (Table 4 and Table 5). This may be attributed to physiological adaptations

Table 1. Comparison of the results of the analysis of the ECG Holter parameters carried out in winter (I) and in summer (II) in all winter swimmers qualified for the study

Descriptive statistics (database)	Study I			Study II			p
	median	IQR (25-75%)		median	IQR (25-75%)		
HR min	46.5	42	50	45.5	41	51	0.614
HR max	134	128	151	139	126	157	0.733
Average HR	72	66	77	74.5	65	78	0.524
VE beats	0	0	5	0	0	2	0.141
Tachycardias (ventricular)	0	0	0	0	0	0	0.180
SVE beats	26	6	104	35	2	75	0.480
Tachycardias (supraventricular)	0	0	2	0	0	2	0.938
pNN50 [%]	6.5	2	16	6	1	15	0.097
RMSSD [ms]	32	24	49	32.5	23	50	0.466
SDNN [ms]	147	119	166	141.5	114	178	0,837
SDNN index [ms]	61.5	48	77	59	46	74	0.703
SDANN [ms]	138.5	113	153	121.5	106	160	0.280
Tiangular index [ms]	39	32	51	39.5	30	51	0.829
Min. QT [ms]	312.5	298	330	313.5	281	333	0.574
QT max [ms]	441	411	465	430.5	415	471	0.616
Average QT [ms]	384	365	404	379	366	411	0.959
Min. QTc [ms]	379.5	362	395	380.5	362	401	0.329
QTc max [ms]	486.5	464	513	478	458	515	0.837
Average QTc [ms]	416	403	438	422	410	439	0.829

Source: Own materials

Table 2. Statistically significant differences by comparing parameters in the subgroup of individuals over and under 45 years of age

Age	<45			≥45			p
	median	IQR (25-75%)		median	IQR (25-75%)		
SDNN [ms]	8	0	32	-14.5	-28	5	0.042
SDNN index [ms]	1	-2	4	0	-6.5	3.5	0.546
SDANN [ms]	7.5	-6	26	-18	-33.5	-3.5	0.014

Source: Own materials

Table 3. Statistically significant differences in the parameters of male and female winter swimmers

Sex	Men			Women			p
	median	IQR (25-75%)		median	IQR (25-75%)		
VE beats	0	-15	0	0	-1	2	0.077
QTc max [ms]	-9	-32	10	12	4	37	0.028

Source: Own materials

Table 4. Comparison of HR min in individuals practising winter swimming once a week and those practising less frequently than once a week.

Frequency of ice swimming	Once a week			Less than once a week			p
	median	IQR (25-75%)		median	IQR (25-75%)		
HR min	0.5	-3	4	-7	-8	-3	0.029

Source: Own materials

Table 5. Comparison of the ECG parameters among the subjects practising winter swimming more frequently and less frequently than once a week

Frequency of ice swimming	More often than once a week			Less than once a week			
	median	IQR (25-75%)		median	IQR (25-75%)		p
HR min	1	-2	3	-7	-8	-3	0.038
HR max	-5	-13	7	13	-10	15	1
Average HR	1	-4	3	1	-1	2	1
VE beats	-2	-9	0	0	0	26	0.352
Tachycardias (ventricular)	0	0	0	0	0	0	1
SVE beats	-12	-25	75	54	-12	63	1
Tachycardias (supraventricular)	0	-1	3	2	0	2	1
pNN50 [%]	0	-2	0	-1	-4	1	1
RMSSD [ms]	-1	-6	-1	3	-3	5	1
SDNN [ms]	-8	-39	-4	40	16	65	0.039
SDNN index [ms]	-1	-4	2	4	1	6	0.230
SDANN [ms]	-14	-39	-6	39	12	81	0.043

Source: Own materials

of the cardiovascular system to regular exposure to cold. Such adaptations can include stimulation of the sympathetic system, increased metabolism and thermogenesis, or repeated activation of the hypothalamic-pituitary-adrenal (HPA) axis. These factors lead to elevated levels of catecholamines, i.e. adrenaline and noradrenaline, which, in turn, affects the HR min, especially in short-term analyses during the winter swimming season. The relationship of the effect of cold through immersion on the direct and reflex excitability of autonomic centres was investigated as early as 1954 by Koella, Ballin and Gellhorn, and is analogous to the conclusions drawn in the present study [27].

The lower SDNN and SDANN values in individuals practising winter swimming more frequently than once a week may be due to the autonomic system adjusting to the regular stress associated with exposure to cold (Table 5). This activity may lead to increased parasympathetic activity during rest or in the summer season, as well as a reduction in heart rate variability, as reflected by lowered SDNN and SDANN values. Reduced heart rate variability (HRV) may be indicative of negative implications for cardiovascular health. This reduction reflects the limited ability of the ANS to dynamically regulate the heart's activity in response to physiological and environmental stressors. It is characterised by a predominance of the sympathetic over the parasympathetic system's activity (higher HR min and lower SDNN and SDANN values), which may increase the risk of cardiovascular diseases, including hypertension or arrhythmia [28, 29].

Although there are many scientific articles on winter swimming that indicate the benefits discussed above, its effects on HRV in the case of intensive practice require further research.

LIMITATIONS

This study has several limitations that should be considered when interpreting the results. First and foremost, the absence of a control group of individuals not engaged in winter swimming could provide us with additional information for the study. Another limitation is the relatively small sample size (n=30), which affects the statistical power of the analysis and restricts the generalizability of the findings. Additionally, all measurements were conducted within a single year, which prevents the assessment of long-term effects of winter swimming and interannual variability. Future studies should include a control group, a larger number of participants, and long-term follow-up to better understand the impact of regular cold-water immersion on cardiovascular health.

CONCLUSIONS

The findings of the study suggest that the physiological response to winter swimming is highly individualized and influenced by factors such as age, sex, and the frequency of exposure to cold. While certain adaptations to regular cold-water immersion may be beneficial, others may indicate a strain on the autonomic nervous system. Therefore, winter swimming cannot be universally classified as either neutral or beneficial for cardiovascular health; its effects appear to vary depending on personal health characteristics and behavioral patterns. The analysis indicates that both short-term and cumulative physiological responses should be considered when assessing the impact of this activity. Further research is necessary to elucidate the underlying mechanisms and the long-term consequences of regular winter swimming, particularly in relation to cardiovascular regulation and autonomic balance.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

The effect of the phytotherapeutic agent *Desolis* on the cytokine profile in the secretion of paraurethral glands in the complex treatment of women with chronic urethritis

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ABSTRACT

Aim: To investigate the effect of the phytotherapeutic agent *Desolis* on cytokine profiles in the secretion of paraurethral glands as part of combination therapy in women with chronic urethritis.

Materials and Methods: A total of 79 women with chronic urethritis were examined and divided into two groups. The main group (n=40) received standard etiological therapy in accordance with CDC guidelines along with *Desolis* (administered orally twice daily for 10 days). The control group (n=39) received standard treatment only. Cytokine concentrations in the secretion of the paraurethral glands were determined before and after treatment using ELISA.

Results: Women with chronic urethritis demonstrated significantly elevated levels of pro-inflammatory cytokines (IL-8, IFN-γ, IP-10) and reduced concentrations of IL-2, IL-1β, RANTES, and Fractalkine. The addition of *Desolis* to treatment led to normalization of these markers, which did not differ significantly from reference values ($p>0.05$), unlike the control group. Furthermore, patients in the *Desolis* group experienced a shorter duration of clinical symptoms and significantly higher pathogen elimination rates (87.5% vs. 56.4%, $p<0.05$).

Conclusions: The use of *Desolis* in combination therapy contributes to the normalization of the local cytokine profile, improves clinical outcomes, and increases treatment efficacy in women with chronic urethritis.

KEY WORDS: reproductive health, sexually transmitted infections, chronic urethritis in women, cytokine profile, *Desolis*

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INTRODUCTION

Chronic urethritis in women remains one of the current problems of modern urogynecology, given its persistent course, high risk of relapse and negative impact on the quality of life of patients [1-3]. Traditional approaches to treatment, based on the use of antibacterial agents, often prove to be insufficiently effective due to disruption of local immunity, microbiota and the presence of resistant forms of pathogens. In this context, there is growing interest in the use of phytotherapy as an element of complex therapy, which has immunomodulatory, anti-inflammatory and antimicrobial properties. Paraurethral glands, anatomically and functionally related to the urinary canal, play an important role in the formation of the local immune response. Studying the cytokine profile of their secretion opens up new opportunities for understanding the pathogenesis of chronic urethritis and assessing the effectiveness of treatment. Cytokines, as key mediators of inflammation and immune regulation, are important prognostic markers that allow assessing the body's response to therapeutic intervention. Asymptomatic forms of sexually transmitted infections (STIs) are not diagnosed and treated in a timely manner, which causes chronic inflammation of the genitals and increases the risk of HIV infection and the development of infertility. The study of cytokines in the female genitourinary system is of great practical importance, since cytokines play a key role in the regulation of inflammatory processes, immune response and tissue healing [2, 4-6]. It should be emphasized that to date, the question of the influence of immunocorrective therapy on cytokines of the paraurethral glands in women with chronic urogenital infection has not been practically studied. Comprehensive drug anti-inflammatory therapy for asymptomatic urogenital inflammatory processes does not always provide a stable therapeutic effect, since its results depend on the biological properties of pathogens, the state of the immune system, the patient's natural resistance and the state of the antioxidant system. Based on this, in modern conditions, much attention is paid to studying the effectiveness of drugs in the treatment and medical rehabilitation of patients with chronic urogenital pathology. Our attention was drawn to the modern phytotherapeutic agent *Desolis* (manufacturer of PrJSC„Technolog" Ukraine) in the complex treatment of patients with asymptomatic forms of chronic urogenital infection. *Desolis* can be recommended as an additional source of biologically active substances in order to normalize the functional state of the urinary tract: to relieve symptoms of painful burning and

unpleasant sensations during urination, which accompany urinary tract infections and inflammation of the bladder; during exacerbation of chronic urinary tract infections; to prevent recurrence of chronic urinary tract infections during remission; after instrumental interventions on the urinary tract (cystoscopy, urethroscopy, lithotripsy, etc.); to enhance the effectiveness of antibacterial therapy. In urolithiasis: promotes the destruction of urate stones and prevents the re-formation of calcium stones or the increase in their residual fragments; helps relieve symptoms caused by the passage of stones through the urinary tract and after the passage of stone fragments after shock wave lithotripsy. *Desolis* contains standardized extracts of medicinal plant raw materials, which ensures their high quality and effectiveness: vaccine macrocarpon (cranberry) fruit juice dry, resveratrol, D-mannose, sodium bicarbonate, tartaric acid, citric acid, sodium citrate. Vaccinium macrocarpon and resveratrol are a source of biologically active substances proanthacyanidins, which have anti-inflammatory, antimicrobial and antioxidant effects [7]. Vaccinium macrocarpon contains 30% (54 mg), resveratrol contains 80% (200 mg) proanthacyanidins. They also contain a large amount of organic acids and flavonoids, which reduce the content of oxalates in the urine, prevent the connection of calcium and phosphorus ions, which form insoluble compounds, thus preventing stone formation processes. D-mannose is a monosaccharide that is practically not metabolized in the human body. It has antimicrobial and fungicidal properties (mainly against *Escherichia coli, Candida albicans*) [8]. D-mannose prevents the attachment of *E. Coli* (which in 65-95% are the cause of urological inflammatory processes) to the epithelium of the walls of the urinary tract, and, connecting with them, promotes their excretion together with urine. A complex of biochemical compounds: sodium bicarbonate, tartaric acid, citric acid, anhydrous sodium citrate when dissolved in water form sodium hydrocitrate and carbon dioxide. This forms residual alkaline ions, which enter the urine and increase its pH. Reducing the acidity of urine reduces the symptoms of pain and burning during urination.

AIM

The aim of this study was to investigate the effect of the phytotherapeutic agent *Desolis* on cytokine profiles in the secretion of paraurethral glands as part of combination therapy in women with chronic urethritis.

MATERIALS AND METHODS

This study included 79 women with STIs who provided informed consent. Clinical studies were performed in accordance with the laws of Ukraine and the norms accepted in international practice, – ICH GCP (Declaration of Helsinki and the Council of Europe Convention on Patients' Rights and Biomedicine). Eligible women were aged 18-40 years, and were not HIV-infected or pregnant. Women underwent STI screening. A gynecological examination was performed and two swabs were taken from the anterior and posterior fornix and lateral vaginal walls. Samples were tested for bacterial STIs (*Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium, Ureaplasma urealyticum,* and *Trichomonas vaginalis*) and herpes simplex virus (HSV) by PCR. Blood was tested for IgG antibodies to HSV-2 by ELISA (HerpeSelect®, Focus Diagnostics, USA). Treponema pallidum was excluded serologically using the Becton Dickinson Macro-Vue™ Rapid Plasma Reagin card test and the hemagglutination test (ImmuTrep® TPHA, Omega Diagnostics LTD, UK). We therefore aimed to identify women with one of five treatable bacterial conditions (*T. vaginalis, C. trachomatis, M. Genitalium, U. urealyticum* or *N. gonorrhoeae*). Cytokines were determined in the secretions of the paraurethral glands of the women by flow cytometry using magnetic microspheres conjugated to monoclonal antibodies using the BioPlex 200 platform with HRF (Bio-Rad, USA) using Luminex xMAP® technology and corresponding custom kits allowing simultaneous measurement of 28 cytokines. Multivariate analysis was used to determine the cytokine profiles associated with STIs.

Cytokines measured were grouped into the following groups: inflammatory cytokines – interleukin (IL)-1α, IL-1β, IL-6, IL-12p70 and tumor necrosis factor (TNF)-α; chemokines – IL-8, macrophage inflammatory protein (MIP)-1α, MIP-1β, gamma-interferon-induced protein (IP)-10, monocyte chemoattractant protein (MCP)-1, regulated upon activation, normally expressed and secreted T (RANTES), and fractalkine; adaptive cytokines – IL-2, IL-4, IL-5, IL-13, IL-15, IL-17 and interferon (IFN)-γ; growth factors – IL-7, IL-9, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-colony-stimulating factor (G-CSF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF)-bb and anti-inflammatory cytokines - IL-1 receptor antagonist (RA) and IL-10. Cytokine concentrations ranged from 0.08 to 1444.46 pg/ml.

Control parameters of the concentrations of all the above cytokines were obtained during the study of 18 women without clinical signs of the disease, similar in composition and age.

All samples of paraurethral gland secretions from women were stored at 4 °C until processing, which occurred within four hours after collection. Fluid from the urethra was collected after digital massage using an elongated, tapered flocked swab (FLOQ swab, Copan Diagnostics, Murrieta, CA, USA) during pelvic examination. Each swab was allowed to absorb fluid within the urethra for 60 seconds without rotating the swab to prevent microabrasion. The swabs were placed in cryovial tubes containing transport medium provided by the test system manufacturer for transport to the laboratory. In the laboratory, paraurethral gland secretion samples were vortexed for 1 minute to suspend and mix the secretions into the transport medium. All fluid was removed from the swab by gently scraping the swab head against the inside of the tube before disposal. Paraurethral gland secretion was aliquoted and stored at -80° for cytokine measurements.

For the criteria for controlling the effectiveness of treatment with the proposed method, standard methods were used: assessment of the dynamics of the main clinical symptoms

(painful, urethral, dysuric), objective assessment of the general condition of patients (irritability, insomnia, general weakness), and also determination of cytokines in the secretion of paraurethral glands in women with chronic urethritis in dynamics - in the acute period (1-3 days of illness) and in the period of early convalescence (12-14 days) and 1-1.5 months after the end of treatment.

Statistical analysis of the obtained results was performed in the environment of the licensed statistical package STATISTICA v.6.1 (Statsoft Inc., USA) (MedCalc v.11.5.0 (free download); „Microsoft® Office" 2016 Pro Plus (Product ID: 00351-35020-14887-AA217) Microsoft Corporation (All rights reserved). In this case, the χ^2 criterion was used to check the indicators for normal distribution. The median, 25% quartile, 75% quartile, and confidence intervals were calculated. The χ^2 criterion and two-sided critical region were used to compare the indicators. To compare the mean values of the characteristic for two independent samples, the Fisher angular transformation method was used with the Yates correction.To analyze the presence and strength of the relationship, the Kendall pairwise correlation coefficient – τ – was calculated.

RESULTS

The study of cytokine levels indicates that the examined women had a significant increase in the concentration of IL-8 (1231.83±74.27 pg/ml, p<0.001), IFN-γ (36.03±0.23 pg/ml, p<0.001) and interferon-gamma-induced protein IP-10 (195.44±5.15 pg/ml, p<0.001) in the secretion of the paraurethral glands; the multiplicity of the difference was 34.10, 6.73 and 4.32, respectively (Table 1).

At the same time, in women with chronic urethritis, a significant decrease in the concentration of IL-1β (35.14±2.11 pg/ml, p <0.01), IL-2 (5.88±0.69 pg/ml, p <0.001), RANTES (12.65±1.28 pg/ml, p <0.001), Fractalkine (23.27±1.27 pg/ml, p <0.01) in the secretion of paraurethral glands was observed. It should be noted that we did not find a significant difference in the concentration of cytokines in the paraurethral glands of women with chronic urethritis depending on the presence or absence of urethral symptoms and the etiological factor.

To study the effectiveness of the natural herbal remedy *Desolis* on the cytokine profile in the secretion of paraurethral glands in the complex treatment of women with chronic urethritis, we administered it orally twice a day for 10 days (main group, n=40). Before using *Desolis*, the contents of the sachet were dissolved in 200 ml of room temperature water and thoroughly mixed. The control group (n=39) received only conventional treatment. Etiotropic treatment was carried out according to the recommendations for the treatment of STDs issued by the US Centers for Disease Control and Prevention (CDC) – azithromycin, doxycycline, ofloxacin. Clinical studies have shown that combination therapy with *Desolis* significantly improves the general condition of patients and well-being. The duration of general weakness was shorter on average by (3.3±0.5) days (p<0.05), malaise by (3.2±0.4) days (p<0.05), and irritability and anxiety by (4.1±0.3) days (p<0.01). Moreover, after the completion of treatment, 34 patients (85.03%) had no complaints about their health and considered themselves practically healthy at that time, which was 1.62 times (p<0.05) higher than the effect achieved when using only conventional means (21 patients – 53.85%).

During the re-examination after the completion of the treatment course, the elimination of Ch. trachomatis and U.urealyticum was observed in 35 patients (87.5%) of the main group and in 22 patients (56.4%) of the control group, i.e. 1.59 times more (p<0.05). The remaining subjects of the main group had a decrease in the titers of mycoplasma and ureaplasma infection, so such patients need to undergo repeated courses of etiotropic and pathogenetic therapy.

The study of the concentration of cytokines in the secretion of paraurethral glands in women with chronic urethritis after a course of immunocorrection showed normalization of their levels in patients of the main group (Table 2).

Thus, in the group of patients who took *Desolis*, there was a significant decrease in the levels of the cytokines IL-8, IFN-γ, IP-10 in the secretion of the paraurethral glands and a significant increase in the levels of IL-1β (52.64±0.90 pg/ml, p <0.01), IL-2 (69.45±2.35 pg/ml, p <0.001), RANTES (38.44±2.25 pg/ml, p <0.001), Fractalkine (28.45±1.57 pg/ml, p <0.001). The levels of these cytokines in the main group did not differ from the normative ones (p>0.05). The levels of these cytokines in the secretion of the paraurethral glands in women with chronic urethritis who did not receive *Desolis* only slightly improved and remained significantly different from the normative values (p<0.05) and significantly different from their values in the main group (p<0.01).

By quantifying the effect of the herbal preparation *Desolis* on cytokine profiles in the secretion of paraurethral glands as part of combination therapy in women with chronic urethritis, it has been established that the proposed method reduces the ineffectiveness of treatment by 75.3 % (interval estimate: 61.2-83.5%, p=0.05) compared to commonly used methods. The new method of treatment reduces the risk of ineffective treatment by 8.22 times (interval estimate: 4.45-13.38 times, p=0.05) compared with the control method, and the number of patients need to be treated is 1.3 persons (interval estimate: 1.2-1.6 persons, p=0.05), that is, it should be treated with 1-2 people in order to receive an additional healed patient in comparison with the generally accepted method of treatment.

DISCUSSION

The results of our study showed that the development of such a complication in women as inflammation of the paraurethral glands (skinitis, prostatitis) [9, 10] against the background of chronic urethritis is accompanied by shifts in the cytokine profile in the secretion of the paraurethral glands. Inflammation is usually characterized by increased levels of IL-1β, IL-6, IL-12 and TNF-α [11], however, examination of women with chronic urethritis indicates, on the contrary, a decrease in the level of IL-1β and normal levels of IL-6, IL-12 and TNF-α in the secretion of the paraurethral glands along with lower concentrations of IL-2, RANTES, which may indicate depletion of the local immune system.

Table 1. Immunological parameters of paraurethral gland secretion in women with chronic urethritis (Me ± m [95% confidence interval])

Functional class of cytokines	Cytokine	Cytokine concentration, conditionally accepted as normal, pg/ml (Me±m [95% confidence interval])	Cytokine concentration in women with chronic inflammation in the urogenital tract, pg/ml (Me±m [95% confidence interval])
Pro-inflammatory	IL-1β	56.62±0.81 [50.22; 68.45]	35.14±2.11** [22.01; 42.99]
	IL-1α	86.34±5.43 [61.33; 131.35]	97.23±11.23 [67.32; 111.89]
	IL-6	34.15±1.22 [32.12; 36.78]	39.44±1.45 [24.32; 45.47]
	IL-12	13.16±1.43 [11.38;15.38]	15.09±1.49 [10.58; 22.64]
	TNF-α	7.33±0.25 [5.03;9.27]	7.89±0.25 [4.93; 10.48]
Anti-inflammatory	IL-10	36.31±1.33 [32.25;39.48]	30.38±1.42 [19.18; 38.77]
	IL-1RA	647.28±55.28 [479.37; 905.25]	1267.47±69.25* [988.33; 1525.26]
Adaptive	IL-2	76.25±2.17 [60.14; 89.25]	5.88±0.69 *** [1.73; 6.79]
	IL-4	24.12±1.23 [21.35; 32.26]	22.27±1.46 [19.05; 25.45]
	IL-5	0.98±0.30 [0.34; 1.42]	0.82±0.35 [0.55; 1.22]
	IL-13	0.67±0.32 [0.34; 1.42]	0.49±0.80 [0.28; 1.49]
	IL-15	4.95±0.82 [3.56; 7.74]	5.10±0.40 [3.74; 8.37]
	IL-17	28.13±0.82 [25.62;30.44]	25.18±0.42 [21.80; 29.17]
	IFN-γ	5.35±0.24 [4.10;7.74]	36.03±0.23*** [25.63; 40.89]
Chemokines	IL-8	36.12±1.55 [35.41; 40.34]	1231.83±74.27*** [970.52; 1493.42]
	MIP-1a	13.55±1.68 [11.22; 18.25]	14.85±1.40 [12.19; 19.25]
	MIP-1b	156.52±5.52 [144.35; 178.23]	189.42±6.55* [154.22; 215.19]
	IP-10	45.25±3.51 [38.24; 65.29]	195.44±5.15*** [189.55; 219.12]
	MCP-1	82.43±1.43 [78.8; 80.3]	81.44±1.54 [67.23; 93.33]
	RANTES	40.53±2.27 [37.26;43.45]	12.65±1.28*** [8.58; 13.44]
	Fractalkine	29.42±1.55 [26.15; 32.04]	23.27±1.27** [19.56; 26.32]

Table 1. Cont.

Growth factors	IL-7	5.25±1.02 [4.04; 7.56]	6.03±1.53 [4.15; 8.11]
	IL-9	2.46±0.34 [1.85; 4.24]	2.49±1.12 [2.10; 5.19]
	GMCSF	51.34±2.45 [45.22; 70.24]	57.62±3.45 [48.01; 74.34]
	GCSF	781.43±28.57 [546.28; 949.24]	1125.23±56.44* [969.63; 1378.43]
	VEGF	389.25±11.53 [303.25; 548.35]	408.63±6.48 [379.53; 548.64]
	FGFb	15.01±2.45 [12.35; 22.56]	17.1±1.49 [12.37; 29.00]
	PDGF-bb	9.98±2.09 [7.20; 15.34]	11.84±2.59 [8.59; 15.39]

*Note: the significance of the difference between the indicators of the group of women with chronic urethritis and the indicators accepted as normal at P values: * – <0.05, ** – <0.01, *** – <0.001*

Source: compiled by the authors of this study

In resource-limited settings, STIs are treated syndromically, according to the presence of clinical signs and symptoms, rather than by more expensive laboratory diagnostics [6, 12-15]. However, a large proportion of women with STIs are asymptomatic and therefore not treated [4, 14, 16]. Women with asymptomatic STIs have levels of genital inflammation comparable to women with symptomatic infections, which are higher compared with women without STIs. We found that women with chlamydia or gonorrhea, who were predominantly asymptomatic, had the highest concentrations of genital cytokines, with the cytokines IFN-γ and IL-1RA being elevated compared with women without

Table 2. Dynamics of cytokines that underwent changes in the secretion of paraurethral glands of women with chronic urethritis under the influence of *Desolis* (Me±m [95% confidence interval])

Functional class of cytokines	Cytokine	Norm	Before treatment n=79	After treatment		P
				Main group (n=40)	Control group (n=39)	
Pro-inflammatory	IL-1β	56.62±0.81 [50.22; 68.45]	35.14±2.11** [22.01; 42.99]	52.64±0.90 [48.34; 64.55]	48.56±1.14* [44.26; 50.14]	<0,01
Anti-inflammatory	IL-1RA	647.28±55.28 [479.37; 905.25]	1267.47±69.25* [988.33; 1525.26]	756.23±50.43 [578.22; 967.45]	788.47±62.35 [579.36; 978.23]	>0,05
	IL-2	76.25±2.17 [60.14; 89.25]	5.88±0.69 *** [1.73; 6.79]	69.45±2.35 [58.74; 83.36]	48.96±0.81 * [40.55; 54.26]	<0,01
Adaptive	IFN-γ	5.35±0.24 [4.10;7.74]	36.03±0.23*** [25.63; 40.89]	6.35±0.27 [4.80;8.65]	10.21±0.27* [8.48; 12.59]	<0,01
	IL-8	36.12±1.55 [35.41; 40.34]	1231.83±74.27*** [970.52; 1493.42]	39.48±1.68 [36.59; 44.77]	156.343±22.25** [99.47; 183.54]	<0,01
Chemokines	MIP-1b	156.52±5.52 [144.35; 178.23]	189.42±6.55* [154.22; 215.19]	156.44±5.23 [145.99; 172.55]	159.55±4.45 [150.33; 180.03]	>0,05
	IP-10	45.25±3.51 [38.24; 65.29]	195.44±5.15*** [189.55; 219.12]	54.26±3.24 [41.42; 60.33]	70.37±5.20* [66.48; 79.44]	>0,05
	RANTES	40.53±2.27 [37.26;43.45]	12.65±1.28*** [8.58; 13.44]	38.44±2.25 [32.28;40.37]	26.44±1.34* [21.12; 29.90]	<0,01
	Fractalkine	29.42±1.55 [26.15; 32.04]	23.27±1.27** [19.56; 26.32]	28.45±1.57 [22.90; 30.11]	25.29±1.25* [20.02; 26.99]	<0,01
Growth factors	GCSF	781.43±28.57 [546.28; 949.24]	1125.23±56.44* [969.63; 1378.43]	790.67±24.09 [578.47; 988.36]	823.44±50.22* [593.45; 903.67]	>0,05

*Note: The significance of the difference in indicators compared to the norm P: * – <0.05, ** – <0.01, *** – <0.001; P – significance of the difference between the indicators of the groups*

Source: compiled by the authors of this study

infection, respectively. Women with trichomoniasis had a mixed cytokine profile with increased concentrations of proinflammatory cytokines in paraurethral gland secretions, but also decreased concentrations of chemokines and hematopoietic cytokines. Thus, many women living in resource-limited settings may have STI-related inflammation that remains unresolved, increasing the risk of HIV infection and reproductive complications [6, 16-19]. Thus, there is an urgent need to improve STI treatment strategies for women, especially in resource-limited settings, to more effectively detect usually asymptomatic infections.

These findings support the central role of cytokine dysregulation in the pathogenesis of chronic urethritis in women. High concentrations of pro-inflammatory mediators, in particular IL-8, IFN-γ and IP-10, indicate active infiltration of neutrophils and Th1-dependent inflammation in the paraurethral glands, which causes the persistence of the inflammatory process and slow regeneration of the epithelium.

Of particular note is the significant decrease in IL-2, a key cytokine for T-cell activation, in some patients, which indicates an immunosuppressive state in some patients. The decrease in the levels of RANTES and Fractalkine, responsible for the chemotaxis of T-lymphocytes and NK cells, additionally emphasizes the disruption of immune response mechanisms.

The use of *Desolis* as part of complex treatment contributed to the normalization of the cytokine profile in most patients. The detected decrease in the levels of IL-8, IFN-γ and IP-10 to values that do not differ from the control ones indicates the inhibition of chronic inflammation. At the same time, the increase in the levels of IL-2, RANTES and Fractalkine after treatment indicates the restoration of immunoregulatory function.

Thus, the results of the study demonstrate the potential of the phytotherapeutic agent *Desolis* as an immunomodulatory agent with antibacterial and anti-inflammatory effects. This effect is not only confirmed biochemically, but also manifested in the clinical improvement of the patients' condition, reduction of complaints, and increase in the level of pathogen elimination. Compared with traditional treatment, the combination with *Desolis* provides a more complete restoration of local immunity and a decrease in the frequency of relapses.

The obtained data can be used to improve the treatment regimens for chronic urethritis, in particular in cases of infections caused by *Chlamydia trachomatis* and *Ureaplasma spp.*, when pathogenetic therapy plays an equally important role than etiotropic therapy.

CONCLUSIONS

In women with chronic urethritis, significant disturbances of the local cytokine balance in the secretion of the paraurethral glands were found: a significant increase in the levels of pro-inflammatory mediators (IL-8, IFN-γ, IP-10) and a decrease in the levels of key immunoregulatory cytokines (IL-2, IL-1β, RANTES, Fractalkine), which indicates an active inflammatory process and a deficiency of the effector immune response.

Oral use of the phytotherapeutic agent *Desolis* as part of the complex therapy of chronic urethritis in women provides a significant normalization of the cytokine profile in the paraurethral secretion, in particular, a decrease in the excessive production of IL-8, IFN-γ and IP-10 and an increase in the levels of IL-2, RANTES, IL-1β and Fractalkine to reference values ($p>0.05$).

Clinical improvement with the use of *Desolis* is manifested in a reduction in the duration of symptoms such as weakness, malaise, anxiety, as well as in a higher level of satisfaction with treatment (85.03% vs. 53.85% in the control group, $p<0.05$).

The use of *Desolis* increases the efficiency of pathogen elimination (87.5% in the *Desolis* group vs. 56.4% in the control group, $p<0.05$), which indicates its positive effect on the pathogenetic mechanisms of chronic urethritis.

The proposed method reduces the ineffectiveness of treatment by 75.3 % (interval estimate: 61.2-83.5 %, $p=0.05$) compared to commonly used methods.

The results obtained confirm the feasibility of including the phytotherapeutic agent *Desolis* in the complex therapy of chronic urethritis in women, in order to optimize immunocorrection, reduce inflammation and increase the effectiveness of treatment.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

The profile of the resistance of *Staphylococcus aureus* against selected antibiotics in Najaf

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ABSTRACT

Aim: In this study, we examine and discuss about the resistance of *Staphylococcus aureus* to common antibiotic classes in Najaf.

Materials and methods: Information on *Staphylococcus aureus's* resistance to drugs was collected from the directorate of health and analyzed.

Results: It was found that *Staphylococcus aureus* exhibited resistance to cephalosporins that was comparable to that of penicillin. On the other hand, significant resistance to cefoxitine, ceftazidim, and penicillin was seen, further studies are required to evaluate the mechanism of antibiotic resistance responsible for such resistance.

Conclusions: the profile of resistance of *Staphylococcus aureus* is variable across antibiotic families. Inter-member differences have been noticed within the group, a pattern that more likely indicates resistance at the level of intracellular concentration of antibiotic rather than the mechanism of action. In addition, it has been noticed that the development of resistance is directly proportional to the frequency of use of antibiotics. Further studies are required to investigate the molecular mechanism of resistance.

KEY WORDS: *Staphylococcus aureus*, bacterial resistance, rational use of antibiotics

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INTRODUCTION

Staphylococcus aureus is a common pathogen found in hospitals and the general population. It can cause diseases such as pneumonia and infectious endocarditis [1]. It exhibits positive Gram stain results and can grow both aerobically and anaerobically, but it thrives at 37°C and pH 7.4 [1-2]. The majority of them are hemolytic and surround the colonies on blood agar plates with a translucent hemolytic ring [1-3]. Furthermore, *Staphylococcus aureus* contains a capsule rather than spores or flagella, can produce golden yellow pigment, and degrade mannitol [3-4]. Additionally, tests for lactose fermentation, plasma coagulase, and deoxyribonuclease have been shown to be positive for *Staphylococcus aureus* [4-6]. Fleming started treating patients with antibiotics after discovering penicillin in the 1940s [7-9]. *Staphylococcus aureus* can manufacture penicillinase, which can hydrolyze the antibiotic's β-lactam ring and reduce its effectiveness, when it develops resistance to penicillin. Researchers went on to create methicillin, a novel semisynthetic penicillin that is resistant to β-lactamase hydrolysis [6, 10-11]. Methicillin successfully treated penicillin-resistant *Staphylococcus aureus* infections when it was introduced to the clinic in 1959 [12-14].

Furthermore, in a number of international locations, such as North Africa, the Middle East, East Asia, Europe, and the United States, Methicillin-resistant *Staphylococcus aureus* (MRSA) has rapidly become the most often found resistant infection [15-17]. Hospital-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA) are the two categories into which MRSA is divided according to its initial source [18-120]. According to a couple of studies [21-23], hospitals in China account for 50.4% of MRSA infections. Moreover, MRSA infections was reported to have a higher death rate than AIDS and Parkinson's disease [24-25]. Since then, antibiotic resistance has grown to be a major global concern. As a result, careful analysis of the *Staphylococcus aureus* resistance pattern can help direct the choice of antibiotics and therapeutic strategies. This study was designed to assess the resistance profile of *Staphylococcus aureus* against selected antibiotic families.

MATERIALS AND METHODS

CHARACTERIZATION OF BACTERIA ISOLATES

All the clinical samples obtained were cultured on CHROMagar, MacConkey agar and Blood agar and the incubated at 37°C for 24 hrs. Identification of bacterial strain each isolate was morphologically, microscopically and biochemically characterized (Oxidase, Catalase, Indol and Simmon Citrate test). The Vitek-2 system allows accurate identification of all bacterial isolates (99%). Subsequently, the isolates were molecularly identified based on 16srRNA gene.

ANTIBIOTICS SUSCEPTIBILITY TEST

The test was done using disc diffusion method for 10 antibiotics following the method of the Clinical and Laboratory Standards Institute (CLSI)(2021) using the prescribed method [26]. Colonies were suspended in 3 cc of normal saline from an overnight Muller-Hinton agar plate culture. The turbidity was adjusted to 0.5 McFarland or 1.5108CFU/ml. The bacterial suspension was spread using a sterile cotton swab and excess fluid was removed by snapping the brush against the wall of the tube. The bacterial solution was seeded onto Muller Hinton agar plates and dry for 15 min. Various antibiotic discs were placed and a maximum of six discs were set on the medium surface using a sterilized needle and a very small amount of pressure in order to place the disk. Thereafter, the plate was incubated for 24h at 37°C and then, the test was performed using the 10 antibacterial disks.

DATA COLLECTION AND ANALYSIS

Data about antibiotics were gathered from the Directorate of Health/Najaf. The data included a wide variety of topics, including the usage of antibiotics (where specified), identified bacterial strains, antibiotic resistance, regimen, and combination of medicines. GraphPad Prism 9.3.1 was utilized for the classification and analysis of the data. Data was gathered and the study was carried out at the medical facilities in Najaf between October 25, 2021, and January 25, 2023. Data on antibiotic usage in 2021 and 2022 were gathered during this time. Both data analysis and presentation were performed using the latest GraphPad Prism software (version is 9.3.1), USA. Data are presented as percent.

OFFICIAL PERMISSION

After receiving permission from the Najaf health directorate, statistics were legally collected as part of the collaboration between the University of Alkafeel and the latter.

RESULTS

Figures 1 shows the resistance of *Staphylococcus aureus* against selected antibiotics; penicillin, cephalosporins, aminoglycosides, carbapenems, macrolides, quinolones, tetracyclines and miscellaneous antibiotics, respectively. Among penicillin, the highest resistance was reported against amoxicillin and amoxicillin plus clavulanic acid while the lowest resistance was against piperacillin.

Regarding cephalosporins, the highest resistance was reported against ceftazidime and cefotaxime while the lowest resistance was against ceftriaxone and cefixime (Fig. 2).

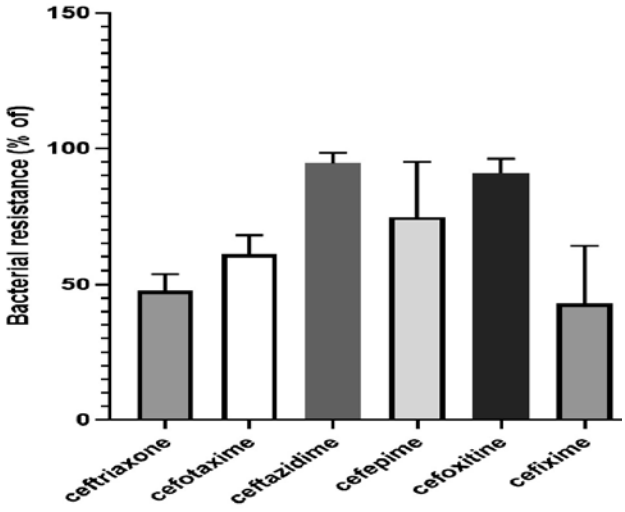

Fig. 2. The resistance of *Staphylococcus aureus* against cephalosporins

Source: Own materials

Among aminoglycosides, it is shown in figure 3 from the highest to the lowest against amikacin, gentamycin and tobramycin.

In regards to carbapenems, about equal resitsnce of *Staphylococcus aureus* against imipinem and aztreonam while its resistance against meropenem was the lowest (Fig. 4).

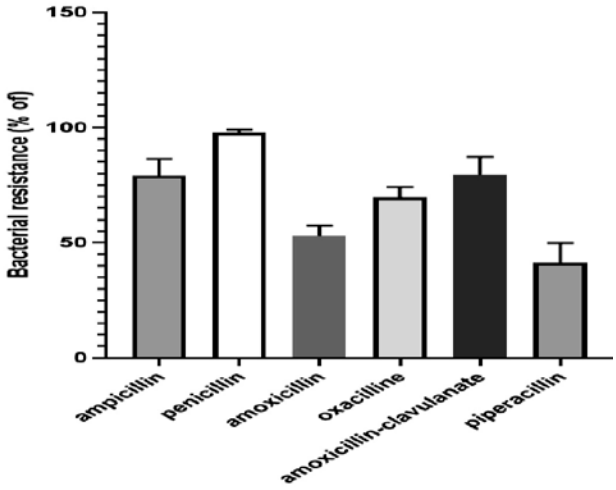

Fig. 1. The resistance of *Staphylococcus aureus* against selected penicillin

Source: Own materials

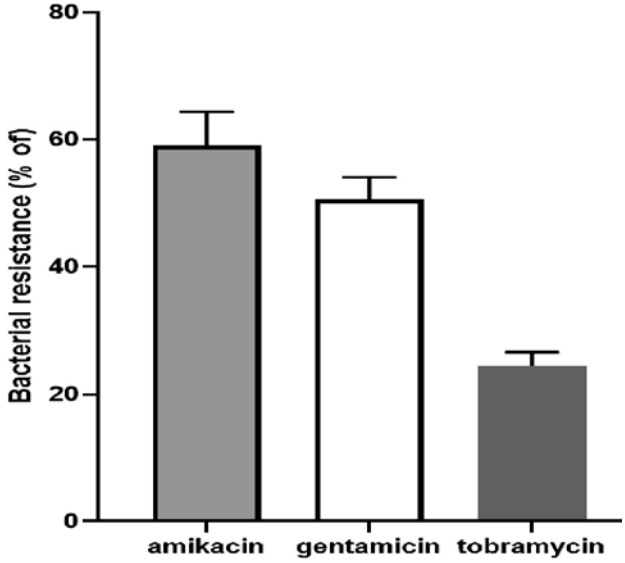

Fig. 3. The resistance of *Staphylococcus aureus* against aminoglycosides.

Source: Own materials

When it comes to macrolides, the resistance of *Staphylococcus aureus* is arranged from the lowest to the highest against clarithromycin, azithromycin and erythromycin as shown in figure 5.

We reported that *Staphylococcus aureus* is resistant against Fluoroquinolones as follows; its resistance was low against moxifloxacin, high against levofloxacin and the highest against ciprofloxacin (Fig. 6).

Staphylococcus aureus showed very low resistance against tigecycline compared to other tetracyclines, higher against doxycycline and the highest against tetracycline (Fig. 7).

Staphylococcus aureus resistance against several miscellaneous antibiotics was also assessed. We found that its resistance from the lowest to the highest as follows; rifampicin, trimethoprim plus sulfamethoxazole, nitrofurantoin and clindamycin as shown in figure 8.

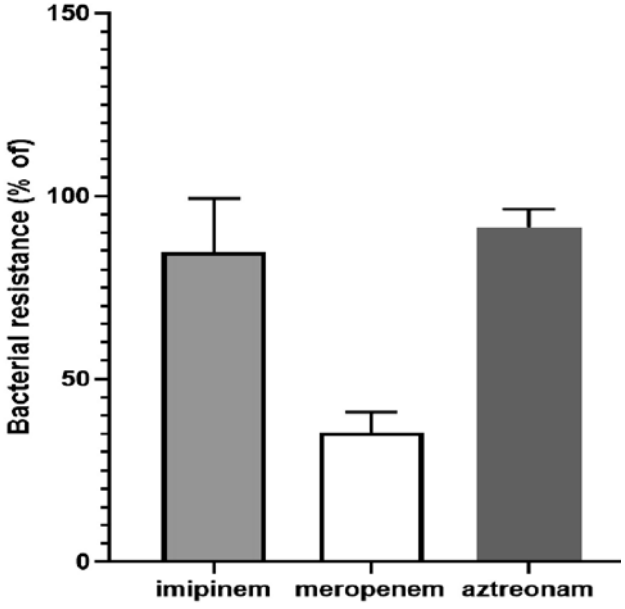

Fig. 4. The resistance of *Staphylococcus aureus* against carbapenems

Source: Own materials

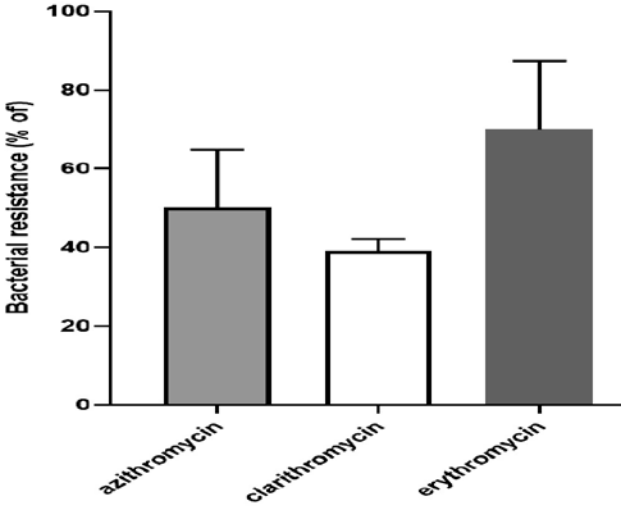

Fig. 5. The resistance of *Staphylococcus aureus* against macrolides

Source: Own materials

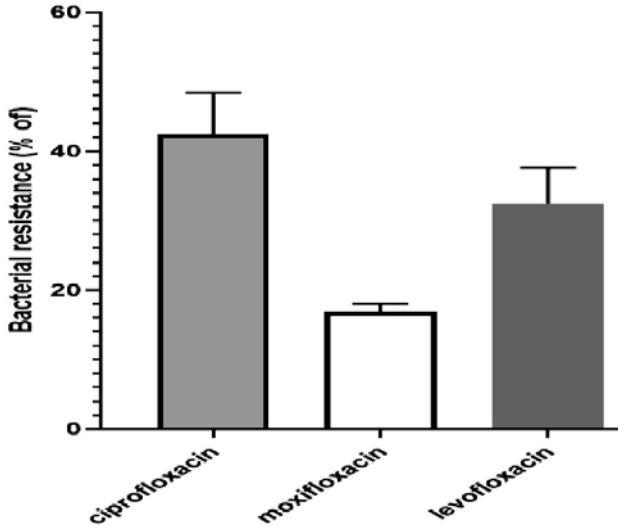

Fig. 6. The resistance of *Staphylococcus aureus* against quinolones

Source: Own materials

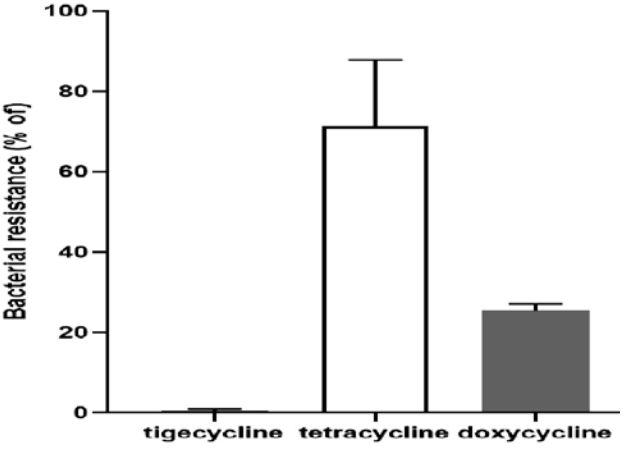

Fig. 7. The resistance of *Staphylococcus aureus* against tetracycline

Source: Own materials

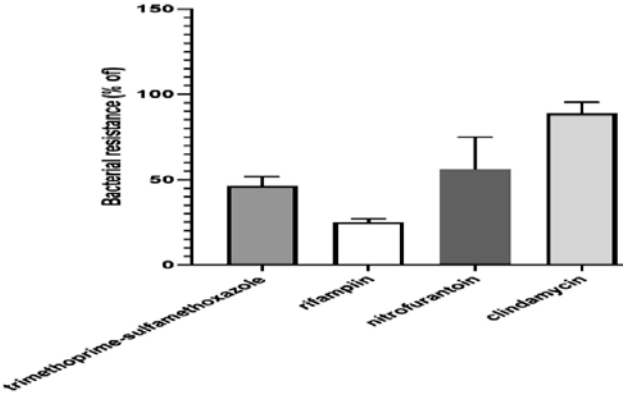

Fig. 8. The resistance of *Staphylococcus aureus* against miscellaneous antibiotics

Source: Own materials

DISCUSSION

The bacterium *Staphylococcus aureus* is abundant in the human body and may be found on the skin's surface as well as in the mucosa of the upper respiratory tract [27]. *Staphylococcus aureus* is still a significant human pathogen even though only 20% of the population is a long-term carrier and the majority of carriers do not exhibit clinical signs [28]. According to Edwards and Massey, *Staphylococcus aureus* is the most prevalent bacteria in hospitals worldwide and may infect both hospitals and the general public [29-30]. In the 1840s, Fleming, a British bacteriologist, created penicillin, which was used in clinical settings to treat infections caused by *Staphylococcus aureus* [2, 31]. Since then, new antimicrobial medications have been created. However, this significant study has also revealed a hidden threat to human society. The prevalence of bacterial resistance has increased due to the increased use of antibiotics, starting with the emergence of multidrug resistant strains like MRSA, which has attracted significant attention from both domestic and international research experts and is considered a clinically significant problem [8, 32]. Even though the fatality rate from MRSA infections has significantly decreased in several European countries, MRSA remains a serious global public health problem [10]. MRSA's characteristics of easy infection, high mortality, and antibiotic resistance have made it difficult to treat in clinical settings [6]. As a result, the best ways to stop and manage MRSA are currently a popular subject in study. Science and technology have advanced over time, and medical advancements have persisted. Outstanding progress has been achieved by humans in the study of MRSA pathogenic factors. Vancomycin is probably still the best medication available today to treat MRSA infections [33]. However, research involving humans has become much more challenging due of MRSA's antibiotic resistance [34]. In order to further advance the creation of novel medications to combat MRSA infection, more research is required to continually examine MRSA's capacity for infection as well as its routes for developing antibiotic resistance. The creation of new medications has expanded the treatment choices available to physicians for MRSA infections, improving patient safety. However, further clinical study is needed to determine the safety and effectiveness of medications. The main inhibitory target site of beta lactam antibiotics in *S. aureus* is frequently the two-way functional transglycolylase transpeptidase PBP2. The domain of the enzyme that includes the transglycolylase coordinates the transfer of the disaccharide pentapeptide source material of peptidoglycan from membrane-bound lipid II to budding polysaccharide chains. The transpeptidase domain facilitates attachment to the glycine cross-bridge of the adjacent chain's fourth D-alanine [35]. Penicillin, oxacillin, methicillin, and cephalosporin are members of this antibiotic family. They stop the peptidoglycan synthesis process' transpeptidation step by binding to and deactivating the penicillin binding proteins in the bacterial cell wall. Aminoglycosides function as bactericidal antimicrobials by interfering with protein synthesis when they bind to the 30S ribosomal subunit. Resistance to aminoglycoside arises as a result of an in vitro mutation in the ribosomal subunit. Similarly, it has been proposed that the acquisition of an enzyme that alters aminoglycosides facilitates the development of resistance to them [35-36]. To stop DNA transcription and replication, Fluoroquinolones target the enzymes Topoisomerase II and IV, which are DNA gyrases. Studies have shown that resistance to quinolone derivatives may arise through the efflux pump system or through mutation of the target Topoisomerase II and IV. Furthermore, it has been demonstrated that a single target mutation does not result in quinolone resistance; rather, a series of mutations linked to an elevated minimum inhibitory concentration (MIC) of Fluoroquinolones is responsible [36]. Aminoglycosides function as bactericidal antimicrobials by interfering with protein synthesis when they bind to the 30S ribosomal subunit. Resistance to aminoglycoside arises as a result of an *in vitro* mutation in the ribosomal subunit. Similarly, it has been proposed that the acquisition of an enzyme that alters aminoglycosides facilitates the development of resistance to them [35-36]. To stop DNA transcription and replication, Fluoroquinolones target the enzymes Topoisomerase II and IV, which are DNA gyrases. Studies have shown that resistance to quinolone derivatives may arise through the efflux pump system or through mutation of the target Topoisomerase II and IV. However, this does not result in the development of lincosamide or streptogramin resistance. A vast array of significant antibiotics and other harmful substances can be resisted by pathogenic bacteria thanks to a variety of innate mechanisms that make them resilient or hardy in the face of harsh environments. Long-term usage of antibiotics has been shown during the past 60 years to trigger a variety of genetic and metabolic mechanisms in bacteria that enable them to evade the harmful effects of antibiotics present in their immediate surroundings. As a kind of evolutionary reaction to the usage of antibiotics, clones of bacteria with acquired or inherent resistance traits have been employed repeatedly.

CONCLUSIONS

In conclusion, the profile of resistance of *Staphylococcus aureus* is variable across antibiotic families. Inter-member differences have been noticed within the group, a pattern that more likely indicates resistance at the level of intracellular concentration of antibiotic rather than the mechanism of action. In addition, it has been noticed that the development of resistance is directly proportional to the frequency of use of antibiotics. Further studies are required to investigate the molecular mechanism of resistance.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Depression, PTSD and psychological distress among Ukrainian youth: The impact of war on mental health

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ABSTRACT

Aim: To determine the prevalence of traumatization, depression, stress, and anxiety during the war in the rear western region of Ukraine.

Materials and Methods: For the study of the war's impact on the psychological state of medical students to be successful, it is essential to analyze various influencing factors and explore possible ways of supporting students in difficult situations duringmilitary conflict. The 1 to 6-year students of the Medical Faculty of I. Horbachevsky Ternopil National Medical University, who voluntarily completed the DASS-21 survey scale, participated in our research on students' mental health. The statistical sample was 716 students.

Results: To compare the degree of the emotional state of depression, anxiety, and stress in medical students, we have used a survey conducted among the students (716 people). Horbachevsky Ternopil National Medical University in 2019 and 2024. In 2019, the degree of depression severity among the students was determined to be 50.9%, anxiety – 48.9%, and stress – 50.7%. After two years of the war, in 2024, this indicator is already 65.8%, 65.9 %, and 74.7%, respectively, which is 1.3 times higher than the degree of depression and anxiety severity and 1.5 times higher than the degree of stress severity in 2019. Withinan extensivesurvey of I. Horbachevsky Ternopil National Medical Universitystudents, 98% said they had been affected by the war in some way, 86% suffered from war-related nightmares, 49% experienced symptoms of insomnia, and 27% had symptoms of post-traumatic stress disorder. However, the mental health of young people who were close to the combat zone or directly participated in hostilities was significantly worse. At the same time, another study on the mental state of students in Ukraine revealed that symptoms of psychological disorder were observed in 52.7% of respondents, with anxiety being characteristic of the majority of participants – 54.1%. Almost half of the young respondents reported experiencing depression – 46.8%. The conducted studies established a connection between mental health disorders among young Ukrainians and factors such as gender, place of residence (urban or rural area), whether they lived in territory occupied by Russian forces, as well as the presence of their own family or elderly relatives.

Conclussions: As the trauma of war can persist for years after its end, there is a need to monitor the psychological state and well-being of students systematically. It is equally important to study the aspects of strengthening psychological health and the resources that may be needed for this. Maintaining students' mental health in martial law requires all types of resources (personal, physical, informational, and other), psychological competence, social support, cognitive training, and simulation modeling methods.

KEY WORDS: Depression, post-traumatic stress, psychological distress, mental health, anxiety, Ukraine, war, young

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INTRODUCTION

The full-scale invasion of Russia significantly affected and changed all spheres of life both on the front line and forward area, as well as in the rear of Ukraine. The development of anxiety, depression, and traumatization of the population [1], especially the young generation of millions of Ukrainians, is facilitated by constant threats to life and health associated with hostilities, missile bombings, and frequent air raid alarms. Psycho-emotional experiences lead to various types of disorders and mental traumas [2], which are caused not only by the direct impact of military actions but also indirectly: by watching war scenes on television or the internet, reading news on social networks, and through communication [3-6]. The pain of loss due to the death of loved ones on the battlefield or from shelling, parting with relatives, financial difficulties, uncertainty about the future – all this significantly affects the mental health of Ukrainians [7-10].

Young people group, which is one of the most vulnerable to stress.Vulnerability to stress, in general, shows a predisposition to undergo intense episodes of distress, exhaustion, and negative emotions, and it is also a risk factor for the development of depression or anxiety [11-13]. «Anxiety and depression are negative categories, and therefore their lowest possible value is desired» [14]. Preserving mental health is an urgent problem because it helps maintain a person's general well-being. The good mental health of students is a key to their success in studies, modern society, and the opportunity to realize themselves in many spheres of life.

According to sociological surveys conducted by the National Institute of Strategic Studies, up to 71% of Ukrainians experience post-traumatic stress disorder (PTSD), up to 95% – anxiety,

and up to 40% – depression. Themain reasons are the full-scale war with Russia (72%) and financial difficulties (24%). The aspects of war that lead to stress or extreme nervousness are, first of all, the safety of relatives and friends (63%) and the loss of a job or source of income (35%) [15, 16].

According to various studies, 40-50% of the Ukrainian population will need psychological help. In certain population groups, the number of such people will be: among the military personnel and veterans – 1.8 million people; among older adults – 7 million; among children and adolescents – about 4 million people. It is projected that 27 million people will need psychological support in the institutions ofprimary medical care. At the same time, about 3-4 million Ukrainians will have in future specific moderate or severe mental health disorders [17-19].

The country needs highly qualified doctors and supporting medical staff with sufficient theoretical and practical knowledge [20-22]. The physical and mental health of future medical specialists is an essential component of their qualified training since students are occupied with a busy schedule, experience problems in keeping pace with the amount of information that they need to gain proficiency in, feel too much workload, and a large number of problematic issues during the practical part of their training [23-25]. For example, challenges during the clinical practice of medical students in healthcare institutions include working with adults and children who were first affected by COVID-19 and later by the war, and as a result, exhibit behavioral disorders or negative habits [26, 27]. A particularly negative impact on students in wartime conditions is the destruction of the value system: what people once considered important and unshakable (human life, peace, justice, truth, mercy, etc.) is now often no longer unquestioningly upheld. During wartime, long-established life guidelines, including those shaped within the family and through life experience, lose their relevance as society finds itself in conditions of dehumanization, violence, and the destruction of stability [28. 29]. People are forced to operate in survival mode, pushing moral principles into the background, while propaganda and information manipulation undermine faith in truth and justice. The loss of loved ones, constant fear, and lack of resources deepen cynicism, disappointment, and apathy.The aggressor state spreads disinformation and commits war crimes based on the narcissistic and other negative traits of its leadership, driven by an excessive desire for power and control, with the usurper achieving success at the expense of oppressing others. In the modern world, there is a collapse of public sphere ethics, leading to abuses and appropriations committed by authoritative figures, as well as a struggle against„modesty"in social life. This, in turn, negatively affects the mental well-being of ordinary people.

For the high-quality training of future doctors during the war, it is crucial to pay more attention to post-traumatic stress disorders,depression, and anxiety in students.

AIM

The aim of the study is to determine the prevalence of traumatization, depression, stress, and anxiety during the war in the rear western region of Ukraine.

MTERIALS AND METHODS

For the study of the war's impact on the psychological state of medical students to be successful, it is essential to analyze various influencing factors and explore possible ways of supporting students in difficult situations duringmilitary conflict. The 1 to 6-year students of the Medical Faculty of I. Horbachevsky Ternopil National Medical University, who voluntarily completed the DASS-21 survey scale, participated in our research on students' mental health. The statistical sample was 716 students.

The degree of depression, anxiety, and stress has been measured using the Depression, Anxiety, and Stress Scale (DASS)-21 [30]. The DASS-21 scale consisted of 21 items that included three self-assessment scales designed to measure emotional states of depression, anxiety, and stress. Each scale countedseven items, divided into subscales with similar content. The values of the DASS-21 rating scale were: 0- does not apply at all; 1- applies to a certain extent or during a specificperiod; 2- applies to a large extent or during a significantperiod; 3- applies very often. This scale is characterized by high reliability (Cronbach's alpha): (depression ($\alpha = 0.92$), anxiety ($\alpha = 0.95$), stress ($\alpha = 0.87$)). According to the results of the questionnaire analysis, regular, mild, moderate, severe, and very severe degrees of depression, anxiety, and stress have been distinguished.

To compare the degree of the emotional state of depression, anxiety, and stress in medical students, we have used a survey conducted among the students (716 people) of I. Horbachevsky Ternopil National Medical University in 2019 and 2024.

Processing of the obtained statistical data has been carried out using the SPSS program version 21. To determine the severity of stress, anxiety, depression, and the degree of post-traumatic stress disorder, we have used the descriptive statistical method (average value, standard deviation). The frequency of the studied parameters was indicated as the absolute value (n) and the percentage (%). Pearson's chi-square test ($\chi 2$) was used to compare indicators. Quantitative indicators were compared using Student's t-test. Differences are generally accepted to bereliable at $p<0,05$.

RESULTS

The prevalence of depression, anxiety, and stress among medical students in the western region of Ukraine after 24 months of the war, according to the results of the analysis of the DASS-21 questionnaire, is presented in the Table. 1.

In 2019, the degree of depression severity among the students was determined to be 50.9%, anxiety – 48.9%, and stress – 50.7%. After two years of the war, in 2024, this indicator is already 65.8%, 65.9 %, and 74.7%, respectively, which is 1.3 times higher than the degree of depression and anxiety severity and 1.5 times higher than the degree of stress severity in 2019 (Table 1).

We consider that war is not only about military actions or physical conflict, but

also profound psychological trauma that affects individuals on all levels. As a result of daily stressors, experiences of loss, forced displacement and uncertainty about the future, people

Table 1. Prevalence of severity degrees of depression, anxiety, and stressamong medical students in the western region of Ukraine in 2019 and 2024

Indicator degree	General data, n=716			
	n	%	n	%
	2019		2024	
		Depression		
Normal	350	48.7	243	33,8
Mild	137	19.0	137	19,0
Moderate	140	19,5	148	20.6
Severe	56	7.8	107	14.9
Very severe	33	4.6	81	11.3
		Anxiety		
Normal	364	50.6	242	33.6
Mild	92	12.8	104	14.5
Moderate	92	12.8	136	18.9
Severe	58	8.0	56	7.8
Very severe	110	15.3	178	24.7
		Stress		
Normal	351	48.8	179	24.8
Mild	121	16,8	99	13.7
Moderate	113	15.7	181	25.2
Severe	105	14,6	194	27.0
Very severe	26	3.6	63	8.8

Source: compiled by the authors of this study

face tremendous emotional burdens. Constant air raid alerts, shelling, the threat of death and fear for loved ones lead to a persistent state of anxiety. Many individuals suffer from sleep disturbances, hypersensitivity to noise and heightened reactivity, which are often accompanied by stress and depression.

In 2019, severe and very severe depression was found in 12.4%, anxiety in 23.3%, and stress in 18.2% of students, while in 2024, these indicators were 26.2%, 32.5%, and 35.8%, respectively (Fig.1 and 2).

When comparing the prevalence of depression, anxiety, and stress in male and female medical students, it was found that those symptoms were more common in women than in men. Moreover, the prevalence of depression is 1.7 times higher (p=0.001), and stress and anxiety are 1.3 times higher (p=0.001) in female students due to severe and very severe degrees of expressiveness (Table 2).

Stress, depression and anxiety during wartime arise due to the impact of external stimuli on the human body under extreme tension, when external influences exceed the normal thresholds of the human nervous system. Each new difficult situation demands particular attention and specific responses from us.

Research results indicate several stages of stress, beginning with anxiety and depression and culminating in complete exhaustion. A comparison of depression, anxiety, and stress levels among men in the western region of Ukraine in 2019 and 2024 shows that severe and very severe levels of depression have doubled or more (Fig. 3 and 4).

Considering the challenges of conducting combat operations under current conditions, the specific nature of tasks, constant physical and psychological demands, prolonged exhaustion and extreme stress, along with threats to life and safety, lack of rotations, social isolation, alienation from family and society, and demobilization – all of these contribute to the development of stress, anxiety, and depression caused by extreme situations on the front lines. This results in psycho-emotional burnout and physical fatigue, which can later develop into low self-esteem, frustration, fears, a generally negative outlook on life priorities, family conflicts, addiction, substance abuse, depressive disorders and more.

Stress resilience is an important human trait that enables individuals to manage their actions and emotions under stress effectively, maintain focus while under emotional pressure, solve problems successfully, and apply appropriate coping strategies.

Based on the results of our study, we observe a tendency toward decreased stress resilience among women in 2019 and 2024. When a person's stress resilience is at a very low level, they (in this case, women) are unable to find internal or external resources to help them overcome the effects of stress factors on the body (Fig. 5 and 6).

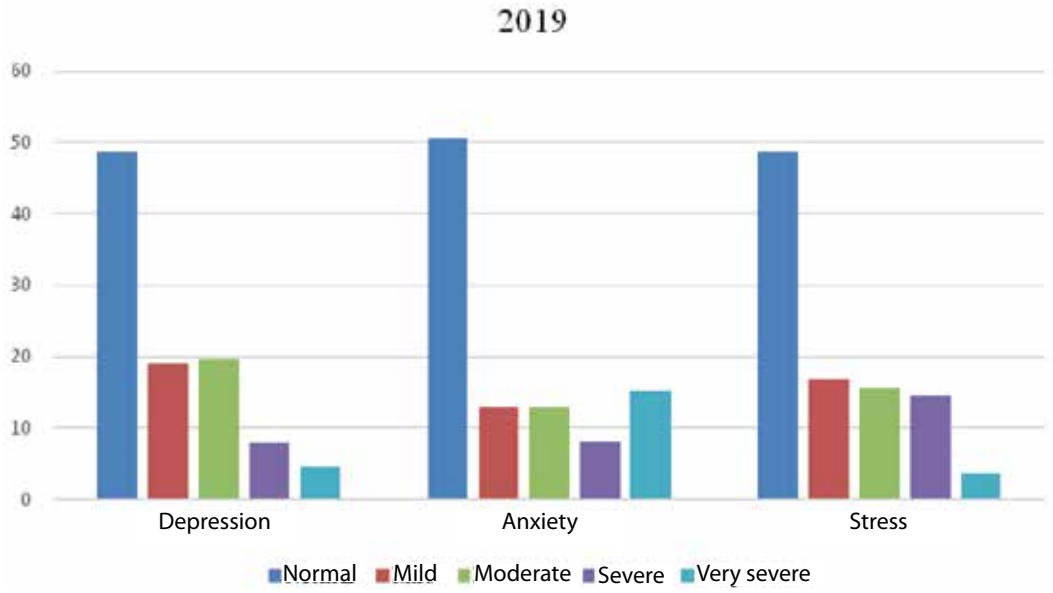

Fig. 1. Degrees of depression, anxiety, and stress severity amongmedical students of the western region of Ukraine in 2019

Picture taken by the authors

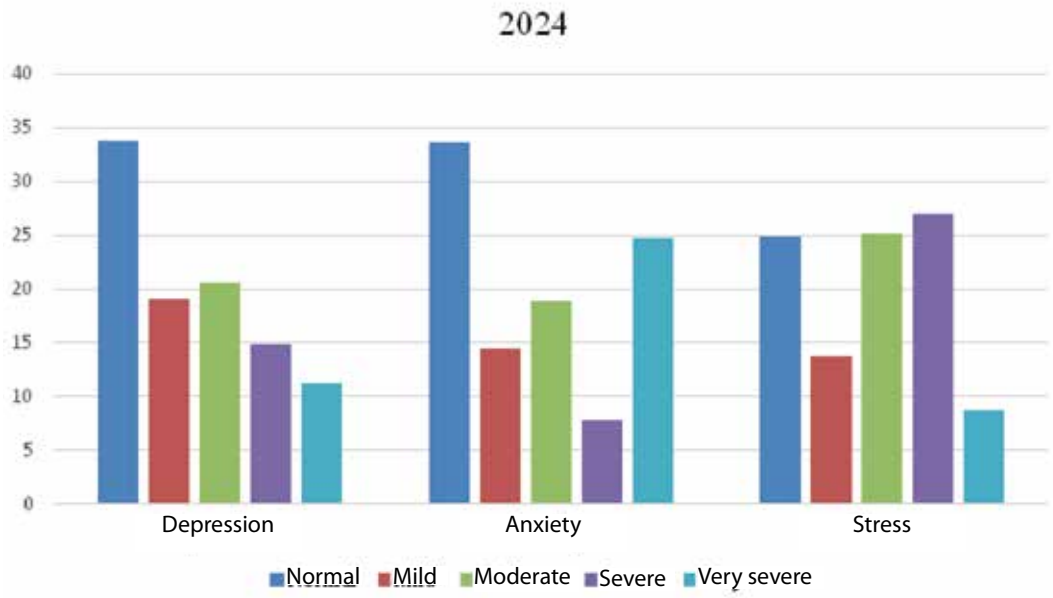

Fig. 2. Degrees of depression, anxiety, and stress severity among medical students of the western region of Ukraine in 2024

Picture taken by the authors

The results of the study show that the female psyche „suffers" significantly more than the male psyche - due to psychophysiological characteristics and greater sensitivity to stress. Women experience depression and emotional problems more frequently than men. In examining the levels of depression, anxiety and stress among women in the western region of Ukraine in 2024, we recorded a wide range of emotional disorders, including increased irritability, anxiety, fear, worry, depressed mood and apathy caused by the loss of loved ones, home, employment, social status, a stable life, uncertainty about the future, and the need to survive in a new and unfamiliar environment.

DISCUSSION

Many factors that negatively affect the state of mental health of students can be singled out. During the war, Ukrainian universities suffered significant human losses: teachers, students, and their relatives died due to military actions and Russian occupation. Several universities have been destroyed or damaged. Thousands of Ukrainian students and teachers were forced to relocate within the country or go abroad [31]. Every day, all those involved in the educational process must overcome war trials: forced interruptions during classes, transition to distance or mixed forms of education, warnings of air raids, and power outages. A full-scale war reduced the

Table 2. Prevalence of severity degrees of depression, anxiety, and stress among medical students in the western region of Ukraine according to gender

Indicator degree	General data, n=716							
	Men				Women			
	180		194		536		522	
	n	%	n	%	n	%	n	%
	2019		2024		2019		2024	
	Depression							
Normal	92	50.6	84	42.8	218	40.5	114	27.8
Mild	37	20.4	30	15.3	90	16.7	75	14.3
Moderate	30	17.0	30	15.3	113	21.0	113	21.5
Severe	11	6.1	24	12.2	75	14.0	120	22.9
Very severe	10	4.9	26	13.3	40	7.4	100	19.1
	Anxiety							
Normal	110	60.5	102	52.0	214	39.8	130	24.7
Mild	25	13.8	28	14.2	77	14.3	77	14.7
Moderate	13	7.2	16	8.1	79	14.6	79	15.1
Severe	16	8.8	19	9.7	62	11.5	72	13.8
Very severe	16	8.8	29	14.8	104	19.3	164	31.3
	Stress							
Normal	98	53.9	90	45.9	203	37.8	98	18.7
Mild	20	11.0	23	11.7	91	17.0	51	9.7
Moderate	39	21.5	32	16.3	114	21.2	104	19.8
Severe	14	7.7	37	18.9	91	17.0	161	30.8
Very severe	9	5.0	12	6.1	37	6.8	108	20.6

Source: compiled by the authors of this study

access to education. People who have been forced to leave Ukraine and study abroad suffer from mental disorders. They feel the pain of losing contact with family and loved ones, the death of family members, difficulties in being understood by foreigners, and the challenge of a language barrier [32]. Medical students may themselves be these people or will work with them during their professional careers. It deepened educational inequality, negatively affected the quality of the educational process and students' academic progress, and, of course, the emotional state of students and academic staff. The mental well-being of students is also influenced by their interaction with teachers, who, due to constant work under stress, may experience professional burnout [33]. Another cause of these disorders in students may be the realization of the need to maintain a balance between a normal level of mental health, work, and personal life, which is extremely difficult in wartime conditions [34].

Withinan extensivesurvey of I. Horbachevsky Ternopil National Medical Universitystudents, 98% said they had been affected by the war in some way, 86% suffered from war-related nightmares, 49% experienced symptoms of insomnia, and 27% had symptoms of post-traumatic stress disorder. However, mental health varied according to closeness to the war zone or direct involvement in it. Another study among the students showed that every second respondent had symptoms of psychological distress (52.7%), anxiety (54.1%), and depression (46.8%). Insomnia was found in 12.1% of participants. Mental health problems were associated with some demographic variables, such as gender, living in an urban area, having children or the elderly, and living in a territory occupied by Russian forces.

It is evident that during martial law, motivation and effective strategies for stress coping play an essential role in the mental health of young people. Higher Education Institution Policy in Ukraine is focused on such aspects: 1) the educational environment should be as comfortable as possible for all participants in the learning process, and the administration of each educational institution is responsible for this by ensuring that ist staff improves their competence in working under martial law conditions; 2) to establish an analytical center to study the impact of stress factors on young people and further work to reduce this impact in the educational process; 3) to ensure conditions for interpersonal interaction and psychological resilience among students in the process of studying academic disciplines by offering stress management workshops.

To improve or maintain mental health, it is necessary to find specific resources that can help you cope with various

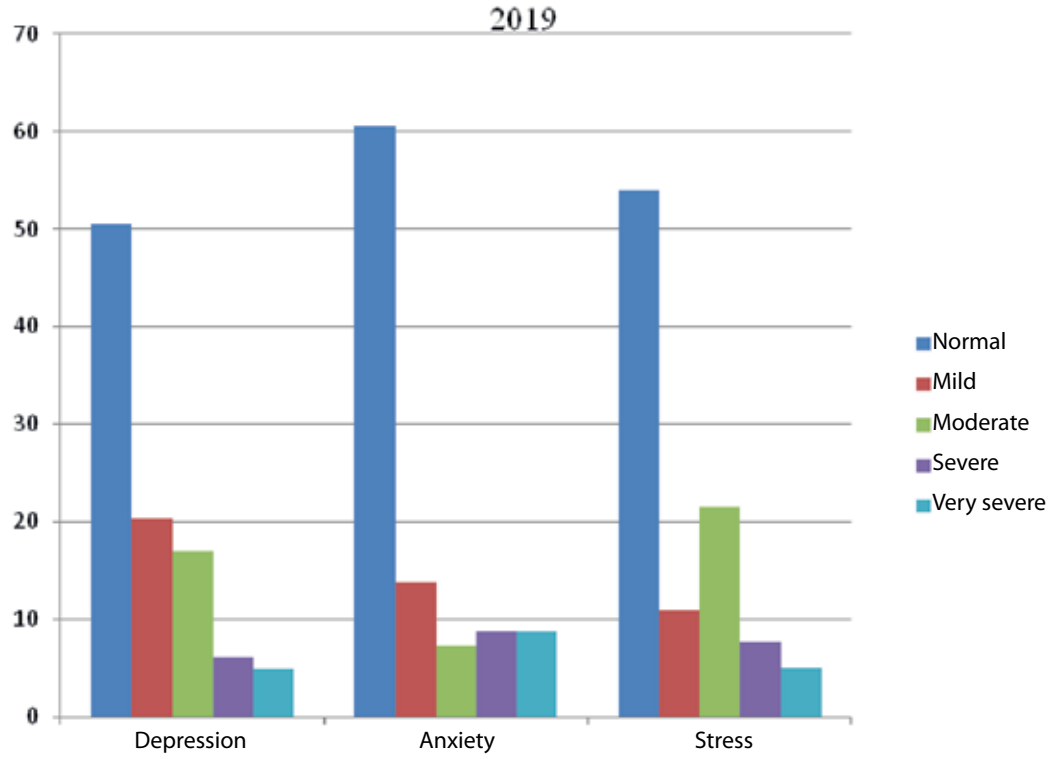

Fig. 3. Degrees of depression, anxiety, and stress severity among men in the western region of Ukraine in 2019

Picture taken by the authors

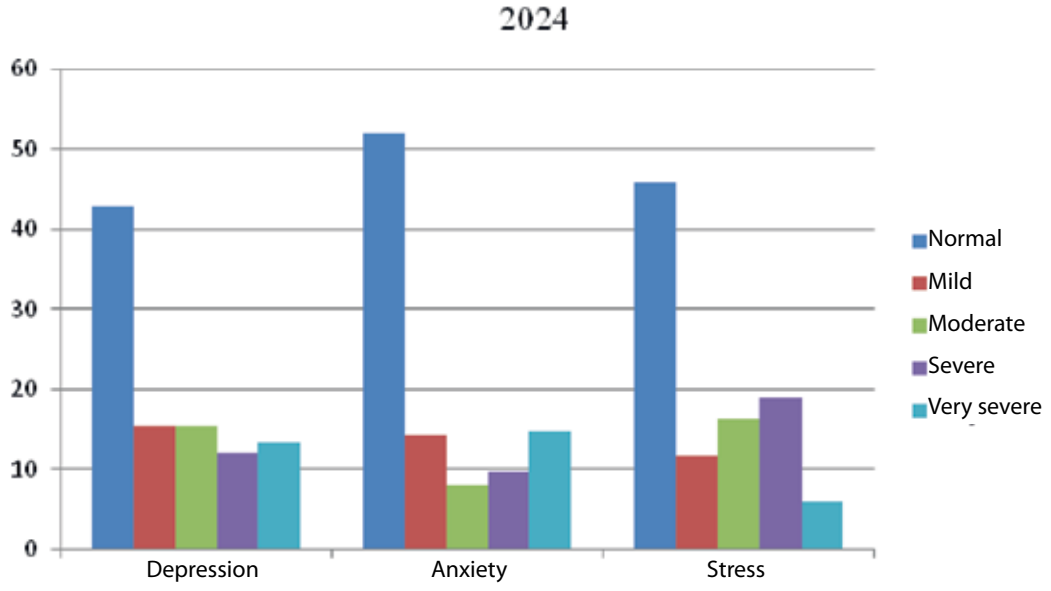

Fig. 4. Degrees of depression, anxiety, and stress severity among men in the western region of Ukraine in 2024

Picture taken by the authors

challenging situations. It is worth paying attention to internal resources that contribute to psychological resilience in stressful situations. Since a person is a social being, one of the most criticalfactors for preserving mental health is social support. An excellent social environment helps a person better tolerate certain difficult situations. This helps to increase psychological stability during martial law [35].

One more source for maintaining mental health is the psychological competence of an individual. This includes the level of psychological education and culture. Other vitalfactors are physical. They include the state of health in general and the attitude towards it as a value. Material means

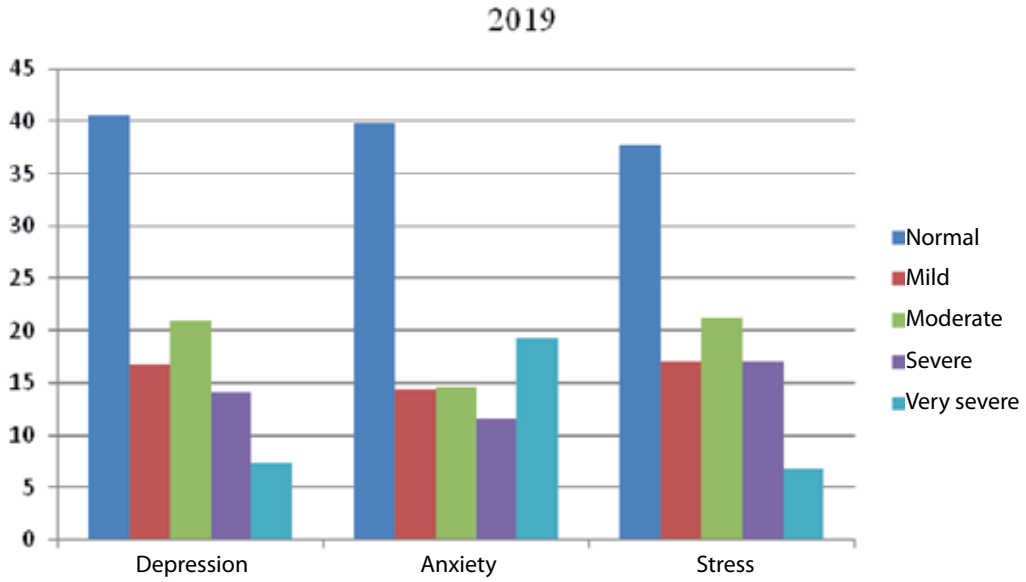

Fig. 5. Degrees of depression, anxiety, and stress severity amongwomen in the western region of Ukraine in 2019

Picture taken by the authors

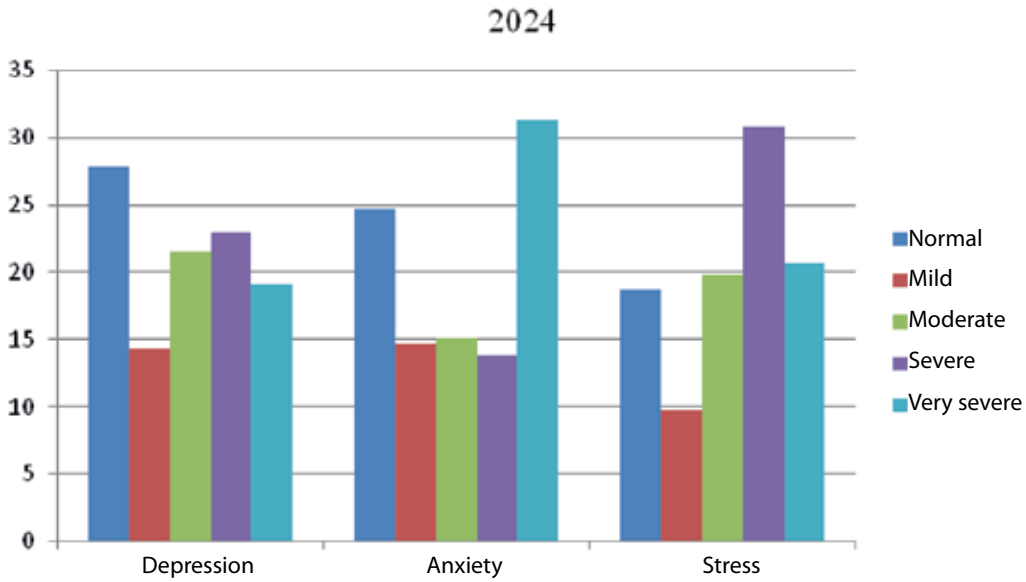

Fig. 6. Degrees of depression, anxiety, and stress severity amongwomen in the western region of Ukraine in 2024

Picture taken by the authors

also have a strong influence on maintaining psychological well-being. For example, people with a goodincome level will feel more confident because they will be sure they can provide for their family.

Students experiencing stress and depression due to war events can overcome these conditions through therapy, such as canistherapy, humor therapy, art therapy, and integrative support sessions, where psychosocial and spiritual needs, problems, and difficult emotions are discussed in a safe and confidential environment based on active listening and genuine empathy.

War can lead to significant psychological stress for medical students who can witness or directly perform medical actions in the context of military conflict. This stress can affect their ability to focus on their studies and learn new material. The following methods and means can be used to overcome psychological stress caused by war: psychological support, group sessions, stress management, the flexibility of the educational process, social support, and independent preparation for stress.Universities can provide students with psychological support and counseling, lettingthem express their feelings and cope with stress. Organizing

group sessions for students to discuss shared concerns and experiences will help them get support from like-minded people. Learning and implementing stress management techniques such as relaxation, meditation, and physical activity can reduce students' stress levels. To relieve academic pressure, universities can consider flexible learning, distance learning, or increased deadlines. Fostering a social support network among students is essential [36].

CONCLUSIONS

Taking into account the results of this study, it can be concluded that the war in Ukraine hurts the mental health and educational abilities of medical students. Maintaining mental health is an essential factor for their academic progress. As the trauma of war can persist for years after its end, there is a need to monitor the psychological state and well-being of students systematically. It is equally important to study the aspects of strengthening psychological health and the resources that may be needed for this. The main aspects of maintaining students' mental health in martial law conditions are all types of resources (personal, physical, informational, and other), psychological competence, social support, as well as methods of mental training and simulation modeling techniques.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

The impact of judo training on the morphofunctional state and physical fitness of healthy adolescents

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ABSTRACT

Aim: The aim is to investigate the impact of an experimental judo training program on the morphofunctional state and physical fitness of healthy adolescents.
Materials and Methods: The study involved 54 male adolescents aged 16-17, who were divided into an experimental group (EG, n=27) and a control group (CG, n=27). The morphofunctional state of the students was evaluated based on the indicators of muscular, cardiovascular, and respiratory system activities, while physical fitness was assessed using physical education tests.
Results: It was found that during the experiment, adolescents' morphofunctional state and physical fitness indicators improved in both groups. However, in the EG, the difference between the initial and final data was significant (p 0.05). Moreover, at the end of the experiment, all the studied indicators in the EG were significantly better than in the CG. The most pronounced impact of judo training was observed on the strength index, Ruffier index, Stange index, Genchi index, Robinson index, and the results in the long jump, pull-ups, push-ups, and trunk lifts.
Conclusions: It was proven that extracurricular judo training sessions, provided that adolescents consciously choose the sport and are motivated to participate, as well as the rational planning of training sessions, are more effective compared to traditional physical education lessons in high school for improving the morphofunctional state and physical fitness of healthy adolescents. The high level of the studied indicators in adolescents will enhance their health and improve their future educational and professional activities.

KEY WORDS: judo, adolescents, morphofunctional state, physical fitness, health, physical education

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INTRODUCTION

Due to the reform of education in Ukraine and the establishment of the New Ukrainian School, radical changes are occurring in all areas of activity, including physical education and sports. This has led to an active search for new forms, methods, and means of physical education that would contribute to strengthening the health of school youth, improving the morphofunctional state of their main body systems, and enhancing their physical fitness levels [1]. Given that Ukraine has been at war with Russian aggressors for over two years, it is particularly important and relevant to improve the physical education of adolescents, specifically high school students – the future defenders of Ukraine [2].

At the same time, research findings from numerous scientists [3, 4] indicate that the level of somatic health, morphofunctional state, and physical fitness of modern adolescents is insufficient for their further educational and professional activities, military service in the Armed Forces of Ukraine, and overall life activities due to a number of problems. According to scientists [5, 6], a person-centered approach, which involves matching the forms, methods, and means of physical education to the individual psychological characteristics of adolescents and allowing the freedom to choose physical activities or sports that best suit their personal abilities, could be the basis for improving physical education in schools.

Scientists [7, 8] claim that various martial arts (aikido, karate, taekwondo, jiu-jitsu, etc.), combat sports (kickboxing, boxing, MMA, hand-to-hand combat, Muay Thai, etc.), and types of wrestling (judo, sambo, combat sambo, freestyle wrestling, Greco-Roman wrestling) are highly popular among adolescents. These sports can be effective means of physical education for adolescents, enhancing their physical fitness levels, improving their morphofunctional state, strengthening their health, and preparing them for life. One of these sports, which has significant practical importance, contributes to the health improvement of adolescents, enhances their physical fitness levels, and fosters motivation for regular physical exercise, is judo [9]. Judo training helps develop speed-strength abilities, general and strength endurance, flexibility, and coordination, increases physical performance, and fosters the formation of volitional qualities in adolescents. The physical fitness achieved by adolescents through judo

training has broad positive carryover and contributes to high achievements in professional activities, daily life, and other types of physical activity [9].

At the same time, experts [10] note that in the process of planning judo classes, it is important to consider the age and anatomical-physiological characteristics of adolescents. According to scientists [11], the age of 16 to 17 is the most favorable for the development and improvement of most physical qualities and abilities of adolescents, particularly speed-strength, which underlies high achievements in this sport. Given the above, the development and testing of an experimental judo training program regarding the impact of this sport on the morphofunctional state and physical fitness of adolescents (high school students) is relevant.

AIM

The aim is to investigate the impact of an experimental judo training program on the morphofunctional state and physical fitness of healthy adolescents.

MATERIALS AND METHODS

The study was conducted in 2023-2024 at Secondary School No. 20 with enhanced physical training (Zhytomyr, Ukraine) and the Department of Physical Education and Sport Improvement of Zhytomyr Ivan Franko State University. The study involved 54 male adolescents (10th-11th grade students aged 16-17), who were divided into an experimental group (EG, n=27) and a control group (CG, n=27). All 54 adolescents were classified as being in the main medical group for physical education classes (i.e., they were healthy).

The adolescents in the EG participated in a school judo sports section following an author's experimental program during extracurricular hours under the guidance of a judo coach-instructor (they were exempted from physical education classes). The adolescents in the CG attended traditional physical education classes conducted by the school's physical education teacher and did not engage in any additional sports activities. The selection of adolescents into groups was carried out by surveying them to provide them with the right to choose the sport they wished to engage in during extracurricular hours, depending on the available sports sections and, accordingly, the coach-instructors at the school.

The number of sessions per week in each group was the same, with 3 sessions per week, each lasting 45 minutes. The duration of the experiment was 9 months (from September 2023 to May 2024).

The author's experimental program was developed according to the age characteristics of 16-17-year-old adolescents (taking into account the sensitive patterns of physical quality development). The program includes: means, methods, and forms of training; methods of dosing physical loads throughout the academic year and during individual training sessions; and aims at fostering harmonious physical development, strengthening health, enhancing the body's functional capabilities, and forming motivation for physical activity considering the adolescents' interests in self-expression and realizing their potential in training activities.

The main tasks of the experimental program include: improving the general physical fitness level of adolescents; mastering judo techniques and enhancing the technical-tactical mastery of judo moves; improving the functional capabilities of adolescents' bodies; and forming positive motivation for regular physical exercise and the chosen sport.

The author's program includes: the distribution of adolescents by levels of physical fitness (low, average, high); variability of means (general developmental and specific preparatory exercises) depending on the adolescents' physical fitness level; learning judo techniques and combinations of techniques; regulation of the volume and intensity of load during training sessions; application of group training with differentiated and individual approaches; use of various teaching methods; use of special movement games with elements of wrestling; use of pedagogical and operational control over students' health, technical, and physical preparation. The application of special movement games with elements of wrestling helps develop speed-strength abilities; physical exercises with elastic bands and ropes ensure high density of judo training sessions; a wide range of techniques with dummies and partners allows for rational dosing of physical loads; controlled increase in physical load according to individual capabilities of adolescents, which contributes to health improvement, increased performance, and enhancement of the morphofunctional state of adolescents' bodies; participation in regional competitions, allowing adolescents to achieve sports ranks and increase their motivation for judo; and a high level of general physical fitness that provides a solid foundation for developing professionally relevant qualities for future professional activity and life skills, are the features of the 9-month author's experimental judo training program.

Research methods: bibliosemantic, medical-biological, testing, and mathematical-statistical methods. The bibliosemantic method was used to determine the state of the problem through the analysis of literary sources and electronic resources. A total of 20 scientific sources were reviewed, most of which are included in scientific databases such as Scopus, Web of Science Core Collection, PubMed, Index Copernicus, and others. Medical-biological methods were used to assess the morphofunctional state of the muscular, cardiovascular, and respiratory systems of adolescents using indices such as the strength index, life index, Ruffier index, Stange index, Genchi index, and Robinson index [12]. The testing method was applied to evaluate the physical fitness of adolescents using tests such as the 30-meter run, standing long jump, pull-ups on a bar, push-ups from a prone position for 1 minute, trunk lifts in a sitting position for 30 seconds, and shuttle run 4x9 meters. Mathematical-statistical methods were used for quantitative processing of the obtained data, qualitative analysis, and evaluation of reliability using the Student's t-test. The reliability for all studies was established at no lower than $p<0.05$. Results are presented as M±m, where M is the arithmetic mean and m is the standard deviation error. All statistical analyses were conducted using IBM SPSS Statistics 21 software, adapted for medical research.

This study adheres to the Academic Integrity Policy of Zhytomyr Ivan Franko State University and the Helsinki Declaration of the World Medical Association. The research topic was approved by the Academic Council of Zhytomyr Ivan Franko State University (protocol No. 2 dated 18.09.2023). Consent for voluntary participation was obtained from all adolescents involved in the study.

RESULTS

A comparative analysis of the morphofunctional state indicators of adolescents in the EG and CG at the beginning and end of the pedagogical experiment, as well as the dynamics of the investigated indicators in each group during the pedagogical experiment, is presented in Table 1.

There was no significant difference ($p>0.05$) between all the investigated morphofunctional state indicators of adolescents in the EG and CG at the beginning of the experiment. During the experiment, most indicators showed a trend towards improvement in both groups of adolescents; however, in the EG, the difference between the indicators at the beginning and end of the experiment was significant for all investigated indices ($p<0.05$-0.001), while in the CG it was not ($p>0.05$), except for the vital index ($p<0.05$). Moreover, at the end of the experiment, all investigated indicators in the EG adolescents were significantly ($p<0.05$-0.001) better than in the CG.

The most pronounced effect of judo training was observed on the following indices in the EG adolescents: strength index, Ruffier index, Stange index, Genchi index, and Robinson index. Specifically, at the end of the experiment, the EG adolescents had better results than the CG by 8.33% in the strength index ($p<0.05$), by 3.59 units in the Ruffier index ($p<0.001$), by 6.71 seconds in the Stange index ($p<0.05$), by 6.13 seconds in the Genchi index ($p<0.001$), and by 3.78 units in the Robinson index ($p<0.05$). The conducted research indicates that judo training sessions, provided there is a conscious choice of sport and motivation for participation, are more effective compared to traditional physical education classes in senior grades for improving the morphofunctional state of 16-17-year-old adolescents.

The level of physical fitness of adolescents in the EG and CG at the beginning and end of the pedagogical experiment, as well as the dynamics of the development of their motor qualities during the study, are presented in Table 2.

At the beginning of the experiment, the level of physical qualities in adolescents from both the EG and CG was not significantly different across all tests ($p>0.05$). At the end of the experiment, adolescents in the EG demonstrated significantly better physical fitness across all tested measures compared to the CG: 0.07 seconds faster in the 30 m sprint ($p<0.05$), 11 cm longer in the standing long jump ($p<0.01$), 4.64 more pull-ups on the bar ($p<0.001$), 4.29 more push-ups ($p<0.05$), 3.51

Table 1. Dynamics of morphofunctional state indicators of adolescents in the EG (n=27) and CG (n=27) throughout the pedagogical experiment (n=54, M±m)

Investigated indicators/ Significance of difference	Groups	Stages of the experiment		Δ	Significance of difference	
		Beginning	End		t	p
Strength Index, %	EG	64.23±1.78	73.57±1.64	9.34	3.86	<0.01
	CG	63.58±1.82	65.24±1.74	1.66	0.72	>0.05
t; p		0.26; >0.05	3.48; <0.05			
Vital Index, ml/kg	EG	61.12±1.84	66.54±1.92	5.42	2.04	<0.05
	CG	61.86±1.82	63.91±1.89	2.05	0.78	>0.05
t; p		0.29; >0.05	0.98; >0.05			
Ruffier Test, units (y.o.)	EG	13.26±0.45	7.72±0.31	5.54	10.14	<0.001
	CG	12.85±0.40	11.31±0.36	1.54	2.86	<0.05
t; p		0.68; >0.05	7.56; <0.001			
Stange Test, s	EG	46.53±1.86	58.17±1.54	11.64	4.82	<0.001
	CG	45.57±2.35	51.46±1.84	5.89	1.97	>0.05
t; p		0.32; >0.05	2.80; <0.05			
Genchi Test, s	EG	30.73±0.66	37.24±0.53	6.51	7.69	<0.001
	CG	29.83±0.54	31.11±0.55	1.28	1.66	>0.05
t; p		1.06; >0.05	8.03; <0.001			
Robinson Index, units (y.o.)	EG	86.91±1.23	81.12±1.07	5.79	3.55	<0.01
	CG	86.55±1.16	84.90±1.11	1.65	1.03	>0.05
t; p		0.21; >0.05	2.45; <0.05			

Note: Δ – increase in indicators over the experimental period; t – value of the Student's t-test; p – significance of the difference between the investigated indicators

Source: compiled by the authors of this study

Table 2. Dynamics of physical fitness of adolescents in the EG (n=27) and CG (n=27) throughout the pedagogical experiment (n=54, M±m)

Tests/ Significance of difference	Groups	Stages of the experiment		Δ	Significance of difference	
		Beginning	End		t	p
30 m Sprint, s	EG	6.04±0.12	5,470,10	0.57	3,65	<0.01
	CG	6.61±0.13	5,54±0,11	0.37	1,94	>0.05
t; p		0.92; >0.05	2.26; <0.05			
Standing Long Jump, cm	EG	204.1±2.77	219,4±2,71	16.3	3,95	<0.001
	CG	201.7±2.58	208,4±2,49	6.7	1,87	>0.05
t; p		0.63; >0.05	2.99; <0.01			
Pull-ups on Bar, times	EG	8.56±0.59	13,72±0,52	5.16	6,56	<0.001
	CG	7.78±0.62	9,08±0,57	1.30	1,54	>0.05
t; p		0.91; >0.05	6.01; <0.001			
Bending the arms in a lying position (1 min), times	EG	22.65±1.12	29,18±1,14	6.53	4.09	<0.001
	CG	21.96±1.07	24,89±1,04	2.93	1.96	>0.05
t; p		0.45; >0.05	2.78; <0.05			
Raising the torso in the saddle (30 s), times	EG	16.55±1.02	24,16±1,05	6.61	4,52	<0.001
	CG	17.04±0.97	20,65±0,99	2.61	1.88	>0.05
t; p		0,35; >0.05	2.43; <0.05			
Shuttle run 4x9 m, s	EG	10.91±0.13	10,12±0,12	0.79	4,47	<0.001
	CG	10.65±0.12	10,43±0,11	0.20	1,23	>0.05
t; p		1,47; >0.05	2.03; <0.05			

Note: Δ – increase in indicators over the experimental period; t – value of the Student's t-test; p – significance of the difference between the investigated indicators

Source: compiled by the authors of this study

more sit-ups (p<0.05), and 0.31 seconds faster in the shuttle run (p<0.05). The greatest effect of judo training was observed in the development of speed-strength qualities, strength endurance, and agility. Over the experimental period, results improved in all tests for both groups, but the changes in the EG were statistically significant (p<0.05-0.001), whereas those in the CG were not (p>0.05). This demonstrates the positive impact of the experimental judo training program on the physical fitness level of adolescents aged 16-17.

DISCUSSION

Given the current low levels of health and physical fitness among students in general education schools, their insufficient motivation for physical activity, non-adherence to healthy lifestyle principles, and the negative impact of the learning conditions during the state of martial law in Ukraine, as well as the inadequate quality of physical education lessons, numerous scientific studies [13] reflect efforts to renew and improve the existing process of physical education for adolescents. Various approaches are proposed for organizing both curricular and extracurricular forms of physical education for students, including those in senior classes.

Our previous research [14, 15] has established that a promising direction for improving the current process of physical education for adolescents is the introduction of sports-oriented health and sports training technologies. The organization of the physical education process based on students' self-selection of physical activities is considered the most progressive form. This approach stimulates interest in specific sports and the development of physical abilities. By providing freedom in choosing physical activities (or any sport), students can demonstrate self-initiative and, consequently, have full autonomy in learning: having chosen the activity themselves, they are more motivated to acquire knowledge and skills in that area. The ability for students to rely on their own feelings and desires in choosing physical activities is of significant importance [16].

At the same time, the analysis of physical education forms in schools indicates that their effectiveness does not meet modern requirements. In many secondary education institutions, physical education and sports events are organized at a low educational and methodological level. The number of students interested in participating in school sports clubs and physical education extracurricular activities is relatively small [17].

When implementing modern sports-oriented technologies in secondary education institutions, it is crucial to remember that, in addition to developing specific sports skills and abilities in adolescents, it is necessary to cultivate vital motor skills, acquire knowledge about a healthy lifestyle, and foster a conscious need for regular physical exercise.

One of the key incentives for students' interest in systematic training in a particular sport includes: improving health and body shape, socializing and forming friendships with peers, participating in competitions and earning medals and awards, and achieving high sports results [18]. Additionally, extracurricular training sessions or physical education classes organized in an individualized format play important roles: promoting and advertising sports and wellness activities, engaging students in productive and enjoyable leisure activities, improving the social and psychological climate in student groups, and setting personal records [19]. Thus, a promising direction for addressing the above-mentioned issues is the implementation of a person-centered approach to physical education in general secondary education institutions, taking into account students' free choice of sport. This approach should consider the material and technical resources available, students' motivation and preferences, and the availability of qualified sports specialists.

Based on a number of studies and considering the high interest among modern adolescents in martial arts, we have developed and substantiated an experimental judo program for school extracurricular activities and implemented it into the physical education curriculum at one of the schools in Zhytomyr.

As a result of implementing the author's experimental judo program into the training process of the school judo section and evaluating its effectiveness over a period of 9 months, we have confirmed the findings of many researchers that adolescents aged 16-17 experience intensive development of speed-strength qualities, muscular endurance, and agility. This facilitates effective acquisition of motor skills and abilities and serves as a prerequisite for the effective execution of judo techniques during training and competitive activities. Additionally, we have expanded upon the data of researchers [7, 9, 11, 17, 20] regarding the organization of the judo training process, the planning of training preparation, and the methodology for teaching and developing physical qualities and abilities of high school students, as well as improving their morphofunctional state and health through judo practice.

CONCLUSIONS

It was found that the indicators of morphofunctional status showed a tendency to improve in both groups of adolescents over the course of the experiment. However, in the experimental group (EG), the difference between the indicators at the beginning and end of the experiment was significant ($p<0.05$-0.001) for all the studied indices, while in the control group (CG) it was not significant ($p>0.05$). Furthermore, at the end of the experiment, all the indicators in the EG were significantly ($p<0.05$-0.001) better than those in the CG. The most pronounced effect of judo training was observed on the indices such as the strength index, Rufier index, Shange index, Genchi index, and Robinson index. At the end of the experiment, the EG showed improvements over the CG of 8.33% for the strength index ($p<0.05$), 3.59 units for the Rufier index ($p<0.001$), 6.71 seconds for the Shange index ($p<0.05$), 6.13 seconds for the Genchi index ($p<0.001$), and 3.78 units for the Robinson index ($p<0.05$).

It was found that the level of physical fitness in adolescents from the experimental group (EG) was significantly better than that in the control group (CG) at the end of the experiment for all the tested measures: by 0.07 seconds in the 30-meter sprint ($p<0.05$), by 11 cm in the standing long jump ($p<0.01$), by 4.64 repetitions in pull-ups ($p<0.001$), by 4.29 repetitions in push-ups ($p<0.05$), by 3.51 repetitions in sit-ups ($p<0.05$), and by 0.31 seconds in the shuttle run 4x9 meters ($p<0.05$). The greatest effect of judo training was observed on the development of speed-strength qualities, muscular endurance, and agility. During the experiment, results improved in both groups for all tests, but in the EG, these changes were significant ($p<0.05$-0.001), whereas in the CG, they were not significant ($p>0.05$).

The conducted research indicates that extracurricular judo training sessions based on the author's experimental program, provided there is a conscious choice of sport and motivation to participate, are more effective compared to traditional physical education classes for improving the morphofunctional state and physical fitness of healthy adolescents aged 16-17. The high level of the studied indicators in adolescents participating in judo is likely to contribute to their health improvement and enhance their future educational and professional activities.

Prospects for further research involve assessing the effectiveness of the author's judo program in improving the morphofunctional state and physical fitness of girls aged 16-17 during extracurricular training sessions.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Evaluation of fructosamine as a new biomarker in the diagnosis of diabetes mellitus

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ABSTRACT

Aim: To evaluate the using of fructosamine as a new biomarker in the diagnosis of diabetes mellitus.

Materials and Methods: This is a cross-sectional case-control study that was conducted at The Medical City, Baghdad/Iraq, from January to May 2024. In this study, 60 diabetic patients were compared with 60 apparently healthy controls. Information was collected from the hospital records and serum fructosamine was measured manually using the nitroblue tetrazolium colorimetric method.

Results: Serum fructosamine levels were significantly higher in diabetic patients (mean=367 µmol/l, SD=12.7) than in the controls (mean=242 µmol/l, SD=22.8), p<0.0001. Logistic regression found that high fructosamine levels were associated with a significantly increased risk of developing diabetes mellitus (odds ratio=1.45; 95% CI: 1.12-1.86; p-value <0.046). Diagnostic performance analysis yielded a sensitivity of 79% and specificity of 73% (p-value=0.033).

Conclusions: Its high levels in the sera of diabetic patients, association with disease risk, and moderate diagnostic accuracy speak for the probable usefulness of this test in clinical practice, these results need confirmation in larger studies.

KEY WORDS: fructosamine, diabetes mellitus, pathophysiology, receiver operating characteristic

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INTRODUCTION

The major global health problem is diabetes mellitus, chronic hyperglycemia due to defecting insulin action, insulin secretion, or both. The two main types of conditions on which this is based are Type 1 diabetes (T1D), and Type 2 diabetes (T2D). These have pathophysiological and immunological mechanisms that are independent [1]. The classification of diabetes becomes critical in diagnosing the type and nature of diabetes. T1D is diagnosed based on autoimmune diseases, where there is evidence that a significant proportion of the pancreatic beta cells have been destroyed. This results in absolute insulin deficiency [2]. Contrastingly, T2D is a form of diabetes that results from insulin resistance juxtaposed to abundantly available insulin, increasingly also in obesity and the metabolic syndrome. Some other special scenarios are gestational diabetes and latent autoimmune diabetes in adults (LADA) because diabetes classification is complicated by another. The latter is commonly misdiagnosed as type 2 diabetes related to LADA because insulin resistance manifests before the need for treatment with insulin since the autoimmune destruction of β-cells also involves few instances of insulin resistance [3-4]. Fructosamine structure is largely that of a protein, mainly albumin, glycated by glucose through a non-enzymatic reaction. Although the general chemical processes of glycation are well documented, there is little specific structural information on fructosamine as an individual entity. Much of the literature covers general glycated proteins rather than fructosamine itself. Performing a more detailed search into the molecular structure of fructosamine may reveal how different variations in glycation affect its biological activity and stability [5-7]. Fructosamine molecules play various explicit and implicit roles, especially as a glycemic biomarker. It can be considered the best substitute for standard glucose evaluations since it calculates the average blood glucose concentration in a more relevant time window. In addition to certain metabolic disease states, and diabetes complications, which further support its wider applicability in clinical treatment [8]. However, such mechanisms and outcomes are unclear, to be signified by proper definitions and clarifications, proper ways to be known. Such gaps thus point toward more focused studies in discovering specific effects at the biological level. The clinical value of fructosamine as a marker for glycemic control is well appreciated, especially in cases where assessing hemoglobin A1c is not feasible [10]. Such as, for example, pathologies related to hemoglobin synthesis, like anemia or hemolysis, which do not allow efficient use of HbA1c as a diagnostic method. Then, fructosamine concentrations provide an interesting alternative view on the assessment

of glycaemia in a given patient. However, the difficulty with fructosamine levels being influenced by conditions like protein turnover and food intake makes its interpretation complex [11]. There exists only a limited, under researched relationship between these two glycemic indicators and the different states of health, stress, or inflammation [12]. Further knowledge of these dependencies would widen the scope of fructosamine applicability in routine diagnostics concerning not only diabetes but other health states as well. The aim of this work is to evaluate the potential use of fructosamine as a new biomarker in the diagnosis of diabetes mellitus.

MATERIALS AND METHODS

PATIENTS AND DATA COLLECTION

This cross-sectional case-control study was conducted at The Medical City in Baghdad, Iraq, from January 2024 to May 2024. Sixty confirmed cases of diabetes mellitus were involved in the study. The control consisted of an equal number of apparently healthy persons identified during the same period. Information related to general data on the patients was collected from the records of the teaching hospital. Fructosamine was measured by a manual colorimetric method using NBT. The method is based on the fact that ketoamines have reducing properties in an alkaline solution at 37°C. The change in absorbance was measured as the difference for 5 minutes around 10-15 minutes at a wavelength of 530 nm. The results were expressed in comparison with a standard that was composed of the Amadori rearrangement product, 1-deoxy-1-morpholino-D-fructose (DMF), in which equivalent 40 g/L human albumin is present, and which has been treated under identical conditions. The DMF standard was synthesized according to the method of Hodge and Rist (Mula-Abed, & Abdul-Razzak, 1999).

STATISTICAL ANALYSIS

Data were subjected to analysis using SPSS statistics version 25.0 software (SPSS, Chicago). The normality test was used to check the level of parametric data (Shapiro Wilk test). Normally distributed data are presented as mean±standard deviation and applied by an independent t-test. Receiver operating characteristic (ROC) curve was applied to test the predictive ability of fructosamine in the prediction of a relapse among DM patients. A probability value of less than 0.05 was considered statistically significant.

ETHICS APPROVAL

The protocol in this study was approved by the ethical committee of the Medical College in the University of Kufa (No. 243 in 2024).

CONSENT TO PARTICIPATE

Prior to collecting samples, all patients involved in the study were required to provide written consent for their participation.

RESULTS

The demographic distribution of diabetes mellitus (DM) patients is highly skewed toward the 60–69 years age group. Here, 35% of the DM group falls into this category compared to 33.33% in the control group. The mean age of DM patients is 46.33±12.47 years, which showcases a slightly younger profile in terms of overall cohorts. With respect to gender distribution, this stands almost even for both males at 53.33% and females at 46.67% of the DM cohort; the same pattern is repeated in the control group where males constitute 48.33% and females 51.67%. Therefore, balanced gender representation and the age-specific prevalence of DM was reiterated by these findings (Table 1).

Serum fructosamine levels are significantly higher in the patients than in the controls. The patients show a mean level of 367 µmol/L (SD=12.7) while the controls show a mean level of 242 µmol/L (SD=22.8). A p-value of less than 0.0001 at this high significance level underlines the potency of fructosamine as a diagnostic biomarker in distinguishing between healthy and diabetic subjects (Fig. 1).

The univariate logistic regression analysis proved that fructosamine levels are significantly associated with the risk of developing diabetes mellitus. In particular, the OR equals 1.45, which can be interpreted to mean a 45% increase in the odds of diabetes mellitus for a unit increase in fructosamine, 1.12-1.86, a very strong point estimate for this relationship. Further, the p-value <0.046 provides

Table 1. Distribution of DM patients by their demographic data

Items	Rating	DM P atients N=60		Control N=60	
		Freq	[%]	Freq	[%]
Age	30-39	13	21.67	15	25
	40-49	15	25	16	26.67
	50-59	11	18.33	9	15
	60-69	21	35	20	33.33
Mean ± SD 46.33 ± 12.47					
Gender	Male	32	53.33	29	48.33
	Female	28	46.67	31	51.67

Source: Own materials

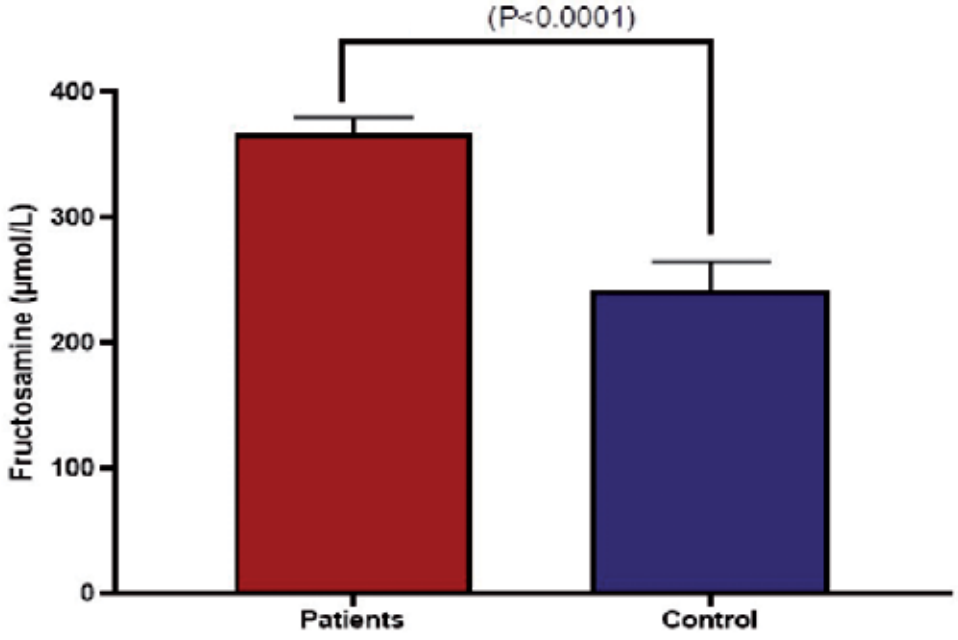

Fig. 1. Differences in serum Fructosamine (µmol/L) between patients and control groups

Source: Own materials

overwhelming evidence regarding the significance of this association and suggests the potential ability of fructosamine as a biomarker for diabetes risk assessment (Table 2).

The diagnostic performance of fructosamine in the diagnosis of DM just places its utility as a diagnostic test, AUC being 0.74, thereby indicating moderate accuracy. Sensitivity at 79% that it will diagnose 79% of the diabetics correctly and specificity at 73% that it will correctly rule out 73% of non-diabetics. The p-value, which is less than 0.05, is an additional statistical validation of fructosamine as a potential biomarker for DM diagnosis (Fig. 2; Table 3).

DISCUSSION

Fructosamine is a useful measure for glycemic control in those circumstances where the long-term index of glycemic control, such as HbA1c, is not reliable. Since albumin is the most abundant serum protein, the most applications of fructosamine are as a measurement of glycated albumin, approximately describing the percentage of albumin that is glycated. The role of fructosamine and GA in the diagnosis, monitoring, and management of diabetes remains to be established [13]. For example, conditions that affect the turnover of red blood cells can make HbA1c results imprecise, which makes fructosamine a much more reliable option for monitoring short-term glycemic control. This will specifically be important in such acute clinical presentations where the levels of fructosamine can yield important insights into patient management [14]. Moreover, research has shown that fructosamine levels correlate well with diabetic complications, a good reason for monitoring this biomarker because it can predict the development of microvascular complications and thus enhance risk stratification in diabetes management [15]. This is proved further by the relationship, as revealed by findings, that high fructosamine levels can relate to increased cardiovascular risks for diabetic patients [16-17]. Fructosamine levels have gained more popularity as an alternative and complimentary measure of glycemic control in the elevation of diabetic patients, more so when traditional metrics like HbA1c show less reliability. Fructosamine reflects the mean level of glucose for the 2- to 3-week time span; therefore, it is best suited to use for short-term follow-up. Various literature showed its applicability in practice [18]. For example, one study by de Oliveira Andrade et al. underscored the mean relationship that exists between fructosamine levels and average glucose in blood, where it was concluded to be predictive. This was further supported by another similar study by John et al. who showed it can be used when there is inadequacy in HbA1c such as in anemia or when there is rapid glycemic changes [7]. Similar comparative studies by Chakrabarti (2023) [8] and Borham et al., (2023) [9] replicated its clinical

Table 2. Univariate logistic regression analysis of fructosamine and the risk of having diabetes mellitus

Biomarker	OR	95% CI	P-value
Fructosamine (µmol/L)	1.45	1.12- 1.86	<0.046

OR: odds ratio, CI: confidence interval

Source: Own materials

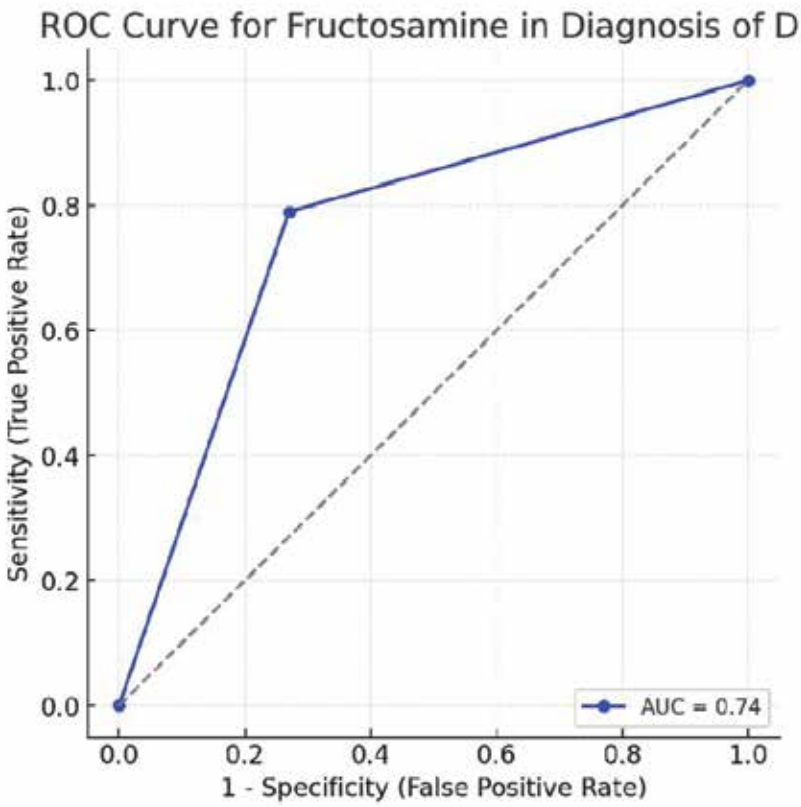

Fig. 2. ROC curve for Fructosamine in the diagnosis of DM

Source: Own materials

Table 3. Sensitivity and specificity of Fructosamine for the diagnosis of DM

Biomarker	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
Fructosamine	0.74	0.033	285	0.79	0.73

AUC: Area Under the curve

Source: Own materials

usefulness, demonstrating the stability of fructosamine as a biomarker high-anemia-associated abnormalities and associated with adverse cardiovascular outcomes in diabetic patients undergoing PCI. In his work in 2022, Singh validated fructosamine accuracy against continuous glucose monitoring systems, thereby underlining its feasibility in resource-limited settings [10]. Another study that further cements this utility was end-stage kidney disease-specific research conducted by Kaminski et al., (2023) [11] on the analytical performance of fructosamine as an indicator of glycemic control. On the other hand, Li et al., (2015) [19] found fructosamine to be highly useful in detecting glucose-sparing therapies for peritoneal dialysis patients. These results are supported by the evidence and argue for the replacement of glycated albumin with fructosamine in routine diabetes care for short-term glycemic monitoring in specific clinical populations Some recent literature, however, continues to note that the use of continuous glucose monitoring provided further evidence of previously undiagnosed hyperglycemia in burnt-out diabetes patients. Fructosamine and GA have superior assessment of glycemic control compared to values of HbA1c, as well as fructosamine, in ESKD patients [11]. The diagnostic cut-off of fructosamine as a diabetes biomarker is its performance at 285 µmol/L, which shows sensitivity of 79% which means it correctly identifies 79% of the diabetic cases, and specificity of 73%, which excludes 73% of nondiabetic cases. Effectiveness in such distinction between diabetic and non-diabetic populations is highlighted by this value. Herein, therefore, the p-value is taken as 0.033 and therefore the statistical finding further enforces the reliability of fructosamine as a biomarker for diabetes diagnostic likelihood. The study finds comparable evidence in previous research that highlighted the possible integration of fructosamine into clinical practice, especially in populations where traditional markers like HbA1c may not be considered useful [19]. Specifically, in their study prospectively outlining the utility of fructosamine as a predictive biomarker for diabetic microvascular complications in populations with a high prevalence of red cell disorders: a retrospective analysis. Their findings indicate that the fructosamine level is significantly associated with the onset of microvascular complications

among diabetic patients and, therefore, it may be of use as a good means of stratifying risk in such populations [20]. These results support the concept that fructosamine produces a balanced diagnostic approach and, thus, proves itself to be valuable in the management of diabetes [21].

CONCLUSIONS

Fructosamine has significant potential for clinical application in the diagnosis and prognosis of diabetes mellitus. Higher levels in diabetic subjects associated strongly with disease risk and only moderate diagnostic accuracy would seem to recommend its use in the clinical laboratory. Further studies, especially in larger populations, are recommended to validate these findings and assess their potential clinical utility.

ABBREVIATIONS

NBT:	Nitroblue Tetrazolium
T1D:	Type 1 Diabetes
T2D:	Type 2 Diabetes
LADA:	Latent Autoimmune Diabetes in Adults
ROC:	Receiver Operating Characteristic
DM:	Diabetes Mellitus
OR:	Odds Ratio
CI:	Confidence Interval
AUC:	Area under Curve

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

The effect of melatonin on antioxidant defense indicators in the blood of rats with insulin resistance

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ABSTRACT

Aim: To determine the effect of melatonin on the activities of glucose-6-phosphate dehydrogenase, glutathione reductase, glutathione peroxidase and the content of reduced glutathione, glucose and insulin levels in the blood of rats with insulin resistance.

Materials and Methods: Research performed in compliance with the Rules of the work using experimental animals (1977) and the Council of Europe Convention on the Protection of Vertebrate Animals used in experiments (Strasbourg, 1986). Sexually mature 18-month-old outbred white male rats were divided into groups: 1) control, 2) insulin resistant rats (dexamethasone at a dose of 0.125 mg/kg for 13 days daily), 3) insulin resistant rats ingested with metformin (200 mg/kg) daily, 4) insulin resistant rats were orally administered melatonin at a dose of 10 mg/kg daily. Measurement of fasting glucose content in the blood from the tail vein (One Touch, USA) and insulin in the blood serum (immunochemiluminescent analyzer Snibe Co., Ltd, the Maglumi test kit, China) was performed on the 14th day. Blood was taken to determine the parameters of glutathione system by using standard methods. Statistical processing was performed using the IBM SPSS Statistics 21 program. Differences were considered statistically significant at $p \leq 0.05$.

Results: Melatonin ingestion as well as metformin were helpful in normalization of insulin level on the background of glucose level restoration and antioxidant system activation.

Conclusions: We have established the hypoglycemic and antioxidant effects of melatonin on the background of dexamethasone-induced insulin resistance.

KEY WORDS: circadian rhythm, animals, glutathione system, dexamethasone diabetes

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INTRODUCTION

Disruption of the circadian rhythm reduces insulin secretion and insulin sensitivity and negatively affects glucose homeostasis. The circadian clock regulates the hypothalamic-pituitary-adrenal axis, an important factor that regulates glucose metabolism and affects the progression of type 2 diabetes [1]. The development of type 2 diabetes is based on the formation of insulin insensitivity [2]. It is known that insulin resistance (IR) is accompanied by hyperglycemia, which leads to impaired blood supply. With a long course of this condition, complications arise in the form of cardiovascular diseases [3]. Vascular endothelial cells are particularly sensitive to high glucose concentrations. In this case, due to the inclusion of an alternative glucose conversion pathway – the sorbitol pathway, the $NADPH_2$ reserve is depleted and the formation of $NADH_2$ increases. This leads to changes in the redox potential, which accelerates glycolysis and increases the synthesis of diacylglycerols, and also provokes the formation of the superoxide anion radical with subsequent oxidation of low-density lipoproteins. The result of such events is a decrease in the availability of nitric oxide and an increase in vascular permeability with the development of dysfunction [2].

Circadian rhythm disturbances can be provoked by chronic stress, which disrupts the functioning of the adrenal cortex-hypothalamic pituitary system. This leads to uncontrolled formation of glucocorticoids [1]. It is known that excessive levels of glucocorticoids can lead to the development of type 2 diabetes mellitus by inducing hyperglycemia, insulin resistance and dyslipidemia (van Raalte and Diamant, 2014). Glucocorticoids cause the development of hepatic insulin resistance and activate gluconeogenesis enzymes, which leads to hyperglycemia (Vegiopoulos and Herzig, 2007). In adipose tissue, glucocorticoids stimulate lipid uptake, triglyceride synthesis, and lipolysis, contributing to the local accumulation of free fatty acids (Wang et al., 2012). In addition, glucocorticoids can reduce insulin sensitivity and glucose uptake in skeletal muscle (Ruzzin et al., 2005). Furthermore, prolonged exposure to glucocorticoids leads to apoptosis of pancreatic β-cells and impairs insulin secretion (Li and Cummins, 2022).

Metformin is the drug of choice for the treatment of type 2 diabetes, as recommended by the American Diabetes Association [4]. Among the side effects of this drug is the accumulation of lactate [5]. Therefore, there is a need for further research to overcome such events.

Melatonin does not have such side effects [6], has chronorythmological [7] and antioxidant [8] properties.

Therefore, it is relevant to study the effect of melatonin on antioxidant defense indicators in the blood of rats with insulin resistance.

AIM

To determine the effect of melatonin on the activity of glucose-6-phosphate dehydrogenase (G6PDH), glutathione reductase (GR), glutathione peroxidase (GP) and the content of reduced glutathione (G-SH) and glucose in the blood of rats with insulin resistance.

MATERIALS AND METHODS

Research performed in compliance with the Rules of the work using experimental animals (1977) and the Council of Europe Convention on the Protection of Vertebrate Animals used in experiments and other scientific purposes (Strasbourg, 1986), according to directions of International Committee of Medical Journals Editors (ICMJE), as well as "Bioethical expertise of preclinical and other scientific research conducted on animals" (Kyiv, 2006). Sexually mature 18-month-old outbred white male rats were divided into three groups: 1) control (intact rats), 2) rats with dexamethasone diabetes, which was induced by daily subcutaneous administration of dexamethasone solution (4 mg/kg, KRKA, Slovenia) at a dose of 0.125 mg/kg for 13 days (O.V. Stefanov, 2001) – IR [9], 3) IR rats ingested with metformin, 4) rats that, against the background of the development of dexamethasone diabetes, were orally administered melatonin (Sigma, USA) at a dose of 10 mg/kg (Mok, J.X., et al., 2019) daily. The hypoglycemic agent metformin (SANDOZ, Poland) was used as a comparison drug, which was administered to animals intragastrically via a gavage in the form of an aqueous suspension at a dose of 200 mg/kg daily. One group of experimental animals was administered metformin (reference drug) simultaneously with dexamethasone, and the other group was administered the study drug. Measurement of fasting glucose content in the blood from the tail vein (by One Touch Ultra Easy, LifeScan, USA) and insulin in the blood serum (by immunochemiluminescent analyzer Snibe Co., Ltd, China using the Maglumi test kit, China) was performed on the 14th day to establish the hypoglycemic effect of melatonin in comparison with metformin. Besides we checked glucose area under the curve (AUC) during oral glucose tolerance test (OGTT) as an index of glucose intolerance [10]. IR index was calculated using homeostasis model assessment (HOMA) index for IR by formula: HOMA-IR = blood glucose (mg/dL) × fasting insulin (μU/mL) ÷ 405. [11]. Rats were sacrificed on the 14th day of experiments. Blood was taken to determine the activity of antioxidant defense enzymes and the content of reduced glutathione, the Thiobarbituric acid (TBC) reactive substances by using standard methods [12, 13].

Statistical processing of the results was performed using the IBM SPSS Statistics 21 program. The significance of the difference between the indicators was assessed using the parametric Student's t-test (with normal distribution) and the non parametric Mann-Whitney U-test (with non-normal distribution). Differences were considered statistically significant at $p \leq 0.05$.

RESULTS

In accordance with results of fasting blood glucose level (Fig. 1) obtained from rats with IR these index was on 170% higher compared to control. Medication with metformin was less successful then the melatonin introduction, because we found decrease of fasting blood glucose level on 32% and on 58% respectively compared to untreated animals. So due to melatonin introduction these index did not differ from control.

A significant increase in glucose tolerance was noted in rats with insulin resistance using the glucose tolerance test (Fig. 2). There was no significant difference between the metformin and melatonin groups, but there was a significant difference compared to untreated rats.

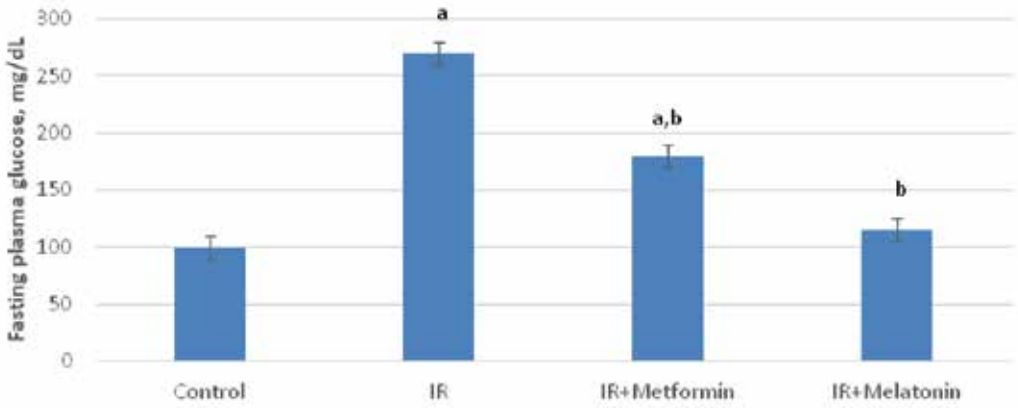

Fig. 1. Fasting plasma glucose, mg/dL (n=6, x±Sx)
1. Changes are reliable (p≤0,05).
2. a – concerning control;
   b – concerning IR

Picture taken by the authors

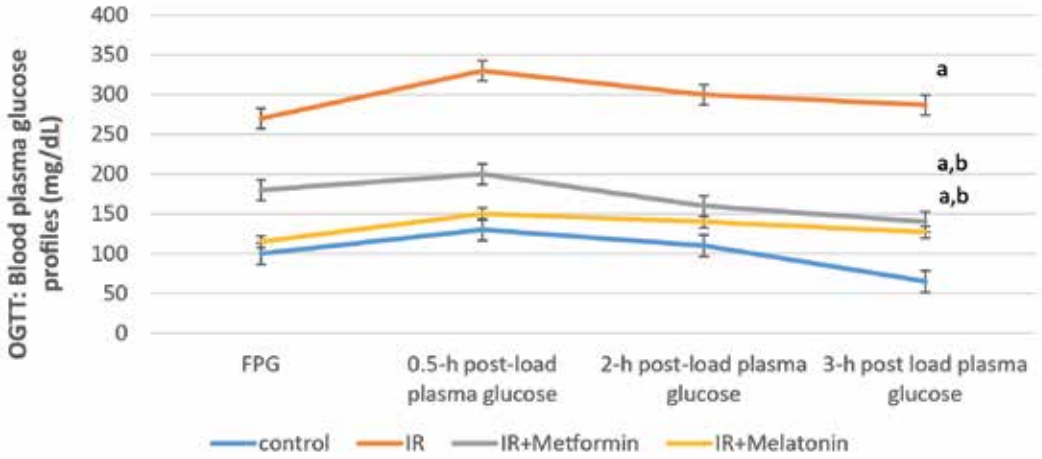

Fig. 2. OGTT: Blood plasma glucose curve (profiles), mg/dL (n=6, x±Sx)
1. Changes are reliable (p≤0,05).
2. a – concerning control;
   b – concerning IR

Picture taken by the authors

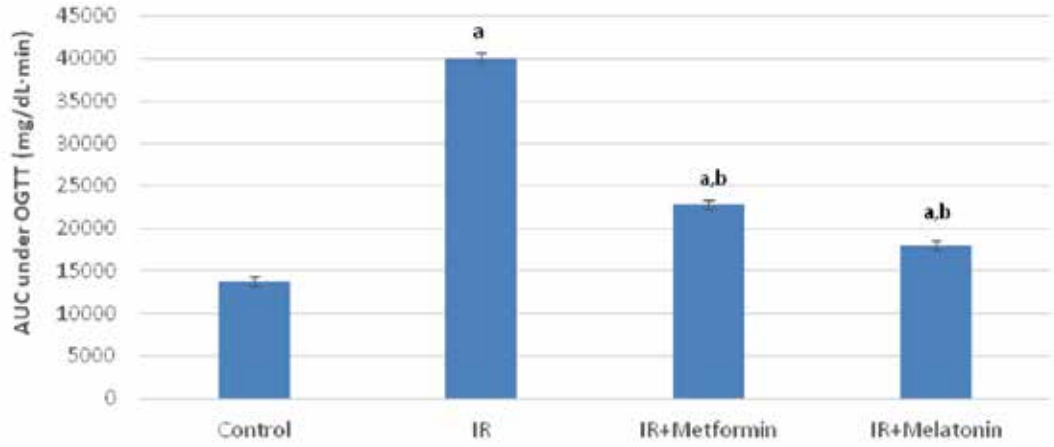

Fig. 3. Area under the curve OGTT, mg/dL·min (n=6, x±Sx)
1. Changes are reliable (p≤0,05).
2. a – concerning control;
   b – concerning IR

Picture taken by the authors

The American Diabetes Association and the International Diabetes Federation guidelines describe the importance of monitoring peak postprandial glucose levels [10]. However, in daily practice, it is difficult to monitor peak postprandial glucose levels because the timing of peak glucose levels is highly dependent on diet and glucose tolerance.

Peak blood glucose values can be measured using the less invasive, time-independent AUC method (Fig. 3). Here we saw a decrease in the indicators in the metformin and melatonin groups by 45% and 52%, respectively, compared to the IR group. Meanwhile these parameters stood higher on 65% and 31% respectively, compared to control.

The development of IR was accompanied by an increase in insulin levels (Fig. 4) and the HOMA-IR index (Fig. 5) by 4.7 and 14 times compared to the control.

This situation was improved by the administration of metformin and melatonin. This is evidenced by a reliable decrease in the corresponding indicators when using metformin or melatonin, respectively. In IR groups with metformin or melatonin serum insulin levels and HOMA-IR did not differ from control.

Dexamethasone administration resulted in a 90% increase in TBC reactive compounds (Fig. 6) compared to control. Introduction of metformin and melatonin helped in decrease of these parameter on 28% and 41% respectively compared to IR group.

The assessment of G6PDH activity (Fig. 7) was reflected in a decrease in the IR group by 21% compared to control and in the normalization of its activity in rats receiving melatonin or metformin.

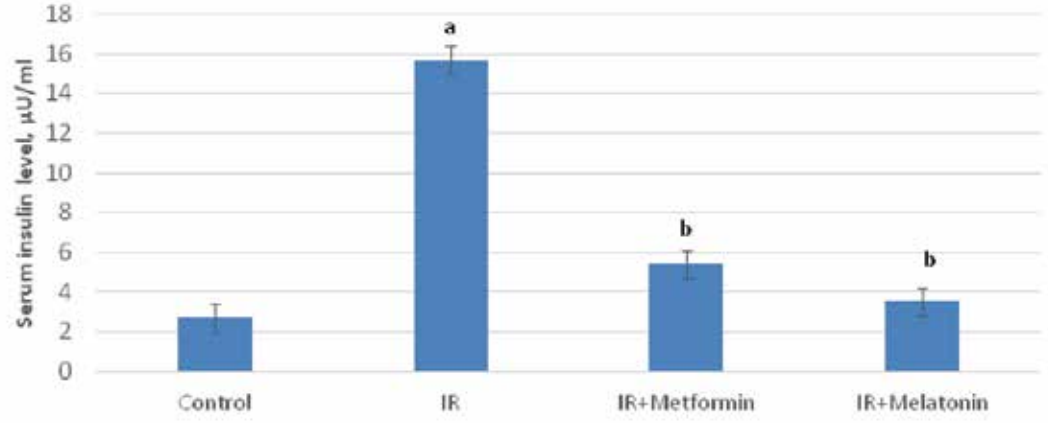

Fig. 4. Serum insulin level, µU/ml (n=6, x±Sx)
1. Changes are reliable (p≤0,05).
2. a – concerning control;
   b – concerning IR

Picture taken by the authors

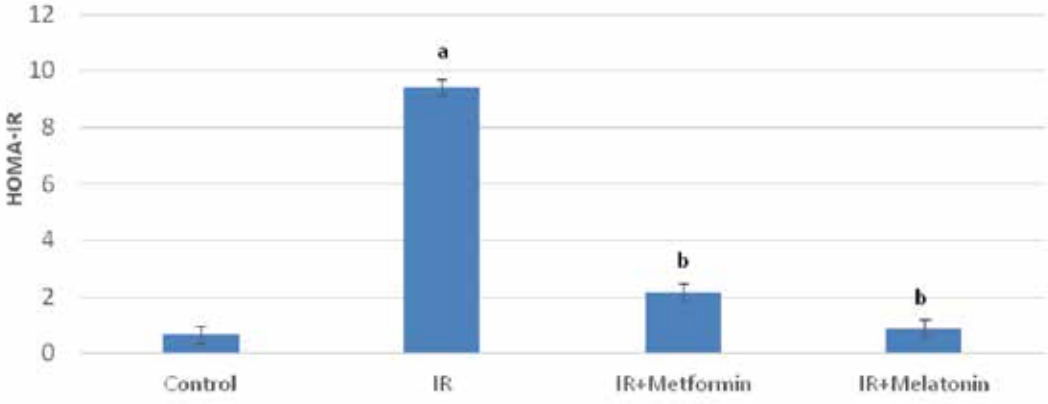

Fig. 5. HOMA-IR (n=6, x±Sx)
1. Changes are reliable (p≤0,05).
2. a – concerning control;
   b – concerning IR

Picture taken by the authors

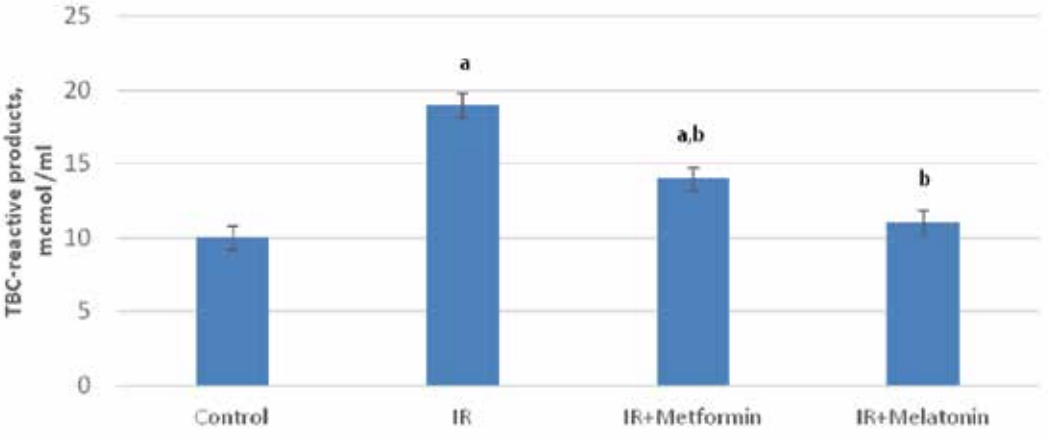

Fig. 6. TBC-reactive products, mcmol /ml (n=6, x±Sx)
1. Changes are reliable (p≤0,05).
2. a – concerning control;
   b – concerning IR

Picture taken by the authors

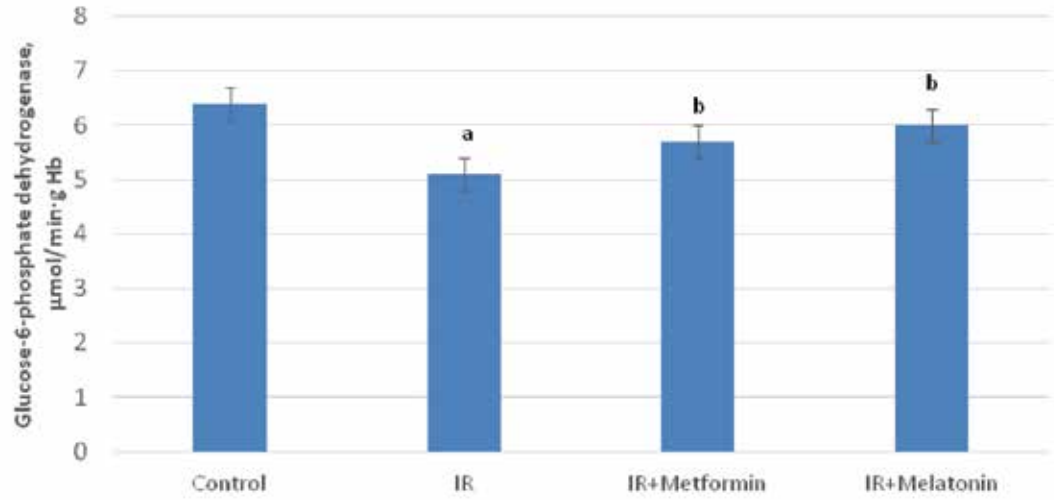

Fig. 7. Glucose-6-phosphate dehydrogenase, µmol/min·g Hb (n=6, x±Sx)
1. Changes are reliable (p≤0,05).
2. a – concerning control;
   b – concerning IR

Picture taken by the authors

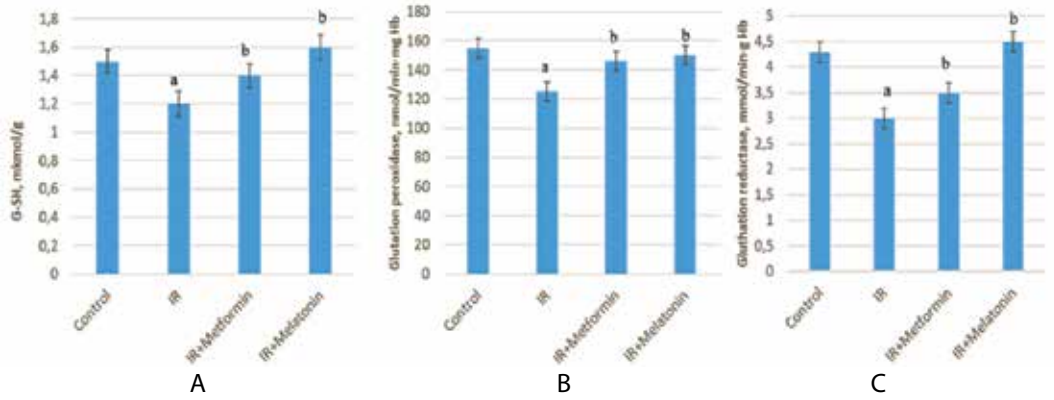

Fig. 8. A) G-SH, mkmol/g; B) Gluthation peroxidase, nmol/min·mg Hb; C) Gluthation reductase, mmol/min·g Hb (n=6, x±Sx)
1. Changes are reliable (p≤0,05).
2. a – concerning control;
   b – concerning IR

Picture taken by the authors

Glutathione system (Fig. 8) weaked by dexamethasone injections. This was accompanied by decrease in content of GS-H on 20% followed by decreased in activities of GP, GR on 20%, 30% respectively, compared to control. IR animals that received metformin or melatonin were characterized by normalization of these parameters.

DISCUSSION

We have found a hypoglycemic effect of melatonin when used under IR conditions. Parameters like fasting glucose level, OGTT and AUC were normalized under its action similar to metformin. This decrease in glucose levels may be associated with the effect of melatonin on glucose transporters. Melatonin receptors are known to be widespread throughout the body. This hormone is able to act through its receptors and modulate insulin-like events in terms of activation of glucose transporters GLUT 2, 4 [14, 15]. Metformin is also able to activate glucose transporters GLUT 4 [16].

Melatonin inhibits glucose synthesis due to its peculiarity of influencing the regulation of gluconeogenesis gene expression [17]. The action of metformin is associated with allosteric inhibition of gluconeogenesis through lactate accumulation [5, 18]. In this order impairment of oxidative phosphorylation happened with less ATP production. Melatonin is a better agent that does not cause acidosis compared to metformin. It can stimulate mitochondria function and energy supply [6, 19].

We found that metformin and melatonin increased G6PDH activity compared to the indicators of IR group animals. This may be due to an increase in glucose uptake by the cells. Regarding melatonin, there is evidence about genes activation of the G6PDH enzyme [20].

The development of IR under the influence of glucocorticoids leads to a disruption of the circadian rhythm (sleep-wake regime, food intake, etc.) [21]. This leads, in addition, to chronic stress and hyperglycemia, to obesity and a decrease in antioxidant defense systems. To restore the circadian rhythm and reduce obesity, it is advisable to use melatonin, which is decreased in conditions of IR development [1, 22]. The physiological relationship between glucocorticoid and melatonin maintains neuronal homeostasis in the regulation of circadian rhythms. However, stress-inducing levels of glucocorticoids cause mitochondrial dysfunction, including defective mitophagy, by increasing the activity of glucocorticoid receptors, which leads to neuronal cell death [23].

Our studies have shown a decrease in the activity of glutathione system enzymes and the content of reduced glutathione in rats with IR. The consequence of the pro- and antioxidant system imbalance was an increase in the content of TBC reactive compounds [24] in the blood of animals with IR. The introduction of melatonin and metformin allowed to restore these indicators to the level of control animals. This effect of metformin and melatonin may be associated with the activation of G6PDH with the subsequent formation of $NADPH_2$, which is necessary for the restoration of glutathione content [25].

We determined an increase of insulin level, HOMA-IR in rats with diabetes induced by dexamethasone (IR). Metformin ingestion as well as melatonin were helpful in normalization of insulin level, HOMA-IR on the background of glucose level restoration and antioxidant system activation. The results showed that melatonin administration reduces plasma insulin levels in vivo and, in addition, there is insulin-melatonin antagonism [26].

CONCLUSIONS

We have established the hypoglycemic effect of melatonin on the background of dexamethasone-induced insulin resistance. This was accompanied by a decrease in insulin levels and activation of the glutathione antioxidant defense system.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Analysis of the men's sexual dysfunctions impact on different aspects of their quality of life

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ABSTRACT

Aim: To study different aspects of quality of life depending on the type and severity of sexual disorders in men.

Materials and Methods: An observed case-control study was carried out during 2023-2024, at three private-funded out-patient health care facilities of the Ivano-Frankivsk region of Ukraine. A survey of the quality of life of 402 men with sexual dysfunctions and 200 men without ones was carried out. The control group included men who visited the health care facilities for the check-up and were recognized as practically healthy. The study data were analyzed using Microsoft Excel data analysis and the Statistica10.0 software packages. Statistical processing of qualitative data was carried out by calculating their prevalence per 100 respondents, and the reliability of their differences in different observation groups was assessed by calculating the chi-square ($\chi 2$) test. The research design and programs were reviewed and approved by the Ethics Commission of the Ivano-Frankivsk National Medical University (protocol No. 133/23 dated March 29, 2023).

Results: The quality-of-life integral index in sexual dysfunctions was (64.9±7.14) % of the maximum possible 100% vs (92.4±3.52) % in the control group. The progression of erectile dysfunction was accompanied by a decrease of the quality-of-life integral index from -25.2% in mild to -33.3% in moderate and -41.6% in severe, and the presence of premature ejaculation reduces the quality of life by 38.6%, hypoactive sexual desire disorder by 38.0%, orgasmic dysfunction by 39.8%. The greatest impact on the men`s quality-of-life reduction in sexual dysfunctions was the dissatisfaction with sexual drive, interest and/or performance (on average 2.1 points on a 5-point scale, compared to 4.9 points in the control group), especially expressed in hypoactive sexual desire disorder (1.6 points, respectively), orgasmic dysfunction (1.7) and severe erectile dysfunction (1.5). Respondents with sexual dysfunctions were the least satisfied with the psychological components of the quality-of-life, in particular in case of severe erectile dysfunction (3.0 points), premature ejaculation (2.9), hypoactive sexual desire disorder (3.0) and orgasmic dysfunction (3.0).

Conclusions: Male sexual dysfunctions negatively affect the psychological component of the quality of life without significant impact on the physical and socio-economic. The complex of treatment measures for men`s sexual dysfunctions must necessarily include psychological interventions.

KEY WORDS: quality of life, sexological care management, sexual dysfunctions of men

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INTRODUCTION

Sexual health is an integral part of everyone`s quality of life, as it is esential for the physical and mental health and well-being of individuals, couples, families, and, accordingly, for the social and economic development of communities and countries.

Sexual dysfunctions (SDs) can negatively affect male fertility, which is of strategic socio-demographic importance [1, 2].

The main SDs in men are erectile dysfunction, premature ejaculation, hypoactive sexual desire disorder, and orgasmic dysfunction.

According to epidemiological studies, erectile dysfunction (ED) is the most common of these, although its prevalence rates vary depending on the study methodology, age of participants, and socioeconomic and cultural status of the populations studied [3, 4]. Thus, according to the results of the Massachusetts study (MMAS), the prevalence of ED in the group of men aged 40 to 70 years was 52%, of which 17.2% – minimal ED, 25.2% – moderate and 9.6% – severe ED. The probability of developing ED increases with the age of men [5]. Most researchers emphasize that ED negatively affects mood, lowers self-esteem, causes anxiety and self-doubt, depression, and neuroses based on male inferiority and thus negatively affects almost all aspects of life [6, 7].

The second place among sexual disorders in men is premature ejaculation (PE), the prevalence of which also varies significantly around the world, ranging from 4% to 39% [8]. PE in men is also accompanied by associated psychological disorders (depression, stress, excessive excitement), which negatively affect not only the patient himself, but also his sexual partner [9-12].

The next most common is low libido (hypoactive sexual desire disorder, HSDD), prevalence of which in the world varies from 3 to 28% [13, 14] It is known that sexual desire gradually decreases with age due to a natural decrease in testosterone levels [15]. However, HSDD is also described in young men (18-29 years old) with prevalence rates from 6 to 19% [16].

Another component of male sexual dysfunctions is orgasmic dysfunction (OD), which is more common in women than in men. However, according to research conducted in the USA, from 5 to 14% of men reported some difficulties in achieving orgasm and 8% of men were

unable to achieve orgasm during the last year [17, 18]. This disorder is also accompanied by pronounced distress and tension in interpersonal relationships [18, 19].

Despite the relationship between mental and sexual health established by many scientists, there is still insufficient research on the interrelation between the various types of sexual disorders and the quality of life, in general and its certain components.

AIM

The research was to study different aspects of quality of life depending on the type and severity of sexual disorders in men.

MATERIALS AND METHODS

An observed case-control study was carried out during 2023-2024, at three private-funded out-patient health care facilities of the Ivano-Frankivsk region of Ukraine.

The study included 402 men with sexual dysfunctions and 200 men without ones.

The International Index of Erectile Function (IIEF) was used for the diagnosis of erectile dysfunction and its severity, hypoactive sexual desire disorder and orgasmic dysfunction. A Premature Ejaculation Diagnostic Tool (PEDT) was used to detect premature ejaculation.

The distribution of the main group – men with sexual dysfunctions – was as follows: ED – 232 patients (57.7%), of which 65 (28.0%) had mild ED, 130 (55.9%) – moderate ED and 37 (16.1%) – severe ED; PE – 89 (22.1%); HSDD – 61 (15.2%); and OD – 20 (5.0%).

The control group included men who visited the health care facilities for the check-up and were recognized as practically healthy.

The comparison groups – with and without SD, did not differ in age and place of residence ($p>0.05$). The majority of people in both groups were under the age of 50 (89.8% and 89.5%) and urban residents (78.9% and 80.5%). At the same time, the median age of male with ED increased with its severity and amounted to 26 [23;29] years old for mild ED, 36 [31;42] for moderate ED, and 51 [46;57] for severe ED. The median age of men with PE was 33 [26;39] years, with HSDD – 32.5 [25.0;40.5], with OD – 33 [26;40], and in the control group – 33 [27;42].

The assessment of quality of life (QoL) was carried out on the basis of a Quality-of-Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) [20], which consists of 14 questions about satisfaction with various components of the quality of life and two additional questions about satisfaction with treatment and life in general. For each of the questions, respondents chose one of the following answers: very poor, poor, satisfactory, good, very good, which corresponded to a score from 1 to 5.

According the results of study was created the database contained a categorical distribution of this answer options to each question of the questionnaire of separate subgroups by type of sexual dysfunctions (mild, moderate and severe ED, PE, HSDD, OD), the total SD and control groups. This made it possible to find both the percentage distribution of answers to each question, as well as the mean of the scores (from 1 to 5).

Each respondent was also assigned their individual quality of life integral index for the main 14 questions as a percentage of the maximum score (70) and its percent decrease from the maximum possible 100%.

To summarize and analyze the main components of QoL (physical, socio-economic and psychological well-being), we calculated the geometric mean of the average scores for individual questions in the comparison groups, except for the answer to satisfaction with sexual life as the main symptom of SD. Accordingly, physical well-being was assessed by the geometric mean of the average scores of the answers to the questions about satisfaction with physical health, work, household activities, ability to function in daily life and ability to get around physically without feeling dizzy or unsteady or falling; socio-economic well-being – according to satisfaction with the economic status, living/housing situation and overall sense of well-being; psychological well-being – based on mood satisfaction, social and family relationships, leisure time activities and himself vision in terms of ability to do work or hobbies.

The study data were analyzed using Microsoft Excel data analysis and the Statistica10.0 software packages.

The quantitative data obtained in the study were first checked for the type of their distribution using the the Shapiro-Wilk's W test. Since all QoL parameters followed the law of normal distribution, the mean (M) and standard deviation (±SD) were chosen to determine the measure of central tendency, and the parametric t-test was used to assess the reliability of the data between the treatment and control groups. The reliability of the data in erectile dysfunction of varying severity (mild, moderate and severe) was assessed using the nonparametric Kruskal-Wallis ANOVA test.

Statistical processing of qualitative data was carried out by calculating their prevalence per 100 respondents, and the reliability of their differences in different observation groups was assessed by calculating the chi-square ($\chi 2$) test.

The research design and programs were reviewed and approved by the Ethics Commission of the Ivano-Frankivsk National Medical University (protocol No. 133/23 dated March 29, 2023).

Informed consent was obtained from all subjects at the time of their enrollment. All participants were informed about the purpose and scope of the study.

RESULTS

It was established that in the main group the quality-of life integral index was significantly lower than in the control one: (64.9±7.14) % of the maximum possible 100%, vs (92.4±3.52) % ($p<0.001$). However, as can be seen in Fig. 1, among the respondents with ED, the quality-of life integral index worsened with the progression of dysfunction severity from (74.8±5.83) % in mild ED to (66.7±4.72) % in moderate ED and to (58.4±3.60) % in severe ED ($p<0.001$). The overall rate for the entire group of EDs was (67.7±7.23) %.

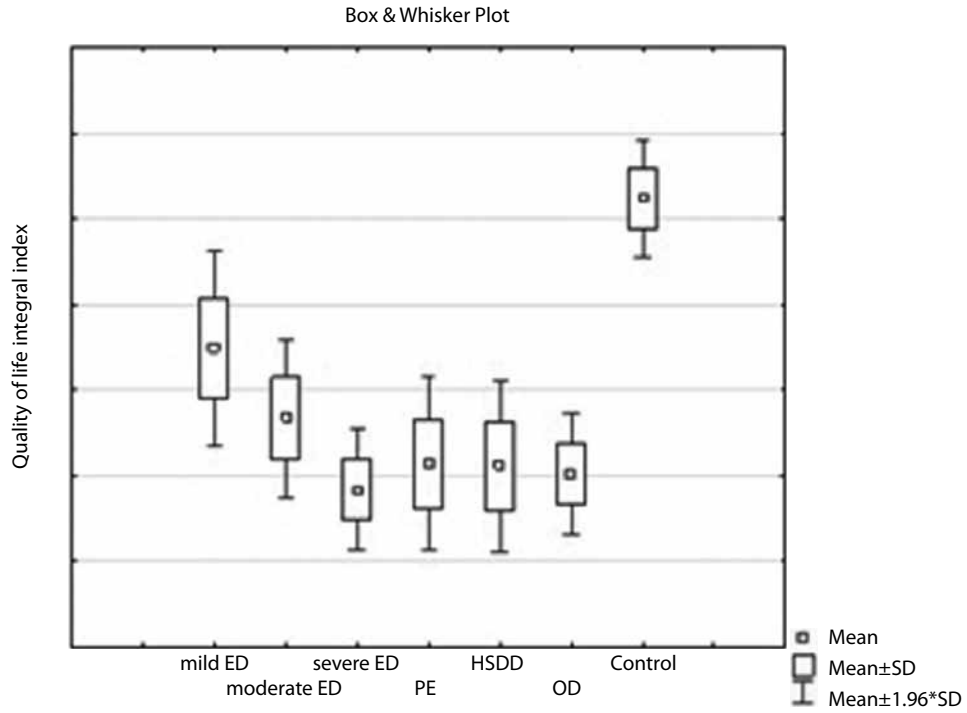

Fig. 1. Quality of life integral indices in comparison groups
NB: ED – erectile dysfunction; PE – premature ejaculation; HSDD – hypoactive sexual desire disorder; OD – orgasmic dysfunction

Picture taken by the authors

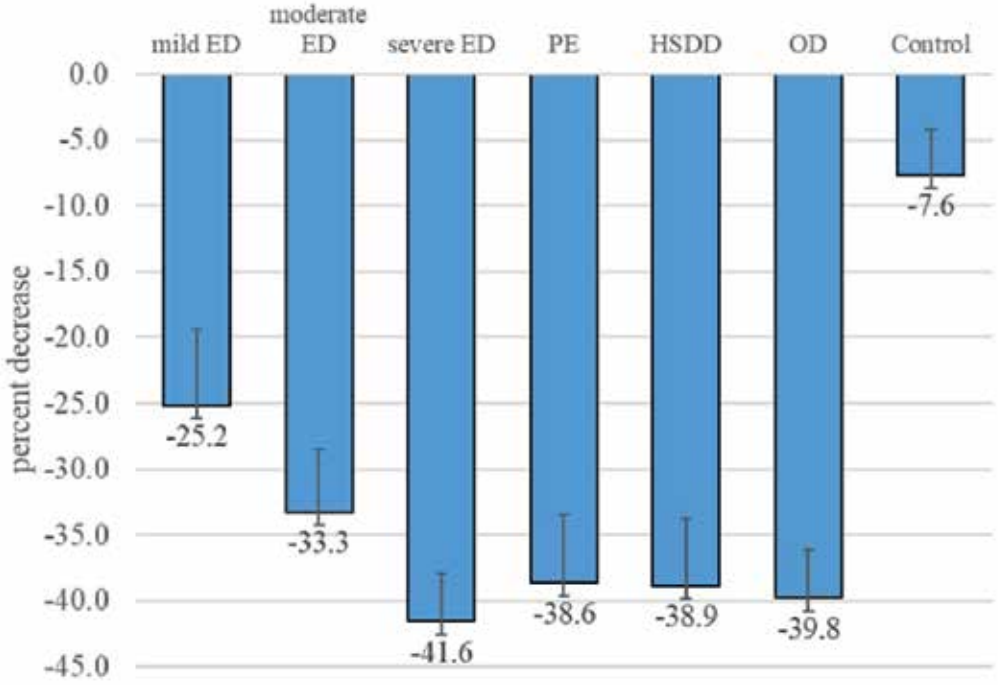

Fig. 2. Percent decrease of quality of life in comparison groups
NB: ED – erectile dysfunction; PE – premature ejaculation; HSDD – hypoactive sexual desire disorder; OD – orgasmic dysfunction

Picture taken by the authors

In other types of sexual dysfunctions, the QoL integral indices almost did not differ from each other and amounted to (61.4±5.15) % in PE, (61.1±5.11) % in HSDD and (60.2± 3.64) % in OD.

Accordingly, the percent decrease from the maximum possible 100% of quality of life in men without sexual dysfunctions was on average only -7.6%, while among respondents with erectile dysfunction it deepened from -25.2% in mild to -33.3% in moderate and up to -41.6% in severe cases (Fig. 2). The presence of PE reduced quality of life by 38.6%, HSDD by 38.0%, and OD by 39.8%.

Considering the answers to certain questions of the questionnaire (Fig. 3), it was found that in the main group all components of QoL were significantly worse than in the control group ($p<0.001$). This difference was especially significant when the respondents assessed their satisfaction with sexual drive, interest and/or performance – (2.1±0.72) points in the main group vs (4.9±0.34) points in the control group.

It should be noted that the most dissatisfied with sexual drive, interest and/or performance were respondents with HSDD – (1.6±0.53) points and OD – (1.7±0.56) points, although patients with PE and ED also complained about it – (1.9±0.54) points and 2.3±0.74) points, respectively. The progression of ED was accompanied by a deepening of dissatisfaction with sexual drive, interest and/or performance from (2.7±0.55) points in mild to (1.5±0.50) points in severe ED.

As we can see at the fig.3, the SDs significantly worsened the mood of the respondents - (2.8±0.88) points vs. (4.5±0.50) points, respectively; caused dissatisfaction with leisure time - (3.0±0.83) points vs. (4.4±0.64) points, their physical health - (3.1±0.81) points vs. (4.6±0.50) points, and other aspects of QoL.

The type of sexual disorder did not affect only satisfaction with household activities, ability to function in daily life and ability to get around physically without feeling dizzy or unsteady or falling ($p>0.05$). For the rest of the QoL aspects, the difference was significant ($p<0.001$) due to a slightly better assessment by all patients with ED compared to other types of sexual disorders. However, the assessment of most aspects of QoL among the respondents with ED worsened with the development of its severity.

Grouping the rest of the answers into three main components of QOL (physical, socioeconomic and psychological well-being) showed that respondents of all subgroups of the main group rated the psychological component of QOL the worst (Fig. 4). Moreover, in the ED group, all components of QoL deteriorated with the deepening of the disorder, and respondents with severe ED, as well as with PE, HSDD, and OD assessed the psychological problems accompanying SD at almost the same level: 2.9-3.0 points.

DISCUSSION

The study was conducted on a sample of men with the SDs, whose structure generally corresponds to the scientific data regarding the prevalence of their various types (ED, PE, HSDD and OD) in the population [5, 8, 13, 18].

In our study, as well as in other similar studies found that men`s SDs negatively affect their quality of life.

However, since the most common SD in men is ED, most studies have also focused on the assessment of QoL in ED. For example, a study by Agaba PA et al. [7] using COOP/ WONCA diagrams [21] also demonstrated the negative

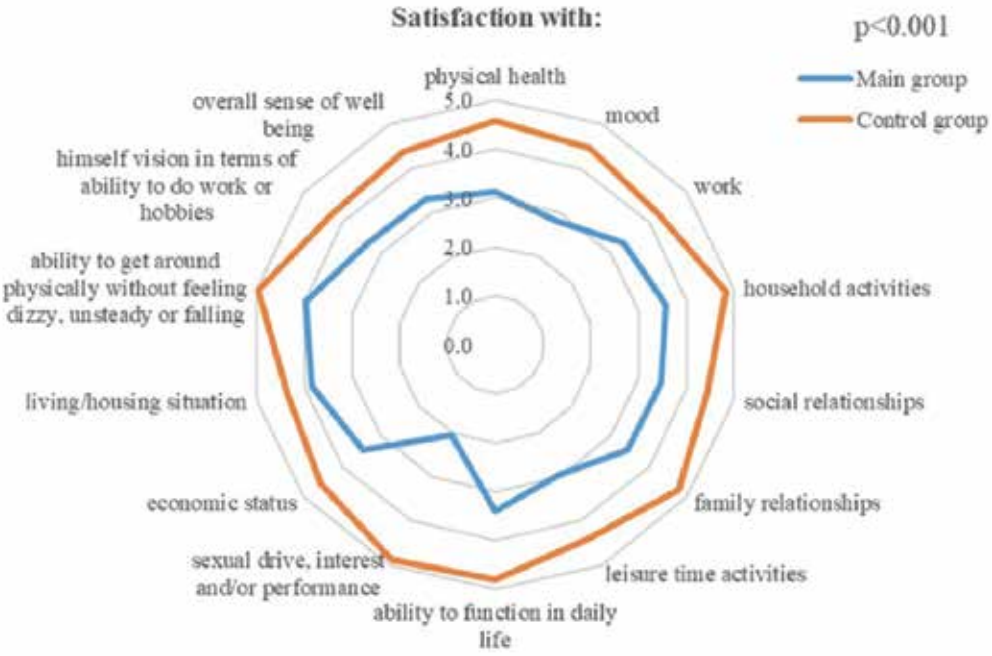

Fig. 3. Mean scores on a 5-point scale of quality-of-life certain components by respondents of the main and control groups

Picture taken by the authors

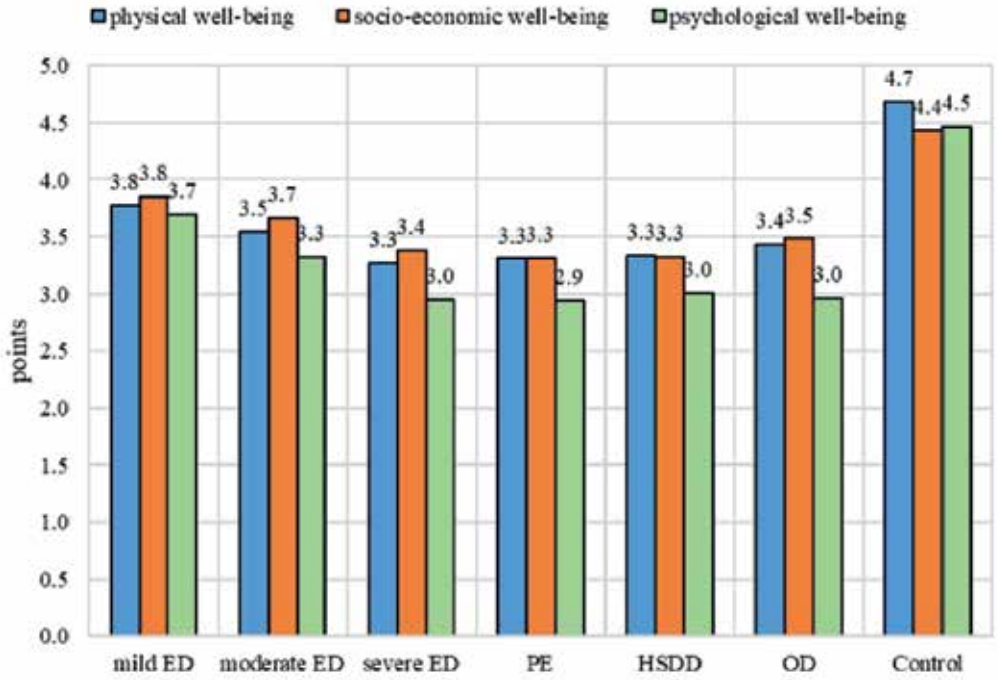

Fig. 4. Characteristics of physical, socio-economic and psychological quality of life components in comparison groups
NB: ED – erectile dysfunction; PE – premature ejaculation; HSDD – hypoactive sexual desire disorder; OD – orgasmic dysfunction

Picture taken by the authors

impact of ED on quality of life, mainly in the areas of social activity and overall health, in the absence of a relationship with physical condition, daily activities and feelings. At the same time, the methodology we used to assess the QoL of patients with SDs in our study differed from the COOP/WONCA charts, which assess QoL only for the last two weeks. The Q-LES-Q-SF questionnaire used by us covered a much wider range of parameters of physical, social and mental well-being and allowed us to analyze the reduction of QoL [20].

In particular, we confirmed the findings of other researchers that ED worsens with age [5, 22], and also showed that the intensification of this SD is accompanied by a decrease in QoL from -25.2% in mild to -41.6% in severe.

In our study, in addition to ED, we also conducted a detailed analysis of the impact of other SDs – PE, HSDD and OD – on the men`s QoL. However, in the scientific community, such SD as HSDD and OD are more often studied in the female population, as these disorders are more common among them [18, 23, 24].

We found that the QoL integral indices in PE, HHSD and OD are also low, almost at the level of QoL in severe ED, although we are talking mainly about young people (the median age of those examined with these SD was 30-33 years compared to 53 years in severe ED), and the decrease of QoL in men with PE, HSDD, and OD was -38.6%, -38.9%, and -39.8%, respectively.

It is logical that, since the object of study was SDs, the study confirmed the greatest impact on the reduction in QoL of such a component as dissatisfaction with sexual drive, interest and/or performance (mean 2.1 points on a 5-point scale, compared to 4.9 points in the control group), especially pronounced in HSDD (1.6 points respectively), OD (1.7) and severe ED (1.5).

As for other QoL components, like in other similar studies [7, 25, 26], ours showed a lower impact of SD on physical and socio-economic aspects of QoL, while the emotional and mental components suffered the most. According to numerous scientific data, this has negative consequences, as it can contribute to depression and anxiety in men, lead to distress in their partners, the development of interpersonal problems and the breakdown of relationships [10, 11, 27].

The findings indicate the need for further more detailed study of the impact of sexual dysfunctions on mental health, the search for determinants of sexual health, including behavioral risk factors, and obstacles in providing accessible and quality sexological care.

Our study has several limitations. The results of this study may not be applicable to all men with SDs, as the results are specific to patients who were treated at the private-funded healthcare facilities where the research was conducted and who consented to participate and for whom paid services are available in such settings. In addition, Ukraine is under war, which have negative impact on mental health of all population. Despite this limitation, the study serves as a valuable guide for understanding the impact of different type and severity of sexual dysfunctions on QoL certain components.

CONCLUSIONS

It was confirmed that sexual dysfunctions in men negatively affect their quality of life, as the QoL integral index in SD

is (64.9±7.14) % of the maximum possible 100%, while in the control group it is (92.4±3.52) %.

It was established that the progression of erectile dysfunction is accompanied by a decrease of the quality-of-life integral index from -25.2% in mild to -33.3% in moderate and -41.6% in severe, and the presence of premature ejaculation reduces the quality of life by 38.6%, hypoactive sexual desire disorder by 38.0%, orgasmic dysfunction by 39.8%.

It was found that the greatest impact on the men`s QoL reduction in sexual dysfunctions is the dissatisfaction with sexual drive, interest and/or performance (on average 2.1 points on a 5-point scale, compared to 4.9 points in the control group), especially expressed in hypoactive sexual desire disorder (1.6 points, respectively), orgasmic dysfunction (1.7) and severe erectile dysfunction (1.5).

It was shown that of the three main components of quality of life (physical, socioeconomic and psychological well-being), men with sexual dysfunctions are least satisfied with the psychological one, in particular in case of severe erectile dysfunction (3.0 points), premature ejaculation (2.9), hypoactive sexual desire disorder (3.0) and orgasmic dysfunction (3.0).

The complex of treatment measures for men`s sexual dysfunctions must necessarily include psychological interventions, and improvement of the psychological component of the quality of life can serve as an indicator of the effectiveness of treatment.

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CONFLICT OF INTEREST
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ORIGINAL ARTICLE

Emotional burnout, anxiety, and depression in patients with chronic pain undergoing rehabilitation during the war in Ukraine: A clinical-psychological study

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ABSTRACT

Aim: To evaluate emotional burnout, anxiety, and depression in men with chronic pain undergoing rehabilitation during wartime in Ukraine, with attention to age and pain duration.

Materials and Methods: The study included 35 male military personnel aged 25-60 years, undergoing inpatient rehabilitation at the State Institution «Veteran Mental Health and Rehabilitation Center «Forest Glade» Ministry of Health of Ukraine (Kyiv, Ukraine) (January-May 2025). The mean age was 43±10 years; average pain duration was 23±17 months. Data were collected via structured questionnaires and clinical interviews. Standardized instruments included the Maslach Burnout Inventory (MBI), State-Trait Anxiety Inventory (STAI), and Hospital Anxiety and Depression Scale (HADS).

Results: Most participants exhibited moderate-to-high levels of emotional exhaustion (88,6%), depersonalization (80%), and reduced personal accomplishment (85,7%) (by MBI). More than 70% showed moderate-to-high levels of both state and trait anxiety (by STAI). Close to half of patients (48,6%) demonstrated borderline or abnormal depression patterns. Participants with pain lasting over 12 months showed significantly higher anxiety score, with 78,9% experiencing clinically relevant anxiety versus 37,5% in the short-term (3-12 months) group (p=0,018). Strong (or close to strong) correlations were identified between burnout, anxiety, and depression subscales (ρ=0,68-0,89; p<0,001 [n=35]).

Conclusions: Chronic pain in wartime conditions is linked to severe psychological distress. Extended pain duration increases anxiety. The strong interplay between burnout and affective symptoms underscores the need for integrative, multidisciplinary rehabilitation tailored to psychological needs.

KEY WORDS: burnout, chronic pain, anxiety, depression, rehabilitation

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INTRODUCTION

Chronic pain is a major global health issue, affecting over 1,5 billion people and contributing to disability and loss of quality of life [1]. The World Health Organization forecasts that its prevalence will rise from 619 million in 2020 to 843 million by 2050 [1]. In war settings, chronic pain is worsened by trauma, injuries, and prolonged stress, leading to higher rates of pain-related syndromes [2, 3]. Among Iraq and Afghanistan war veterans, up to 70% of those with chronic pain also suffer from anxiety or depression [4, 5], complicating treatment and increasing long-term disability risks [6, 7].

In Ukraine, the ongoing conflict has caused a surge in cases of chronic pain due to combat trauma, musculoskeletal damage, and post-traumatic stress disorder (PTSD) among both military and civilian populations [8, 9]. Although emotional burnout has been widely studied in healthcare workers, its prevalence in patients with chronic pain during wartime remains underexplored [10, 11]. Anxiety and depression are key mediators between pain and functional disability, yet the roles of age, pain duration, and resilience under military conditions require further investigation [12, 13].

AIM

The aim of this study is to evaluate emotional burnout, anxiety, and depression in men with chronic pain undergoing rehabilitation during wartime in Ukraine, with attention to age and pain duration.

MATERIALS AND METHODS

The study was conducted from January to May 2025 at the State Institution «Veteran Mental Health and Rehabilitation Center «Forest Glade» Ministry of Health of Ukraine (Kyiv, Ukraine). The final sample consisted of 35 male military personnel aged 29 to 60 years, with a mean age of (mean±standard deviation) 43±10 years. The

average duration of combat-related chronic pain was 23±17 months (range: 3 to 58 months). The inclusion criterion was the absence of acute psychosis or severe cognitive impairment. Patients were stratified by age (25-40 years [n=18] and 41-60 years [n=17]) and pain duration (3-12 months [n=16] and >12 months [n=19]).

The validated Ukrainian versions of standardized instruments were used. The Maslach Burnout Inventory (MBI) [4, 10] assessed three dimensions of occupational burnout: emotional exhaustion (EE) – emotional overload (scoring per subscale [SpS]: low ≤16, moderate 17-26, high ≥27); depersonalization (DP) – impersonal attitude toward patients (SpS: low ≤6, moderate 7-12, high ≥13; personal accomplishment (PA) – sense of work success (SpS [reverse-scored]: high ≥39, moderate 32-38, low ≤31).

The State-Trait Anxiety Inventory (STAI) [5, 6] measured state anxiety (STAI-S) (transitory situational anxiety) and trait anxiety (STAI-T) (general tendency toward anxiety). Each scale includes 20 items rated on a 4-point Likert scale (total score: 20-80). Interpretation: low ≤37, moderate 38-44, and high ≥45 (cut-offs may vary by population).

The Hospital Anxiety and Depression Scale (HADS) [6, 8, 9] evaluated anxiety (HADS-A) and depression (HADS-D), excluding somatic symptoms. Each subscale consists of 7 items (total score: 0-21). Interpretation: 0-7: normal; 8-10: borderline abnormal (borderline case); ≥11: abnormal (case).

These instruments are well-established in clinical and research practice and have demonstrated good reliability and validity in both international and Ukrainian samples [3, 18]. Data were collected through self-report questionnaires and structured interviews at rehabilitation intake.

The data were analyzed by the use of Statistica v. 14.0 (TIBCO Software Inc., USA), IBM SPSS Statistics v. 27.0 (Armonk, NY: IBM Corp., USA), and RStudio v. 2025.05.1+513 for R v. 4.5.1. The quantitative parameters were presented as median (Me) with interquartile range (IQR). The qualitative data were presented as absolute and relative (%) frequency. To compare two independent samples, we used the Mann-Whitney U test (for quantitative variables) and the Fisher`s exact test (for binary qualitative data). The correlation analysis was performed using the Spearman`s rank correlation coefficient (ρ), being interpreted as follows: $|\rho|<0,3$ – weak; $0,3\leq|\rho|<0,7$ – moderate; and $|\rho|\geq0,7$ – strong correlation. A p-value <0,05 was considered as statistically significant.

RESULTS

According to the MBI, most participants exhibited moderate-to-high levels of EE (88,6%), DP (80,0%), and reduced PA (85,7%) at rehabilitation intake (Fig. 1). Specifically, 37,2% had high EE, 28,6% showed high DP, and 31,4% demonstrated low PA (i.e., high level of reduced PA) – the indicators of chronic stress and long-term burnout. The dominant profile reflected moderate burnout, particularly in emotional and interpersonal functioning (Fig. 1).

Table 1 shows that both age groups (25-40 and 41-60 years) had comparable average scores and similar distributions of burnout severity. Most participants exhibited moderate to high levels of emotional exhaustion (EE) and depersonalization (DP). Although the older group showed slightly higher rates of high DP and a low degree of reduced personal accomplishment (PA), none of the differences were statistically significant (Table 1).

As shown in Table 2, no statistically significant differences in burnout severity were found between patients with short-term (3-12 months) and long-term (>12 months) pain

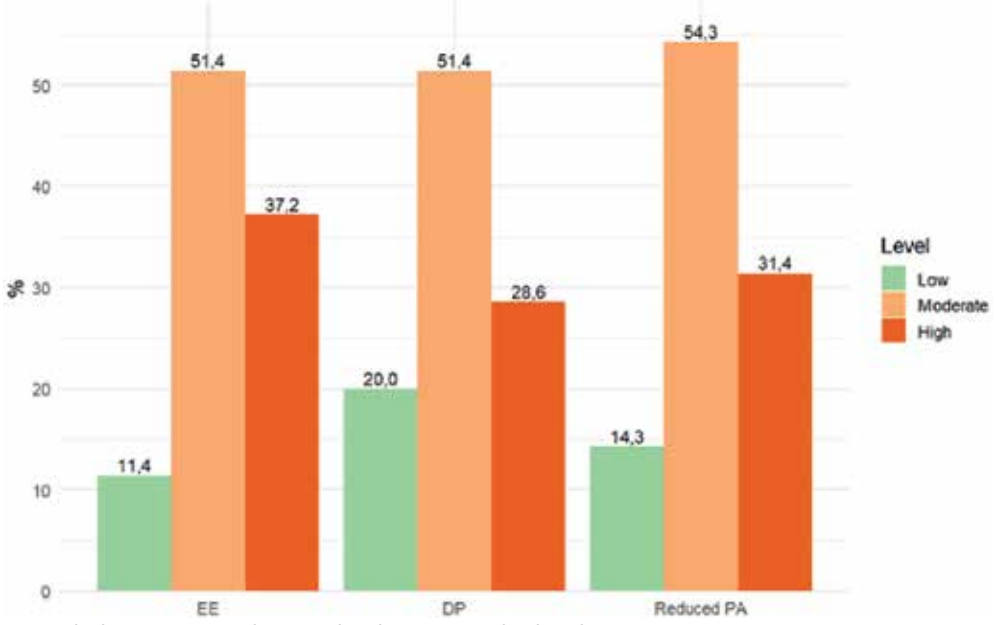

Fig. 1. The burnout severity by MBI subscales: EE, DP, and reduced PA (n=35)

Picture taken by the authors

Table 1. The distribution of MBI subscales by age groups (n=35)

Subscale			Age group (years)		p
			25-40 (N=18)	41-60 (N=17)	
EE	Average value, score		23 (20-32)	25 (17-31)	0.807
	Level, n (%)	L	1 (5.6)	3 (17.6)	0.338
		M	11 (61.1)	7 (41.2)	0.318
		H	6 (33.3)	7 (41.2)	0.733
		[M+H]	17 (94.4)	14 (82.4)	0.338
DP	Average value, score		10 (9-12)	11 (7-16)	0.935
	Level, n (%)	L	3 (16.7)	4 (23.5)	0.691
		M	11 (61.1)	7 (41.2)	0.318
		H	4 (22.2)	6 (35.3)	0.471
		[M+H]	15 (83.3)	13 (76.5)	0.691
PA	Average value, score		36 (33-39)	37 (33-41)	0.636
	Level*, n (%)	L	2 (11.1)	3 (17.6)	0.658
		M	11 (61.1)	8 (47.1)	0.505
		H	5 (27.8)	6 (35.3)	0.725
		[M+H]	16 (88.9)	14 (82.4)	0.658

*Note: L – low; M – moderate; H – high; *– of the reduced PA*

Source: compiled by the authors of this study

Table 2. Distribution of MBI subscales by pain duration groups (n = 35)

Subscale			Pain duration (months)		p
			3-12 (N=16)	>12 (N=19)	
EE	Average value, score		21 (20-26)	27 (17-34)	0.271
	Level, n (%)	L	2 (12.5)	2 (10.5)	1.000
		M	11 (68.8)	7 (36.9)	0.092
		H	3 (18.7)	10 (52.6)	0.078
		[M+H]	14 (87.5)	17 (89.5)	1.000
DP	Average value, score		10 (7-11)	11 (8-17)	0.367
	Level, n (%)	L	4 (25.0)	3 (15.8)	0.677
		M	9 (56.2)	9 (47.4)	0.738
		H	3 (18.8)	7 (36.8)	0.285
		[M+H]	12 (75.0)	16 (84.2)	0.677
PA	Average value, score		36 (33-39)	37 (33-41)	0.636
	Level*, n (%)	L	3 (18.8)	2 (10.5)	0.642
		M	10 (62.5)	9 (47.4)	0.500
		H	3 (18.8)	8 (42.1)	0.167
		[M+H]	13 (81.3)	17 (89.5)	0.642

*Note: L – low; M – moderate; H – high; *– of the reduced PA*

Source: compiled by the authors of this study

duration. However, high EE tended to be more frequent in >12 months group, while moderate levels predominated in the 3-12-month group. In addition, high DP was numerically, but non-significantly more common in the long-term group, with fewer individuals in the low range, as compared to the alternative group. For the reduced PA, we observed the share of those with high burnout rose from 18,8% to 42,1% in the 3-12 and >12 months groups, respectively (Table 2).

Although the differences did not reach statistical significance, the findings suggest a possible increase in EE, DP, and PA among patients with longer pain duration, highlighting the cumulative toll of chronic pain.

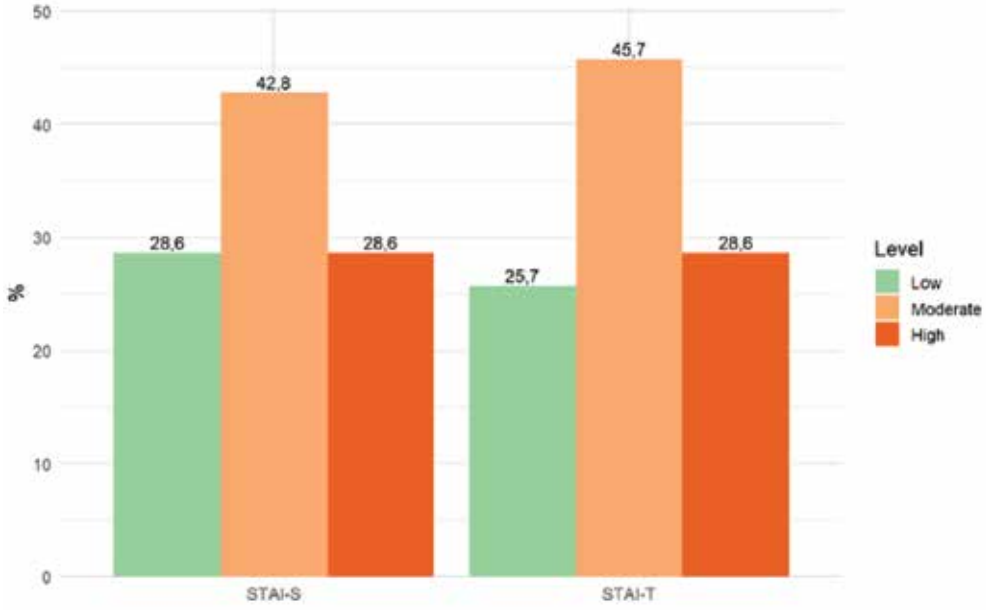

Fig. 2. Anxiety Levels According to STAI-S and STAI-T (n=35)

Picture taken by the authors

Table 3. The distribution of STAI subscales by age groups (n = 35)

Subscale			Age group (years)		p
			25-40 (N=18)	41-60 (N=17)	
STAI-S	Average value, score		40 (35-45)	44 (35-54)	0.273
	Level, n (%)	L	5 (27.8)	5 (29.4)	1.000
		M	9 (50.0)	6 (35.3)	0.500
		H	4 (22.2)	6 (35.3)	0.471
		[M+H]	13 (72.2)	12 (70.6)	1.000
STAI-T	Average value, score		40 (35-45)	44 (37-48)	0.369
	Level, n (%)	L	5 (27.8)	4 (23.5)	1.000
		M	9 (50.0)	7 (41.2)	0.738
		H	4 (22.2)	6 (35.3)	0.471
		[M+H]	13 (72.2)	13 (76.5)	1.000

Note: L – low; M – moderate; H – high

Source: compiled by the authors of this study

As shown in Fig. 2, moderate anxiety levels were the most common among the enrolled participants. Overall, more than 70 % showed moderate-to-high anxiety in both dimensions, highlighting its prevalence in individuals with chronic pain and emotional burnout (Fig. 2).

According to Table 3, no statistically significant differences were found between younger (25-40 years) and older (41-60 years) participants. However, older participants had slightly higher average scores for both state and trait anxiety. Although not statistically significant, this may reflect the impact of age-related factors such as cumulative stress, chronic pain, or military experience. Moreover, over 70% of participants in each age group showed moderate-to-high levels of anxiety, indicating a widespread psychological burden regardless of age. In addition, while moderate anxiety was numerically more common in the younger group, high anxiety levels were more prevalent among older participants, possibly due to reduced emotional resilience with age (Table 3). These findings highlight a shared psychological burden across age groups, with no apparent protective effect of youth. The age-related rise in anxiety, though not statistically significant, is clinically meaningful and should inform age-sensitive approaches to managing anxiety and emotional regulation in individuals with chronic pain and burnout.

Table 4 presents the relationship between chronic pain duration and anxiety severity among the enrolled participants.

While no statistically significant differences were found, the data reveal clinically meaningful findings. In particular,

participants with pain lasting over 12 months showed higher median scores for both state (43 vs. 38) and trait anxiety (44 vs. 39), indicating a growing emotional burden with prolonged pain. Additionally, high anxiety levels were twice as common in the >12-month group (36,8%) compared to the 3-12-month group (18,7%) for both state and trait anxiety, suggesting emotional deterioration over time. Finally, we observed a decrease in the frequency of low anxiety cases in the long-term group compared to the short-term group, indicating reduced psychological resilience with increasing pain duration.

Despite the lack of statistical significance, the results from Table 4 suggest that longer pain duration could be linked to increased anxiety. These findings support previous research on the psychological toll of chronic nociceptive input and highlight the importance of early psychological assessment and intervention in chronic pain management [3, 5, 11, 14].

The HADS results reveal a relatively high prevalence of emotional disturbances among participants (Fig. 3). Specifically, 60% reported borderline abnormal-to-abnormal anxiety, aligning with STAI findings and reflecting a substantial anxiety burden in chronic pain patients. Importantly, 51,4% of respondents showed a normal pattern of HADS-D scores, but 48,6% had borderline or abnormal symptoms, highlighting that depression remains clinically significant (Fig. 3).

The distributions of HADS subscale levels among the enrolled participants (Fig. 3) underscore the emotional impact of war-related chronic pain, with anxiety indicating acute

Table 4. The distribution of STAI subscales by pain duration groups (n = 35)

Subscale			Pain duration (months)		p
			3-12 (N=16)	>12 (N=19)	
STAI-S	Average value, score		38 (33-45)	43 (37-61)	0.117
	Level, n (%)	L	7 (43.8)	3 (15.8)	0.132
		M	6 (37.5)	9 (47.4)	0.734
		H	3 (18.7)	7 (36.8)	0.285
		[M+H]	9 (56.2)	16 (84.2)	0.132
STAI-T	Average value, score		39 (34-45)	44 (38-56)	0.102
	Level, n (%)	L	6 (37.5)	3 (15.8)	0.245
		M	7 (43.8)	9 (47.4)	1.000
		H	3 (18.7)	7 (36.8)	0.285
		[M+H]	10 (62.5)	16 (84.2)	0.245

Note: L – low; M – moderate; H – high

Source: compiled by the authors of this study

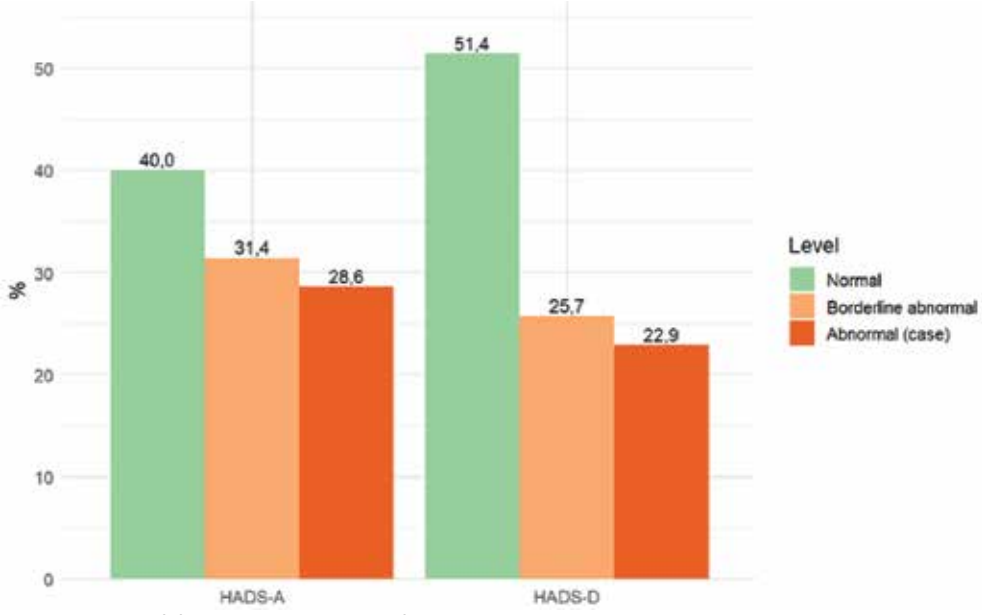

Fig. 3. Anxiety and depression severity according to HADS (n=35)

Picture taken by the authors

distress and depression suggesting long-term affective strain. These findings support routine psychological screening and integrated mental health support in rehabilitation programs, particularly for veterans.

Table 5 shows that anxiety and depression levels (HADS) did not differ significantly between younger (25-40) and older (41-60) participants, though some clinically meaningful findings emerged.

Despite comparable average scores and similar frequencies of pooled borderline and abnormal anxiety patterns in the studied groups, the older group presented with numerically more frequent abnormal cases, suggesting that emotional vulnerability increases with age. Additionally, the older group was characterized by more frequent pooled borderline and abnormal depression patterns compared to the younger group, with over 20% of abnormal depression cases in both groups (Table 5). These findings support the need for age-sensitive psychological assessment and care, especially in individuals with chronic pain or combat-related stress.

Table 6 compares the HADS subscale patterns in patients with short-term (3-12 months) versus long-term (>12 months) pain, revealing significant findings, particularly for anxiety.

According to the obtained data, the HADS-A subscale score was significantly higher in the long-term group compared to the short-term patients. Furthermore, a normal HADS-A pattern was more common in the short-term group, while borderline-to-abnormal cases were more frequent in the long-term group (Table 6). This confirms a link between prolonged pain and increased anxiety.

The long-term pain group also demonstrated numerically higher HADS-D subscale scores, with a tendency for the pooled borderline-to-abnormal pattern to be more frequent compared to the short-term group, suggesting a trend toward worsening emotional health with increasing pain duration (Table 6).

Table 5. Distribution of HADS subscales by age groups (n = 35)

Subscale			Age group (years)		p
			25-40 (N=18)	41-60 (N=17)	
HADS-A	Average value, score		9 (4-10)	8 (5-12)	0.782
	Level, n (%)	N	7 (38.9)	7 (41.2)	1.000
		BA	7 (38.9)	4 (23.5)	0.471
		A	4 (22.2)	6 (35.3)	0.471
		[BA+A]	11 (61.1)	10 (58.8)	1.000
HADS-D	Average value, score		7 (4-10)	8 (5-10)	0.483
	Level, n (%)	N	10 (55.6)	8 (47.1)	0.740
		BA	4 (22.2)	5 (29.4)	0.711
		A	4 (22.2)	4 (23.5)	1.000
		[BA+A]	14 (44.4)	9 (52.9)	0.740

Note: N – normal; BA – borderline abnormal (borderline case); A – abnormal (case)

Source: compiled by the authors of this study

Table 6. The distribution of HADS subscales by pain duration groups (n = 35)

Subscale			Pain duration (months)		p
			3–12 (N = 16)	>12 (N = 19)	
HADS-A	Average value, score		5 (4-10)	10 (8-15)	0.041
	Level, n (%)	N	10 (62.5)	4 (21.1)	0.018
		BA	3 (18.75)	8 (42.1)	0.167
		A	3 (18.75)	7 (36.8)	0.285
		[BA+A]	6 (37.5)	15 (78.9)	0.018
HADS-D	Average value, score		6 (4-9)	8 (5-12)	0.142
	Level, n (%)	N	11 (68.75)	7 (36.85)	0.092
		BA	2 (12.5)	7 (36.85)	0.135
		A	3 (18.75)	5 (26.3)	0.700
		[BA+A]	5 (31.25)	12 (63.15)	0.092

Note: N – normal; BA – borderline abnormal (borderline case); A – abnormal (case)

Source: compiled by the authors of this study

Fig. 4. The correlation matrix (ρ) the studied surveys` subscales among the enrolled respondents (heatmap). All the correlations are significant at p<0,001 (n=35)

Picture taken by the authors

Therefore, pain duration significantly impacts emotional well-being, especially anxiety, which rises sharply after 12 months. While depressive symptoms also increase, further study is needed. These results support early psychological screening and interventions within the first year of chronic pain, particularly for those with military-related trauma.

Fig. 4 shows the correlations of the studied surveys' subscales among the enrolled respondents (n=35). Strong (or close to strong) positive correlations (ρ=0.68-0.89; p < 0.001) emerged between burnout (MBI), anxiety (STAI, HADS-A), and depression (HADS-D), suggesting a shared emotional burden across these dimensions.

Although age and pain duration showed no significant correlations with psychological variables and were excluded from the heatmap (Fig. 4), this absence may be due to the small sample size or specific psychosocial traits of the enrolled population. Nonetheless, earlier analyses indicated that prolonged pain correlates with higher anxiety and depressive symptoms, highlighting the likely impact of chronic nociceptive stress on emotional health [3, 5, 9, 11, 14].

The currently obtained results emphasize a close relationship among anxiety, depression, and burnout in chronic pain patients. The lack of statistically significant relationships between the studied parameters and age or pain duration should not negate the clinical relevance of pain chronicity in shaping emotional responses. Larger studies are needed to confirm these associations and explore how chronic pain dynamics influence psychological well-being.

DISCUSSION

This study offers important insight into the psychological burden of chronic pain in wartime conditions. Moderate-to-high levels of EE (88,6%), DP (80%), and reduced PA (85,7%) were observed, alongside clinically relevant anxiety (71,4%) and depression (74,3%) per MBI and HADS assessments, respectively. These findings align with previous research in military settings – e.g., J. Vollert et al. [2], D. Langford et al. [5], and H. Li et al. [4], – and confirm similar trends in Ukraine (O. Shynkaruk et al. [3], P. Rogozhan et al. [8]).

Age-related differences in burnout and affective symptoms were not statistically significant, being partially contrasted to H. Varina and S. Shevchenko [14], who found younger adults more vulnerable due to limited coping strategies.

Pain duration showed a clearer pattern: those with >12 months of pain experienced significantly higher anxiety score and a higher prevalence of borderline-to-abnormal anxiety cases, alongside with the trend towards increased depression and burnout. These findings mirror M. Haack et al. [13] and J. De La Rosa et al. [6], who highlighted the emotional toll of chronic stress and comorbid pain-mood disorders.

The correlation analysis showed no significant links between psychological outcomes and age or pain duration, possibly due to small sample size and the uniformity of wartime stress exposure. A ceiling effect may have obscured group differences. Still, mostly strong intercorrelations were found between trait/state anxiety, EE, and DP, indicating a tightly connected emotional distress network. These patterns support integrative models of chronic pain and emotional dysregulation (M. Haack et al. [13]; S. Kim et al. [11]).

Clinically, our results once again underline the necessity of multidisciplinary rehabilitation that prioritizes psychological care. Burnout and affective symptoms should be treated as core components, not secondary effects. This aligns with C. Maslach and M. Leiter [10], J. Gewandter et al. [15], and J. Lim et al. [16], L. Butska et al. [17], who advocate

for systemic and patient-centered approaches. Gender-sensitive cognitive-behavioral therapy and quality-of-life focused care (J. Lim et al. [16]; M. Hadi et al. [18]) are also crucial. Ukrainian researchers [17, 19] similarly stress the importance of psychological education and context-specific strategies during war.

The limitations of the current study include the small sample size and cross-sectional design, limiting generalizability and causal inference. The wartime setting introduces uncontrollable psychosocial variables but offers a unique perspective – comparable to challenges noted by M. Moore et al. [7] and A. McGuire et al. [9] in conflict zones.

Future research should focus on larger, longitudinal studies exploring psychological symptom trajectories in chronic pain patients, factoring in resilience, coping, and access to support.

Finally, this study reveals a pronounced psychological burden in individuals with chronic pain under wartime stress, with a strong interplay between anxiety, depression, and burnout. These findings call for holistic, integrated care tailored to the complex needs of this vulnerable group.

CONCLUSIONS

A high level of psychoemotional distress was observed in most chronic pain patients affected by military operations: over 70% had moderate-to-high levels of burnout and anxiety, and close to half of patients (48,6%) demonstrated borderline or abnormal depression patterns.

Pain duration >12 months was significantly associated with higher anxiety, with 78,9% experiencing clinically relevant anxiety versus 37,5% in the short-term group (p=0,018).

The correlation analysis revealed strong (or close to strong) links between burnout (MBI), anxiety (STAI, HADS-A), and depression (HADS-D), pointing to systemic emotional dysregulation in chronic pain patients.

These findings highlight the importance of multidisciplinary rehabilitation, where psychological care is essential alongside physical treatment. The results further support individualized approaches that consider pain duration, psychological traits, personal history, and the combat context.

Future research should include larger, longitudinal samples and emphasize integrated psychophysiological strategies for veterans and war-affected populations.

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The authors confirm their full responsibility for adhering to ethical and legal standards in conducting biomedical research. This includes a strict compliance with the Law of Ukraine «Fundamentals of Health Legislation of Ukraine», the principles of the Declaration of Helsinki on ethical standards for biomedical research involving human subjects, and Directive 2001/20/EC of the European Parliament and the Council of the EU (April 4, 2001, as amended). The study protocol was approved by the local ethics committee. All responses were provided voluntarily and anonymously by the participants.

CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Detection and prevention of gambling disorder among Ukrainian law enforcement personnel under high operational stress: Institutional experience and comparative analysis

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ABSTRACT

Aim: To conduct a comparative institutional analysis of existing practices for detecting and preventing gambling disorder among Ukrainian law enforcement personnel under conditions of high operational stress.

Materials and Methods: The study involved 342 employees (average age 34,1±5,2 years; 86,5% males and 13,5% females) from four Ukrainian law enforcement agencies, performing investigative, operational-search, counterintelligence, analytical, and administrative-control functions. The study was conducted during 2023-2025 and employed the Problem Gambling Severity Index (PGSI) and Gambling Disorder Identification Test (GDIT) screening tools, an anonymous survey, structured psychological interviews, behavioural observation, and digital monitoring.

Results: According to the PGSI, 7,1% of respondents demonstrated pathological gambling behaviour. The use of the GDIT revealed an elevated score (≥15) in 40 (11,7%) respondents, with 19 of them (5,6%) exhibiting clinically relevant symptoms. Respondents with a GDIT score ≥15 (vs. <15 score group) showed 1,3 times higher anxiety levels (by HADS-A score), 3,4 times greater frequency of disciplinary incidents, and systematic interaction with gambling platforms during off-duty hours. Significant correlations were found between elevated gambling risk levels (by PGSI and GDIT) and symptoms of anxiety (HADS-A), impulsive financial decisions, and increased disciplinary infractions.

Conclusions: The implementation of a comprehensive system for the prevention of gambling disorder, integrating psychometric, behavioural, and digital indicators, is advisable to enhance psychological resilience and prevent a decline in operational reliability among Ukrainian law enforcement personnel under high operational stress.

KEY WORDS: gambling disorder; PGSI; GDIT; behavioural indicators

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INTRODUCTION

Under martial law, the effective performance of Ukraine's law enforcement agencies depends on their personnel's professional competence, psychological resilience, and behavioural stability. Addictive behaviours, particularly gambling disorder (ludomania), are increasingly noted among employees of the National Police, State Bureau of Investigation, Bureau of Economic Security, and Security Service of Ukraine due to high operational stress and emotional overload.

Gambling disorder, marked by compulsive gambling behaviour, is classified by the World Health Organization (WHO) as a mental disorder (ICD-10: F63.0; ICD-11: 6C50) [1]. Its growing prevalence in Ukraine necessitated the adoption of a clinical protocol, *Gambling Disorder (Ludomania)*, by the Ministry of Health (Order No. 1201, 10 July 2024) [2], based on international guidelines by the Problem Gambling Research and Treatment Centre [3].

The protocol recommends screening for gambling disorder among at-risk individuals using:

- Brief tools (1-3 items): BBGS [4], Lie-Bet Questionnaire [5], NODS-CLiP [6];
- Moderate tools (4-12 items): Problem Gambling Severity Index (PGSI) within the CPGI [7];
- Comprehensive tools (>13 items): SOGS [8], VGS [9], PPGM [10].

Additionally, patients should be assessed for comorbidities such as anxiety, depression, substance use, personality disorders, and domestic violence [11].

Gambling disorder reflects chronic stress and often remains unaddressed within institutions, endangering both personal and institutional reliability [11]. In a large-scale North American study of 43 093 people, Petry et al. [12] found high co-occurrence of gambling disorder with depression (37 %, odds ratio [OR]=3,0), anxiety (41 %, OR=3,4), alcohol dependence (73 %, OR=6,3), illicit drug

use (38 %, OR=5,4), nicotine dependence (60 %, OR=7,2), and personality disorders (61 %, OR=9,1).

A meta-analysis by F. Lorains et al. [13] confirmed frequent comorbidities among gamblers: nicotine (60,1 %), other substances (57,5 %), mood (37,9 %), and anxiety disorders (37,5 %).

Validated international screening tools, such as the PGSI and the Gambling Disorder Identification Test (GDIT), meet modern psychometric standards and are used for psychological assessment [14-16]. When combined with behavioural markers (e.g., disciplinary incidents, impulsive financial behaviour, cognitive decline), they enhance early detection. Regulatory steps in Ukraine now include gambling access restrictions for military personnel and public officials, along with online gambling bans during martial law [17].

AIM

The aim of this study is to conduct a comparative, institutional analysis of existing practices for detecting and preventing gambling disorder among Ukrainian law enforcement personnel under conditions of high operational stress.

MATERIALS AND METHODS

During 2023-2025, a comprehensive interdisciplinary study was conducted involving employees of the National Police of Ukraine, the State Bureau of Investigation, the Bureau of Economic Security of Ukraine, and the Security Service of Ukraine.

The study involved 342 employees from four Ukrainian law enforcement agencies, performing investigative, operational-search, counterintelligence, analytical, and administrative-control functions, all of whom voluntarily agreed to participate in the survey. The average age of respondents was (mean±standard deviation) 34,1±5,2 years); 86,5% were men and 13,5% were women. The majority of participants (64,6%) had between 5 and 15 years of service, 21,2% had more than 15 years, and only 14,2% had less than 5 years of experience. In terms of professional duties, 58% of respondents performed operational, counterintelligence, or investigative functions, 25% were engaged in analytical activities, and 17% held administrative and supervisory roles.

The study utilized standardized screening tools, specifically the PGSI to quantify risky gambling behavior, and the GDIT to identify its clinical, behavioral, and social manifestations within the professional activities of law enforcement personnel.

PGSI is a quantitative assessment tool used to evaluate the level of problematic or risky gambling behavior. It is applied in psychology, psychiatry, sociology, and public health to identify individuals at risk of developing gambling addiction. The PGSI consists of 9 questions that assess the frequency, consequences, and self-perception of gambling behavior over the past 12 months. Score interpretation: 0 points – no gambling problems, 1-2 points – low risk (some problems possible), 3-7 points – moderate risk (negative consequences may already be present), 8 or more points – high level of problem gambling behavior (likely gambling disorder) [18].

GDIT is a standardized test designed to detect gambling-related disorders. It is used for screening, diagnosis, and monitoring the severity of gambling addiction in both clinical and research settings. The test includes 18 items grouped into three core domains: gambling intensity, gambling-related harms, and clinical criteria for gambling disorder. Interpretation is based on the number of positive responses in each of the three domains. The test allows differentiation between normal, risky, and clinically significant gambling behavior [19].

The study involved the analysis of psycho-emotional, behavioral, and digital risk indicators, the assessment of the effectiveness of PGSI and GDIT screening tools, and the formulation of an interdisciplinary prevention strategy adapted to the specifics of law enforcement.

Subsequently, among respondents with an elevated risk level, the level of anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS). This scale allows for the identification of emotional disorders in patients, as it excludes somatic symptoms that are often present in both physical illnesses and depression/anxiety. HADS is a universal tool for initial psycho-emotional screening (HADS-A and HADS-D for anxiety and depression, respectively) [12].

Structured psychological interviews and digital monitoring were also conducted to analyze gambling-related online activity. Behavioural markers such as disciplinary fluctuations, impulsive financial actions, and emotional destabilization were assessed.

Statistical analysis was performed using IBM SPSS Statistics v. 27.0 and Jamovi v. 2.3. Quantitative variables were presented as mean±standard deviation. Qualitative data were summarized as absolute values (n) and percentages (%). Comparative analyses of continuous variables between independent groups were conducted using the Student's t-test or the Mann-Whitney U test. Differences in proportions were analyzed using the Fisher's exact test. Correlational analysis was conducted using the Spearman's rank correlation coefficient (ρ). The correlation coefficients were interpreted as follows: $|\rho|<0,3$ – weak; $0,3\leq|\rho|<0,7$ – moderate; and $|\rho|\geq0,7$ – strong correlation. A p-value of $<0,05$ was considered statistically significant in all analyses.

The research complied with internationally recognized principles of bioethics, including the provisions of the World Medical Association's Declaration of Helsinki and the Convention on Human Rights and Biomedicine. Data processing was conducted in anonymized form in accordance with confidentiality and data protection standards.

RESULTS

Analysis of the PGSI scale showed that 65,0% (n=222) of respondents exhibited no signs of gambling behavior (0 points), 13,7% (n=47) showed a low risk (1–2 points), 14,3% (n=49) a moderate risk level (3–7 points), and 7,0% (n=24) pathological gambling behavior (8+ points), requiring institutional intervention (Fig. 1).

The use of the GDIT revealed an elevated score (≥15) in 40 (11,7%) respondents, with 19 of them (5,6%) exhibiting clinically relevant symptom complexes, including loss of

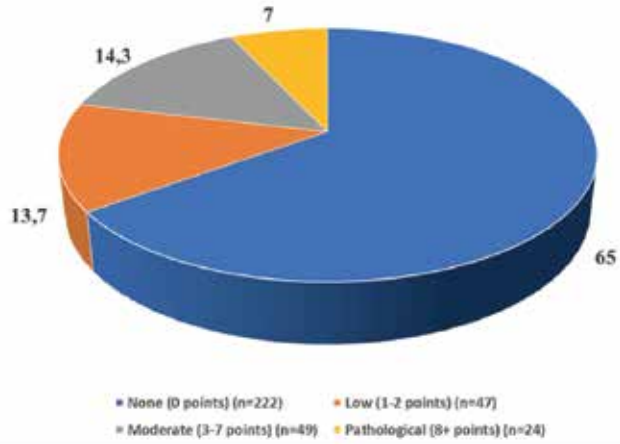

Fig. 1. The distribution of respondents (%) by the level of gambling behavior (PGSI) (n=342)

Picture taken by the authors

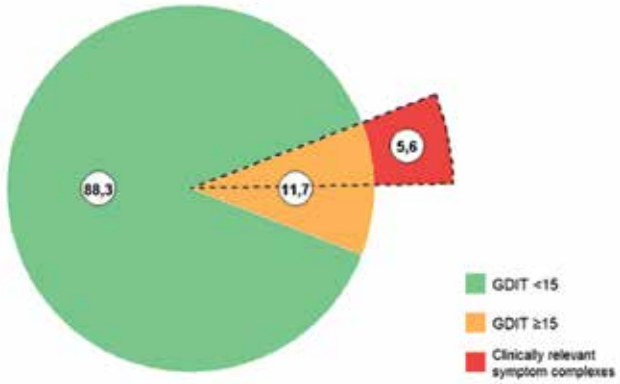

Fig. 2. The frequency (%) of elevated GDIT score patterns among the respondents (n=342)

Picture taken by the authors

control, compulsive urges to recoup losses, and social isolation (Fig. 2). In these cases, there were also multiple instances of skipping physical training sessions, disciplinary sanctions, and communication problems with colleagues. This trend is also reflected in the frequency of disciplinary incidents depending on the GDIT level, demonstrating that the frequency of disciplinary incidents is 3,4 times higher among respondents with a GDIT score ≥15 compared to the GDIT <15 group (42,5% vs. 12,6%, respectively; p<0,001).

The group analysis showed that employees under the age of 30 had the highest frequency of gambling risks – 21,8% in the «at-risk/pathological behavior» category – whereas in the 45+ age group it was only 6,2%. Employees with less than 5 years of service had average GDIT scores three times higher than those with over 15 years of experience (17,2 vs. 5,8 points, respectively; p<0,05).

Among women, the frequency of gambling manifestations was lower; however, a distinctive feature was the use of gambling as a means of emotional compensation, particularly in cases of chronic stress or fatigue. In 83% of such cases, involving female respondents who reported gambling as a means of emotional compensation in situations of chronic stress or fatigue, elevated anxiety levels were detected on the HADS scale score (7,1±0,6), indicating the need for psychological support

Psychological indicators on the HADS scale also demonstrated a statistically significant difference. The GDIT ≥15 group demonstrated a higher average anxiety score (HADS-A), as compared to GDIT<15 respondents (6,2±0,4 vs. 4,8±0,5, respectively; p<0,05), indicating the impact of gambling behavior on emotional state.

Among respondents with high GDIT levels (GDIT ≥ 15 points), additional clinically significant physiological disorders were recorded, including sleep disturbances (such as reduced sleep duration to 4-5 hours and frequent awakenings), chronic fatigue, tension headaches, increased heart rate, dyspeptic symptoms (nausea, decreased appetite), and signs of neurovegetative instability. Somatic symptoms were associated with levels of psycho-emotional destabilization, and in 9,2% of individuals, signs of hypertensive stress response were identified.

Behavioural indicators among individuals with elevated GDIT included disruptions in duty schedules of Ukrainian law enforcement personnel, impulsive conflicts, risky financial behavior (including use of credit resources), and reduced quality of reporting and official correspondence. Digital monitoring showed that in the group with GDIT ≥15, the average weekly time spent engaging with gambling content was 4,2±1,1 hours, with typical activity periods occurring after 10:00 p.m. In 7,9% of respondents, systematic transactions to gambling platforms from personal accounts (including Monobank, Wise, Skrill) were detected, which in several cases correlated with temporary insolvency.

The correlational analysis demonstrated a moderate (not far from strong) positive association between GDIT scores and HADS-A anxiety levels (ρ=0,64; p<0,05), indicating a close link between elevated gambling risk and heightened emotional distress. A strong positive correlation was observed between GDIT scores and the number of recorded disciplinary infractions (ρ=0,72; p<0,01), suggesting that increased gambling-related vulnerability is associated with deteriorating professional conduct. Moreover, impulsive financial behavior exhibited a moderate positive correlation with GDIT scores (ρ=0,61; p<0,05), further supporting the diagnostic relevance of behavioral indicators in identifying at-risk individuals within law enforcement settings (Table 1).

A moderate positive correlation was identified between PGSI scores and anxiety levels measured by the HADS-A scale (ρ=0,41; p<0,05), confirming the association between gambling intensity and psycho-emotional destabilization. In our study, PGSI scores did not show a statistically significant correlation with the markers of impulsive financial behavior (ρ=0,37; p > 0,05) or frequency of disciplinary infractions (ρ=0,34; p > 0,05), as assessed through digital monitoring and personnel records (Table 1).

The obtained data confirm the presence of gambling-related behavioural dysregulation in Ukrainian law enforcement personnel and highlight structural vulnerabilities that may

Table 1. The risk levels and correlation analysis of the studied indicators

Indicator	PGSI (n=342)	GDIT (n = 342)
Risk level	Moderate – 14.3%	Elevated – 11.7%
	Pathological gambling behavior – 7.1%	Clinically relevant symptom complexes – 5.6%
	Correlations	
HADS-A	Moderate positive: ρ=0.41 ($p<0.05$)	Moderate positive: ρ=0.64 ($p<0.05$)
Disciplinary infractions	NS	Strong positive: ρ=0.72 ($p<0.01$)
Impulsive financial behavior	NS	Moderate positive: ρ=0.61 ($p<0.05$)

Note: NS – non-significant

Source: compiled by the authors of this study

be addressed through prevention strategies involving periodic assessment and digital observation tools.

DISCUSSION

The systematization of markers allows for the identification of three clinical-behavioral profiles of individuals with gambling disorders: the impulsive gambler (high anxiety, young age, lack of experience), the compensatory gambler (exhaustion, search for emotional release, sleep disturbances), and the rationalized dependent (high level of denial, demonstrative disregard for service norms, avoidance of control).

The impulsive gambler typically belongs to the younger age group (under 30), has insufficient service experience, and is characterized by a high level of emotional lability. This category often exhibits mood instability, underdeveloped self-control, and a tendency toward conflict behavior. Medical consequences frequently include autonomic dysfunction, sleep disorders, and intermittent anxiety-depressive states.

The compensatory gambler is a person who engages in gambling as a mechanism of psychological compensation in response to chronic stress, professional burnout, or interpersonal problems. Characteristic symptoms include appetite disturbances, chest pain, sleep disorders, and a constant sense of psychophysiological exhaustion. This gambler type requires timely psychological intervention and support.

The rationalized dependent exhibits externally ordered behavior but is marked by a high level of denial, psychological rigidity, manipulative tendencies, and avoidance of responsibility. This type often violates organizational norms, demonstrates disregard for procedures, and is prone to chronic addiction and the development of psychological resistance to preventive measures.

The obtained results of the empirical study confirm that gambling addiction among employees of Ukrainian law enforcement agencies (National Police of Ukraine, State Bureau of Investigation, Bureau of Economic Security of Ukraine, and Security Service of Ukraine) is not only a psychological issue but also an organizational problem affecting institutional resilience, discipline, and security [20-22]. The PGSI and GDIT scale indicators correlated with the level of anxiety (HADS-A), indicating psycho-emotional exhaustion, which becomes a contributing factor to the development of behavioral addictions. Importantly, the obtained results support the clinical validity of PGSI and GDIT scales in operational environments and emphasize their relevance for early identification of destabilized personnel under high-stress conditions.

Specialized organizations – the WHO [23, 24], American Psychological Association (APA) [25], and the Ministry of Health of Ukraine (Order No. 1201 dated 10.07.2024 [2]) – emphasize the importance of early detection of such conditions as markers of deepening behavioral addiction and high risk for cardiovascular and gastrointestinal diseases in individuals with gambling disorders.

Our findings are consistent with the conclusions of NICE, which reports that up to 14% of individuals in security structures exhibit symptoms consistent with gambling disorder, and under conditions of chronic stress and irregular schedules, the risks nearly double [26]. Similar trends are documented by Public Health England, which emphasizes the need to integrate gambling screening into standard psychological assessment procedures [26, 27].

In the Republic of Poland, gambling is recognized as a risk factor not only for the civilian population but also for law enforcement personnel. A report by the Mental Health Center of the Institute of Occupational Medicine in Łódź notes that behavioral addictions are increasingly recorded among police officers and border guards, particularly in the form of online betting and casinos, which leads to a rise in disciplinary violations and professional burnout. The Polish Psychiatric Association, in cooperation with the Ministry of the Interior of Poland, also recommends mandatory gambling screening during the annual medical and psychological evaluation of personnel [28, 29].

In the Republic of Lithuania, according to the State Gambling and Gaming Control Commission, an anonymous register of self-restricted players has been in place since

2020, which includes a special category for "public servants with critical responsibilities". At the level of the Ministry of the Interior of Lithuania, it has been proposed to adapt the procedure of electronic monitoring of digital transactions for security sector employees who fall within the risk zone [30, 31].

In the Federal Republic of Germany, the issue of gambling behavior in law enforcement structures is actively studied within the framework of BZgA (Federal Center for Health Education) programs. According to a 2021 study, up to 9,1% of police officers show signs of moderate gambling activity, which is associated with service-related stress and night shifts. The Federal Ministry of Health of Germany recommends integrating elements of the PGSI, Lie/Bet, and South Oaks Gambling Screen questionnaires into regular screening programs for service members [32, 33].

CONCLUSIONS

The study validated the effectiveness of an interdisciplinary institutional approach to identifying and preventing gambling disorder among Ukrainian law enforcement personnel exposed to high operational stress. Both the PGSI and GDIT proved to be reliable screening tools for risky and pathological gambling behaviour.

Significant correlations were found between gambling risk levels and anxiety symptoms (HADS-A), impulsive financial behaviour, and disciplinary infractions. Higher GDIT scores were associated with increased anxiety, more frequent rule violations, and regular interaction with gambling platforms during off-duty hours.

The integration of psychometric assessments with behavioural and digital markers allows for accurate identification of at-risk individuals. These findings highlight the clinical relevance of gambling-related behavioural dysregulation within security-sector institutions and support the development of tailored, context-specific prevention strategies.

Thus, the study findings lead to a recommendation for the introduction of regular gambling behaviour screening, integration of digital behaviour monitoring, and establishment of psychological support systems within law enforcement agencies. This will enhance psychological resilience, institutional reliability, and operational security during martial law and in peacetime.

The results of our study highlight the necessity of an interdisciplinary approach involving collaboration with general practitioners, cardiologists, and neurologists to pay closer attention to somatic complaints that may be secondary to gambling addiction – such as headaches, tachycardia, hypertension, sleep disturbances, and loss of appetite. It is essential to ensure timely referrals for psychological assessment when these somatic symptoms are accompanied by emotional instability or behavioural traits suggestive of compulsive tendencies. Clinical psychologists, psychotherapists, and psychiatrists should be involved in the comprehensive management of such patients.

The conducted study has practical significance for the early identification of risk factors and development of gambling addiction, as well as their association with somatoform disorders and the impact on individuals' fitness for duty.

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ORIGINAL ARTICLE

Hospital stay duration prediction score system for Covid-19 patients: Evaluation of proposed practical models

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ABSTRACT

Aim: Evaluate the prognostic value of the proposed scale on determining hospital stay duration of patients with COVID-19. Establish baseline values of the scale for further implementation into primary care.

Materials and Methods: We gathered and analyzed data of 140 hospitalized patients who underwent treatment in Uzhhorod CMCH and had a positive COVID-19 test from the start of the pandemic and until January of 2022. 4 models were proposed, each patient was analyzed based on a point system determined by the model, to compare the number of accumulated points with hospital stay duration.

Results: Linear regression results showed that models I and IV provide a low practical usage as per R2. Models II and III are most promising showing a high prognostic value (R^2 are 0.0703 and 0.111 respectively). Models II and III showed a statistically significant increase in hospital stay for scores 2 and 5 compared with 0. The accumulated data shows that scores 2 and 5 show a significant increase in hospital stays, while 1, 3 and 4 did not show any significant increase for practical usage.

Conclusions: Overall, this analysis showed that middle scores and maximum scores showed significance compared to hospital stays, while Models II and III showed the highest practical usage coefficients in COVID-19 scenarios. Despite the fact that the number of asthma and COPD patients was low, these models may prove useful for practical usage in triage scenarios and primary care.

KEY WORDS: COVID-19, non-communicable disease, diagnostic tools, outcomes, primary care

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INTRODUCTION

During the pandemic the main focus of healthcare providers and researchers alike was aimed at evaluating COVID-19 patients that are already hospitalized. It has been shown that timely hospitalization and start of treatment improve patient prognosis. Thus, there are tools to assess patients that are receiving inpatient care, such as BCRSS, qCSI, NEWS and NEWS2. But these scores are difficult to implement in an outpatient setting, because they evaluate rapid deterioration of the patient's condition and use metrics that rapidly change as well, such as SpO2, ventilation rate and body temperature. [1-4] These vital signs can provide information on the patient`s wellbeing currently and can show a provider that the patient needs immediate care. Unfortunately, these metrics may stay in normal ranges at the moment of measurement, but may rapidly deteriorate in the next few days for certain patients with chronic conditions. Also, we should take into account that the primary care physician is the first point of contact for these patients in most cases, where such metrics are unreliable. Therefore, the goal of this score is to evaluate the prognostic role of such criteria and to provide primary care physicians and other first response providers with a comprehensive, easy to use tool to quickly assess the risk of rapid worsening of COVID-19 infection and apply necessary measures to prevent that.

AIM

Evaluate the prognostic value of the proposed scale on determining hospital stay duration of patients with COVID-19. Establish baseline values of the scale for further implementation into clinical practice of primary care physicians.

MATERIALS AND METHODS

We gathered and analyzed data of 140 hospitalized patients who underwent treatment in Uzhhorod city multidisciplinary clinical hospital and had a positive COVID-19 test from the start of the pandemic and until January of 2022. Hospital stay duration was calculated in days. There were several criteria used in the score model development. Age was considered a factor for patients older than 65 years. Chronic medical conditions were also taken into account: diabetes mellitus, obesity, chronic obstructive pulmonary disorder (COPD), asthma, arterial hypertension, heart and liver issues.

To determine, how these diseases and conditions influence hospital stay duration, we developed 4 scale models:

Model I – each of the following criteria was calculated as 1 point: age 65+, diabetes, heart issues and/or hypertension (combination or one of them counts as 1 point), obesity, COPD.

Model II – each of the following criteria was calculated as 1 point: age 65+, diabetes, heart issues, hypertension (as separate 1 point each), obesity, COPD.

Model III – the same calculations as Model I, but heart issues and hypertension count as separate points and with the addition of liver problems (count as 1 point).

Model IV – the same calculations as same as Model I, but taking into account that studies showed asthma to be a beneficial factor in hospital stay duration for COVID-19 patients, we will deduct 1 point if the patient also has asthma. [5]

Statistical analysis was performed using Spearman's correlation (with a positive correlation hypothesis) and a linear regression analysis. Jamovi 2.3 was used for statistical calculations [6].

RESULTS

Out of 140 patients 83 were female and 57 - male. Medium age was 61 (SD=13,8 years). The medium COVID-19 hospital stay duration was 17 days (SD=11,4 days).

The number of individual conditions and states were as follows: age 65+ - 67 patients, hypertension - 63, diabetes mellitus – 60, heart issues – 27, obesity – 37, liver issues – 29. Asthma and COPD had the lowest numbers – 2 of each diagnosis. There were 22 patients with 0 criteria, 33 patients with 1 criterion, 36 – with 2 criteria, 23 – with 3 criteria, 17 – with 4 criteria, and 9 with 5 criteria (Fig. 1).

MODEL EVALUATION

When comparing hospital stay duration in days with the score on each model, we used Spearman`s correlation, which showed that all models had statistical significance ($p<0.05$) with Model II and Model III having a stronger correlation coefficient (0.257 and 0.253 respectively) compared to Models I and IV (0.165 and 0.157 respectively).

To determine how the number of points is correlated to hospital stay duration and how each additional point affects the number of days spent in the hospital, we used linear regression for every model. Model I and Model IV due to their design patients accumulated point in the range of 0 to 4. Models II and III had patients accumulated point in the range of 0 to 5.

For model I the analysis showed that there is a statistically significant increase in hospital stay duration for patients that scored 1 and 4, when comparing to patients, who scored 0 (estimated increase of 5.89 days, p=0.033, and 7.15 days, p=0.04 respectively). All other comparisons were not statistically significant. For model I, the intercept was statistically significant ($p<0.001$) in all comparison models with $R^2 = 0.0437$ (Table 1).

For Model II, statistical analysis showed that there is a statistically significant increase in hospital duration for patients who scored 2 and 5 compared to patients with 0 (estimated increase of 7.09 days, p=0.025 and 12.93 days, p=0.008 respectively) and for patients who scored 5 compared to ones, who scored 1 (estimated increase of 9.58, p=0.035). Other comparisons didn`t show any statistical significance. For model II, the intercept was statistically significant ($p<0.001$) in all comparison models with $R^2 = 0.0703$ (Table 2).

Model III showed statistical significance in more comparison points: increase in hospital stay of patients with a score of 2 and 5 compared to 0 (7.53, p=0.012 and 14.81, $p<0.001$ respectively) as well as compared to 1 (5.344, p=0.043 and 12.626, p=0.003 respectively). Also, people, who scored 5 showed statistical significance compared to ones, who scored 3 (12.227, p=0.005) and 4 (10.63, p=0.021). For model III, the intercept was statistically significant ($p<0.001$) in all comparison models with $R^2 = 0.111$ (Table 2).

For the last model – Model IV, there was no statistically significant correlation between score comparisons and hospital stay duration with $R^2 = 0.0265$ (Table 1).

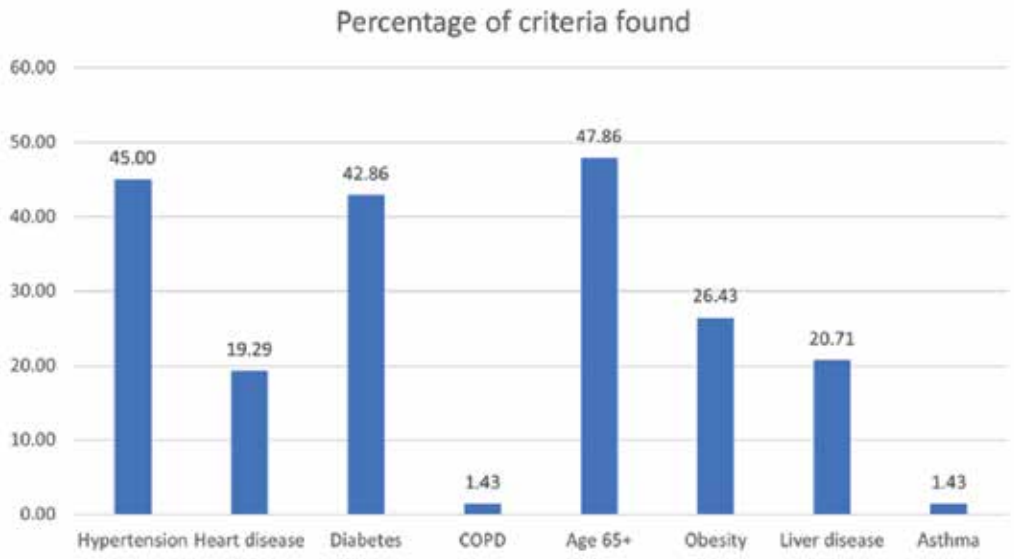

Fig. 1. Percentage of patients with each criterion

Picture taken by the authors

Table 1. Linear regression for Models I and IV: model fit measures and model coefficients

Model I		
R	R^2	
0.209	0.0437	
Predictor	Estimate	p
1 – 0	5.89	0.033
2 – 0	3.1	0.344
3 – 0	4.36	0.214
4 – 0	7.15	0.04
2 – 1	-2.79	0.322
3 – 1	-1.53	0.62
4 – 1	1.26	0.675
3 – 2	1.26	0.724
4 – 2	4.05	0.25
4 – 3	2.79	0.454

Model IV		
R		R^2
0.163		0.0265
Predictor	Estimate	p
1 – 0	4.08	0.135
2 – 0	2.11	0.524
3 – 0	3.15	0.369
4 – 0	5.94	0.087
2 – 1	-1.973	0.494
3 – 1	-0.927	0.765
4 – 1	1.862	0.541
3 – 2	1.05	0.773
4 – 2	3.83	0.285
4 – 3	2.789	0.458

Source: compiled by the authors of this study

Table 2. Linear regression for Models II and III: model fit measures and model coefficients

Model II		
R		R^2
0.265		0.0703
Predictor	Estimate	p
1 – 0	3.25	0.244
2 – 0	7.09	0.025
3 – 0	4.79	0.151
4 – 0	5.63	0.126
5 – 0	12.93	0.008
2 – 1	3.84	0.164
3 – 1	1.54	0.603
4 – 1	2.38	0.476
5 – 1	9.68	0.035
3 – 2	-2.3	0.484
4 – 2	-1.46	0.687
5 – 2	5.84	0.222
4 – 3	0.838	0.825
5 – 3	8.143	0.098
5 – 4	7.305	0.156

Model III		
R		R^2
0.333		0.111
Predictor	Estimate	p
1 – 0	2.18	0.47
2 – 0	7.53	0.012
3 – 0	2.58	0.43
4 – 0	4.18	0.247
5 – 0	14.81	< .001
2 – 1	5.344	0.043
3 – 1	-1.342	0.893
4 – 1	0.648	0.551
5 – 1	12.626	0.003
3 – 2	-4.94	0.091
4 – 2	-3.35	0.308
5 – 2	7.28	0.076
4 – 3	1.595	0.655
5 – 3	12.227	0.005
5 – 4	10.63	0.021

Source: compiled by the authors of this study

DISCUSSION

The criteria and conditions were picked based on previous data showing that their impact on COVID-19 duration. Patients with diabetes mellitus have been shown to have a prolonged duration of infection depending on glycemic levels and increased inflammation. [7] Patients age was also shown to be a factor of prolonged hospital stay and increased risk of complications, specifically 65 years old or higher. Cardiovascular diseases and hypertension are both widespread and have a significant effect on the overall health, contributing to inflammation progression and slower recovery [8, 9].

Spearman`s correlation showed us, that all models have a statistically significant correlation, when comparing hospital stay duration with the number of points that any individual patient has, with the hypothesis being a positive correlation.

When examining the Linear regression results, models I and IV showed low practical usage as per R^2 (0.0437 and

0.0265 respectively). Model I is of particular interest in the context of solidifying the theory of the other models. It showed a correlation when comparing patients that scored 0 with patients that scored 1 and 4. This may be due to the fact that model I counted hypertension and/or heart disease as one point, these scores are consistent with models II and III, but with less significance.

Models II and III are most promising regarding prognostic value (R^2 are 0.0703 and 0.111 respectively). Unlike Model III, Model II did not include liver diseases. This model was included, because some previous studies showed that liver disease was not a prognostic factor for risk of hospitalization, since it mainly determined how well the patients would tolerate treatment. [10-12] Both models II and III showed a statistically significant increase in hospital stay duration of patients that scored 2 and 5 compared to patients with 0.

The accumulated data shows that scores 2 and 5 (4 for model I as being the highest) show a significant increase in hospital stays, while 1, 3 and 4 (3 for model I) did not show any significant increase for practical usage.

There was also an interesting trend, that occurred in the models – a decrease in hospital stay duration for patients with a higher number of points. For models I and IV this occurred when comparing patients who scored 2 and 3 points, when comparing to patients with a score of 1. For model II this occurred for patients who scored 3 and 4, when comparing to patients with a score of 2. And lastly, for model III this occurred for patients, who scored 3 compared to patients, who scored 1, and also the same trend as for model II – 3 and 4 points compared to 2. There was no statistical significance related to these finds, but it might be an indicator that one or more criteria may have a more meaningful impact on hospital stay duration compared to other factors. How this would influence the final practical model prompt further investigation.

CONCLUSIONS

Overall, this analysis showed that middle scores (1 and 2, depending on the model) and maximum scores (4 and 5) showed significance compared to hospital stays, while Models II and III showed the highest practical usage coefficients (R^2 – 7.03 and 11.1 % respectively) in COVID-19 scenarios. Despite the fact that the number of asthma and COPD patients was low, these models may prove useful for practical usage in triage scenarios and primary care. Further studies are warranted to establish baseline scores for implementation in practice.

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ORIGINAL ARTICLE

Study of ophthalmologists' opinions on the influence of current conditions in Ukraine on the organization of medical care for glaucoma patients

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ABSTRACT

Aim: To investigate the professional opinions of ophthalmologists who provide medical care to glaucoma patients in current conditions in Ukraine, particularly regarding the impact of Russia's full-scale invasion of Ukraine on the organization, quality, and timeliness of medical care for these patients.

Materials and Methods: The research materials were data from a voluntary anonymous questionnaire survey of 322 ophthalmologists from various regions of Ukraine who work in public and private medical institutions. Data from the Kyiv City Information and Analytical Center of Medical Statistics were also analyzed.

Results: According to the ophthalmologists, the proportion of patients with secondary glaucoma (62,9±3,5%) and open-angle glaucoma (34,4±3,5%) has increased, as well as the proportion of patients with stage III glaucoma (61,6±3,4%). Since the onset of the full-scale invasion, the number of glaucoma patients seeking ophthalmological help late (74,8±2,4%) or irregularly (83,5±2,1%) has increased. A total of 62,7±2,7% of ophthalmologists report that glaucoma patients are effectively refusing surgical treatment, mostly due to a lack of financial resources to undergo the operation (82,7±2,7%).

Conclusions: The war has had a negative impact on the ability to provide quality ophthalmologic care, particularly to patients with open-angle glaucoma. The findings may be used to identify opportunities and strategies for improving the quality of ophthalmologic care.

KEY WORDS: Ophthalmology, glaucoma, medical care, ophthalmologists, prevention

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INTRODUCTION

Glaucoma is a leading cause of irreversible blindness worldwide [1, 2]. Between 1990 and 2019, the global prevalence of glaucoma increased to 7,47 million cases, and the global disease burden measured in DALYs (disability-adjusted life years) rose to 0,75 million – an increase of 92,5% and 69,2%, respectively. It has been established that the disease burden caused by glaucoma is closely associated with socioeconomic status, age, and gender [3]. In 2022, the global incidence rate of open-angle glaucoma was 23,46 cases per 10 000 person-years among individuals aged 40 to 79. Specifically, the incidence was 5,51 cases per 10 000 person-years in the 40-44 age group, and 64,36 per 10 000 person-years in the 75-79 age group [4].

It is known that many people with glaucoma are unaware that they have a progressive yet preventable disease [5, 6]. As the severity of glaucoma increases, its progression becomes more difficult to control, and the cost of treatment rises with the stage of the disease [7]. Therefore, early, rapid, and accurate diagnosis of glaucoma is crucial. Currently, diagnosis is typically made through opportunistic case detection, usually by optometrists or general ophthalmologists. Optimal screening-based diagnosis allows for early detection of glaucoma in patients who are at high risk of developing the disease or are particularly vulnerable to vision impairment and decreased quality of life. Screening also helps determine the most effective treatment among the various available options [8].

Russia's full-scale military invasion of Ukraine has significantly affected various aspects of life across all regions of the country – not only those located near the front lines. The war's negative socio-economic impact is the result of extensive infrastructure destruction, reduced workforce availability, inflation, population debt, unemployment, social fragmentation, and large-scale population migration [9].

A direct correlation has been established between the presence of glaucoma and worsening socio-economic indicators, particularly in relation to the patient's ability to bear direct treatment costs (such as purchasing medications, attending regular medical appointments, undergoing diagnostic examinations, and having surgery) [10].

AIM

To investigate the professional opinions of ophthalmologists who provide medical care to glaucoma patients in current conditions in Ukraine, particularly

regarding the impact of Russia's full-scale invasion of Ukraine on the organization, quality, and timeliness of medical care for these patients.

MATERIALS AND METHODS

The study employed a questionnaire-based survey using a custom-designed questionnaire consisting of 33 questions. The questionnaire aimed to assess the physician's ability to ensure timely and comprehensive medical examinations for diagnosis, prescribe appropriate treatment, and organize disease monitoring. Part of the questionnaire focused on patient adherence to collaboration with ophthalmologists, including compliance with medical prescriptions and timeliness in seeking care when glaucoma symptoms arise. The survey also provided insight into ophthalmologists' perceptions of how the full-scale Russian invasion of Ukraine has affected the quality of medical care for glaucoma patients. The data from the Kyiv City Information and Analytical Center of Medical Statistics were also analyzed.

The primary source of data for the study was a questionnaire survey completed by 322 ophthalmologists. Among the surveyed ophthalmologists, women predominated (88,2%). In terms of age distribution, the majority (53,2%) were between 40 and 59 years old, while nearly one-third (30,5%) were under 40. Notably, more than a quarter (26,3%) of respondents were of retirement age. It is important to note that 43% of ophthalmologists had more than 26 years of total medical experience; 24,3% had between 16 and 25 years of experience; and the remaining 32,7% had up to 15 years of experience. As for their experience specifically as ophthalmologists, the corresponding distribution was as follows: 38,6%, 25,0%, and 36,4%, respectively. Data were presented as absolute and relative (rate per 100 respondents [%] ± standard error [SE]) frequency.

ETHICS

The research was conducted in accordance with the standards and principles of the Council of Europe Convention on Human Rights and Biomedicine, the World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current Ukrainian regulatory documents. The questionnaire used in this study was approved by the Ethics Committee of Bohomolets National Medical University, Protocol No. 190, dated 23.12.24. The survey was voluntary and anonymous.

RESULTS

Glaucoma is a fairly common eye disease, and only five respondents (1,6%) reported that they had not encountered this condition in their practice – most likely due to their limited professional experience. More than half of the surveyed ophthalmologists (57,8%) stated, based on their observations, that the epidemiological structure of glaucoma has changed since the beginning of the full-scale invasion. They primarily believe that there has been an increase in the proportion of patients with glaucoma, particularly with secondary glaucoma (60,2±3,6%) and open-angle glaucoma (34,4±3,5%). Nearly two-thirds of the physicians (63,0%) believe that the distribution of glaucoma cases by stage has changed since the onset of the full-scale invasion, specifically noting a significant increase in the proportion of patients with stage III glaucoma (61,6±3,4%) (Table 1).

The majority of doctors consider the quality of ophthalmological care provided in the healthcare institutions where they work to be high (30,4 ± 2,6%) or rather high (31,1 ± 2,6%). However, 36,3 ± 2,7% of respondents believe that the quality of ophthalmological care has changed since the beginning of the war. Opinions among doctors regarding the direction of these changes were divided: overall, 56,4% believe that the quality of care has improved, while 29,1% think it has worsened. Furthermore, 59,6% of respondents believe that all necessary resources for providing quality ophthalmological care are available in healthcare institutions, although 32,6% think these resources have changed since the start of the war, with 65,7% of them considering these changes to be improvements. These resources are largely determined by the state of material and technical equipment in healthcare institutions. A significant portion of ophthalmologists evaluate this state, particularly regarding glaucoma diagnosis and treatment, as excellent (15,2 ± 2,0%) or good (39,4 ± 2,7%). Only 31,1% of respondents believe that the material and technical support for glaucoma diagnosis and treatment has changed during the war, with 68,0% of them stating that it has improved.

Table 1. Assessment by ophthalmologists of changes in the glaucoma patient population related to the war

No.	Question	Answer	Distribution of respondents by answers, N (% ± SE)
1	How has the epidemiological structure of glaucoma in practice changed after the full-scale invasion? (n=186)	Increased percentage of open-angle glaucoma	64 (34.4 ± 3.5)
		Increased percentage of angle-closure glaucoma	10 (5.4 ± 1.7)
		Increased percentage of secondary glaucoma	112 (60.2 ± 3.6)
2	How has the distribution of patients by stage of glaucoma changed after the full-scale invasion? (n=203)	Increased percentage of patients with early-stage I-II glaucoma	45 (22.2 ± 2.9)
		Increased percentage of patients with advanced stage III glaucoma	125 (61.6 ± 3.4)
		Increased percentage of patients with terminal stage IV glaucoma	33 (16.2 ± 2.6)

Source: compiled by the authors of this study

Only 18,2% of respondents indicated that the equipment and materials they work with do not meet modern scientific and technical standards or current ophthalmological care standards for patients with glaucoma (Table 2).

An integral and critically important part of an ophthalmologist's work is preventive care, especially in terms of secondary and tertiary prevention. Only timely and regular examinations by an ophthalmologist can ensure the early detection of glaucoma, as believed by the vast majority of respondents (95,9%). The key to stabilizing glaucoma and preventing its progression is undoubtedly the strict adherence to the ophthalmologist's prescribed treatment, which is supported by 94,1% of respondents. In cases where non-surgical treatment methods are ineffective, timely surgical treatment is considered essential for stabilizing glaucoma and preventing its progression, according to 92,9% of the surveyed ophthalmologists (Table 3).

The analysis of respondents' answers to questions about changes in the behavior of patients with glaucoma regarding the implementation of doctors' recommendations turned out to be important. Physicians note that since the beginning of the full-scale invasion, the number of glaucoma patients who seek ophthalmological care late (74,8±2,4%) and irregularly (83,5±2,1%) has increased. According to 73,9±2,5% of respondents, the number of glaucoma patients who violate the ophthalmologist's treatment prescriptions has also risen. Furthermore, 62,7±2,7% of ophthalmologists report that glaucoma patients often refuse surgical treatment. The main reasons for this refusal are lack of financial resources to undergo surgery (82,7±2,7%), psychological problems related to the war (51,9±3,5%), and residence in occupied territories with logistical difficulties (42,6±3,5%). The least significant factors were distrust of the ophthalmologist (4,5±1,5%) or the ophthalmic surgeon (4,9±1,5%) (Table 4).

According to available data on glaucoma morbidity in Kyiv, the prevalence of this disease has decreased: if in the pre-war year 2021 it was 69,1 per 10,000 population, by 2024 it had dropped to 52,2 per 10,000 population. Thus, during the period of full-scale invasion, the prevalence of glaucoma decreased by 24,5%. However, at the same time, the incidence of newly diagnosed cases during this period increased from 3,7 to 5,6 cases per 10 000 population (an increase of 51,3%). Therefore, not all previously established glaucoma cases were registered, but the number of newly detected cases increased. Such divergent trends can be explained by the untimely and irregular visits to ophthalmologists, which is

Table 2. Results of the survey of ophthalmologists regarding the organization of ophthalmological care in healthcare institutions where they work and changes after the full-scale invasion of Russia into Ukraine and the introduction of martial law in Ukraine

No.	Question	Answer	Distribution of respondents by answers, N (% ± SE)
1	Assess changes in the quality of ophthalmological care related to the war (n=117)	Significantly improved	19 (16.2±3.4)
		Improved	47 (40.2±4.5)
		Worsened	28 (23.9±3.9)
		Significantly worsened	6 (5.2±2.0)
		Difficult to answer	17 (14.5±3.3)
2	Assess changes in opportunities for quality ophthalmological care for glaucoma patients related to the war (n=105)	Significantly improved	11 (10.5±3.0)
		Improved	58 (55.2±4.9)
		Worsened	34 (32.4±4.6)
		Significantly worsened	2 (1.9±1.3)
3	Assess the state of material and technical support for glaucoma diagnosis and treatment (n=322)	Excellent	49 (15.2±2.0)
		Good	127 (39.5±2.7)
		Satisfactory	124 (38.5±2.7)
		Unsatisfactory	22 (6.8±1.4)
4	Assess changes in the state of material and technical support for glaucoma diagnosis and treatment related to the war (n=100)	Significantly improved	12 (12.0±3.3)
		Improved	56 (56.0±4.9)
		Worsened	30 (30.0±4.6)
		Significantly worsened	2 (2.0±1.4)
5	Assess the compliance of the equipment and materials you work with to modern scientific and technical standards and current standards of ophthalmological care for glaucoma patients (n=322)	Compliant	132 (40.9±2.7)
		No	58 (18.2±2.1)
		Partially	132 (40.9±2.7)

Source: compiled by the authors of this study

Table 3. Ophthalmologists' assessment of the importance of secondary and tertiary glaucoma prevention measures (n=322)

No.	Question	Distribution of respondents by answers, N (% ± SE)				
		Definitely yes	Probably yes	Probably no	Definitely no	Difficult to answer
1	Is timely and regular examination by an ophthalmologist the key to early detection of glaucoma?	272 (84.5±2.0)	36 (11.2±1.8)	11 (3.4±1.0)	0	3 (0.9±0.5)
2	Is strict adherence to the ophthalmologist's prescriptions the key to stabilizing and preventing progression of glaucoma?	218 (67.7±2.6)	85 (26.4±2.5)	6 (1.9±0.8)	3 (0.9±0.5)	10 (3.1±0.9)
3	Is timely surgical treatment, in case of ineffectiveness of non-surgical methods, the key to stabilization and prevention of glaucoma progression?	178 (55.3±2.8)	121 37.6±2.7)	10 (3.1±0.9)	1 (0.3±0.3)	12 (3.7±1.1)

Source: compiled by the authors of this study

Table 4. The ophthalmologists' assessment of changes in patient behavior regarding adherence to doctors' recommendations (n=322)

No.	Question: Do you observe in your practice since the full-scale invasion an increase in the number of glaucoma patients who	Distribution of respondents by answers, N (%±SE)		
		yes	no	difficult to answer
1	seek ophthalmological care late?	241 (74.8±2.4%)	44 (13.7±1.9%)	37 (11.5±1.8%)
2	seek ophthalmological care irregularly?	269 (83.5±2.1%)	24 (7.5±1.5%)	29 (9.0±1.6%)
3	violate the ophthalmologist's treatment recommendations for glaucoma?	238 (73.9±2.5%)	38 (11.8±1.8%)	46 (14.3±1.9%)
4	do not comply with the ophthalmologist's recommendations regarding surgical treatment of glaucoma?	202 (62.7±2.7%)	48 (14.9±1.9%)	72 (22.4±2.3%)

Source: compiled by the authors of this study

confirmed by the results of the study. Additionally, during the war, there was a qualitative change in the population of Kyiv: part of the native population left the city, while it was replenished by internally displaced persons [11, 12].

The number of ophthalmologists in Kyiv has slightly increased to 340 (by 6%), and the number of ophthalmological hospital beds also rose to 183 (by 14,3%) against the backdrop of a decreasing city population, the exact size of which cannot currently be determined. Therefore, the accessibility of ophthalmological care requires further analysis. It should also be noted that the situation in Kyiv is not fully representative of the entire country, as it is the capital where the largest concentration of the best resources is located [11, 12].

DISCUSSION

The data obtained in this study from the survey of ophthalmologists are consistent with the results of other studies. For example, non-compliance with treatment regimens is observed in 32% of patients [13]. Risk factors for non-adherence to ophthalmologist visit schedules among glaucoma patients include lower levels of education and income, cost-saving on medications, and concerns about differing opinions on diagnosis and treatment among various doctors [14].

Ophthalmologists have also identified an insufficient level of patient knowledge about glaucoma and its treatment methods. The lack of knowledge was associated with a low level of education, a short duration of the disease, advanced age, and the absence of the Internet as a preferred source of information. A study of information needs and preferred providers revealed that a patient education program should cover a wide range of topics with an emphasis on general information through written materials and information tailored to the needs of each glaucoma patient. The ophthalmologist should be the key

person, but others (nurses, optometrists, and members of glaucoma patient associations) also play an important role in patient education [15].

Access to glaucoma treatment is influenced by early intervention in at-risk patients, duration of treatment, and patient adherence to treatment regimens. Socioeconomic factors such as insurance status, education, income, marital status, and access to technology can significantly impact the diagnosis and long-term treatment of patients with glaucoma. People facing these barriers tend to avoid annual eye examinations, leading to a higher incidence of untreated glaucoma. Therefore, the severity and urgency of treatment are important for patients' adherence to ophthalmologist visits and glaucoma therapy. Thus, regular eye care leads to earlier detection and may improve treatment outcomes and reduce disease severity [16].

The paradigm of glaucoma treatment is beginning to shift from a more reactive approach, which relies on topical medications, to a more interventional one involving minimally invasive procedures with lower risk, such as laser trabeculoplasty. However, this transition is accompanied by an increasing need for early, rapid, and accurate diagnosis based on cutting-edge technologies. These include home-based intraocular pressure monitoring, new visual field platforms, photo-based imaging and optical coherence tomography, mitochondrial flavoprotein fluorescence imaging, detection of apoptotic retinal cells, collector channel imaging, and genetic testing enhanced by artificial intelligence [17].

Nevertheless, there are differences within each diagnosis, and optimal treatment requires a personalized approach. As a result of thoughtful application of these recommendations, the benefit to the patient becomes more significant than the ophthalmologic service itself – meaning that a more patient-centered approach should be adopted in glaucoma care [18]. The choice of treatment should aim at long-term intraocular pressure reduction while remaining reasonable and manageable. Currently, approximately 5–10% of glaucoma patients undergo surgical treatment [13].

Glaucoma poses a significant burden on healthcare systems. To reduce glaucoma incidence and prevent blindness – which presents an even greater public health threat among glaucoma patients – it is essential to implement regular screening, including genetic counseling for individuals with high-risk factors. Additionally, efforts should focus on improving patient education, promoting telemedicine for glaucoma care, and increasing the number of scientific studies on both pharmacological and surgical interventions [1].

Timely and effective glaucoma treatment that slows disease progression can reduce the long-term economic burden of this chronic condition on the healthcare system [7]. Direct patient costs associated with ophthalmologist visits, glaucoma surgeries, and medications increase with disease severity. Notably, medication expenses account for the largest share of total direct costs across all stages of the disease (24%-61%). Ophthalmologists bear primary responsibility for understanding and implementing treatment strategies that provide the highest quality of care and quality of life for patients [19].

A holistic approach, including lifestyle modifications and the reduction of chronic stress, should be an integral part of the treatment of patients with glaucoma, as this may help prevent disease progression [20].

The extraordinary situation in Ukraine due to the war has further exacerbated problems related to ophthalmic health and care. Extensive bombing across the country has resulted in numerous serious eye injuries and has exposed millions of civilians and military personnel to clouds of fragmented debris and harmful irritants. Unsanitary conditions in combat zones, shelters, and during population displacement have increased the risk of eye infections. In many regions, access to ophthalmological care has been disrupted due to the destruction of healthcare facilities and the migration of both the population and medical personnel [21].

CONCLUSIONS

The study of ophthalmologists' professional opinions regarding the current state of ophthalmic care provision has made it possible to assess the impact of the full-scale invasion of Russian troops into Ukraine on changes in the epidemiological situation related to glaucoma, the quality of medical care for glaucoma patients, and their adherence to treatment. According to the ophthalmologists, there has been an increase in the proportion of patients with secondary glaucoma and open-angle glaucoma, as well as patients in stage III of the disease. Since the beginning of the full-scale invasion, the number of glaucoma patients who seek ophthalmic care late or irregularly has increased, and many patients are effectively refusing surgical treatment due to a lack of financial resources.

Two-thirds of surveyed physicians consider the quality of ophthalmic care to be high or relatively high, and rate the state of material and technical resources as excellent or good. This paradox can be explained by the incredible dedication of Ukrainian doctors, who, even under extremely difficult conditions, continue to improve technologies and enhance their professional qualifications. The war has had a negative impact on the ability of glaucoma patients to receive quality ophthalmic care. Preserving vision in glaucoma patients depends on timely diagnosis, which largely relies on the technical capabilities of medical facilities. Equally important, however, is patients' adherence to doctors' prescriptions, which, in turn, depends on the accessibility of ophthalmic services and medications for glaucoma treatment. The results obtained may be used to identify opportunities and strategies for improving the quality of ophthalmic care.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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REVIEW ARTICLE

Assessment of the impact of air pollution with heavy metals on the composition of thrombi in peripheral vascular ischemia

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ABSTRACT

Air pollution currently plays a vital role in the increase in the number of deaths in the world. The problem of air pollution is now a very important public health problem. The effects of this pollution on the cardiovascular system have long been known. This impact is known in the field of PM2.5 and PM10 particulate matter. There are fewer reports on this impact in the field of heavy metals. The authors of this study present a brief description of acute ischemia of the lower limb and the possible effect of heavy metals from polluted air on the formation of thrombus in the arteries of the lower limbs and thus on acute ischemia of the lower limbs. The authors present an outline of the possible impact of polluted air elements on the formation of thrombus. This process can be combined with coagulation inside the peripheral arteries. The above problem requires research in the future. The authors plan such studies. This issue requires further research, and the authors plan to conduct such studies in the future

KEY WORDS: air pollution, heavy metals, acute limb ischemia

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INTRODUCTION

Air pollution significantly affects health, causing up to 7 million premature deaths annually worldwide. It also increases the number of hospitalizations and sick leave. Climate change is changing the distribution of primary pollutants, in particular sus-pended dust. It causes secondary pollution [1]. According to data from the World Health Organization (WHO), air pollution is currently the largest environmental threat to health in the European Union (EU). It contributes to around 400,000 premature deaths each year and costs hundreds of billions of euros for health. People living in urban areas are particularly vulnerable [2].

Particulate matter, nitrogen dioxide and ozone are the greatest threats. Particulate matter PM 10 and PM 2.5 is a very important element of the adverse impact on human health due to its specific impact on all living organisms. PM10 and PM 2.5 particles are suspended solid pollutants in the air with the corresponding dimensions of 10μm and 2.5μm. They come mainly from the combustion of solid fossil fuels [3]. Reports in recent years raise the problem of heavy metals such as arsenic, cadmium and nickel contained in PM2.5 and PM10 with a significant impact on health, especially in the field of the cardiovascular system. Heavy metals transported with inhaled air significantly contribute to the increase in the incidence of arterial hypertension, accelerate coronary atherosclerosis, increase the incidence of ischemic heart disease, and contribute to the electrical instability of the heart [3-5].

Arterial thrombosis most often occurs in connection with atherosclerosis. In some cases, arterial thrombosis may have an anatomical or cardiovascular basis, where the source of clots are thrombi, e.g. from the left atrial appendage [6]. There are various causes of thrombotic changes in the arteries. One of the common causes is thrombo-philia, a group of hereditary and acquired diseases causing hypercoagulability [7]. Acquired thrombo-philia associated with thrombosis include antiphospholipid syndrome (APS), heparin-induced thrombocytopenia (HIT), myeloproferative neoplasms (MPN), solid organ tumors, vasculitis and paroxysmal nocturnal hemoglobinuria [8]. Thrombotic changes in peripheral arteries may also result from the presence of aortic wall thrombi [7]. Such a thrombus may originate from an atherosclerotic lesion in the aortic wall or an aortic aneurysm. In some cases, primary aortic mural thrombus occurs. It is then attached to the aortic wall in the absence of atherosclerotic lesions or aortic aneurysms. The incidence of thoracic aortic thrombi in peripheral embolism is estimated at 9% [9]. In most such cases, the course of the disease is asymptomatic. Diagnosis follows an embolic event involving the extremities [10]. We use echocardiography to diagnose these events, but CT angio-gram remains the method of choice [11, 12].

Acute limb ischemia (ALI) is defined as a sudden and critical loss of limb perfusion, with symptoms lasting <2 weeks [13]. The incidence of this condition is ap-proximately 500-1000 per million/year in the European and North American population [14] . Symp-toms develop over hours or days. Patients develop or worsen intermittent claudication. Pain in the lower limbs occurs. Initially, these symptoms occur during physical exertion. Then the pain occurs at rest. Paresthesia and muscle weak-ness appear. In extreme cases, symptoms of paresis may occur [15].

Most cases of acute limb ischemia result from progression of chronic limb ischemia, proximal thrombus embolism, or thrombus formation following trauma [16]. Rarely does a doctor encounter patients with acute limb ischemia without an obvious cause. Current guidelines require diagnostic tests to identify the potential source of cardioembolic dis-eases [16].

AIM

In this short review article, we outline the mechanisms of thrombus formation in a peripheral arterial vessel. We want to investigate the content of heavy metals in the thrombus. This is of great importance in proving the participation of these particles in the intravascular coagulation process.

MATERIALS AND METHODS

Patients with ALI are exposed to various degrees to the accumulation of heavy metals in the body due to the pollution of the environment in which they live. The penetration of heavy metal ions through the plasma membranes into the blood plasma, and then into erythrocytes, enables the formation of chelating compounds in which Fe is displaced from hemoglobin and replaced with heavy metal (Fig. 1). The sequence of these reactions may be a factor in the formation of blood clots, the cause of which is shown to be the release of steroid substances causing the formation of fibrin from atherosclerotic plaques.

We know that iron is essential for many proteins and enzymes in human physiology. In the etiology of atherosclerosis, iron contributes to the formation of many reactive oxygen free radicals. These radicals, in turn, contribute to the modification of lipids, which in turn promotes the progression of atherosclerotic processes [17]. On the other hand, there are reports confirming the relationship between air pollution and thrombosis [18, 19]. Activation of the thrombotic process under the influence of air pollution has been re-ported in humans and in animal experiments [20, 21]. The result of thromboembolic changes in this case may be acute myocardial ischemia and thromboembolism of peripheral vessels [22-24].

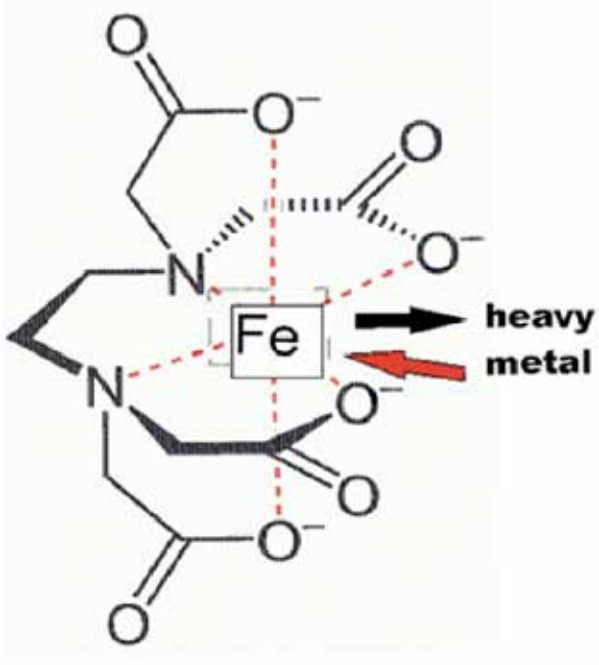

Fig. 1. Mechanism of chelate formation

Source: Own materials – M. A. Jóźwik, M. Jóźwik

Blood clotting is a necessary part of hemostasis where platelets build up to form a temporary vessel closure and fibrinogen is converted into a network of fibrin polymers to stop bleeding, but both of these processes are also associated with increased clotting. Determining the presence of heavy metals, their quantitative and qualitative analysis will answer the question to what extent air pollution with heavy metals affects the formation of a thrombus**.**

Atherosclerosis and thrombosis of the arteries of the lower extremities occur in about 6% of adults worldwide. It is then diagnosed as peripheral arterial disease (PAD). The incidence of this condition is increasing. Symptoms of the disease include: pain in the lower limbs, immobility, deterioration of the quality of life, high risk of injury and falls. As a result of the disease, myocardial infarction, ischemic stroke, amputation of the limb and death may occur [25].

Critical limb ischemia is an indication for rapid revascularization. Failure to perform this revascularization may result in increased ischemia, which is associated with an increase in mortality. In the first year after diagnosis, 25% (45% with amputation) will die, 30% will have a limb amputation. Only 45% of patients survive with both legs. After 5 years, 60% of patients die [26].

If acute limb ischemia occurs, it is necessary to quickly restore vascular flow. The preferred method in these cases is endovascular thrombectomy and thrombus export. The rules and indications for this procedure in Poland are set out in the Guidelines of the Polish Society of Vascular Diseases, the last one from 2018 [27].

REVIEW AND DISCUSSION

Acute limb ischemia usually develops on the basis of one of two processes. Older patients (about 85% of arterial obstructions) develop these disorders as a result of atherosclerotic processes occurring in the lumen of the artery. On the other hand, embolism not resulting from atherosclerosis causes acute ischemia in 10 to 15% of cases [28]. Arterial embolisms causing acute limb ischemia may be caused by cardiac arrhythmias, aneurysms and dissections [29-31].

A review of Polish and foreign literature includes studies on the usefulness of this method for the treatment of acute limb ischemia. In the study by Berger et al. ICAI (Ischemia Critica degli Arti Inferiori) of 2019 among the 1560 patients enrolled: 298 patients died within one year and 187 after amputation after 6 months. In the study, prior revascularization was associated with lower mortality but a higher likelihood of amputation. Among the basic risk factors for the cardiovascular system, diabetes in-creased mortality and reduced the likelihood of recovery [32].

Patients with acute limb ischemia should be treated immediately with anticoagulants. Treatment depends on the classification of ischemia. Currently, it is believed that surgical treatment and thrombolytic treatment with the use of catheters is the most effective. We do not have large randomized trials on this subject. The guidelines suggest the choice of the method of revascularization depending on the anatomical location, etiology and possibilities of surgical therapy. A very important factor is the time it takes to restore blood flow [33].

There are still some answers to the definition of the etiology of limb ischemia. Classic risk factors play a very important role. In addition to these factors, attention has also recently been paid to environmental pollution as a factor that can modify and accelerate atherosclerotic processes.

Currently, the classic risk factors for heart and vascular diseases are well under-stood. However, we are paying more and more attention to less classic factors. They are also believed to play an important role. As reported by Wolska et al. one of these non-classical factors is atmospheric air pollution. Sielski et al. et al. observed the important role of heavy metal air pollution in the case of sudden prehospital cardiac arrest (OHCA) [34].

In connection with the above, attention was paid to the analysis of the composition of the thrombus in terms of heavy metal content. The aim of the study is to test the hypothesis: whether we are currently observing an increased content of heavy metals in the arterial thrombus. Indirectly, such an increased content of metals in the thrombus can affect its destabilization and acute limb ischemia.

The process of intravascular coagulation is complicated. Its main elements are observed on two pathways: plasma and platelet. The effect of classic cardiovascular risk factors on the coagulation process has been observed and known for a long time. These mechanisms involve plasma elements and platelets, as well as leukocytes, mast cells and other morphotic elements of the blood [35-38].

The role of environmental elements in this process is not fully understood. There are many publications in the literature describing the effect of PM 2.5 particles on the coagulation process, both in the process of thrombus formation in veins and arteries. Dales et al. report a short-term increase in admissions in the emergency room of a hospital in Santiago de Chile due to venous thrombosis and pulmonary embolism, which was proportional to the concentration of PM 2.5 particulate matter and gaseous pollutants in the atmosphere [39]. Italian studies also show a relationship between the con-centration of PM2.5 and PM10 in the atmosphere and a higher number of admissions to the emergency room due to thromboembolism [40].

The relationship between arterial thrombosis and the concentration of particulate matter in the atmosphere is mainly known in the case of heart attack. Numerous studies by Peters et al. can be cited here. [41, 42]. Less known in the literature is the relationship between peripheral arterial thrombosis and the concentration of PM2.5 in the atmosphere. This association has been well documented in large population studies such as MISA and APHEA-2 [43, 44].

In this short presentation of the problem, the authors focus on drawing attention to air pollution and the possible impact of this pollution on cardiovascular disease. It is possible that this influence affects thrombi in peripheral vessels and thus peripheral embolism. However, the whole issue requires numerous studies in the future. This can be difficult because the impact of pollution is not only air, but also water and soil.

CONCLUSIONS

In the formation of a thrombus in peripheral vessels, we have many complex mechanisms. One of the possible mechanisms promoting thrombosis in peripheral arterial vessels is the participation of heavy metals. Detection and proof of this phenomenon will be very important due to the problem of air pollution with heavy metals.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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REVIEW ARTICLE

Rehabilitation of patients after acute coronary syndromes

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ABSTRACT

Cardiac rehabilitation is a comprehensive approach aimed at preventing heart disease, supporting treatment and improving the quality of life of patients and their functional abilities. Its goals include slowing the progression of cardiovascular diseases and reducing mortality associated with these diseases. Physiotherapy is a key element of cardiac rehabilitation, complemented by appropriate pharmacological treatment, psychotherapy, nutritional counseling, patient education about the cardiovascular system and lifestyle modifications tailored to individual needs. Cardiac rehabilitation in the prevention of the occurrence, in addition to other forms of treatment, has an additional impact on reducing mortality and morbidity of patients with sequelae, especially patients after myocardial infarction. The importance of cardiac rehabilitation has increased in recent years due to the increasing number of patients successfully treated for acute coronary syndromes. Rehabilitation in this group of patients helps to alleviate the immediate negative effects of myocardial infarction and reduces the risk of re-hospitalization. Combining pharmacotherapy with well-structured physical training and lifestyle changes improves the efficiency of the cardiovascular system, improves the quality of life and reduces the occurrence of adverse cardiovascular events. The importance and benefits of cardiac rehabilitation in patients after a heart attack have been known for many years. Physiotherapists play a significant role in these activities, their work is related to helping patients in taking preventive measures - both from risk groups and after cardiac incidents.The role of the physiotherapist is also to persuade the patient to change their lifestyle.

KEY WORDS: rehabilitation, myocardial infarction, acute myocardial infarction, kinetic therapy, interval training

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INTRODUCTION

Cardiovascular diseases are among the most significant health problems of modern times, leading to both disability and death. Among them, the most common cause of death is coronary artery disease. Due to their common occurrence, course characteristics and consequences, circulatory system diseases are a special area of interest for researchers analyzing the quality of life of patients. Not only the health status of patients, the effectiveness of therapy or the effect of new drugs are assessed, but also whether the treatment improved everyday functioning, reduced suffering and allowed for a return to family, social and professional activity.

A heart attack is an event for most patients that significantly changes their future life, as well as the lives of their loved ones. A direct threat to life often makes patients reflect on the causes and effects of the disease. Patients wonder how to reduce the risk of another incident, how to modify their habits and lifestyle to stay healthy for longer. Answers to these questions can be found during cardiac rehabilitation, which, under the supervision of specialists, allows not only regaining fitness, but also returning to normal life, provided that the principles of a healthy lifestyle are followed.

Cardiac rehabilitation, when done properly, offers benefits that go far beyond improving physical fitness. It promotes lifestyle changes, encouraging physical activity, giving up stimulants, weight loss, and dietary modifications. This can help lower blood pressure, improve lipid profiles and glucose metabolism, and even inhibit or reverse atherosclerotic changes. Rehabilitation also improves the efficiency of the cardiorespiratory system, the efficiency of the musculoskeletal system, and overall physical condition. It also strengthens the cooperation of patients with medical personnel and their commitment to following therapeutic recommendations. In the first, difficult months after a heart attack, rehabilitation is also an important source of psychological support for patients [1].

AIM

The aim of the article is to present the rehabilitation method in Poland for patients after a heart attack. The

work, explaining the basic terminology in the field of rehabilitation, will go through the stages of rehabilitation, its models and recommendations. Then we will focus on the description of the optimal model of comprehensive rehabilitation and secondary prevention in patients after acute coronary syndrome. We will focus on the problems and effectiveness of these exercises.

MATERIALS AND METHODS

This publication is based on research published in PubMed and Google Scholar. A thorough literature search was conducted, covering publications from 1993-2024, to provide a comprehensive and up-to-date review of relevant findings. The search strategy included the use of specific keywords „cardiac rehabilitation", „Recommendations for the implementation of comprehensive cardiological rehabilitation" and „effectiveness of cardiac rehabilitation after myocardial infarction". The initial search yielded approximately 40 articles. After a detailed review, 27 articles related to the subject of the article were selected. The selection process gave priority and focus to articles that provided direct information on rehabilitation and its effectiveness after acute coronary syndromes.

The remaining 13 articles were excluded because they were irrelevant or did not focus on important aspects of patient rehabilitation. The selection of 27 key articles forms the basis of this review, ensuring that the conclusions drawn are both justified and consistent with current scientific knowledge.

REVIEW AND DISCUSSION

THE FIRST STAGE OF CARDIAC REHABILITATION

The first stage of rehabilitation takes place in a hospital setting and lasts until the patient is discharged home. It begins as soon as possible, immediately after the patient's health condition has stabilized, often still in the intensive care unit. At the beginning, it includes passive exercises in bed, then active sitting, using a wheelchair to move to the toilet, and eventually standing and walking near the bed and around the room. Exercises during this period focus on respiratory gymnastics, relaxation and strengthening specific muscle groups [1].

In the following days, depending on the patient's condition, the intensity of activity is gradually increased, up to controlled exercises. The pace of introducing new forms of movement depends on the course of the acute phase of the disease and possible complications. Rehabilitation at this stage can be carried out according to the A1, A2 or B model [1, 2].

Before discharge, each patient after a heart attack, unless there are contraindications, should undergo an exercise test. This is a submaximal test, performed up to 70% of the maximum heart rate or to moderate fatigue (13 points on the Borg scale). The test results are used to qualify patients for the next stages of rehabilitation. It is also worth remembering that, in addition to pharmacotherapy, psychological support, education of the patient and his family play a key role in the recovery process [2].

SECOND STAGE OF CARDIAC REHABILITATION

Cardiac rehabilitation, which is the second module of comprehensive care after a heart attack, includes the early second stage of rehabilitation and should last from 4 to 12 weeks. According to the guidelines of the KOS-zawał program, it should be started within 14 days of the patient's discharge after the completion of full revascularization. Centers performing this rehabilitation receive an additional 10% of remuneration from the National Health Fund. The program can be carried out in various forms: in-patient (in cardiac rehabilitation departments, sanatoriums or cardiology spa hospitals), in day mode or at the patient's home as part of hybrid cardiac telerehabilitation, preceded by training in the facility. In order for the patient to qualify for in-patient rehabilitation, in addition to the main diagnosis (e.g. STEMI, NSTEMI, or subsequent heart attack), a coexisting diagnosis or disability at level 3 according to the modified Rankin scale is also required. These conditions limit the number of patients who can benefit from this form of therapy [2, 3].

Daily rehabilitation is available for people who do not meet these criteria. Unfortunately, the number of centers offering daily cardiac rehabilitation in Poland is too small, especially in smaller towns. This leads to difficulties with transport, which often discourages patients from completing the therapy. An alternative is hybrid cardiac telerehabilitation at home, but its availability is also currently limited, although it may become more common in the future.

The Polish Cardiac Society (PTK) recommends qualifying patients for one of the rehabilitation models (A, B, C or D) based on their physical fitness and the level of risk of cardiovascular events. It is worth emphasizing that patients after a heart attack, unassisted and after coronary angioplasty, have a much harder time getting into inpatient rehabilitation under the KOS-zawał program. However, patients with coronary stents inserted, but outside the KOS program, may qualify for this form of rehabilitation if they are diagnosed with arterial hypertension [1-3].

THE THIRD STAGE OF CARDIAC REHABILITATION

After completing the second stage of rehabilitation, the third stage begins, which should last the patient's entire life. During this period, regular physical activity should not be a major burden for either the patient or their family. The main goals are: improving exercise tolerance, maintaining the achieved effects of therapy, and reducing the risk of disease relapse. Rehabilitation should take place under the constant care of specialists from the cardiac rehabilitation clinic and the cardiology clinic [1, 2] (Table1-2).

OUT-OF-HOSPITAL REHABILITATION MODELS

There are different out-of-hospital rehabilitation models (Table 1). Table 2 present criteria for selecting a kinesiotherapy model depending on the module efficiency and risk level.

Aerobic endurance training is the basic form of physical activity for cardiology patients. It consists of dynamic exercises involving large muscle groups, which are based on oxygen processes, such as walking, cycling or ergometer, climbing stairs, swimming, slow running or team games.

Patients should avoid anaerobic and static exercise, which involves lifting, holding or pushing heavy objects. Activities

Table. 1. Out-of-hospital rehabilitation models

Depending on the qualifications for individual models, kinesiotherapy is performed as follows:
Model A – the basic form of load is continuous endurance training (3-5 times a week) lasting 30-45 minutes; it is supplemented by resistance training (2-3 times a week), which should constitute approximately 10% of the training volume;
Model B – endurance training (continuous or interval) with the frequency as in Model A, but the intensity is maintained at 50-60% of the heart rate reserve appropriate to the patient's age; resistance training is also used here, but with a proportionally lower load;
Model C – the intensity of endurance training (interval form) is 40–50% of the heart rate reserve; additionally, a set of general fitness exercises with elements of resistance and breathing;
Model D – kinesiotherapy is performed in the form of individual exercises (mainly general fitness and breathing) with an intensity below 20% of the heart rate reserve appropriate to the patient's age

Source: [1, 2]

Table. 2. Criteria for selecting a kinesiotherapy model depending on the module efficiency and risk level

Model	Exercise tolerance	Risk of complications	Intensity
A	Good ≥ 7MET ≥ 100W	low	60-80% heart rate reserve or 50-70% max load
B	Good and average ≥ 5MET ≥ 75W	medium	50-60% heart rate reserve or 50% max load
C	low 3-5MET 50-75W	medium	40-50% heart rate reserve or
	good ≥ 6MET >75MET	high	40-50% of maximum load
D	very low < 3MET <50W	medium	less than 20% heart rate reserve or
	medium, low and very low < 6MET ≤ 75W	high	below 10-15% acceleration of resting heart rate

Source: [2]

requiring strong emotions and competition should also be avoided. Depending on exercise tolerance, training can take the form of intervals for people with average tolerance or continuous for people with good tolerance. It is recommended that exercises be performed at least 6 times a week for at least 30 minutes, with 2-3 minutes of rest breaks [3, 4].

Compared to endurance exercises, resistance training has a smaller effect on reducing cardiovascular risk, but in appropriate doses it allows for improvement of muscle strength and endurance, which has a beneficial effect on the overall fitness of the body. In cardiology patients, resistance exercises should be synchronized with breathing. It is recommended to perform 10-15 repetitions in 1-3 series, with a load of 30-50% of maximum muscle strength. Such exercises should be performed 2-3 times a week, but they should only be introduced after at least a week of well-tolerated endurance training. In cardiac rehabilitation, resistance training of large muscle groups should be dynamic in nature to avoid a sudden increase in blood pressure. The third stage of rehabilitation begins 2-4 months after the onset of the disease and lasts for the rest of life. The patient should walk, cycle and perform general fitness exercises 3 times a week for 30-60 minutes, depending on the recommendations for the exercise model to which they have been qualified. The goal is to maintain good physical and mental condition [5, 6] (Table 3).

Interval training, which has gained immense popularity in recent years, is an excellent form of physical activity not only for healthy people, but also for patients undergoing rehabilitation, especially those with circulatory system problems. Studies show that after just one interval training session, positive effects on the autonomic work of the heart can be observed, both in healthy people and patients with heart failure. The effectiveness of such exercises can be adjusted by changing the intensity and length of the exercise and rest phases, which affects the time the heart works at a high oxygen level.

The biggest advantage of interval training is the ability to achieve better results in a shorter time compared to continuous training. In the case of cardiac patients, an

Table. 3. Intensity of selected physical activities

PHYSICAL ACTIVITY	MET
washing, shaving, washing dishes	1.5-2
light housework (cooking, vacuuming)	2-4
heavy housework (washing windows, carrying heavy objects)	3-6
sexual activities	3-5
garden work	4.5-10
snow removal	6-15
Marching on flat terrain 3-4 km/h 5,5 km/h 7.5 km/h	 2.5-3.5 4.5 7
climbing stairs	6-8
swimming	4-8
cycling (flat terrain 8-15 km/h)	3-7
running on flat terrain 8-10km/h	8-11

Source: [5, 6]

additional advantage is the ease of monitoring blood pressure and heart rate, as well as individual adjustment of the intensity of the load. In cardiac rehabilitation, alternating load periods lasting from 0.5 to 4 minutes, interspersed with 1-3 minute breaks, are used as part of a training that usually lasts 15- 30 minutes.

Recommended forms of exercise include: walking on a treadmill (with simultaneous alternating effort and rest lasting 60 seconds) or cycling on a cycloergometer (30 seconds of effort at an intensity of 50% of maximum physical capacity and a 60-second break, during which the patient rides with a load of 10 W). Cardiac rehabilitation brings numerous benefits, including improved physical condition, the efficiency of the musculoskeletal system and the efficiency of the circulatory and respiratory system. Additionally, regular physical exercise contributes to reducing the risk of ischemic heart disease and atherosclerosis, improving body weight, lowering blood pressure and favorably changing the lipid profile and carbohydrate metabolism, which leads to reduced insulin resistance. An important aspect is also the patient's motivation to continue treatment and change their lifestyle. These effects are referred to as the pleiotropic effect of physical training, which, supported by patient education, results in a reduced risk of acute cardiac events, a shorter treatment time, and a delay in the development of cardiovascular diseases. As a result, patients experience fewer hospitalizations, and their quality of life and life expectancy are improved [6, 7]. The optimal model of comprehensive rehabilitation and secondary prevention in patients after acute coronary syndrome is presented in figure 1

CARDIOLOGICAL PROBLEMS AND PATIENT REHABILITATION

In patients with recent acute coronary syndrome and primary coronary angioplasty, coronary angioplasty in patients with acute coronary syndrome with ST elevation and without ST elevation with moderate to high risk is the preferred therapeutic option [7]. However, cardiac rehabilitation combined with risk factor assessment is a key element in the patient's recovery and daily activity. After a procedure that has been uneventful, physical activity (walking around the ward) can be started the next day. In the case of a complicated coronary angiography or angioplasty procedure, it is necessary to wait until the patient's condition stabilizes. After the patient is discharged from the hospital, the cardiac rehabilitation regimen should be continued according to the possibilities of the given medical center. For patients with severe left ventricular dysfunction, an approximately 4-week in-hospital rehabilitation cycle may be considered. Patients with stable coronary artery disease and after elective coronary angioplasty should be made aware of the importance of properly conducted cardiac rehabilitation.

Properly planned exercises should be conducted while still in the hospital and then continued as part of outpatient care. Cooperation between the interventional cardiology physician and the clinicians treating patients in the department is important. The common goal is the well-being of the patient, which is why from the first contact with the patient, they should be encouraged to change their lifestyle and participate in cardiac rehabilitation.

Patients after coronary artery bypass grafting or heart valve surgery, in the case of patients undergoing cardiac surgery, it is worth focusing on a cardiac rehabilitation program before the procedure. This allows the patient's condition to be optimized so that the procedure is carried out with a limited number of complications. As with other patients, cardiac rehabilitation should be planned based on an individual assessment [8].

EFFECTIVENESS OF REHABILITATION

A common consequence of a heart attack is reduced myocardial efficiency and reduced exercise tolerance

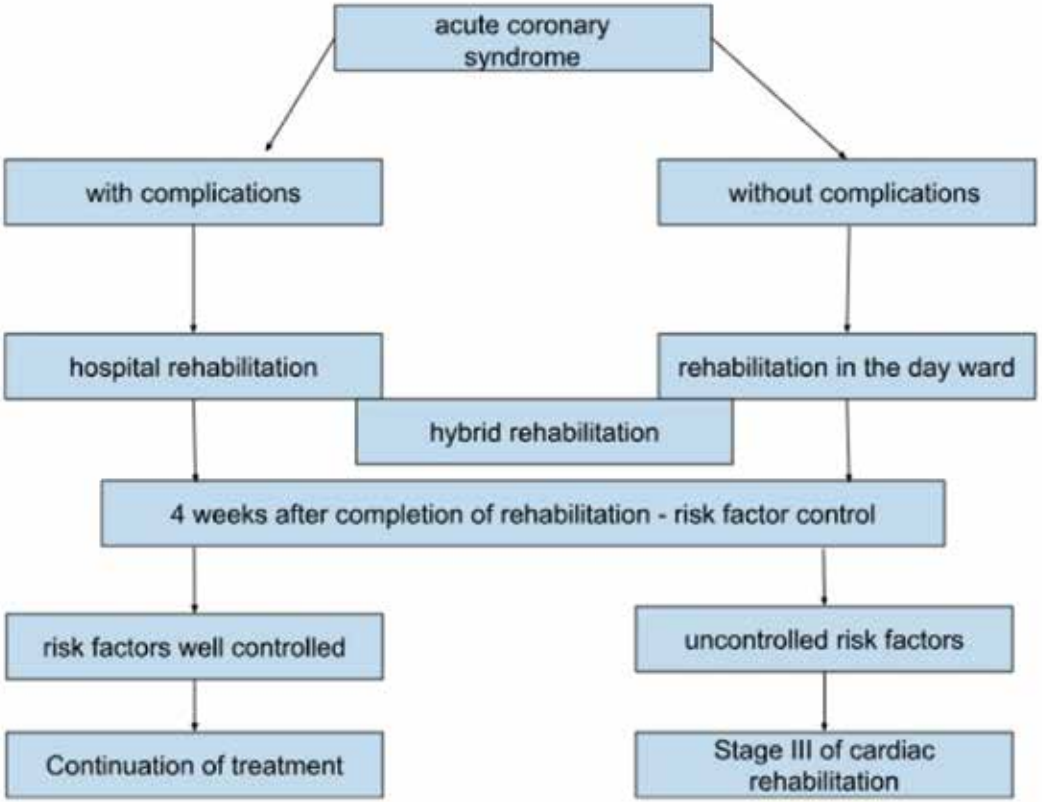

Fig. 1. Optimal model of comprehensive rehabilitation and secondary prevention in patients after acute coronary syndrome
Source: [5-7]

leading to a limitation of daily activity. The desired effect of cardiac rehabilitation is to achieve improved efficiency in order to regain asymptomatic functionality, as well as a favorable prognosis [9, 10].

The results of the study conducted by the authors indicate that outpatient rehabilitation had a beneficial effect on improving the physical efficiency of patients in both age groups and additionally on a significant improvement in the EF level in the group of older patients. In the group of men up to 65 years of age, the MET value increased by 2.71 units, i.e. by 39.74%, and in the group of men over 65 years of age by 2.38 units, i.e. by 48.77%.

Regular participation in comprehensive cardiac rehabilitation programs significantly reduces mortality among patients with coronary artery disease, primarily through improvement in exercise capacity and modification of risk factors [11]. After examining 188 people with ischemic heart disease aged 31-82, including 54 people who had a myocardial infarction, they found that after an 8-week training at the lactate threshold, the efficiency of all patients significantly improved, but the lowest efficiency was characteristic of patients from the oldest age group, and the highest in the youngest.

These results were also confirmed in the study by Fontes-Oliveira et al., where the efficiency parameters of men after a myocardial infarction improved after rehabilitation [12]. An increase in physical efficiency after the use of various rehabilitation programs in patients after a myocardial infarction was obtained by Adam, Wu and Zhang et al. [13-15].

In other reports, an 8-week rehabilitation also improved efficiency after the completion of the exercise program [16, 17]. The occurrence of a negative correlation after rehabilitation suggests a significant improvement in performance among younger men from the group of over 65 years of age, which additionally confirms the improvement in performance in this group of patients. A negative correlation between the performance of older men and age occurred after physical training, confirming the biological negative relationship between age and performance.

The subject of changes in the level of physical performance in men with ischemic heart disease depending on the initial EF was addressed by, among others, Rybicki and Malina [18]. They examined 62 men after myocardial infarction or coronary artery bypass grafting, assessing physical performance before and after rehabilitation. The patients were divided into 2 groups with lower (≤40%) and higher (≥50%) EF. A significant increase in performance was observed after the applied rehabilitation in both groups, but no linear correlation was found between the initial EF and performance and its increase after rehabilitation. In the group of younger men, an upward trend in EF was noted from 58.06% to 59.18%, while in the group of older patients, the increase in EF was significantly greater after rehabilitation – from 49.38% to 52.63%, i.e. over 6%. The lack of significant improvement in younger patients after

training may result from the normal initial EF, while the increase in EF in older men after rehabilitation may result from its lower initial value.

Several reports have shown that a 5% decrease in EF increases the mortality of patients almost twice, while an increase above 5% reduces the risk of death by approximately 10% within a year [11, 18, 19]. Recent studies have confirmed that structured cardiac rehabilitation programs lasting 8-12 weeks can support body weight reduction and improve body composition. For example, the OPTICARE XL CR randomized trial showed significantly greater short-term weight loss in overweight and obese patients compared with standard rehabilitation, while blended and remote lifestyle interventions integrated into CR demonstrated favorable changes in fat mass and body composition [22, 23]. Hushcha et al., in turn, studied overweight and obese patients participating in a 12-week outpatient cardiac rehabilitation program and showed that about one quarter of participants achieved significant weight loss (≥3% of body weight), which was associated with younger age, higher baseline BMI, and healthier dietary habits. These findings confirm that comprehensive cardiac rehabilitation can play an important role in weight management, especially in patients with metabolic risk factors [24]

Cardiac rehabilitation should bring patients benefits in the form of improved quality of life, increased functional capacity, mental stabilization, and return to social or professional life. To this end, efforts should be made to increase the threshold of perceived fatigue during physical activity. Studies have not found any significant changes in the perception of effort load after cardio training despite the increased load in the exercise test.

CONCLUSIONS

Although professional recommendations for the prevention of circulatory system diseases have existed for many years, their use in everyday practice is still insufficient. In European countries, only one third of patients with diagnosed coronary artery disease undergo any form of cardiac rehabilitation programs [25].

The results of the EUROASPIRE audit on the prevention of circulatory system diseases in the last 12 years indicate unfavorable changes in the lifestyle of European society: an increased percentage of smokers in the group of people under 50 years of age, an increased percentage of obese people and people with diagnosed diabetes. Blood pressure control has not changed during this time, while lipid control has improved [26].

The problem with implementing cardiac rehabilitation programs is their short-term effect. After completing rehabilitation, the patient does not have support from the health service and returns to unfavorable elements of lifestyle. In summary, there is evidence available for the effectiveness of cardiac rehabilitation in the prevention of circulatory system diseases. It is important to encourage patients to cooperate with well-known centers that deal with rehabilitation in a broad sense, taking into account psychosocial, dietary and pharmacological aspects.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

Occupational burnout among interventional radiologists – prevalence, risk factors and interventions

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ABSTRACT

Interventional radiology (IR) is one of the fastest growing medical subspecialties, offering minimally invasive procedures associated with reduced postoperative complications and faster recovery. However, the rapid expansion of this field has increased physicians' workload, contributing to a rising risk of occupational burnout (OB). Burnout, recognized as a distinct disorder in ICD-11, adversely affects physicians' mental and physical health, professional performance, and patient safety. This narrative review aimed to summarize current findings on the prevalence, risk factors, and potential interventions regarding OB among interventional radiologists worldwide. A systematic search of PubMed, Embase, and Web of Science, complemented by an additional manual search, identified seven eligible original research articles. According to available data, the prevalence of OB among IRs ranges from 44% to 71.9%, depending on applied methodological criteria. Key risk factors include excessive workload, administrative burdens, disturbed work-life balance, younger age, limited IR experience, dysfunctional coping strategies, and lack of time for academic activities. Proposed interventions can be divided into systemic changes, such as workload reduction and improved departmental organization, and individual strategies aimed at resilience-building, including mindfulness training, physical exercise, and structured group discussions. Evidence suggests that combined approaches yield the most sustainable results. Despite methodological limitations, the reviewed studies highlight the alarming scale of burnout in IR. Further standardized research is urgently needed to inform effective prevention strategies. Addressing burnout is crucial not only to protect physician well-being but also to improve patient outcomes and sustain healthcare system efficiency.

KEY WORDS: radiology, epidemiology, occupational stress

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INTRODUCTION

Interventional radiology is currently one of the most rapidly advancing subspecialties in medicine [1, 2]. Minimally invasive procedures performed under image guidance are often associated with a lower risk of postoperative complications and faster patient recovery representing potential alternatives for conventional open surgery approaches [3-5]. A comprehensive meta-analysis published in *The Lancet* in 2016 revealed that neurothrombectomy in patients with large vessel occlusion significantly reduced disability, improved long-term outcome, creating new first–line treatment in acute ischemic stroke patients [6, 7]. Since this breakthrough, endovascular techniques have established their position as an integral part of every high profiled hospital. The rapid advancement of this field causes growing demand for physicians skilled in minimally invasive techniques [8]. As a result of increased workload the risk of occupational burnout for practicing physicians rises [9-16].

Occupational burnout has been attracting increasing attention within the medical community. Even though some researchers emphasize that the distinct features between OB and other diagnoses, e.g. depression, need more clarification, OB was acknowledged as a separate disorder in ICD-11 [17, 18]. According to available data, physicians are associated with a higher risk of burnout compared to the general population and it is more common among physicians working on the front lines of patient care [19]. Burnout adversely affects not only the well-being of physicians but also the quality of care they provide. Among physicians, it is associated with an increased risk of court cases, early retirement, impaired performance, substance abuse, sleep deprivation, depression, suicidal thoughts and attempts [16, 19–24]. Burnout was associated not only with a higher risk of mental health problems, but also with development of somatic disorders, such as Type 2 Diabetes, hypercholesterolemia, gastrointestinal issues, coronary heart disease, etc. [16]. From the patient's perspective, physician burnout increases the risk of medical errors and contributes to lower satisfaction with care. Consequently, there is growing emphasis on early detection and the implementation of interventions aimed at mitigating the risk of burnout.

AIM

In this review, we aim to summarize current findings about OB among interventional radiologists worldwide. Specifically, we plan to: (1) determine the prevalence of OB and assess how widespread the problem is within IR consultants, (2) identify the major risk factors contributing to its development, and (3) evaluate proposed interventions that may help physicians mitigate OB impact. Is there anything that can be done to mitigate OB, and reduce everyday stress? Given burnout's negative consequences for both healthcare providers and their patients, this review seeks to highlight potential solutions that could enhance physicians' well-being, improve their professional performance, and ultimately strengthen the healthcare system as a whole.

MATERIALS AND METHODS

PubMed, Embase and WoS were searched in order to find original research articles. Search time-frame involved articles published till the end of 2024 year. Only articles written in English were included. Used search phrases were "interventional radiology AND burnout"; "interventional radiologist AND burnout"; "interventional radiographers AND burnout".

Original research papers, articles focusing on IR consultants, and articles measuring OB (validated questionnaires, custom surveys) were primarily selected (included) for this review. Review articles, studies that did not focus specifically on interventional radiologists or did not report data for them as a separate subgroup were excluded from this review, e.g. papers focusing solely on diagnostic radiologists or papers about radiologists in general without distinguishing them on subspecialties were excluded.

A total of 79 records were identified through database searches. After removal of duplicates and application of the predefined inclusion and exclusion criteria, 6 articles were deemed eligible for this review [9-11, 13-15]. In addition, one relevant article was identified through independent searching on the ResearchGate platform [12].

The extracted data included participants' demographics (age or age range, years of professional experience, and level of training), study characteristics (methodological details, sample size, study population), reported outcomes of questionnaires and surveys (e.g. MBI scores and subscores), and identified risk factors. Data were described in text and presented in the form of tables.

This study was designed as a narrative review, structured further into results (prevalence of OB and identified risk factors), discussion (proposed interventions), and conclusions. Selected articles are shown in Table 1.

REVIEW

TESTS AND QUESTIONNAIRES USED IN THE REVIEWED STUDIES

OB can be measured using several validated standardized tests with Maslach Burnout Inventory being the most widely used [25]. The original version of this test was formed in 1981 by Christina Maslach and Susan E. Jackson [26, 27]. Since then special versions of the test emerged, including the Maslach Burnout Inventory-human services survey (MBI-HSS) composed especially for human services and healthcare workers [17]. MBI consists of 22 items that measure 3 components of burnout, that is depersonalization (DP), emotional exhaustion (EE) and personal accomplishment (PA). The higher scores of DP and EE, and the lower score of PA the greater risk of burnout.

Some researchers employed GAD-7 scale and Brief-COPE questionnaire. GAD-7 is used to measure the severity of generalized anxiety disorder (GAD) symptoms and Brief-COPE is used to assess coping strategies [28, 29].

Finally, other authors used custom questionnaires to assess wellbeing of surveyed interventional radiologists.

Table 1. Original research articles describing OB among IRs

Nr	First author	Sample size	Consistent of study group	Country	Used questionnaires/ surveys
1.	Murphy M et al. [14]	40	Interventional radiographers	Ireland	Custom questionnaire (no standardized tool)
2.	Woerner A et al. [13]	422	Interventional radiologists and trainees	Multinational (15 countries – most authors from the USA)	GAD-7, Brief-COPE
3.	Justaniah AI et al. [12]	80	Interventional radiologists	Saudi Arabia	Maslach Burnout Inventory (MBI)
4.	Bundy JJ et al. [11]	339	Interventional radiologists	United States	Maslach Burnout Inventory – HSS version
5.	Haridass S et al. [10]	137	Interventional radiologists	International (mostly Indian origin regardless country of practice)	Custom survey (Work–Family–Health relations)
6.	Bastian MB et al. [9]	172	General radiologists (incl. 26.2% of IRs)	Germany	German-adapted Maslach Burnout Inventory
7.	Al Rekabi A et al. [15]	223	Interventional radiologists	United Kingdom	Maslach Burnout Inventory – HSS version

Source: Own study

Table 2. Prevalence of OB among IRs based on MBI

First Author	Sample size	Prevalence of OB	Burnout Criteria (Based on MBI)
Bastian MB et al.	172 (45 IRs)	84.4%	mean score ≥10 (German-adapted MBI)
Bundy JJ et al.	339	71.9%	EE ≥27 or DP ≥10 (MBI–HSS)
Justaniah AI et al.	80	approx. 50%	Full MBI (22 items); no cutoff thresholds specified
Al Rekabi A et al.	223	44%	EE ≥27 or DP ≥10 (MBI–HSS)

Source: Own study

PREVALENCE OF BURNOUT AMONG IRS

According to the available data, between 44-84.4% of surveyed radiologists met the criteria for OB based on the Maslach Burnout Inventory (MBI) [9, 11, 12, 15]. Results are shown in Table 2.

It should be emphasized, however, that the OB criteria applied by the authors varied. Researchers from Germany considered a mean MBI score of at least 10 points as sufficient to indicate burnout [9]. In contrast, investigators from the USA and the UK classified burnout as present when participants exhibited either severe depersonalization (DP) scores (≥10) or severe emotional exhaustion (EE) scores (≥27) [11, 15].

We are not the first who noticed such methodological inconsistencies [25]. Since there are methodology differences among studies, it makes the obtained results hard to compare directly. Considering that authors from the UK and USA used the same cut-off points and gathered relatively large samples, OB among IRs might be estimated between 44-71.9%.

Woerner A. et al. investigated IRs' workload and mental health during COVID-19 pandemic [13]. According to their findings 41.9% of surveyed IRs had a measurable level of anxiety (GAD-7 score ≥5). Brief-COPE questionnaire results showed that the mostly used coping strategies were acceptance and active coping. Dysfunctional strategies were less common among respondents with exception of self-distraction being the third most common strategy.

Authors from Ireland also focused on physical and mental wellbeing of IRs during pandemic [14]. Before the global outbreak of SARS-CoV-2 only 7.5% of surveyed radiographers described their perceived stress level as high, whereas during pandemic this percent increased to 50%. Similarly, before the pandemic 37.5% of radiographers stated that working in the IR didn't have any impact on their physical, mental and social wellbeing. During the pandemic this proportion decreased to 7.5%. The majority of respondents (95%) were afraid about passing the virus on to relatives or friends and 85% were afraid of getting sick themselves. A similar percentage noticed either improvement (22.5%) or deterioration (20%) in their relationship with work colleagues and the rest (57.5%) didn't notice any change. In contrast, 60% of IRs noticed deterioration in their relationship with personal (outside of work) friends.

Gomez F et al. researched the general influence of the pandemic upon interventional radiology practice with OB not being their primary focus [30]. Nonetheless, 54% of surveyed IRs described their stress level during pandemic as either "very much" or "quite a bit". Moreover, 43% of respondents declared extreme concern about the health of their families.

According to Haridass S et al., a significant level of stress was reported by 67.1% of respondents and occupation related health problems were observed in 25% of participants with backache being the most relevant [10].

DESCRIBED RISK FACTORS ASSOCIATED WITH BURNOUT AND INCREASED ANXIETY LEVELS

Factors confirmed to be statistically significant were increased workload, administrative and organizational challenges, disturbed work–life balance, younger physician's age and lack of IR experience, implementation of dysfunctional coping strategies and feeling unavailable for research or teaching. Reports concerning gender influence upon OB seem contradicting.

Most often mentioned situations associated with increased workload and burnout were working over 80-hrs a week, increased call coverage and out of hour IR cover, increased time pressure, prolonged working hours and shortage of IR clinicians [10, 11, 13, 15].

Regarding administrative and organizational challenges the most often mentioned factors were lack of adequate departmental adjustments or lack of adjustments in a timely manner, suboptimal working conditions and tough times with administration [9, 10, 13].

Disturbed work–life balance was also a contributor to risk of OB development. Multivariate analysis performed by Haridass et al. revealed that being unable to spend time on activities that one enjoys was associated with risk of burnout [10]. Sleep quality also played an important role with sleep duration <5 hours having significant association with lower PA scores [9, 12].

Regarding the impact of the age and experience upon burnout, the physicians between 30-40 years old achieved higher DP scores than those older than 51 years old. Physicians with short IR practice (<4 years) had their DP scores significantly higher as well [12]. Those findings align with results from the UK, which showed that DP scores decreased from the youngest to oldest participants and the lowest EE scores were achieved by the participants older than 60 [15]. On the other hand PA scores presented the opposite trend, with oldest respondents showing the highest scores.

Implementation of dysfunctional coping strategies (most of all disengagement and self-blame) significantly increased risk of reporting anxiety [13].

IRs, who stated that they don't have sufficient time and energy to engage in teaching, training or research achieved higher DP scores and had significantly increased risk for OB [15].

Opposing conclusions arise from works of researchers from the USA and UK regarding gender influence on OB. A study from the USA showed that being female was significantly associated with an increased risk of OB and study of Woerner et al. reported that female participants were more likely to experience anxiety [11, 13]. These findings are consistent with some previous research [31, 32]. On the other hand, a study from the UK showed that male respondents achieved significantly higher DP scores in the survey than females [15].

DISCUSSION

In this review we summarized the latest findings concerning OB among IRs. Taking into account that OB doesn't solely affect suffering physicians, but also their surroundings, the proportion of IRs affected by burnout is concerningly high. Since problems and risk factors leading to it are defined, proper solutions might be suggested.

Proposed interventions can be divided into two main categories - those associated with systemic changes and those associated with developing individual's resilience [33]. Decreasing working hours has improved EE and DP scores among studied residents and interns [34]. Though, systemic changes, such as reduction of workload or administrative burden are not always possible. While night and weekend duties are immanent part of IRs' work, some authors propose reduction of weekly working hours to compensate time spent on night and weekend duties [10]. Workload could also be reduced by hiring more IR consultants. Unfortunately, in some countries IR is not broadly recognized, even among medical students and some physicians [35–39]. Therefore fewer of them decide to choose IR training. Moreover, some countries do not offer separate training for residents interested in radiologic interventions, additionally decreasing inflow of IR consultants.

Increasing an individual's internal resources and resilience is a complementary strategy. Implementation of approach-coping strategies instead of dysfunctional ones and spending quality time on things that one enjoys are crucial to maintain work–life balance. Authors mention also solutions such as mindfulness training, physical exercises and small group discussions [11]. Based on original research, physical exercise has been proven to significantly reduce risk of OB [31]. Group discussions combined with mindfulness training significantly lowered high DP scores with effects that sustained even after 12 months since the end of intervention period [40]. Even though building internal resources is important, it has to be emphasized that it is not a substitute for systemic changes and both strategies have to be developed simultaneously.

An interesting perspective was shown by Japanese researchers that evaluated general job satisfaction among their IRs. They revealed that reported job satisfaction was negatively correlated with absence of "IkuBoss" [41]. IkuBoss is a special kind of supervising manager that takes care of the job environment to support work–life balance among employees, e.g. by monitoring workload, encouraging particular employees to use their vacation etc. Such kind of management, if done properly, might be a bridge between systemic and individual approaches to mitigate OB.

Our study has some limitations. First of all, Interventional Radiology is a relatively young medical specialty, so there's a little research focused on performing physicians and their workplace. More original studies using standardized methodologies and based on evaluated tests should be performed. Secondly, cited original research publications are based on surveys, which introduces the potential for sampling bias, e.g. physicians with advanced burnout neither found energy nor motivation to answer sent questionnaires. Since then, it is possible that the percentage of physicians affected by OB might be even higher than shown.

CONCLUSIONS

Estimated between 44%-71.9% prevalence of OB among IRs is concerningly high. Factors confirmed to increase risk of OB are increased workload, administrative and organizational challenges, disturbed work–life balance, younger physician's age and lack of IR experience, implementation of dysfunctional coping strategies and feeling unavailable for research or teaching. Based on EBM, interventions found to be effective against OB, are small group discussions combined with mindfulness training, physical exercises and decreasing workload. Building an individual's resilience is a complementary strategy to systematic changes and both strategies should be developed parallelly. Since there is a little research addressing this matter we need more original studies focused on wellbeing and prevention of OB among IRs.

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COFLICT OF INTEREST
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CASE STUDY

Clinical and radiological manifestations of listeriosis of the nervous system – three cases report

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ABSTRACT

Listeria monocytogenes, a Gram-positive bacterium, can cause infections of the nervous system, such as meningitis or encephalitis, with a particular tendency to affect the posterior part of the brain. It can rarely lead to brain abscesses as well. This microorganism is most commonly pathogenic for fetuses, newborns, older individuals, alcoholics, and immunocompromised individuals. The aim of the study was to present three cases of central nervous system listeriosis. Two of presented cases were rhombencephalitis in males without identified predisposing factors. The third case involved a female patient with listerial meningitis during treatment for lymphoma with monoclonal antibodies and vincristine. Neuroimaging of the central nervous system, lumbar punctures, and additional tests were performed in all patients. Antibiotic therapy was administered to all patients according to the literature recommendations. The patient with meningitis was transferred for further treatment to the infectious diseases department. Both patients with rhombencephalitis required treatment in the Intensive Care Unit. One of them unfortunately passed away, while the other required surgical decompression of the posterior cranial fossa and ventricular cerebrospinal fluid drainage, and survived. Listeriosis of the central nervous system is a serious disease, and the number of diagnoses has been increasing in recent years, with cases of rhombencephalitis associated with significant mortality rates. Timely diagnosis is crucial for successful treatment, which is facilitated by the availability of molecular tests in modern times. Diagnosis and treatment require a multidisciplinary approach involving neurologists, radiologists, intensivists, and sometimes even neurosurgeons.

KEY WORDS: neurolisteriosis, molecular diagnosis, surgical decompression

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INTRODUCTION

Listeriosis is an infectious disease of humans and animals that can occur in an acute or latent manner. It is classified as a typical zoonotic disease, and due to its mode of spread, it is defined as a sapronosis [1]. It is caused by the bacterium *Listeria monocytogenes* (*L. monocytogenes*), which is a typical intracellular pathogen. It is a small, facultatively anaerobic, gram-positive rod, capable of surviving in a wide range of temperatures, and is inactivated only at temperatures above 75°C. It can survive for many years in unfavorable conditions, and under favorable conditions, it becomes a dangerous pathogen attacking, among others, the central nervous system (CNS) [2]. One of the reasons for the high pathogenicity of *L. monocytogenes* is the presence of specific virulence factors. Among them are internalins, membrane proteins that facilitate the entry of bacteria into macrophages and endothelial cells, listeriolysins, responsible for breaking the membranes of phagolysosomes, phospholipases enabling the infection of subsequent cells without the risk of destruction by immune cells, and the surface protein ActA [3, 4]. The vast majority of listeriosis infections result from the consumption of contaminated food. It can also penetrate through damaged skin, mucous membranes, or the placenta. Epidemics and sporadic cases of *Listeria* infections worldwide have often been the result of consuming unpasteurized milk, insufficiently washed fruits and vegetables, meat products, raw meat, fish, seafood, fast-food products, and ready meals that have not undergone proper heat treatment [5, 6]. The incubation period for listeriosis lasts from 3 to 70 days, on average 31 days [1]. *L. monocytogenes* penetrates the body through the intestinal epithelium, and then can spread through the blood and reach the CNS. It is also believed that retrograde transport through nerves, such as the trigeminal nerve or other cranial nerves, is possible [7, 8]. Listeriosis is considered a rare disease, with an estimated incidence ranging from 0.1 to 10 cases per million people. In the USA, about 1600 cases are reported annually [7], and in Poland, according to the KOROUN register for the years 2011-2020, about several dozen cases per year [9]. Mortality associated with listeriosis is estimated at 16%, and in the case of CNS infections, it increases to 30% [7]. In recent years, there has been an increase in the number of *L. monocytogenes* infections, which is probably due to the aging of societies and changes in dietary habits [5, 6, 10]. Listeriosis can

take two types of infections: non-invasive, which manifest as gastroenteritis, and invasive, which occur mainly in people with a weakened immune system, in the elderly, pregnant women, and newborns [3]. The most common invasive forms of listeriosis in humans are bacteremia, accounting for about 50% of all cases, neurolisteriosis, accounting for about 20-25%, and perinatal infections, which occur in about 10-15% of cases [10]. Endocarditis, arthritis, bone infection, peritonitis, pneumonia, and liver abscesses and inflammations are less commonly observed [1, 2]. Neurolisteriosis most often manifests as meningitis, less often as rhomboencephalitis, and very rarely as a brain abscess, occurring in about 1-10% of cases [10-12]. Meningitis in the course of neurolisteriosis is characterized by a gradual increase in consciousness disorders, the appearance of epileptic seizures, motor disorders, such as muscle tremors and ataxia. The classic triad of symptoms (fever, neck stiffness, and consciousness disorders) occurs only in some patients. In some cases, the cerebrospinal fluid examination may not show changes, and the detectability of bacteria in direct preparations and cultures is also limited. Blood cultures are more valuable for diagnostics. Neuroimaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), often show nonspecific changes that can support the diagnostic process [7]. The second form of neurolisteriosis, rhomboencephalitis, is characterized by gradual dysfunction of the brainstem. The clinical symptoms of this form appear in two phases. In the first phase, lasting from 4 to 10 days, nonspecific symptoms such as headaches, dizziness, nausea, and vomiting occur. In the next phase, there is asymmetric damage to cranial nerves V, VII, IX, X, and XII, leading to the appearance of cerebellar symptoms, hemiparesis, hemisensory disturbances, and meningeal signs [13-15]. Magnetic resonance imaging (MRI) often shows characteristic changes in this form of neurolisteriosis [10]. MRI of the head often shows a characteristic image of signal disturbance, in the form of small, ring-enhancing changes in the brainstem, with punctate-central diffusion restriction, as in forming microabscesses, and patchy foci of elevated T2/FLAIR signals with a high dynamic of changes over time, in the brainstem and partially in the cerebellar hemispheres. Interestingly, this form of listeriosis most often affects healthy adults [7]. The rarest form of neurolisteriosis is a brain abscess, which is associated with high mortality. The brain abscess often localizes in atypical places, such as subcortical areas, thalamus, pons, or medulla oblongata. The course of this form of the disease is subacute and is often accompanied by meningitis. Brain abscess most often affects patients with immune disorders [16, 17]. The diagnosis of listeriosis can be difficult due to its rarity and often insidious character of symptoms. Delay in proper treatment can negatively affect the patient's prognosis.

AIM

The purpose of the study was to present three cases of neurolisteriosis that were diagnosed in our center recently.

CASE REPORTS

CASE 1

A 51-year-old male, a citizen of Belarus, working in Poland in a construction company, was admitted to the Department of Neurology due to dizziness and balance disorders, which occurred a few days after returning from a two-month vacation in his home country. Upon admission, the patient was conscious, had proper verbal contact, but complained of swallowing problems and difficulty maintaining balance while walking. In the neurological examination upon admission, the following deviations from the norm were found: nystagmus more pronounced when looking to the right, shallower left nasolabial fold, left-sided paresis (4 on the Lovett scale), ataxia in the left limbs, bilateral Babinski sign, wide-based gait, and instability during the Romberg test. Laboratory tests in blood serum revealed a slightly lowered level of sodium and potassium. In the magnetic resonance imaging (MRI) of the head, irregular areas of hyperintensity in the T2 sequence were observed in the cerebellar peduncles on the left side, the left cerebellar hemisphere, and the medulla oblongata. These changes did not show signs of ischemia in the diffusion study and had a slight mass effect. A lumbar puncture was performed and clear and colorless cerebrospinal fluid was obtained at normal pressure. The analysis of the cerebrospinal fluid showed the presence of 507 cells and an elevated protein concentration (66 mg/dl). Samples were sent for testing for Lyme disease, syphilis, PCR panel for 12 species of meningitis pathogens, autoimmune encephalitis, and cytology. At this stage, a neuroinfection of an unknown factor was diagnosed, and empirical antibiotic therapy (cefotaxim at a dose of 2 g/day) and antiviral treatment (acyclovir at a dose of 3x750 mg) were initiated in the patient. On the second day of hospitalization, the patient's condition worsened – a fever of up to 38.5°C, upper respiratory tract problems, and changes in blood pressure occurred. Speech became dysarthric, double vision occurred when looking straight and to the right, swallowing difficulties increased, and the Babinski sign on the left side was more pronounced. Deep reflexes in the upper and lower limbs were weakened, while the palatopharyngeal reflexes were preserved. The MRI of the head was repeated with an extension to MR spectroscopy (Fig. 1). Unfortunately, the examination was interrupted due to the patient's anxiety. Based on the initial radiological assessment, it was concluded that the changes in the brainstem had expanded, but no metabolite activity readout was obtained. The patient had a fever reaching 39°C, and additional laboratory tests showed slightly elevated CRP and ESR values of 70 mm/h. Chest X-ray revealed band-like consolidations, and abdominal ultrasound examination showed no abnormalities. Due to the deterioration of the patient's condition, an autoimmune cause of brainstem inflammation was also considered, and steroid therapy and immunoglobulin therapy were initiated. Unfortunately, the patient's condition continued to deteriorate and on the fourth day of hospitalization,

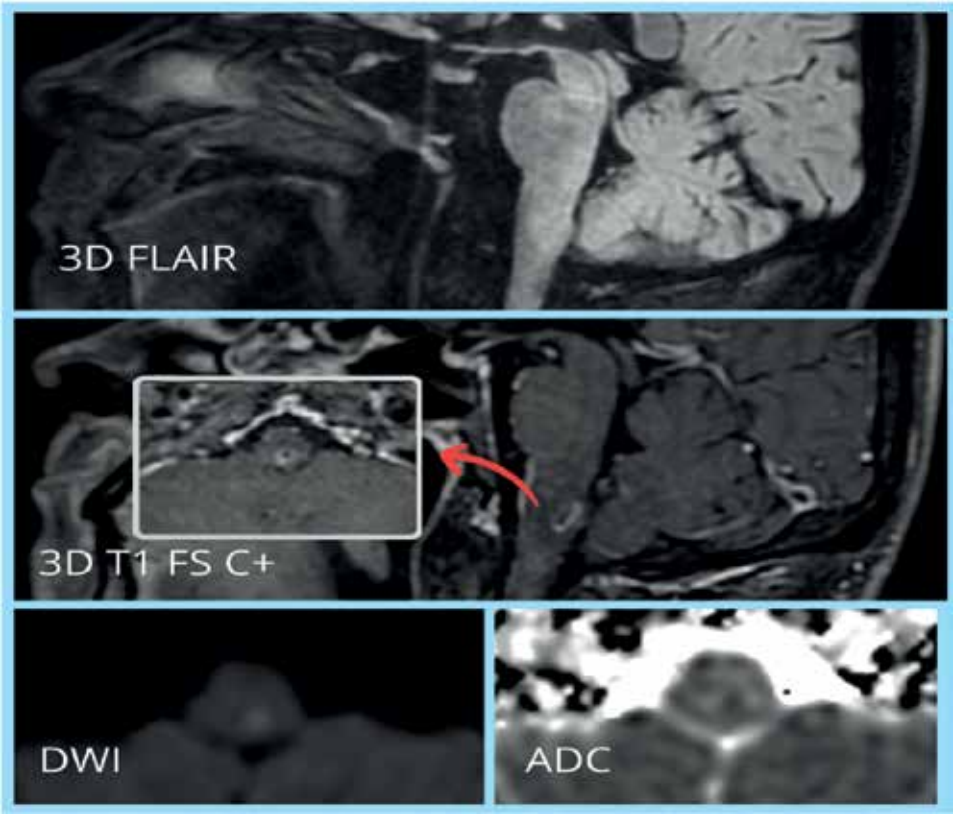

Fig. 1. MRI of the head of the Case No.1

Source: Own materials

he required intubation and connection to a respirator. The patient was transported to the Intensive Care Unit, where he died after three days. The final results of the cerebrospinal fluid examination taken during the stay in the Intensive Care Unit, which were available about 10 days after the sample was taken, showed the presence of *Listeria monocytogenes* in molecular tests.

CASE 2

A 66-year-old urologist was admitted to the Department of Neurology after an outpatient magnetic resonance imaging (MRI) examination due to increasing weakness, gait disturbances, speech, and double vision, occurring for a week. A few days before the onset of neurological symptoms, the patient and his family had a gastrointestinal infection. The MRI of the head described a contrast-enhancing focal change in the medulla oblongata and the pons, along with an area of edema of unclear character, requiring broad differentiation (Fig. 2). Upon admission to the Department, the patient was in good general condition. In the neurological examination, deviations from the norm were found: dysarthria, damage to both abducent nerves, bilateral coarse nystagmus with a predominance to the right, wide-based gait, instability in the Romberg test. Hiccups were observed. In laboratory tests, leukocytosis (11.5k/µl), elevated CRP (14.5 mg/l) and ESR (40 mm/h) values, and slightly elevated potassium concentration were noted. The collected cerebrospinal fluid was clear, flowed out under normal pressure, and did not show deviations in the basic examination. Tests for HIV infection, syphilis, Lyme disease, antibodies against gangliosides, antibodies for autoimmune encephalitis, onconeural antibodies, tumor markers, ANA1, and ANA2 were negative. The results of these tests were received after a few days. On the third day of hospitalization, the patient's condition worsened, shortness of breath occurred, the patient was restless, and the family reported a change in behavior. Performed computed tomography of the chest and abdomen, angiography of the intra- and extracranial arteries, and ultrasound of the abdomen did not reveal abnormalities. Inflammatory parameters were normal. In the subsequent MRI of the cervical spine, progression of changes in the brainstem was observed, including the appearance of a new 8 mm diameter lesion in the pons, ring-enhancing and causing significant edema in the posterior-right part of the pons. Additionally, infiltrative changes were observed bilaterally towards the cerebellar peduncles, predominantly on the left side and involving the dentate nucleus. Based on this subsequent MRI, a suspicion of purulent rhombencephalitis was raised. From the moment of patient admission, empirical antibiotic therapy (ceftraxon 2 g), steroid therapy, and antiviral therapy (acyclovir) were applied. Then, due to the lack of response to treatment the range of antibiotic therapy was expanded to include vancomycin and penicillin (5 million units). Due to the further deterioration of the patient's general condition, the occurrence of fever and confusion, a decision was made to transfer the patient to the Intensive Care Unit. The result of the examination for meningitis, including the presence of *Listeria monocytogenes*, was negative, which was

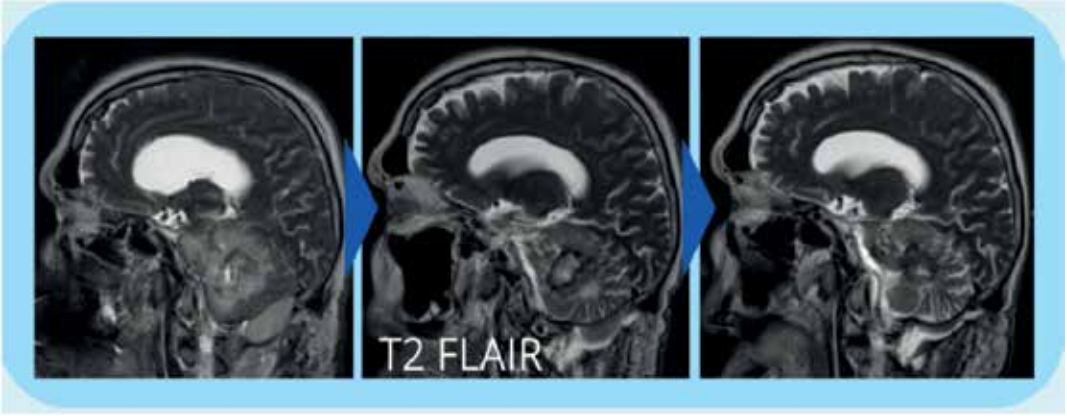

Fig. 2. MRI of the head of the Case No.2
Source: Own materials

confirmed after the patient's discharge. However, further tests conducted in the Intensive Care Unit revealed the presence of *Listeria monocytogenes*. Despite treatment (ampicillin, gentamycin, meropenem), the patient's condition worsened, intubation was necessary, and then, due to the increasing mass effect in the posterior cranial fossa and the expansion of the supratentorial ventricular system in the computed tomography examination, a decision was made for neurosurgical treatment. The procedure consisted of a wide decompression of the posterior cranial fossa without aspiration of inflammatory changes and external drainage of cerebrospinal fluid. Additionally, a tracheostomy was performed. Over the next 8 weeks, the patient's condition gradually improved, MRI examinations showed a gradual reduction of inflammatory changes, patency of the fourth ventricle, and the patient gradually regained consciousness. He was transferred to a rehabilitation center, and after another three months, he is in full logical contact, moves with a walker, and brainstem symptoms are gradually receding.

CASE 3

An 83-year-old female patient was admitted to the Department of Neurology due to disturbances in consciousness, loss of logical contact, and psychomotor agitation, which had been increasing for three days before hospitalization. In her medical history, the patient had a diagnosis of small B-cell lymphoma, stage III according to the Ann Arbor classification. Two weeks earlier, she had received the first cycle of chemotherapy with vincristine and a monoclonal antibody, but the next chemotherapy administration was postponed due to the occurrence of agranulocytosis. Additionally, the patient had comorbidities related to hypertension, type 2 diabetes, hyperlipidemia, hypothyroidism, and previous surgical procedures, such as strumectomy, appendectomy, and cholecystectomy. Upon admission to the hospital, the patient was conscious, had eye contact, but did not establish verbal contact and showed psychomotor agitation. The neurological examination revealed neck stiffness and the presence of oromandibular dyskinesias. The patient had a fever up to 38°C, but her circulation and breathing were normal. In basic laboratory tests, elevated inflammatory parameters such as leukocytosis (12k/µl) with a predominance of neutrophils, elevated CRP (47.2 mg/l), thrombocytopenia (121k/µl), hyponatremia (126 mmol/l) with hypokalemia (2.89 mmol/l), and elevated random blood glucose (197.51 mg/dl) were noteworthy. In the performed contrast-enhanced MRI of the head, no other foci of pathological enhancement were found apart from the enhancement of the dura mater, especially above the frontal lobes (Fig. 3). The EEG examination did not show seizure-

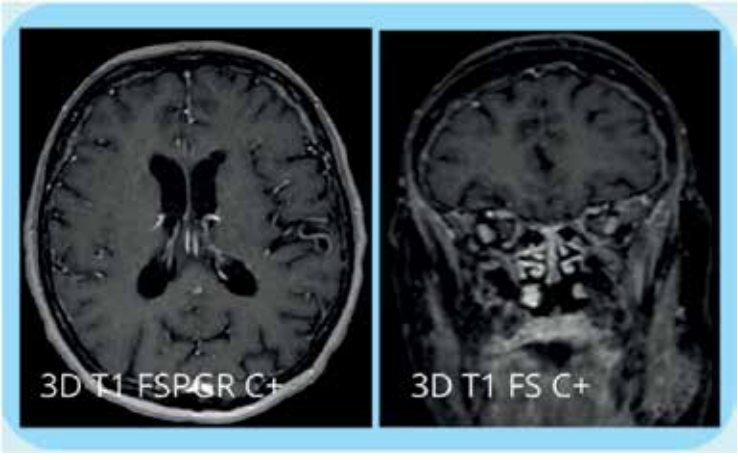

Fig. 3. MRI of the head of the Case No. 3
Source: Own materials

like changes. The patient underwent a lumbar puncture, during which straw-colored and turbid cerebrospinal fluid was obtained with cytosis (1062 cells/μl), CSF protein level of 293 mg/dl, and glucose level of 43 mg/dl. Samples were taken from the cerebrospinal fluid for culture and a PCR panel for 12 species of meningitis pathogens. The patient was started on empirical antiviral treatment – acyclovir at a dose of 800 mg every 8 hours, as well as broad-spectrum empirical antibiotic therapy – ceftriaxone 2g every 12 hours, vancomycin 1g every 12 hours, and ampicillin 2g every 4 hours. In the review radiological examination of the chest, bilateral changes of interstitial pathology with probable bacterial superinfection and hilar lymphadenopathy were described. A test for SARS-CoV-2 infection was performed, which was negative. The patient was also consulted by a psychiatrist, who diagnosed delirium or confusion of exogenous origin (CNS infection). The administration of quetiapine at a dose of 2 x 25 mg was recommended, with a possible gradual increase in the dose under the control of blood pressure and the patient's general condition. Both in the culture of CSF and in the molecular examination of CSF, a positive result was obtained for *Listeria monocytogenes* infection, while blood and urine cultures were negative. On the third day of stay, after confirming bacterial meningitis, the patient was transferred to the Infectious Diseases Department in a severe general condition. There, her general and neurological condition gradually began to improve over the next several days until healed.

DISCUSSION

Cases of nervous system listeriosis pose a serious threat to patients, as nervous system listeriosis is a disease that can lead to significant disability and cause considerable mortality. Mortality rates vary in the literature, as brain and spinal cord inflammation caused by *L. monocytogenes* are generally rare diseases and it is difficult to find statistically representative case series. In one case review, 100% of untreated patients died; among those who were treated early with ampicillin or penicillin, mortality rates were less than 30%. According to this report, mortality rates were higher in patients with accompanying cancers [10]. CNS listeriosis can have diverse clinical and radiological manifestations. The three cases of this disease presented above confirm this diversity. The diagnosis in cases of neurolisteriosis is based on neuroimaging studies, which sometimes give pathognomonic images for this neuroinfection, microbiological examinations of cerebrospinal fluid, and molecular tests. The first two of our cases concerned healthy men without significant potential immune disorders in the history and both had radiological features of posterior brain inflammation. The unfavorable course, ending in death, affected the patient with smaller changes in MR. This was a person whose diagnosis was established the latest, due to the fact that at that time we did not yet have rapid molecular diagnostics. In the second patient, the MR examination showed a lesion of a descending abscess in the medulla oblongata, pons, and cerebellum. This case also required intensive treatment, including indirect and direct neurosurgical decompression, but we ultimately achieved a cure burdened only with a slight neurological deficit, which is withdrawing in several months of observation giving hope for a complete cure. Only the third of the described cases concerned a person burdened with the occurrence of a risk factor for listeriosis neuroinfection - confirmed in the history of immunosuppression in an elderly woman treated with chemotherapy for lymphoma. In this case, the MR head examination did not reveal significant interstitial changes, only meningeal enhancement in the frontal areas, but in the cerebrospinal fluid, the presence of *Listeria monocytogenes* was found, both molecularly and later microbiologically. It should be emphasized that the diagnosis in all our cases was primarily obtained by molecular tests, which significantly accelerated the implementation of appropriate treatment in the last two patients. Molecular tests, such as PCR (Polymerase Chain Reaction) techniques, have played a significant role in improving the speed and precision of listeriosis diagnostics. These techniques involve the amplification (duplication) of specific pathogen DNA sequences, which allows for rapid and precise detection of the presence of the bacterium responsible for listeriosis. One of the biggest advantages of molecular tests is their ability to deliver results quickly. Traditional microbiological diagnostic methods, such as bacterial cultures, can take several days, which can delay the start of appropriate treatment. On the other hand, molecular tests can deliver results within a few hours, significantly speeding up the diagnostic process. In addition, molecular tests are very precise and can detect even small amounts of pathogen DNA, making them particularly useful in cases where bacteria are present only in small amounts [18, 19]. One of the biggest benefits after the C-19 pandemic is the proliferation and facilitation of access to molecular diagnostics. Until the wider availability of molecular tests, the diagnosis required differentiation from autoimmune or viral inflammations and could lead to improperly targeted therapy, especially at the beginning of the disease, and all presented cases confirm that rapid diagnosis and appropriate treatment are key to improving prognosis and achieving success. These latter, increasingly available, seem to be a breakthrough accelerating early diagnosis and implementation of appropriate treatment and are key to improving the prognosis of patients. In the context of treatment, the main approach to treating CNS listeriosis is antibiotic therapy, not surgical treatment, even in cases with formed abscesses. *Listeria monocytogenes* is sensitive to many different antibiotics, including ampicillin, gentamicin, and cotrimoxazole. Long-term antibiotic treatment is often required to cure the infection. The first drugs of choice for *L. monocytogenes* infections are ampicillin or penicillin G. in combination with gentamicin, because although aminoglycosides have poor penetration into the central nervous system (CNS), a large, prospective observational study from 2017 showed possible benefits for reducing mortality when they are used in combination with beta-lactam antibiotics in patients with neurolisteriosis or bacteremia, which heralds a higher risk of CNS infection [20]. Bactrim is an acceptable second-line therapy for those patients who are allergic to penicillin or beta-lactam antibiotics.

L. monocytogenes is resistant to all cephalosporins, and some strains have developed full resistance to vancomycin. Less commonly used antibiotics, such as meropenem and linezolid, are effective against *L. monocytogenes*, however, they are used sporadically and only in severe circumstances. The duration of antibiotic therapy largely depends on the degree of spread, however, neurolisteriosis requires at least six weeks of antibiotic therapy [21]. Another therapeutic controversy is steroid therapy, often used, for example, in autoimmune brain inflammations. One study found that treating neurolisteriosis with dexamethasone in combination with antibiotics significantly increased mortality. Therefore, steroids are not recommended in the treatment of brain and spinal cord inflammation caused by *Listeria*, and if they were included symptomatically at the beginning of therapy, their use should be discontinued immediately after confirming *L. monocytogenes* infection [10]. In our patient number two, we observed a deterioration of the clinical condition in connection with the introduction of steroid therapy before we established the diagnosis. In cases of posterior brain inflammation associated with listeriosis, not only intensive antibiotic treatment may be necessary, but even neurosurgical interventions to avoid secondary damage to the brainstem. They can both involve the treatment of hydrocephalus by external drainage, and posterior fossa decompressions, and even abscess aspirations. In the cases presented by us, we decided on neurosurgical treatment only in relation to the second patient, who in subsequent control imaging studies demonstrated symptoms of rapid mass increase in the posterior cranial fossa with obturation of the fourth ventricle lumen and enlargement of the supratentorial ventricular system. The surgical intervention was limited only to external drainage and bone decompression of the posterior cranial fossa, obtaining within a few days the recovery of the fourth ventricle patency allowing first closure, and then removal of the ventricular drainage. During the surgical intervention, the subarachnoid space was not explored, nor was the aspiration of the forming cerebellar abscess decided, considering that the MR image indicates that we were at this stage with too early a phase of abscess formation. Subsequent MR examinations showed a decrease in its mass and shrinkage without intervention, which positively verified the first decision not to explore the cerebellar parenchyma and to focus on conservative treatment - especially since the final course of treatment in this case turned out to be successful (Fig.3). The literature referring to issues related to surgical intervention in cases of neurolisteriosis is so modest [22] that it seems that the experience gained even in this one of the cases presented is valuable.

CONCLUSIONS

Nervous system listeriosis is a rare but serious health threat. In recent years, there has been an increase in the number of cases of posterior brain inflammation associated with this disease, which is associated with high mortality. Thanks to advances in molecular testing and neuroimaging studies, diagnosis is becoming easier. Rapid diagnosis remains a key factor for effective treatment, which is based on a relatively simple, albeit long-term, antibiotic therapy, but requires integrated cooperation of a neurologist, radiologist, intensivist, infectious disease specialist, and sometimes even a neurosurgeon.

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CONFLICT OF INTEREST
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