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ORIGINAL ARTICLE

Histomorphological changes in gunshot wounds using the developed method of surgical debridement of soft tissue defects in amputation stumps after gunshot traumatic amputations of lower extremities

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ABSTRACT

Aim: To study histomorphological changes in gunshot wounds when applying the developed technique of surgical debridement of soft tissue defects in amputation stumps following gunshot traumatic amputations of the lower extremities.

Materials and Methods: A histomorphological study of soft tissue defects in amputation stumps was carried out in 40 patients, including 20 patients in the main group who were treated according to the developed surgical debridement technique involving pulse lavage, ultrasonic cavitation, proposed dermatotension sutures, and early plastic closure. Tissue samples were obtained during hospitalization – on day 1; during the second debridement – on day 4; and during the fourth one – on day 12.

Results: On day 1, histomorphological changes were similar in the patients of both groups, presenting as deep defects, an extensive damage region with necrosis in the centre, diffuse polymorphonuclear inflammatory infiltration, and signs of oedema with marked perifocal inflammatory changes. On day 4, a decreased volume of necrotic tissue was noted in the patients of the main group as compared to the control group; the infiltrate contained segmented neutrophils in low quantities, and there was significant development of granulation tissue. On day 12, the patients of the main group showed complete resolution of the inflammatory process with healing of soft tissue defects and formation of a fully epithelialised connective tissue scar.

Conclusions: The histomorphological study of soft tissue defects in amputation stumps in patients treated by the developed surgical debridement technique demonstrated rapid elimination of necrotic tissue, a decrease in signs of inflammation, early development of mature granulation tissue, and wound healing.

KEYWORDS: wounds, trauma, infectious complications, histomorphological study

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INTRODUCTION

Today, in the context of the ongoing full-scale war in Ukraine, there is a significant increase in the number of military and civilian victims with blast trauma and blast injuries [1]. Shotgun wounds to the limbs appear to be the most common type of injury caused by explosive trauma, accounting for up to 70,0% of all injuries [2, 3], while those followed by traumatic amputations of the lower extremities occur in 4,9-8,1% of cases [4]. The major method of surgical treatment of these wounds at the Role 2 level is primary surgical debridement (PSD) of soft tissue gunshot defects without stump formation [5, 6]. In recent years, surgical debridement has undergone certain changes and improvements for all types of gunshot wounds, involving vacuum-assisted closure (VAC) therapy, among others [7-10]. To date, no current literature presents a detailed microscopic analysis of soft tissue gunshot defects in amputation stumps of the lower extremities depending on the surgical debridement technique.

AIM

The aim of the work was to study histomorphological changes in gunshot wounds when applying the developed technique of surgical debridement of soft tissue defects in amputation stumps following gunshot traumatic amputations of lower extremities.

MATERIALS AND METHODS

The research conducted complies with the provisions of the Helsinki Declaration, the Council of Europe Convention on Human Rights and Biomedicine, the relevant provisions of the WHO and the Ministry of Health of Ukraine, and the ethical standards established by the Bioethics Committee of National Pirogov Memorial Medical University, Vinnytsya, Protocol No. 8 of September 15, 2025. Permission for the study was obtained, as reflected in the informed consent.

A histomorphological study of soft tissue defects in amputation stumps following gunshot traumatic amputations was performed in 40 patients undergoing an in-patient course of treatment at the Military Medical Clinical Center of the Central Region. All patients were divided into two groups: the control group consisted of 20 patients treated according to conventional methods of staged repeated or secondary surgical debridement followed by the closure of defects with secondary sutures; and the main (experimental)

group included 20 patients treated according to a specially developed technique of complex repeated (secondary) surgical debridement of soft tissue defects of amputation stumps after gunshot traumatic amputations of the lower extremities (registration certificate of copyright for work № 125791 dated 18 April 2024), involving pulse lavage, ultrasonic cavitation, proposed dermatotension sutures, and early plastic closure with secondary sutures using local tissues.

Tissue samples from the regions of soft tissue gunshot defects of amputation stumps were obtained during hospitalization – on day 1, i.e. during the first in succession repeated surgical debridement (ReSD) or secondary surgical debridement (SSD); during the second in succession ReSD or SSD, i.e. on day 4; and during the fourth in succession ReSD or SSD, i.e. on day 12. The excision of soft tissue sections measuring 1,0 × 1,0 × 0,3 cm was performed, followed by fixation in 10% neutral formalin solution, passage of specimens through alcohols of increasing concentration, and embedding in paraffin. Serial sections 5-7 μm thick were cut from the paraffin blocks and then stained with haematoxylin and eosin. The microscopic structure of the specimens was examined using an OLYMPUS BX41 light microscope, which provides magnifications of 100×, 200×, 400×, and 1000×.

FRAMEWORK

The study was conducted as a fragment of the scientific project of the Department of Surgery, Medical Faculty No. 2, National Pirogov Memorial Medical University, Vinnytsya, „Evaluation of the effectiveness of minimally invasive techniques and the use of various energy sources in the treatment of gastrointestinal diseases" (state registration number 0120U101673; term: 2020-2024).

RESULTS

On day 1, the area of damage in the soft tissues of gunshot wounds was rather extensive in the control group, with no distinct margins and the development of necrosis in the centre (thickness of the necrotic tissue layer being about 5 mm), as well as marked perifocal reactive changes in the form of significant inflammation. In addition, severe microcirculation disorders were observed. The dermis beneath the epithelium consisted of bundles of collagen and elastic fibres oriented in different directions. Dermal blood vessels in the affected area around the wound defect were dilated, with marked dystrophic changes in the endothelium. The vessels appeared plethoric, with marginal leukocytes present. Diffuse polymorphonuclear inflammatory infiltration and signs of moderate tissue oedema were observed in the wounds. The surface layer of necrotic tissue was separated from the underlying tissues by a clearly defined demarcation leukocyte ridge. In some patients, necrotic tissue in the wounds had already been rejected, with only a thin layer of fibrinoid substance remaining on the surface. The inflammatory cellular infiltrate included neutrophilic leukocytes, with eosinophilic leukocytes in low quantities, tissue macrophage elements, and lymphocytes. In the peri-wound area, young and not numerous fibroblasts were identified. Regenerative proliferation of stratified squamous epithelium from the wound edges was not seen. The structure of the underlying hypodermis was damaged by foci of necrosis and significant inflammatory cell infiltration. Accumulation of edematous fluid was detected in the hypodermis, as well as mononuclear cells of the blood monocyte type, lymphocytes, and segmented leukocytes in large quantities (Fig. 1).

Histomorphological changes in gunshot defects to the soft tissues of amputation stumps in the patients of the main group were similar to those in patients of the control group (Fig. 2).

On postoperative day 4, i.e. during the second in succession ReSD (or SSD), weak proliferation of young epithelium was observed at the edges of wound defects in the patients of the control group. Its layer grew on granulation tissue.

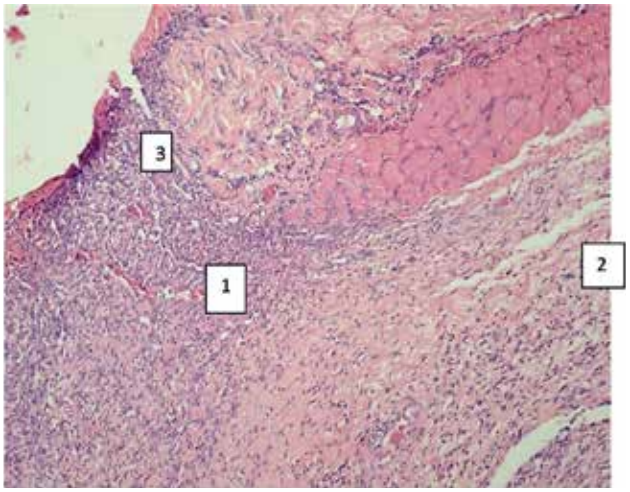

Fig. 1. Histomorphological changes in the tissues of the central part of the wound defect. Day 1, the control group. Diffuse polymorphocellular inflammatory infiltration (1), signs of moderate tissue edema (2), thin layer of fibrinoid (3) in the tissues of the wound bed

Picture taken by the authors

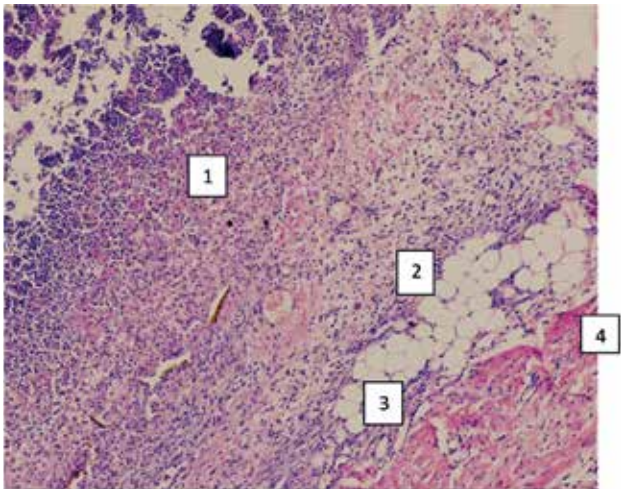

Fig. 2. Histomorphological changes in the tissues of the wound defect region. Day 1, the main group. Leukocyte-necrotic layer (1), layer of functional blood vessels (2), fibrous layer (3), hypodermis with inflammatory changes (4)

Picture taken by the authors

Inflammatory processes were present in the skin, extending to the subcutaneous tissue and even to muscle tissue. Insufficient development of granulation tissue was seen at the site of dead tissue in the region of the gunshot wound. Its main components were vertical vascular loops and a leukocytic-necrotic zone. Formation of new small-sized vessels was observed along with proliferation of capillary endothelial cells, known as angioblasts, which initially formed cell strands and later vascular tubes for blood supply. Blood corpuscles and edematous fluid leaked from the newly formed vessels into the surrounding tissues. Reactive inflammatory infiltration was observed in the hypodermis. The cellular composition of the infiltrate was represented mostly by segmented neutrophils; low counts of lymphocytes and monocytic cells (macrophages, giant multinucleated cells of foreign bodies) were also identified. Wound contraction was moderate. The vascular reaction in the area of inflammation was characterised by moderate hyperemia, oedema of the hypodermis, and the reticular layer of the dermis. Single bundles of collagen fibres of organised dense fibrous connective tissue of the dermis, with signs of oedema, stratification, and fragmentation of fibres, were identified as well. The surface layer of necrotic tissue was separated from the underlying tissue by a clearly defined demarcation leukocyte ridge. However, over most of the wound area, the necrotic tissue had already been rejected, leaving only a thin zone of superficial deposits of fibrinoid substance. Small numbers of active fibroblasts were identified in the peri-wound region (Fig. 3).

In the patients of the main group, moderate proliferation of young epithelium was observed at the edges of wound defects on postoperative day 4 (during the second in succession ReSD or SSD). The epithelium grew over granulation tissue, covering about one-third of the wound surface by that time. Inflammatory changes were present in the skin tissues, extending to the subcutaneous tissue. At the site of dead tissue, considerable development of granulation tissue was observed. Its main components were vertical vascular loops and a narrow leukocytic-necrotic zone. Formation of new small-sized blood vessels was observed along with proliferation of capillary endothelial cells (angioblasts), which initially formed cell strands and later vascular tubes for blood supply. Blood cells and edematous fluid leaked from the newly formed vessels into the surrounding tissues. Young forms of fibroblasts were identified among the inflammatory cells. Mild reactive inflammatory infiltration was observed in the hypodermis. The cellular composition of the infiltrate was represented by few segmented neutrophils, moderate amounts of lymphocytes, and monocytic cells (macrophages, giant multinucleated cells of foreign bodies). Wound contraction was moderate. The vascular reaction in the area of inflammation was characterised by moderate hyperemia, oedema of the hypodermis and the reticular layer of the dermis. Single bundles of collagen fibres of dense fibrous connective tissue of the dermis, with signs of oedema, stratification, and fragmentation of fibres, were identified as well. The surface layer of necrotic tissue was separated from the underlying tissue by a clearly defined demarcation leukocyte ridge. However, over most of the wound area, the necrotic tissue had already been rejected, leaving only a thin zone of superficial deposits of fibrinoid substance. Small numbers of active fibroblasts were identified in the peri-wound area (Fig. 4).

On postoperative day 12, i.e. during the fourth in succession ReSD, insufficient resolution of inflammation was observed in the patients of the control group, as well as insufficient healing of soft tissue defects. A connective tissue scar with an epithelializing thin dystrophic epidermis was formed in the area of inflammation. Under the scar tissue, a layer of organised fibrous tissue with diffuse lymphohistiocytic

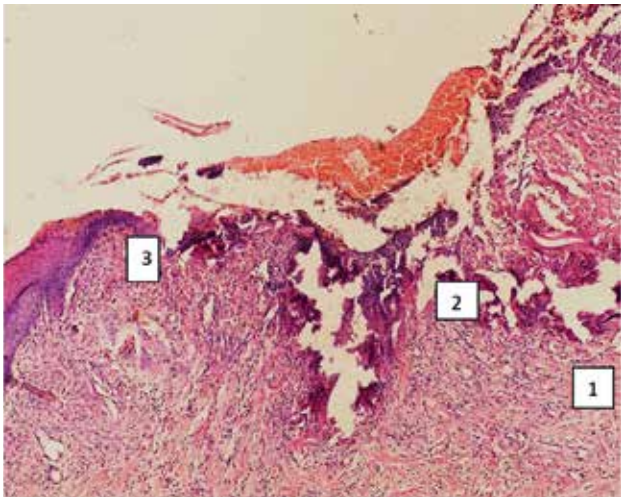

Fig. 3. Histomorphological changes in the tissues of wound defect region. Day 4, the control group. Mature granulation tissue (1), rather wide layer of necrotic tissue (2), newly formed epithelium with dystrophic changes (3) at the edges of the wound defect

Picture taken by the authors

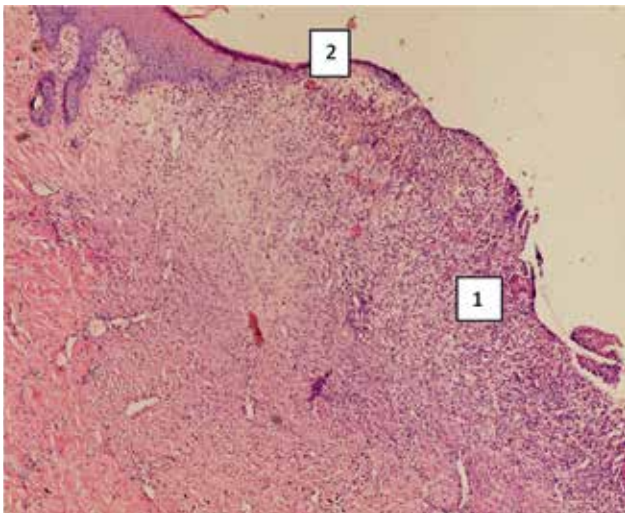

Fig. 4. Histomorphological changes in tissues of wound defect region. Day 4, main group. Mature granulation tissue (1) with moderate inflammation; newly formed proliferation epithelium (2)

Picture taken by the authors

infiltration was identified. Dermal papillae, hair follicles, sebaceous glands, and sweat glands were not identified. The scar tissue consisted of numerous fibrocytes and collagen fibres. There was a reduction of blood vessels in the scar tissue area, with closure of their lumens. The scar was undergoing the remodelling process. A thin layer of hypodermis was identified beneath the fibrous tissue. Minor signs of microcirculation disorders were observed in the hypodermis in the form of moderate hyperemia.

Thus, these changes in the patients of the control group are indicative of incomplete resolution of inflammatory changes in soft tissue defects of amputation stumps, connective tissue scarring, and scar remodelling processes (Fig. 5).

On postoperative day 12, i.e. during the fourth in succession ReSD, almost complete resolution of inflammation and healing of the wound defect was observed in the patients of the main group. In the area of inflammation, a completely epithelialized connective tissue scar with no inflammatory cell infiltration was formed. A layer of mature fibrous tissue was identified beneath the scar tissue. The scar tissue consisted of large amounts of fibrocytes and collagen fibres. In the scar tissue region, there was a reduction of blood vessels with closure of their lumens. The scar was undergoing the remodelling process. A thin layer of hypodermis was identified beneath the fibrous tissue. Minor signs of microcirculation disorders were observed in the hypodermis.

Thus, these changes are indicative of almost complete resolution of inflammatory changes, with the formation of a connective tissue scar and ongoing scar remodelling processes. In the patients of the main group, unlike those in the control group, an almost mature scar was formed as a result of the wound healing process and resolution of inflammation, with no inflammatory cell infiltration and only minor microcirculation disorders (Fig. 6).

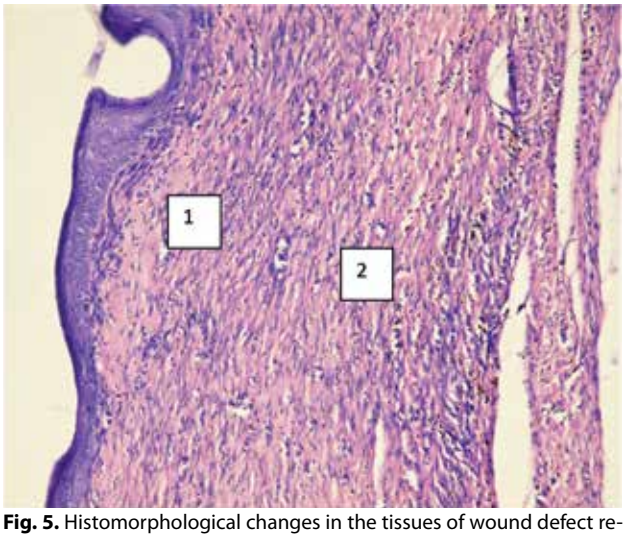

Fig. 5. Histomorphological changes in the tissues of wound defect region. Day 12, the control group. Newly formed epidermis (1) covering scar tissue (2) with oriented fibrous bundles and moderate lymphohistiocytic infiltration

Picture taken by the authors

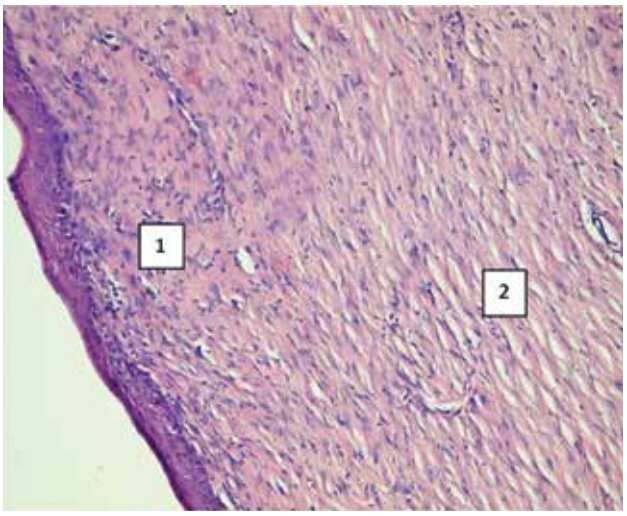

Fig. 6. Histomorphological changes in the tissues of wound defect region. Day 12, the main group. Newly formed epidermis (1) covering scar tissue (2) with reduced blood vessels

Picture taken by the authors

DISCUSSION

According to many researchers, the treatment of soft tissue gunshot wounds remains a complex and unresolved problem worldwide [8-10]. All existing surgical debridement techniques may be associated with purulent-inflammatory complications. Histomorphological studies carried out by the authors [11, 12] have demonstrated the effective use of surgical debridement of gunshot wounds combined with physical methods, including ultrasonic cavitation, hyperbaric oxygenation, and vacuum therapy. However, there are no morphological studies demonstrating the effectiveness of pulse lavage with decamethoxine followed by ultrasonic cavitation and vacuum therapy. Furthermore, there is no information regarding the histomorphological examination of soft tissue gunshot defects, specifically those in amputation stumps of the limbs, with the additional use of dermatotension sutures during each stage of repeated surgical treatment for faster closure with secondary sutures, as well as assessment of their healing dynamics.

The data obtained during our histomorphological studies of soft tissue defects in amputation stumps after traumatic amputation of the lower extremities as a result of gunshot wounds demonstrated that on day 1, histomorphological changes in patients of both groups were similar and manifested as deep defects, extensive areas of damage with necrosis in the centre, diffuse polymorphic inflammatory infiltration, signs of oedema with marked perifocal inflammatory changes, and significant microcirculation disorders. These data are comparable with the results presented by Khomenko I.P. et al. (2017) [13], in which morphological examination of gunshot wounds at the time of hospitalization in experimental and control groups showed a similar morphological pattern: areas of damage containing randomly located collagen fibres with foci of cellular infiltration. In some areas, the absence of ground substance was observed, as well as excessive

accumulation of coarse collagenous fibres, isolated fibroblasts, and cellular elements [13].

According to the results of our study, on postoperative day 4, necrotic tissues and inflammatory infiltrate were still present in the region of soft tissue defects of amputation stumps of the lower extremities in the control group patients, along with insufficient development of granulation tissue and moderate wound contraction. By contrast, at this stage of examination, the patients of the main group showed a smaller volume of necrotic tissue, which had been mostly rejected; the infiltrate consisted of a small number of segmented neutrophils, and considerable development of granulation tissue was observed.

According to the microscopic findings of Khomenko I.P. et al. (2018) [13], after surgical debridement of gunshot wounds on days 3-5 using the traditionally employed technique, randomly arranged collagen fibres were observed, with areas of moderate cellular infiltration, while the soft tissue defect itself remained unchanged. Vacuum therapy applied on days 3-5 resulted in an increased number of erythrocytes per unit of blood volume and a significantly increased number of fibroblasts. However, marked cellular lymphohistiocytic infiltration was still present. Proliferation of young mesenchymal elements and neovascularization were observed, suggesting activation of reparative processes [13].

On day 12, incomplete resolution of inflammation was observed in the patients of the control group, along with the formation of a connective tissue scar undergoing remodelling processes, absence of skin appendages, preservation of minor inflammatory cell infiltration, and minor microcirculation disorders. By contrast, the patients of the main group demonstrated complete resolution of inflammatory changes at this stage of wound management, healing of the soft tissue defect, and complete epithelialization of the connective tissue scar, with no inflammatory cell infiltration and only minor microcirculation disorders.

According to Gerasymenko O.S. et al., the process of wound healing and epithelialization was 1.5-2 times faster in the patients of the main group compared with those treated by traditional methods, the findings being consistent with our study. Furthermore, uncomplicated wound healing was observed in only 26 (74.3%) patients [12].

CONCLUSIONS

Thus, histomorphological examination of soft tissue defects in amputation stumps following traumatic amputation of the lower extremities in patients undergoing complex surgical debridement using the developed method demonstrated better results compared with the control group. After the second surgical debridement (day 4), a smaller amount of necrotic tissue was observed, the inflammatory infiltrate consisted of a small number of segmented neutrophils, and there was considerable development of granulation tissue with moderately marked contraction of the soft tissue defect. The fourth in succession surgical debridement (day 12) resulted in complete resolution of the inflammatory process, healing of the soft tissue defect, and formation of a connective tissue scar with no inflammatory cell infiltration and only minor microcirculation disorders.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Scientific rationale for the use of calcium pectate in foods for special medical purposes under conditions of lead exposure

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ABSTRACT

Aim: To study the complexing ability of pectins of different origins towards calcium ions (Ca^{2+}) and lead ions (Pb^{2+}), in order to justify the introduction of calcium pectate into product formulations for special medical purposes and the subsequent medical use of such products for therapeutic and prophylactic purposes under conditions of lead exposure.

Materials and Methods: The complexation ability of six different fruit and vegetable pectins with calcium (Ca^{2+}) and lead (Pb^{2+}) ions was investigated using the atomic emission method.

Results: It was found that the highest complexing ability towards Ca^{2+} ions was observed in sugar beet pectin: 5,02±0,04 mmol Me/g pectin; the complexing ability of quince, citrus, apple, carrot, and pumpkin pectins ranged from 3,07±0,02 to 3,91±0,03 mmol Me/g pectin. The complexing ability of sugar beet pectin towards Pb^{2+} ions was 1,40±0,01 mmol Me/g pectin, while other pectins exhibited complexing abilities from 1,00±0,01 to 1,31±0,01 mmol Me/g pectin. The study of pectins' complexing ability in an aqueous medium in vitro, in the simultaneous presence of Ca^{2+} and Pb^{2+} ions, did not reveal a statistically significant change in complexing ability towards Pb^{2+} ions in sugar beet pectin (p=0,052), citrus pectin (p=0,054), carrot pectin (p=0,072), or pumpkin pectin (p=0,061); however, a decrease in complexing ability with Pb^{2+} ions was observed in quince pectin (p=0,036) and apple pectin (p=0,048).

Conclusions: Calcium pectates of fruit and vegetable origin can be added to dietary products for special medical purposes to reduce lead exposure.

KEYWORDS: pectin, complexation, calcium, lead

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INTRODUCTION

Lead, by decision of the World Health Organization (WHO), is included in the list of the 10 most dangerous chemicals due to its toxic effects on the nervous, reproductive, and cardiovascular systems, hematopoiesis, gastrointestinal tract, and kidneys. Worldwide, the most common form of lead exposure is chronic [1].

For Ukraine, which has been engaged in a large-scale war for a long time, the main sources of lead are ammunition, lead-acid batteries in mechanical vehicles and unmanned aerial vehicles, various pigments, paints, and other sources. Studies conducted between 2022 and 2024 revealed a wide range of pollutants directly associated with the war, with heavy metals occupying a prominent position among them [2-4]. A significant increase in exposure to lead compounds has been found in military personnel in combat zones and in the population living in adjacent areas [5, 6].

Under conditions of chronic lead exposure, approaches aimed at enhancing the body's natural detoxification mechanisms become increasingly relevant. This can be achieved through the consumption of foods for special medical purposes based on pectins, the value of which lies in their unique biological properties and ability to complex with heavy metal ions [7]. Calcium pectate deserves special attention, as it has a proven high complexing ability towards lead ions [8-10]. However, despite the long history of the use of pectins in food products, there is insufficient data in the scientific literature on the quantitative characteristics of effective sorption of lead ions by pectins of various origins. Today, such indicators are necessary for the development of product formulations for special medical purposes aimed at the treatment and prevention of pathological conditions in individuals exposed to lead.

AIM

To study the complexing ability of pectins of different origins towards calcium ions (Ca^{2+}) and lead ions (Pb^{2+}), in order to justify the introduction of calcium pectate into product formulations for special medical purposes and the subsequent medical use of such products for therapeutic and prophylactic purposes under conditions of lead exposure.

MATERIALS AND METHODS

An analysis of sources from the scientometric databases PubMed, Medline, and Elsevier was conducted, and WHO publications on the impact of lead on human health were reviewed. The object of the study is calcium and lead chelates

obtained by complexing with pectins derived from various fruit and vegetable raw materials. The subject of the study is the complexing ability of pectins derived from various fruit and vegetable raw materials towards calcium ions (Ca^{2+}) and lead ions (Pb^{2+}).

As a source of pectin, pectin-containing extracts and juices of pumpkin, apple, quince, citrus, and carrot, as well as pectin-containing extracts of sugar beet, were used (manufacturer of raw ingredients – LLC MANZANA-FOOD, Ukraine). Only low-esterified pectins were used.

The safety of raw materials (extracts and juices) was investigated according to microbiological and sanitary-chemical safety indicators, using instrumental methods of chemical analysis, and for compliance with the State Sanitary Rules and Norms "Maximum Permissible Levels of Certain Pollutants in Food Products," the technical requirements "Permissible Levels of Radionuclides ^{137}Cs, ^{90}Sr in Food Products and Drinking Water," and the manufacturer's specifications.

To determine the content of pesticide residues, the method of ultra-high-performance liquid chromatography with electrospray ionization mass spectrometry (UPLC-MS/MS, Waters, USA) was used. The content of lead, cadmium, mercury, zinc, copper, and calcium was determined by the atomic emission method (SHIMADZU ICPE-9820, Japan). To determine radionuclides, spectrometers of domestic production were used. According to the results of the research, it was found that the raw materials (extracts and juices), in terms of the content of heavy metals, radionuclides, and pesticide residues, met the established medical safety criteria.

The complexing ability of pectins was determined in the following units: mg Me/g pectin is the mass of metal ions (in milligrams) that 1 gram of dry pectin can bind; and in mmol Me/g pectin is the amount of metal (in millimoles) per 1 gram of pectin.

Statistical analysis of the data was performed using Microsoft Excel 2019. Quantitative variables were presented as the mean (M) and standard error (m), and were compared using the Student's t-test for independent samples. A $p<0,05$ was considered as statistically significant.

ETHICS

In this work, in vitro methods were used. The Commission approved the protocol of this study on Ethics of Medical and Biological Research of the State Enterprise «L.I. Medved's Research Center of Preventive Toxicology, Food and Chemical Safety of the Ministry of Health of Ukraine».

FRAMEWORK

The research was carried out in accordance with the research work "Scientific substantiation of medical criteria for chemical and food safety; toxicological and hygienic studies of chemicals, pesticides and agrochemicals, polymers, materials and products; medical and sanitary regulation of hazardous factors in objects of the human environment" (No. 0123U102087 of state registration; date: 2023-2027). The research was carried out at the expense of the State Enterprise "Scientific Center for Preventive Toxicology, Food and Chemical Safety named after Academician L.I. Medved of the Ministry of Health of Ukraine".

RESULTS

It was found that pectins made from different vegetable and fruit raw materials have different complexing abilities towards Ca^{2+} and Pb^{2+} ions. Thus, the highest complexation indicators for Ca^{2+} ions were found in beet pectin – 5,02±0,04 mmol Me/g pectin; other pectins showed similar complexation rates, ranging from 3,02±0,02 to 3,91±0,03 mmol Me/g pectin;

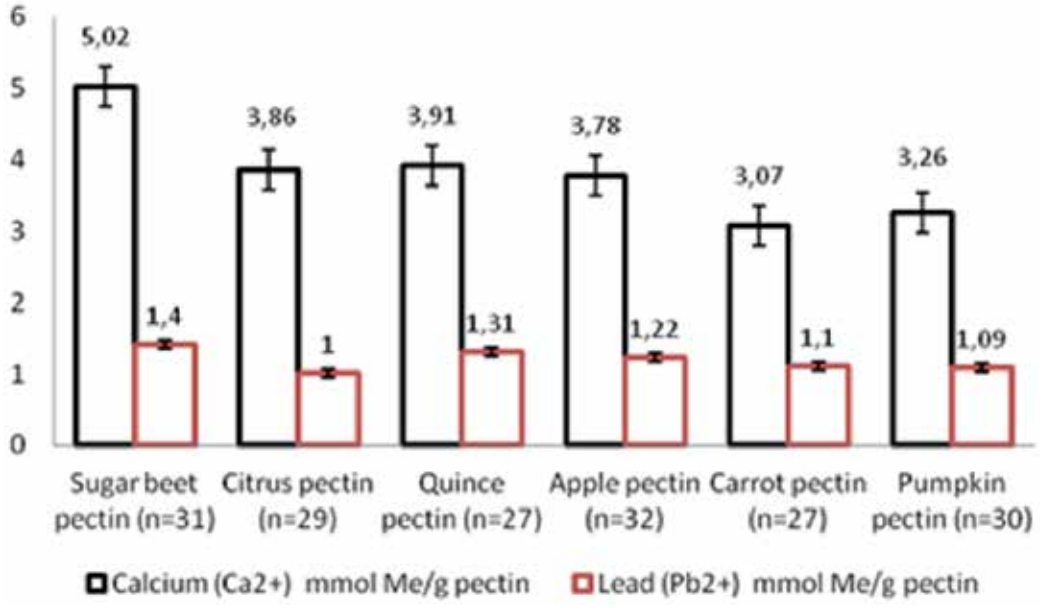

Fig. 1. Complexation abilities (mmol Me/g pectin) of different pectins towards Ca^{2+} and Pb^{2+} ions (M±m)

Picture taken by the authors

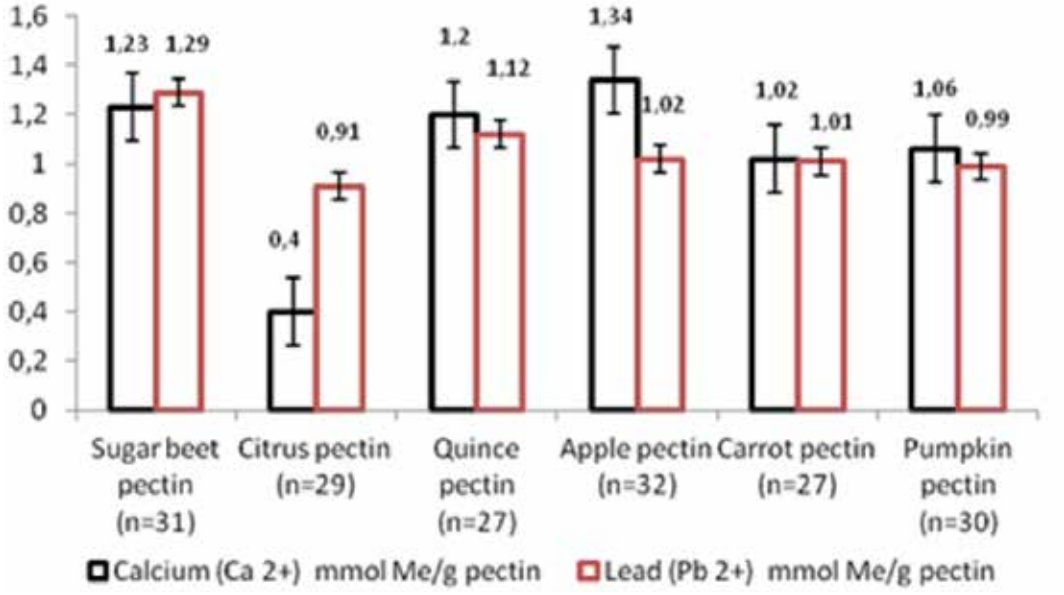

Fig. 2. Complexation abilities (mmol Me/g pectin) of different pectins towards a mixture of Ca^{2+} and Pb^{2+} ions (M±m)

Picture taken by the authors

in relation to Pb^{2+} ions, beet pectin was 1,40±0,01 mmol met/g pectin, other pectins showed similar complexation indicators, ranging from 1,00±0,01 to 1,31±0,01 mmol Me/g pectin (Fig. 1).

At the next stage of the study, measurements were made of the complexing ability of pectins towards a mixture of Ca^{2+} ions and lead Pb^{2+}. It was found that the highest complexing ability to Ca^{2+} ions in an aqueous medium, in the simultaneous presence of Ca^{2+} and Pb^{2+}ions, was demonstrated by beet pectin – 1,23±0,01mmol Me/g pectin; its complexing ability was also the highest towards Pb^{2+} ions – 1,29±0,02 mmol Me/g pectin in this solution (Fig. 2).

The next step was to compare the complexing ability of pectins towards Ca^{2+} ions in different aqueous solutions: the first solution contained only calcium ions, the second – simultaneously Ca^{2+} and Pb^{2+} ions. It was found that the decrease in complexing ability of all studied pectins towards Ca^{2+} ions in the conditions of the simultaneous presence of Ca^{2+} and Pb^{2+} ions (Fig. 3).

The complexing ability of pectins towards Pb^{2+} ions was determined in different aqueous solutions: the first solution contained only Pb^{2+} ions, the second simultaneously contained Ca^{2+} and Pb^{2+} ions. It was found that in the second solution there were changes in the values of the complexing

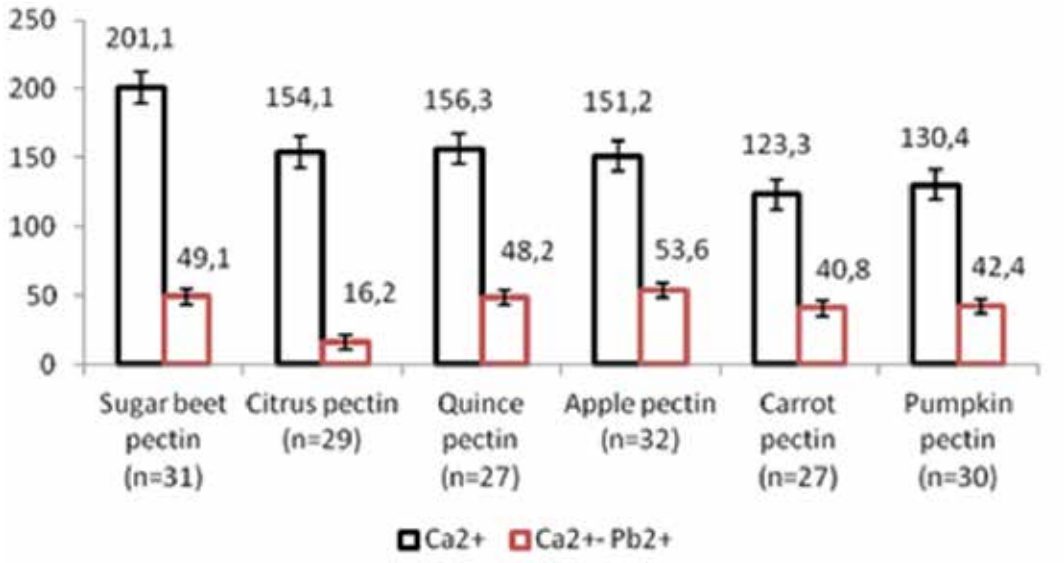

Fig. 3. Comparative analysis of the complexing ability (mg Me/g pectin) of pectins in a solution containing only Ca^{2+} ions and in a solution containing simultaneously Ca^{2+} and Pb^{2+} ions (M±m; $p<0,01$ for all comparisons)

Picture taken by the authors

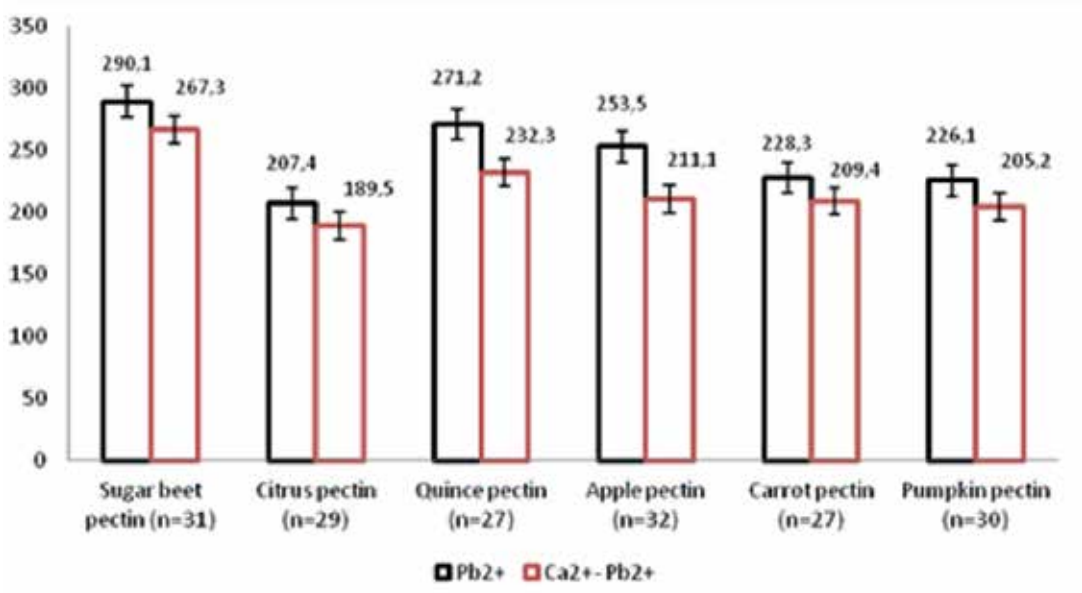

Fig. 4. Comparative analysis of the complexing ability (mg Me/g pectin) of pectins in a solution containing only Pb^{2+} ions and in a solution containing simultaneously Ca^{2+} and Pb^{2+} ions (M±m)

Picture taken by the authors

ability of all the studied pectins (Fig. 4), however, all pectins in the conditions of the simultaneous presence of Ca^{2+} and Pb^{2+} ions showed high adsorption rates of lead Pb^{2+} ions.

No statistically significant changes in the complexing ability were observed for beetroot (p = 0,052), citrus (p = 0,054), carrot (p = 0,072), and pumpkin pectins (p = 0,061); however, a decrease in the complexing ability was detected for quince pectin (p = 0,036) and apple pectin (p = 0,048). Thus, beetroot, pumpkin, citrus, and carrot pectins can be considered as priority sources for the preparation of calcium pectates, which, in turn, can be used in product formulations for special medical purposes under conditions of lead exposure.

DISCUSSION

The decrease in the complexing ability of pectins towards Ca^{2+} ions in the presence of Pb^{2+} ions can be explained by the fact that lead actively interacts with the surface layer of the pectin globule, which limits the free access of Ca^{2+} ions to the pectin. Studies show that calcium pectates can act as effective sorbents with ion-exchange properties, binding lead ions within the gastrointestinal tract.

To create a product with high complexing properties for Pb^{2+} ions, it is also necessary to consider that complexing ability is influenced by: the degree of esterification, with lower esterification leading to higher complexing ability due to the presence of more free carboxyl groups capable of binding metals; the type of metal, since pectins most actively bind polyvalent metal cations such as Pb^{2+}, Cu^{2+}, Co^{2+}, and Sr^{2+} [7]; and the pH of the medium, as the complexing ability of low-esterified pectins and their pectates towards Pb^{2+} ions occurs across a wide pH range, from slightly acidic to alkaline conditions [11].

Currently, in the search for universal adsorbents for toxins, scientists are exploring complex polymer compositions based on dextrins, gelatin, polyethylene glycol, cyclodextrins, chitosan, hyaluronic acid, alginate, polygalacturonic acid, carrageenan gum, carboxymethylcellulose, gellan gum, and others [12, 13].

One research direction is the enhancement of pectin's complexing ability through modification. For example, to increase the complexing ability of pectins towards Pb^{2+}, special microspheres – pectin/poly(m-phenylenediamine) – have been developed, exhibiting a maximum adsorption capacity of 390,9 mg Me/g pectin [14]. Other researchers, by modifying calcium pectates, increased the adsorption capacity to 325 mg/g for Pb^{2+} in aqueous solution at pH 5,0 [15].

The following authors created hydrogels based on pectin and sodium acrylate-co-N-isopropylacrylamide with a maximum adsorption capacity of up to 265,49 mg/g for the adsorption of methyl violet, methylene blue, and heavy metals [16]. Some studies have demonstrated the improvement of the adsorption characteristics of pectin-based hydrogels using nanoparticles, leading to the development of hydrogel nanocomposites. Aerogels exhibited several advantageous properties, including a high maximum adsorption capacity for Pb^{2+} ions (373,7 mg/g, tested at pH 5,0), ultra-light weight (up to 63,4 mg/cm^3), high mechanical strength (stress over 0,24 MPa at 50 % strain), and ease of processing [16, 17].

All of the above-mentioned modified pectin complexes are highly effective adsorbents for industrial applications, particularly for the treatment of wastewater containing dyes and heavy metals, including lead. Beyond industrial applications, pectins are also considered promising adsorbents of heavy metals in the livestock sector. For instance, through a sequential enzymatic-ultrasonic process, additives based on pectin-rich fiber from sisal waste (11,8 % pectin) are being developed for the removal of lead from the animal body [17].

Pectin is attractive for various applications due to its technical, functional, and biological properties, such as gelling and thickening abilities or modulation of the microbiota in both animals and humans. These properties make pectin suitable for a wide range of applications in the food chain, including its use as packaging, as carriers of nutrients in food products, or for direct use as a functional ingredient, such as dietary fiber [18]. Calcium pectates, through modification, can form complex matrices and trap molecules within them (the "egg carton" principle). Positively charged biopolymers, such as chitosan, are used to reinforce the matrix framework [19]. Recent studies have begun to investigate the therapeutic properties of foods for special medical purposes in the prevention and treatment of certain diseases [20].

Pectin is a natural biopolymer that can be extracted from the processing products of various plant raw materials. On this basis, raw materials with a more complex structure than other polysaccharides can be created. As a natural polymer, pectin possesses useful hydrogel properties, and therefore it can be considered not only as a basis for creating adsorbents of heavy metals and toxins, but also as a multifunctional matrix for the delivery of proteins and drugs, as well as for cell immobilization, opening new prospects for regenerative medicine and tissue engineering.

PROSPECTS FOR FURTHER RESEARCH

The large-scale war launched by the Russian Federation against Ukraine has generated a new range of chemical threats, particularly critically elevated levels of lead contamination in the environment. This necessitates the development of effective means of protecting the health of military personnel and civilians in conditions of exposure to heavy metals. Calcium pectates can be the basis for a wide range of food formulations for special medical purposes.

CONCLUSIONS

1. It was established that beet pectin had the highest complexing ability towards Ca^{2+} ions – 5,02±0,04 mmol Me/g pectin; the complexing ability of quince, citrus, apple, carrot and pumpkin pectins ranged from 3,07±0,02 to 3,91±0,03 mmol Me /g pectin.
2. It was established that all the studied pectins had a high complexing ability towards Pb^{2+} ions, however, beet pectin had the highest indicators – 1,40±0,01 mmol Me/g pectin, other pectins had indicators in the range of 1,00±0,01 to 1,31±0,01 mmol Me/g pectin.
3. The study of the complexing ability of pectins in an aqueous medium in vitro in the simultaneous presence of Ca^{2+} and Pb^{2+} ions did not reveal a statistically significant change in the complexing ability towards Pb^{2+} ions for sugar beet, citrus, and carrot pectins. However, a decrease in the complexing ability towards Pb^{2+} ions was observed for quince and apple pectins, while an increase was noted for pumpkin pectin.
4. The results of the study confirm the feasibility of creating calcium pectates based on various fruit and vegetable pectins for subsequent use in dietary products for special medical purposes under conditions of lead exposure.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Resveratrol improves cognitive function and quality of life in postmenopausal women

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ABSTRACT

Aim: To evaluate the effect of trans-resveratrol on cognitive function and quality of life in postmenopausal women.

Materials and Methods: A prospective controlled clinical study involved 88 women aged 52.1±2.5 years, postmenopausal for 2.3±1.2 years, who were randomized into two groups: study (n=55) and comparison (n=33). All patients underwent laboratory and psychometric examinations.

Results: Compared with the control group, resveratrol intake was associated with an increase in serum magnesium levels (p 0.05). Resveratrol administration in the study group resulted in positive changes in cognitive function ($p<0.001$), unlike in the control group, where no significant changes were observed ($p>0.05$). Improvements in quality of life according to the EQ-5D-3L scale occurred in both groups, but with an advantage in the study group (p 0.05).

Conclusions: The results of the study indicate a significant positive effect of resveratrol on cognitive functioning, as confirmed by an increase in MoCA scores, as well as an improvement in quality-of-life parameters according to the EQ-5D-3L and MENQOL questionnaires. The data obtained provide grounds for asserting that resveratrol can help slow age-related cognitive decline in postmenopausal women.

KEYWORDS: resveratrol, postmenopause, arterial hypertension, cognitive function, quality of life.

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INTRODUCTION

Menopause is a physiological process in a woman's life, bringing her closer to the stage of reproductive aging [1]. Menopause itself is diagnosed retrospectively 12 months after the cessation of menstruation [2]. The clinical importance of this period lies both in temporary (vasomotor symptoms, sleep disturbances, depression) and long-term changes in health (decreased bone mineral density, urogenital symptoms, increased blood pressure), which lead to a decrease in quality of life and hinder adaptive aging [3-6]. Estrogens play an important role in cognitive processing and neuronal function. It is hypoestrogenism in the perimenopausal period that is associated with a number of cognitive changes, in particular, a decrease in the speed of information processing and deterioration of verbal memory [7, 8].

There are three main estrogens: estradiol (E2), estrone (E1), and estriol (E3). E2 is the most physiologically significant because it has the highest affinity for the intracellular estrogen receptors ERα and ERβ [9]. The brain is one of the key target organs for the action of sex hormones. It has been found that classical estrogen receptors (ERα/β) are localized in areas responsible for cognitive functions [10]: in the hippocampus [11, 12], medial prefrontal cortex [13], basal forebrain [14], and the striatum [15, 16]. Estrogens are considered neuroprotective hormones that participate in the regulation of the cholinergic and dopaminergic systems of the brain, ensuring the processes of memory, learning, attention, and cognitive flexibility [17].

Brain aging and associated cognitive dysfunction occur simultaneously with endocrine aging. Memory impairment is common in the postmenopausal period, negatively affecting women's psychophysical health [18, 19]. The proportion of postmenopausal women in the general population is increasing due to global population aging [20, 21]. At the same time, women are more likely to develop chronic degenerative diseases of the nervous system, such as Alzheimer's disease, compared to men of the same age [22].

Polyphenols are secondary plant metabolites that have a wide range of mechanisms, such as antioxidant, anti-inflammatory, immunomodulatory, regulation of intestinal microbiota, and others [23-25]. Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a natural phenolic compound found in red wine, has attracted considerable attention for its potential to prevent cognitive decline [26, 27]. This property of resveratrol, especially its biologically active isomer – trans-resveratrol, can be implemented through several mechanisms, including its activation of estrogen receptors (ER), which increases the bioavailability of nitric oxide and thereby promotes endothelium-dependent vasodilation necessary for cerebral perfusion [28]. In studies on rats, resveratrol has demonstrated a protective effect against neurodegenerative diseases by enhancing neurotransmitter secretion, increasing the production of new neurons, and reducing neuroinflammation and oxidative stress [29-31]. Several studies have shown that resveratrol intake in

the postmenopausal period led to improved mood and cognitive function, accompanied by enhanced neurovascular interaction [32, 33]. These data indicate the potential ability of regular resveratrol consumption to slow cognitive aging in postmenopausal women [34]. Resveratrol is also known to have a positive effect on molecular markers of myocardial stress and cardiovascular risk [35, 36], preventing the development of chronic heart failure [37], which is associated with cognitive decline [38].

AIM

The aim of the study was to evaluate the effect of trans-resveratrol on cognitive function and quality of life in postmenopausal women.

MATERIALS AND METHODS

A prospective randomized controlled clinical study was conducted in parallel groups. The study involved 88 postmenopausal women.

The inclusion criteria were as follows: female gender, postmenopausal period, grade I-II arterial hypertension (AH), stage I-II.

Exclusion criteria were as follows: presence of neurological disorders, clinical depression, suspected dementia, artificial early menopause, alcohol/drug dependence, intolerance or allergic reaction to microcrystalline cellulose, grapes, red wine or blueberries, verified oncological, endocrine, rheumatic diseases, significant renal or hepatic impairment, stage C or D heart failure.

Patients were examined at the clinical base of the Department of Propaedeutics of Internal Medicine of Poltava State Medical University at the Municipal Enterprise "3rd City Clinical Hospital of Poltava City Council" in Poltava.

The study was guided by the principles and provisions of the Helsinki Declaration, the Council of Europe Convention on Human Rights and Biomedicine, and other founding documents on medical and biological research and the principles of bioethics. All patients signed an informed consent form to participate in the study.

Patients were randomized into two groups: study (n=55) and comparison (n=33). All patients received drug treatment for arterial hypertension, ACEI/ARB (angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and β-blockers), in accordance with the current recommendations of the European Society of Cardiology (ESC) for the treatment of high blood pressure and hypertension [39]. Patients in the study group were additionally prescribed resveratrol at a dose of 500 mg once a day for 3 months. Revers from the pharmaceutical company OmniPharma was chosen as the resveratrol preparation.

The examination of patients before and after the three-month course of treatment included clinical, laboratory, and psychometric methods. Patients underwent body weight registration, anthropometry with subsequent calculation of body mass index (BMI), and blood pressure (BP) measurement. Blood pressure was measured in a sitting position after a 10-minute rest three times at two-minute intervals during monthly visits using a Microlife BP AG 1-30 mechanical tonometer (Switzerland), as well as through home monitoring with recording of readings in a BP diary issued at the beginning of the study.

Laboratory tests included assessment of the lipid profile (total cholesterol (TC), mineral and vitamin status with determination of magnesium, ionized calcium, and 25-hydroxyvitamin D levels in blood serum and were performed in a certified (ISO 10012:2005) clinical diagnostic laboratory of the private enterprise Medical Laboratory "Analityka".

Psychometric assessment methods included the Montreal Cognitive Assessment (MoCA) test, the EQ-5D-5L (EuroQol Group) and MENQOL (Menopause-Specific Quality of Life Questionnaire) questionnaires.

The MoCA test is a standardized screening tool for detecting mild cognitive impairment by assessing key domains of cognitive functioning (memory, attention, language, executive functions, orientation, and visuospatial skills). The maximum score is 30, with a score of 26 or higher considered normal cognitive functioning. Lower scores indicate possible mild or moderate cognitive impairment [40, 41].

Health-related quality of life was assessed using the EQ-5D-5L questionnaire [42]. The methodology included two components: the EQ-5D index, which reflects health status across five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and the EQ-5D-VAS, a visual analog scale for self-assessment of overall health, where 0 points corresponds to the worst possible health condition and 100 points corresponds to the best possible health condition [43].

Menopause-related quality of life was assessed using the MENQOL questionnaire, which contains 29 items grouped into four domains: vasomotor, psychosocial, physical, and sexual. Each item is rated on a 7-point scale, where higher scores reflect more severe symptoms and lower quality of life [44, 45].

Statistical calculations were performed using KyPlot 6.0 software. The Shapiro-Wilk test was used to assess the normality of the distribution. In the case of normal distribution, the paired Student's t-test was used; in the case of distribution that differed from normal, the Mann-Whitney U-test was used. The data were presented as M±SD, where M is the mean and SD is the standard deviation. In the case of a distribution that differed from normal, the results were presented as the median (Me) and interquartile range (IQR), (Q1; Q3), where Q1 and Q3 are the first and third quartiles, respectively. The difference in data was considered significant at a significance level of $p<0.05$.

ETHICS

This work complies with the principles of the Declaration of Helsinki.

FRAMEWORK

This research work is a part of the clinical study "Clinical and pathogenetic aspects of the development of chronic heart failure in postmenopausal women and ways to correct

the identified disorders" on the effect of trans-resveratrol on cardiometabolic markers, bone mineral density, cognitive function, and well-being in postmenopausal women.

RESULTS

At the beginning of the study, all patients in the cohort had elevated blood pressure, which was mainly systolic. In 37.5% of women, insufficient levels of 25(OH)D were found in the blood, 23.9% had a deficiency, and the entire cohort had elevated total blood cholesterol. In addition, 70.5% of women were overweight, 22.7% were obese (grade I), 6.8% were obese (grade II), and the rest of the patients were of normal weight.

No statistically significant differences in the studied indicators were found between the study and comparison groups. The baseline indicators of the study cohort are shown in Table 1.

When assessing key micronutrients involved in the regulation of cognitive functions after three months of therapy, no statistically significant dynamics of 25(OH)D levels were found in both study groups (p=0.498): in the study group and the comparison group, the values of this indicator were 25.90±9.45 ng/mL and 27.33±9.72 ng/mL, respectively. Blood cholesterol levels also did not change significantly: in the study group – 6.28±1.11 mmol/L; p=0.247, in the comparison group – 6.37±1.25 mmol/L; p=0.296.

However, under the influence of resveratrol, a positive trend was observed in serum magnesium levels, which amounted to 0.80±0.06 mmol/L; p=0.0013, in contrast to the comparison group, where there were no statistically significant changes in this indicator (0.79±0.05 mmol/L; p=0.1941).

The level of ionized calcium in the study group decreased (1.27±0.05 mmol/L; p=0.009), while in the comparison group, the value of this indicator did not change statistically (1.28±0.04 mmol/L; p=0.707).

At the end of the three-month course of therapy, a significant decrease in systolic BP was noted in both the study group (128.74±6.08 mmHg; p=0.0001) and the control group (129.12±4.66 mmHg; p=0.0001). However, diastolic BP decreased significantly only in group I under the influence of resveratrol and amounted to 80.00±7.54 mmHg; p=0.0001.

According to the results of cognitive function screening using the MoCA scale, it was found that 20% of participants (18 people) had preserved cognitive function, while 80% (70 people) had mild cognitive dysfunction. No moderate or severe cognitive impairment was detected (Fig. 1).

In the study group, after three months of resveratrol administration, a positive trend in cognitive function was observed (25.92±1.98 vs. 23.74±1.73; p<0.001), unlike the comparison group (25.24±1.69 vs. 25.25±1.47; p>0.05), where no significant changes were recorded.

According to the EQ-5D-3L questionnaire, before the start of therapy, the EQ-5D index in the study group was 0.825 (0.755; 0.870), EQ-5D-VAS was 70 (60; 80), in the comparison group – 0.825 (0.785; 0.845) and 70 (60; 70), respectively. No statistically significant differences between the groups were found.

At the end of the three-month treatment course, patients who took resveratrol reported a reduction in fatigue, increased energy levels, and improved performance more often than those in the control group. This was accompanied by a significant improvement in quality-of-life indicators: the EQ-5D index in group I was 0.885 (0.825; 0.985) (p<0.001), EQ-5D-VAS – 80 (70; 85) (p<0.001).

Positive changes in these indicators also occurred in group II (comparison): the EQ-5D index increased significantly and amounted to 0.825 (0.785; 0.93), p<0.05, the EQ-5D-VAS value also increased – 70 (60; 80), p<0.01, but to a lesser extent than under the influence of resveratrol (p<0.05) (Fig. 2, Fig. 3).

Table 2 shows the scores for all MENQOL domains. At the beginning of the study, the entire cohort reported night sweats, anxiety/nervousness, and difficulty sleeping, which resulted in significantly higher scores in the physical and vasomotor domains. The average scores for the psychosocial and sexual domains were slightly lower. The values of the studied domains in the comparison group before and

Table 1. Clinical and laboratory characteristics of the study groups

Indicator, unit of measurement	Statistical indicator	Study group study (n=55)	Group comparison (n=33)	P-value
Age, years	M±SD	51.6±0.5	52.4±0.3	p = 0.147
Duration of postmenopause, years		2.2	2.3±0.1	p = 0.575
Systolic blood pressure, mmHg		147.65±0.8	146.5±0.8	p = 0.391
Diastolic BP, mmHg		83.69±0.8	81.6	p = 0.135
BMI, kg/m2		29.9±1.2	27.8±0.6	p = 0.118
Total 25(OH)D, ng/mL		28.27±9.37	24.93±8.99	p = 0.168
Ionized calcium, mmol/L		1.29±0.04	1.28±0.04	p = 0.460
Magnesium, mmol/L		0.76±0.05	0.77±0.04	p = 0.331
Total cholesterol, mmol/L		6.45±0.14	6.22±0.20	p = 0.349

Source: compiled by the authors of this study

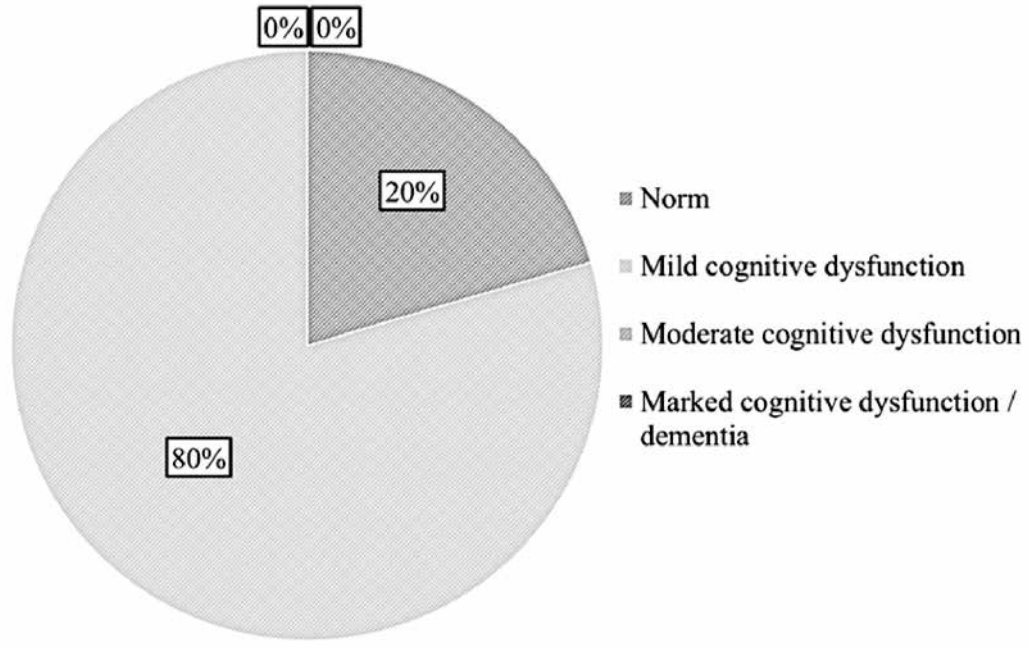

Fig.1. Distribution of patients according to MoCA test results

Picture taken by the authors

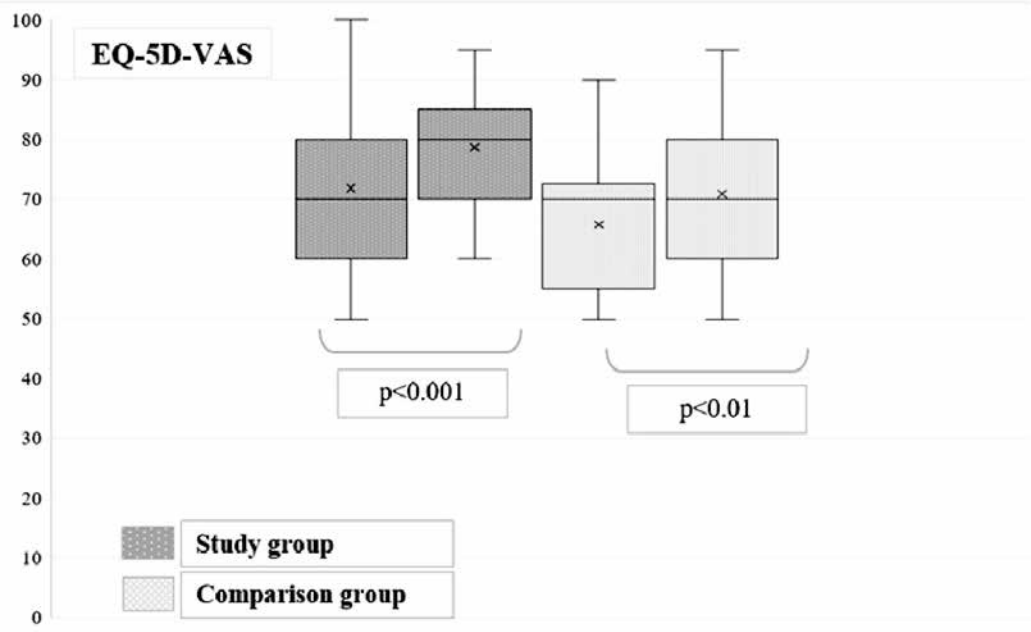

Fig. 2. Dynamics of the subjective status of patients under the influence of therapy according to the EQ-5D-3L questionnaire (according to the EQ-5D-VAS scale)

Picture taken by the authors

after the three-month course of treatment did not differ statistically. In contrast, the study group showed positive dynamics in the vasomotor, psychosocial, physical, and sexual domains (p=0.001).

DISCUSSION

Our results suggest that one of the key mechanisms of resveratrol action is its ability to activate cerebral estrogen receptors, particularly ERα and ERβ. Activation of these receptors can modulate synaptic transmission and neuronal activity in structures critical for cognitive processes, such as the hippocampus. Previous experimental data indicate that stimulation of estrogen receptors promotes an increase in dendritic spine density and the formation of new synaptic contacts on pyramidal neurons, reflecting enhanced neuroplasticity [46, 47]. Probably due to these mechanisms, our study observed a significant improvement in cognitive performance on the MoCA scale in the group of women who received resveratrol, which may indicate its potential neuroprotective and cognitive-modulating effects. Other clinical studies have found that taking resveratrol at a dose of 75 mg twice daily for 12 months improved cognitive function and vascular reactivity in the brain in menopausal women [33].

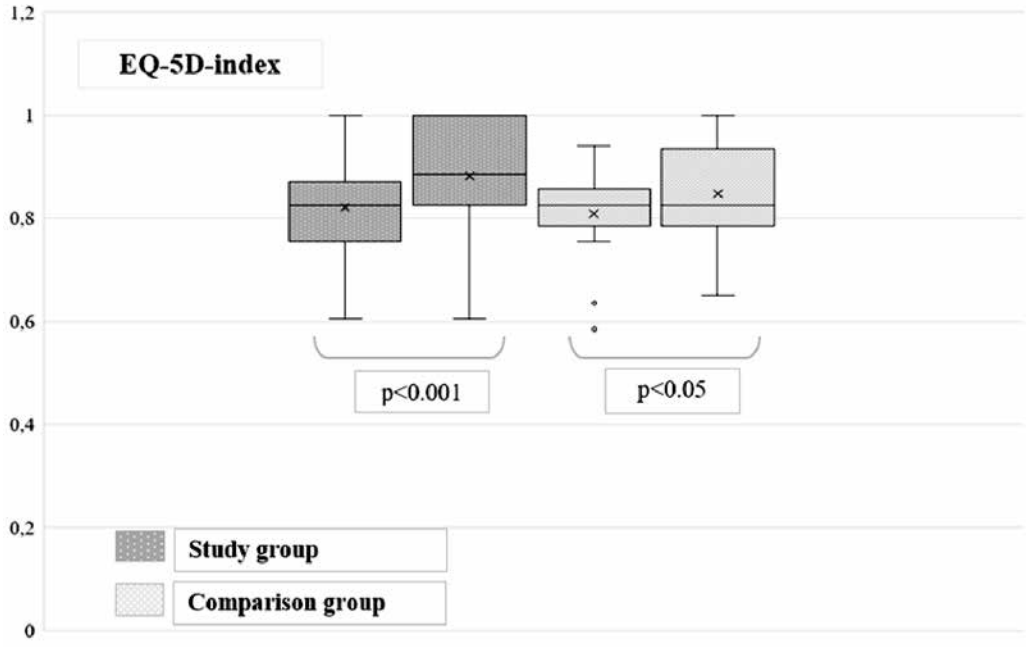

Fig. 3. Dynamics of patients' subjective status under the influence of therapy according to the EQ-5D-3L questionnaire (according to the EQ-5D index)

Picture taken by the authors

Table 2. Dynamics of menopause symptom scores and related quality of life in the study groups

Group / Indicator*	Statistical indicator	MENQL: vasomotor domain		MENQL: psychosocial domain		MENQL: physical domain		MENQL: sexual domain	
		pre-Tx	post-Tx	pre-Tx	post-Tx	pre-Tx	post-Tx	pre-Tx	post-Tx
Study group I, n=55	M±SD	4.20±1.87	3.09±0.24	3.62±1.54	2.60±1.18	4.0±1.27	2.94±1.29	3.62±1.78	2.69±1.45
	p	<0.001		<0.001		<0.001		<0.001	
Comparison group II, n=33	M±SD	3.11±1.77	3.40±1.94	3.77±1.28	3.99±1.44	4.20±1.14	3.94±1.14	2.89±2.00	3.10±2.02
	p	>0.05		>0.05		>0.05		>0.05	

*Note: * - data presented in points*

Source: compiled by the authors of this study

Despite the fact that there were no changes in 25(OH)D levels, it can be assumed that resveratrol does not affect hydroxylation in the liver, but rather on the local activity of calcitriol (1,25(OH)$_2$D) or on the expression of vitamin D receptors (VDR), which may alter the balance between Ca^{2+} absorption in the intestine and its utilization in tissues [48].

The dynamics of calcium content under the influence of resveratrol probably occurred through the influence on cellular calcium metabolism by stimulating osteoblast activity and increasing the transition of Ca2+ from plasma to bone tissue [49, 50].

No scientific literature sources have been found that would indicate a direct effect of resveratrol on the regulation of magnesium levels in blood or tissues. However, the increase in this indicator in the study group is probably due to the indirect effect of resveratrol on the expression of Claudin-16/19 transport proteins and Transient Receptor Potential Melastatin 6/7 (TRPM6/TRPM7) magnesium, which is confirmed by data from a number of researchers [51]. With its anti-inflammatory and antioxidant effects, resveratrol is able to exert corresponding effects in the intestine by modulating the intestinal microbiome through an increase in the number of Akkermansia and Lactobacillus bacteria, potentially improving the absorption and transport of Mg^{2+}, especially in cases of initially reduced absorption [52, 53].

The improvement in the MENQOL domains (vasomotor, psychosocial, physical, and sexual) in the study group can be explained by several interrelated biological mechanisms of resveratrol.

Firstly, resveratrol is a phytoestrogen that can act as a selective estrogen receptor modulator, improving endothelial function and vasodilation, which is especially important in postmenopausal conditions [54].

Secondly, resveratrol improves endothelial function and nitric oxide bioavailability [55], which mediates a reduction in vasomotor symptoms of menopause (hot flashes) and improves quality of life, which is also confirmed by the results obtained on the EQ-5D-VAS scale and the EQ-5D index.

Thirdly, resveratrol activates signaling pathways associated with the protein sirtuin-1 (SIRT1) and coactivator 1 gamma receptor activated by peroxisome proliferator alpha (PGC-1α), which support mitochondrial function, reduce oxidative stress and chronic inflammation, which may contribute to improving both physical condition and cognitive functioning. For example, in cell studies, resveratrol activated the relevant pathways of aging and cell survival [56].

These numerous effects of resveratrol-modulation of estrogen receptors, improvement of endothelial function, neuroprotection, antioxidant activity, etc.–may cause positive changes, which are reflected in the correction of MENQOL domain values: a reduction in vasomotor symptoms, improvement in psychoemotional state, physical energy, sexual comfort, and quality of life according to the EQ-5D-VAS scale and EQ-5D index.

CONCLUSIONS

The results of the clinical study demonstrate the positive effect of trans-resveratrol at a dose of 500 mg per day on cognitive functioning according to the MoCA test and quality of life according to the EQ-5D-3L and MENQOL questionnaires. The use of resveratrol can counteract age-related and reproductive aging-related cognitive decline in women.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Health service accessibility and psychological distress among displaced populations during the armed conflict: A cross-sectional survey

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ABSTRACT

Aim: To quantify barriers to access to essential health services and describe patterns of psychological distress and help-seeking among displaced populations during the armed conflict in Ukraine.

Materials and Methods: A cross-sectional questionnaire captured displacement status, linkage to primary care (declaration), perceived accessibility, barriers in the previous 6 months, awareness of reimbursement medicines, unmet service needs, and psychological symptoms within the last 2 weeks. The dataset (n=450) comprises anonymized real-world responses collected in this study.

Results: The 48,4% of respondents were classified as currently displaced, and 75,8% reported a primary care declaration. Primary care was rated fully accessible by 20,9%, whereas 42,7% reported difficult/very difficult access. Appointment unavailability (61,6%), lack of medicines (49,8%), and high service costs (40,0%) were common barriers. Sleep disturbance (37,6%) and anxiety/panic (36,2%) were frequent; 18,7% reported seeking any support for mental health needs.

Conclusions: In this cross-sectional survey, access constraints clustered around appointment availability, medicine supply, and affordability, while psychological symptoms were frequent and support-seeking remained limited. Interventions should combine primary care navigation and capacity measures with integrated, stigma-sensitive mental health pathways.

KEYWORDS: primary health care, mental health, refugees

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INTRODUCTION

The armed conflict in Ukraine has driven unprecedented internal and cross-border displacement, increasing vulnerability to interruptions in essential health services and worsening mental health outcomes [1, 2]. Displaced populations experience cumulative access barriers including administrative constraints, limited-service capacity, affordability barriers, and disrupted continuity with primary care providers [2, 3]. Health system resilience – the ability to maintain core functions during shocks and adapt through learning – has become a central framework for evaluating service delivery under crisis [4]. In conflict-affected contexts, primary care typically serves as the entry point to care and referral coordination, but performance is sensitive to workforce shortages, supply chain disruptions, and patient navigation gaps [5, 6]. Psychological symptoms frequently co-occur with unmet physical health needs, while stigma and low awareness of available pathways constrain help-seeking [7, 8].

AIM

The aim of the study was to quantify barriers to access to essential health services and describe patterns of psychological distress and help-seeking among displaced populations during armed conflict in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN

Cross-sectional survey instrument including displacement status, demographic characteristics, primary care linkage (declaration), perceived accessibility of primary care, barriers to care in the prior 6 months, awareness/use of medication reimbursement, unmet needs for selected services, and psychological symptoms and help-seeking within the last 2 weeks.

DATA SOURCE

This manuscript reports findings from a real-world cross-sectional survey (n=450). Responses were collected using a structured questionnaire and anonymized prior to analysis. No direct personal identifiers were included in the analytical dataset. Data collection was conducted in 2025 using a structured questionnaire administered both online and offline through partner healthcare facilities and community networks. Respondents reported current residence across multiple Ukrainian regions; the largest shares were from Dnipropetrovsk region, Kharkiv region, Kyiv, Zaporizhzhia region, Lviv region, Odesa region and Kyiv region.

The age groups and sex distribution of the total sample of respondents (n=450) is presented in Table 1.

Table 1. The age groups and sex among the enrolled respondents (n=450)

Characteristics		N	%
Males		185	41,1
Females		265	58,9
Age group (years old)	18-29	124	27,6
	30-44	163	36,2
	45-59	108	24,0
	60+	55	12,2

Source: compiled by the authors of this study

STATISTICAL ANALYSIS

All analyses were performed in Python 3.13.9 within the Anaconda Distribution (version 25.11.1.). Qualitative indicators as absolute frequency and relative frequency (%). Multi-select questions were decomposed into binary items and summarized with multiple-response frequencies. The multivariate associations were evaluated using the $\chi 2$ test with effect size as Cramér's V criterion; bivariate ones – by the use of Fisher`s exact test and φ criterion. Monotonic associations between the rank variables were assessed by Spearman's correlation coefficient (ρ). The two-sided p-value <0,05 was considered as statistically significant.

ETHICS

The present manuscript is based on anonymized real-world data collected from adult participants using a structured questionnaire. The study was conducted in accordance with the Declaration of Helsinki and the Convention on Human Rights and Biomedicine (Oviedo Convention) [9, 10]. Participation was voluntary, and informed consent was obtained from all participants prior to questionnaire completion. No directly identifying information was collected, and the dataset was fully de-identified prior to analysis; personal identifiers and any linkage keys were not retained, and the analytical dataset is stored separately from any contact or administrative information. Where required by local regulations and institutional policies, the study protocol was reviewed and approved by an appropriate local (bio)ethics committee, and data handling complied with applicable data protection requirements.

FRAMEWORK

The study was conducted as a fragment of the scientific project «Medical and social justification, development and implementation of the «Center of innovative healthcare technologies» model based on the trinity of science, education and practice in the work of a multidisciplinary healthcare institution and determining its role in the formation of a single medical space» (state registration number: 0125U000318; term: 2025-2029).

RESULTS

Among the total sample of respondents (n=450), 48,45 % were classified as currently displaced, and 8,0% as previously displaced (Fig. 1). A primary care declaration was reported in 75,8% (341/450), and the use of reimbursement medicines program – by 148 (32,9 %) respondents.

Perceived primary care accessibility was rated as fully accessible in 20,9% (94/450), rather accessible in 36,4% (164/450), mostly difficult in 26,0% (117/450), and very difficult in 16,7% (75/450) (Fig. 2). Therefore, more than 40 % of respondents reported the difficult access pattern. It should be noted that, the reported access difficulty did not differ significantly by the displacement status.

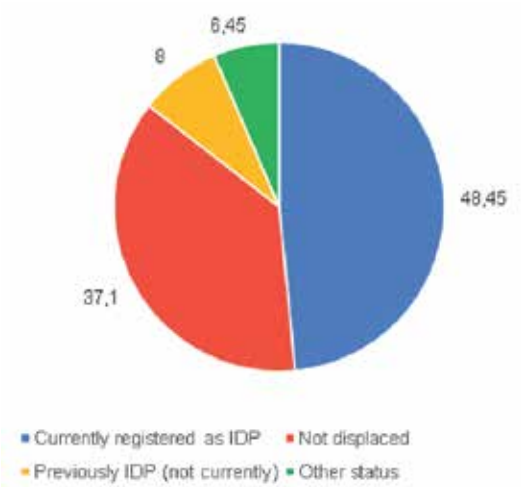

Fig. 1. The displacement status distribution (%) among the enrolled participants (n=450)

Note: IDP – internally displaced person
Picture taken by the authors

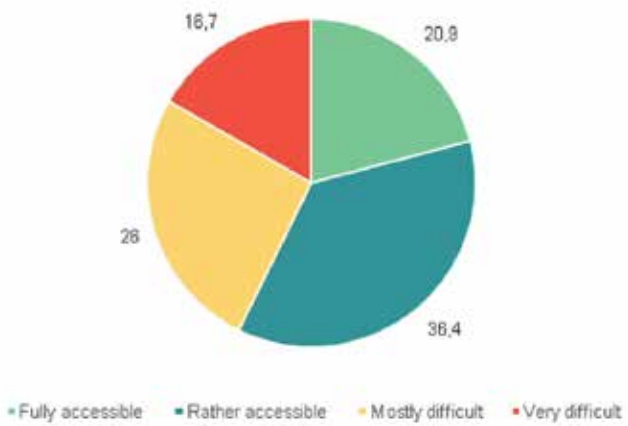

Fig. 2. The perceived accessibility patterns of primary care services (%) among the enrolled participants (n=450)

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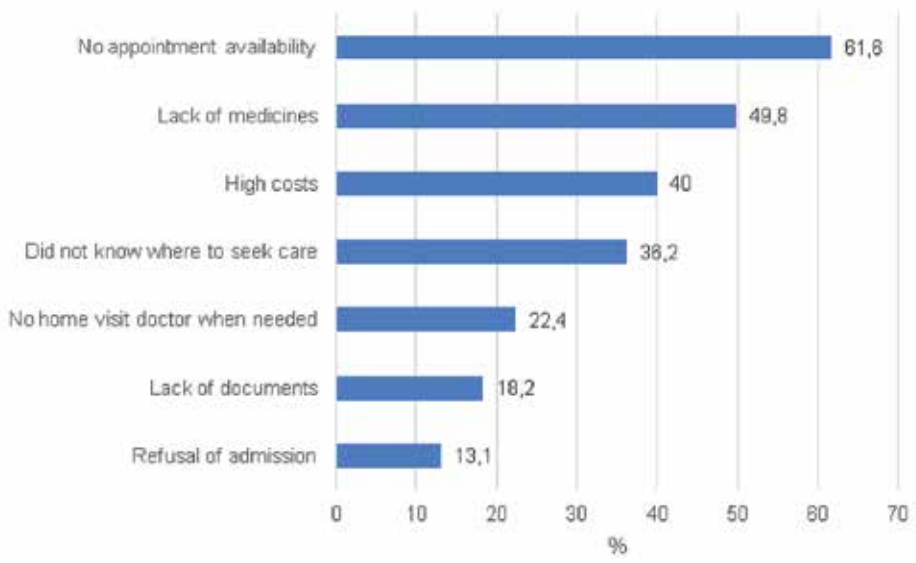

Fig. 3. Reported barriers to health care access in the last 6 months (multiple responses [%]; n=450)

Picture taken by the authors

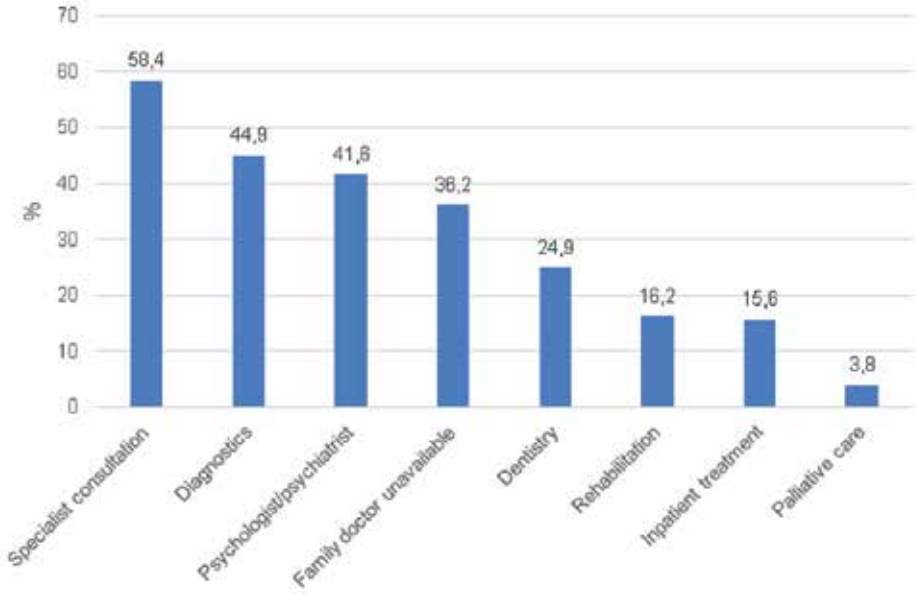

Fig. 4. Reported unmet needs for selected health services (multiple responses [%]; n=450)

Picture taken by the authors

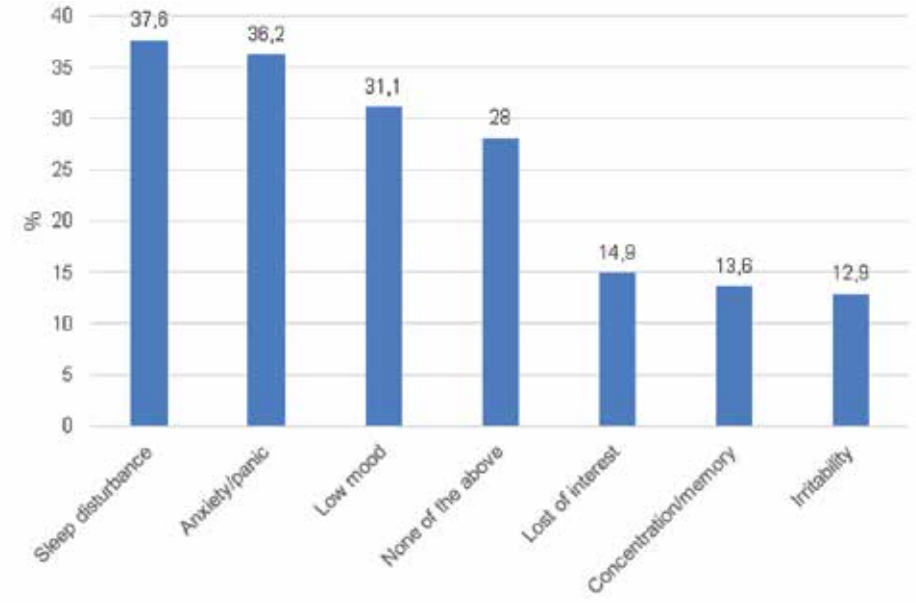

Fig. 5. Self-reported psychological symptoms in the last 2 weeks (multiple responses [%]; n=450)

Picture taken by the authors

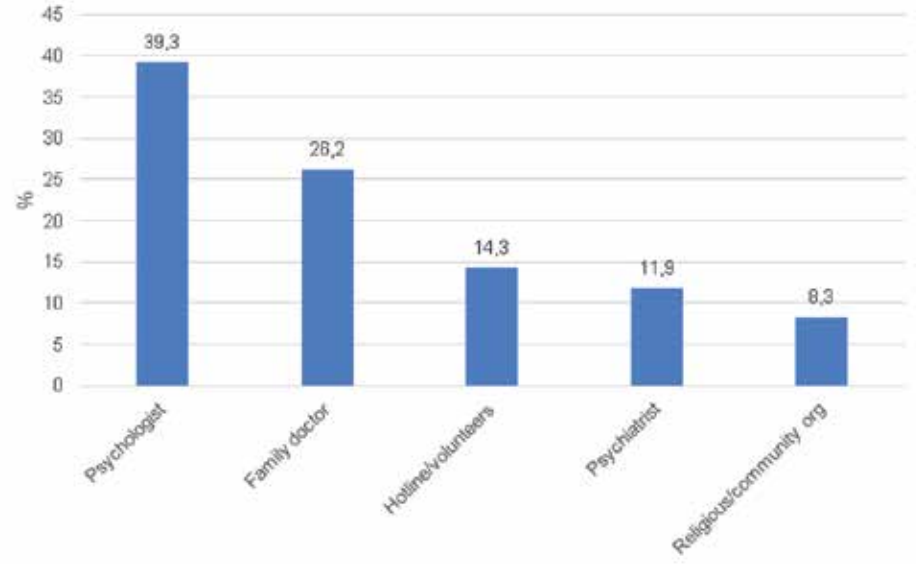

Fig. 6. The reported sources of support for mental health needs among the respondents who mentioned any support (multiple responses [%]; n=84)

Picture taken by the authors

The most frequent barriers to health care access in the prior 6 months were inability to book an appointment (61,6%), lack of medicines (49,8%), and high cost of services (40,0%) (Fig. 3). Moreover, the barrier burden was associated with higher access difficulty (ρ=0,64; p<0,001).

The unmet needs most for selected health services frequently included specialist consultations (58,4%), diagnostic services (44,9%), and psychologist/psychiatrist consultations (41,6%) (Fig. 4).

Among the self-reported psychological symptoms, sleep disturbance (37,6%), persistent anxiety/panic (36,2%), and low mood (31,1%) were the most frequent ones (Fig. 5).

Importantly, only 84 (18,7%) respondents reported seeking any support for mental health needs. Furthermore, the need for psychologist assistance was mentioned as the most frequent option for the responders who reported the need for mental health support (Fig. 6).

DISCUSSION

The present cross-sectional survey provides a concise real-world snapshot of access to health services and psychological distress among adults living in a conflict-affected setting in Ukraine. Three findings are particularly salient. First, perceived difficulty of accessing primary care was common: more than 40% of respondents rated access as mostly or very difficult. Second, the most frequently reported barriers clustered around appointment availability, medicine supply, and affordability. Third, psychological symptoms were prevalent, whereas formal help-seeking for mental health needs remained low.

Notably, perceived access difficulty did not differ significantly by displacement status. In the context of a protracted conflict, this pattern may reflect system-wide constraints affecting both displaced and non-displaced residents, where generalized capacity limitations (workforce shortages, disrupted referral pathways, and constrained diagnostic/medicine supply) can dominate over individual legal status or place of origin. This finding also suggests that "displacement" alone may be an insufficient stratifier for access inequities in Ukraine and should be complemented by more granular determinants, such as displacement duration, housing stability, settlement type, socioeconomic vulnerability, and local service density, which have been linked to heterogeneous access patterns in displaced populations [2, 3, 11-13].

The barrier profile reported in the prior 6 months highlights a combined administrative-supply-financial bottleneck: inability to book an appointment (61,6%), lack of medicines (49,8%), and high cost of services (40,0%). The observed monotonic association between barrier burden and perceived access difficulty supports an interpretation that barriers accumulate and jointly shape access experience rather than acting as isolated obstacles. From a health systems and resilience perspective, this "stacking" of constraints is consistent with shock-driven disruptions in routine service delivery, increased demand, and reduced responsiveness under stress [4, 14]. Practically, it implies that addressing a single bottleneck (e.g., scheduling) may have a limited effect unless accompanied by parallel measures in supply continuity (essential medicines, diagnostics) and financial protection.

Unmet needs were most frequently reported for specialist consultations (58,4%) and diagnostic services (44,9%), indicating pressure points beyond primary care. This finding aligns with a common pathway in disrupted health systems: primary care may remain the formal entry point (with 75,8% reporting a declaration), yet downstream service capacity – specialist availability, diagnostic throughput, referral logistics – can remain constrained, translating into delayed or foregone care. Strengthening referral pathways, expanding diagnostic capacity (including contracted/outsourced diagnostics where feasible), and establishing transparent triage criteria may therefore be as important as improving first-contact access.

Mental health findings reinforce a well-documented paradox in crisis-affected populations: high symptom burden

alongside low professional help-seeking. Sleep disturbance (37,6%), persistent anxiety/panic (36,2%), and low mood (31,1%) were frequent, but only 18,7% reported seeking any support. Reported preferences among those seeking support emphasize demand for psychologist services, which may signal perceived acceptability of psychological counseling relative to psychiatric care, as well as stigma and limited awareness of available pathways [7, 8, 15]. For service planning, these results support "no-wrong-door" approaches: brief screening and psychoeducation embedded in primary care, clear referral algorithms to community-based mental health services, and proactive communication about where and how to obtain support, particularly in settings where formal service navigation is difficult.

Methodologically, the study benefits from a structured instrument, multi-region coverage, and analysis strategies appropriate for cross-sectional survey data (multiple-response decomposition, effect size reporting, and multivariable modeling). Nevertheless, the findings should be interpreted with caution due to self-reporting, potential recall bias (especially for 6-month barriers), and non-probability sampling; therefore, results should not be treated as population-level prevalence estimates. Future analyses would be strengthened by stratification and interaction testing (e.g., sex × displacement; declaration × access difficulty), sensitivity analyses using alternative outcome specifications for access difficulty, and approaches that account for clustering by region or recruitment channel (facility/community network) to improve policy relevance and inference.

CONCLUSIONS

Perceived difficulty in accessing primary care was reported by over 40% of respondents. The leading barriers in the prior 6 months were appointment unavailability, lack of medicines, and service unaffordability, and a higher cumulative barrier burden was strongly associated with greater perceived access difficulty. Unmet needs were most frequently reported for specialist consultations and diagnostic services, while psychological symptoms – particularly sleep disturbance, anxiety/panic, and low mood – were common. Despite this symptom burden, formal help-seeking for mental health needs was limited.

Health system responses in conflict-affected settings should prioritize: (1) improving appointment availability through practical scheduling and triage pathways; (2) strengthening continuity of essential medicines and diagnostic capacity; (3) reducing financial barriers via targeted protection mechanisms and clear patient navigation support; and (4) integrating stigma-sensitive mental health screening, psychoeducation, and referral routes into primary care and community entry points, supported by routine monitoring with standardized indicators and clear visual reporting. The introduction of compulsory health insurance establishes institutional conditions for reducing financial barriers to accessing medical services and ensuring their sustainable financing. This, in turn, contributes to improving the availability and quality of healthcare – particularly at the primary care level – for internally displaced persons and individuals affected by military actions.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Dynamics of psychosomatic health indicators in future law enforcement officers under the influence of high-intensity loads

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ABSTRACT

Aim: To investigate the impact of high-intensity interval training (HIIT) on cadets' somatic and mental health indicators during their academic training under martial law.

Materials and Methods: The research involved 98 male cadets, who were divided into three groups: group No. 1 (n=21), whose cadets engaged in HIIT; Group No. 2 (n=53), whose cadets were involved in other sports; Group No. 3 (n=24), whose cadets did not engage in additional sports. Research methods: theoretical analysis and generalization of literature, biomedical methods, psychological methods, statistical methods.

Results: In most tests, cadets in Group No. 1 had significantly better somatic and mental health indicators during their senior training years than those in Group No. 3, indicating a more pronounced effect of HIIT on the morphofunctional and psycho-emotional state of cadets during their academic training. At the same time, no significant difference was found between the indicators of cadets in Group No. 1 and Group No. 2, which indicates the effectiveness of additional motor activity and sports training sessions in improving the psychosomatic health of cadets.

Conclusions: The positive effect of HIIT on indicators of psychosomatic health among future law enforcement officers has been demonstrated. This underscores the advisability of the broader implementation of HIIT in the physical training of future law enforcement officers during their academic training at higher educational institutions with a specific learning environment, to improve their psychosomatic health and, accordingly, increase the effectiveness of their future service activities.

KEYWORDS: somatic health, mental health, cadets, future law enforcement officers, HIIT

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INTRODUCTION

The crisis Ukraine is currently experiencing affects all components of society. Therefore, the educational sphere is a key factor in training specialists who can quickly adapt to the constant or situational conditions of the professional environment and perform their professional activities at a high level [1]. At the same time, political and socio-economic changes, the fight against the pandemic, and the ongoing war in Ukraine require new approaches to solving educational and applied tasks in the training of future specialists. A critical task under current conditions is the development of a new system for training law enforcement specialists, which is conditioned by the current military and political situation in Ukrainian society [2, 3].

Scientists classify the activities of law enforcement agencies as a mixed profession, which is carried out in specific, complex external conditions, requiring law enforcement officers to have high mental stability, developed motor skills (strength, speed, endurance, and agility), readiness to use all available means to prevent offences, and the ability to act at any time and under any conditions [4]. Therefore, one essential task of the educational process for future law enforcement officers is to develop their physical and psychological readiness for law enforcement activities under extreme conditions and to strengthen their somatic and mental health throughout academic training [5].

As scientists point out [6], the Russian-Ukrainian war has led to the spread of signs of emotional instability and numerous cases of PTSD among the population, including law enforcement officers, which reduces their quality of life and negatively affects their somatic health. Therefore, scientists [7] note that in wartime, the issue of preserving the psychosomatic health of young people, including cadets – future law enforcement officers – becomes particularly relevant. From a psychological point of view, cadets are a particularly vulnerable group due to high academic requirements, social pressure, stress, and other factors that can affect their mental and somatic health [8, 9]. Regular physical exercise and participation in health- and recreational-motor activities by cadets can help address this problem, accelerating their adaptation to adverse living conditions and mitigating the negative effects of stress [10].

Today, high-intensity interval training (HIIT) is widely popular worldwide, including among cadets in higher educational institutions with a specific learning environment [11, 12]. HIIT is a model of physical activity that combines short intervals of intense exercise with periods of low-intensity recovery. This training format increases endurance, accelerates metabolism, and effectively burns calories even after the training session [13, 14]. HIIT is suitable for law enforcement officers across a

range of physical fitness levels, as its intensity and duration can be adapted to individual capabilities. According to experts [15, 16], HIIT is also popular due to its short training duration. HIIT can be effective in improving both the somatic and mental health of cadets during their academic training under martial law conditions (e.g., in distance-learning environments, during prolonged alarms, in shelters, etc.).

AIM

The aim is to investigate the impact of high-intensity interval training on cadets' somatic and mental health indicators during their academic training under martial law.

MATERIALS AND METHODS

PARTICIPANTS

The research, conducted in the 2022-2025 years, involved 98 male 1st – 3rd year cadets from the Odesa State University of Internal Affairs (OSUIA, Odesa, Ukraine) majoring in 262 "Law Enforcement Activities" specialty.

To achieve the research aim, based on the results of the introductory survey in the 1st training year (2022), we formed three groups of cadets: Group No. 1 (n=21) included cadets who attended a sports club on HIIT under the guidance of a coach during their sporting and mass participation activities (SMPAs); Group No. 2 (n=53) included cadets from the same training year who also participated in various sports (combat sambo, kettlebell lifting, functional multi-event competitions, volleyball, futsal) during their SMPAs hours; Group No. 3 (n=24) included cadets who, during their academic training, attended only compulsory physical training sessions and did not engage in additional sports; their SMPAs were conducted according to the standard program. The amount of physical activity per week (in hours) across the study groups did not differ and was 12 hours. The main difference was the content of the training sessions across groups. The groups were formed exclusively at the cadets' own request. Inclusion criteria: male cadets, willingness to engage in a particular sport during their academic training (determined by a survey at the beginning of the first semester), no health contraindications to sports; exclusion criterion: the cadet's desire to withdraw from the research at any time. Each cadet signed an informed consent form for voluntary participation in the research.

RESEARCH METHODS

Theoretical analysis and generalization of literature, biomedical methods, psychological methods, statistical methods. The method of theoretical analysis and generalization of literature was used to study scientific sources on the topic of research (24 sources from MedLine, Scopus and Web of Science databases were studied).

Biomedical methods were used to assess cadets' somatic health according to the following indicators: body mass index (BMI), vital index (VI), strength index (SI), and Robinson index (RI), somatic health level (SHL). The body mass index was calculated as body weight divided by height squared. The vital index was determined by the ratio of vital lung capacity to body weight. The ratio of the dynamometry of the stronger hand to body weight determined the strength index. The Robinson index was determined by the ratio of the product of the resting pulse and systolic blood pressure to 100. Somatic health level was determined as the sum of points for each of the above indices: 3 points or less – low SHL; 4-6 points – below average level; 7-11 points – average level; 12-15 points – above average level; 16-18 points – high level [17, 18].

Psycho-diagnostic methods were used to assess the mental health of cadets. Three methods were used: the PSM-25 Psychological Stress Scale (Lemur-Tessier-Fillion), the Stress Resilience Self-Assessment Test (S. Cohen and G. Willianson), Reactive (Situational) Anxiety Scale (C. D. Spielberger and Yu. L. Khanin) [19, 20]. The PSM-25 Psychological Stress Scale is designed to measure the structure of stress experiences. It contains 25 statements, to which respondents indicated the frequency of occurrence and rated them on a 1-8 scale, where 1=never and 8=constantly. Subsequently, the total score for all statements was calculated. Stress was assessed as follows: 99 points or less – low stress level; 100-124 points – average stress level; 125 points or more – high stress level. The Stress Resilience Self-Assessment Test required cadets to complete 10 questionnaire items. Cadets had to choose one of the suggested answers, which were evaluated as follows for questions 1, 2, 3, 7, 9, 10: never – 0, rarely – 1, sometimes – 2, quite often – 3, often – 4; for questions 4, 5, 6, 8 – never – 4, rarely – 3, sometimes – 2, quite often – 1, often – 0. The level of stress resilience was assessed based on the total number of points scored: 6.8 points and less – excellent level of stress resilience; 6.9-14.2 – good level; 14.3-24.2 – satisfactory level; 24.3-34.2 – poor level; 34.3 points and above – very poor. The Reactive Anxiety Scale included cadets' responses to 20 statements in the questionnaire, depending on how they felt at the time of testing: no, that's not true; probably true; true; entirely true. Reactive anxiety (RA) was determined by the formula: $RA=\Sigma 1 - \Sigma 2 + 50$, where $\Sigma 1$ is the sum of the numbers marked on the form for items 3, 4, 6, 7, 9, 12, 13, 14, 17, 18; $\Sigma 2$ is the sum of the numbers marked on the form for items 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20. The assessment of reactive anxiety among cadets was carried out as follows: 30 points or less – low level of reactive anxiety; 31-45 points – moderate level; 46 points or more – high level.

STATISTICAL METHODS

Statistical methods were used to process the data obtained. The compliance of the sample data distribution with the Gauss' law was assessed using the Shapiro-Wilk W test. The reliability of the difference between the indicators was determined using the Student's t-test. The reliability of the difference was set at $p<0.05$. All statistical analyses were performed using SPSS software, version 10.0, adapted for medical and biological research.

ETHICS

The procedure for organizing the study and the topic of the article were previously agreed with the Committee on compliance with Academic Integrity and Ethics of the OSUIA. Also this study followed the regulations of the World Medical Association Declaration of Helsinki. Informed consent was received from all cadets who took part in this study.

FRAMEWORK

This scientific article was carried out according to the plan of the research work of the Lviv State University of Internal Affairs for 2020-2026 „Psychological, pedagogical and sociological support of law enforcement officers» (state registration number 0113U008196).

RESULTS

The results of the dynamics of somatic health indicators of cadets from the three study groups during the academic training process are presented in Table 1.

The BMI analysis showed that in the 1st and 2nd training years, there were no significant differences among the groups ($p>0.05$). In the 3rd training year, a significant difference was observed in cadets' indicators between Group No. 1 and Group No. 3 (1.76 kg/m2; $p\leq0.05$). At the same time, no significant difference was found between Group No. 1 and Group No. 2, as well as between Group No. 2 and Group No. 3 ($p>0.05$). Overall, the analysis of the obtained indicators indicates that, in the 3rd training year, cadets' BMIs across all studied groups are within the normal range. Still, cadets who did not participate in additional sports clubs have a significantly worse BMI compared to cadets who systematically engage in sports, including using HIIT methods. During the research period, BMI remained stable in Group No. 1. In contrast, in Group No. 2 and Group No. 3, BMI increased significantly ($p\leq0.05$), underscoring the effectiveness of HIIT in burning calories in cadets' bodies.

Analysis of the VI in the study groups shows that in the 1st training year, the indicators did not differ significantly ($p>0.05$). However, in the 2nd and 3rd training years, the VI of cadets in Group No. 1 was considerably better than that of cadets in Group No. 3, by 4.31 ml/kg ($p\leq0.05$) and 5.79 ml/kg ($p\leq0.01$), respectively. Also, in the 3rd training year, the VI indicators in cadets of Group No. 2 were significantly better than in Group No. 3 by 3.51 ml/kg ($p\leq0.05$). Throughout the research, a positive trend in the VI was observed in Group No. 1 and Group No. 2, although the difference was not significant ($p>0.05$). In Group No. 3, there is a tendency toward deterioration in the VI ($p>0.05$). The analysis indicates that HIIT sessions are more effective than traditional training in improving respiratory function among cadets during their academic training. Accordingly, in cadets of Group No. 1 and Group No. 2, the level of functional capabilities of the respiratory system in the 3rd training year is assessed as "above average", and in Group No. 3, an "average" level is recorded in all training years.

The study of the SI indicators, which reflect the development of arm muscle strength relative to body weight, shows that the indicators of cadets in the 1st and 2nd training years in all groups do not differ significantly from each other ($p>0.05$). In the 3rd training year, Group No. 1 showed significantly better results than Group No. 3, with a 6.6 % difference ($p\leq0.05$). No significant differences were found between Group No. 1 and Group No. 2 ($p>0.05$). Throughout the research, the SI of cadets in all groups showed positive dynamics, but in Group No. 1 and Group No. 2, the changes were significant ($p\leq0.05$). At the same time, in Group No. 3, the effect was insignificant ($p>0.05$), confirming the more pronounced impact of conscious sports activities on the strength indicators of future law enforcement officers. The development of the muscular system in cadets in Group No. 1 is assessed as "average", in Group No. 2 – as "below average", and in Group No. 3 – as "low", which gives the right to recommend HIIT methods for the development of cadets' strength indicators during their academic training.

Assessment of the functional reserves of the cardiovascular system of cadets according to the RI indicators shows that in the 1st and 2nd training years, the indicators of cadets in all study groups do not differ significantly ($p>0.05$). In the 3rd training year, a significant difference was found between cadets in Group No. 1 and Group No. 3, amounting to 5.66 c. u. ($p\leq0.01$). No difference was found between Group No. 1 and Group No. 2. During the research, the RI indicators of cadets in all study groups improved significantly. Still, the most pronounced changes were observed in Group No. 1. Based on the RI, it can be stated that, in the 1st training year, the functional reserves of the cardiovascular system across all study groups were at the "average" level. Already in the 3rd training year, in Group No. 1 and Group No. 2, they correspond to the "above average" level, and cadets in Group No. 3 correspond to the "average" level.

The analysis of the SHL showed that, in the 1st training year, it did not differ significantly across cadets in any study group ($p>0.05$). In the 2nd training year, cadets in Group No. 1 had a substantially better SHL than cadets in Group No. 3 ($p\leq0.05$). In the 3rd training year, Group No. 1 showed the best SHL (7.06 points), which is significantly better than that of Group No. 3 by 3.54 points ($p\leq0.001$); Group No. 2 also showed a significantly better SHL than Group No. 3 ($p\leq0.001$), which indicates the positive impact of training sessions and HIIT, as well as other sports, on the health of cadets during their academic training. This is confirmed by the absence of a significant difference between Group No. 1 and Group No. 2 ($p>0.05$). During the research, the SHL of cadets in Group No. 1 and Group No. 2 significantly improved ($p\leq0.001$), whereas in Group No. 3, it did not change significantly. The SHL of cadets in Group No. 1 and Group No. 2 in the 3rd training year is assessed as average, while in Group No. 3 it is below average.

The results of the dynamics of mental health indicators of cadets in the three study groups are presented in Table 2.

Assessment of stress levels using the PSM-25 method indicates that in the 1st and 2nd training years, no significant differences were observed among the indicators across the three study groups ($p>0.05$). At the same time, the stress levels of cadets in all three groups in the 1st and 2nd training years correspond to the average level. In the 3rd training year, the stress levels in Group No. 1 and Group No. 2 were significantly lower than in Group No. 3 by 6.3 and 5.9 points, respectively ($p\leq0.05$). Still, no significant difference was found between the stress levels in Group No. 1 and Group No. 2 ($p>0.05$). Moreover, during the research period, stress levels decreased significantly among cadets in Group No. 1 and Group No. 2 ($p\leq0.05$), whereas in Group No. 3 the changes were not significant ($p>0.05$). In Group No. 1 and Group No. 2, the stress level

Table 1. The dynamics of somatic health indicators of cadets during the academic training process (n=98), X±m

Training year	Group No.1 (n=21)	Group No. 2 (n=53)	Group No.3 (n=24)	Significance of the difference		
				t1-2 (p)	t1-3 (p)	t2-3 (p)
Body mass index, kg/m2						
1st	22.00±0.39	22.71±0.16	23.01±0.33	1.68 (p>0.05)	1.91 (p>0.05)	0.82 (p>0.05)
2nd	22.28±0.41	23.17±0.18	23.38±0.41	1.91 (p>0.05)	1.90 (p>0.05)	0.47 (p>0.05)
3rd	22.55±0.44	23.39±0.23	24.31±0.49	1.69 (p>0.05)	2.67 (p≤0.05)	1.45 (p>0.05)
t1-3 (p)	0.94 (p>0.05)	2.43 (p≤0.05)	2.20 (p≤0.05)			
Vital index, ml/kg						
1st	61.48±1.31	59.34±0.86	58.43±1.45	1.37 (p>0.05)	1.56 (p>0.05)	0.54 (p>0.05)
2nd	62.14±1.20	60.14±0.83	57.83±1.38	1.37 (p>0.05)	2.36 (p≤0.05)	0.81 (p>0.05)
3rd	63.18±1.09	60.90±0.74	57.39±1.27	1.73 (p>0.05)	3.46 (p≤0.01)	2.39 (p≤0.05)
t1-3 (p)	1.00 (p>0.05)	1.37 (p>0.05)	0.54 (p>0.05)			
Strength index, %						
1st	58.6±2.15	58.8±1.22	57.6±2.24	0.08 (p>0.05)	0.32 (p>0.05)	0.47 (p>0.05)
2nd	61.2±1.88	59.1±1.07	57.7±2.06	0.97 (p>0.05)	1.25 (p>0.05)	0.60 (p>0.05)
3rd	64.7±1.34	62.0±0.86	58.1±1.98	1.70 (p>0.05)	2.76 (p≤0.05)	1.81 (p>0.05)
t1-3 (p)	2.41 (p≤0.05)	2.14 (p≤0.05)	0.17 (p>0.05)			
Robinson index, c. u.						
1st	87.67±1.24	86.89±0.78	88.07±1.26	0.55 (p>0.05)	0.25 (p>0.05)	0.80 (p>0.05)
2nd	83.54±1.20	84.86±0.72	86.77±1.22	0.94 (p>0.05)	1.89 (p>0.05)	1.35 (p>0.05)
3rd	78.89±1.15	80.71±0.64	84.55±1.11	1.38 (p>0.05)	3.54 (p≤0.01)	3.01 (p≤0.01)
t1-3 (p)	5.19 (p≤0.001)	6.13 (p≤0.001)	2.10 (p≤0.05)			
Somatic health level, points						
1st	2.62±0.54	2.93±0.28	2.96±0.58	0.51 (p>0.05)	0.36 (p>0.05)	0.04 (p>0.05)
2nd	4.85±0.52	4.15±0.27	3.07±0.53	1.19 (p>0.05)	2.40 (p≤0.05)	1.82 (p>0.05)
3rd	7.06±0.46	6.84±0.25	3.52±0.47	0.42 (p>0.05)	5.28 (p≤0.001)	6.24 (p≤0.001)
t1-3 (p)	6.23 (p≤0.001)	10.36 (p≤0.001)	0.75 (p>0.05)			

Notes: X – arithmetic mean; m – error of arithmetic mean; t – Student's test value; p – reliability value
Source: compiled by the authors of this study

in the 3rd training year is assessed as low; in Group No. 3, it is estimated as average. This indicates that additional sports activities have a positive effect on reducing stress in future law enforcement officers during their academic training in wartime conditions.

According to the stress resilience self-assessment methodology, lower scores indicate higher stress resilience among cadets. Thus, when studying the level of stress resilience of cadets, we found that in Group No. 1 and Group No. 2, already in the 2nd and 3rd training years,

Table 2. The dynamics of mental health indicators of cadets during the academic training process (n=98), X±m, points

Training year	Group No.1 (n=21)	Group No. 2 (n=53)	Group No.3 (n=24)	Significance of the difference		
				t1-2 (p)	t1-3 (p)	t2-3 (p)
Stress level						
1st	104.2±2.19	103.9±1.84	105.1±2.20	0.10 (p>0.05)	0.29 (p>0.05)	0.41 (p>0.05)
2nd	101.8±2.16	101.3±1.79	104.6±2.16	0.18 (p>0.05)	0.92 (p>0.05)	1.18 (p>0.05)
3rd	97.6±2.12	98.2±1.77	103.9±2.18	0.22 (p>0.05)	2.07 (p≤0.05)	2.03 (p≤0.05)
t1-3 (p)	2.17 (p≤0.05)	2.23 (p≤0.05)	0.39 (p>0.05)			
Stress resilience level						
1st	16.1±0.93	16.4±0.77	16.5±0.96	0.25 (p>0.05)	0.30 (p>0.05)	0.08 (p>0.05)
2nd	14.3±0.87	14.9±0.73	16.2±0.92	0.53 (p>0.05)	1.50 (p>0.05)	1.11 (p>0.05)
3rd	13.8±0.85	14.1±0.69	15.9±0.90	0.27 (p>0.05)	1.79 (p>0.05)	1.59 (p>0.05)
t1-3 (p)	1.85 (p>0.05)	2.22 (p≤0.05)	0.46 (p>0.05)			
Reactive anxiety level						
1st	42.6±0.86	43.1±0.69	42.3±0.88	0.45 (p>0.05)	0.24 (p>0.05)	0.72 (p>0.05)
2nd	40.7±0.83	41.2±0.67	41.9±0.85	0.47 (p>0.05)	1.01 (p>0.05)	0.65 (p>0.05)
3rd	38.5±0.80	38.6±0.66	41.2±0.84	0.10 (p>0.05)	2.35 (p≤0.05)	2.43 (p≤0.05)
t1-3 (p)	3.49 (p≤0.01)	4.71 (p≤0.001)	0.90 (p>0.05)			

Notes: X – arithmetic mean; m – error of arithmetic mean; t – Student's test value; p – reliability value
Source: compiled by the authors of this study

the level of stress resilience is higher than in Group No. 3. Still, no significant difference between the indicators of the study groups was found (p>0.05). It is also essential to add that in the 1st and 2nd training years, the level of stress resilience of cadets in all three groups was assessed as satisfactory, and in the 3rd training year, it was assessed as good in Group No. 1 and Group No. 2 and satisfactory in Group No. 3. During the research period, an increase in stress resilience was observed in all three groups of cadets. Still, more pronounced changes occurred in Group No. 1 and Group No. 2, where cadets additionally engaged in HIIT and other types of sports and motor activity.

According to the study of reactive anxiety among cadets, no significant differences were found among the three study groups in the 1st and 2nd training years (p>0.05). In the 3rd training year, the reactive anxiety scores in Group No. 1 and Group No. 2 were significantly better than in Group No. 3 by 2.7 and 2.6 points, respectively (p≤0.05). This indicates that additional training in HIIT and other sports effectively reduces anxiety among future law enforcement officers during their academic training. Moreover, during the research period, anxiety levels in Group No. 1 and Group No. 2 decreased significantly (p≤0.01-0.001), while in Group No. 3 they remained unchanged (p>0.05), which proves the effectiveness of additional training sessions in health and recreational physical activities and sports for improving the mental health of future law enforcement officers.

DISCUSSION

Scientists [21] note that among the main tasks of the educational process in physical training for future law enforcement officers is to improve their physical fitness, develop physical qualities, enhance whole-body function, and develop the ability to be ready for action under any conditions at any time. A modern police officer must ensure public safety, using, if necessary, sufficient force and methods; be able to distinguish between dangerous situations; and act without prejudice in all circumstances, guided by ethical standards [1].

According to scientists [22], the individual ability of specialists comprises three components: specialized, psychological, and physical training. The latter, in turn, involves the body's functional capabilities, motor skills and abilities, the development of physical qualities, and somatic health.

We believe that it is impossible to achieve a high level of specialized training (professional skills) for a law enforcement officer without a solid foundation in physical fitness and somatic health. The health of a law enforcement officer and their physical condition significantly affect their level of psychological preparedness (mental state) and specialized preparedness, as well as the quality of their professional performance. In this regard, as some researchers have rightly pointed out [3, 10], physical training plays a vital role in preparing future law enforcement officers. However, in conditions of martial law, during constant air raid alerts, in conditions of distance learning, etc., it is essential to use such means and methods of physical training that would be effective in the absence of full-fledged conditions for training (in shelters, in limited space, in field conditions), lack of equipment, and time. High-intensity interval training (HIIT) can be an effective and contemporary method of physical training for future law enforcement officers during their academic training under conditions of martial law [13]. This is proven by the indicators we have obtained.

Summarizing the research data of many scientists [14, 15], the main advantages of HIIT for cadets have been identified: high-intensity physical activities in a short period of time (10-30 minutes); the possibility of using a wide range of exercises (with weights, body weight, on gymnastic equipment, etc.); the possibility of performing exercises both outdoors and in basements, bomb shelters, checkpoints, etc.; diverse and comprehensive development of motor skills; formation of service-related motor skills; improvement of the functional capabilities of cadets' bodies; loss of excess (fat) body weight of cadets; improvement of the physical condition of cadets; improvement of somatic health; improvement of psychological state, psychological hardening; improvement of well-being, self-confidence, and stability of actions in extreme situations. In particular, our analysis demonstrates the effectiveness of HIIT sessions in improving the functioning and functional reserves of cadets' respiratory and cardiovascular systems during their academic training, as well as the more pronounced effect of deliberate sports activities on the strength indicators of future law enforcement officers.

The results of our research confirm the conclusions of many scientists [16, 18, 23, 24] and supplement them with information on the positive effects of HIIT sessions on body mass index, vital index, strength index, and Robinson index, improvements in cadets' stress resilience, and reductions in stress and anxiety. Thus, based on the results of the study of the dynamics of cadets' psychosomatic health indicators during their HIIT sessions, it was established that they effectively influence the improvement of the functional capabilities of the central systems of cadets' bodies, as well as indicators of their psychological state (primarily, a decrease in anxiety and the impact of stress on the body, increased stress resilience, etc.). The vast majority of the indicators studied for cadets in Group No. 1 were significantly better in the 3rd training year than in Group No. 3.

CONCLUSIONS

It was found that in most tests, cadets in Group No. 1 had significantly better somatic and mental health indicators during their senior training years than those in Group No. 3, indicating a more pronounced effect of HIIT on the morphofunctional and psycho-emotional state of future law enforcement officers during their academic training. The most pronounced effects of HIIT were observed in indicators of cadets' respiratory and cardiovascular systems, as well as in their stress resilience and anxiety levels. At the same time, no significant difference was found between the indicators of cadets in Group No. 1 and Group No. 2, which indicates the effectiveness of additional motor activity and sports training sessions in improving the psychosomatic health of cadets.

The positive effect of HIIT on indicators of psychosomatic health among future law enforcement officers has been demonstrated. This underscores the advisability of the broader implementation of HIIT in the physical training of future law enforcement officers during their academic training at higher educational institutions with a specific learning environment, to improve their psychosomatic health and, accordingly, increase the effectiveness of their future service activities.

PROSPECTS FOR FURTHER RESEARCH

It is planned to investigate the impact of HIIT sessions on physical fitness indicators and body composition among female cadets during their academic training under martial law conditions.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

Academic performance and preclinical skills in the dental students of Ukrainian University

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ABSTRACT

Aim: To identify the relation between academic performance and preclinical skills in pediatric dentistry, and which skills need to be refined

Materials and Methods: This is a cross-sectional study conducted among the second year students of Poltava state medical university (PSMU) in the 2023/2024 academic year. Oral questions used for knowledge assessment, and academic performance was calculated as average score of grades for all classes. Preclinical skills were estimated with developed assessment at two stations during objective structural phantom exam (OSFE). The $\chi 2$ test for proportions and Spearman`s rank correlation coefficient were calculated.

Results: The assessment of practical skills found that the students with excellent level of skills showed same academic performance ($P<0,05$). The students with weak satisfactory skills prevailed among the students with same academic performance ($P<0,05$). Spearman`s rank correlation coefficient ($p=0,7$) showed moderate relation between preclinical and academic performance ($P<0,01$). At the station «Fissure sealing», the worst skill was plaque removal and saliva isolation ($P<0,05$). At this station «Finishing and polishing of composite restoration», the worst skill was the second using of occlusal paper and filling finishing with a bur ($P<0,05$). The average grade for station «Fissure sealing» $4,22\pm0,05$ was higher than the grade for «Finishing and polishing of composite restoration» $3,76\pm0,07$ ($P<0,0001$).

Conclusions: A moderate association was found between academic performance and preclinical skills in prevention of dental diseases with propaedeutic of pediatric dentistry. During classes, students` skills in finishing of composite restorations need to be improved, also students need more practice and feedback from the teacher at fissure sealing.

KEYWORDS: academic performance, practical skills, dentistry

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INTRODUCTION

In the past decade, Ukrainian dental programs have strongly changed due to introducing of university autonomy. Also Ukraine's healthcare system underwent substantial transformation [1], resulting in a reduction of dentists who work in a public sector and introduction new dental technologies in academic process to prepare competitive specialists. To address the student preclinical skills acquisition, Faculty of Dentistry of PSMU introduced OSFE in propaedeutic dental disciplines at the end of the 2023/2024 academic year. During OSFE, the students demonstrated their skills and past two stations in each of the four propaedeutic dental disciplines.

The structure of dental disciplines in PSMU includes classes, lectures, self-directed activities and clinic practices. Theoretical component is a background for development of clinical skills of students, and both of components are essential for preparation to OSFE and clinical practice. Unfortunately, Russian-Ukrainian war brought forth abrupt and radical changes in educational process, and classes might be interrupted by air raids necessitating both teachers and students be in the shelter which decreased class time.

Medical students usually have a good academic performance as compared to non-medical students [2]. Recent studies have studied the associations between academic performance and preclinical skills in endodontics [3, 4], operative dentistry [5, 6, 7], restorative dentistry [4], orthodontics and prosthodontics [5]. To date, there was no study in the literature that has demonstrated an association between academic performance and preclinical technique skills in pediatric dentistry. Moreover, the authors interested about students` lacks in skills in order to improved them next academic year.

AIM

Thus, the aim of this study was to identify the relation between academic performance and preclinical skills in pediatric dentistry, and which skills need to be refined.

MATERIALS AND METHODS

This is an institution-based cross-sectional study conducted among PSMU students of the second year of study in the 2023/2024 academic year.

In PSMU, prevention of dental diseases with propaedeutic of pediatric dentistry is the discipline which includes the fundamental principles of preclinical pediatric dentistry. The module included 21 two-hours-long live classes, 3 records of lectures and 6 short online presentations for self-directed activities. Each class consisted of assessment of students` knowledge and practical exercises. In this study, a portion of the assessment for students` knowledge

was oral questions. The simulation exercises, through the use of acrylic and extracted teeth, allowed the students to apply learned principles and concepts. A short 10-min demonstration preceded each simulation exercise.

Grading system in PSMU is based on the 5 to 2 scale, criteria of which are described in the syllabus of discipline. Academic performance of the examined students was calculated as an average score of grades for all classes. According academic performance, the students were categorized into 4 groups: the first group with excellent score 4,5-4.9, the second group with good score 4.0-4.49, the third group with satisfactory score 3.5-3.99, the fourth group with weak satisfactory score 3.0-3.49. 2 students with poor score below 3.0 were excluded. Finally, 182 students were enrolled in this study.

Practical skills were assessed in the standardized OSFE at the end of the fourth semester. Recently erupted molars often hurted by caries due low mineralisation, limited child`s ability to care of teeth [8] and plaque accumulation with different microbial species [9]. Previous studies showed that permanent [10] and deciduous molars [11] have the highest caries risk in the early stages after their eruption, so fissure sealing is a crucial preventive procedure to be acquired by students. Students were given 30 min to perform two skills on the plastic teeth at the stations «Fissure sealing» and «Finishing and polishing of composite restoration». Initially, students made an acquaintance with algorithms and criteria of preclinical skills` assessment.

At the station «Fissure sealing», skills included (1) the choice of instruments (was graded from a scale of 0-0.5, 0 was not done and 0,5 was done), (2) the choice of material (0-0.5), (3) the plaque removal (0-1), (4) the saliva control (0-0.5), (5) the enamel etching (0-0.5), (6) the sealant application (0-1), and (7) the sealant polymerization (0-1). Maximal sum of grades was 5 for each station, and a pass mark of 3.0 was applied.

At the station «Finishing and polishing of composite restoration», skills included (1) the application of occlusal paper, (2) the filling finishing with burs, (3) the second application of occlusal paper, (4) the filling polishing with rubber point, (5) the filling polishing with a paste. Each treatment step was graded from a scale of 0-1, with 0 was not done, 1 was done. According the recommendations [12], the assessments were done independently by two pediatric faculties, and the graders were blinded to each other assessments. Therefore, each faculty assigned two grades to each student and the final grade was calculated by averaging the grades of the two faculties who evaluated two stations. To assess practical skills, students were categorized into 4 groups as they were to assess academic performance.

Statistical analysis of the data was executed using Excel 2016 (Microsoft Corp). The χ^2 test for proportions and Spearman`s rank correlation coefficient were calculated. Statistical significance was established at $P<0.05$.

ETHICS

This work complies with the principles of the Declaration of Helsinki.

RESULTS

The details of the academic performance and preclinical skills of the students are presented in Table 1. The assessment found that the rate of students with excellent practical skills prevailed in the first group (p=0.03). The most of students of the second group past preclinical exam with excellent and good scores. The third group with satisfactory academic performance demonstrated various practical skills and one student failed. The rate of students with a weak satisfactory practical skulls prevailed in the fourth group of students (p=0.03). Moreover, Spearman`s rank correlation coefficient (p=0.699857) showed a moderate relation between preclinical and academic performance ($P<0.01$).

Practical skills at the station «Fissure sealing» are shown in Table 2. From skills which were estimated from the scale 0-1, the worst skill was plaque removal as compared to sealant application and polymerization (P=0.0001). From skills which estimated from the scale 0-0.5, the worst skill was saliva isolation as compared to enamel etching and choice of instruments and material ($P<0.0001$).

At this station «Finishing and polishing of composite restoration» (Table 3), the worst skill was the second using of occlusal paper as compared to all other skills (P=0.0001). In addition, filling finishing was worse compared to polishing ($P<0.05$).

Average grade for station «Fissure sealing» 4.22±0.05 was higher than grade for station «Finishing and polishing of composite restoration» 3.76±0,07 ($P<0.0001$). Average grade for two stations was 3.99±0.04.

Table 1. Academic performance and practical skills of the examined students

Academic performance	Number of students	Score of practical skills (N, %)				
		4.5-4.9	4.0-4.49	3.5-3.99	3-3.49	<3
4.5-4.9	31	20 (64.51)[2]	10 (32.26)[1,2]	1 (3.23)[1,2]	0	0
4.0-4.49	40	12 (30)[2]	15 (37.5)[2]	7 (17.5)	6 (15)[2]	0
3.5-3.99	69	9 (13.04)[1]	21 (30.43)[2]	19 (27.54)	19 (27.54)[2]	1 (1.45)
3.0-3.49	40	5 (12.5)[1]	5 (12.5)[1]	10 (25)[1]	(50)	0

Note:[1]p<0,05 – intragroup difference, [2]p<0,05 – difference compared to the group with weak satisfactory academic performance
Source: compiled by the authors of this study

Table 2. Practical skills of the students at the station «Fissure sealing»

Statistic parameters	Skills							
	Plaque removal (0-1)	Choice of instruments (0-0.5)	Choice of material (0-0.5)	Saliva control (0-0.5)	Enamel etching (0-0.5)	Sealant application (0-1)	Sealant polymerization (0-1)	Average score
Average mean	0.808	0.486	0.497	0.206	0.379	0.934	0.940	4.217
Average error	0.03	0.006	0.003	0.019	0.016	0.018	0.018	0.052
p^1		<0.0001	<0.0001		<0.0001	0.0001	0.0001	
p^2								

Note: p^1 – difference with plaque removal, p^2 – difference with saliva isolation
Source: compiled by the authors of this study

Table 3. Practical skills at the station «Finishing and polishing of composite restoration»

Statistic parameters	Skills (estimated from the scale 0-1)					
	Using of occlusal paper	Filling finishing with burs	The 2d using of occlusal paper	Polishing with rubber point	Polishing with paste	Average grade
Average mean	0.758	0.706	0.511	0.940	0.832	3.761
Average error	0.03	0.03	0.04	0.02	0.03	0.07
p^1	0.0001	0.0001		0.0001	0.0001	
p^2				<0.0001	0.005	

Note: p^1 – difference with the second using of occlusal paper, p^2 – difference with filling finishing
Source: compiled by the authors of this study

DISCUSSION

In the course of propaedeutic disciplines, junior dental students are expected to develop some practical skills before dealing with real patients. Acquiring these skills ensures dental students can undertake safe and competent procedures.

In PSMU, the students simultaneously discuss themes and make simulation exercises in the classrooms, but they have less time for these activities due to the war. OSFE, which has been recently introduced at our university, has practical tasks close to preclinical practical exams in other countries [3-7]. To assess whether students acquired preclinical skills in fissure sealing and finishing and polishing of composite restoration, a valid and reliable assessment was developed that employs an appropriate standard setting.

During the preclinical course, dental students may perform within the first two phases of the motor skills learning theory by Fitts and Posner [3]. A student learnt how to make fissure sealing and filling finishing and polishing, focusing on steps, during cognitive phase. Each of these steps requires concentration, and with practice and feedback from the teacher, the student moved to associative phase where knowledge was integrated into motor behavior. It is clear that theoretical component could improve student`s ability to perform dental manipulations. Therefore, the authors tried to match grades of the practical stations with individual`s average academic performance during studying of the discipline.

This study found that the students with excellent academic performance mostly showed same practical skills, whereas the students with weak satisfactory academic performance mostly showed weak practical skills ($P<0.05$).

The current study is the first which demonstrated a moderate correlation between academic performance and preclinical skills in dental propaedeutic disciplines. This finding is consistent with the researches which showed a moderate correlation between didactic and practical scores for the dental anatomy course [5] and between academic and clinical courses of the five year students [7]. In contrast, a few studies found a weak association between academic performance and preclinical skills in endodontics [3], preparation of dental hard tissues [6], operative dentistry and prosthodontics [5], and restorative dentistry [4]. The results of academic performance at previous studies may be attributed to the different number of multiple choice questions (MCQs) [3, 4, 5, 7] or the focus on certain themes [3, 6]. Moreover, individual differences in motor skill learning during classes [13] could influence the results of practical assessment.

The studied students more often missed treatment steps of plaque removal and saliva control at the station «Fissure sealing» as compared to other steps ($P<0.05$). This station was the first and the lacks might be associated with stress that was found in the study of Elsawaay et al. [14]. At the second station «Finishing and polishing of composite restoration», the students had the lowest grade for the second application of occlusal paper as compared to other steps ($P<0.05$). Moreover, the students had better grade for filling polishing as compared to filling finishing ($P<0.05$). A statistically significant difference between the average scores of stations does not only demonstrated lacks in the

simulation exercises during the classes, but also reflects different grades for each step of the station. Therefore, educators have to emphasize on these low level skills next academic year, and the assessment of fissure sealing needs to be changed.

We could not evaluate impact of the war on the results of the students because OSFE was organized firstly in our university. One limitation of this study was that only two stations in pediatric dentistry were available in the 2023/2024 academic year. Therefore, more stations are required to increase the representability of the results.

CONCLUSIONS

Within the limitation of this study, a moderate association was found between academic performance and preclinical skills in pediatric dentistry. During classes, students` skills in finishing of composite restorations need to be improved, also students need more practice and feedback from the teacher at fissure sealing.

Sum up, this study highlights the importance of using theoretical component and practical exams to provide a comprehensive evaluation of students' knowledge and skills in the field of pediatric dentistry.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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REVIEW ARTICLE

Cultural competence in healthcare: A systematic review of perceptions, assessment, and mental health interventions among professionals/students in Greece/Cyprus

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ABSTRACT

Aim: This systematic review examined the cultural competence among healthcare professionals, focusing on: (I) the assessment of cultural competence among healthcare professionals; (II) the education and assessment of cultural competence among healthcare students; (III) healthcare professionals' perceptions and experiences regarding cultural competence; (IV) healthcare students' perceptions and experiences regarding cultural competence; and (V) educators' perspectives on teaching cultural competence.

Materials and Methods: A systematic review was conducted according to PRISMA 2020 guidelines. Databases searched included PubMed, Google Scholar, Elsevier, and ProQuest from 2017 to 2024. From 15, 053 studies identified initially, 31 studies met inclusion criteria after screening and were analyzed in depth.

Conclusions: Healthcare professionals and students acknowledge the benefits of cultural competence training; however, undergraduate programs and curricula remain underdeveloped. Educators frequently rely on anecdotal methods rather than structured frameworks. Further systematic integration and evidence-based strategies are essential.

KEYWORDS: assessment, education, diversity

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INTRODUCTION

The continuous sociocultural diversification of patient populations globally has rendered cultural competence an essential skill for healthcare professionals. It plays a critical role in delivering equitable, effective, and patient-centered care [1-4]. Educational interventions aimed at fostering cultural competence contribute significantly to reducing health disparities, enhancing patient safety, and improving satisfaction among diverse populations [4, 5]. Cultural competence is not limited to acquiring theoretical knowledge; rather, it entails self-awareness, attitudes, sensitivity, and communication skills, which enable providers to engage meaningfully with individuals from varying cultural backgrounds.

Recent studies emphasize that theoretical instruction alone is insufficient to develop true cultural competence. Instead, the combination of formal education with practical exposure and direct interactions with culturally diverse patients has proven to be more impactful in cultivating cultural sensitivity, awareness, and confidence [6–12]. For example, Byrne (2020) demonstrated that undergraduate nursing students who participated in both lectures and simulation scenarios with culturally diverse standardized patients scored significantly higher in cultural competence compared to those who attended lectures alone [7].

Despite the international recognition of cultural competence as a vital component of quality care, research in Greece and Cyprus remains limited, particularly in terms of assessing current levels of competence and educational strategies. A significant number of healthcare professionals report feeling inadequately prepared to manage culturally complex situations, especially in regions with limited exposure to multicultural populations [5, 13, 14]. For instance, Červený et al. (2020) revealed that only 28% of Slovak nurses considered themselves culturally competent, and a striking 68% had received no cultural diversity training [14].

Various validated tools have been developed to assess cultural competence in healthcare, including the Nurses' Cultural Competence Scale (NCCS) [15], the Self-Assessment of Perceived Level of Cultural Competence (SAPLCC) [16], the Inventory Assessing the Process of Cultural Competence Among Healthcare Professionals – Student Version (IAPCC-SV) [7, 11], and the Medical Science Graduates' Cultural Competency Questionnaire [17] However, the application of these tools often lacks consistency across institutions and countries. Educational integration remains fragmented, and in many cases, structured frameworks or guidelines are absent [18, 19].

Cultural competence development also encompasses personal insight and the recognition of diversity as a fundamental value. Programs that foster self-reflection, critical thinking, and emotional engagement have shown greater success in preparing students and professionals for real-world practice [12, 20, 21]. In contrast, the lack of structured training often leads to professional insecurity,

passive attitudes, and, at times, detached or indifferent responses to culturally diverse patients [22, 23].

Professional experiences consistently indicate that practical, real-world engagement with culturally diverse populations plays a more decisive role than traditional classroom learning in enhancing cultural competence [5, 6, 12, 24]. For example, nurses often report that their cultural awareness evolved not through academic instruction but through daily interactions with patients from minority or immigrant backgrounds [6, 13, 22]. In emergency care settings, as Yadollahi et al. (2020) noted, over 90% of Canadian nurses had not received Indigenous cultural health training, and many felt more confident in their technical skills than in delivering culturally appropriate care [13].

Among healthcare students, international clinical placements, multicultural clinical settings, and experiential learning methods have been linked to significantly higher levels of competence [8, 10, 11, 25]. Gower et al. (2019) further noted that these improvements can persist for at least 12 months following an overseas clinical placement, indicating long-term benefits of immersive programs [25].

Overall, the literature highlights the urgent need for systematic incorporation of cultural competence into healthcare curricula through both theoretical content and experiential learning. Clear, standardized guidelines and educator training are essential to ensure that cultural competence is not treated as peripheral or anecdotal but as a core component of healthcare education [4, 18, 19, 26-28].

AIM

This systematic review examined the cultural competence among healthcare professionals, focusing on: (I) the assessment of cultural competence among healthcare professionals; (II) the education and assessment of cultural competence among healthcare students; (III) healthcare professionals' perceptions and experiences regarding cultural competence; (IV) healthcare students' perceptions and experiences regarding cultural competence; and (V) educators' perspectives on teaching cultural competence.

MATERIALS AND METHODS

This systematic review follows the PRISMA 2020 guidelines. A detailed research protocol was developed to outline objectives, inclusion/exclusion criteria, search strategies, selection processes, and data extraction methods.

ELIGIBILITY CRITERIA

Inclusion criteria:

- Publications from reputable databases (PubMed, Google Scholar, Elsevier, ProQuest)
- Studies published from 2017 to 2024
- Language limited to English and Greek
- Availability of full text
- Clinical trials, quantitative or qualitative studies
- Exclusion criteria:
- Publications before 2017
- Inaccessible full texts
- Studies not relevant to cultural competence in healthcare

INFORMATION SOURCES

Literature searches were conducted between January and February 2024 in PubMed, Google Scholar, Elsevier, and ProQuest. Keywords included: cultur*, healthcare, competen*, students, education*, profession*, training, Greece, Cyprus. Boolean operators (AND, OR, NOT) as well as in Greek language were applied to refine search outcomes. The identified studies' titles and abstracts were screened, followed by a full-text review of studies meeting inclusion criteria. Specific data were collected regarding cultural competence levels, assessment tools, educational strategies, and perceptions of professionals, students, and educators. Synthesized data were categorized into five thematic areas.

ETHICS

All sources used in this literature review are publicly available.

REVIEW AND DISCUSSION

From 15, 053 initial records, 31 studies (Appendix – Table 1) were included after rigorous screening are presented in PRISMA Flow Diagram (Fig. 1) above. Studies were grouped into five thematic categories, addressing assessment, education, perceptions, experiences, and teaching practices related to cultural competence.

I.ASSESSMENT OF CULTURAL COMPETENCE AMONG HEALTHCARE PROFESSIONALS

The quantitative research of Zarzycka et al. (2020), based on an adapted diagnostic program aimed at the preliminary assessment of cultural competence using the Polish version of the NCCS scale (Nurses Cultural Competence Scale) in nurses. The results revealed a moderate level of competence in cultural knowledge, a low level of competence in skills, and a high level of competence in awareness and sensitivity [15].

A study of Chen et al. (2018) in Taiwan examined nurses' cultural competence over one year, revealing that formal education alone did not develop this skill. Instead, competence was gained through direct interactions with patients from diverse cultural backgrounds [6].

Researchers evaluated the Persian Cultural Competence Scale for Iranian nurses by assessing its psychometric properties. This reliable tool allows for measuring cultural competence, evaluating related interventions and improving nursing care quality [15].

Yadollahi et al. (2020) in their study resulted that Canadian emergency nurses working with Indigenous patients showed limited cross-cultural preparedness: 90% lacked Indigenous health training and felt more confident providing technical than culturally competent care [13].

A qualitative study of Harrison et al. (2019) attempted to analyse the role of cultural competence in healthcare professionals working with patients from ethnic minorities. It concluded that cultural competence and effective consumer engagement were closely linked to ethnic minority populations and ensured equitable quality healthcare [31].

Majda et al. (2021) used the Cross-Cultural Competence Inventory (CCCI) to evaluate cultural competence among Polish healthcare professionals. Nurses scored lowest,

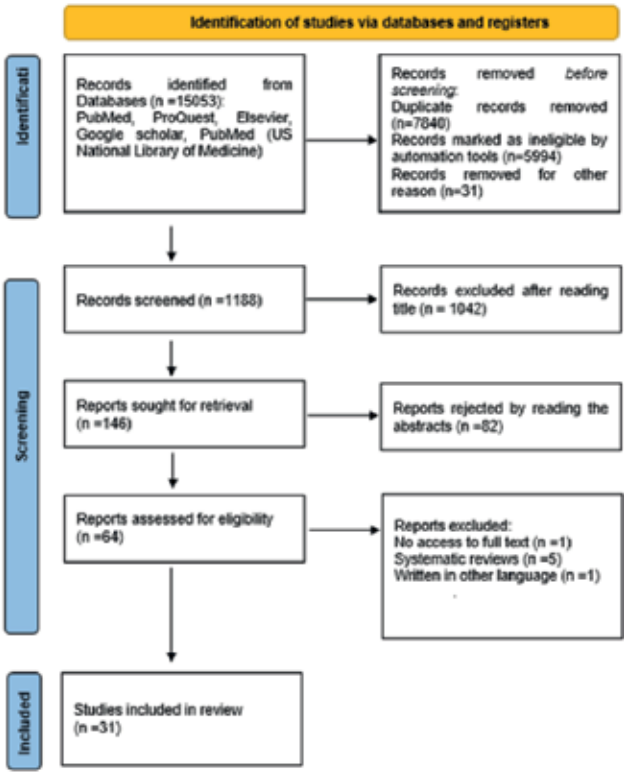

Fig. 1. Prisma flow diagram

Source: compiled by the authors based on [29, 30]

physicians highest on positive refugee attitudes, and all categories (nurses, physicians, paramedics) had minimal participation in training workshops [32].

II. THE EDUCATION AND ASSESSMENT OF CULTURAL COMPETENCE AMONG HEALTHCARE STUDENTS

Effective strategies combined lectures with simulations or international exposure. Common assessment tools included IAPCC-SV and SAPLCC.

Byrne (2020) conducted a quantitative study on U.S. undergraduate nursing students using the Inventory Assessing the Process for Cultural Competence Among Healthcare Professionals -Student Version IAPCC-SV tool to compare self-reported cultural competence. Students who experienced both lectures and simulations with culturally diverse standardized patients scored higher than those who attended lectures alone, indicating that incorporating simulations effectively enhanced cultural competence [7].

In a study of Echeverri et al. (2017) a Self-Assessment of Perceived Level of Cultural Competence (SAPLCC) tool was used to assess perceived cultural competency among medical and pharmacy students. Pharmacy students had significantly higher scores in assessing their attitudes regarding discriminatory practices, developing treatment plans, providing culturally sensitive education and counselling services, and better cultural communication [16].

A study was conducted by Naghizadeh et al. (2020) to develop and validate the Medical Science Graduates' Cultural Competency Questionnaire among medical graduates which was found a valid and reliable tool [17].

Wang et al. (2021) compared healthcare students in a short-term study abroad program with those who stayed in Australia and found that international exposure may enhance students' cultural knowledge [10].

Forsyth et al. (2018) analysed indigenous cultural competency training in dental programs at the University of Sydney. Their study, involving school staff and dental students, found that although the curriculum includes domestic cultural competence content, there is a need for a comprehensive, evidence-based framework to better prepare graduates [26].

Using cohort study, an attempt was made by Jones et al. (2017) to determine the level of cultural competence among newly enrolled students and graduating students in health sciences separately. As a result, a significant difference in the level of cultural competence was observed among them [33].

Cruz et al. (2018) evaluated nursing students' cultural competence on an international scale. Overall, they found a moderate level of competence, with students scoring highest in teaching, guiding, and demonstrating culturally appropriate behavior. However, their ability to consult with patients about health beliefs received lower ratings. Factors such as country of residence, gender, year of study, experience in caring for multicultural patients, and living in a multicultural environment influenced these competence levels [8].

Liu et al. (2018) evaluated both immediate and long-term outcomes of daily workshops aimed at enhancing cultural competence among 40 Chinese undergraduate nursing students. Qualitative feedback indicated that participants found the workshops effective, while quantitative results revealed significant improvements in scores on the Chinese Version of the Cultural Competence Inventory for Nurses (CCIN) after the intervention [9].

Göl et al. (2019) examined the relationship between cultural sensitivity and the level of intelligence among nursing students. The Intercultural Sensitivity Scale and the Cultural Intelligence Scale were used. Nursing students with prior contact with different cultures and aspirations to work abroad scored higher on both cultural sensitivity and intelligence, exceeding 75% on the respective scales [21].

III. HEALTHCARE PROFESSIONALS' PERCEPTIONS AND EXPERIENCES REGARDING CULTURAL COMPETENCE

Professionals often felt inadequately prepared, with training significantly improving self-awareness and culturally competent behaviors.

Researchers (Lin et al. 2019) attempted to create a descriptive theoretical framework regarding the experiences in cultural competence of clinical nurses in Taiwan. The results revealed issues related to multiple levels of cultural competence experienced by nurses, as well as the importance of understanding cultural diversity among patients and caregivers [5].

Kaihlanen et al. (2019) explored how cultural competence training impacts Registered and Enrolled Nurses by focusing on awareness of their own cultural traits. The study found that the training increased self-awareness and prompted reflective thinking, with participants considering it useful.

This enhanced sensitivity is seen as vital for improving communication with patients and ultimately supporting high-quality healthcare delivery [20].

A qualitative study of Amiri et al. (2017) was also conducted to explore the experiences of nurses in caring for individuals from different cultures. The nurses' experience in caring for these patients revealed that minorities have been somewhat neglected in the city of Mashhad (Iran), and the nursing care for such individuals in hospitals and other clinics lacks a specific framework [22].

A quantitative study of Aboshaiqah et al. (2017) was conducted with nurses to examine their cultural competence before and after training implementation using an assessment tool. The results showed no significant difference in the average scores before and after the training [34].

In another study, an attempt was made by Červený et al. (2020) to assess the perception of cultural competence among Slovak nurses. Only 28% perceived themselves as culturally competent and 68% reported no training in cultural diversity. Age and prior training were significantly linked to culturally competent behaviours, indicating a strong need to enhance these skills in the Slovak healthcare system [14].

A qualitative study (Markey et al. 2017) examined how nurses manage concerns when caring for patients from diverse cultural and ethnic backgrounds. It revealed that nurses often adopt coping strategies like -detached indifference- to manage their insecurities and are more inclined to blame others for their own oversights and shortcomings [23].

A study by Fair et al. (2021) aimed to present an evaluation of the ORAMMA training model in Greece and explore midwives' experiences. The evaluation involved midwives who underwent training, and those qualitatively investigated regarding their experiences. A significant improvement was observed in the median score before and after the test on midwives' knowledge, skills, and self-perceived cultural competence. Qualitative results revealed that the cultural training topics were found suitable and applicable. Three additional themes emerged concerning supportive care, collaboration with colleagues, and how challenges could be addressed [35].

IV. HEALTHCARE STUDENTS' PERCEPTIONS AND EXPERIENCES REGARDING CULTURAL COMPETENCE

Clinical experiences and direct cultural interactions substantially increased students' cultural competence compared to theoretical teaching alone.

In a study of Knecht et al. (2018), an attempt was made to investigate whether participation in different clinical environments in a nationally diverse city would significantly increase the level of cultural competence of nursing students (qualitative and quantitative study), as measured by the Inventory for Assessing the Process of Cultural Competence Among Healthcare Professionals-Student Version (IAPCC-SV) tool. The composite study showed a statistically significant difference in the mean score of the IAPPCC-SV between the groups. Students who participated in the integrated program scored higher compared to students who participated in more traditional, less diverse clinical experiences [11].

Mukhalalati et al. (2020) conducted a mixed-method study with pharmacy students and educators to assess cultural competence in pharmaceutical education. While both groups showed cultural awareness and sensitivity, their holistic awareness was limited, suggesting that theoretical education alone may not be enough to fully prepare them as culturally competent professionals [27].

Choi et al. (2018) identified how cultural education and personal experiences influence cultural competence in nursing students. The study concluded that cultural competence improves when education is combined with personal cultural experiences with the direct contact with diverse cultures as the most beneficial factor [12].

Gower et al. (2019) quantitatively examined the long-term effects of an international clinical placement on nursing students' cultural competence. Their findings revealed that students' cultural competence increased immediately after the placement and remained elevated even 12 months later [25].

Forsyth et al. (2019) explored dental and oral health students' perceptions of including Indigenous content in their curricula to identify barriers and inform future strategies for developing Indigenous cultural competence. The study found that enhancing cultural competence requires an informed history of Indigenous Australians, a commitment to Indigenous communities, and reflective practice on these experiences [36].

Antón-Solanas et al. (2021) analyzed European nursing students' experiences learning cultural competence through interactions with patients from diverse backgrounds. The study found that students' perceived levels of cultural competence varied, prompting recommendations for tailored learning strategies and the integration of intercultural content into undergraduate nursing curricula [37].

V. EDUCATORS' PERSPECTIVES ON TEACHING CULTURAL COMPETENCE

Educators frequently used anecdotal and case-study methods, with limited structured curricula or comprehensive frameworks.

The qualitative study of Antón-Solanas et al. (2021) explored the perceptions and experiences of nursing educators in teaching cultural competence. Cultural competence was not clearly integrated into educational curricula. Instead, educators used examples and case studies to illustrate theory [18].

Paric et al. (2021) examined factors influencing the integration of cultural competence in nursing education from educators' perspectives. Their findings underscore the need for greater transparency and collaboration between educators and university administration, training educators in cultural competency and evidence-based teaching and courses or workshops with clear objectives and assessments [19].

Chen et al. (2020) conducted a mixed-method study on cultural competence in nursing students, focusing on teaching perspectives. The qualitative results highlighted a need for broader support in teaching cultural competence, noting a shortage of teaching examples and resources, as well as a general lack of student knowledge in this area [28].

Cultural competence is essential for delivering effective, culturally responsive healthcare services, significantly contributing to the reduction of health disparities, enhanced patient safety, and increased satisfaction among diverse populations [4, 5]. Consequently, it is vital for undergraduate health professional students to develop cultural competence through structured education [1-4] and evidence-based training programs [38].

Integrated healthcare service-learning within undergraduate curricula enhances students' cultural awareness, knowledge, skills, and motivation. Such educational approaches equip students to deliver improved care to diverse populations and effectively address the socio-political factors contributing to health inequalities [11, 37]. Nursing curricula specifically should be systematically evaluated and revised to include comprehensive cultural content. Clear guidelines and standardized frameworks are necessary to ensure consistent and meaningful inclusion of diversity education [14, 18]. Furthermore, healthcare service provisions must emphasize cultural awareness and sensitivity to adequately meet the needs of diverse patient populations [26, 27, 36].

Short-term study-abroad programs have demonstrated potential in enhancing healthcare students' cultural knowledge, although they primarily improve cultural knowledge rather than awareness, attitudes, or skills [10]. Given the critical importance of cultural competence for healthcare professionals, it is imperative to utilize validated assessment tools even at the undergraduate level to timely address gaps in cultural competence development [17].

Current evidence reveals that most healthcare professionals lack formal training in cultural competence. Therefore, employing standardized and psychometrically validated tools for reliably assessing cultural competence and cultural intelligence is highly recommended [32]. Frontline nurses have emphasized the necessity for greater cultural competence to effectively understand and meet the healthcare needs of multicultural patient populations [5]. Additionally, routine cultural health assessments conducted by healthcare providers themselves can further support culturally competent care [39].

Research indicates significant improvements in cultural competence when theoretical education is combined with direct cultural experiences [12]. In contrast, healthcare professionals who lack adequate cultural competence training frequently exhibit challenges in managing care for culturally diverse patients, often leading to passive attitudes, indifference, and professional insecurity [22, 23]. Thus, establishing cultural competence as an essential component of healthcare systems and professional practice is critical for ensuring equitable, high-quality healthcare services across all cultural and ethnic groups [31].

Commonly utilized assessment tools identified in this systematic review include the Inventory Assessing the Process of Cultural Competence Among Healthcare Professionals-Student Version (IAPCC-SV) [7, 11], the IAPCC-R for healthcare professionals [28], the Nurses' Cultural Competence Scale (NCCS) [15], the Medical Science Graduates' Cultural Competency Questionnaire [17], the Self-Assessment of Perceived Level of Cultural Competence (SAPLCC) [16], the Cultural Intelligence Scale, and the Intercultural Sensitivity Scale [21].

From an educational perspective, cultural competence trainers at the undergraduate level require targeted training in cultural competencies and evidence-based teaching methodologies [28]. Curricula should explicitly incorporate structured courses or workshops on cultural competence, clearly defining learning objectives and measurable assessment criteria [19], supported by comprehensive guidelines and standards for the systematic integration of cultural content [18].

Enhancing cultural competence among healthcare professionals and students is crucial for addressing the diverse healthcare needs of multicultural populations. Structured education, combined with practical cultural exposure and standardized assessments, is key to developing sustainable competencies. It is essential to foster comprehensive, evidence-based curricula and targeted training for educators to systematically integrate cultural competence into healthcare education, ensuring equitable and quality healthcare services for all populations.

CONCLUSIONS

This systematic review highlights the essential role of cultural competence in healthcare education and practice. Although healthcare professionals and students increasingly recognize its importance, formal training and structured educational approaches remain limited, especially in Greece and Cyprus. Undergraduate programs often lack clear frameworks, resulting in fragmented teaching methods that rely heavily on anecdotal experiences rather than evidence-based strategies. The integration of cultural competence into curricula is frequently superficial, and many educators feel underprepared to teach it effectively. Moreover, healthcare professionals often report greater confidence in technical skills than in culturally responsive care. This gap points to the need for comprehensive curriculum reform that incorporates both theoretical foundations and experiential learning opportunities. Evidence from the reviewed studies emphasizes that real-world exposure, such as clinical placements and interactions with diverse populations, significantly enhances cultural awareness and sensitivity. To support this, validated assessment tools and standardized teaching practices should be more widely implemented. Developing cultural competence is not optional – it is fundamental to delivering ethical, person-centered, and equitable care. Moving forward, healthcare education must prioritize structured cultural training, support educators through professional development, and create environments that reflect and respect the diversity of the populations they serve.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Appendix

Table 1. Table of the results of systematic review

A/A	Author, Year, Country	Title	Number of participants	Purpose	Method	Results
1	Aboshaiqah et al., 2017 Saudi Arabia	Enhancing culturally competent nursing care in Saudi Arabia.	584 nurses	Examination of cultural competency among nurses before and after training, using an individual assessment tool.	Quantitative	There was no significant difference between the average scores before and after the test; however, the cultural competency reported by the nurses themselves was enhanced through the designed educational training program.
2	Amiri et al., 2017, Iran	Nurses' experiences of caring for patients with different cultures in Mashhad, Iran	12 nurses	Exploration of nurses' experiences in caring for individuals from different cultures.	Qualitative	The experience of nurses in the care of patients from other cultures has shown that minorities have been neglected in Mashhad, and nursing care for such individuals in hospitals and other clinics lacks a specific framework.
3	Antón-Solanas, Tambo-Lizalde et al., 2021, Spain, Belgium, Turkey, Portugal	Nursing students' experience of learning cultural competence.	40 undergraduate nursing students: 12 Spanish, 11 Belgians, 10 Turks, 7 Portuguese.	Analysis of the experience of European nursing students regarding the learning of cultural competence through working with patients from different cultural backgrounds.	Qualitative	The perceived level of cultural competence among nursing students was variable. However, their learning needs were identified, and strategies were proposed for integrating intercultural nursing content into the undergraduate nursing curriculum.
4	Antón-Solanas, Huércanos-Esparza et al., 2021, Spain, Portugal, Belgium, Turkey	Nursing lecturers' perception and experience of teaching cultural competence: A European qualitative study	24 Nursing lecturers	Exploration of the perception and experience of nursing faculty regarding the teaching of cultural competence in four undergraduate nursing programs.	Qualitative with semi-structured interviews	Cultural competence was not clearly integrated into the educational programs. Instead, instructors primarily used examples and case studies to illustrate theory. The integration of cultural content was unplanned and not based on a specific model.
5	Byrne, 2020, USA	Evaluating cultural competence in undergraduate nursing students using standardized patients.	38 undergraduate nursing students	Description of the level of self-reported cultural competence of undergraduate nursing students and comparison of the competence level between students who participated only in lectures versus students who participated in both lectures and simulations with standardized patients (SPs) from different cultures.	Quantitative, using the tool Inventory Assessing the Process for Cultural Competence Among Healthcare Professionals – Student Version (IAPCC-SV)	Students who underwent the intervention showed a higher average score of cultural competence. The results after the intervention indicated that the lecture and/or program incorporating cultural competence increased the level of cultural competence among undergraduate students.
6	Červený et al., 2020, Slovakia	Self-reported cultural competence of nurses providing nursing care in Slovakia.	267 nurses	Identification and evaluation of perception of cultural competence among nurses in the Slovak healthcare system.	Cross-sectional quantitative study using Cultural Competency Assessment Questionnaire	28% perceive themselves as culturally competent. 68% received no training related to cultural diversity. Age and prior training showed significant correlation with culturally competent behaviour.
7	Chen et al, 2018, Taiwan	Exploring the growth trajectory of cultural competence in Taiwanese paediatric nurses.	10 nurses	Examination of the evolution of cultural competence among paediatric nurses in Taiwan over a period of one year.	Qualitative	The cultural competence of the nurses was not achieved through formal education on cultural competence. Instead, their experience in this area relied solely on their interaction with multicultural patients.
8	Chen et al., 2020, USA	Exploring faculty perceptions of teaching cultural competence in nursing	13 individuals from nursing schools in the quantitative group and 7 individuals in the qualitative group.	Investigation of the cultural competence of the nursing school and understanding the prospects of teaching culturally competent care to students.	Qualitative and quantitative using the tool IAPCC-R (Inventory for Assessing the Process of Cultural Competence Among Healthcare Professionals-Revised)	The results of the quantitative study indicated that the school was culturally informed and culturally competent, based on Campinha-Bacote's definitions (2007). On the other hand, the results of the qualitative study showed overall support for teaching cultural competence but highlighted a lack of examples and resources for application/teaching, as well as a lack of knowledge of cultural competence among students.

Table 1. Cont.

9	Choi et al., 2018, Korea	Effects of cultural education and cultural experiences on the cultural competence among undergraduate nursing students	236 nursing students	Identification of how cultural education and personal experiences influence cultural competence in nursing students.	Cross-sectional, quantitative	Cultural competence increased when cultural experiences were added to cultural education. Contact with different cultures is what benefits students' cultural competence the most.
10	Cruz et al., 2018, 9 countries (Chile, India, Iraq, Oman, Philippines, Saudi Arabia, South Africa, Sudan, and Turkey)	A multicountry perspective on cultural competence among baccalaureate nursing students.	2,163 nurses from April to November 2016.	Assessment of cultural competence in nursing students aimed at providing an international perspective on cultural competence.	Quantitative study using the Cultural Capacity Scale tool.	There was a moderate range of cultural competence among students. However, their ability for teaching and guidance, as well as demonstration of culturally appropriate behaviour, received the highest ratings. Lower ratings were related to consulting patients on health belief issues. Factors such as country of residence, gender, year of study, experience in caring for patients from multicultural backgrounds, and living in a multicultural environment influenced cultural competence.
11	Echeverri et al., 2017, USA	Racial dynamics and cultural competence training in medical and pharmacy education	254 medical students, 285 pharmacy students	Assessment of perceived level of cultural competence and creation of student profiles using the tool.	Quantitative, using the Self-Assessment of Perceived Level of Cultural Competence (SAPLCC) tool.	Pharmacy students had significantly higher ratings than medical students in assessing their attitudes towards discriminatory practices, developing treatment plans, and providing culturally sensitive education and counselling services, demonstrating better cultural communication. African Americans had a higher awareness of racial discrimination compared to Caucasians. Overall, participants had a moderate overall rating of cultural competence.
12	Fair et al., 2021, Greece	Midwives' experiences of cultural competency training and providing perinatal care for migrant women a mixed methods study: Operational Refugee and Migrant Maternal Approach (ORAMMA) project	35 midwives - (ORAMMA training), 12 midwives - interviews	Presentation of an evaluation of the ORAMMA training model and exploration of the experiences of midwives regarding training and provision of care within the framework of the ORAMMA project.	Quantitative and qualitative. Cultural competence was assessed before and after training (ORAMMA – compassionate and culturally sensitive maternity care education in three different European countries).	The interviews explored the experiences. There was a significant improvement in the mean score after compared to before the intervention, where improvement was observed in the midwives' knowledge, skills, and self-perceived cultural competence. The exploration of midwives' experiences (using qualitative methods) from the training revealed that they found the cultural education topics appropriate and applicable, "made a difference," and addressed educational gaps. Data from the ORAMMA project experiences identified three additional issues regarding supportive care, collaboration with colleagues, and that challenges can be addressed. Midwives gained positive experiences from the Oramma care model.
13	Forsyth et al., 2018, Australia	Indigenous cultural competence: A dental faculty curriculum review.	69 employees and 191 dental students	Provide a basic analysis of the indigenous cultural competence curricula to identify the necessary changes in the dental school programs at the University of Sydney to enable students to become culturally competent upon graduation.	Quantitative	There is domestic content on cultural competence in the dental curriculum. However, there is a need for a comprehensive, evidence-based domestic framework for teaching cultural competence. The main pedagogical method of the curriculum was lectures, followed by case studies and group discussions.

Table 1. Cont.

14	Forsyth et al., 2019, Australia	Students don't know what they don't know: Dental and oral health students' perspectives on developing cultural competence regarding indigenous peoples	15 dental and oral health students	The identification of students' perceptions regarding the inclusion of Indigenous content in current dental and oral health curricula. Perception of barriers and support for the development of Indigenous cultural competence in students and strategies for updating education in the future.	Qualitative	The findings indicated that increasing cultural competence among dental and oral health students requires an informed understanding of the history of Indigenous Australians, engagement with Indigenous communities, and reflection on these experiences.
15	Göl et al., 2019, Turkey	Association between cultural intelligence and cultural sensitivity in nursing students: A cross-sectional descriptive study	336 nursing students	Determining the relationship between cultural sensitivity and the level of cultural intelligence among nursing students.	Cross-sectional descriptive study using the Intercultural Sensitivity Scale and the Cultural Intelligence Scale	The overall scores on both the Intercultural Sensitivity Scale and the Cultural Intelligence Scale were higher among those students who had come into contact with individuals from different cultural backgrounds and those who intended to work abroad. More than 75% scored high on cultural sensitivity and intelligence.
16	Gower et al., 2019, Australia	One year on: Cultural competence of Australian nursing students following international service-learning.	50 nursing students	Exploring the gap (long-term impact) and describing the quantitative influence of an international clinical placement experience on the cultural competence of participants, both in the short term and 12 months later.	Quantitative assessment immediately before, immediately after, and 12 months after the international clinical placement.	Overall, the cultural competence of the students increased immediately after their placement, and the score was maintained 12 months later. Targeted activities are recommended before placement to develop specific aspects, especially cultural desire.
17	Harrison et al., 2019, Australia	What is the role of cultural competence in ethnic minority consumer engagement? An analysis in community healthcare.	21 healthcare professionals	The analysis of the role of cultural competence in healthcare professionals working with patients from ethnic minorities.	Qualitative, using semi-structured interviews.	Cultural competence and effective consumer engagement are closely linked to populations of ethnic minorities. Cultural proficiency is critical to ensuring equitable, quality healthcare for patients from diverse ethnic backgrounds.
18	Jones et al., 2017, USA	Assessing health professional students' cultural competence using a global perspective	146 new-entry students and 59 graduates in health sciences.	Assessment of the level of cultural competence in new-entry and graduating students of health sciences.	2 cohort studies for each group separately using the Global Worldview Cultural Competence Survey (GWCCS).	A significant difference in the level of cultural competence was observed among the graduates compared to the incoming students.
19	Kaihlanen et al, 2019, South Finland	Increasing cultural awareness: Qualitative study of nurses' perceptions about cultural competence training.	14 registered nurses (RNs) and 6 nursing assistants (NAs).	Investigation of nurses' perceptions regarding the content and usefulness of cultural competence training, focusing on their awareness of their own cultural characteristics.	Qualitative	The training increased healthcare professionals' awareness of their own cultural characteristics, was considered useful, and prompted reflection. Enhanced sensitivity can facilitate communication between healthcare professionals and patients, constituting a critical component of a quality healthcare.
20	Knecht et al., 2018, USA	An investigation of the development of cultural competence in undergraduate nursing students: A mixed-methods study.	58 nursing students	Investigating whether participation in diverse clinical settings in a nationally diverse city would significantly increase students' level of cultural competence.	Qualitative and quantitative (composite) study, using the Inventory for Assessing the Process of Cultural Competence Among Healthcare Professionals-Student Version (IAPCC-SV)	The study showed a statistically significant difference in mean scores on the IAPPCC-SV measuring cultural competence between the groups. Students who participated in the embedded program scored higher compared to students who participated in more traditional and less diverse clinical experiences.
21	Lin, et al., 2019, Taiwan	Exploring the experiences of cultural competence among clinical nurses in Taiwan.	30 nurses	To create a descriptive theoretical framework on the experiences in cultural competence of clinical nurses in Taiwan.	Qualitative	It highlighted the multiple levels of cultural competence experienced by nurses and the importance of understanding cultural diversity among patients and caregivers.

Table 1. Cont.

22	Liu et al., 2018, China	Increasing undergraduate nursing students' cultural competence: An evaluation study.	40 nursing students	Evaluation of immediate and long-term outcomes following the implementation of day-long workshops designed to improve cultural competence in Chinese undergraduate nursing students.	Qualitative using Chinese Version of Cultural Competence Inventory for Nurses (CCIN)	Participants found the workshop effective (qualitative study results). After implementing the workshop, CCIN scores increased significantly in total scores, as well as in the components of cultural awareness, knowledge, understanding, cultural skills, but not in cultural respect (quantitative study results).
23	Majda et al., 2021, Southern Poland	Cultural competence and cultural intelligence of healthcare professionals providing emergency medical services.	308 doctors, 439 nurses and 305 paramedics	Measurement and assessment of cultural competence and intelligence among health professionals in emergency departments and clinics	Quantitative using the multidimensional Cross-Cultural Competence Inventory (CCCI)	Nurses had the lowest scores while doctors had the highest scores on positive attitudes towards refugees. All three categories of health workers had low rates of previous participation in training workshops.
24	Markey et al., 2017, Ireland	Resigned indifference: the importance of cultural competence education.	30 nurses	Exploring how nurses address their primary concern when caring for patients from different cultural and ethnic backgrounds.	Qualitative	Participants adopted disengagement strategies on issues that caused them insecurity and resigned indifference; in terms of rationalization behavior, it was easier to blame someone else for their own oversights and shortcomings.
25	Mukhalalati et al., 2020, Qatar	Cultural awareness and competence of pharmacy educators and learners from the perspective of pharmacy students at Qatar University: A mixed-methods approach.	70 pharmacy students in the quantitative phase, 23 students in the qualitative phase	Examining the level of cultural awareness and competency of pharmacy educators and students and the impact of cultural diversity on pharmacy education.	Quantitative using the Cultural Awareness Scale (CAS) tool and qualitative	Teachers and students in general are culturally aware and culturally sensitive. However, the demonstration of a holistic awareness has been hampered. It appeared that theoretical education provides cultural sensitivity to students, which proves insufficient in preparing them to become culturally competent health professionals
26	Naghizadeh et al., 2020, Iran	Psychometric evaluation of the Medical Science Graduates' Cultural Competency Questionnaire.	542 medical students	Development and validation of a questionnaire to assess cultural competence in medical seniors.	Quantitative using the Medical Science Graduates' Cultural Competency Questionnaire	The Medical Science Graduates' Cultural Competency Questionnaire proved to be a valid and reliable tool for measuring cultural competence in medical students.
27	Paric et al., 2021, Finland	Nurse teacher's perceptions on teaching cultural competence to students in Finland: a descriptive qualitative study.	12 Nurse teachers	Examination of the elements influencing the implementation of cultural competency content in nursing education from the perspective of the nursing educator.	Qualitative descriptive with semi-structured interviews	More transparency and collaboration between faculty and university administration is needed to ensure the inclusion of cultural competence in nursing education. Faculty should receive training on cultural competencies and evidence-based teaching methods. The curriculum should include a course or workshop on cultural competencies with clear learning objectives and assessment criteria. Finally, the educational institution should be committed to developing a culturally competent organization through internationalization and maintaining a multicultural environment.
28	Sarkhani, et al., 2022, Iran	Psychometric properties of the Persian version of the cultural competence scale in clinical nurses.	303 nurses	Investigating psychometric properties of the Persian version of the cultural competence scale in Iranian nurses	Quantitative	Valid assessment of nurses' cultural competence provides the ground for evaluating the effectiveness of various interventions to promote their cultural competence and, consequently, the quality of nursing care.
29	Wang et al., 2021, Australia	Improvement in the cognitive aspects of cultural competence after short-term overseas study programs.	Group 1 (n=32) of health care students participated in a study abroad program. Group 2 (n=46) health care students remained in Australia	Examining whether short-term study abroad programs for healthcare students increase their cultural competence	Quantitative	Group 1 had higher scores than Group 2 on cultural knowledge, but not on cultural awareness, attitudes or skills. Short-term study abroad programs can increase students' cultural knowledge.

Table 1. Cont.

30	Yadollahi et al., 2020, Canada	Evaluation of cultural competency in clinical nurses: A descriptive study.	30 ER nurses	Description of cross-cultural health practices of Canadian emergency room nurses working with Indigenous populations (patients)	Descriptive	About 90% of nurses had not received specific training on indigenous health. They were more confident in their ability to provide technical care than in their knowledge of the cultural aspects of providing care.
31	Zarzycka et al, 2020, Poland	Nurse cultural competence -cultural adaptation and validation of the polish version of the nurse cultural competence scale and preliminary research results.	238 nurses	Preliminary assessment of cultural competence based on the Polish version of the NCCS scale	Quantitative study based on a customized-diagnostic multidisciplinary project -NCCS	Medium level of proficiency in knowledge, low level of proficiency in skill, high level of proficiency in awareness and sensitivity.

Source: compiled by the authors of this study

REVIEW ARTICLE

Biomarkers of cellular senescence in bone tissue

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ABSTRACT

Aim: To summarize the biomarkers of cellular senescence in bone tissue and discuss their potential relevance for clinical risk stratification and outcomes related to bone remodeling and implant osseointegration.

Materials and Methods: A narrative literature review was performed using PubMed and Google Scholar searches focused on osteoblast, osteocyte and mesenchymal stem cell senescence, DNA damage response, senescence-associated secretory phenotype, oxidative stress, and epigenetic regulation in bone. Eligible peer-reviewed publications were screened for evidence on established and emerging senescence biomarkers, detection methods (histochemical, immunohistochemical, molecular, and secretory profiling), and mechanistic links to impaired osteogenesis and enhanced osteoclastogenesis. Findings were synthesized into practical biomarker categories (molecular, cellular/tissue, and functional) with emphasis on translational implications for dental implant planning and peri-implant bone stability.

Conclusions: Bone cellular senescence is characterized by increased SA-β-gal activity, upregulation of cell-cycle inhibitors (p16INK4a, p21CIP1/WAF1, p53-related pathways), persistent DNA damage signaling, and a proinflammatory secretory phenotype that promotes osteoclast activation and suppresses osteogenesis. Tissue-level changes include reduced osteoblast function, osteocyte loss, and a shift toward resorptive remodeling reflected by an elevated RANKL/OPG ratio. Emerging signals (e.g., selected long non-coding RNAs and innate immune sensors such as TLR9) may complement classic markers in future panels. Integrating senescence-related biomarkers into clinical assessment may support individualized protocols for patients with biologically compromised bone and inform targeted preventive strategies.

KEYWORDS: cellular senescence, bone remodeling, dental implants

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INTRODUCTION

Cellular aging (senescence) in tissues is associated with chronic inflammation, immune dysregulation, and a shift towards a proinflammatory secretory profile [1]. In bone, the accumulation of senescent cells can disrupt the balance of bone remodeling, leading to reduced regenerative capacity and age-related bone loss [2]. This is particularly relevant in the jaw, where bone quality is a key determinant of dental implant success. Expanding diagnostic capabilities to detect cellular senescence in the jawbone is clinically important for identifying high-risk patients and enabling preventive measures during dental procedures, such as bone augmentation or implantation. Traditional methods – including histology, histochemical staining for senescence-associated β-galactosidase, and cell cycle assays –provide only a general indication of the presence of senescent cells [3]. Modern multi-modal approaches now combine molecular biomarkers and secretory factor profiling to quantify the intensity and impact of cellular aging in tissues [4].

Most currently known senescence biomarkers are indirect, as they may also reflect prolonged inflammation or immune imbalances within the tissue microenvironment. Nevertheless, identifying elevated levels of bone aging biomarkers prior to implant surgery could allow clinicians to optimize the implantation site. For example, preconditioning the bone with osteoinductive growth factors or selecting an implant design that ensures primary stability in compromised bone may mitigate the effects of cellular senescence [5]. Furthermore, minimally invasive monitoring of these biomarkers during the osseointegration period could help identify implants at risk of early failure. In such cases, adjusting the loading protocol or administering senolytic therapies to modulate the peri-implant environment may improve clinical outcomes [6].

AIM

The aim of this review is to systematize the potential biomarkers of cellular senescence in bone tissue that can be identified during dental implant planning, and to interpret these markers as factors potentially associated with the prognosis of implant osseointegration.

MATERIALS AND METHODS

This study is a structured literature review. We searched for relevant publications using Google Scholar and PubMed, with

keywords such as «bone senescence», «osteoblast senescence», «osteocyte senescence», «senescence markers in bone», «SASP bone», and «LncRNA bone aging». Peer-reviewed articles reporting on specific cellular aging markers in bone tissue were included, with no restriction on publication year to capture both classic studies and up-to-date research. From an initial pool of 146 papers, 30 relevant studies were selected based on the presence of data on bone aging markers, analysis of their diagnostic or prognostic value, and any reported links between marker changes and bone formation or resorption processes. Data from these sources were extracted and categorized into: (1) laboratory and clinical markers of bone cell senescence; (2) methods for their detection; and (3) their potential significance for bone remodeling and implant osseointegration.

ETHICS

This review article is based on the analysis of publicly available scientific evidence published in peer-reviewed journals, clinical guidelines, and bibliographic databases. No patient-identifiable information was used, and ethics committee approval was not required because the work did not involve new clinical interventions or primary collection of patient data. The authors adhered to the ethical principles of the World Medical Association Declaration of Helsinki and to international standards for medical publishing, including the recommendations of the International Committee of Medical Journal Editors (ICMJE). The manuscript contains no plagiarism or data fabrication. All sources of information are properly cited and formatted in accordance with the journal requirements.

REVIEW AND DISCUSSION

CATEGORIES OF SENESCENCE MARKERS

The known biomarkers of bone cellular aging can be grouped into three broad categories: molecular, cellular/tissue, and functional [7] (see Table 1).

MOLECULAR MARKERS

These include SA-β-gal, the classic enzymatic marker of senescent cells; cell cycle inhibitors p16INK4a, p21CIP1/WAF1, p19ARF and p53, whose upregulation mediates irreversible growth arrest; DNA damage markers such as γH2AX foci and 53BP1, and telomere shortening, a hallmark of replicative senescence . Molecular markers also encompass secretory factors associated with senescence – the senescence-associated secretory phenotype (SASP) – including proinflammatory cytokines (e.g. IL-6, IL-8, TNF-α), chemokines, growth factors and matrix metalloproteinases that senescent osteoblasts/osteocytes secrete. In addition, epigenetic changes like altered expression of certain long non-coding RNAs (LncRNAs) (for example, upregulation of LncRNAs HOTAIR, MEG3, MALAT1, RUNX2-AS1 and downregulation of ANCR) and shifts in specific microRNA levels (e.g. miR-34a, miR-29, miR-218) have recently been associated with osteoblast and MSC senescence in bone [8].

CELLULAR/TISSUE MARKERS

At the cell and tissue level, senescence is indicated by reduced osteoblast function (such as decreased RUNX2 expression, alkaline phosphatase activity and osteocalcin production, reflecting impaired bone formation) and increased osteoclast activity (elevated tartrate-resistant acid phosphatase and cathepsin K, reflecting enhanced bone resorption) [9]. An accumulation of senescent osteocytes leads to osteocytic dysregulation, evidenced by empty osteocyte lacunae and a reduced number of viable osteocytes in aged bone. An imbalance in the RANKL/OPG ratio – with higher RANKL and lower osteoprotegerin – is also observed, shifting bone remodeling toward resorption in the aging bone microenvironment [10]. Notably, osteocytes in aged bone exhibit biomechanical and morphological changes (such as altered cytoskeleton stiffness and dendritic network) consistent with cellular senescence [11].

FUNCTIONAL MARKERS

These refer to systemic or tissue-level functional indicators of bone aging. Senescent bone tissue often shows decreased mineralization, for example a reduced calcium/phosphorus (Ca/P) ratio in the bone matrix, corresponding to inferior bone quality [12]. Chronic oxidative stress is another hallmark: aged osteoblastic cells accumulate reactive oxygen species (ROS) and oxidative DNA damage (8-oxo-dG), alongside a decline in antioxidant enzymes, resulting in elevated oxidative stress levels [13]. Mitochondrial dysfunction, including increased mitochondrial DNA mutations, is also a feature of cellular senescence affecting bone's energy metabolism [14]. Excessive ROS production in bone cells can damage DNA and telomeres, activating p53/p21 and p16 pathways that enforce growth arrest, and can also stimulate osteoclastogenesis via the RANK–RANKL signaling axis [15].

KEY SENESCENCE MARKERS AND THEIR EFFECTS

Among the molecular markers, p16INK4a is especially noteworthy: its expression rises dramatically (often by >3–5-fold) in senescent osteoblasts and MSCs, accumulating in nuclei and reliably indicating irreversible cell cycle arrest [16]. p21CIP1/WAF1 increases more moderately (~2–3-fold) at earlier stages of stress-induced senescence as part of the p53 pathway, serving as an early, dynamic marker of DNA damage response [17]. Upregulation of these cyclin-dependent kinase inhibitors, along with p19ARF and persistent p53 activation, leads to permanent exit of osteogenic cells from the cell cycle. The functional consequence is a reduction in osteoblast proliferation and differentiation, directly limiting new bone formation on implant surfaces [18]. Consistently, areas of bone with high p16/p21high cell populations show impaired regenerative capacity.

Senescent bone cells can be identified histochemically by their senescence-associated β-galactosidase (SA-β-gal) activity, which accumulates in the lysosomes of aging cells. Osteoblasts and osteocytes exhibiting high SA-β-gal activity – typically detected at pH 6.0 – have largely lost their proliferative and osteogenic potential. An increased proportion of SA-β-gal$^+$ osteocytes correlates with the presence of non-viable ("empty") lacunae in bone, and mesenchymal stem cells (MSCs) positive for SA-β-gal demonstrate impaired osteogenic differentiation, contributing to osteoporotic changes. Thus, SA-β-gal

Table 1. Main markers of cellular senescence in bone tissue (grouped by category) and their features

Category	Markers	Features and Effects
Molecular	SA-β-gal (senescence-associated β-galactosidase)	Enzymatic marker of senescent osteoblasts/osteocytes (histochemical detection; indicates loss of proliferative capacity)
	p16INK4a, p21CIP1/WAF1, p19ARF, p53	Cell cycle inhibitors/tumor suppressors; upregulated in senescent bone cells (p16 and p53 increase >3–5×; p21 ~2–3×) leading to irreversible growth arrest
	γH2AX, 53BP1 foci	DNA damage response markers; accumulation signifies genomic stress and telomere dysfunction in aging cells
	Short telomeres	Telomere attrition associated with replicative senescence (limited cell divisions)
	SASP factors: IL-6, IL-8, TNF-α, MMP-1, -3, -13, etc.	Senescence-associated secretory phenotype; proinflammatory cytokines and proteases that create chronic inflammation and promote osteoclast-mediated resorption
	LncRNAs: HOTAIR, MEG3, CCAT1, RUNX2-AS1 (↑in aging); ANCR, MALAT1 (↓in aging)	Epigenetic regulators of senescence and differentiation; altered expression modulates osteogenic potential (e.g. high HOTAIR/MEG3 activate p16/p53 pathways, low ANCR indicates lost osteogenesis)
	microRNAs: miR-34a, miR-29, miR-218 (altered in aging)	Post-transcriptional regulators affecting osteoblast/osteoclast activity; contribute to the senescent phenotype in bone cells
Cellular/Tissue	Osteoblast dysfunction: ↓RUNX2, ↓ALP, ↓osteocalcin	Senescence impairs osteoblast differentiation and bone-forming activity (markers of osteogenesis are reduced)
	Osteoclast activation: ↑TRAP, ↑cathepsin K	Senescent milieu tilts balance toward bone resorption (osteoclast enzyme levels rise, indicating increased resorptive activity)
	Osteocyte degeneration: empty lacunae, ↑viable osteocytes	Loss of osteocyte network viability in aged bone; fewer functional osteocytes and microstructural deterioration
	RANKL/OPG imbalance: ↑RANKL, ↓OPG	Favors osteoclastogenesis and bone resorption ("inflammaging" effect); seen in aging and chronic inflammatory conditions
Functional	Reduced mineralization: low Ca/P ratio	Aged bone shows lower mineral content and quality, reflecting impaired mineral deposition and increased porosity
	Oxidative stress: ↑ROS, ↑8-oxo-dG, ↓antioxidants	Accumulation of reactive oxygen species and oxidative DNA damage in senescent cells; overwhelms antioxidant defenses, leading to DNA/tissue damage and activation of senescence pathways (p53/p16)
	Mitochondrial dysfunction: ↑mtDNA mutations	Aging cells accumulate mitochondrial DNA damage; contributes to energy metabolism decline and enhanced apoptosis/senescence signals
	Altered mechanics: osteocyte cytoskeletal changes	Senescent osteocytes show reduced mechanosensitivity and structural changes, potentially impacting bone's adaptive remodeling to mechanical load

Notes: SA-β-gal – senescence-associated β-galactosidase; p16INK4a – p16 inhibitor of cyclin-dependent kinase 4A; p21CIP1/WAF1 – p21 cyclin-dependent kinase inhibitor 1/wild-type p53-activated fragment; p19ARF – p19 alternative reading frame; p53 -tumor protein p53; γH2AX – phosphorylated histone H2A.X (gamma H2AX); 53BP1 -tumor protein p53-binding protein 1; DNA -deoxyribonucleic acid; SASP -senescence-associated secretory phenotype; IL-6 -interleukin 6; IL-8 -interleukin 8; TNF-α – tumor necrosis factor alpha; MMP – matrix metalloproteinase; lncRNA / lncRNAs – long non-coding RNA(s); HOTAIR – HOX transcript antisense RNA; MEG3 – maternally expressed gene 3; CCAT1 – colon cancer-associated transcript 1; RUNX2-AS1 – RUNX2 antisense RNA 1; ANCR – anti-differentiation non-coding RNA; MALAT1 – metastasis-associated lung adenocarcinoma transcript 1; miRNA – microRNA; RUNX2 – runt-related transcription factor 2; ALP – alkaline phosphatase; TRAP – tartrate-resistant acid phosphatase; RANKL – receptor activator of nuclear factor kappa-B ligand; OPG -osteoprotegerin; Ca/P -calcium-to-phosphorus ratio; ROS -reactive oxygen species; 8-oxo-dG (also reported as 8-OHdG) -8 oxo-2′-deoxyguanosine; mtDNA -mitochondrial DNA
Source: compiled by the authors of this study

serves as a general marker confirming the accumulation of senescent cells in bone [19].

A prominent feature of senescent osteoblasts and osteocytes is the development of a senescence-associated secretory phenotype (SASP). Senescent bone cells secrete a specific set of proinflammatory and matrix-degrading factors, including IL-6, IL-8, TNF-α, and proteases such as MMP-1, -3, and -13, along with other cytokines and chemokines [20]. This SASP creates a chronic inflammatory environment in bone tissue and disrupts normal remodeling. Elevated cytokines and MMPs promote osteoclast activation and bone matrix degradation while inhibiting new bone formation by osteoblasts. For instance, an increase in baseline RANKL, accompanied by a decrease in OPG, is commonly observed in aging or chronically inflamed bone, shifting the balance toward bone resorption [21]. In a periodontal bone aging model, high local levels of RANKL, together with the cell-cycle inhibitor p21, were predictive of accelerated bone loss, indicating that senescent osteoblasts ($RANKL^+$) and proinflammatory T cells (Th17 producing IL-17) jointly drive osteoclastic resorption. Similarly, a recent meta-analysis reported significantly elevated IL-1β and IL-17 concentrations in the peri-implant milieu of failed or loosened mini-implants, reinforcing the concept that an "inflammaging" profile contributes to early implant failure [22].

In addition to protein markers, DNA damage sensors and innate immune receptors can contribute to bone senescence. One example is Toll-like receptor 9 (TLR9), which detects unmethylated DNA fragments. TLR9 expression is normally low in young osteoblastic cells but increases markedly (2-4×) in aged or diseased bone. Over-activation of TLR9 by accumulating mitochondrial DNA fragments or other damage-associated molecular patterns has been shown to promote senescence and inflammaging in periodontal bone, concurrently elevating p16, p21, p53, and SASP cytokines. While TLR9 is not a classical senescence marker, its upregulation reflects an immune-driven response to tissue damage that can exacerbate bone aging processes [23].

EPIGENETIC AND NON-CODING RNA MARKERS

Recent studies highlight that epigenetic changes in aging bone cells can serve as important biomarkers. Notably, several long non-coding RNAs (LncRNAs) have been implicated in regulating osteoblast and MSC senescence. For instance, HOTAIR and MEG3 lncRNAs are significantly upregulated in senescent osteogenic cells, promoting expression of p21/p16 or activating p53 signaling, respectively. Elevated CCAT1 and RUNX2-AS1 lncRNAs have been linked to inhibition of osteogenic differentiation (e.g. via Wnt/β-catenin pathway suppression or direct RUNX2 inhibition), consistent with an aging-related shift toward adipogenic or non-osteogenic cell fates. In contrast, the lncRNA ANCR (anti-differentiation non-coding RNA) is markedly downregulated (by ~50-70%) in aged MSCs; low ANCR is considered a marker of lost osteogenic potential in these cells. High levels of MALAT1, another lncRNA, are associated with a "younger" osteoblastic phenotype, whereas a significant decrease in MALAT1 accompanies progressive senescence. These lncRNA biomarkers, though newly identified, may reflect the epigenetic state and remaining regenerative capacity of bone cell populations. In addition to lncRNAs, certain microRNAs have been tied to bone aging. For example, miR-34a, miR-29, and miR-218 have been reported to influence osteoblast and osteoclast function during aging, acting as small regulatory markers of cellular senescence in bone [24].

This review identifies a spectrum of cellular senescence biomarkers in bone tissue that could be utilized to assess implant-related risk and guide clinical decision-making. The presence of multiple senescent cell markers in a patient's jawbone – for instance, high p16^INK4a expression coupled with a proinflammatory SASP profile – indicates an osteogenic environment with diminished regenerative capacity. Such a senescent bone microenvironment can compromise the healing and osseointegration of dental implants. Early recognition of this state allows for a personalized, preventive approach. For example, a patient with elevated p16^INK4a and inflammatory cytokines in a pre-implant bone biopsy might benefit from preoperative interventions to rejuvenate the site. These could include improving the local bone milieu with growth factor-rich plasma or other osteoinductive materials, and selecting implant designs or surfaces that achieve maximal primary stability even when secondary bone formation may be delayed.

During the healing phase, patients exhibiting high senescence marker levels may require modified implant loading protocols (e.g., extended unloaded healing periods) or adjunctive therapies to modulate peri-implant inflammation. Indeed, recent research in periodontics has demonstrated that administering senolytic drugs, such as dasatinib and quercetin, can reduce gingival cell senescence, inflammation, and alveolar bone loss. By extension, similar senolytic or osteoprotective strategies could potentially improve implant integration in aging or medically compromised patients [25].

The findings also highlight that senescence biomarkers could serve as early warning signals for implant failure. Monitoring peri-implant crevicular fluid or biopsy samples for spikes in SASP factors (e.g., IL-6, IL-1β) or other senescence indicators may allow clinicians to identify implants at risk of osteolysis and loss before clinical failure becomes evident. In severe periodontitis and peri-implantitis, accumulations of senescent ($RANKL^+$) osteoblasts and proinflammatory T cells have been directly linked to accelerated bone destruction. Similarly, orthodontic mini-implants under load have shown localized senescence, and targeting these senescent cells has been proposed as a means to prevent root resorption [26]. These observations underscore that controlling cellular senescence and the associated inflammatory milieu is critical for maintaining peri-implant bone health.

It must be noted that there is currently no single "gold standard" senescence marker in bone with a defined threshold value for risk stratification. The heterogeneity of patient factors and study methodologies means that interpreting these biomarkers requires careful clinical context. For instance, systemic conditions such as diabetes can amplify cellular senescence pathways in bone – for example, hyperglycemia-induced p53 activation in MSCs impeding their osteogenic differentiation [27] – thereby compounding the risk of implant complications. Similarly, loss of anti-aging factors, such as sirtuins, can predispose bone cells to premature senescence; for instance, knockdown of SIRT6 has been shown to induce senescence in human MSCs. These systemic and molecular influences should be taken into account when evaluating senescence marker levels in implant patients.

Despite these complexities, integrating multiple biomarker readings holds promise for improving implant prognostics. A composite analysis of senescence markers alongside clinical and imaging data could yield a more robust predictive model than any single marker alone [28]. For example, combining molecular biomarker screening with implant stability testing or bone density measurements may better identify patients at high risk of osseointegration failure. Such an approach aligns with the principles of personalized medicine: by quantitatively profiling an individual's bone senescence status, clinicians can tailor implant treatment plans – including timing of loading and use of adjunctive therapies – to that patient's biological capacity for bone healing [29].

In summary, cellular senescence represents a convergence of pathways – DNA damage response, chronic inflammation, and epigenetic alterations – that adversely affect bone

regeneration. The biomarkers discussed, from classical p16^INK4a staining to advanced genomic and secretory profiles, provide insight into the "aging state" of the bone-implant interface. Applied in practice, they could become valuable tools for risk assessment and guiding interventions. Further clinical research is warranted to establish standardized assays and threshold values for these biomarkers in implant dentistry, and to test interventions such as senolytics, antioxidants, or anti-inflammatory protocols aimed at mitigating the negative effects of cellular senescence on implant outcomes [30].

CONCLUSIONS

Cellular aging of bone tissue is a critical factor influencing the success of dental implants. Accumulation of senescent osteogenic cells in the jaw can compromise the healing and remodeling necessary for stable osseointegration. Among the key biomarkers of bone senescence, p16^INK4a, p21^CIP1/WAF1, p19^ARF, and p53 are particularly significant, as their upregulation reflects activation of cell-cycle arrest mechanisms and the irreversible transition of cells into a senescent state. Elevated levels of these markers correlate with reduced proliferative activity of osteoblasts and MSCs, directly limiting new bone formation on implant surfaces.

SA-β-galactosidase serves as a broad indicator of senescent cell accumulation in bone; a high proportion of SA-β-gal$^+$ cells at an implant site suggests diminished regenerative potential. A proinflammatory SASP profile – characterized by increased IL-6, IL-8, TNF-α, MMP-13, and an imbalanced RANKL/OPG ratio – is also detrimental, as it promotes chronic inflammation and shifts bone metabolism toward resorption rather than formation. Additional factors, such as elevated ROS and TLR9 activation, further propagate inflammatory and senescence pathways in response to oxidative DNA damage and mitochondrial stress. Emerging epigenetic markers, including specific lncRNAs (e.g., HOTAIR, MEG3, MALAT1, ANCR), provide further insight into the aging status of bone cells and their residual osteogenic capacity.

Overall, a comprehensive assessment of these senescence biomarkers in bone can serve as a valuable tool for predicting dental implant outcomes. It enables identification of patients at high risk of poor osseointegration due to an "aged" bone microenvironment. Such patients may benefit from prophylactic or concurrent interventions – such as senolytic drugs, bone anabolic agents, or tailored implant protocols – to improve the likelihood of long-term implant stability. By incorporating biomarker analysis into implant dentistry, clinicians can adopt a personalized approach to treatment that anticipates biological challenges associated with tissue aging and proactively addresses them, ultimately enhancing the success and longevity of dental implants.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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REVIEW ARTICLE

Protection of the right to human dignity in medical relations in the practice of the European Court of Human Rights

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ABSTRACT

Aim: To investigate the negative and positive obligations of the state in ensuring the right of an individual to respect for human dignity in medical and legal relations, taking into account the practice of the European Court of Human Rights, and to reveal the protection of this right among drug addicts.

Materials and Methods: The research methodology involves the analysis of national regulatory provisions, international treaties, legislative acts of Ukraine, and legal positions of the ECHR on the problems of implementing the right to respect for human dignity in medical and legal relations, as well as the case law of the European Court of Human Rights. Data analysis was conducted using open sources, mainly for the period 2010-2025. The main search keywords were „ECHR", „protection of rights", „health care", „legal regulation", „the right of an individual to respect for human dignity". The search criteria focused on modern scientific approaches and practical experience in ensuring the right of individuals to respect for human dignity in medical and legal relations. Sources that do not focus on medical-legal relations, that do not take into account the current practice of the ECHR, that do not comply with international human rights standards, legal acts or regulatory documents that contradict the practice of the ECHR were excluded from consideration.

Conclusions: The study highlights cases of failure to fulfill negative obligations of a material nature of the studied right of individuals, among which the following are identified: improper performance by officials of their duties due to inaction (failure to provide medical services, which led to serious consequences); improper performance of official duties by officials of state bodies, as well as unlawful actions of law enforcement agencies of a deliberate nature (physical and psychological violence against persons in custody). An approach is proposed in which adherence to the principle of the supremacy of the law under study, taking into account the practice of the European Court of Human Rights, is the basis for respecting human rights and freedoms.

KEYWORDS: European Court of Human Rights; protection of rights; healthcare

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INTRODUCTION

One of the current global human problems is the problem of human rights and their implementation, especially regarding such an important aspect as the prohibition of torture in the healthcare sector, the solution of which is possible only through joint efforts of states and the international community [1, 2]. By ratifying the Convention for the Protection of Human Rights and Fundamental Freedoms, Ukraine simultaneously recognized the binding nature of the European Court of Human Rights' (ECHR) case law. As a participant in international relations, Ukraine has constitutional obligations to ensure the security and quality of life of its citizens (Articles 3, 49), including the right to health care and medical care [3]. In addition, law is not static by its nature; it changes as a result of social development and transformations [4]. In this regard, the practice of the ECHR regarding the implementation of the right to respect for dignity in medical and legal relations is important. However, it should be noted that in Ukraine, some key problems of protection and implementation of the right mentioned above have not been theoretically developed and have not been scientifically researched. The above indicates the relevance of the chosen topic of the publication.

AIM

To investigate the negative and positive obligations of the state in ensuring the right of an individual to respect for human dignity in medical and legal relations, taking into account the practice of the ECHR, to reveal the protection of this right among drug addicts.

MATERIALS AND METHODS

The research methodology is an analysis of national regulatory legal acts and international documents ensuring the right to respect for human dignity in medical and legal relations, case law of the ECHR. Scientific and analytical sources on the problems of ensuring the right to respect for human dignity in medical and legal relations were also used. A system of methods and techniques of scientific knowledge was applied, namely: dialectical, formal-legal, systemic, hermeneutic, comparative-legal, empirical. The formal-legal method was applied in the analysis of regulatory provisions of international treaties, legislative acts of Ukraine, and legal positions of the ECHR. Dialectical and systemic methods contributed to establishing connections between the normative provisions of European documents in the field of human rights, the practice of the ECHR and the national legislation of Ukraine in the context of protecting

the rights of an individual to respect for dignity in medical and legal relations. When analyzing the practice of the ECHR, formal-legal, hermeneutic, and empirical methods were used to determine the content of the Court's legal positions and their interrelationships in the context of protecting the rights of an individual to respect for dignity in medical-legal relations. Data analysis was conducted using open sources, mainly for the period 2010-2025. The main search keywords were „ECHR", „protection of rights", „health care", „legal regulation", „the right of an individual to respect for human dignity". The search criteria focused on modern scientific approaches and practical experience in ensuring the right of individuals to respect for human dignity in medical and legal relations. Sources that do not focus on medical-legal relations, that do not take into account the current practice of the ECHR, that do not comply with international human rights standards, legal acts or regulatory documents that contradict the practice of the ECHR were excluded from consideration. The initial database consisted of 85 sources, of which 45 were included in the final analysis. The materials of the publication form the basis for systematizing legislation on issues of ensuring the right to respect for human dignity in medical and legal relations, the key ones of which are the Constitution of Ukraine, the Criminal Procedure Code of Ukraine, the Civil Code of Ukraine, and the ECHR.

ETHICS

This review is based on an evaluation of publicly available evidence from peer-reviewed publications, clinical guidelines, and scientific databases. No identifiable patient information was used; accordingly, ethics committee review was not required because the work involved neither new clinical interventions nor primary data collection. The authors complied with the World Medical Association Declaration of Helsinki and standard publication principles for medical journals, including ICMJE recommendations. No part of the manuscript involves plagiarism or data fabrication. All sources are cited and formatted in line with applicable publication standards.

FRAMEWORK

The work is a fragment of a comprehensive target program of the Department of Administrative Law and Administrative Activities, Yaroslav Mudryi National Law University, "Constitutional and legal problems of ensuring the rule of law in the functioning of the mechanism of public power in Ukraine" (№ state registration 0111U000966; deadline: 2022-2025).

REVIEW AND DISCUSSION

The right to respect for human dignity in medical and legal relations is provided for by both national and international legislation [5]. Dignity, according to the Constitution of Ukraine, is recognized as the highest social value (Article 3) [6]; no one has the right to encroach on it. In the event of such unlawful actions, any person may seek help from the court, and the guilty person must be held responsible in accordance with the law. The right to respect for dignity and honor is also provided for in the Civil Code of Ukraine, which stipulates that an individual has the right to apply to a court with a statement to protect their dignity and honor (Article 297) [7].

The Criminal Procedure Code of Ukraine also provides for respect for human dignity (Article 11). Each State Party shall take effective legislative, administrative, judicial, and other measures to prevent acts of torture in any territory under its jurisdiction. An order from a superior or a state authority cannot be a justification for torture (Article 2) [8]. Everyone has the right to defend, by all means not prohibited by law, their human dignity, rights, freedoms, and interests that have been violated during criminal proceedings. However, the above grounds do not allow us to conclude that there is an effective mechanism for the legal protection of public relations from torture in the field of medical and legal relations.

According to Article 3 of the Convention for the Protection of Human Rights and Fundamental Freedoms, the state is obliged to comply with both negative and positive obligations. In the professional literature and case law, substantive and procedural aspects of violations under Article 3 of this Convention are distinguished. In particular, the scope of application of Article 3 of the Convention for the Protection of Human Rights and Fundamental Freedoms in Medical Legal Relations is given in Table 1 [9-12].

The right to respect for human dignity in medical and legal relations is also provided for by the norms of international law. In particular, it is enshrined in the Universal Declaration of Human Rights of 1948, the International Covenant on Civil and Political Rights of 1966, the Convention for the Protection of Human Rights and Fundamental Freedoms of 1950, and other generally recognized international documents [9].

According to Article 3 of the Convention [9], prohibited forms of treatment include torture, inhuman treatment, and degrading treatment. According to Article 7 of the Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment [13], no one shall be subjected to torture or cruel, inhuman, or degrading treatment or punishment. In particular, no one shall be subjected to medical or scientific experiments without their free consent. The prohibition of torture is also enshrined in Article 7 of the International Covenant on Civil and Political Rights, which states that no one shall be subjected to torture or cruel, inhuman, or degrading treatment or punishment, as well as in the Declaration for the Protection of All Persons from Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment, adopted by the UN General Assembly on December 9, 1975.

According to Article 11 of the European Charter of Patients' Rights [14], everyone has the right to be free from suffering and pain, as far as possible, at every stage of their illness. According to the provisions of Article 5 (Parts 10, 11) of the Declaration on Policy on Respecting Patients' Rights in Europe, patients have the right to relief of suffering to the extent permitted by the current level of medical knowledge. A dying person has the right to humane treatment and to die with dignity.

Table 1. Scope of application of Article 3 of the Convention for the Protection of Human Rights and Fundamental Freedoms in Medical Legal Relations

№	Components	№	Components
I	Being under state control	XIII	Infection with a deadly disease
II	Investigating complaints of ill-treatment	XIV	Use of special means and weapons, use of force
III	Investigation of facts indicating ill-treatment	XV	Emergencies, state of emergency
IV	Compensation for mistreatment	XVI	Planning and conducting operations involving the use of force, disappearance of a person
V	All matters of being in custody and/or under the control of state authorities	XVII	Threat of ill-treatment, prevention of ill-treatment by civilians
VI	Expectation of punishment	XVIII	Persons under guardianship and care
VII	Detention of persons with serious physical disabilities	XIX	Domestic violence
VIII	Disciplinary punishments	XX	Guardians and custodians, adoption
IX	Treatment of persons with mental disorders	XX	Shelters, kindergartens, schools, boarding schools, children's camps
X	Compulsory medical measures	XXI	Expulsion, deportation, extradition
XI	Force-feeding	XXII	Human trafficking, bondage, sexual slavery
XII	Storage of medical records	XXIII	Discrimination based on race, gender, nationality, religion, or sexual orientation.

Source: compiled by the authors based on [9-12]

The European Convention on Human Rights [9] allows individuals to file formal complaints with the ECHR if their rights have been violated. The ECHR issues binding decisions and can order states to provide compensation to victims [15, 16]. Thus, the European Committee for the Prevention of Torture and Inhuman or Degrading Treatment or Punishment monitors compliance with Article 3 of the European Convention for the Protection of Human Rights and Fundamental Freedoms.

We present the grounds and subject matter of the disputed legal relationship before the ECHR – the right to respect for human dignity in medical and legal relations – in Table 2 [17-21].

The following should be noted concerning the above data. In particular, the ECHR found a violation of Article 3 of the Convention in the case of Wenner v. Germany [17]. It should be noted that this case is symbolic for understanding the standards of treatment of drug addicts in places of detention. The ECHR confirmed that the state bears a special responsibility for the health of persons under its control, and ignoring the specific medical needs of such persons may qualify as inhuman or degrading treatment. The ECHR sets an important precedent that a default abstinence policy without individual assessment violates international human rights obligations [17].

We will also reveal the grounds and subject matter of the disputed legal relationship before the ECHR in the context of protecting the right to respect for human dignity in medical and legal relations, as presented in Table 3 [22-26].

Examples of violations of Article 3 of the Convention [9] in medical and legal relations also include cases such as the refusal to release a cancer patient, although detention caused him "particularly severe suffering" (Case of Moiselle v. France) [27]; significant deficiencies in the provision of medical care to a mentally ill prisoner who was known to be prone to suicide (Case of Keenan v. the United Kingdom) [28]; and failure to provide the applicant with timely and adequate medical care for his HIV infection and tuberculosis (Case of Yakovenko v. Ukraine) [29]. Examples of violations of Article 3 of the Convention [9] in medical and legal relations also include inconsistencies in medical documentation. Furthermore, the use of experimental treatment without the patient's consent can be equated to inhuman treatment (Case of X v. Denmark) [30], among others.

Another example is the ECHR case Kudła v. Poland [31], which is an important precedent in the field of protecting the rights of prisoners and ensuring proper medical care for people suffering from drug addiction. The ECHR found that the refusal to provide substitution therapy and other necessary medical care violates Article 3 of the European Convention, as it creates conditions for serious physical and mental suffering. This decision emphasizes the importance of providing adequate medical care to vulnerable groups of persons, in particular those deprived of their liberty, and requires the state to take all necessary measures to protect their rights and health.

In the judicial system, some researchers note the gradual development of the approach to the principle of subsidiarity and the limits of discretion in assessing decision-making in the field of human rights by the ECHR [10]. In its principled position, the ECHR excludes any considerations of the category of "proportionality or balance" from the application of Article 3 of the European Convention on Human Rights. The right to respect for dignity in the provision of medical care is related to the right to the highest attainable standard of physical and mental health, as well as the realization

Table 2. The grounds and subject matter of the disputed legal relationship of the ECHR, the right to respect for human dignity in medical legal relations

Separate Case European Court of Human Rights				
Case of Wenner v. Germany [17]	Case of Sy v. Italy [18]	Case of D. v. the United Kingdom [19]	Case of McGlinchey and Others v. the United Kingdom [20]	Case of Sanhraoui and Others v. France [21]
Failure to provide the applicant with adequate medical care during his imprisonment, namely the refusal to provide maintenance methadone substitution therapy without a proper medical assessment, contrary to the doctors' recommendations	The prolonged detention of a person with serious mental disorders in ordinary prison conditions without proper medical care and contrary to the decisions of the domestic courts led to the deterioration of his condition and amounted to inhuman and degrading treatment.	The imminent severe suffering and humiliation that the applicant would suffer due to the lack of necessary treatment and support in the country of expulsion, given the terminal stage of his illness and his complete dependence on medical care.	The prison authorities' disregard for her condition and lack of proper medical intervention for her withdrawal syndrome led to her suffering and subsequent death	The applicants' detention conditions are appalling, due to overcrowding in the cells and inadequate sanitary conditions.

Source: compiled by the authors based on [17-21]

Table 3. Violation of Article 3 of the Convention for the Protection of Human Rights and Fundamental Freedoms and the right to human dignity in medical legal relationships

Separate Case European Court of Human Rights			
Case of Salakhov and Islyamova v. Ukraine [22]	Case of Rooman v. Belgium [23]	Case of Kaprykowski v. Poland [24]	Case of Paladi v. Moldova [25]
The doctors' underestimation of the seriousness of the applicant's condition and the unjustified refusal to urgently hospitalise him led to his suffering. The applicant is being kept in handcuffs for a long time in the hospital, despite his critical health condition and the lack of reasonable grounds for such security measures	Failure to provide the applicant, who suffered from a serious mental disorder and was incapacitated, with adequate psychiatric treatment in his native language (German, which is one of the official languages of Belgium)	Failure to provide the applicant, who required specialized medical care and constant assistance from another person in daily activities due to his health condition, with adequate medical care and proper conditions of detention in a pre-trial detention center	Failure to provide the applicant, who suffered from some serious illnesses while in detention, with adequate medical care, which posed a risk to his health and caused him suffering

Source: compiled by the authors based on [22-26]

of the right to freedom from torture and cruel, inhuman, and degrading treatment, and other human rights [1, 32].

Scientific doctrine has not developed a unified understanding of the categories of "dignity," "personal dignity," and "human dignity," or of the right to respect for dignity in medical and legal relations. Current national legislation does not contain a definition of the concept of dignity, since it is a moral and ethical category and, at the same time, a personal non-property right. In particular, human dignity is above human rights, is the core of all human rights and freedoms, and serves as an argument in their interpretation and concretization [33]. The term "personal dignity" should be understood as recognition of the value of each individual as a unique biopsychosocial being [33, 34]. From the standpoint of civil law regulation of legal relations concerning personal dignity, the social or class attitude towards the individual is important, regardless of the individual himself [35-37].

Therefore, some scholars define the category of "dignity" as the basis of the entire system of human and civil rights and freedoms. The category of "human dignity" plays an important role in law by promoting specific methods of interpreting and considering issues of human rights protection [38]. Some authors criticize the category of the "prohibition of torture and cruel, inhuman, and degrading treatment" in the context of its "absoluteness" and the "exhaustiveness" of the list from the point of view of international law [5, 39]. In the case law of the ECHR, ill-treatment is defined as a certain degree of physical pain or mental suffering. In the case of torture, this level is very high. Such pain or suffering is inflicted by certain methods or by creating particular circumstances.

Therefore, ensuring the right of an individual to respect for human dignity during illness is vital, as it directly affects the realization of the human right to health and the functioning of the health care system. During criminal

proceedings, respect for the human dignity, rights, and freedoms of each person must be ensured [40, 41]. This system also assumes the absence of harm and abuse, as well as effective communication [42-44]. Therefore, the right to respect for the dignity of the person in medical and legal relations is defined as the ability to realize and feel one's value as a person, to have a positive moral assessment of oneself, not to be subjected to torture, to be free from cruel, inhuman, or degrading treatment, to be free from degrading punishment, and to freely consent to medical, scientific, or other experiments [45].

CONCLUSIONS

In the practice of the ECHR, it is possible to identify non-compliance with negative obligations regarding the right to respect for human dignity in medical and legal relations in the following categories of material violations, namely: failure to provide medical care when a person is seriously ill, which may, under certain circumstances, amount to inhuman treatment; cases such as the refusal to release a cancer patient even though detention caused him "particularly severe suffering"; significant deficiencies in the provision of medical care to a mentally ill prisoner who was known to be suicidal; cases where the failure to assist led to a life-threatening condition or otherwise caused the victim "severe and prolonged suffering"; inconsistencies in medical documentation, which may be recognized as a violation; experimental treatment, which may amount to inhuman treatment if carried out without the patient's consent; and others.

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CONFLICT OF INTEREST
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REVIEW ARTICLE

Protection of personal medical data in the context of GDPR implementation

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ABSTRACT

Aim: To analyse the challenges of protecting personal medical data in European Union (EU) Member States and other European countries during the implementation of Regulation 2016/679 (General Data Protection Regulation [GDPR]).

Materials and Methods: The study is based on an analysis of international and national legal frameworks governing personal medical data protection, focusing on the GDPR, the case law of the European Court of Human Rights (seven relevant judgments), and national data protection legislation. Statistical data from reports of national Data Protection Authorities were analyzed to identify dominant categories of infringements related to unlawful processing, storage, disclosure, and security breaches of medical data. The methodology included a comparative analysis of European Court of Human Rights judgments and an overview of enforcement activities of data protection authorities in 27 EU Member States. Dialectical, hermeneutic, comparative, analytical, and systemic analysis methods were applied.

Conclusions: To comply with the GDPR, healthcare institutions must ensure lawful and secure processing of personal medical data: organize internal procedures, appoint a Data Protection Officer, implement technical and organizational measures, obtain informed consent from patients, and guarantee their rights to access and protect such sensitive information. The protection of personal medical data is ensured through a multi-level system that combines the GDPR, the European Court of Human Rights case law, and national institutions. It is essential to develop and implement clear data protection policies that define responsibilities, data handling procedures and incident response. Many countries still have low awareness among medical personnel regarding personal data protection.

KEYWORDS: public administration, ethical standards, personal data

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INTRODUCTION

A growing number of countries are applying digitalization processes in healthcare systems, which leads to an increase in the volume of personal medical data processing. The protection of personal medical data is highly specific and requires legal regulation. This is important because medical information belongs to the sensitive category, and its illegal disclosure violates the rights of patients and may carry legal risks for the organization that has not provided such protection [1, 2].

AIM

The aim of the study is to analyse the challenges of protecting personal medical data in the European Union (EU) Member States and other European countries during the implementation of the General Data Protection Regulation (GDPR).

MATERIALS AND METHODS

This study was conducted to analyze the legal regulation of personal medical data protection, with a particular focus on the implementation of Regulation (EU) 2016/679 General Data Protection Regulation (GDPR) and the relevant case law of the European Court of Human Rights (ECHR).

A comprehensive literature search was conducted using the following databases: Google Scholar, PubMed, Scopus, Web of Science, and SpringerLink. The search covered publications from 2016 to 2025, corresponding to the period of GDPR implementation, while the analysis of ECHR case law encompassed decisions from 1997 to the present.

The search included combinations of the following keywords: personal data protection, medical data, GDPR enforcement, healthcare privacy, data breaches in healthcare, public administration, ethical standards, personal data, and GDPR compliance.

Studies were selected based on the following inclusion criteria: peer-reviewed scientific articles, official EU legal acts, analytical and monitoring reports of data protection authorities, and ECHR judgments related to personal medical data protection. The following were excluded from the review: conference abstracts, editorials, opinion pieces, non-peer-reviewed publications, and unofficial commentaries.

The initial search yielded more than 60 potentially relevant sources. After relevance screening, 28 sources were included in the final review, fully corresponding to the reference list. In addition, the study provided a comparative overview of enforcement activities of data protection authorities in 27

EU Member States, with an analysis of administrative fines imposed for unlawful processing, storage, disclosure, or security breaches of medical data, enabling identification of dominant categories of violations and enforcement trends in healthcare.

The research employed dialectical, hermeneutic, comparative, analytical, synthetic, and system analysis methods.

ETHICS

This review article is based on an analysis of publicly available scientific data published in peer-reviewed journals, clinical guidelines, and databases. No patient-identifying data were used during the work, and no approval from an ethics committee was required, as the study did not involve new clinical interventions or primary collection of patient information. The authors adhered to the ethical principles of the Declaration of Helsinki of the World Medical Association and international standards for publication in medical journals, including the recommendations of the ICMJE (International Committee of Medical Journal Editors).

No element of the work contains plagiarism or fabrication of data. All sources of information are appropriately cited and properly formatted.

FRAMEWORK

The study was conducted as a fragment of the complex scientific project of the Bogomolets National Medical University «Forensic medical assessment of the impact of subclinical alcohol intoxication on human cognitive functions» (state registration number 0125U000571; term: 2025-2027).

REVIEW AND DISCUSSION

Personal medical data are subject to legal protection that establishes a special regime of compliance with confidentiality and security standards. This is important for medical institutions. Any action with such data (collection, recording, organisation, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction) may be carried out exclusively in accordance with the law [1-4].

The protection of personal medical data within the EU is ensured through a multi-level system that combines the ECHR, the EU institutions, and national supervisory bodies. At the national level, these principles are implemented by Data Protection Authorities (DPAs) and courts, which apply both the GDPR and national legislation, guided by the case law of the ECHR. National courts frequently refer to both the GDPR and the ECHR's case law when resolving disputes related to personal medical data. Among the case law of the ECHR are Z. v. Finland (1997) [5], M.S. v. Sweden (1997) [6], Von Hannover v. Germany (2002) [7], Poltoratsky v. Ukraine (2003) [8], Birzykowski v. Poland (2006) [9], S. and Marper v. the United Kingdom (2008) [10], and Jilberg v. Sweden (2012) [11], which are compared in Table 1.

Table 1 illustrates the growing body of case law of the ECHR concerning the protection of the right to privacy and the confidentiality of personal medical data. The ECHR, both in practice and in principle, recognizes that personal medical data constitute sensitive information and that the protection of this right is closely linked to safeguarding human dignity and personal integrity. Beginning with the case Z. v. Finland (1997) [5], the ECHR emphasized that any disclosure of medical information must be justified, necessary, and proportionate, as derived from Article 8 of the Convention for the Protection of Human Rights

Table 1. ECHR Cases Protecting Personal Medical Data

ECHR Case	Z v. Finland [5]	M.S. v. Sweden [6]	Von Hannover v. Germany [7]	Poltoratsky v. Ukraine [8]	Birzykowski v. Poland [9]	S. and Marper v. the United Kingdom [10]	Jilberg v. Sweden [11]
Year	1997	1997	2002	2003	2006	2008	2012
Country Involved	Finland	Sweden	Germany	Ukraine	Poland	United Kingdom	Sweden
Core Issue	Disclosure of HIV status during criminal proceedings	Sharing of medical data by authorities without consent	Publication of private health and family details of public figures	Improper access to prisoner's medical records	Disclosure of hospital medical reports in court	Retention of DNA and biometric data by authorities	Use of patient records for research without proper anonymization
ECHR Findings (Article 8)	Violation of the right to respect for private life	Violation found	Violation found	Violation found	Violation found	Violation found	Violation found
Content	Medical data is highly sensitive; any disclosure must be justified, necessary, and proportionate	Protection of health data requires strict confidentiality and limiting the purposes of disclosure	Even public figures enjoy protection of private and medical information	State must ensure confidentiality of medical data even in detention settings	Unauthorized sharing of hospital records breaches privacy rights	Genetic and biometric data fall under sensitive personal data requiring strict safeguards	Research use of medical data must ensure effective anonymization and consent mechanisms

Source: compiled by the authors based on [5-11]

and Fundamental Freedoms (1950). The case law is not limited to a single decision; the specificities of different types of personal medical data are emerging in new ECHR judgments (for example, in cases related to the retention or use of genetic data).

When the EU adopted the GDPR in 2016 [12], it incorporated many of the safeguards already formulated in ECHR judgments. The legal framework for the protection of personal medical data of EU citizens was harmonised, as each national regime had its own specific features, which in turn required unification. Since 2016, EU healthcare institutions have been obliged to write their internal compliance policies in such a way that they comply with the GDPR. First of all, this rule requires the appointment of data protection officers (DPOs) and the implementation of technical and organisational measures (TOMs) to ensure the lawful processing of medical data, notification of breaches of personal medical data protection to supervisory boards within 72 hours, etc. Core GDPR principles: explicit consent, data minimisation, purpose limitation, and security of processing – reflect the same rationale developed through ECHR jurisprudence: that the handling of personal medical data must always be lawful, transparent, and proportionate to a legitimate purpose. The GDPR represents not a departure from, but rather a continuation of the human rights-based standards for medical data protection first established by the ECHR.

The GDPR is mandatory for organizations that work with personal medical data of EU residents (including residents located outside the EU). Such strictness is not accidental; it should ensure adequate "legal steps" to change social relations towards their digital transformation (namely, the rapid growth of data processing on the Internet and the development of "big data" systems, as well as the gradual unification of medical information systems). Thus, it is important that:

– firstly, the GDPR has an extraterritorial principle of operation and applies to all organizations (including medical institutions, private clinics, pharmaceutical companies, research centers and non-profit organizations) that process, use or store personal medical data of EU residents [13, 14]. Even if the organization has no physical establishment in Europe, it is still required to implement appropriate legal, organizational, and technical measures to ensure the protection of personal medical data. In other words, if a medical company, clinic or telemedicine platform does not have an office in the EU, but provides remote consultations or laboratory services to patient's resident in the EU, uses their medical data (anamnesis, test results, electronic prescriptions, telemedicine consultation records etc.) or stores this data in its information systems, such activities automatically fall under the GDPR. For example, if a Ukrainian private laboratory performs tests for patients from Poland or Germany, sending results by email or via an online platform, then despite the fact that the laboratory is physically located outside the EU, it processes personal medical data of EU residents and therefore must comply with the GDPR requirements;
– secondly, compliance (or GDPR compliance programs) plays a crucial role in mitigating these risks. Establishing a robust compliance framework enables medical institutions and organizations to systematically implement all necessary legal, technical, and organizational measures [15, 16]. If the personal data controller has not implemented appropriate technical and organizational measures to ensure the protection of the rights of data subjects, has not taken into account data protection by design or has not notified the data breach incident to the supervisory authority within 72 hours of becoming aware of the breach, and such incident has resulted in a violation of the rights or freedoms of individuals, fines of up to 20 000 000 euros or 4% of the company's global annual revenue (whichever is higher) are provided for. The supervisory authority has the right to apply additional corrective measures, such as issuing an order to stop processing personal data, temporarily or permanently restricting access to the data or requiring the deletion of data that was processed in violation;
– thirdly, in order to minimize the risk of liability, it is advisable for medical institutions processing personal medical data of EU residents to take the following steps:
  1) ensure compliance of internal processes with the requirements of the GDPR, namely to determine that the full cycle of processing personal medical data (from collection to storage and transfer or destruction) must comply with the principles of proportionality and data minimization. In case of processing outside the EU, the destination country must be granted the status of one that ensures an adequate level of data protection;
  2) take the necessary measures to ensure appropriate security measures, for example, by including special clauses in contracts with partners, suppliers, laboratories or insurance companies, special conditions for processing and storing personal medical data should be provided, as well as determine the liability of the subjects for violation of these conditions. Internal policies of medical institutions should contain provisions on the role and responsibilities of the DPO;
  3) receive and/or process personal medical data with the informed consent of the individual whose data is being processed. Such consent must be clear, freely and consciously given, in writing or in electronic form with the possibility of its verification and withdrawal. Exceptions are permitted only in cases expressly provided by law, such as for the protection of an individual's life or public health;
  4) inform the subject of medical data about the purpose of processing, storage periods, categories of persons to whom the data may be transferred, and also ensure the patient's right to access their data, correct or delete inaccurate information, restrict or object to processing, and transfer data (data portability);
  5) ensure compliance with technical and organizational requirements for the implementation of the above rights, in particular through electronic patient acco-

unts in the system (for example, in Ukraine, this is the eHealth and Health24 systems);

– fourthly, the main problems that remain unresolved in countries that are at the stage of implementing the GDPR (in particular, Ukraine) include:
  1) insufficient awareness of medical personnel with the principles of personal medical data protection. A significant part of doctors, nurses and administrative staff do not have proper training in the practical application of GDPR requirements. Most medical institutions lack training programs on confidentiality and ethical handling of patient data. As a result, medical personnel often violate the principles of data minimization, incorrectly determine the purpose of their processing or violate the security of their transmission;
  2) technical vulnerability of electronic medical data storage systems. The vulnerability of such systems makes them a target for cybercriminals. There is also a lack of effective control over illegal data dissemination.

Promising directions identified in recent regulatory practice include the harmonisation of standards for the exchange of medical data, ensuring the right of patients to confidentiality. Each person who transfers their personal data should be granted the rights (and not only declaratively):

a) to request the destruction of their personal data if they are no longer needed for the purposes for which they were collected;
b) to receive information about what data is processed, for what purpose, and to request their correction;
c) to request the temporary cessation of data processing under certain conditions (for example, if the data is contested);
d) to object to the use of data, for example, for direct marketing purposes.

Each medical institution that processes patients' medical data must develop and approve an internal privacy policy [17–19]. Such a document must determine the procedure for collecting, storing, processing, transferring, and destroying personal data; categories of persons who have access to information; and responding to incidents of leakage or unauthorised access. Internal regulations and contracts must be reviewed and adapted to the requirements of the law. This applies to both contracts with clients and with IT contractors and services. It is important to develop a clear procedure for reporting data leaks. It is seen that the introduction of certification of medical information systems according to international standards (ISO/IEC 27701, which is a certification for Privacy Information Management Systems), in particular for countries that are not EU members, will increase their compatibility with European platforms.

The protection of personal medical data is a right guaranteed to everyone. In Article 4 of the GDPR, the term "data concerning health" is used. Such data are classified as special categories of personal data that require a higher level of protection. These include information about «personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about his or her health status» [12]. The processing of such data is permitted only if there is a clear legal basis – the consent of the data subject or the need to provide medical services in accordance with the requirements of the law.

The issues of personal medical data protection are relevant both at the general theoretical [20-25] and regulatory levels [12]. The relevance of scientific research is confirmed by statistical data on the volume of fines imposed for violations of the GDPR. National data protection authorities of EU member states [26], including the Spanish Data Protection Agency, the French Commission Nationale de l'Informatique et des Libertés, and the Italian Garante per la protezione dei dati personali, among others, apply sanctions to medical institutions, pharmaceutical companies, and individual medical practices for violating the GDPR.

Fig. 1 and Fig. 2 present the data from the EnforcementTracker.com database for the period 2018-2025, illustrating the distribution of GDPR administrative fines by economic sector and by type of violation [27]. These figures reflect both the scale and the diversity of challenges related to personal data protection, including the healthcare sector. The analysis is based on publicly available enforcement decisions adopted by national data protection authorities under Regulation (EU) 2016/679. The data systematized by the authors according to sector, number of cases, and total amount of fines. Only finalized enforcement decisions were included in the analysis.

As we can see, although the healthcare sector is not among the leaders in terms of the total amount of fines, it has a large number of incidents (257), which indicates existing problems in the processing of personal medical data (for comparison: in the financial sector there are fewer cases, but significantly larger fines. However, these indicators may be affected by the type of activity and the size of the user base, and the amount of financial liability depends on this) (Fig. 1).

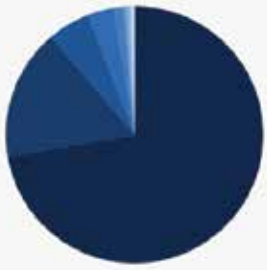
Fig. 2 presents the distribution of administrative fines by main categories of GDPR infringements, including unlawful processing, violations of general data processing principles, and insufficient technical and organisational measures. An analysis of the three main categories shows that most violations stem from unlawful or insufficiently legal grounds for data processing (e.g., processing without proper patient consent or unlawful transfer to third parties). The high rate of non-compliance with the general principles of processing indicates violations ranging from opaque privacy policies to data retention longer than necessary. The third most important category, insufficient technical and organisational protection, directly affects healthcare institutions, which often lack modern encryption systems, access auditing, or leak response procedures.

In the annual report Protecting Personal Data in a Changing Landscape (2024), it is stated that the 2024-2027 Strategy provides a comprehensive roadmap to address emerging challenges, safeguard fundamental rights, and adapt to the rapid evolution of digital technologies. National DPAs

Statistics: Fines by sectors
The following statistics show how many fines and what sum of fines have been imposed to date in each sector.

Note: Only fines with valid information on the amount of the fine and on the the corresponding sector are taken into account.

1. By total sum of fines:



Sector	Sum of Fines
Media, Telecoms and Broadcasting	**€ 4,905,920,868** (at 346 fines)
Industry and Commerce	**€ 1,120,852,727** (at 540 fines)
Employment	**€ 360,498,217** (at 174 fines)
Transportation and Energy	**€ 222,367,521** (at 153 fines)
Finance, Insurance and Consulting	**€ 82,423,108** (at 297 fines)
Health Care	**€ 31,093,279** (at 257 fines)
Public Sector and Education	**€ 30,885,763** (at 290 fines)
Accomodation and Hospitality	**€ 22,699,248** (at 83 fines)
Individuals and Private Associations	**€ 4,257,481** (at 323 fines)
Not assigned	**€ 3,614,609** (at 198 fines)
Real Estate	**€ 3,001,571** (at 79 fines)

Fig. 1. Statistics on GDPR administrative fines for 2018-2025, including the health care sector

Source: compiled by the authors based on [27]

Statistics: Fines by type of violation
The following statistics show how many fines and what sum of fines have been imposed per type of GDPR violation to date.

Note: Only fines with valid information on the amount of the fine and on the type of violation are taken into account.

1. By total sum of fines:

Violation	Sum of Fines
Insufficient legal basis for data processing	**€ 3,004,692,817** (at 773 fines)
Non-compliance with general data processing principles	**€ 2,511,690,330** (at 717 fines)
Insufficient technical and organisational measures to ensure information security	**€ 877,952,537** (at 508 fines)
Insufficient fulfilment of information obligations	**€ 252,723,860** (at 202 fines)
Insufficient fulfilment of data subjects rights	**€ 103,012,766** (at 274 fines)
Unknown	**€ 24,325,341** (at 19 fines)
Insufficient cooperation with supervisory authority	**€ 7,089,169** (at 154 fines)
Insufficient fulfilment of data breach notification obligations	**€ 3,985,392** (at 48 fines)
Insufficient data processing agreement	**€ 1,128,510** (at 14 fines)
Insufficient involvement of data protection officer	**€ 978,000** (at 25 fines)
Lack of appointment of data protection officer	**€ 35,670** (at 6 fines)

Fig. 2. Distribution of fines by type of GDPR violations for 2018-2025

Source: compiled by the authors based on [27]

should prioritise the information security of medical IT systems that use personal health data, including electronic patient records, telemedicine services, mobile applications for health monitoring, and information exchange systems between hospitals [28]. European regulators consider such breaches to be among the most dangerous, since the leakage of even a limited amount of health data can lead to a violation of personal dignity, discrimination, misuse of medical information, or a violation of medical confidentiality. For example, in 2024, the Croatian Data Protection Authority conducted 623 investigations, received 1 280 complaints, issued 153 compliance orders, and adopted 191 sanctions, including 38 fines. Several complaints were filed by data subjects who had requested copies of their health data. The hospital concerned failed to provide these copies, claiming that the requested medical documentation had been irretrievably lost. As the hospital had not implemented adequate backup mechanisms for personal data, access to the data subjects' information was permanently lost, constituting a breach of Article 32(1)(b) of the GDPR. Furthermore, the Agency concluded that the hospital had violated several provisions concerning data security and integrity. The Croatian DPA imposed an administrative fine of €190 000 [28].

CONCLUSIONS

1. The protection of personal medical data within the EU is ensured through a multi-level system that combines the ECHR, the EU institutions, and national supervisory bodies. National courts frequently refer to both

the GDPR and the ECHR's case law when resolving disputes related to personal medical data.

2. The GDPR has extraterritorial effect and covers any activity related to the processing of personal medical data of EU citizens, even if such processing is carried out outside its territory.
3. In order to comply with the GDPR, healthcare providers must ensure the lawful, transparent, and secure processing of personal medical data. This entails appointing Data Protection Officers, implementing appropriate technical and organizational measures, obtaining valid informed consent from patients where required by law, and effectively guaranteeing data subjects' rights to access, rectify, erase, restrict, or object to the processing of their personal medical data. Furthermore, healthcare institutions should develop and implement comprehensive internal data protection policies that clearly define responsibilities, data handling procedures, incident response mechanisms, and staff training programs to ensure consistent and effective GDPR compliance. At the same time, many European countries continue to face persistent challenges in GDPR implementation within the healthcare sector, including insufficient awareness among medical personnel regarding personal data protection requirements, technical vulnerabilities of healthcare information systems, and inadequate oversight of confidentiality compliance.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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CASE STUDY

Rare demyelinating diseases of the central nervous system: A diagnostic and therapeutic challenge – based on the case of a young woman with MOGAD

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ABSTRACT

Demyelinating diseases of the central nervous system constitute a heterogeneous group of diseases. The best known is multiple sclerosis, while neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are rare diseases. A 19-year-old female patient was admitted to the neurology department due to rapidly progressing memory and speech disorders. Mild mixed aphasia and right-sided pyramidal syndrome were diagnosed. Magnetic resonance imaging (MRI) of the brain revealed acute nodular demyelination in the left hemisphere. Intravenous methylprednisolone was administered. After approximately 2 months, the patient was readmitted due to several generalized epileptic seizures. At that time, the patient was transferred to a clinical center, where extensive diagnostics was performed. Among others, acute disseminated encephalitis, autoimmune encephalitis, tumefactive multiple sclerosis, and tumor were taken into consideration. MRI with spectroscopy and angiography revealed degenerative changes following acute demyelination. General examination of the cerebrospinal fluid was normal. No anti-neuronal antibodies were detected. However, positive anti-MOG antibodies were detected (and antibodies against aquaporin 4 were negative), which led to a suspicion of MOGAD. The patient was discharged home with a recommendation to use antiepileptic drugs and oral steroids. It is important to remember about rare demyelinating diseases, such as MOGAD, which require differentiation from multiple sclerosis. The prognosis for this condition is generally better, but the disease can lead to permanent neurological damage.

KEYWORDS: MOGAD, demyelination, seizures, cerebral cortical encephalitis

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INTRODUCTION

Inflammatory demyelinating diseases of the central nervous system (CNS) encompass a spectrum of disorders, primarily including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), and acute disseminated encephalomyelitis (ADEM) [1]. These disorders often share overlapping clinical presentations (e.g. optic neuritis, transverse myelitis) and MRI findings, which can make differential diagnosis challenging [2]. Accurate early distinction among them is critical, however, as their treatments and prognoses differ significantly [2]. Recognizing the correct diagnosis is particularly important in atypical or severe cases, where misdiagnosis (for example, labeling NMOSD or MOGAD as MS) cannot lead to optimal therapy [3].

MOGAD, in particular, has recently been established as a distinct CNS demyelinating condition characterized by autoantibodies targeting myelin oligodendrocyte glycoprotein [4, 5]. Historically, patients with what is now recognized as MOGAD were often misdiagnosed as having atypical MS or seronegative NMOSD [3]. MOGAD can present with a wide range of demyelinating syndromes - including optic neuritis (often bilateral), longitudinally extensive transverse myelitis, ADEM-like encephalomyelitis with encephalopathy, brainstem syndromes, or even cerebral cortical encephalitis with seizures [5, 6]. This broad clinical spectrum, combined with the relative infrequency of MOGAD, contributes to diagnostic uncertainty. Indeed, MOGAD is a rare disorder with an estimated prevalence of approximately 1.3-2.5 per 100,000 population [7], yet it poses a significant diagnostic and therapeutic challenge in neurology [3]. Confirming the diagnosis relies on detection of MOG-IgG antibodies in serum (typically via live cell-based assay), but variability in assay methods and cutoff titers, as well as an expanding clinical phenotype, can complicate interpretation [4]. Thus, a high index of suspicion is required: clinicians must consider MOGAD in patients with inflammatory demyelination that is seronegative for aquaporin-4 (AQP4) or otherwise atypical for MS, and pursue appropriate antibody testing to establish the correct diagnosis [3]. In the following case, we illustrate these principles through the diagnostic and therapeutic course of a young woman with MOGAD.

CASE REPORT

A 19-year-old patient was admitted to the municipal neurology department due to rapidly progressing memory, speech and behavioral disorders. Neurological examination at admission revealed mild sensorimotor aphasia and a discrete right-sided pyramidal syndrome. Magnetic resonance imaging (MRI) of the brain showed an area of acute nodular demyelination with enhancement in the left hemisphere (Fig. 1-3). There were no abnormalities in laboratory tests (blood count, inflammatory markers, glucose, transaminases, creatinine, electrolytes, antinuclear antibodies, thyroid hormones, vitamin B12) and in the general examination of the cerebrospinal fluid (CSF). During the stay in hospital, the patient's condition worsened, speech disorders and paresis of the right limbs increased. Due to the suspected demyelinating disease (tumefactive form of multiple sclerosis), the patient was given steroids (1 g methylprednisolone intravenously for 5 days). Partial improvement was observed and control MRI demonstrated clear regression of the changes.

After approximately 2 months, the patient was readmitted to the department due to the occurrence of several generalized tonic-clonic seizures. Another MRI was performed, which revealed no new lesions. The EEG demonstrated seizure-like lesions. Anti-epileptic drugs (valproic acid, lamotrigine and levetiracetam) were initiated. The patient's condition stabilized and the seizures stopped.

But subsequently, due to the exhaustion of diagnostic possibilities in the municipal neurology department, the patient was transferred to a clinical center.

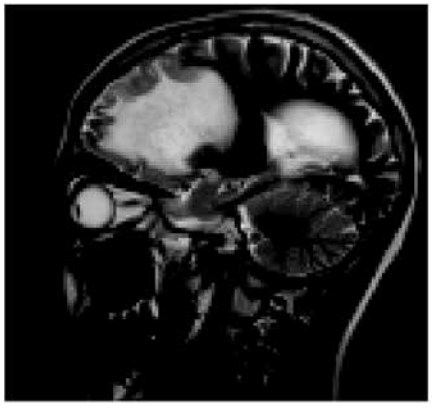
The differential diagnosis included, among others, ADEM, autoimmune encephalitis, tumefactive form of multiple sclerosis, primary brain tumor and central nervous system lymphoma.

Neurological examination at admission showed mild sensorimotor aphasia and a moderate right-sided paresis. Psychological examination revealed cognitive impairment at the level of mild dementia. A control MRI of the brain with spectroscopy and angiography revealed retrograde degenerative and malacic changes after the active phase of the demyelinating disease (Fig. 4). Thus, a proliferative process was excluded. MRI of the cervical spine did not reveal any abnormalities.

There were also no abnormalities in serum laboratory tests (blood count, electrolytes, CRP, creatinine, glucose, TSH, anti-TPO, vitamin B12, ANA1, ANA2, ANA3) and in the general examination of CSF as well as in PCR testing for viral and bacterial pathogens. No oligoclonal bands in CSF were found. Moreover, no anti-Borrelia antibodies in the IgG and IgM classes by ELISA method were detected as well as no anti-neuronal antibodies or tumor markers were found in either serum or CSF. However, positive anti-MOG antibodies were detected (anti-aquaporin 4 antibodies were negative). Based on the clinical characteristics and additional tests, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) was diagnosed. The patient was discharged home with a recommendation to use antiepileptic drugs (lamotrigine 50 mg twice a day and levetiracetam 750 mg twice a day) and oral steroids (prednisone at a initial dose of 1 mg per kg of body weight daily for one month, then gradually reduced to maintain a total treatment duration of 6 months). The patient remains under the supervision of the Neurology Clinic. Her neurological condition has been stable for a year, with sporadic seizures (so lamotrigine dose was increased to 100 mg twice daily and levetiracetam to 1000 mg twice daily). A follow-up psychological examination showed improvement in cognitive functions (test results at the level of mild cognitive impairment).

DISCUSSION

MOGAD is an immune-mediated demyelinating condition of the central nervous system, now recognized as a distinct entity that can overlap clinically with MS, NMOSD, or ADEM [8]. Most commonly, MOGAD presents with optic neuritis, myelitis, or an ADEM-like polysymptomatic attack, whereas purely cortical presentations are uncommon. A subset of patients - such as the young adult in our case – develop an encephalitic picture with cortical lesions and seizures, a rare phenotype often referred to as cerebral cortical encephalitis (CCE) or „FLAMES" (FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures) [9]. Such cases typically manifest with acute onset of seizures, headaches, and focal neurologic deficits (e.g., aphasia or cognitive impairment) and can initially be misdiagnosed



a

b

Fig. 1. T2-weighted images in sagittal (a) and coronal (b) planes. Extensive hyperintense areas of white matter mainly in the left cerebral hemisphere with extension through the corpus callosum

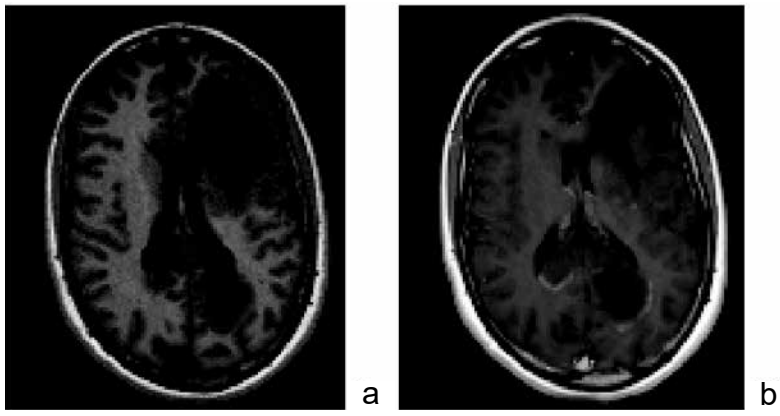


Fig. 2. T1-FSPGR images before (a) and after (b) contrast administration showing partial peripheral enhancement

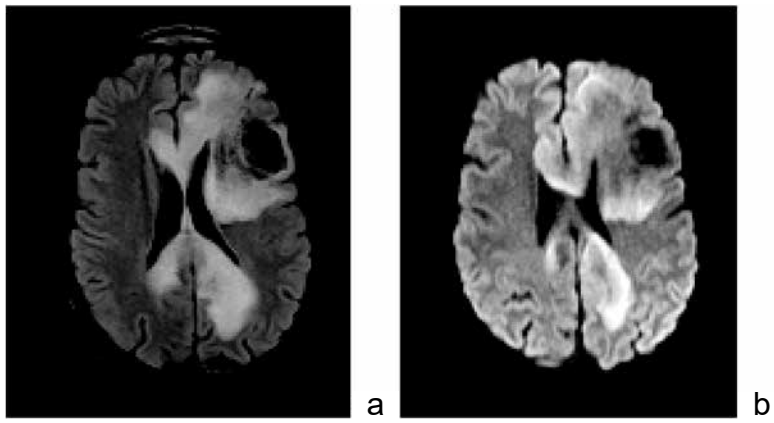


Fig 3. T2 FLAIR (a) and DWI (b) images in axial plane. Extensive areas of abnormal signals in the left cerebral hemisphere with corpus callosum involvement and peripheral bands of increased water molecule restriction in the extracellular space

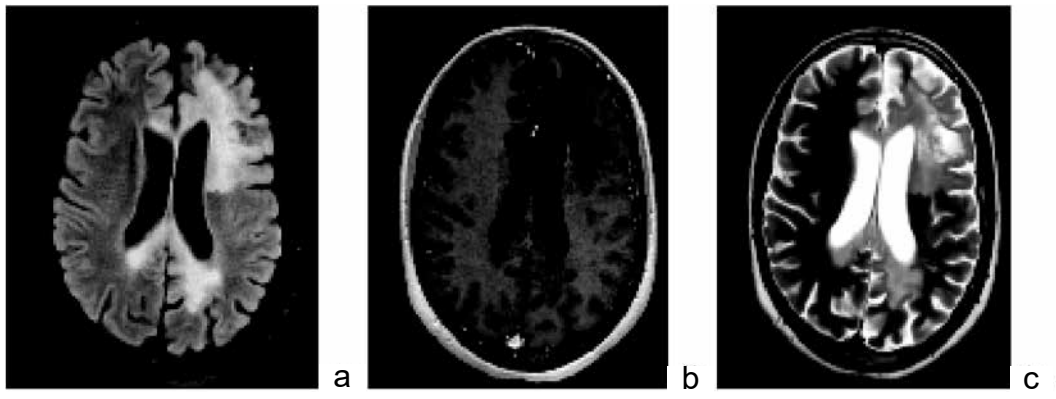


Fig. 4. T2 FLAIR (a), T1 (b) and T2 (c) images showing regression of edema with accompanying gliosis

as viral or autoimmune (paraneoplastic) encephalitis [9]. Indeed, recent literature reviews have identified only 33-50 reported patients with MOG-IgG-positive CCE, with most presenting with seizures and unilateral cortical MRI lesions, and almost all showing a favorable response to immunotherapy [9, 10]. This underscores the rarity of the cortical seizure-onset presentation in MOGAD, especially in adults, and highlights the importance of considering MOGAD in the differential diagnosis of encephalitic episodes.

In the present case, the diagnostic workup needed to exclude more common pathologies that can mimic MOGAD. The differential diagnosis for a young patient with an inflammatory brain lesion and neuropsychiatric symptoms included ADEM, autoimmune encephalitis, a tumefactive form of MS, and even a central nervous system neoplasm. The initial brain MRI revealed an acute nodular, contrast-enhancing lesion in the left hemisphere, raising concern for a tumefactive demyelinating plaque or a glial tumor.

Notably, MOGAD itself has been reported to cause solitary „tumefactive" demyelinating lesions that mimic brain tumors, with tumefactive lesions occurring in approximately 22% of MOGAD patients [11]. In general, a steroid trial can be informative in such scenarios: demyelinating lesions typically show marked clinical and radiological improvement with high-dose corticosteroid therapy, whereas true neoplasms will not. Consistent with this, our patient improved after intravenous methylprednisolone, and follow-up MRI demonstrated a regression of the lesion (with residual gliotic/malacic changes). Such an evolution is characteristic of a demyelinating process and effectively ruled out an underlying proliferative lesion [11].

Infectious etiologies and paraneoplastic autoimmune encephalitis were also considered given the subacute cognitive decline and seizures; however, the lack of fever, normal cerebrospinal fluid (CSF) profile, and negative anti-neuronal autoantibodies made those diagnoses unlikely. While a small subset of MOGAD patients with seizures have been reported to harbor coexisting anti-NMDA receptor antibodies [12], no such findings were present in this case. Ultimately, the detection of serum MOG-IgG – in the appropriate clinical context – confirmed the diagnosis of MOGAD, after aquaporin-4 IgG and other potential causes had been excluded.

Distinguishing MOGAD from MS is particularly important, as the two disorders differ in prognosis and management despite some overlapping features. Certain MRI characteristics can help: brain lesions in MOGAD are often larger, ill-defined („fluffy"), and located in cortical or deep gray matter regions (such as thalami or brainstem), whereas MS lesions are typically smaller, well-demarcated, and periventricular/juxtacortical with an ovoid shape oriented perpendicular to the ventricles [13]. In our patient, the MRI lesions were more consistent with an acute demyelination of the kind seen in MOGAD, and there were no classic periventricular MS plaques. Moreover, leptomeningeal enhancement on MRI – seen in this case – is an imaging feature that strongly favors MOGAD encephalitis over MS, found in approximately 89% of reported MOGAD-CCE cases [9]. The clinical course also provided clues: the acute encephalopathic presentation with seizures is atypical for MS (seizures occur in only 2-5% of MS patients), but is a recognized feature of cortical presentations of MOGAD, occurring in approximately 10% of MOGAD patients [14]. By contrast, our patient's age (19 years) made MS a consideration, but the combination of clinical and radiologic features pointed away from MS. Additional laboratory findings supported this distinction as well: notably, no oligoclonal bands were detected in CSF. This is in line with MOGAD, which usually lacks persistent intrathecal IgG synthesis (positive in only 5% of cases), whereas up to 95% of MS cases classically exhibit CSF oligoclonal bands [13]. Together, these factors favored the diagnosis of MOG-antibody-associated encephalitis over an MS or other demyelinating conditions.

Proper identification of MOGAD has direct implications for therapy and prognosis. High-dose corticosteroids are the cornerstone of acute treatment in MOGAD, typically leading to rapid improvement [8]. Our patient's partial recovery after intravenous methylprednisolone and the radiologic improvement on the subsequent MRI are consistent with the known steroid-responsiveness of MOGAD lesions. In contrast to MS, there is no role for chronic MS disease-modifying drugs in MOGAD; instead, immunotherapy is guided toward preventing relapses. Although MOGAD can be monophasic, a significant proportion of patients – especially adults – experience relapses over time [14]. For this reason, maintenance immunosuppressive therapy is often considered after a first MOGAD attack in adults. Therapeutic options include a prolonged taper of oral corticosteroids and/or introduction of steroid-sparing agents such as azathioprine, mycophenolate mofetil or rituximab, while intravenous immunoglobulin (IVIG) has also shown efficacy – particularly in pediatric cases [15]. The optimal regimen is individualized based on the patient's risk factors and tolerance, but the goal is to reduce the risk of further demyelinating episodes that could accumulate neurological deficits.

Finally, the overall prognosis in MOGAD tends to be more favorable than in MS or aquaporin-4 positive NMOSD, provided that acute attacks are appropriately managed. Unlike MS, MOGAD does not typically lead to a chronically progressive deterioration – there is usually no insidious progression outside of relapses [8]. Most patients regain near-normal function after attacks, and long-term disability rates are low in comparison to NMOSD. Children in particular often recover well, whereas adult patients may have slightly higher risk of residual deficits or relapse. Nevertheless, MOGAD is not benign: severe attacks can cause permanent neurological damage, and each relapse carries a risk of cumulative disability. Therefore, recognizing this rare demyelinating disease and differentiating it from MS is critical, as it prompts the appropriate immunotherapy and close follow-up. In our patient's case, timely steroid treatment and seizure control led to a good recovery, and she remains stable on follow-up. Ongoing surveillance and a low threshold for immunotherapy escalation will be important given the possibility of relapse, but her prognosis for maintaining a high level of function is optimistic in light of the generally better outcomes observed in MOGAD.

CONCLUSIONS

It is important to remember about rare demyelinating diseases, such as MOGAD, which require differentiation from multiple sclerosis. The prognosis in this condition is generally better, but the disease can lead to permanent neurological damage. Early recognition and appropriate treatment are crucial for optimal patient outcomes.

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16. Written informed consent was obtained from the patient for publication of this case report and accompanying images

CONFLICT OF INTEREST

The Authors declare no conflicts of interest

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CASE STUDY

Acute pancreatitis as a severe complication of scoliosis surgery in pediatric patient: A case report and literature review

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ABSTRACT

Acute pancreatitis (AP) in children is a rare but severe inflammatory disease of the pancreas. Unlike in adults, where alcohol consumption and gallstones are the most common causes, pediatric AP results from various factors such as abdominal trauma, infections, biliary tract disease, systemic disorders, genetic predisposition, and drug-induced injury, with many cases remaining idiopathic. Adolescent idiopathic scoliosis (AIS) is the most common form of pediatric scoliosis. Treatment options include physical therapy, bracing, and surgical correction in severe cases. A case of an adolescent patient with AIS who developed severe (AP) after scoliosis surgery was analyzed, alongside a review of the relevant literature. We report the case of a 14-year-old male with severe AIS and additional risk factors, including malnutrition and hypertension, who underwent transpedicular stabilization and spondylodesis from Th2 to L4. In the early postoperative period, he developed severe (AP) as a rare but serious complication. Conservative treatment involved withdrawal of oral feeding, initiation of parenteral nutrition, and subsequent transition to enteral feeding. Multidisciplinary management addressed associated liver abnormalities, gastrointestinal ulcerations, neurological findings, and persistent hypertension, leading to gradual clinical recovery.We present the case of an adolescent patient with (AIS) who developed severe (AP) as a complication of surgery. In addition, a review of the relevant literature is presented and discussed, demonstrating that multiple perioperative abnormalities associated with scoliosis surgery may represent significant risk factors for the development of AP and contribute to the occurrence of this complication.

KEYWORDS: acute pancreatitis, complication, scoliosis surgery, pediatric

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INTRODUCTION

Acute pancreatitis (AP) in children is a rare condition, with an estimated incidence of 13 cases per 100,000 individuals. The most common symptoms of pediatric AP include acute abdominal pain, nausea, and vomiting, and the majority of cases are characterized by elevated serum levels of pancreatic amylase and/or lipase. Radiological imaging of the abdomen often reveals abnormalities. The etiology of AP in children differs from that in adults, in whom alcohol consumption and gallstones are the most common causes. In children, known etiological factors include abdominal trauma, viral infections, biliary tract diseases, medications or toxins, genetic abnormalities, and systemic diseases such as sepsis, inflammatory bowel disease, or hemolytic uremic syndrome. However, a significant proportion of pediatric AP cases still remain idiopathic [1, 2].

Adolescent idiopathic scoliosis (AIS) is the most common form of pediatric scoliosis. Approximately 2-3% of children under the age of 16 have a spinal curvature of ≥10 degrees, with 0.3-0.5% progressing to a curvature of 20 degrees or more - the threshold at which therapeutic intervention is generally recommended [3]. AIS is associated with an increased risk of health issues in adulthood, including reduced quality of life, cosmetic deformity, physical disability, pain, and progressive functional limitations [4]. Consequently, timely and appropriate treatment is crucial. Management strategies for AIS include conservative approaches such as physical therapy and bracing, as well as surgical correction [4].

We present a case of severe AP as a rare complication of scoliosis surgery, developing in a pediatric patient in the early postoperative period.

MATERIAL SAND METHODS

A case of an adolescent patient with AIS who developed severe (AP) after scoliosis surgery was analyzed, alongside a review of the relevant literature.

CASE REPORT

A 14-year-old male patient (height: 168.5 cm, weight: 47 kg; BMI: 16.6 kg/m^2, 13th percentile) was admitted in September 2023 for surgical treatment of AIS [5].

Idiopathic scoliosis in this patient was located in the thoracolumbar region from Th10 to L3, with the apex at Th12 and a significant disturbance of curvatures in the

sagittal plane. Before surgery, the scoliosis angle measured from Th10 to L3 was 82 degrees, and in the lumbar section, kyphosis was present with an angle of 34 degrees. The length of the spine measured from Th1 to S1 was 455 mm (Fig. 1-3).

The patient underwent surgical correction of scoliosis involving transpedicular stabilization and spondylodesis from thoracic vertebra 2 to lumbar vertebra 4 (Th2-L4) using titanium instrumentation (Expedium, Johnson & Johnson). Transpedicular screws were inserted on the left side at levels Th2, Th3, Th5-Th9, Th11-L4, and Th10, Th12-L2 (rigid screws at Th12-L2, the others polyaxial), and on the right side at levels Th2, Th3, Th5-Th7, Th9, Th11, L3, and L4 (all polyaxial). The procedure lasted a total of 8 hours and 15 minutes and was performed under general anesthesia. After the surgery, the scoliosis angle was reduced to 34 degrees, lumbar lordosis was restored to an angle of 16 degrees, and the length of the spine measured from Th1 to S1 increased to 522 mm (Fig. 4).

Prior to admission, elevated blood pressure values had been observed during the final week of September 2023, reaching up to 150/100 mmHg, but no further diagnostic procedures or treatment were initiated. In the early postoperative period, the patient developed signs of acute liver failure, including markedly elevated aspartate aminotransferase (AST) to 4,997 U/L, 125-fold above the upper normal range (UNR), and alanine aminotransferase (ALT) to 63-fold above the UNR. These abnormalities resolved over several days. Subsequently, the patient began experiencing epigastric and periumbilical pain, abdominal distension, and intensive vomiting. Laboratory tests revealed elevated pancreatic enzyme levels (amylase 246 U/L, 2.5-fold above the UNR; lipase 1,173 U/L, 19-fold above the UNR) and mild hyponatremia.

Physical examination showed a distended abdomen, reduced peristalsis, and tenderness on palpation in the right and left middle abdomen, as well as in the central epigastrium. Additionally, the patient presented with elevated arterial blood pressure (143/86 mmHg). Computed tomography (CT) of the abdomen revealed enlargement of the pancreas, particularly in the head region, a fluid collection near the tail of the pancreas and the splenic hilum, and dilation of the stomach and duodenum.

Oral feeding was discontinued and parenteral nutrition was introduced. Over the subsequent days, pancreatic enzyme levels gradually decreased. Follow-up abdominal ultrasonography showed normalization of the pancreatic parenchyma, aside from some irregular margins.

Persistent abdominal distension and severe pain prompted an abdominal radiograph, which revealed air-fluid levels in the stomach and jejunum. Treatment with intravenous proton pump inhibitors (PPIs) and itopride was initiated. Gastroscopy revealed esophagitis, gastritis, and duodenitis with crater-like ulcers in the gastric body and pre-pyloric area.

Following the introduction of treatment, the patient's gastric residuals decreased over the next several days and abdominal pain subsided. A gradual transition from parenteral to enteral nutrition via a nasogastric tube was

Fig. 1. Patient before scoliosis operation

Fig. 2. Patient before scoliosis operation

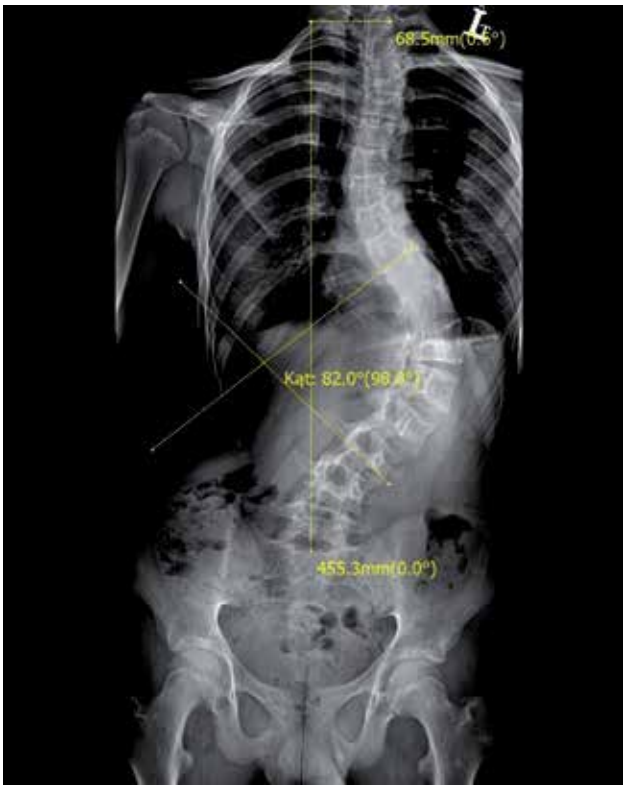

Fig. 3. Radiological assessment before scoliosis operation

Fig. 4. Radiological assessment after scoliosis operation

successfully achieved. Additionally, ursodeoxycholic acid was prescribed due to a slight elevation in gamma-glutamyl transpeptidase (GGT) levels, which subsequently normalized. A follow-up gastroscopy after 3 weeks showed regression of the previously observed inflammatory lesions.

During hospitalization, the patient required high doses of analgesics, which were later tapered, and received antihypertensive therapy with amlodipine and metoprolol succinate. Periodic fluctuations in liver aminotransferases led to the initiation of hepatoprotective therapy with ornithine aspartate and silymarin.

Discharge recommendations included continuation of the ongoing treatment and partial enteral nutrition via a nasogastric tube with a high-calorie diet, combined with an oral diet enriched with nutritional support formulas.

The patient gradually gained weight (up to 58 kg, with a height of 178 cm and a BMI of 18.3 kg/m^2 at the six-month follow-up visit), and control gastroscopy showed complete regression of the earlier lesions. The patient remained on PPI, essential phospholipids, silymarin, and vitamin B supplementation for 3 months. Nevertheless, he has remained under multispecialty care, including orthopedic and rehabilitation clinics, and is under nephrological supervision due to hypertension.

DISCUSSION

Although surgical treatment for AIS carries a lower risk of complications compared to adult spinal deformity surgery, complications can still occur. The frequency of complications varies depending on the type of scoliosis and the specific surgical approach. A review by Reames et al. reported the highest complication rates in neuromuscular scoliosis (17.9%), followed by congenital scoliosis (10.6%) and idiopathic scoliosis (6.3%) [6]. According to data reported by Menger et al., postoperative complication rates in AIS surgery were as follows: gastrointestinal complications (2.7%), respiratory complications (2.8%), neurological issues (0.9%), cardiac complications (0.8%), infections (0.4%), and venous thromboembolic events (0.1%) [7].

Gastrointestinal complications following scoliosis surgery may include prolonged paralytic ileus, dysphagia, gastroparesis, and acute pancreatitis [8]. The development of AP following scoliosis surgery is a rare but significant complication, with reported incidence rates varying across studies. A prospective clinical study by Feng et al. identified AP in 7.6% of 176 patients who underwent posterior spinal correction surgery [9]. Similarly, a study by Laplaza et al. found that 9% of 80 patients developed AP [10]. However, El Bouyousfi et al. reported AP in 14 out of 571 pediatric patients (2.4%) who had undergone scoliosis surgery [11]. Scoliosis surgery is not the only procedure after which AP has been reported. Cases have also been documented following cardiac valve surgery, thoracic and thoracoabdominal aortic repairs, laparoscopic sleeve gastrectomy, and even pancreatectomy or parathyroid surgery [12-17].

The precise mechanism underlying the development of AP following scoliosis correction surgery remains uncertain. It has been hypothesized that increased spinal rigidity and tension after correction may contribute to neuropathy affecting visceral nerves and the spinal cord [8]. One of the primary mechanisms proposed for postoperative AP is mechanical trauma to the pancreas. Spinal surgical

procedures, particularly those involving correction or fusion, may inadvertently cause direct pancreatic injury. Additionally, the prone positioning commonly used during spinal surgeries may result in mechanical compression of the pancreas, increasing the risk of trauma and subsequent inflammation [9, 10, 18-20].

Another significant factor contributing to AP is hemodynamic instability during surgery. Intraoperative hypotension and reduced splanchnic blood flow can lead to pancreatic ischemia, compromising perfusion and triggering inflammatory responses. Studies indicate that lower intraoperative mean arterial pressure correlates with an increased risk of AP due to inadequate pancreatic tissue perfusion [9, 10]. This risk is particularly elevated in patients with a low body mass index, as they have reduced adipose tissue surrounding the pancreas, making it more susceptible to compression and ischemic injury [9, 18]. Furthermore, malnourished patients generally have reduced physiological reserves, increasing their susceptibility to perioperative and postoperative stressors.

Additionally, metabolic and electrolyte imbalances may play a role in postoperative AP. Surgical stress can disrupt metabolic homeostasis, leading to fluctuations in calcium and triglyceride levels, both established risk factors for pancreatitis [21]. Furthermore, the perioperative administration of certain medications, particularly opioids, has been implicated in AP development, although the precise mechanisms remain unclear [22-24].

In summary, the development of AP following spinal surgery appears to result from a multifactorial interplay of mechanical trauma, hemodynamic instability, and metabolic dysregulation.

Acute pancreatitis following major orthopedic interventions is rare and presents both diagnostic and clinical challenges, particularly in an adolescent with multiple concurrent issues, including transient liver enzyme disturbances, gastrointestinal ulcerations, persistent hypertension, and neurological symptoms. Laplaza et al. observed that patients who developed pancreatitis were typically older and taller, had a lower BMI, and experienced longer hospital stays [10]. Moreover, while low mean intraoperative arterial pressure is another well-established risk factor, De La Garza Ramos et al. also identified a history of hypertension as a predisposing factor for complications following scoliosis correction surgery, a condition present in our patient prior to the procedure [25].

Although the exact etiology of AP in the presented patient remains uncertain, several contributing risk factors must be considered, including age over 14 years, a low BMI of 16.6 kg/m^2 with relatively tall stature, as well as prolonged fasting and extensive spinal fusion segments [9,10,26]. This case also illustrates that even mild electrolyte disturbances (e.g., hyponatremia) and subtle intravascular volume shifts can disrupt splanchnic circulation, predisposing the pancreas to ischemic injury. The complexity and duration of the surgical procedure, along with potential intraoperative hemodynamic fluctuations, may have contributed to visceral hypoperfusion, leading to pancreatic ischemia. While direct pancreatic trauma was unlikely due to the surgical approach, prolonged anesthesia and prone positioning may have compromised microcirculatory perfusion. Furthermore, altered anatomical conditions following spinal correction may have exerted pressure on the celiac trunk, further contributing to AP development. The role of anesthetic agents and perioperative medications as potential triggers of AP must also be considered.

Moreover, the patient's transient acute liver failure-like picture with markedly elevated transaminases may suggest significant but self-limiting hepatic impairment, which could also have resulted from compression of the celiac trunk. Although none of the hepatotropic infections could be identified, one cannot rule out an element of transient ischemic hepatitis or drug-induced liver injury.

According to the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) criteria, the diagnosis of AP requires the presence of at least two of the following: abdominal pain consistent with AP, serum amylase and/or lipase levels ≥3 times the upper limit of normal, and imaging findings characteristic of AP [27]. The presented patient met all three diagnostic criteria, including the presence of abdominal pain, a serum lipase level of 1,173 U/L, and abdominal CT findings showing pancreatic enlargement, along with a fluid collection near the tail of the pancreas and the splenic hilum.

Ghisi et al. described a similar case involving a 15-year-old female who developed AP following scoliosis surgery. The patient had severe right thoracic scoliosis and underwent a two-stage posterior arthrodesis with growing magnetic rod instrumentation, followed by posterior fixation. The day after surgery, she developed nausea and mild abdominal pain. Similar to our patient, she presented with elevated liver and pancreatic enzyme levels, vomiting, and abdominal pain. However, unlike our patient, she did not have hypertension and had a normal BMI (21.85 kg/m^2). A CT scan of the abdomen revealed a more extensive distribution of fluid within the abdominal cavity compared to our patient. Additionally, she experienced significant intraoperative blood loss requiring transfusion of blood and fresh frozen plasma. Her treatment included a hypolipidic diet, oral hydration, somatostatin, rifaximin, and ursodeoxycholic acid. However, she did not require a nasogastric tube or further nutritional support [16].

Another case report by Hewavitharane et al. described a 13-year-old girl with severe proximal thoracic scoliosis (T3–T6) and a BMI of 16.32 kg/m^2, comparable to our patient [28]. Intraoperatively, she required blood and crystalloid transfusion. Her symptoms, including nausea, vomiting, and low-grade fever, emerged on postoperative day three. Similar to our patient, CT imaging revealed pancreatic head swelling and peripancreatic fluid. However, she also developed mild bilateral pleural effusions and lung base consolidation. Notably, this case report does not provide information on the long-term nutritional management of the patient with a low BMI.

The severity of AP and the range of necessary interventions can vary significantly among patients. A case series by Aborashed-

Amador et al. highlighted three instances of AP following spinal surgeries. Two of these cases were successfully managed with appropriate hydration and parenteral nutrition until significant clinical improvement was observed. However, the oldest patient in the series required urgent drainage due to a large peripancreatic collection identified on abdominal CT [22]. In our case, the patient initially required parenteral nutrition, which was successfully transitioned to enteral feeding, and no abdominal surgical interventions were necessary for the management of AP.

Furthermore, Ruparelia et al. described a case of AP resulting from surgery unrelated to the pancreatic region [29]. The authors reported a 15-year-old girl who developed symptoms of AP on the first day after a craniotomy for tumor excision. The clinical course, symptoms, abdominal CT findings, and treatment used were very similar to our case; however, her liver function parameters were within normal limits. Moreover, in Ruparelia's case, the likely etiology of postoperative AP was attributed to medications used, including prednisolone, propofol, and sodium valproate. This case highlights the importance of excluding common causes of AP, such as trauma, biliary stone disease, and hypertriglyceridemia. Additionally, since their patient had been hemodynamically stable throughout the operative period, splanchnic hypoperfusion was also not suspected. Therefore, in our case, the range of medications administered to the patient during the perioperative period should also be considered.

Compared to the cases mentioned above, our patient's spectrum of symptoms was more complex. The clinical presentation was not limited to AP but also included symptoms associated with esophagitis, gastritis, and duodenitis, as well as non-gastrointestinal issues such as hypertension and neurological symptoms.

Therefore, compared to the cases described in the literature, our patient required management of a much broader range of symptoms and the implementation of a more extensive diagnostic workup, including gastroenterological, neurological, cardiological, nephrological, and orthopedic assessments. The progression of this clinical case, along with other similar reports, underscores the importance of promptly evaluating pancreatic and liver enzyme levels to facilitate early diagnosis when symptoms suggest an abdominal complication [18,20,26].

CONCLUSIONS

This case illustrates a pediatric patient with severe AP as a serious complication of scoliosis surgery. AP, although rare, should be considered in the differential diagnosis when unexpected abdominal symptoms and organ dysfunction occur in the postoperative period.

Multiple risk factors, such as low BMI, hypertension, and transient perioperative abnormalities in hepatic and splanchnic circulation, can combine to produce severe gastrointestinal and systemic complications.

Successful resolution of inflammatory lesions requires early diagnosis and multidisciplinary therapy, including parenteral and enteral nutritional treatment, hemodynamic support, physical therapy, and long-term nutritional follow-up.

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The patient's parents provided written informed consent for the publication of this case report and the inclusion of photographs.

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CASE STUDY

Myocardial work indices and cardiac magnetic resonance in the diagnosis and follow-up of Lyme carditis presenting with intermittent complete heart block

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ABSTRACT

This case report explores the spectrum and mechanisms of myocardial involvement in Lyme carditis, integrating clinical and imaging findings to better understand the disease course and its management implications. While conduction abnormalities are the most well-recognized cardiac manifestation of Lyme carditis, our findings highlight the importance of myocardial work assessment by echocardiography in the early stage of the disease and by cardiac magnetic resonance in the late stage. These insights may guide clinicians in early recognition, targeted therapy, and prevention of adverse cardiac outcomes in Lyme carditis and other forms of myocarditis. We report the case of a 44-year-old male presenting with complete atrioventricular block. Myocardial work assessment by echocardiography was performed to investigate the underlying etiology, revealing findings suggestive of an inflammatory myopericardial syndrome as the cause of the conduction abnormality. The Suspicious Index in Lyme Carditis Suspicious (SILC) score indicated an intermediate probability of Lyme infection, which was subsequently confirmed by laboratory testing. The patient was treated with intravenous ceftriaxone, resulting in resolution of the conduction disturbance and obviating the need for pacemaker implantation. During follow-up, myocardial work parameters were reassessed, and cardiac magnetic resonance imaging was performed, both supporting remission with residual changes and providing additional prognostic insights.

KEYWORDS: cardiac magnetic resonance, Lyme carditis, late gadolinium enhancement, myocardial work, SILC score

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INTRODUCTION

Lyme carditis (LC) is one of the multisystem manifestations of Lyme disease (LD), a tick-borne infection caused by Borrelia burgdorferi (BB). The pathophysiology of LC involves direct cardiac invasion by the spirochete, leading to an inflammatory response. This inflammation frequently affects the cardiac conduction system, particularly the atrioventricular (AV) node, and may result in varying degrees of heart block [1, 2]. Myocardial work (MW), assessed by echocardiography, is a useful tool for detecting subclinical left ventricular (LV) dysfunction. It is calculated using pressure – strain loop analysis, which integrates non-invasively estimated LV pressure, derived from brachial artery cuff measurements, with two-dimensional speckle-tracking echocardiography (2D-STE) assessment of global longitudinal strain (GLS) [3]. Cardiac magnetic resonance (CMR), as recommended by international guidelines, is a sensitive and non-invasive imaging modality for evaluating inflammatory myopericardial syndromes. Advanced CMR techniques such as late gadolinium enhancement (LGE) enable differentiation between active inflammation and fibrotic scar tissue [4-6]. We investigated MW combined with CMR as complementary tools to support diagnosis, guide therapy, and inform prognosis in LC.

MATERIALS AND METHODS

We report the case of a 44-year-old male presenting with complete atrioventricular block. Myocardial work assessment by echocardiography was performed to investigate the underlying etiology, revealing findings suggestive of an inflammatory myopericardial syndrome as the cause of the conduction abnormality.

CASE STUDY

A 44-year-old previously healthy man was admitted with fatigue, dizziness, and complete AV block on electrocardiogram (ECG). He reported a tick bite without rash or other accompanying symptoms during a canoe trip three months prior to admission. On presentation, he was afebrile, and the physical examination was unremarkable except for a heart rate of 30 bpm and a blood pressure of 167/86 mmHg. Laboratory findings revealed elevated C-reactive protein at 19.8 mg/L (reference <5), N-terminal pro-B-type natriuretic peptide at 184 pg/mL (reference

<125), and normal high-sensitivity troponin I at 5.0 pg/mL (reference <34.2). Transthoracic echocardiography (TTE) demonstrated a left ventricular ejection fraction (LVEF) of 60% (reference ≥50) and a global longitudinal strain (GLS) of -22.8% (reference -20.5±1.9), with normal chamber dimensions, wall thickness, and no pericardial effusion (Table 1). Most MW parameters were elevated, except for global work efficiency (GWE), which remained within normal limits (Fig. 1A-B, Table 1). Given the suspicion of an inflammatory myocardial process, the Suspicious index in Lyme carditis (SILC) score, summarized by the mnemonic COSTAR (Constitutional symptoms=2; Outdoor activity=1; Sex [male]=1; Tick bite=3; Age <50=1; Rash [erythema migrans]=4) was applied.

The patient's total score was 6, indicating an intermediate probability of LC [7]. Serological testing using enzyme-linked immunosorbent assay and Western blot confirmed BB infection. Intravenous ceftriaxone 2 g daily was administered for four weeks in accordance with the 2020 Guidelines for the prevention, diagnosis, and treatment of Lyme disease [1]. Continuous intravenous salbutamol was initiated to improve conduction but discontinued after two days due to an increased heart rate. By the second day of antibiotic therapy, AV conduction improved to a 2:1 block and

Table 1. Echocardiographic parameters, including myocardial work indices, assessed during hospitalization and follow-up

	At admission	Before discharge	11 months later
GLS [%]			
GWI [mmHg%]	↑2831	↑2666	1651
GCW [mmHg%]	↑3707	↑3348	1962
GWW [mmHg%]	↑152	↑218	115
GWE [mmHg%]	95	↓93	↓94
LVEF [%]	60	63	61

Values beyond ranges are indicated with arrows. GLS (reference -20.5±1.9), global longitudinal strain; GWI (reference 1900±317), global work index represents average myocardial work derived from the mean pressure-strain loop area of all segments (total work done), it is derived from peak GLS and afterload; GCW (reference 2267±327), global constructive work describes the total work during segment shortening in systole (positive work) and segment lengthening during isovolumetric relaxation (negative work); GWW (reference 58-122.5), global wasted work describes segment lengthening in systole (negative work) and segment shortening at isovolumetric relaxation (positive work); GWE (reference 95-97), global work efficiency represents ratio of GCW divided by the sum of GCW and GWW; LVEF (reference ≥ 50), left ventricle ejection fraction

Source: Own materials

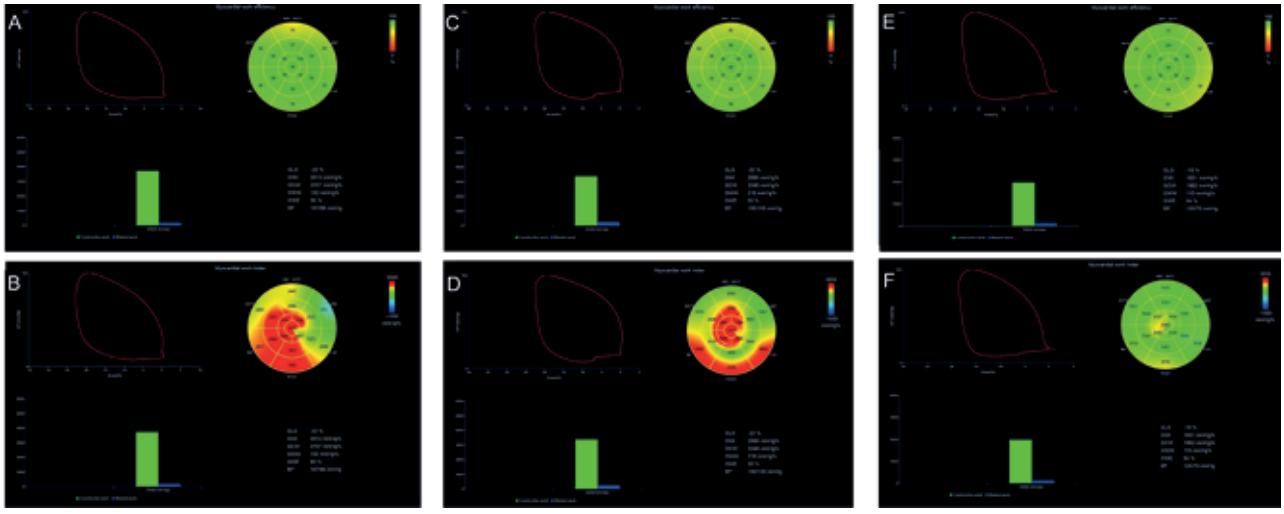

Fig. 1. Measurement of myocardial work parameters by two-dimensional speckle-tracking echocardiography
Panels A-B at admission, C-D before discharge, and E-F at 11 months show LV pressurestrain loops, bull's-eye plots of GWE or GWI, bar graphs of GCW and GWW, and results from myocardial work analysis.
GLS, global longitudinal strain; GWI, global work index represents average myocardial work derived from the mean pressure-strain loop area of all segments (total work done); GCW, global constructive work describes the total work during segment shortening in systole (positive work) and segment lengthening during isovolumetric relaxation (negative work); GWW, global wasted work describes segment lengthening in systole (negative work) and segment shortening at isovolumetric relaxation (positive work); GWE, global work efficiency represents ratio of GCW divided by the sum of GCW and GWW; BP blood pressure

Source: Own materials

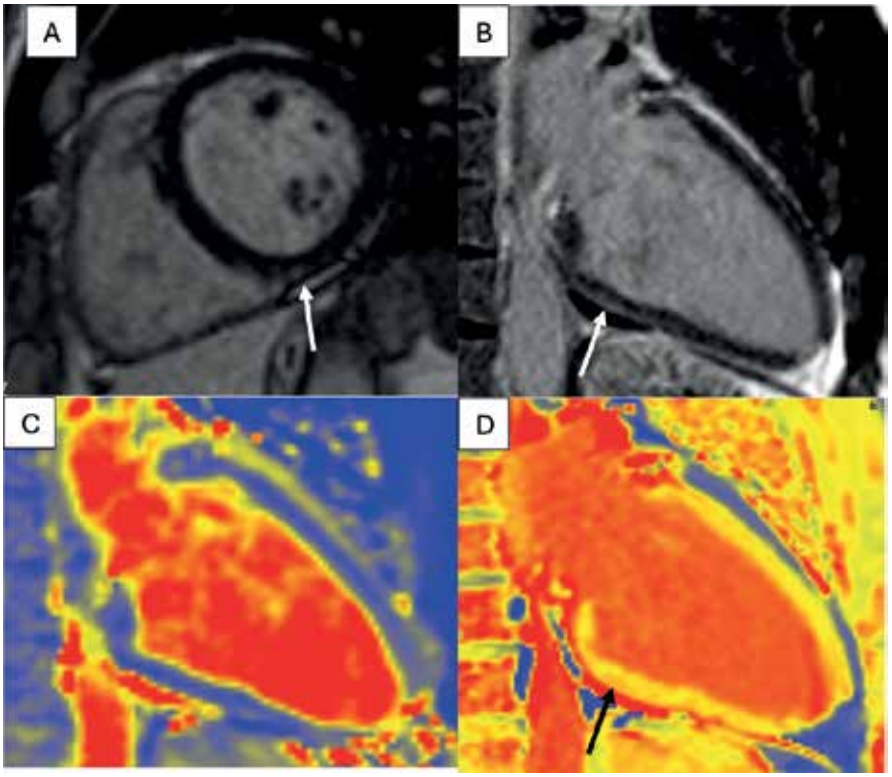

Fig. 2. Cardiac magnetic resonance images at 11-month follow-up
Myocardial fibrosis at the right ventricular insertion point in the short-axis LGE sequence, white arrow; (B) subepicardial fibrosis in the basal inferior left ventricle segment in the two-chamber LGE sequence, white arrow; (C) myocardium without edema in the two-chamber T2 mapping sequence; (D) myocardial fibrosis in the basal segment of the inferior wall in the two-chamber native T1 mapping sequence, black arrow. The examination included cine sequences to assess myocardial function, followed by T1 and T2 mapping sequences. LGE, late gadolinium enhancement sequences were acquired 10 minutes after contrast agent injection (gadobutrol) to evaluate tissue characterization

Source: Own materials

subsequently to Mobitz type I, accompanied by rapid resolution of symptoms. Prior to discharge, Holter ECG monitoring revealed 561 episodes of Mobitz type I block without significant pauses. LVEF and GLS remained within normal limits, as did LV size and wall thickness. MW indices remained elevated compared with baseline but showed a trend toward normalization, with minimally reduced GWE (Fig. 1C–D, Table 1). The patient was discharged in good clinical condition after four weeks of hospitalization. Follow-up demonstrated stable heart rate and normal blood pressure. At 11 months, Holter ECG revealed six nocturnal episodes of Mobitz type I block without significant pauses. TTE showed a preserved LVEF of 61%, GLS of –18.5%, and normalization of MW indices, except for a slightly reduced GWE (Fig. 1E–F, Table1). CMR revealed LGE in the basal segment of the inferior wall, consistent with residual post-inflammatory changes (Fig. 2).

DISCUSSION

The diagnosis of LC presenting with AV block is often challenging, particularly because LV systolic function is typically preserved and clinical manifestations are usually limited to conduction abnormalities. BB infiltrates the connective tissue at the base of the heart, predominantly affecting the subepicardial and mid-wall regions of the myocardium, which correspond to the circumferential and rotational myocardial fibers [1]. This infiltration may lead to subtle myocardial deformation detectable by advanced 2D-STE. In contrast, the subendocardial longitudinal fibers are usually spared, explaining why LS values generally remain within normal limits [8]. Nonetheless, some authors have reported reduced GLS in myopericardial syndromes with preserved LVEF. Meindl et al. observed significantly lower GLS (mean±standard deviation) in patients with acute myocarditis compared with healthy controls (-19.1±1.8 vs. -22.1±1.7) [9]. In the present case, both LVEF and GLS were normal at admission and remained stable during follow-up. MW assessment provides a more load-independent evaluation of LV performance by integrating afterload, estimated from brachial artery blood pressure, with strain-derived myocardial deformation. While GLS predominantly reflects subendocardial function, which tends to remain preserved in inflammatory conditions, elevated MW indices may indicate compensatory activity in response to dysfunction of the outer myocardial layers. Unlike ischemic heart disease, where myocardial injury

progresses from the endocardium toward the epicardium, the inflammatory process in LC, as in other forms of infective myocarditis, typically involves the subepicardial and mid-myocardial layers with relative sparing of the endocardium. The pattern likely explains the preservation of LVEF despite myocardial involvement [1]. In this case, MW indices were elevated during the acute phase and gradually decreased over time. Detailed analysis revealed increased regional MW values in the inferior and posterior LV segments, and to a lesser extend in the apical and septal segments (Fig.1B-D). Comparable findings have been reported by Stöbe et al., who observed elevated regional MW indices in the apical and basal posterior segments in patients with acute myocarditis [10], whereas Kalesi et al. reported reduced GWI and GCW compared with healthy controls [11]. Serial MW imaging in the present case demonstrated elevated indices at admission, progressive improvement following antibiotic therapy, and normalization at 11 months. These temporal changes paralleled electrocardiographic recovery and were consistent with an effective antibiotic response. Collectively, these findings suggest that elevated MW indices may represent a compensatory mechanism counterbalancing dysfunction of the outer LV layers during the acute inflammatory phase. Although not specific to LC, MW analysis appears to be a valuable adjunct for assessing myocardial involvement and functional recovery in LC and other inflammatory myocardial syndromes.

The role of CMR imaging in LC remains incompletely defined. In early stages of LC presenting with AV block, CMR may reveal focal LGE in the basal anteroseptal region near the AV node, but data on late-stage imaging are limited. In reported cases, mid-wall or subepicardial LGE, and occasionally persistent myocardial edema, have been described between four and twelve months after presentation [12, 13]. In the ITAMY study, the presence of mid-wall LGE in the anteroseptal segments of patients with acute myocarditis and preserved LVEF was associated with worse outcomes [14]. In the present case, CMR performed 11 months after diagnosis demonstrated subepicardial LGE in the basal inferior segment, corresponding to regions with prior MW abnormalities (Fig. 1B). According to the 2025 European Society of Cardiology (ESC) Guidelines for the management of myocarditis and pericarditis, the persistence of LGE supports a diagnosis of remission with residual myocardial changes [5]. While extensive scar burden has been associated with an increased risk of hypokinetic cardiomyopathy, either dilated or nondilated, and ventricular arrhythmias [4], the absence of substantial scarring in this patient suggests a favorable prognosis.

CONCLUSIONS

The present findings highlight the potential utility of MW as a noninvasive tool for the diagnosis and monitoring of early-stage LC and other forms of inflammatory myopericardial syndromes. MW assessment may also assist in optimizing antibiotic therapy and reducing the need for permanent pacemaker implantation. In addition, CMR performed during the later stages of LC appears to have prognostic value in predicting subsequent LV dysfunction and arrhythmic risk. To the best of our knowledge, this is the first reported case of LC evaluated and quantified using MW analysis.

LEARNING OBJECTIVES

Recognize the diagnostic challenges of Lyme carditis, particularly when atrioventricular block is the sole manifestation.

Understand the role of myocardial work assessment by echocardiography as an additional diagnostic tool in the initial stage of the disease.

Highlight the value of cardiac magnetic resonance imaging during follow-up as a prognostic modality.

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CASE STUDY

Case report of extramedullary plasmacytoma within the left palatine tonsil in a 31-year-old female patient

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ABSTRACT

Extramedullary plasmacytoma (EMP) is an uncommon variant (rare presentation) of plasma-cell neoplasia characterized by the proliferation of clonal plasma cells outside the bone marrow microenvironment. EMP most frequently arises in the head and neck region, particularly within soft-tissue structures of the upper aerodigestive tract. Herein, we present a case report of a 31-year-old patient diagnosed with a localized extramedullary plasmacytoma (EMP) of the left palatine tonsil at the University Hospital in Kraków. We are also presenting a summary of the EMP of the tonsil case reports from the PubMed database. This article aims to present a clinical case of extramedullary plasmacytoma involving the palatine tonsil in a 31-year-old woman, with a detailed description of the diagnostic process and therapeutic management. In addition, the article reviews alternative diagnostic approaches and treatment modalities reported in the literature.

KEYWORDS: extramedullary plasmacytoma, palatine, tonsillectomy, hematology

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INTRODUCTION

The International Myeloma Working Group (IMWG) has established stringent criteria for the diagnosis of EMP 1) Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells 2) Normal bone marrow with no evidence of clonal plasma cells 3) Normal skeletal survey and MRI (or CT) of the spine and pelvis, except for the primary solitary lesion 4) Absence of end-organ damage, such as CRAB (hypercalcemia, renal failure, anemia, and osteolytic bone lesions) that can be attributed to a lymphoplasma cell proliferative disorder. [1]Liebross et al. found that among the 1,354 individuals treated for plasma cell neoplasms at the MD Anderson Cancer Center between 1963 and 1996, 1,272 patients (94%) were diagnosed with multiple myeloma (MM), 60 (4%) with solitary bone plasmacytoma (SBP), and 22 (2%) with extramedullary plasmacytoma (EMP).[2]

Given the rarity of EMP, the evidence base supporting optimal therapeutic decision-making remains limited, with most available information derived from retrospective cohorts or single-institution experiences. The feasibility of surgical intervention is frequently restricted by the intricate anatomy of the head and neck - the predominant site of EMP - where achieving negative margins may necessitate procedures associated with substantial morbidity and, at times, significant disfigurement [3]. Consequently, radiotherapy has traditionally constituted the principal treatment modality. Although prospective studies are lacking, multiple reports indicate that radiation doses of 40-60 Gy are associated with high rates of local disease control [4]. Neoadjuvant chemotherapy is generally not recommended, as existing data do not demonstrate a clear therapeutic advantage (Fig. 1) [5].

In the study conducted by Kilciksiz et al., which included 80 individuals diagnosed with solitary plasmacytoma (SP), 40 patients (50.0%) underwent radiotherapy (RT) as the sole treatment modality, whereas 38 patients (47.5%) received combined surgical resection followed by RT. The median radiation dose administered was 46 Gy (range, 30-64 Gy). Median progression-free survival (PFS) and multiple myeloma-free survival (MMFS) were 3.5 and 4.8 years, respectively. Notably, younger patients experienced more favorable outcomes following RT with or without surgery. In comparison, older patients exhibited a higher likelihood of progression to multiple myeloma, underscoring the prognostic significance of age within this cohort [6].

EMP has also been incorporated into pediatric-specific classification systems, underscoring its distinct clinical features in younger patients [7]. In a representative series of 13 individuals (8 males and five females) aged 3–18 years, Waldeyer's ring constituted the most common site of involvement (n = 9), with less frequent localization in the larynx (n = 2) and the ocular adnexa (n = 1). One patient demonstrated synchronous disease affecting both the epipharynx and conjunctiva. Notably, a child with tonsillar EMP was concurrently diagnosed with Epstein–Barr virus infection, suggesting a potential viral contribution in select cases. Management in this pediatric cohort was predominantly surgical. Among the 12 patients with

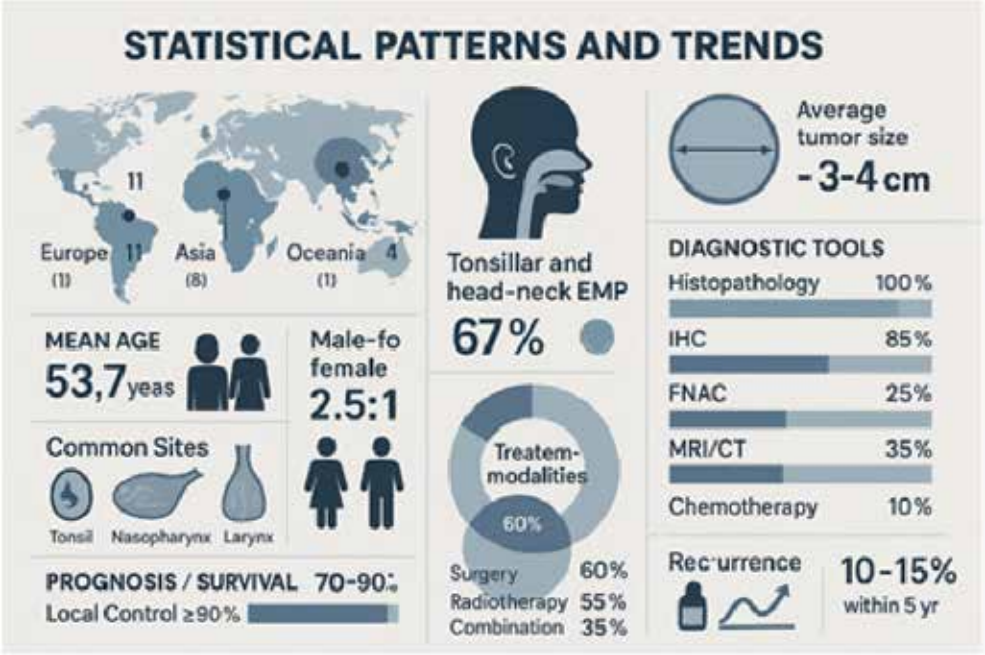

Fig 1. EMP Statistics

Source: Schematic diagram generated using the ChatGPT (OpenAI) artificial intelligence tool, based on the author's description

available follow-up data, complete and durable remission was achieved following resection, with a median follow-up duration of 38 months. Nevertheless, local recurrence occurred in three individuals, highlighting the importance of continued surveillance even in the context of initially favorable treatment outcomes.

AIM

This article aims to present a clinical case of extramedullary plasmacytoma involving the palatine tonsil in a 31-year-old woman, with a detailed description of the diagnostic process and therapeutic management. In addition, the article reviews alternative diagnostic approaches and treatment modalities reported in the literature.

CASE REPORT

This case report presents a female 31 year old patient who was admitted with pain in her left palatine tonsil increasing for six months. On admission, the patient was in good general condition, of normosthenic build, cardiorespiratory efficient, in good mental status with no abnormalities on physical examination; peripheral lymph nodes were not palpable. Hashimoto's thyroiditis with thyroxine therapy was the only concurrent disease, and inflammatory markers were negative. A bilateral tonsillar biopsy was performed due to persistent unilateral tonsillar symptoms. On histopathological analysis, a suspected focal extramedullary plasmacytoma within the left palatine tonsil was found. In this case, further work-up was performed to exclude systemic multiple myeloma. Laboratory results were found to be within normal ranges: ionized calcium: 0.96 mmol/l [N], protein: 73.9 g/l [N], calcium: 2.48 mmol/l [N], phosphorus: 0.84 mmol/l [N], creatinine: 55.3 umol/l [N], ALT: 41 U/l [N], alkaline phosphatase: 59 U/l [N] ferritin: 101 ug/l [N], CRP 3.32 mg/l. As such, markers of organ involvement (hypercalcemia, renal failure, anemia) were excluded. Monoclonal protein was not detected in serum by electrophoresis, total protein was 74.7 g/l with albumin 43.03 g/l [N], gamma globulin 10.46 g/l [N], and the albumin-globulin ratio (A/G) 1.36 [N]. Serum protein immunofixation was negative. On bone marrow immunophenotype, no specific CD cell marker profile ($CD38^{+++}$, $CD138^{+}$ plasma cells with κ/λ restriction, CD19–, $CD56^{+}$ (±CD117), CD45 dim/–) for multiple myeloma specific plasmocytes was found. A CT scan of the neck and skeletal system (WBLDCT) was performed. The neck scan did not reveal significantly enlarged lymph nodes. Still, there was a noticeable asymmetry in the size of the submandibular lymph nodes (group Ib: left side diameter up to 7 mm in the short axis, right side diameter up to 4 mm) and along the neck vessels (group IIIa: left side diameter up to 9 mm, right side diameter up to 7 mm). Contrast enhancement of the nodal groups was quite symmetrical – warranting further examination. The remaining neck lymph nodes were up to 6 mm in the short axis. The left palatine tonsil was more prominent than on the right side, with minor calcification and a slight narrowing of the air column in the airway on that side. Small polypoid lesions up to 5 mm thick were present in the alveolar recess of the left maxillary sinus. The bones were free of suspicious focal lesions. The cervical spine showed no significant degenerative changes. Following a comprehensive evaluation of diagnostic findings and multidisciplinary consultation, the patient was scheduled for surgical intervention under general anesthesia. In the absence of evidence for systemic involvement of multiple myeloma and in the presence of localized plasma-cell

infiltration within the left tonsillar specimen, surgical intervention in the form of tonsillectomy was deemed to be indicated. A bilateral tonsillectomy was performed without intraoperative complications, and the excised tissue was submitted for histopathological analysis. The perioperative and postoperative courses were uneventful, with no adverse events observed. The patient was discharged in stable general and local condition and provided with detailed instructions regarding postoperative care, follow-up assessments, and further management considerations.

Histopathological analysis of the right palatine tonsil revealed reactive lymphoid tissue without increased plasma-cell density, clustering, or morphological features suggestive of neoplastic involvement. Examination of the left palatine tonsil demonstrated largely preserved lymphoid architecture. The lymphoid component consisted predominantly of small CD3+/CD5+/CD43+ T lymphocytes and CD20+/CD5-/CD43-/MUM1-/CD23-/cyclin D1-/CD38- B lymphocytes, arranged in well-formed lymphoid follicles with reactive germinal centers. These germinal centers were supported by a regular network of CD23+/CD21+ follicular dendritic cells, consistent with reactive follicular hyperplasia. In selected areas, particularly near the biopsy incision line, irregular, band-like aggregates of plasma cells were identified. These plasma cells exhibited mild cytologic atypia and expressed the following immunophenotype: CD138±, CD38+, CD20–, MUM1+, CD43+, cyclin D1–. Light-chain restriction with lambda positivity and absence of kappa expression confirmed monoclonality. Proliferative activity within the plasmacytic population was low, with Ki-67 expression ranging from 5% to 10%. Importantly, no architectural or immunophenotypic features indicative of an underlying B-cell lymphoma were detected, thereby excluding a lymphomatous process with secondary plasmacytic differentiation. Instead, the presence of a localized, monotypic (lambda-restricted) plasma-cell infiltrate – occurring in the absence of systemic disease or concurrent lymphoid malignancy – supports the diagnosis of a neoplastic plasma-cell proliferation confined to the tonsil. Correlation of the histopathological findings with the clinical presentation, in the absence of systemic involvement, supports the diagnosis of a localized extramedullary plasmacytoma (EMP) of the left palatine tonsil, in accordance with the 2022 World Health Organization (WHO) classification of hematolymphoid neoplasms. The histological findings primarily support the diagnosis of focal extra-skeletal neoplastic growth of plasma cells (extramedullary plasmacytoma), distinguishing the less probable (in view of plasma cell atypia) – extranodal marginal zone lymphoma (EMZL) with B-intensified (in the specimen) plasmacytic differentiation; the least probable – local, monoclonal activity of plasma cells, which occurs as a result of infection.

On follow-up after one year, the patient is without clinical signs of disease. Laboratory findings for organ involvement (CRA) remain within normal limits, and control WBLDCT is without findings. The patient has yearly scheduled follow-up consultations.

DISCUSSION

Extramedullary plasmacytoma is a sporadic tumor that, as the name suggests, occurs outside the bone marrow and most commonly affects the head and neck [3]. EMP most commonly presents at a median age of approximately 55 years, with a clear male predominance, as about 75% of affected patients are men. Nearly 80% of cases arise in the head and neck region – particularly involving the nasal cavity, paranasal sinuses, and nasopharynx – while less frequent sites include the gastrointestinal tract, lungs, breasts, testes, and skin [31]. Owing to the infrequency of EMP, robust evidence to suggest optimal treatment decisions is lacking, and the available knowledge is largely based on retrospective studies and reports from individual centers. This case underscores several essential principles in the management of localized EMP of the palatine tonsil. The enlargement of the organ and significant pain prompted biopsy and histopathological examination which allowed for differential diagnosis. The standard of care consists of moderate-dose radiotherapy (40-50 Gy), with surgical intervention reserved for selected circumstances [4]. Ge Wen states that EMP should be treated with involved-site radiotherapy of no less than 45 Gy [3]. Today, CAR-T treatment has not been used in the Extramedullary Plasmacytoma. In this case, malignancy was successfully identified, and appropriate therapy was initiated. Due to isolated infiltration by the plasmacytoma, surgical intervention alone was performed.

Given the documented risk of MM recurrence and progression, long-term follow-up is essential. A multidisciplinary approach involving otolaryngology, pathology, hematology, and radiology remains critical to ensure optimal outcomes. The findings are within the reference range, and the patient's previous complete blood count (CBC) analyses revealed no deviations from reference values and were consistent with the data presented in the tables. In this case, the treatment was surgical. Despite the lesion's lack of progression, the patient should undergo periodic check-ups. Table 1 shows the reported EMP cases in the literature from around the world from the PubMed database (Appendix – Tabela 1).

CONCLUSIONS

In the majority of cases, EMP localizes to the head and neck region. In our patient, the tumor was confined to the palatine tonsil and detected at an early, localized stage. In case, surgical excision alone was chosen given the localized disease, absence of systemic involvement, and accessible tumor location. Although the patient was able to detect and diagnose an extramedullary plasmacytoma at an early stage, it is essential to undergo appropriate medical check-ups. Given that some cases of progression may occur beyond 5 years post-diagnosis, follow-up protocols should be extended over the long term. Many cases are manageable, and patients don't experience recurrence or progress to multiple myeloma.

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32. The work uses illustrations generated using the ChatGPT artificial intelligence. The graphics were provided for illustrative purposes only; their content was reviewed and approved by the authors

CONFLICT OF INTEREST
The Authors declare no conflict of interest

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Appendix
Table 1. The reported EMP cases in the literature from around the world from the pub med database

Author/Year	Title/Source	Location of EMP	Patient(s)	Diagnosis /Method	Treatment	Outcome /Follow-up
Oschlies et al., 2025 (Europe)	EMP in children [7]	Waldeyer's ring incl. the tonsil	13 (3-18 yrs)	Histology + genetics	Surgery ± RT	12/13 complete remission
Zehlicke&Gramer, 2002 (Germany)	Extramedullary plasmocytoma of the left tonsil [8]	Left tonsil (oropharynx)	Single case	Histopathology, immunohistology	Tonsillectomy	Diagnostic certainty; negative follow-up
Tisner Nieto et al., 1995 (Spain)	Primary extramedullary plasmacytomas of the upper respiratory tract [9]	Tonsils (2), rhinopharynx, maxillary sinus	4 cases (45-73 yrs)	Histologic biopsy	Tonsillectomy ±radiotherapy (40 Gy)	All asymptomatic after 12-53 mo
Çelebi et al., 2018 (Turkey)	Tonsillar Plasmacytoma: clues on MRI [10]	Tonsil	42 F	MRI, histology	Surgery	Disease-free at follow-up
Nishida et al., 1987 (Japan)	A case of extramedullary plasmacytoma [11]	Tonsil + multiple soft tissues	51 M	Histology, immunohistology	Chemo + radiotherapy	Tumors reduced markedly
Bjelkenkrantz et al., 1981 (Sweden)	Extramedullary plasmacytoma of the larynx [12]	Larynx + tonsil	Single	Histopathology	Radiotherapy + tonsillectomy	7-year disease-free
Bregni et al., 2012 (Brazil)	MALT lymphoma with plasma cell differentiation [13]	Palatine tonsil	34 M	Histology + immuno	–	Suggested link to EMP
Basavaiah et al., 2019 (India)	Clinicopathological spectrum of solitary plasmacytoma [14]	Tonsil (rare among sites)	29 total (subset tonsil)	Histopathology + IHC	Various	Good prognosis; male preponderance
Hashimoto et al., 1983 (Japan)	EMP with crystal inclusions [15]	Left palatal tonsil	51 F	Histology + EM	Surgical excision	No recurrence at 1 yr

Table 1. cont.

Bhat et al., 2010 (India)	Tonsil EMP diagnosed by FNAC [16]	Right tonsil	43 M	FNAC + IHC	Surgery	FNAC useful; confirmed by histology
González et al., 2003 (Spain)	EMP of head and neck (3 cases) [17]	Upper airway (incl. tonsil)	3	Histology + bone marrow	Surgery ± radiotherapy	No recurrence
Straetmans& Stokroos, 2008 (Netherlands)	EMP in head & neck [18]	Subglottis, middle ear, epiglottis	3	Histology + imaging	Surgery ± RT	Good prognosis if localized
Yang et al., 2006 (China)	Solitary plasmacytoma: 43 cases [19]	Tonsil (2 EMP cases)	43 total	IHC (CD79a+, CD20-)	–	Distinct immunophenotype
Bazaadut et al., 2010 (Australia)	EMP of tonsil with nodal involvement [20]	Tonsil + lymph node	58 M	FNAC, IHC	Surgery only	Disease-free; no RT needed
Jaheddine et al., 2024 (Morocco)	EMP of nasopharynx [21]	Nasopharynx	55 M	MRI + pathology	Radiotherapy	Favorable prognosis
Sakai et al. 2007 (Japan)	Extramedullary plasmacytoma of the tonsil diagnosed by fine-needle aspiration cytology [22]	Left tonsil	53 M	MRI + FNAC + IHC	Excision	Accurate cytologic diagnosis
Cortez et al., 1979 (USA)	Unilateral tonsillar enlargement [23]	Tonsil	16 reviewed	Clinical review	–	EMP is rare, but a key differential
Suska et al., 2019 (Poland)	Solitary EMP of the palatine tonsil [24]	Palatine tonsil	Single	Histology + IHC	Surgery	Rare, good prognosis
Junquera et al., 2009 (Spain)	Synchronous SCC + EMP [25]	Maxillary sinus, tonsil	Single	Histopathology	Surgery + chemo	No recurrence at six months
Kalan et al., 2012 (UK)	Solitary EMP of tonsil [26]	Tonsil	Single	Histopathology + IHC	Surgery	Rare site; good outcome
Huoh et al., 2011 (USA)	EMP of the tonsil [27]	Palatine tonsil	Single	Histology + imaging	Surgery	–
Yüce et al., 2025 (Turkey)	Head and neck EMP (11 pts) [28]	Tonsil, sinonasal, larynx	11 (mean 55 yrs)	Histology + flow cytometry	RT (44–50 Gy) ± surgery	RT effective; 45 Gy sufficient
Dong Hoon et al., 2025 (Korea)	Extramedullary Plasmacytoma of the Head and Neck Region in a Single Institution [29]	Tonsil + others	10 (mean 58 yrs)	Histology + staging	RT + surgery (70%)	5-yr OS 60-80%; higher stage worse
Alabdulaaly et al., 2024 (USA)	Jaw SBP & oral EMP review [30]	Gingiva & tonsil are common	161 cases	Literature review	RT (⅓ cases)	Remission 73% for oral EMP

VARIA

Legal qualification of collaborationism in healthcare

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ABSTRACT

Aim: To investigate approaches to the criminal legal qualification of collaborationism in the field of healthcare, taking into account the norms of international humanitarian law.

Materials and Methods: The research methodology involves an analysis of current legislative documents on the qualification of criminal liability for collaborative activities, as well as regulatory legal acts in the healthcare field, and documents of international humanitarian law. The data analysis was conducted using open sources, mainly for the period 2013–2025, with an emphasis on the period of the active phase of the war in Ukraine. The main search keywords were „human rights", „collaborationism", „criminal liability", „crimes against the foundations of national security", „medical immunity in international humanitarian law", and „healthcare". The initial database consisted of 70 sources, of which 34 were included in the final analysis. The materials of the publication form the basis for the systematization of criminal legislation on the problems of protecting the rights of persons accused of collaborative activities in the field of healthcare, the key ones being the Constitution of Ukraine, the Criminal Code of Ukraine, and the European Convention on Human Rights.

Conclusions: The study emphasizes the need to improve the approach to the criminal legal qualification of collaborationism in the health sector, which covers both legal and organizational components, as well as mandatory compliance with the norms of international humanitarian law. The social danger of this phenomenon lies not only in the fact that it encroaches on the defense capability and foundations of national security, but also in the fact that it poses a threat to other objects of criminal law protection.

KEYWORDS: human rights, collaborationism, criminal liability, healthcare

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INTRODUCTION

According to the Constitution, Ukraine is a sovereign and independent state. The sovereignty of Ukraine extends to its entire territory, which is integral and inviolable within the existing borders [1]. However, on 24 February 2022, Russia invaded Ukraine as part of a so-called "special military operation," and despite significant losses, Russian troops remain in Ukraine, and the war continues. The presence on the territory of Ukraine of units of the armed forces of other states in violation of the procedure established by the Constitution [1] and laws of Ukraine, the Hague Conventions of 1907, the IV Geneva Convention of 1949, and also contrary to the Memorandum on Security Guarantees in Connection with Ukraine's Accession to the Treaty on the Non-Proliferation of Nuclear Weapons of 1994 [2], the Treaty on Friendship, Cooperation and Partnership between Ukraine and the Russian Federation of 1997, and other international legal acts, is the occupation of part of the territory of the sovereign state of Ukraine and an internationally unlawful act with all the consequences provided for by international law. One of the threats to the national security of Ukraine is collaborative activity, which is a crime against the foundations of national security.

In the current conditions of war, the phenomenon of collaborationism in Ukraine has transformed from a historical category into a modern legal problem [3-5]. The World Health Organization, in its 2024 report, notes that during the war, Ukraine's healthcare sector was targeted by Russian forces, as 2 207 attacks on medical facilities were documented, resulting in 205 deaths and 698 injuries. These attacks by Russian forces disrupted the work of 1 860 medical facilities, further complicating the provision of services and exacerbating existing inequalities in healthcare [6]. At the end of 2024, more than 1 442 verdicts in cases of collaborative activity were registered in the Register of Court Decisions. The number of open criminal proceedings in 2023 for collaboration is significantly higher than in 2022 (12 031 were registered, 620 were sent to courts, and the number of verdicts issued was 268) [6].

The fighting has already created incredible conditions and risks to public health [7] and violated the mechanism for implementing the human right to healthcare [8]. In addition, armed conflicts highlight some limitations of international humanitarian law in protecting forward-deployed field hospitals from deliberate shelling [9-11]. Collaborationist activities under martial law in Ukraine significantly undermine the state's defence capabilities, the foundations of national security, and the right of individuals to healthcare [3, 4, 12, 13]. One of the pressing problems in the conditions of martial law in Ukraine is individual cases of voluntary cooperation of medical workers with Russian occupiers in temporarily occupied territories. Therefore, the

study of the legal aspects of the qualification of „medical collaborationism" – its content, forms, and characteristics – is an important social and scientific problem, given that medical activities in temporarily occupied territories are ensured by the norms of international humanitarian law.

AIM

To investigate approaches to the criminal legal qualification of collaborationism in the field of healthcare, taking into account the norms of international humanitarian law.

MATERIALS AND METHODS

The methodological basis of the study is the analysis of current regulatory and legal documents on the legal qualification of criminal liability for collaborative activities, as well as regulatory documents in the field of health care, documents of international humanitarian law. The work used a system of general scientific and special legal methods, including analysis and synthesis, formal legal, and comparative legal methods. In particular, the comparative law method allowed us to compare the norms of Ukrainian law regarding criminal liability for collaborationism with the norms of international humanitarian law. The data analysis was conducted using open sources, mainly for the period 2013-2025, with an emphasis on the period of the active phase of the war in Ukraine. The main search keywords were „human rights", „collaborationism", „criminal liability", „crimes against the foundations of national security", „medical immunity in international humanitarian law", and „healthcare". The search criteria focused on modern scientific approaches and practical experience in delineating the legal qualification of collaborationism and the grounds for legal liability for such acts in the healthcare sector. Sources primarily focused on administrative and legal measures to counter collaborationism, and the problems of administrative liability in this area were excluded from consideration. The initial database consisted of 70 sources, of which 34 were included in the final analysis. The materials of the publication form the basis for the systematization of criminal legislation on the problems of protecting the rights of persons accused of collaborative activities in the field of healthcare, the key ones being the Constitution of Ukraine, the Criminal Code of Ukraine, and the European Convention on Human Rights.

ETHICS

This review article is based on a critical analysis of publicly available scientific evidence retrieved from peer-reviewed journals, clinical practice guidelines, and authoritative databases. No patient-identifiable data were accessed or used. Ethical approval was therefore not required, as the study did not involve prospective clinical interventions, human participant enrollment, or primary collection of patient information. The authors conducted the work in accordance with the ethical principles of the World Medical Association Declaration of Helsinki and internationally accepted standards of medical publishing, including the recommendations of the International Committee of Medical Journal Editors (ICMJE). The manuscript contains no plagiarism and no fabricated or falsified data. All sources are appropriately cited and formatted to comply with applicable publication requirements.

FRAMEWORK

The work is a fragment of a comprehensive target program of the Department of Administrative Law and Administrative Activities, Yaroslav Mudryi National Law University, "Constitutional and legal problems of ensuring the rule of law in the functioning of the mechanism of public power in Ukraine" (№ state registration 0111U000966; deadline: 2022-2025).

REVIEW AND DISCUSSION

The provision of medical assistance to the population in occupied territories during armed conflicts is ensured by the norms of international humanitarian law [14, 15]. The concept of „collaborative activity" was introduced into national legislation from the moment of the adoption of a special legislative act establishing criminal liability for such actions in 2022, and since then the Criminal Code of Ukraine provides for its forms, as well as grounds for liability [16], and has two new articles – collaborationism (Article 111-1) and aiding and abetting an aggressor state (Article 111-2). Until 2022, persons suspected of collaborationism were charged under Article 111 of the Criminal Code of Ukraine, "High Treason" [16]. In a general sense, collaborationism is conscious, voluntary, and deliberate cooperation with the enemy in their interests and to the detriment of one's own state [4, 12, 16-18]. The legislator's definition of a subject in various clauses of offences of Article 111-1 of the Criminal Code of Ukraine has a differentiated approach; as a rule, a subject can only be a citizen of Ukraine, but in some clauses there are no restrictions on citizenship [4, 16].

It should be noted that medical activities are one of the most protected types of activities under international humanitarian law, providing basic medical services to the population of the occupied territory [19, 20]. In our opinion, medical collaborationism is voluntary and deliberate cooperation with the enemy to facilitate armed aggression and temporary occupation to the detriment of one's own state in the field of healthcare. Let us outline the components of the term ‚collaboration' in medical-legal relations in Table 1 [16, 21, 22].

In accordance with the provisions of international law, in particular those relating to the protection of victims of international armed conflicts [23], it is established that under no circumstances may any person be subjected to punishment for the performance of medical functions compatible with medical ethics, regardless of the person in whose interests these functions are performed (Part 1 of Article 16) [24]. Also, punishing a person for performing medical duties in accordance with medical ethics is prohibited by Norm 26 of Customary International Humanitarian Law. In particular, the organisational actions of chief doctors in managing relevant healthcare facilities in temporarily occupied territories are the fulfilment of their duties, but do not pose a public danger. In view of Article 16 of the Additional Protocol to the Geneva Conventions [24], actions of medical personnel that consist of performing medical functions compatible with medical ethics, if they do not

Table 1. Components of the term «collaboration» in medical legal relations

Elements
An act committed under conditions of occupation
An act carried out in the form of cooperation with an aggressor state. A characteristic feature of cooperation is voluntariness
An act carried out in cooperation may be aimed at facilitating the implementation of armed aggression and temporary occupation, avoiding the responsibility of certain persons for the implementation of such aggression and occupation, etc.
An act carried out in cooperation by representatives of the state's population (both citizens and non-citizens)
An act carried out in collaboration to cause harm to the state of Ukraine, its patriots, or allies

Source: compiled by the authors of this study

constitute another criminal offence, cannot be qualified under Article 111-1 of the Criminal Code of Ukraine [16]. However, in Ukraine, there are cases of court decisions and criminal proceedings against healthcare officials for collaborationism [25]. Analysing the judicial practice regarding collaborationism in the healthcare sector, it should be noted that the investigation applies the same part of the article on collaborationism in cases that are „disproportionate" in terms of the severity of the criminal offence. For example, Part 5 of Article 111-1 of the Criminal Code of Ukraine incriminates a doctor who served as the "Minister of Health" of Crimea during the Russian occupation. He is accused of supplying Russian military equipment, medicines, and transport, and supporting the aggression of the Russian Federation. Under the same part of the article of the Criminal Code of Ukraine, a doctor from Balakliya (Kharkiv region) is charged, who, during the occupation, headed the „medical service" and „acted as the head" of the local hospital. However, the justification for the „suspicion" that Ukrainian investigators raise against medical workers in the occupied territories mostly concerns the functions of ensuring the operation of hospitals. In most such examples, officials of healthcare institutions in the temporarily occupied territories are charged under Part 5 of Article 111-1 of the Criminal Code of Ukraine [16] – holding a leadership position in an occupation authority. Among other things, they are accused of participating in the re-registration of Ukrainian medical institutions in Russian registers and working under Russian programs.

Problematic issues of criminal liability for collaborative activities can be identified in four groups: (1) problems related to understanding legislative terms (establishing the content of the law); (2) problems of distinguishing between Article 111-1 of the Criminal Code of Ukraine and related articles when qualifying; (3) problems of fairness of sanctions and effectiveness of punishment application [26]. In national legislation, it is advisable to distinguish the grounds for liability of medical professionals for „high treason," aiding and abetting an aggressor state (Article 111-2), and collaborative activities (Article 111-1). In some scientific works, treason is considered a type of collaborative activity [27]. Important criteria for distinguishing collaboration from aiding an aggressor state are the presence of an international armed conflict and its application regardless of citizenship. The object of criminal offences provided for in Article 111-1 of the Criminal Code of Ukraine is the foundations of Ukraine's national security. Given the content of Article 111-1 of the Criminal Code of Ukraine, an additional object of criminal offences is the life and health of people and property rights [16]. The subject of collaborative activity belongs to a special category, namely: it can be a sane individual who has reached the age of 16 and is a citizen of Ukraine. High treason is possible only in those forms that are directly listed in the disposition of Article 111 of the Criminal Code of Ukraine [16]. These acts can be committed both in peacetime and during martial law and under conditions of temporary occupation. Treason consists of defecting to the enemy, espionage, and assisting a foreign state in carrying out subversive activities against Ukraine.

The forms and types of collaboration in medical-legal relations remain undefined in legal doctrine. Modern researchers distinguish between collaborationism, which involves a political agreement with the occupier; „cooperation" with the occupation authorities in civilian areas; collaborationism as a „joint war" on the side of the occupation forces; humanitarian collaborationism; internal political collaborationism, etc. [12, 18]. It should be noted that collaborationist activities can be carried out only during periods of armed conflict or occupation of territories. In particular, the legislation of most countries of the world and the EU classifies the category of „collaborationism" as a crime against one's own state, high treason [14, 19]. In our opinion, medical collaborationism is the voluntary and intentional cooperation with the enemy by medical workers to promote armed aggression and temporary occupation to the detriment of one's own state while performing official duties in the field of healthcare.

Another problem is determining whether the category of "ethical medical activity in occupied territories" is carried out under international humanitarian law for a humanitarian purpose, and whether it is a socially beneficial activity or a criminal one [14, 15, 28-33]. The issue of doctors' liability for collaborationism and the qualification of such actions in national legislation is ambiguous [4, 12]. In scientific works, separate approaches to resolving this issue have been formed. Supporters of the first approach note that criminal liability of medical workers is excluded in connection with the fulfilment of their professional duty to provide medical care [4]. The second approach also provides for the exclusion of criminal liability of such persons; however, due to the presence of extreme necessity or physical or

mental coercion when committing an act (Articles 39, 40 of the Criminal Code of Ukraine [16, 12, 28]. At the same time, some scientists adhere to the third scientific approach, noting that the criminal liability of medical professionals is excluded due to the insignificance of the act [18, 21]. However, national judicial practice provides for cases of criminal liability for „administrative" collaborationism in the healthcare sector in conjunction with other crimes committed by this category of persons in temporarily occupied territories. In particular, when a doctor holds a management position in healthcare institutions in temporarily occupied territories, they do so voluntarily. Conventionally, this type of collaborationism in the healthcare sector is called «administrative», and such actions are subject to criminal liability under national law. In this case, the case is heard in absentia. However, in the future, the accused may file a lawsuit to protect his rights with the European Court of Human Rights [34]. Therefore, given the nature of „administrative" collaborative activities in the medical field and in the context of human rights protection, it is advisable to introduce a separate definition of such criminal offenses, as well as determine the level of their public danger. It is necessary to harmonize the norms of national criminal law with the norms of international humanitarian law for collaborationism in the field of health care.

CONCLUSIONS

Medical collaborationism is the voluntary and intentional cooperation of medical professionals with the enemy in order to facilitate armed aggression and temporary occupation to the detriment of one's own state while performing their official duties in the field of healthcare. Medical activities in wartime are most protected by the norms of international humanitarian law, while national legislation defines the limits of criminal liability for such acts. The social danger of voluntary "administrative" collaborationism in the healthcare sector lies not only in the fact that it encroaches on the defence capability and foundations of national security of Ukraine, but also in that it creates a threat to other objects of criminal law protection. In particular, this concerns human life and health, the preservation of property rights, ensuring public safety, and the implementation of human rights in the field of healthcare. Increasing the effectiveness of countering this phenomenon is possible through improving the legislative framework, using modern technologies, cooperating with international structures, and active participation of civil society.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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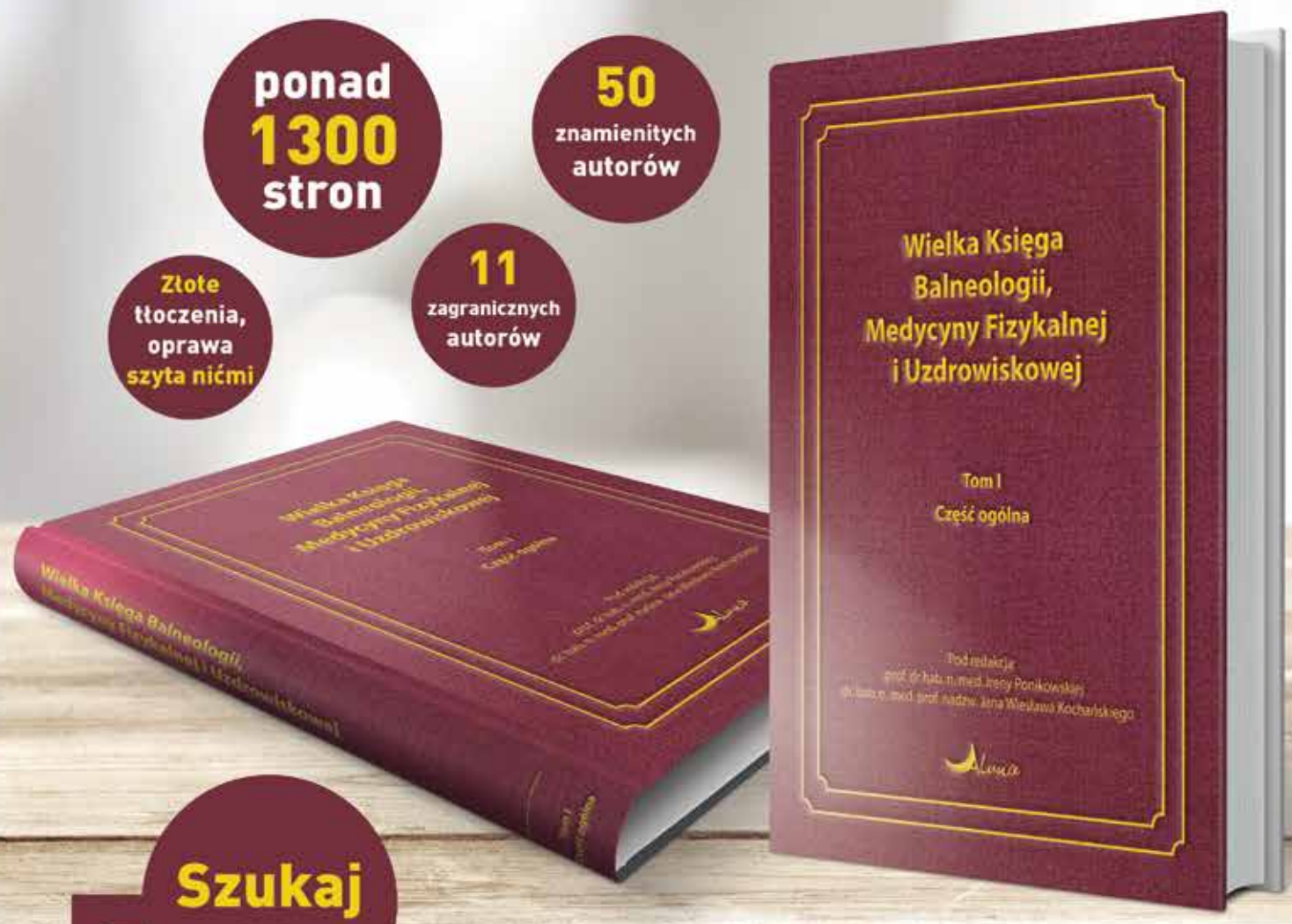

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