Polski Merkuriusz Lekarski

POLISH MEDICAL JOURNAL

ISSN 1426-9686

VOLUME LIII, ISSUE 4, JULY-AUGUST 2025

Polski Merkuriusz Lekarski

POLISH MEDICAL JOURNAL

ISSN 1426-9686

VOLUME LIII, ISSUE 4, JULY-AUGUST 2025

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a.luczynska@wydawnictwo-aluna.pl

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ORIGINAL ARTICLE

Comparison of the ONSTEP and Lichtenstein techniques for inguinal hernia repair–early results of a prospective study

Konrad Pielaciński[1], Katarzyna Pruszczyk-Matusiak[2], Jan Pielaciński[3], Agata Bosak Pielacińska[4], Andrzej B. Szczepanik[1]

[1]DEPARTMENT OF GENERAL, ONCOLOGIC AND METABOLIC SURGERY, INSTITUTE OF HEMATOLOGY AND TRANSFUSION MEDICINE, WARSAW, POLAND
[2]DEPARTMENT OF HEMATOLOGY, INSTITUTE OF HEMATOLOGY AND TRANSFUSION MEDICINE, WARSAW, POLAND
[3]INDEPENDENT PUBLIC SPECIALIST WESTERN HOSPITAL OF ST. JOHN PAUL II, GRODZISK MAZOWIECKI, POLAND
[4]LUX MED, WARSAW, POLAND

ABSTRACT

Aim: The study aims to evaluate the impact of the ONSTEP technique on the intensity of the systemic inflammatory response syndrome (SIRS) and the outcomes of inguinal hernia treatment compared to the Lichtenstein technique.

Materials and Methods: In 41 men randomized into 2 study groups, unilateral inguinal hernia repair was performed using the ONSTEP technique in group O and the Lichtenstein technique in group L. A total of 34 men met the full inclusion criteria, with each group consisting of 17 patients. Data were collected prospectively during hospitalization, as well as on day 7 and at 3 and 12 months postoperatively. Pain intensity was assessed using the Numerical Rating Scale (NRS). The severity of the systemic inflammatory response syndrome (SIRS) was evaluated based on changes in the following parameters: leukocyte and platelet counts, levels of interleukin-6, C-reactive protein (CRP), and fibrinogen at 6, 24, 46, and 168 hours postoperatively.

Results: No statistically significant differences were observed between the study groups in the incidence of CPP, the need for analgesics, recurrence rates, SIRS severity, or operative time. However, the ONSTEP technique was associated with significantly lower acute postoperative pain intensity and a quicker return to daily activities compared to the Lichtenstein technique.

Conclusions: Compared with the Lichtenstein technique, the ONSTEP technique shows similar intensity of SIRS and mostly comparable results in treatment, however the intensity of intense acute postoperative pain is lower and the return to preoperative activity proceeds faster.

KEY WORDS: classical inguinal hernia repair, preperitoneal space, ONSTEP, Lichtenstein technique

Pol Merkur Lek,2025;53(4):437-443 doi: 10.36740/Merkur202504101

INTRODUCTION

In current practice, inguinal hernia repair in adults is most commonly performed using synthetic mesh, as its implantation improves treatment outcomes and reduces recurrence rates to approximately 1-5% [1, 2, 3]. Nevertheless, postoperative pain in the groin area, particularly chronic postoperative pain (CPP) persisting for at least three months after surgery, remains an unresolved issue [3, 4]. Currently, the vast majority of inguinal hernia repairs are performed with the use of the classical Lichtenstein technique. This method is technically simple, repeatable, and has a short learning curve. However, it is not an optimal technique, as CPP is observed in up to 30% of patients following this procedure [3, 5, 6]. Significantly lower rates of CPP (approximately 4-6%) have been reported in patients undergoing minimally invasive techniques such as laparoendoscopic TAPP or TEP techniques. Unfortunately, these methods are associated with a much higher level of technical complexity and an extended learning curve, making them less popular [2, 7-9]. Given this context, it seems beneficial to develop a technique that combines the advantages of the open Lichtenstein method with those of minimally invasive laparoendoscopic approaches. One of the newer methods with the potential to meet these criteria is the Open New Simplified Totally Extraperitoneal (ONSTEP) technique. ONSTEP is an open procedure performed without the use of optical guidance, utilizing a single incision in the groin. It is characterized by a moderate level of technical difficulty and involves the use of a specialized flat mesh with an additional elliptical component that facilitates its placement in the preperitoneal space [10-12].

AIM

The aim of this study was to compare the ONSTEP and Lichtenstein techniques in inguinal hernia repair, focusing on pain intensity, time to return to normal activity, risk of hernia recurrence, and the intensity of systemic inflammatory response syndrome (SIRS).

MATERIALS AND METHODS

Patients requiring elective inguinal hernia repair were admitted on schedule. Inclusion criteria included men aged

18 to 80 years with primary unilateral inguinal hernias and an ASA status of 1-3. Exclusion criteria included irreducible or scrotal hernias and a general health condition with ASA grade of 4 or higher. All patients provided informed consent to participate in the study. The study protocol and objectives were approved by the local Bioethics Committee (Protocol 29/2021). Randomization into two groups was performed using a list generated at http://www.randomization.com. The ONSTEP group (O) consisted of patients treated using the ONSTEP technique with Onflex™ Mesh (Bard, Warwick, USA). The Lichtenstein group (L) consisted of patients treated with the Lichtenstein technique using Ultrapro™ Mesh (Ethicon, Diegem, Belgium). The ONSTEP group used Onflex™ meshes sized 8.6 × 14.2 cm (medium) or 10.2 × 15.7 cm (large), while the Lichtenstein group used Ultrapro™ meshes sized 10 × 15 cm. During surgery, both Ultrapro™ and Onflex™ meshes were tailored and placed around the spermatic cord, with incisions in the meshes sutured using non-absorbable polypropylene 2-0 sutures. All surgeries were performed by a single surgeon following available technical descriptions [13, 14]. In patients with additional risk factors, preventive measures were applied, including a single dose of cefazolin (2.0 g, i.v.) for patients with additional risk factors for bacterial infections and nadroparin (0.3 ml, s.c.) for the prevention of venous thromboembolism.

Surgeries were conducted under general or spinal anesthesia. Postoperative pain management included paracetamol, metamizole, and dexketoprofen. For statistical calculations, one standard dose of the aforementioned drugs was considered equivalent to 1 g of paracetamol. Patients were allowed to walk and drink fluids 6 hours postoperatively. Discharge was permitted no earlier than the first postoperative day, contingent upon the patient's general condition. Postoperative care did not restrict daily activity but discouraged driving a car within the first 7 days and lifting objects heavier than 10 kg for 6 weeks [15, 16]. Data for the study was collected during hospitalization and at follow-up visits on the 7th day and at 3 and 12 months postoperatively. The severity of SIRS was assessed based on peripheral blood measurements, including leukocyte, lymphocyte, neutrophil, and platelet counts, as well as serum levels of interleukin-6 (IL-6), C-reactive

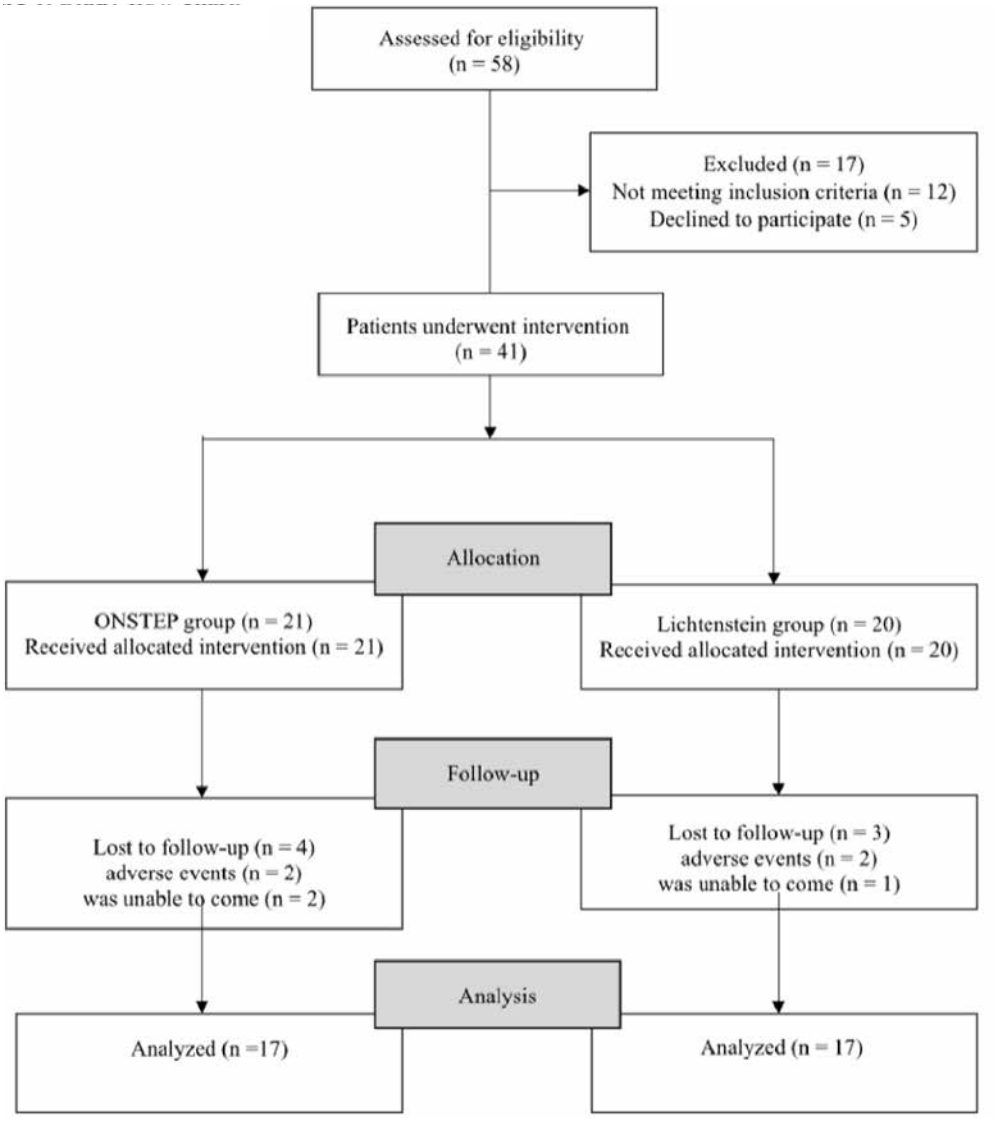

Fig. 1. Study flow chart

Table 1. Characteristics of the study group. The data are presented as the number of patients (n) and percentages (%)

Parameter	O group (n=17)	L group (n=17)	p-value
Age, years: median (range)	63 (40-76)	64 (33-74)	>0.99[a]
BMI			
Normal	9 (52.94%)	7 (41.18%)	0.56[b]
Overweight	5 (29.41%)	8 (47.06%)	
Obese	3 (17.65%)	2 (11.76%)	
Previous surgery			
Yes	6 (35.29%)	4 (23.53%)	0.45[b]
No	11 (64.71%)	13 (76.47%)	
ASA classification			
I	6 (35.29%)	4 (23.53%)	0.72[b]
II	9 (52.94%)	10 (58.82%)	
III	2 (11.76%)	3 (17.65%)	
Smoker			
Yes	7 (41.18%)	4 (23.53%)	0.27[b]
No	10 (58.82%)	13 (76.47%)	
Hernia side			
Right sided	6 (35.29%)	7 (41.18%)	0.72[b]
Left sided	11 (64.1%)	10 (58.82%)	
Hernia type – EHS classification			0.36[b]
L1	3 (17.65%)	5 (29.41%)	
L2	9 (52.94%)	6 (35.29%)	
M1	5 (29.41%)	4 (23. 53%)	
M2	0 (0%)	2 (11.76%)	
Time from diagnosis until herniorrhaphy weeks; median (range)	60 (12-520)	42 (4–520)	0.19[b]
Incarceration			
Yes	7 (41.18%)	6 (35.29%)	0.72[b]
No	10 (58.82%)	11 (64.71%)	
Pain intensity before surgery median (range)			
assessed using NRS	5 (0-9)	5 (0-8)	0.58[a]
assessed using sf-IPQ	3 (0-6)	2 (0-6)	0.10[a]
Parameter: median (range)			
White blood count [G/L]	6.22 (3.42-11.99)	6.45 (4.29-9.23)	0.94[b]
Platelets [G/L]	224 (149-343)	211 (124-304)	0.54[b]
Neutrocytes [G/L]	4.3 (1.9-8.91)	4.1 (1.76-5.78)	0.35[b]
Lymphocytes [G/L]	1.77 (0.97-2.7)	1.55 (0.9-3.94)	0.81[b]
Fibrynogen [g/L]	2.98 (1.54-4.5)	2.81 (1.9-3.41)	0.27[b]
C-reactive protein [mg/L]	1.62 (0.6-8.9)	1.5 (0.6-4.56)	0.78[b]
Interleukin 6 [pg/mL]	2.2 (1.5-6.5)	2.2 (1.5-10)	0.65[b]

[a]compared using Mann-Whitney test, [b]calculated with Pearson's chi-squared test, EHS – European Hernia Society, ASA – American Society of Anesthesiologists, BMI – Body Mass Index, NRS – Numerical Rating Scale, sf-IPQ – Short-Form Inguinal Pain Questionnaire

protein (CRP), and fibrinogen at 6, 24, 46, and 168 hours postoperatively. Pain intensity in the groin was evaluated using the Numerical Rating Scale (NRS) and the Short-Form Inguinal Pain Questionnaire (SF-IPQ) [17]. The SF-IPQ also assessed the extent to which groin pain restricted activity prior to surgery and at 3 and 12 months postoperatively.

ETHICS

The study was approved by the local ethics committee (Protocol 29/2021).

Patients provided written informed consent to participate in the study.

STATISTICAL METHODS

Statistical analysis was performed using Statistica 13.3 (Dell Inc., StatSoft Polska Sp. z o.o., Kraków, Poland). The Mann-Whitney U test was used for numerical data analysis, while Pearson's chi-square test was applied for categorical data. Results were considered statistically significant at $p<0.05$.

RESULTS

A total of 58 patients were admitted for elective surgery. Of these, 41 met the inclusion criteria and were randomized into two study groups. The ONSTEP group (Group O) included 21 patients, and the Lichtenstein group (Group L) included

Table 2. Overall comparison of surgery-related parameters and outcomes

Parameter	O group (n=17)	L group (n=17)	p-value
Anesthesia general subarachnoid (spinal)	 10 (58.82%) 7 (41.18%)	 8 (47.06%) 9 (52.94%)	 0.27[b]
Duration of operation (min): median (range)	40 (30-78)	51 (32-62)	0.28[a]
Analgesic consumption: median (range)* on: 1st postoperative day 2nd postoperative day 7th postoperative day	 2 (0-5) 2 (0-7) 0 (0-3)	 2 (0-6) 2 (0-5) 0 (0-4)	 0.15[a] 0.13[a] 0.11[a]
Return to pre operative activity (days): median (range)	2 (1-5)	4 (3-11)	<0.0001[a]
Length of postoperative stay (days): median (range)	2 (1-3)	2 (2-3)	0.41[a]
Local hematoma – groin – scrotal	 2 (11.76%) 2 (11.76%)	 4 (23.57%) 1 (5.88%)	 0.77[b]
Subcutaneous hematoma	4 (29.41%)	3 (17.65%)	0.47[b]
Urinary retention	1 (5.88%)	0	0.31[b]
Other causes of groin discomfort pulling sensation pricking sensation foreign body sensation	 1 (5.88%) 1 (5.88%) 0	 2 (11.76%) 1 (5.88%) 1 (5.88%)	 0.69[b]

*[a]compared using Mann-Whitney test, [b]calculated with Pearson's chi-squared test, *conversion Paracetamol g/day*

Table 3. Postoperative pain intensity measured using the NRS or sf-IPQ

Pain scoring method	Time	O group	L group	p-value
NRS median (range)	1. day 2. day 7. day	3 (1-9) 3 (1-8) 1 (0-4)	5 (2-10) 3 (1-10) 3 (1-6)	0.0195[a] 0.15[a] 0.0019[a]
sf-IPQ median (range)	3. month 12. month	0 (0-4) 0 (0-2)	0 (0-4) 0 (0-4)	0.25[a] 0.54[a]

NRS – Numerical Rating Scale, sf-IPQ – Short-Form Inguinal Pain Questionnaire, [a]compared using Mann-Whitney test

20 patients. Seven patients (17%) were excluded from the study, including four (19%) from Group O and three (15%) from Group L. The reasons for exclusion were: deterioration of general health due to concomitant

conditions in three patients (one [4.8%] in Group O and two [10%] in Group L), back pain in one patient (4.8%) from Group O, and failure to attend follow-up visits in three patients (two [9.5%] from Group O and one [5%] from Group L). The frequency of these events did not differ significantly between groups (Fisher's Exact Test). The treatment outcomes of 34 patients (17 in Group O and 17 in Group L) were further analyzed. The study scheme is illustrated in Figure 1, and the patient characteristics for each group are presented in Table 1. No statistically significant differences were observed in patient characteristics. During the surgeries and postoperative periods, no serious complications or signs of surgical site infection were observed. Over a year-long follow-up observation, no hernia recurrences were noted in either group. There were no statistically significant differences between the groups regarding operative time, length of hospital stay, incidence of hematomas, urinary retention, or discomfort related to the sensation of a foreign body (mesh) or pulling in the operated groin (Table 2). Additionally, the results obtained via the SF-IPQ questionnaire showed no statistically significant differences in chronic pain intensity or activity limitations at 3 and 12 months postoperatively (Table 3). However, the return to preoperative ("daily") activity was significantly faster in Group O, occurring most frequently on postoperative day 2 compared to day 4 in Group L (Table 2). The intensity of postoperative pain was significantly greater in

Group L on postoperative days 1 and 7. In contrast, differences in the demand for analgesics on postoperative days 1, 2, and 7 were not statistically significant. There were no statistically significant differences between the groups in changes in leukocyte, lymphocyte, neutrophil,

Table 4. Changes in the levels of interleukin 6 (IL-6), C-reactive protein (CRP), fibrinogen, as well as the count of platelets, white blood cells, neutrophils, and lymphocytes at 6, 24, 48, and 168 hours post-surgery compared to preoperative values. The values are expressed as medians and ranges

Parameter	Time after surgery (hours)	O-group	L-group	p-value
IL-6 [pg/mL]	6-0	50 (15.8-151.7)	39.6 (8.4-134.7)	0.865064
	24-0	58.7 (14.4-124.8)	46.2 (14.44-139.9)	0.339392
	48-0	25.88 (5-71.7)	17 (2.4-59.05)	0.375281
	168-0	1.8 (-4.4 to 11.1)	0 (-5.5 to 6.7)	0.078857
CRP [mg/L]	6-0	0.4 (-0.5 to 57.4)	0.6 (-0.34 to 3.27)	0.658382
	24-0	39.97 (0.37-101.35)	35.4 (14.28-115.03)	0.785665
	48-0	61.9 (9.8-174.35)	68.4 (13.32-139.03)	1.000000
	168-0	4.58 (0.26-25.41)	3.82 (-0.75 to 13.7)	0.181577
FIBR [g/L]	6-0	n/a	n/a	n/a
	24-0	0.61 (0.04-5.16)	0.62 (0.21-1.71)	0.733861
	48-0	1.55 (0.49-3.22)	1.45 (0.88-2.59)	0.683212
	168-0	0.69 (-0.27 to 3.27)	0.69 (0.11-4.56)	0.865064
PLT [G/L]	6-0	-25 (-53 to 29)	-23 (-97 to -3)	0.517724
	24-0	-20 (-38 to 22)	-12 (-116 to 12)	1.000000
	48-0	-9 (-44 to 20)	-17 (-46 to 16)	0.245085
	168-0	20 (-3 to 60)	16 (-77 to 132)	0.759632
WBC [G/L]	6-0	3.72 (0.95-10.6)	4.56 (1.13-6.97)	0.708380
	24-0	3.41 (-0.72 to 10.97)	2.27 (-0.54 to 9.29)	0.193217
	48-0	2.94 (-0.14 to 11.23)	2.12 (-1.54 to 3.78)	0.057468
	168-0	0.65 (-4.31 to 3.3)	0.31 (-0.95 to 1.21)	0.322280
NEU [G/L]	6-0	3.15 (0.77-8.7)	4.37 (0.2-7.41)	0.394049
	24-0	2.9 (-1.44 to 11.65)	2.76 (0.48-9.64)	0.540078
	48-0	2.1 (-1.04 to 12.05)	2.1 (-2.67 to 5.33)	0.891870
	168-0	0.25 (-3.36 to 2.82)	0.32 (-2.21 to 1.14)	0.838409
LYMPH [G/L]	6-0	0.17 (-1.76 to 1.23)	-0.18 (-1.22 to 0.66)	0.149706
	24-0	-0.52 (-1.4 to 0.65)	-0.37 (-1.65 to 0.7)	0.865064
	48-0	-0.13 (-0.6 to 12.43)	-0.27 (-1.1 to 0.4)	0.159832
	168-0	-0.03 (-1.02 to 1.29)	0.08 (-1.32 to 0.84)	0.658382

IL-6 – interleukin 6, CRP – C-reactive protein fibrinogen, FIBR – as well as the count of platelets, PLT – the count of platelets white blood cells, WBC – white blood cells, NEU – neutrophils, LYMPH – lymphocytes

or platelet counts, or in serum levels of interleukin-6 (IL-6), C-reactive protein (CRP), and fibrinogen at 6, 24, 46, and 168 hours postoperatively (Table 4).

DISCUSSION

CPP remains a significant issue in inguinal hernia repair. Its presence, especially in severe cases, limits daily activities and negatively impacts the quality of life. CPP occurs in 1-16% of patients undergoing the Lichtenstein technique, with an average prevalence of 6-8% in patients undergoing surgery [6, 9, 18, 19]. In our search for a method that is both more advantageous for patients than the Lichtenstein technique and technically simpler and less demanding than laparoendoscopic techniques, we examined the ONSTEP technique. This method places the implant partially in the preperitoneal space, a potential advantage over the Lichtenstein technique, while remaining less complex than laparoendoscopic approaches. Moreover, the published results of a limited number of studies on the ONSTEP technique are promising, indicating outcomes at least comparable to those of the Lichtenstein technique [3, 13]. In our study, patients who underwent hernia repair using the ONSTEP technique reported significantly lower acute pain levels on the 1st and 7th postoperative days and returned to normal activity faster. However, at 3 and 12 months postoperatively, no statistically significant differences in

pain intensity or activity restriction were observed between the two groups. Notably, the pain assessments in the ONSTEP group appeared to indicate less intense pain at 12 months post-surgery. While these findings suggest that the ONSTEP technique may offer certain advantages for patients, as supported by some studies [12, 20-23], other research does not confirm these benefits compared with the Lichtenstein technique [23-25]. Moreover, our results did not demonstrate any statistically significant differences in other outcomes, such as the need for pain medications, frequency of foreign body sensation, rate of adverse events, or duration of surgery. These observations align with the findings of other studies [24-25]. Furthermore, no evidence of a reduced SIRS reaction was found in the ONSTEP group during the first postoperative week, indicating that both methods are associated with similar levels of surgical trauma and SIRS intensity. This finding is consistent with previous research assessing SIRS in hernia repair surgeries [26]. In the study, no hernia recurrences were observed in either group after one year of follow-up. However, this may reflect the relatively short follow-up period [2, 9]. Based on the available literature and our experience with the Lichtenstein and TEP techniques [28, 29] we believe that the key to preventing hernia recurrence with the ONSTEP technique lies in selecting an appropriately sized implant and ensuring meticulous placement of its "medial part" in the preperitoneal space. Additionally, as in the Lichtenstein technique, the "lateral part" of the implant should be fixed with a nonabsorbable suture. These observations are supported by findings in other studies [1, 9, 21]. Given the placement of the "medial part" of the Onflex™ implant in the preperitoneal space, the ONSTEP technique may be particularly beneficial for treating femoral hernias. However, unlike other preperitoneal techniques performed via an anterior approach (e.g., the TREPP technique-transrectus sheath preperitoneal mesh repair), the ONSTEP technique involves implant placement in both the preperitoneal space and the inguinal canal. This dual approach may pose a disadvantage in cases of hernia recurrence, as it could complicate subsequent repairs [3, 20-23]. In light of these findings, we plan to continue our research comparing the ONSTEP and Lichtenstein techniques. However, due to the high costs, further assessments of SIRS in these patients will not be included.

CONCLUSIONS

Both the ONSTEP and Lichtenstein techniques are equally effective in preventing inguinal hernia recurrence and demonstrate comparable results regarding surgery duration, intensity of SIRS, and chronic postoperative pain. However, compared with the Lichtenstein technique, the ONSTEP technique offers the advantages of reduced acute postoperative pain and a faster return to normal activity. These findings highlight the potential benefits of the ONSTEP technique, but require further confirmation through randomized controlled trials.

ACKNOWLEDGMENTS

The authors extend their gratitude to Professor Piotr Paluszkiewicz and the entire staff of their clinic for their invaluable assistance with data collection and patient follow-up.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Jan Pielaciński
Independent Public Specialist Western Hospital of St. John Paul II
Grodzisk Mazowiecki, Poland
e-mail: janpiel02@gmail.com

ORCID AND CONTRIBUTIONSHIP

Konrad Pielaciński: 0000-0001-8323-9620 A C D F
Katarzyna Pruszczyk-Matusiak: 0000-0002-7646-4931 C D
Jan Pielaciński: 0009-0007-0675-3037 B D
Agata Bosak Pielacińska: 0009-0008-7366-0954 B D
Andrzej B. Szczepanik: 0000-0001-8322-0815 E F

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

RECEIVED: 30.03.2025
ACCEPTED: 15.06.2025

CREATIVE COMMONS 4.0

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ORIGINAL ARTICLE

Digital differential diagnostics of thyroid pathology by interference scanning of ellipticity polarization maps of microscopic images of native histological sections

Oleksandr V. Bilookyi[1], Yurii Ye. Rohovyi[1], Yurii A. Uschenko[2], Oksana V. Kinzerska[2], Valeriy M. Sklyarchuk[2], Viacheslav V. Bilookyi[1]

[1]BUKOVINIAN STATE MEDICAL UNIVERSITY, CHERNIVTSI, UKRAINE
[2]YURIY FEDKOVYCH CHERNIVTSI NATIONAL UNIVERSITY, CHERNIVTSI, UKRAINE

ABSTRACT

Aim: To find out new objective criteria for laser histological differential diagnosis of thyroid pathology based on the use of a digital method of layer-by-layer polarization-interference mapping of polarization ellipticity maps of microscopic images of native histological sections of thyroid biopsy.

Materials and Methods: Four groups of patients were studied: control group 1 – healthy donors (51 patients); study group 2 – patients with nodular goiter (51 patients); study group 3 – patients with autoimmune thyroiditis (51 patients); study group 4 – patients with papillary cancer (51 patients). Methods used: polarization-interference, statistical.

Results: A brief theory and model concepts of the formation of structural optical anisotropy of polycrystalline networks of native histological sections of thyroid biopsy are considered. The structural and logical scheme of the method of polarization-interference layer-by-layer mapping of microscopic images of thyroid biopsies is presented. The statistical analysis of algorithmically reproduced maps of polarization ellipticity of experimental samples of biopsies of donors and patients with nodular goiter, autoimmune thyroiditis and papillary cancer was performed. Statistical objective markers for the differential diagnosis of thyroid pathology have been determined.

Conclusions: An excellent level (~93%-95%) of the balanced accuracy of differentiation of pathological conditions by the method of polarization-interference layer mapping was demonstrated.

KEY WORDS: thyroid gland, nodular goiter, autoimmune thyroiditis, papillary cancer, differential diagnosis, polarization-interference method

Pol Merkur Lek,2025;53(4):444-451 doi: 10.36740/Merkur202504102

INTRODUCTION

Optical methods for diagnosing various biological tissues and visualizing their optically anisotropic structure (fibrillar networks, optically active molecular domains) occupy a prominent place due to their high information content and the possibility of multifunctional photometric, spectral, polarization, and correlation monitoring [1]. Polarimetric studies [2] have emerged as a separate area in the field of optical analysis of biological tissues. Analysis of the polarization characteristics of scattered radiation allows to obtain a qualitatively new understanding of the morphological and physiological state of biological tissues [3]. A significant progress in the field of biomedical polarimetric diagnostics was the development of Mueller matrix methods, which led to the creation of a separate field of Mueller matrix microscopy (MMM) [4-7]. The fundamental results obtained within the framework of MMM [7] of biological tissues are promising for applied clinical and preclinical studies of the polycrystalline structure of biological tissues. In particular, the possibility of obtaining quantitative optical parameters to characterize the evolution of gastric tissue from a healthy state through inflammation to cancer using Mueller microscopy of gastric biopsies has been demonstrated [4]. At the same time, the main information limitation of polarimetric mapping is the dependence of experimental data on the degree of laser depolarization, which distorts the relationship between microscopic images and morphological parameters of biological layers [8-16]. Therefore, the development of new, well reproducible and more accurate laser polarimetry methods remains very relevant.

AIM

To find out new objective criteria for laser histological differential diagnosis of thyroid pathology based on the use of a digital method of layer-by-layer polarization-interference mapping of polarization ellipticity maps of microscopic images of native histological sections of thyroid biopsy.

MATERIALS AND METHODS

The methodology of the polarization-interference method is based on the use of an optical laser polarization-modified interferometer platform. Here, a 50% light splitter is used to divide the laser beam into two beams – an irradiating beam and a reference beam. Using a linear polarizer-quarter-

wave plate system, the circularly polarized states of the irradiating and reference coherent laser beams are formed. A rotating mirror is used to direct the circularly polarized irradiation beam to the thyroid tissue under study.

The polarization-modulated image of the drug is projected by the micro-lens into the plane of the light-sensitive pixels of the digital camera. A second rotating mirror directs a circularly polarized reference coherent wave into the plane of the microscopic image of the test specimen. As a result, a polarization-interference pattern of the microscopic image is formed. This pattern is polarization filtered by a linear analyzer, the transmission axis of which is consistently oriented relative to the plane of incidence by angles 0 and $\pi/2$.

The resulting polarization-filtered interference patterns are recorded by a set of pixels of a digital CCD camera. Digital polarization-interference distributions are accumulated in the interface of the computer analysis unit. On this basis, layer-by-layer maps of polarization ellipticity of the microscopic image of the native histological section of the thyroid biopsy are calculated. Table 1 illustrates the structural and logical scheme of the polarization-interference method.

Four groups of patients were studied: Control group 1 – healthy donors (51 patients). Study group 2 – patients with nodular goiter (51 patients). Study group 3 – patients with autoimmune thyroiditis (51 patients). Study group 4 – patients with papillary cancer (51 patients). The objects of the study were native histological sections of thyroid tissue biopsies. After an appointment with an endocrinologist and a surgeon, if the indications are clearly indicated, the patient is prescribed a fine needle aspiration biopsy of the thyroid nodule. The patient lies down on the couch, on his back. The neck skin is treated with a special antiseptic solution "Sterilium". Four groups of patients were studied: The surgeon places an ultrasound sensor on the patient's neck and performs the examination. After that, the image of the required node is displayed on the monitor. Under the control of ultrasound, a thin needle (size 23G) from a 10 ml syringe is inserted through the skin into the nodule. The patient holds the injection site with a finger for 15 minutes. Anesthesia is not required during the thyroid nodule biopsy. The test results can be obtained in 5-10 days. After the surgeon deciphers the data, the patient is prescribed appropriate treatment. The instructions after the nodule puncture are as follows: it is forbidden to shout and sing during the day; you cannot perform heavy physical activity; it is not advisable to take a hot shower and go to the bath. Restrictions apply only for the first day after the procedure.

Table 2 shows the optical and geometric parameters of the study objects.

RESULTS

Fig. 1 shows the results of measurement by polarization mapping of maps (fragments-1) and histograms (fragments-2) of coordinate distributions (m,n) of random values of the polarization ellipticity β(m,n) of digital microscopic images of native histological sections of thyroid biopsies of donors and patients with nodular goiter, autoimmune thyroiditis, and papillary cancer.

The obtained results demonstrated the presence of statistical structure in the coordinate distributions of the polarization ellipticity value of digital microscopic images of histological sections of the thyroid gland (Fig. 1, fragments -1).

Comparative comparison of histograms (Fig. 1, fragments -2) of distributions of random values of polarization ellipticity revealed a tendency of increasing structural anisotropy of fibrillar networks of connective tissue of the thyroid parenchyma from control group 1 to experimental groups 2 (nodular goiter); 3 (autoimmune thyroiditis) and 4 (papillary cancer). This fact is indicated by a consistent "shift", as well as the expansion of the range of change, towards higher values of the main extremes of the histograms of

Table 1. Structural and logical scheme of polarization-interference mapping

Unit for optical formation of thyroid irradiating agent and reference coherent laser radiation
Unit for formation of circularly polarized states of irradiating thyroid preparation and reference coherent laser radiation
Unit for projecting a polarizing laser microscopic image of a biological thyroid preparation into the plane of a digital CCD camera
Unit for optical mixing of microscopic image of thyroid biological preparation and reference coherent beam
Unit for formation of interference distribution of digital microscopic image of thyroid gland preparations in the plane of digital CCD camera
Unit of polarization analysis of interference distribution of digital microscopic image of thyroid gland preparations in the plane of digital CCD camera
Unit of digital registration of polarization-filtered coordinate intensity distributions of interference microscopic image of thyroid gland preparations
Unit of computer accumulation of polarization-filtered coordinate intensity distributions of interference microscopic image of thyroid gland preparations

Table 2. Optical and geometric parameters of biological products

Geometric thickness, d, μm	40±0.4
Attenuation coefficient, τ	0.26±0.08
Degree of depolarization, Δ,%	37-44

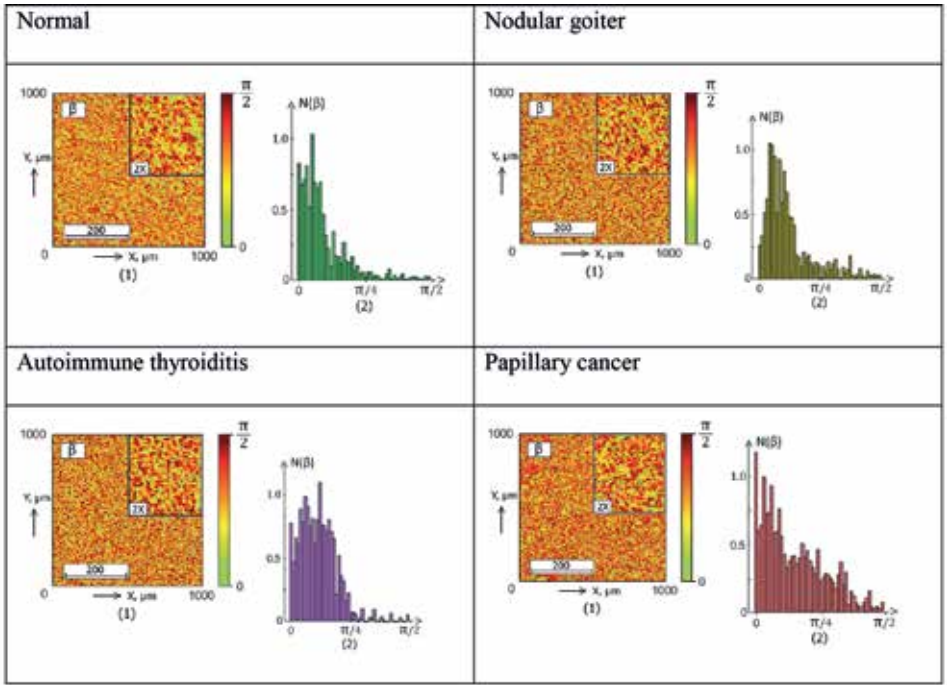

Fig. 1. Polarization maps (1) and histograms (2) of the distributions of the polarization ellipticity of digital microscopic images of native histological sections of thyroid biopsy from all groups

Table 3. Statistical parameters of polarization ellipticity maps of digital microscopic images of native histologic sections of thyroid biopsy from donors and patients with different pathologies

Group	Group 1 (51 sample)	Group 2 (51 sample)	Group 3 (51 sample)	Group 4 (51 sample)
Average, SM_1	0,230,013	0,280,016	0,310,018	0,370,021
p_{ik}	$p_{12;13;14} \le 0{,}05; p_{23;24;34} \le 0{,}05$			
Dispersion, SM_1	0,140,006	0,160,008	0,190,009	0,220,012
p_{ik}	$p_{12;13;14} \le 0{,}05; p_{23;24;34} \le 0{,}05$			
Asymmetry, SM_1	0,910,039	0,780,035	0,630,028	0,420,025
p_{ik}	$p_{12;13;14} \le 0{,}05; p_{23;24;34} \le 0{,}05$			
Excess, SM_1	1,330,061	1,040,047	0,820,039	0,610,034
p_{ik}	$p_{12;13;14} \le 0{,}05; p_{23;24;34} \le 0{,}05$			

the polarization ellipticity distributions (Fig. 1, fragments-2).

The quantitatively identified scenario is illustrated by the results of statistical analysis of the polarization ellipticity maps of microscopic images of native histological sections, which are presented in Table 3.

The experimentally determined dynamic ranges of changes in statistical markers of polarization ellipticity maps made it possible to effectively diagnose thyroid pathologies differentially (Table 4).

The achieved level of results was improved due to the phase layer-by-layer reproduction of polarization ellipticity maps against a significant depolarized background, which are more clearly related to the structural anisotropy of the thyroid parenchyma.

Fig. 2 illustrates the results of experimental layer-by-layer (phase parameter ϑ) polarization mapping (fragments -1) and histograms (fragments -2) of distributions (m,n) of random values of polarization ellipticity $\beta(\vartheta,m,n)$ of digital microscopic images of native histological sections of biopsy specimens from donors and patients with various thyroid pathologies.

Comparison of the coordinate and probabilistic structure of the layer-by-layer maps of the ellipticity of polarization $\beta(\vartheta,m,n)$ of birefringent (connective tissue networks, fibrous cords, etc.) structures of the thyroid parenchyma revealed a more pronounced tendency of consistent increase in optical anisotropy or linear birefringence from control group 1 (normal) to the set of experimental groups 2 (nodular goiter); 3 (autoimmune thyroiditis) and 4 (papillary cancer).

The quantitatively experimentally identified scenario illustrates an increase in the mean and interval of changes in the histograms of distributions of random values of polarization ellipticity of layer maps $\beta(\vartheta,m,n)$ of digital microscopic images of native histological sections of the thyroid gland – Table 5.

Table 4. Balanced accuracy according to statistical analysis of polarization ellipticity maps of thyroid biopsies

Average, SM_1		
a=85	a=88	a=89
b=17	b=14	b=13
Ac_{12}=84,3%	Ac_{13}=86,3%	Ac_{14}=87,3%
a=80	a=82	a=83
b=22	b=20	b=19
Ac_{23}=78,4%	Ac_{24}=80,4%	Ac_{34}=81,4%
Dispersion, SM_2		
a=85	a=88	a=89
b=17	b=14	b=13
Ac_{12}=84,3%	Ac_{13}=86,3%	Ac_{14}=87,3%
a=80	a=82	a=83
b=22	b=20	b=19
Ac_{23}=78,4%	Ac_{24}=80,4%	Ac_{34}=81,4%
Asymmetry, SM_3		
a=93	a=94	a=95
b=9	b=8	b=7
Ac_{12}=91,2%	Ac_{13}=92,1%	Ac_{14}=93,1%
a=89	a=90	a=91
b=13	b=12	b=11
Ac_{23}=87,3%	Ac_{24}=88,2%	Ac_{34}=89,2%
Excess, SM_4		
a=93	a=94	a=95
b=9	b=8	b=7
Ac_{12}=91,2%	Ac_{13}=92,1%	Ac_{14}=93,1%
a=89	a=90	a=91
b=13	b=12	b=11
Ac_{23}=87,3%	Ac_{24}=88,2%	Ac_{34}=89,2%

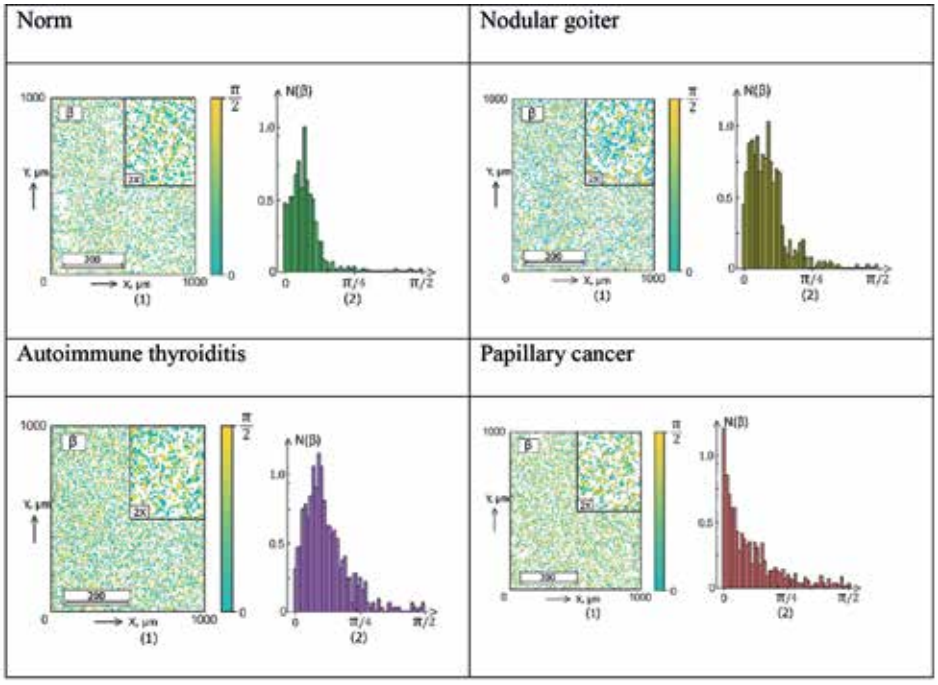

Fig. 2. Phase polarization maps (1) and histograms (2) of the distributions of polarization ellipticity values of digital microscopic images of native histological sections of thyroid biopsy

The peculiarity of the analysis of our results is the fact that in this case, the algorithmically reconstructed layer maps β(ϑ,m,n) are "devoid" of the distorting effect of the depolarized background and are almost uniquely related to the optically anisotropic properties of the birefringent polycrystalline structure of the thyroid parenchyma. Therefore, as the birefringence of the parenchyma increases ("normal – nodular goiter – autoimmune thyroiditis – papillary cancer"), the dynamics of changes in the value of statistical markers increases. As a result, the balanced accuracy of the differential diagnosis of thyroid pathologies increases (Table 6).

The use of polarisation biomedical optics methods makes it possible to increase the angle of view in assessing the development of pathological processes in the thyroid gland, such as goiter, autoimmune thyroiditis and papillary cancer from 20% to 100%. In particular, the optical model of the morphological structure of thyroid tissue is a two-component amorphous-anisotropic matrix. The amorphous component (parenchyma formed by epithelial tissue – T thyrocytes) is polarisation inactive and does not change the polarisation state of the laser irradiating beam. The anisotropic component (optically active globulin protein complexes – follicles filled with a colloid of thyroglobulin proteins) forms coordinately distributed polarisation ellipticities or polarisation ellipticity maps. The statistical structure of polarization ellipticity maps is determined by the concentration of optically active thyroglobulin protein chiral molecules of the follicle colloid and does not depend on their coordinate distribution in the volume of the thyroid tissue sample parenchyma. The polycrystalline component (layers of the connective tissue network in the parenchyma – supramolecular fibrillar connective tissue protein networks) has structural optical anisotropy. Pathological changes in the thyroid gland lead to transformation of the parenchyma structure due to: follicle enlargement and formation of polycrystalline structural anisotropy due to nodular growth of connective tissue, which leads to nodular goiter with activation of T thyrocytes as an amorphous component in patients with nodular goiter as a result of activation of the dysregulatory pathological process.

Pathological changes in the thyroid gland lead to transformation of the parenchyma structure due to: follicle shrinkage and reduction of polycrystalline structural anisotropy and its simultaneous growth due to connective tissue proliferation as a result of autoimmune inflammation.

Pathological changes in the thyroid gland lead to transformation of the parenchyma structure due to: follicle shrinkage with a decrease in polycrystalline structural anisotropy due to papillary growth of transformed T thyrocytes, which leads to papillary thyroid cancer.

DISCUSSIONS

The analysis of the results of statistical analysis of integral polarization ellipticity maps of digital microscopic images of native histological sections of thyroid biopsy revealed:

Statistically significant (p_{ik}≤0,05) change in the magnitude of all central statistical moments of the 1st – 4th orders, which characterize the integrated maps of polarization ellipticity $\beta(m,n)$.

The value of the average SM_1 increases within 1.5 times – from 0.23 to 0.37.

The value of the Dispersion SM_2 increases within 1,75 times – from 0,14 to 0,22.

Asymmetry SM_3 of the polarization ellipticity distributions is statistically significant (p_{ik}≤0,05) and varies in the range from 0,91 to 0,42.

Excess SM_4 coordinate distributions $\beta(m,n)$ also statistically significant (p_{ik}≤0,05) varies in the range from 1,33 to 0,61.

Diagnostics of thyroid pathology (control group 1 and the totality of all study groups "2-4"):

"Norm – Nodular goiter" Ac_{12} (SM_3;SM_4)~87% – "good" level;

"Norm – autoimmune thyroiditis" Ac_{13} (SM_3;SM_4) ~88% – "excellent" level;

"Norm – papillary cancer" Ac_{14} (SM_3;SM_4)~89% – "good" level.

Differential diagnosis:

" Nodular goiter – autoimmune thyroiditis" Ac_{23} (SM_3;SM_4) ~87% – "good" level;

" Nodular goiter – papillary cancer" Ac_{24} (SM_3;SM_4) ~88% – "good" level";

Table 5. Statistical parameters of phase maps of polarization ellipticity of digital microscopic images of native histological sections of the thyroid gland

Group	Group 1 (51 sample)	Group 2 (51 sample)	Group 3 (51 sample)	Group 4 (51 sample)
Average, SM_1	0,170,009	0,210,11	0,260,15	0,310,17
p_{ik}	$p_{12;13;14} \le 0{,}05; p_{23;24;24} \le 0{,}05$			
Dispersion, SM_1	0,090,005	0,110,007	0,130,008	0,1450,009
p_{ik}	$p_{12;13;14} \le 0{,}05; p_{23;24;24} \le 0{,}05$			
Asymmetry, SM_1	0,930,051	0,770,043	0,610,034	0,450,031
p_{ik}	$p_{12;13;14} \le 0{,}001; p_{23;24;34} \le 0{,}001$			
Excess, SM_1	1,610,092	1,230,069	0,910,052	0,730,038
p_{ik}	$p_{12;13;14} \le 0{,}001; p_{23;24;34} \le 0{,}001$			

Table 6. Balanced accuracy of differential diagnosis of thyroid pathology based on the analysis of layer-by-layer polarization ellipticity maps

Average, SM_1		
a=89	a=89	a=90
b=13	b=13	b=12
Ac_{14}=87,3%	Ac_{14}=87,3%	Ac_{14}=88,3%
a=80	a=82	a=83
b=22	b=20	b=19
Ac_{23}=78,4%	Ac_{24}=80,4%	Ac_{34}=81,4%
Dispersion, SM_2		
a=89	a=89	a=90
b=13	b=13	b=12
Ac_{14}=87,3%	Ac_{14}=87,3%	Ac_{14}=88,3%
a=80	a=82	a=83
b=22	b=20	b=19
Ac_{23}=78,4%	Ac_{24}=80,4%	Ac_{34}=81,4%
Asymmetry, SM_3		
a=95	a=96	a=97
b=7	b=6	b=5
Ac_{12}=93,1%	Ac_{13}=94,1%	Ac_{14}=95,1%
a=90	a=91	a=92
b=12	b=11	b=10
Ac_{23}=88,3%	Ac_{24}=89,2%	Ac_{34}=90,2%
Excess, SM_4		
a=95	a=96	a=97
b=7	b=6	b=5
Ac_{12}=93,1%	Ac_{13}=94,1%	Ac_{14}=95,1%
a=90	a=91	a=92
b=12	b=11	b=10
Ac_{23}=88,3%	Ac_{24}=89,2%	Ac_{34}=90,2%

" Autoimmune thyroiditis – papillary cancer " Ac_{34} (SM_3;SM_4) ~89% – "good" level".

The obtained results correlate well with prognostic scenarios of pathological changes in the structural anisotropy of the thyroid parenchyma.

Namely, "nodular goiter" – an increase in polycrystalline structural birefringence due to nodular proliferation of connective tissue; "autoimmune thyroiditis" – due to squamous cell metaplasia of follicular cells, an increase in their size, an increase in the level of polycrystalline structural birefringence is formed due to the formation of a network of fibrous strands; "papillary cancer" – the predominant influence of structural birefringence increases due to hyperplasia in the form of oblong papillary formations.

Statistical analysis of the data of digital holographic reproduction of layer-by-layer maps of polarization ellipticity revealed:

Consistent and statistically significant (p_{ik}<0,05) increase in the value of the 1st order statistical moment (average) SM_1 of the layer-by-layer polarization distributions $\beta(\vartheta,m,n)$ from 0,17 to 0,31.

The value of the 2nd order statistical moment (dispersion) SM_2 is statistically significant (p_{ik}<0,05) and grows in the range from 0,09 to 0,145.

Maximum diagnostic sensitivity to changes in the statistical structure of layer maps $\beta(\vartheta,m,n)$ have asymmetry SM_3 and excess SM_4, which characterize the asymmetry and sharpness of the peak of the distributions of the ellipticity of polarization of microscopic images of histological sections of thyroid biopsy.

Statistical moment of the 3rd order – asymmetry $SM_3(\vartheta, \beta)$ statistically significant ($p_{ik}\leq$0,001) varies within a wide range (up to two times) of eigenvalues from 0,45 to 0,93.

Statistical moment of the 4th order – excess $SM_4(\vartheta, \beta)$ similarly statistically significant ($p_{ik}\leq$0,001) varies within the range of 2,15 times – from 0,73 to 1,61.

The results of the information analysis of the data of the method of polarization-interference mapping of layer-by-layer maps of polarization ellipticity demonstrated

the following levels of balanced accuracy of differential diagnosis of thyroid pathologies:

"Norm – Nodular goiter" Ac_{12} $(SM_3;SM_4)$~93% – "good" level;

"Norm – autoimmune thyroiditis" Ac_{13} $(SM_3;SM_4)$ ~94% – "excellent" level;

"Norm – papillary cancer" Ac_{14} $(SM_3;SM_4)$~95% – "good" level.

Differential diagnosis:

" Nodular goiter – autoimmune thyroiditis" Ac_{23} $(SM_3;SM_4)$ ~87% – "good" level;

" Nodular goiter – papillary cancer" Ac_{24} $(SM_3;SM_4)$ ~88% – "good" level";

" Autoimmune thyroiditis – papillary cancer " Ac_{34} $(SM_3;SM_4)$ ~89% – "good" level".

Thus, the most important idea of our study is the integration of biophysical methods with clinical studies, which is manifested in the use of optical methods to confirm the features of pathogenesis for three pathological processes of the thyroid gland the use of biophysical methods made it possible to confirm the features of pathogenesis for three pathological processes of the thyroid gland. In patients with nodular goiter, caused by the activation of T thyrocytes, as an amorphous component, as a result of the activation of the dysregulatory pathological process due to violations of the principle of direct and negative feedback of the regulation of endocrine functions [17-28]. In autoimmune Hashimoto's thyroiditis, as a result of the influence of genetic factors, stress, excess iodine and barrier disruption, autoimmune inflammation of the thyroid gland develops with a decrease in the number of colloids, squamous metaplasia of follicular cells – T thyrocytes, proliferation of connective tissue in the interstitium, infiltration of the stroma by lymphocytes and the formation of Hurtle cells [29]. In patients with papillary cancer, caused by the papillary proliferation of transformed T thyrocytes, as an amorphous component, as a result of the activation of tumor progression with intensive processes of growth, invasion, and the formation of vessels to ensure the blood supply to the tumor [30].

CONCLUSIONS

1. The experimental results of polarization mapping of ellipticity maps of digital microscopic images of native histological sections of thyroid biopsies of donors and patients with nodular goiter, autoimmune thyroiditis and papillary cancer are presented and analyzed within the framework of the statistical approach.
2. The optimal markers of the method of mapping the polarization ellipticity maps of digital microscopic images of thyroid biopsies were identified, which provided a good level of accuracy of differential diagnosis (~87.3%-89.2%).
3. The results of polarization-interference mapping of layer-by-layer coordinate distributions of ellipticity of polarization of native histological sections of thyroid biopsy are presented and analyzed within the framework of the statistical approach.
4. The results of the information analysis of layer-by-layer mapping of microscopic images of native histological sections of thyroid biopsy revealed an increase in the sensitivity of this method to an excellent level (~93%-95%).

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This research was carried out according to the research work of Bukovinian State Medical University for 2019-2024 on the theme of "New technologies for diagnosis and pathogenetic treatment of proximal nephron dysfunction under the conditions of development of systemic and renal classical and dysregulatory pathological processes" (state registration number 0120U102805).

The authors gratefully acknowledge the support of the National Research Foundation of Ukraine, Project 2022.01/0034; Scholarship of the Verkhovna Rada of Ukraine for Young Doctoral Students.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Oleksandr V. Bilookyi
Bukovinian State Medical University
2 Teatralna Square, 58002 Chernivtsi, Ukraine
e-mail: bilookyi.olexandr@bsmu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Oleksandr V. Bilookyi: 0000-0002-4190-313X B
Yurii Ye. Rohovyi: 0000-0001-7119-9190 F
Yurii A.Uschenko: 0000-0003-1767-1882 A
Oksana V. Kinzerska: 0000-0003-1722-1216 C
Valeriy M. Sklyarchuk: 0000-0001-8211-4391 D
Viacheslav V. Bilookyi: 0000-0001-9921-7178 E

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

RECEIVED: 10.01.2025
ACCEPTED: 22.06.2025

CREATIVE COMMONS 4.0

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ORIGINAL ARTICLE

Evaluation of Vitamin D3 as a diagnostic marker in hypothyroidism

Karar Nadhm Obaid Aljabry[1], Yasseen Abdulurda Yasseen[1], Nibras Hussein Abdulsada Al-Ghuraibawi[2], Ali A. Al-Fahham[3]

[1]INTERNAL MEDICINE DEPARTMENT, MEDICINE COLLEGE, UNIVERSITY OF KUFA, NAJAF, IRAQ
[2]DEPARTMENT OF PHARMACOLOGY, COLLEGE OF PHARMACY, UNIVERSITY OF KUFA, NAJAF, IRAQ
[3]FACULTY OF NURSING, UNIVERSITY OF KUFA, NAJAF, IRAQ

ABSTRACT

Aim: To investigate the role of serum vitamin D3 in the pathogenesis and diagnosis for hypothyroidism.

Materials and Methods: Cross-sectional study was conducted at the Outpatient Analytics Center of Al-Nokhba and Al-Sadder Teaching Hospital, Najaf, Iraq, between October 2021 and February 2022. A total of two groups, Group I (49 hypothyroid patients; mean age 47.69±8.961 years) and Group II (49 healthy controls; mean age 47.43±9.89 years), were included. The estimation of serum T3, T4, TSH, calcium, and 25(OH) vitamin D levels was performed by GP1100 immunofluorescence quantitative analyzer. Serum Calcium levels were determined by the spectrophotometric method.

Results: Hypothyroid patients had much lower serum 25(OH) vitamin D levels; mean value was 12.45±0.95 ng/ml whereas for controls it was 31.35±0.87 ng/ml (P<0.000). T3, T4, and calcium levels were also significantly low in the hypothyroid patients, as opposed to the high levels of TSH. The sensitivity and specificity of vitamin D3 in the diagnosis of hypothyroidism is 71% and 65% respectively.

Conclusions: This study underlines a strong association between hypothyroidism and low serum levels of vitamin D. The results support the notion that, in fact, vitamin D deficiency may be involved in the pathophysiology of hypothyroidism, thus indicating the significance of monitoring and correcting the status of this vitamin in such patients. Further studies should be directed to the casual pathways and therapeutic benefits of vitamin D supplementation.

KEY WORD: Hypothyroidism, Vitamin D3, calcium, serum levels T3, T4

Pol Merkur Lek,2025;53(4):452-457 doi: 10.36740/Merkur202504103

INTRODUCTION

Deficiency of vitamin D has been related as contributing to the pathogenesis of several autoimmune and endocrine diseases, including hypothyroidism. Understanding the link between hypothyroidism and vitamin D might provide new insight into the etiopathogenesis of this thyroid pathology and eventually open new directions for therapy. Hypothyroidism, a disorder characterized by reduction thyroid hormone secretion, is caused by multifactorial aspects and complex diagnostic pathways. Hypothyroidism results from several factors such as autoimmune diseases, iodine deficiency, and congenital abnormalities. The American Association of Clinical Endocrinologists (AACE) in conjunction with the American Thyroid Association (ATA) has defined a need for proper diagnosis to enhance the treatment of patients with this condition. Prevalence of autoimmune causes is found mainly for Hashimoto's thyroiditis, but in areas of iodine intake which are less than sufficient, it will have an important effect as well [1]. Consideration for the early detection of congenital hypothyroidism (CH) requiring immediate prevention toward retardation features important genetic defects of synthesis involving the ways of thyroid hormones and their functions [2]. Apart from genetic factors, the increasing prevalence of congenital hypothyroidism is worrisome due to possible environmental impingement and genetic predisposition [3]. It infers additional studies in understanding the interaction of genetic and environmental factors contributing to the rising rates of CH. Hypothyroidism can occur in three ways: primary, secondary, or tertiary. Primary hypothyroidism results from a decreased production of thyroid hormones by the cells of the thyroid gland. The tertiary is seen in cases with pituitary diseases, whereas secondary hypothyroidism occurs in people with hypothalamic disorders [4]. Diagnosis of hypothyroidism is based on serum TSH levels in the first instance. Indeed, Thyroid-stimulating hormone (TSH) is the primary screening test for thyroid disorders. Furthermore, hypothyroidism at the peripheral level is diagnosed when free levels of tri-iodothyronine (T3) and thyroxine (T4) are measurable. Clinical symptoms of hypothyroidism may manifest in relation to a situation when biochemical assays are normal. The condition may result from peripheral tissue genetic defects, allowing the manifestation of synthesis diseases with sensitivity to peripheral tissues or due to enhanced tumor cell production of deiodinase 3 that inactivates thyroid hormones. The symptoms of these patients differ, depending on the origin of the tumor [5]. The diagnostic process can, however, be complicated by the presence of comorbidities that drive clinicians to undertake comprehensive clinical and laboratory

evaluations to determine the underlying etiology. Subclinical hypothyroidism is even more challenging as the diagnosis relies on fairly subtle clinical judgment and individualized treatment strategies. Specific diagnostic considerations are also involved in congenital hypothyroidism where neonatal screening protocols and biochemical markers need to be assessed [6]. Early identification and management are especially important in cases of congenital hypothyroidism given low rates of optimal outcomes when compared to prompt L-T4 supplementation. Moreover, central hypothyroidism (CeH), resulting from impaired pituitary or hypothalamic function, poses particular challenges in diagnosis due to the inconsistent sensitivity of clinical parameters [7]. This emphasizes the need for developing expert consensus guidelines to improve the diagnosis and patient care strategies for all forms of hypothyroidism [8]. Conversely, Vitamin D is a steroid-like fat-soluble substance that regulates important functions in the balance of phosphorus and calcium homeostasis and is important in healthy bones. Vitamin D deficiency or insufficiency affects about 1 billion of the world's population [9]. The vitamin is normally produced in response to ultraviolet radiation exposure and this process involves conversion in the liver and kidney to its active form, calcitriol [10]. Vitamin D levels have long been associated with thyroid pathologies, such as Hashimoto thyroiditis and autoimmune disease of the thyroid. Few studies exist on the relationship between hypothyroidism and the level of vitamin D in the body [11].

AIM

Accordingly, the current study aims to investigate the role of serum vitamin D3 in the pathogenesis and diagnosis for hypothyroidism.

MATERIALS AND METHODS

Ninety-eight subjects who were residents of the Najaf region and recruited to the Outpatient Analytics Center of Al-Nokhba and Al-Sadder Teaching Hospital during the period from Oct.2021 to Feb.2022 were included in this study. All participants provided written informed consent, they were divided into two main groups:

Group I: This group comprised 49, with mean age±S.D (47.69±8.961) years. The patients were diagnosed as hypothyroid, having TSH higher than 5.0 mU/L with lowered levels of T3 and T4 compared to their normal values.

Group II: Consisted of 49 apparently healthy individuals (control group). Mean ages±S.D were (47.43±9.89) years.

All the cases enrolled in this study were subjected to thorough history taking, a complete general physical examination, and laboratory investigations including serum T3, T4, TSH, calcium and vitamin D. The levels of serum T3, T4, TSH and 25 (OH) D levels (D3) were measured by Immunofluorescence Quantitative analyzer technique (Getein, Biotech, Inc.). Serum Calcium levels were determined by the spectrophotometric method (Huma Count, Germany). Vitamin D deficiency was defined as a serum level of 25OHD of <=20 ng/ml and insufficiency as a serum level between >20 ng/ml and<30 ng/ml and normal > or=30 ng/ml.

STATISTICAL ANALYSIS

Resultant data were statistically analyzed by SPSS 11.5 for Windows. The mean±SD for all variables was calculated. The significance of mean differences for each tested variable was tested by student's "t" test. Correlations between serum vitamin D, calcium, TSH T3, and T4, were presented using the correlation coefficient (r). Results were considered as significant or non-significant if P> 0.05 or P<0.05, respectively.

RESULTS

SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Socio-demographic characteristics in patients and healthy controls were displayed in table 1. This table illustrates an important gender distribution difference P=0.044 wherein more males are accounted for in the control group and more females in the patient group. However, there is no difference in the mean age between the two groups (patients: 47.69±8.961 years, controls: 47.43±9.89 years, P=0.890), which means that these groups can be seen as matched with respect to age. The groups have been designed to be balanced statistical comparisons, at least from the point of view of sample sizes (n=49).

The distribution of patients according to the assessment of vitamin D3 revealed that a huge 77% is deficient in vitamin D, while only 23% have a normal level of vitamin D, fig. 1.

Major differences in clinical biomarkers were noted among hypothyroid patients and healthy controls, as shown in Table 2. An increase in TSH level (8.71±7.81 mU/L) was recorded in patients when compared to the control group (3.48±1.16 mU/L). This proved the typical regulation loss characteristic of hypothyroidism (P<0.000). On the contrary, significantly reduced levels were recorded for T3, T4, Ca, and Vitamin D3 for patients. T3 and T4 for patients were 1.06±0.48 Pg/ml and 2.68±1.21 µg/dl,

Table 1. Socio-demographic characteristics in patients and healthy controls

		Patients (n=49)	Control (n=49)	P value
Gender	Male	16	23	0.044
	Female	33	27	
Age (Years)*		47.69 ± 8.961	47.43 ± 9.89	0.890

** Result expressed as mean ± S.D*

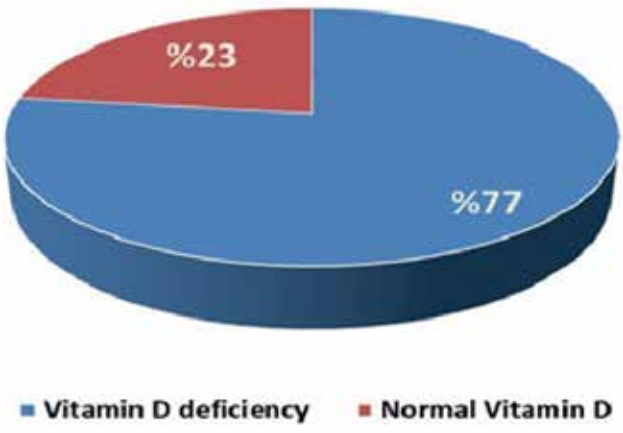

Fig. 1. Distribution patients according to the assessment of vitamin D3

respectively, against 3.31±0.61 Pg/ml and 8.40±1.87 µg/dl for normal subjects (P<0.000). Equally low in patients were Ca (6.30±1.64 mg/dl vs. 9.20±0.69 mg/dl) and Vitamin D3 (12.45±0.95 ng/ml vs. 31.35±0.87 ng/ml) (P<0.000). These highlight how deeply biochemical changes take place in hypothyroidism, which may be a sign for an extended application for these biomarkers in the diagnosis and monitoring of the disease (Table 2).

Results of univariate logistic regression analysis depicting the association of different biomarkers with vitamin D deficiency risk amongst hypothyroid patients are presented in Table 3. Both TSH (OR=1.21, 95% CI: 1.04-1.65) and Ca++ (OR=1.52, 95% CI: 1.13-1.26) show significant associations with vitamin D deficiency at P<0.11 and P<0.001, respectively. A very strong and significant association is also noticed for T3 (OR=1.11, 95% CI: 1.11-1.68). T4 manifests a borderline association with vitamin D deficiency (P=0.066), thereby suggesting a probable role for it in predicting such a condition amongst hypothyroid subjects. Further research is warranted to confirm these findings.

The sensitivity and specificity values of vitamin D levels for the detection of hypothyroidism, at a cutoff of 20 have been calculated using the Youden index (Table 4). The sensitivity for the cut-point reached is 71%, meaning that the test will pick up 71% of hypothyroid patients with vitamin D deficiency. The specificity stands at 65%, indicating that it will exclude 65% of non-hypothyroid cases. The AUC is 71%, which is considered fair in giving the accuracy of vitamin D as a marker for diagnosing hypothyroidism. This finding implies that vitamin D may be fairly good as a diagnostic tool; however, more biomarkers would be needed to enhance overall diagnostic accuracy.

DISCUSSION

The current study demonstrated a gender-dependent differences between hypothyroid patients and healthy individuals (control). These findings come in line with previous studies which found that the hypothyroidism more common in female than male and this may be because of women may experience a high flux of hormones during pregnancy and again at menopause [12-13]. The epidemiology of hypothyroidism shows marked gender differences with a larger number of women being affected compared to men. This effect is consistent with the findings in related fields, like chronic kidney disorders, where the influence of sex and gender disparities is seen on outcomes and prevalence rates [14]. A meta-analysis conducted on thyroid-

Table 2. Differences in clinical biomarker between hypothyroid patients and healthy controls

Biomarkers	Patients (n=49)	Control (n=49)	p-value
TSH (mU/L)	8.71 ± 7.81	3.48 ± 1.16	< 0.000
T3 (Pg/ml)	1.06 ± 0.48	3.31 ± 0.61	< 0.000
T4 (µg/dl)	2.68 ± 1.21	8.40 ±1.87	< 0.000
Ca (mg/dl)	6.30 ± 1.64	9.20 ± 0.69	< 0.000
Vitamin D3 (ng/ml)	12.45 ± 9.95	31.35 ± 0.87	< 0.000

Table 3. Univariate logistic regression analysis of the association biomarkers in hypothyroid patients and the risk of having vitamin D deficiency

	OR	95% CI	P-value
TSH	1.21	1.04- 1.65	<0.11
T3	1.11	1.11- 1.68	< 0.000
T4	1.34	1.02- 1.83	0.066
Ca++	1.52	1.13- 1.26	<0.001

OR: odds ratio, CI: confidence interval

Table 4. The sensitivity and specificity of vitamin D in the diagnosis of hypothyroidism

	Cutoff point	Sensitivity	Specificity	AUC[1]
Vitamin D	20	71%	65%	71%

[1]Area under the curve; cutoff point calculated using Youden index method

related phenotypes also brought out specific differences by gender in the regulation of thyroid function, indicating that perhaps biological and genetic factors contribute to these disparities [15]. Gender disparities in health outcomes have also been established in hypothyroidism. Kaushik et al., (2023) investigated the association of subclinical hypothyroidism with the risk of coronary heart disease, and came to find that women might undergo dissimilar cardiovascular risks compared to men. This difference is very important when considering the long-term consequences of hypothyroidism on the health of males and females [16]. Vitamin D deficiency has gained importance worldwide, especially among certain populations, for instance those with hypothyroidism, reflecting low circulating free thyroid hormones that mask metabolic aberrations. These might include some insulin resistance and disturbed calcium metabolism. A literature review study by Vieira et al., (2020) seemingly reiterated a marked relationship between vitamin D levels and TSH levels among patients with subclinical hypothyroidism. Which in turn suggests a plausible argument that the observed elevated TSH levels relate with low D3 vitamin levels [17]. It is suggested that this may occur through insulin resistance: indicating a situation where already existing metabolic disturbance is worsened by vitamin D deficiency among those suffering hypothyroid diseases. This finding relates to the growing body of evidence supporting vitamin D as vital to preserving good metabolic health, its action possibly protective against conditions such as hypothyroidism. Moreover, the physiological linkage between vitamin D and the homeostasis of calcium may also be related to thyroid functionality [18]. The current study is consistent with the findings of previous studies which observed lower circulating 25(OH) vitamin D3 levels in patients with hypothyroidism [19-21]. These observations find their rationalization through the biological actions of vitamin D, mediated through its receptor termed vitamin D receptor (VDR) [22] and which are under the regulation of the vitamin D-binding protein [23] and the CYP27B1 hydroxylase enzyme [24]. Vitamin D has immunomodulatory action on many cells of the immune system both of the innate and adaptive immune response, since most of these cells express the VDR. Indeed, it inhibits immune function through dendritic cell initiation of T cell function; promoting rather a tolerogenic phenotype that prefers regulatory T cells over effector T cells [25]. This mechanism is particularly pertinent to the pathogenesis of Hashimoto's thyroiditis, the most frequent form of hypothyroidism in which auto reactive T cells are induced against antigens of the thyroid. Impairment of central or peripheral immune tolerance may result from genetically determined immunodeficiency or a lack of suppressive immune function-related regulatory T cells and has been linked to Vitamin D3 deficiency in hypothyroid patients [26], however, our finding is in contrast to the findings some other studies, which proposed that the association between hypothyroidism and low levels of D3 might not be causal. They suggested that hypothyroidism can lead to 25(OH)D malabsorption. Other factors such as limited sun exposure in certain regions, will independently add to the 25(OH)D pool, contain by itself vitamin D deficiency being prevalent even among healthy individuals without thyroid diseases. It underlies the complexity of interrelations between hypothyroidism and vitamin D3 levels and motivates further research in this area [27-28]. The regression result of calcium exhibited a association between calcium content and vitamin D deficiency. As documented by Holick et al., in discussing the role of vitamin D with calcium metabolism, the main point is that its deficiency can bring about the disease of secondary hyperparathyroidism, which may further worsen the issue with thyroid performance and also a person's whole metabolic condition [29]. Vitamin D is fundamental for the regulation of homeostasis in calcium and phosphorus. According to Bouillon et al., (2018), vitamin D is very important in promoting optimal absorption of calcium by the intestines and maintaining proper bone health. Vitamin D deficiency demands surrogates of intake and sources of alternative pathways concerning better risk for fractures to even greater turnover of the bone. This was consistent with the classical view that vitamin D functioned primarily to facilitate absorption of calcium. Thus, it supported the integrity of the skeleton [30]. Sassi et al., (2018) later elaborated the multifaceted role of vitamin D, the principal impact on immune function and inflammation, which could indirectly affect calcium metabolism. The fact that immune cells express receptors for vitamin D establishes a link between immune health and calcium homeostasis, further suggesting that the key driver to ensure both immune health and bone health is maintaining adequate levels of vitamin D [31]. Gil et al., (2018) also underscore the well-known role of vitamin D in calcium absorption regulation while introducing the possibility that vitamin D might express some effect on the cellular level mechanisms beyond mineral metabolism. This more general view reinforces the concept that vitamin D should be at a sufficient level not only because of calcium regulation but also for health in general [32]. Giustina et al., (2018) further testify to the complexity of the role of vitamin D in calcium metabolism by asserting that its effects on bone mineral density and fracture site, actual condition, and different health conditions contrast with the unequivocal positive effects of vitamin D and calcium intake on fracture risk in

the elderly population. In essence, this is an indication that the interrelationship between vitamin D and calcium is not just a linear one but seems to depend on several different factors [33]. It seems that vitamin D levels may be one of the indicators in the diagnosis of hypothyroidism. The sensitivity and specificity of diagnostic tests are crucial in clinical practice. In this context, a study of novel reagents to improve the sensitivity and specificity of vitamin D testing is of great interest. Improved testing of vitamin D levels may indirectly affect the diagnostic accuracy of hypothyroidism. Improved test performance may lead to a better understanding of the role of vitamin D in thyroid function and may help detect vitamin D deficiency in patients with thyroid dysfunction. Moreover, a significant study brought forward the fact that vitamin D could act in the place of a probable biomarker in the diagnosis of hypothyroidism especially in those population groups who have prior risk factors due to the deficiency of both vitamin D and thyroid functioning. Authors express their recommendation for checking the level of vitamin D on routine bases in patients with subclinical hypothyroidism, accentuating its sensitivity concerning metabolic health as well as the onset of early diabetes [34].

CONCLUSIONS

This study underlines a strong association between hypothyroidism and low serum levels of vitamin D. The results support the notion that, in fact, vitamin D deficiency may be involved in the pathophysiology of hypothyroidism, thus indicating the significance of monitoring and correcting the status of this vitamin in such patients. Further studies should be directed to the casual pathways and therapeutic benefits of vitamin D supplementation.

ABBREVIATIONS

AACE:	American Association of Clinical Endocrinologists
ATA:	American Thyroid Association
CH:	Congenital Hypothyroidism
r:	Correlation Coefficient
TSH:	Thyroid-stimulating hormone
T3:	tri-iodothyronine
T4:	thyroxine

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Ali A. Al-Fahham
University of Kufa
299G+HPX, Kufa St, Kufa, Najaf Governorate, Iraq
e-mail: sgahmed1331962@outlook.com

ORCID AND CONTRIBUTIONSHIP

Karar Nadhm Obaid Aljabry: 0009-0009-0406-1963 B C
Yasseen Abdulurda Yasseen: 0009-0001-4664-240X C D
Nibras Hussein Abdulsada Al-Ghuraibawi: 0000-0003-1494-9236 D E
Ali A. Al-Fahham: 0000-0002-6316-6281 A F

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

RECEIVED: 28.12.2024
ACCEPTED: 24.05.2025

CREATIVE COMMONS 4.0

ORIGINAL ARTICLE

The peculiarities of biochemical and morphological changes in the heart of the rats under chronic hypodynamia in the development of adrenalin damage of heart

Olha V. Denefil[1], Roman B. Druziuk[2], Volodymyr Ye. Pelykh[1], Olena O. Kulianda[1], Larysa Ya. Fedoniuk[1], Zoya M. Nebesna[1], Oleh B. Yasinovskyi[1]

[1]I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE
[2]STATE ESTABLISHMENT «LUGANSK STATE MEDICAL UNIVERSITY», RIVNE, UKRAINE

ABSTRACT

Aim: To evaluate the state of oxidation processes and morphological changes in the heart of rats with chronic hypodynamia during the development of epinephrine heart damage (EHD).

Materials and Methods: The study was performed on 144 white male Wistar rats. The animals were divided into two groups: 1 – control, 2 – hypodynamia. For EHD, rats were injected once intraperitoneally with a 0.18% solution of adrenaline hydrotartrate at the rate of 0.5 mg/kg of weight. Stress was induced in rats from 2.5 to 4.0 months of age. The animals were constantly kept in cages with limited living space for 1.5 months. The concentration of diene and triene conjugates (DC, TC), Schiff's bases (SB), TBA-active products (TBA-ap), oxidatively modified proteins (OMP), activity of superoxide dismutase (SOD) and catalase (CAT) were determined in the heart. A morphological study of preparations stained with Azan-trichrome was carried out. All studies were performed in control, 1, 3, 7, 14 and 28 days after adrenaline injection.

Results: In the I series DC and TC increased after 1 day of EHD, fell to control values after 3 days, and then had wave-like character (highest – after 14 days), SB decreased, TBA-ap increase (maximal after 14 days). OMP_{370} increased after 1 and 3 days, after 14 days they were higher than in control, and after 28 days they decreased. OMP_{430} were greater than the control in all terms, except 28 days. The activity of antioxidant enzymes was lower than the control at all times. Hypodynamia caused an increase of lipid peroxidation and a decrease in OMP. Hypodynamia leads to increase of CAT, and decrase of SOD. All indicators of SOD and CAT exceeded hihger level of the antioxidant indicators of animals of the II group at EHD. Biochemical changes are consistent with morphological. After injection of epinephrine, severe vascular disorders, edema, endothelial cell damage, microcirculatory disorders, hemorrhages in the surrounding tissues, and sclerosing of the walls of arteries and venules were observed. Morphological studies established higher disturbances in the II group.

Conclusions: Hypodynamia in rats causes an increase of lipid peroxidation products and catalase activity in the heart, but a decrease in the content of oxidatively modified proteins and superoxide dismutase activity. Adrenaline injection causes activation of lipid peroxidation, especially secondary forms, and an less accumulation in the content of oxidatively modified proteins. During the development of epinephrine heart damage, the activity of antioxidants is significantly higher in animals with chronic hypodynamia. Biochemical changes are consistent with morphological changes, and indicate more damage to the myocardium in the process of development of epinephrine heart damage in animals of the I group.

KEY WORDS: heart, male rats, adrenalin, hypodynamia, biochemical changes, morphological changes

Pol Merkur Lek,2025;53(4):458-466 doi: 10.36740/Merkur202504104

INTRODUCTION

According to research by the European Branch of the World Health Organization (WHO), 60% of adults and 75% of young people suffer from physical inactivity [1, 2]. In recent years, this issue has become even more pressing due to the COVID-19 pandemic [3]. In Ukraine, the problem has intensified further as a result of the war [4].

At the same time, war is undoubtedly a powerful stressor. Moreover, stress can have both chronic and acute effects, which may occur rapidly – almost instantaneously. Therefore, the combined effects of physical inactivity, chronic stress, and acute stress are common phenomenon. Studies are currently being conducted on how these factors affect the cardiovascular system [5, 6].

The combined effect on the myocardium – mediated by β_2-receptor activation through the sympathetic nervous system and elevated adrenaline levels under chronic stress – continues to be studied [7, 8]. One of the models reflecting the development of cardiovascular pathology is the catecholamine model [9]. Catecholamines can induce chronic stress when moderately elevated and acute stress when highly elevated, both of which increase myocardial oxygen demand [10-12]. The development of oxidative stress is a universal mechanism of cell damage, including in the cardiovascular system [13]. Among the various methods for studying oxidative stress in myocardial injury is the determination of the content of medium-weight molecules [14]. This makes the investigation of this issue particularly relevant.

AIM

Aim of the research was to evaluate the state of oxidation processes and morphological changes in the heart of rats with chronic hypodynamia during the development of epinephrine heart damage (EHD).

MATERIALS AND METHODS

The work was doing at the Central Research Laboratory of I. Horbachevsky Ternopil National Medical University. Morphological investigation of heart doing in Histology and Embriology of I. Horbachevsky Ternopil National Medical University.

All experiments were performed in the morning in a specially designated room at a temperature of 18-22 °C, relative humidity of 40-60% and illumination of 250 lux. Animals were kept and experiments on them in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for research and other scientific purposes [15].

The study was performed on 144 white Wistar line male rats, which were kept in one room on a standard diet and a vivarium regime. All animals were divided into two series: 1 – control, 2 – hypodynamia. To modulate EHD, rats were injected once intraperitoneally with a 0.18% solution of adrenaline hydrotartrate at the rate of 0.5 mg/kg of weight (Pharmaceutical company "Darnytsia", Ukraine) [16]. Such dose of adrenaline causes 1 hour after injection responsible regulatory changes in the morphology and functioning of the cardiovascular system, without causing lethality among animals.

Stress was induced in rats from 2.5 to 4.0 months of age. The animals were constantly kept in cages with limited living space for 1.5 months [17]. At the time of the initiation of EHD reproduction, all animals were 4 months old, after injection of adrenaline hydrotartrate in volumes corresponding to body weight, after 1, 3, 7, 14 and 28 days, animals were euthanized under sodium thiopental anesthesia. Design of experiment show in Table 1.

Euthanasia of rats was carried out by total bleeding from the heart after previous thiopental-sodium anesthesia (60 $mg \cdot kg^{-1}$ of the animal's body weight intraperitoneally).

In the heart of animals, the concentration of diene and triene conjugates (DC, TC), TBA-active products (TBA-ap), Schiff's bases (SB), oxidatively-modified proteins (OMP), superoxide dismutase and catalase activity (SOD, CAT) were determined.

The concentration of DC, TC and SB was determined according to the method [18], which is based on the fact that hydroperoxides extracted with a heptane-isopropyl mixture have a certain absorption maximum for DC at λ = 232 nm, for TC – at λ= 278 nm, for SB – at λ = 400 nm. The content of diene and triene conjugates, Schiff bases was expressed in units/g. TBA-ap was determined at a wavelength of 535 nm according to the method [18], expressed in micromoles per kilogram (μmol/kg).

The method of determining the oxidative modification of proteins is based on the interaction of oxidized amino acid residues with 2,4-dinitrophenylhydrazine (2,4-DNPH) with the formation of 2,4-dinitrophenylhydrazones [19]. Ketone-dinitro-phenylhydrazones of a neutral character are registered at 370 nm (OMP_{370}), ketone-dinitro-phenylhydrazones of a basic character – at 430 nm (OMP_{430}), aldehyde-dinitrophenylhydrazones of a neutral character – at 530 nm (OMP_{530}), expressed in nmol/g of protein.

Superoxide dismutase activity in heart homogenate was determined according to the method [18], expressed in conventional units per 1 g. Catalase activity in heart homogenate and blood serum was determined according to the method [18], expressed in mcat/kg.

Transverse sections of the heart, made at the level of both ventricles, were also taken for morphological examination. The preparations were taken immediately

Table 1. Design of experiment – division of experimental animals

Group	Characteristics of the experimental model group	Number of animals
I – Control white rats	Control (Intact)	12
	1 day after adrenaline injection	12
	3 days after adrenaline injection	12
	7 days after adrenaline injection	12
	14 days after adrenaline injection	12
	28 days after adrenaline injection	12
II –White rats with chronic hypodynamia	Control (Hypodynamia)	12
	1 day after adrenaline injection	12
	3 days after adrenaline injection	12
	7 days after adrenaline injection	12
	14 days after adrenaline injection	12
	28 days after adrenaline injection	12
Total		144

after taken blood from the heart of the animal, fixed in a 10% solution of neutral formalin. No earlier than two weeks later, the preparations were washed in the tap water and held in alcohol, poured into paraffin blocks. Sections were stained with azan-trichrome and examined under a light microscope [20].

The significance of the obtained differences between the results (minimum level of significance $p<0.05$) was assessed using the Kruskal–Wallis and Newman–Keuls tests (BioStat program, AnalystSoft Inc.). All results prresented in M±σ.

RESULTS

The products of lipid peroxidation have the following changes (Table 2). When analyzing indicators in I group of rats after 1 day after adrenaline injection, compared to control, the following was noted an increase in DC by 29.5% ($p<0.001$), an increase in TC by 42.5% ($p<0.001$), a decrease in SB by 19.8% ($p<0.001$), an increase in TBA-ap by 74.0% ($p<0.001$). After 3 days of EHD, compared to control, DC and TC indicators have not change SB decreased by 46.0% ($p<0.001$), TBA-ap increased by 96.7% ($p<0.001$). The DC, TC, SB were decrease at that time, compare to results after 1 day, but TBA-ap increased. After the 7 days EHD, compared to control group, the indicators of DC increased by 53.8% ($p<0.001$), TC by 73.4% ($p<0.001$), TBA-ap by 46.4% ($p<0.001$), the most significant decrease in SB indicators was by 71.4% ($p<0.001$). The DC and TC were increase, but SB and TBA-ap were decrease at that time, compare to results after 3 days EHD. After 14 days, compared to control, indicators increased most significantly: DC – by 2.2 times ($p<0.001$), TC – by 2.5 times ($p<0.001$), TBA-ap – by 4.1 times ($p<0.001$), SB indicators decreased by 62.7% ($p<0.001$). All indexes, exept SB, were increase, compare to results after 7 days EHD. After 28 days of EHD, compared to control, the indicators of DC, TC and TBA-ap increased by 73.7% ($p<0.001$), by 95.0% ($p<0.001$) and by 2.5 times ($p<0.001$), respectively; SB was decreased by 54.8% ($p<0.001$). The DC, TC and TBA-ap were decreased, and SB was increased at that time, compare to results after 14 days EHD.

Analyzing the indicators in II groups of rats after 1 day EHD, compared to hypodynamia control, was noted an increase in the indicators of DC, TC and TBA-ap by 35.7% ($p<0.001$), by 76.6% ($p<0.001$) and by 10.2% ($p<0.01$); reduction of SB indicators by 32.8% ($p<0.001$). After 3 days of EHD, compared to hypodynamia control, DC indicators decreased by 48.5% ($p<0.001$), TC increase by 36.3% ($p<0.001$), SB – by 34.5% ($p<0.001$), TBA-ap – by 25.0% ($p<0.001$). The DC and TC were decreased at that time, but SB and TBA-ap – increased compare to results after 1 day. After 7 days EHD, compared to hypodynamia control, there was the most significant decrease in DC indicators by 46.0% ($p<0.001$), TC – by 49.2% ($p<0.001$), less significant decrease in SB – by 52.0% ($p<0.001$), and increase of TBA-ap by 51.4% ($p<0.001$). The TC and SB were decrease, but TBA-ap was increase at that time, compare to results after 3 days EHD. After 14 days of EHD, compared to hypodynamia control, the DC was decreased by 38.7% ($p<0.001$), SB – by 42.9% ($p<0.001$), TC was increased by 11.7% ($p<0.001$), TBA-ap – by 76.4% ($p<0.001$). The DC, TC, TBA-ap and SB increased at that time, compare to results after 7 days EHD.

Table 2. Changes in the content of products of lipid peroxidation in the heart of rats during the development of epinephrine heart damage (M ± σ, n=12)

Group	Index			
	DC, units/g	TC, units/g	SB, units/g	TBA-ap, μmol/kg
Group I – Control				
Control (Intact)	1.56±0.12	1.39±0.10	1.26±0.11	1.81±0.09
1 day EHD	2.02±0.16*	1.98±0.12*	1.01±0,06*	3.15±0.22*
3 days EHD	1.43±0.15**	1.09±0.19**	0.68±0.11*,**	3.56±0.24*
7 days EHD	2.40±0.20*,**	2.41±0.16*,**	0.36±0.02*,**	2.65±0.20*,**
14 days EHD	3.43±0.23*,**	3.45±0.13*,**	0.47±0.02*,**	7.40±0.47*,**
28 days EHD	2.71±0.18*,**	2.71±0.19*,**	0.57±0.03*,**	4.62±0.21*,**
Group II – Hypodynamia				
Control (Hypodynamia)	3,28±0.22$^{\#}$	2,56±0,09$^{\#}$	1,77±0,05$^{\#}$	3,64±0,08$^{\#}$
1 day EHD	4,45±0,20$^{*,\#}$	4,52±0,20$^{*,\#}$	1,19±0,02$^{*,\#}$	4,01±0,22$^{*,\#}$
3 days EHD	1,69±0,11*,**	3,49±0,20$^{*,**,\#}$	2,38±0,09$^{*,**,\#}$	4,55±0,14$^{*,**,\#}$
7 days EHD	1,77±0,09$^{*,\#}$	1,30±0,11$^{*,**,\#}$	0,85±0,03$^{*,**,\#}$	5,51±0,14$^{*,**,\#}$
14 days EHD	2,01±0,10$^{*,**,\#}$	2,86±0,18$^{*,**,\#}$	1,01±0,02$^{*,**,\#}$	6,42±0,21$^{*,**,\#}$
28 days EHD	1,86±0,11$^{*,\#}$	2,36±0,14**	0,86±0,02$^{*,**,\#}$	5,71±0,22$^{*,**,\#}$

*Notes: 1. * – differences with the control within the group; ** – differences with the results of the previous term of the study within the group; # – differences with the corresponding term of group I.*

Table 3. Changes in the content of oxidatively modified proteins in the heart of rats during the development of epinephrine damage to the heart, nmol/g of protein, (M ± σ, n=12)

Group	Index	
	OMP_{370}, nmol/g of protein	OMP_{430}, nmol/g of protein
Group I – Control		
Control (Intact)	0,217 ± 0,011	0,253 ± 0,011
1 day EHD	0,416 ± 0,010*	0,453 ± 0,015*
3 days EHD	0,470 ± 0,021*,**	0,556 ± 0,031*,**
7 days EHD	0,307 ± 0,012*,**	0,378 ± 0,013*,**
14 days EHD	0,362 ± 0,025*,**	0,467 ± 0,022*,**
28 days EHD	0,283 ± 0,009*,**	0,383 ± 0,011*,**
Group II – Hypodynamia		
Control (Hypodynamia)	0,117 ± 0,009#	0,172 ± 0,009#
1 day EHD	0,216 ± 0,010*,#	0,271 ± 0,011*,#
3 days EHD	0,211 ± 0,008*,#	0,242 ± 0,011*,**,#
7 days EHD	0,225 ± 0,008*,#	0,261 ± 0,009*,#
14 days EHD	0,306 ± 0,010*,**,#	0,329 ± 0,021*,**,#
28 days EHD	0,321 ± 0,009*,#	0,365 ± 0,012*

*Notes: 1. * – differences with the control within the group; ** – differences with the results of the previous term of the study within the group; # – differences with the corresponding term of group I.*

After 28 days EHD, compared to castration control, the indicators of DC, and SB was less by 43.3% (p<0.01) and 51.43% (p<0.001), respectively, and TBA-ap indicators increased by 56.9% (p<0.001). Compared to 14 days after EHD, amount of TC, TBA-ap and SB was less.

When we compared results of I, and II groups, we saw, that hypodynamia lead to increase levels of DC, TC, SB and TBA-ap by 2.1 times (p<0.001), by 69.8% (p<0.001), by 40.5% (p<0.002), by 2.0 times (p<0.001), respectively. After 1 day EHD levels of DC, TC, SB and TBA-ap were higher in II group of rats by 2.2 times (p<0.001), by 2.3 times (p<0.001), by 17.8% (p<0.001) and by 27.3% (p<0.001) respectively. After 3 days EHD level of TC was higher in II group by 3.2 times (p<0.001), SB by 3.5 times (p<0.001) and TBA-ap by 27.8% (p<0.001). After 7 days EHD levels of DC and TC were less in II group of rats by 35.6% (p<0.001) and 85.4% (p<0.001), respectively, and levels of SB and TBA-ap were higher in II group by 2.4 times (p<0.001) and by 2.1 times (p<0.001), respectively. After 14 days EHD levels of DC, TC and TBA-ap were less in II group of rats by 41.4% (p<0.001), 17.1% (p<0.001) and 13.2% (p<0.001), respectively, and level of SB and was higher in II group by 2.1 times (p<0.001). After 28 days EHD levels of DC wase less in II group of rats by 31.4% (p<0.001), and levels of SB and TBA-ap was higher in II group by 50.9% (p<0.001) and by 23.6% (p<0.001) respectively.

The changes of oxidatively modified proteins (OMP) we show in Table 3.

When analyzing indicators in I group of rats after 1 day after adrenaline injection, compared to control, the following was noted an increase in all cases: in OMP_{370} by 91.7% (p<0.001), in OMP_{430} – by 79.0% (p<0.001). After 3 days of EHD, compared to control, the indicators of OMP_{370} and OMP_{430} increased by 2.2 times (p<0,001). The level of OMP_{370} and OMP_{430} were higher, compared to previous term of investigation. After 7 days of EHD, compared to control, the indicators of OMP_{370} increased by 41.5% (p<0.001), OMP_{430} increased by 49.4% (p<0.001). The OMP were decrease at that time, compare to results after 3 days of EHD. After 14 days of EHD, compared to control, the indicators of OMP_{370} increased by 66.8% (p<0.001), OMP_{430} increased most significantly by 84.6% (p<0.001). Compared to 7 days after EHD, amount of all indexes were higher. After 28 days of EHD, compared to control, the indicators of OMP_{370} and OMP_{430} were higher than control data, OMP_{370} by 30.4% (p<0.001), in OMP_{430} – by 51.4% (p<0.001).

When analyzing indicators in II group of rats after 1 day after adrenaline injection, compared to hypodynamia control, was noted an increase in the indicators of OMP_{370} by 84.6% (p<0.001), OMP_{430} by 57.6% (p<0,001). After 3 days of EHD, compared to hypodynamia control, the indicators increased less significantly: OMP_{370} – by 80.3% (p<0.001), OMP_{430} – by 40.7% (p<0.001). Compared to 1 day after EHD, amount of OMP_{430} was higher. After 7 days of EHD, compared to hypodynamia control, the indicators of OMP_{370} increased by 92.3% (p<0.001), OMP_{430} by 51.7% (p<0.001). Compared to 3 days after EHD, amount of OMP not changed. After 14 days of EHD, compared to hypodynamia control, indicators increased: OMP_{370} – by 2.6 times (p<0.001), OMP_{430} – by 91.3% (p<0.001), all indexes were higher than in previous

time of invstigation. After 28 days of EHD, compared to hypodynamia control, the indicators of OMP_{370} increased by 2.7 times (p<0.001), OMP_{430} by 2.1 times (p<0.001), compared to 14 days after EHD it were similar.

When we compare results of both groups, we saw, that hypodynamia lead to decrease in all indicators: OMP_{370} by 46.1% (p<0.001), OMP_{430} – by 32.0% (p<0.001). After 1 day of EHD in II group, compared to I group, the indicators of OMP_{370} was less by 48.1% (p<0.001), OMP_{430} – by 40.2% (p<0.001). After 3 days of EHD in II group, compared to I group, the indicators of OMP_{370} was less by 55.1% (p<0.001), OMP_{430} – by 56.5% (p<0.001). After 7 days of EHD in II group, compared to I group, the indicators of OMP_{370} lower by 26.7% (p<0.001), OMP_{430} – by 30.9% (p<0.001). When analyzing indicators after 14 days of EHD in II group, compared to I group, the following was noted an decrease in all cases: in OMP_{370} by 15.5% (p<0.05), in OMP_{430} – by 29.5% (p<0.001). After 28 days of EHD in II group, compared to I group, only the indicators of OMP_{370} was higher by 13.4% (p<0.01).

The changes of superoxide dismutase and catalase activities we demonstrated in Table 4.

Analyzing the indicators of superoxide dismutase activity after adrenaline injection in I group, compared to control, demonstrated it decrease in all term of investigation. Indexes was less after 1 day by 38.6% (p<0.001), after 3 days – by 25.5% (p<0.001), after 7 days – by 48.7% (p<0.001), after 14 days – by 43.5% (p<0.001), and after 28 days – by 33.0% (p<0.001). It increase, compares to previous term, after 3 and 28 days. Analyzing the indicators of catalase activity after adrenaline injection in I series, compared to control, after 1 day was decreased by 30.6% (p<0.001), after 3 days – by 27.9% (p<0.001), after 7 and 14 days – by 28.6% (p<0.001), after 28 days – by 30.6% (p<0.001).

Superoxide dismutase activity after adrenaline injection in II group, compared to hypodynamia control, after 1 day was higher by 38.8% (p<0.001), after 3 days was higher by 2.3 times (p<0.001), after 7th days – by by 2.2 times (p<0.001), after 14 th days – by 2.2 times (p<0.001), after 28th days – by 2.8 times (p<0.001). Catalase activity after adrenaline injection in II group, compared to hypodynamia control, after 1 day was lower by 31.2% (p<0.001), after 3d days – by 51.6% (p<0.001), after 7th days – by 51.3% (p<0.001), after 14th day – by 48.1% (p<0.001), after 28th day – by 54.7% (p<0.001).

Analyzing the indicators of superoxide dismutase activity in both groups of rats without adrenaline injection, the following in II group with hypodynamia rats, compared to I group, indicate less superoxide dismutase activity by 50.3% (p<0.001), but higher catalase activity by 2.4 times (p<0.001). At all terms of investigation, antioxidant activity was higher in II series of rats. Indicators of superoxide dismutase activity after adrenaline injection in II group, compared to I group, after 1 day increased by 12.2% (p<0.001), after 3 days – by 56.1% (p<0.001), after 7 days – by 2.1 times (p<0.001), after 14 days – by 97.7% (p<0.001), after 28 days – by 2.0 times (p<0.001). Indicators of catalase activity after adrenaline injection in II group, compared to I group, after 1 day increased by 2.3 times (p<0.001), after 3 days – by 59.4% (p<0.001), after 7 days – by 61.9% (p<0.001), after 14 days – by 72.4% (p<0.001), after 28 days – by 54.9% (p<0.001).

Table 4. Changes of the antioxidants activity in the heart of rats during the development of epinephrine heart damage (M ± σ, n=12)

Group	Index	
	Superoxide dismutase activity, unit/g	Catalase activity, mcat/kg
Group I – Control		
Control (Intact)	3.06 ± 0.27	1.47 ± 0.11
1 day EHD	$1.88 \pm 0.11^{*}$	$1.02 \pm 0.06^{*}$
3 days EHD	$2.28 \pm 0.15^{*,**}$	$1.06 \pm 0.07^{*}$
7 days EHD	$1.57 \pm 0.10^{*,**}$	$1.05 \pm 0.02^{*}$
14 days EHD	$1.73 \pm 0.11^{*}$	$1.05 \pm 0.02^{*}$
28 days EHD	$2.05 \pm 0.09^{*,**}$	$1.02 \pm 0.02^{*}$
Group II – Hypodynamia		
Control (Hypodynamia)	$1.52 \pm 0.13^{\#}$	$3.49 \pm 0.12^{\#}$
1 day EHD	$2.11 \pm 0.03^{*,\#}$	$2.40 \pm 0.06^{*,\#}$
3 days EHD	$3.56 \pm 0.21^{*,**,\#}$	$1.69 \pm 0.06^{*,**,\#}$
7 days EHD	$3.36 \pm 0.09^{*,\#}$	$1.70 \pm 0.10^{*,\#}$
14 days EHD	$3.42 \pm 0.11^{*,\#}$	$1.81 \pm 0.06^{*,\#}$
28 days EHD	$4.19 \pm 0.28^{*,**,\#}$	$1.58 \pm 0.04^{*,**,\#}$

*Notes: 1. * – differences with the control within the group; ** – differences with the results of the previous term of the study within the group; # – differences with the corresponding term of group I.*

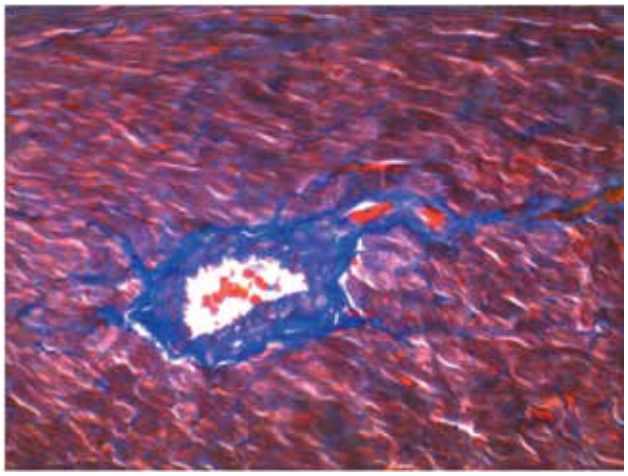

Fig. 1. Structural organization of the heart of the animals of group II, 1 day after adrenalin injection. Stained with Azan-trichrome x 200

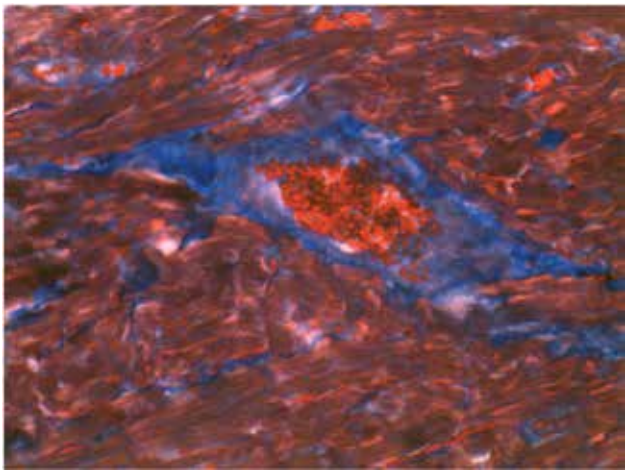

Fig. 2. Structural organization of the heart of the animals of group II, 3 days after adrenalin injection. Stained with Azan-trichrome x 400

The studied biochemical changes in the heart are accompanied by alterative changes in the structural components of the myocardium in the experimental groups.

When studying histological specimens stained with Azan-trichrome, the following was noted after the injection of adrenaline. Pronounced vascular disorders, edema of the adventitia, perivasal edema, damage to the endothelial cells, dilatation of the capillaries lumen, full blood vessels, stasis, hemorrhages, sclerosing of the walls of arteries and venules were observed. Destructive changes in cardiac muscle cells were also noted. Blood vessels wall edema, their shortening, necrosis was partially observed, and myocytolysis was noted in some fields of vision. Edema of the stroma was noted.

When studying the histological specimens of the hearts of animals of the I and II series, the following was noted. 1 day after the injection of adrenaline, in the rats of the I group, there was more intensive growth of connective tissue, edema of the stroma, edema of the arteries wall, structural desorganization of the endothelium, and in the II group (Fig. 1), there was more prominent proliferation of connective tissue, edema of the stroma, arterial walls, and disruption of the integrity of the endothelial structure.

3 days after the injction of adrenaline in rats of the I group, a more pronounced growth of connective tissue, edema of the stroma, cardiac muscle cells, and arteries wall were identifed microscopically. Intravascular hemolysis of erythrocytes was noted. In the II group of rats (Fig. 2), microscopically, more pronounced edema of cardiomyocytes, proliferation of connective tissue around the vessels were detected. Intravascular hemolysis of erythrocytes was noted.

7 days after the injection of adrenaline, microscopically in the myocardium of rats of the I group, there was more prominent edema of stroma and cardiomyocytes, and in some places their necrotic changes were observed. Fibrosis of wall of the arteries, damage of the endothelial cells also was noted. The lumen of blood vesells were empty, without any formed elements of blood. In the II group of

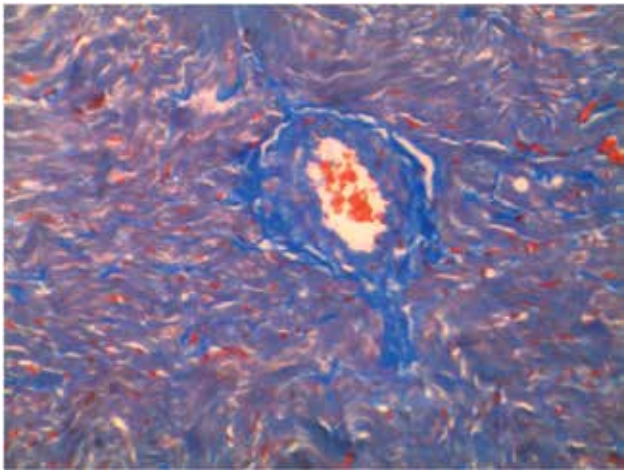

Fig. 3. Structural organization of the heart of the animals of group II, 7 days after adrenalin injection. Stained with Azan-trichrome x 200

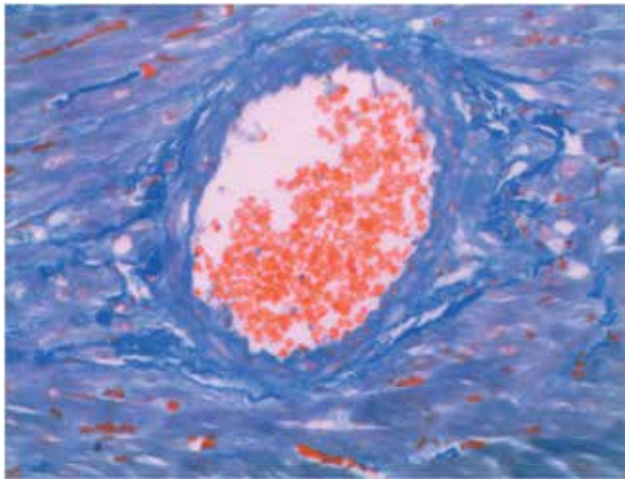

Fig. 4. Structural organization of the heart of the animals of group II, 14 days after adrenalin injection. Stained with Azan-trichrome x 200

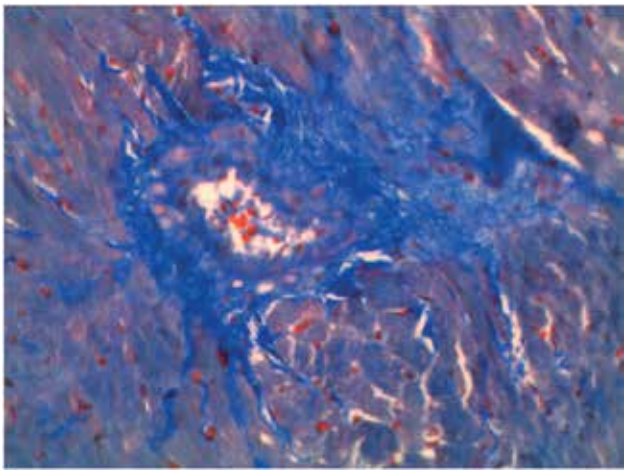

Fig. 5. Structural organization of the heart of the animals of group II, 28 days after adrenalin injection. Stained with Azan-trichrome x 200

rats (Fig. 3), the presence of blood clots and fibrosis of the arterial walls was noted in the vessels.

14 days after the injection of adrenaline microscopically in the myocardium of rats of the I group there was more prominent growth of vascular adventitia and perivascular space, edema of the cardiac muscle cells. Intravascular hemolysis of erythrocytes was noted. In the II group of rats (Fig. 4), there was a more pronounced violation of the endothelial cells of the vascular wall. The presence of blood clots was noted in the vessels.

28 days after the injection of adrenaline microscopically in the rats' heart of the I group, there was a more proprominent growth of connective tissue, edema of the stroma and cardiac muscle cells, wall of the arteries. Blood clots were noted in the blood vessels. In the II group of rats (Fig. 5), there was more pronounced proliferation of connective tissue, edema of the stroma and cardiomyocytes, and arterial walls. The presence of blood clots was noted in the vessels.

So, morphological studies of the hearts of experimental animals established more prominent alterative changes in the II group of animals.

DISCUSSIONS

The literature contains data on the disclosure of mechanisms of damage to the cardiovascular system in various pathological processes, which is combined with neuroendocrine regulation [21, 22], prolonged hypodynamia [23], thermal trauma [24] but there is practically no data on regulatory mechanisms that ensure the processes of adaptation of the cardiovascular system in prolonged hypodynamia and adrenalin heart damage.

In the I group of animals, primary form of lipid peroxidation products increased already after 1 day of EHD, fell to control values only after 3 days, and then the changes had a wave-like character. The highest indicators of DC and TC were registered after 14 days. Such results may indicate an active process of development of adrenaline damage in the heart. It is obvious that after the initial acute phase of the alteration, there was a slight decrease in the activity of the inflammatory process, cardiosclerosis was formed, an active process of fibrosis, which progressed. Other scientist [25] described such connection between epinephrine, protein oxidation, antioxidant status and inflammation. As for changes in SB, this indicator decreased, with a minimum after 7 days, and then the values increased, but did not recover to control indicators. It is obvious that the decrease in the formation of SB indicated the incomplete neutralization of lipid peroxidation products at all times of the study. This was indicated by the increase in TBA-ap, which exceeded the control indicators at all times of the study. The maximum TBA-ap was noted after 14 days.

In the I series of rats, all values of OMP_{370} increased after 1 and 3 days, after 7 days they did not differ from the control, after 14 days they were higher than control level, and after 28 days they decreased and did not differ from the control values. OMP_{430} were greater than the control indicators in all terms, except the last; the maximum was noted after 14 days. The obtained data indicate that, like the processes of lipid peroxidation, the maximum destruction of proteins also occurs after 14 days from adrenaline injection.

The activity of antioxidant enzymes was lower than the control indicators at all times of the study, which could indicate their use at all stages of the development of EHD.

It is know, that female has reduced cardiovasclar risk and a better prognosis [26]. That is why hypodynamia leads to werst prognosis in males that was showed in our exeriment.

In the II group of rats with hypodynamia caused an increase in all indicators of lipid peroxidation, more intermediate products. During the development of EHD, after 1, 3 and 7 days, higher changes were noted as in rats of the II group, but only after 14 days, changes was grater in the I series of rats. It is possible that during this period the higher activity of antioxidants un the II group of animal caused less accumulation of products of lipid peroxidation. The increase in SB indicates the detoxification of lipid peroxidation products to a greater extent than in the I group of rats. After 28 days, a decrease in DC and TC was noted, relative to the control of the II series and the indicators of the animals of the I group at that study period; but TBA-ap was higher, compared to the values of the I group of rats. Such results indicate a more favorable course of EHD in the I series of rats as a result of less damage to the bilipid layer of cardiomyocyte membranes.

In the II group of rats, hypodynamia caused a decrease in OMP indicators. After injection of epinephrine, all values of OMP, compared to the values of rats with hypodynamia, were lower at all times of the study. Such results indicate a more favorable condition of EHD in the II group of rats as a result of less damage to cardiomyocyte membrane proteins.

In the II group of rats after hypodynamia, an decrease in superoxide dismutase increase, but catalase activity – increases, and both activities was observed to increase with the development of EHD. Compared with the I group of rats, in the II group, all indicators of SOD and CAT were higher than the indicators of animals of the I group at all times of the study.

Biochemical changes are consistent with morphological changes, and indicate more damage to the myocardium in

the process of development of EHD in animals of the II group. Vascular and endotelial changed show the development of hypoxia, deseminated intravascular coagulative syndrome, and cardioscleosis.

Similar studies, but on the study of antioxidant protection of the liver, were conducted by other scientists, but they recorded a decrease, not an increase, of the antioxidant system at the beginning of hypokinesia [27], and after 30 days – an increase of it [28], although other authors note the suppression of antioxidant activity against the background of increased lipid peroxidation [29]. We also found a decrease in superoxide dismutase activity, but only in the control group of animals, and in EHD – SOD increased.

CONCLUSIONS

Hypodynamia in rats causes an increase of lipid peroxidation products and catalase activity in the heart, but a decrease in the content of oxidatively modified proteins and superoxide dismutase activity. Adrenaline injection causes activation of lipid peroxidation, especially secondary forms, and an less accumulation in the content of oxidatively modified proteins. During the development of epinephrine heart damage, the activity of antioxidants is significantly higher in animals with chronic hypodynamia. Biochemical changes are consistent with morphological changes, and indicate more damage to the myocardium in the process of development of epinephrine heart damage in animals of the I group.

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The work is carried out within the framework of the initiative research work of the I. Horbachevsky Ternopil National Medical University (Ternopil, Ukraine) "Pathogenetic features of systemic and organ disorders due to the action of extraordinary factors on the body" (state registration number 0121U100071)".

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Larysa Ya. Fedoniuk
I. Horbachevsky Ternopil National Medical University
9 Valova st, 46000 Ternopil, Ukraine
e-mail: Fedonyuk22Larisa@gmail.com

ORCID AND CONTRIBUTIONSHIP
Olha V. Denefil: 0000-0002-3606-5215 A B E F
Roman B. Druziuk: 0000-0001-5451-3184 A B C D E
Volodymyr Ye. Pelykh: 0000-0003-3468-858X B C
Olena O. Kulianda: 0009-0008-2096-4890 D E
Larysa Ya. Fedoniuk: 0000-0003-4910-6888 E F
Zoya M. Nebesna: 0000-0002-6869-0859 B E F
Oleh B. Yasinovskyi: 0000-0002-5121-3140 B E F

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

RECEIVED: 11.01.2025
ACCEPTED: 25.06.2025

CREATIVE COMMONS 4.0

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ORIGINAL ARTICLE

Evaluation of some immune mediators (IL-16, IgE and eosinophils) as diagnostic markers for COVID-19

Sarah Kassab Shandaway Al-Zamali[1], Ruqaya Yahya abd AL-Shaheed[2], Hawraa S. AL- Jobory[3] , Ali A. Al-fahham[4]

[1]DEPARTMENT OF MEDICAL MICROBIOLOGY, HAMMURABI COLLEGE OF MEDICINE, UNIVERSITY OF BABYLON, HILLAH, BABYLON, IRAQ
[2]CRIMINAL EVIDENCE DEPARTMENT, COLLEGE OF SCIENCE, UNIVERSITY OF HILLA, BABYLON, IRAQ
[3]DEPARTMENT OF PHARMACY, TECHNICAL INSTITUTE OF BABYLON, AL-FURAT AL-AWSAT TECHNICAL UNIVERSITY (ATU), KUFA, IRAQ
[4]FACULTY OF NURSING, UNIVERSITY OF KUFA, KUFA, IRAQ

ABSTRACT

Aim: To evaluate clinical applicability of immune mediator's interleukin-16, immunoglobulin E along with eosinophil count in diagnosing COVID-19 and determining its severity.

Materials and Methods: Cross-sectional case-control study was conducted at Al-Najaf General Hospital, Najaf, Iraq between March and August 2024. 120 participants: 60 confirmed COVID-19 cases and 60 healthy controls which matched cases in terms of age and sex. Data collected through direct interviews and hospital records; laboratory investigations were performed following standard protocols. Serum analysis: Serum levels of IgE and IL-16 were determined using an automated system and enzyme-linked immune sorbent assay (ELISA).

Results: A significant difference in levels of immune markers between COVID-19 group and healthy controls. Eosinophil count significantly higher in patients than in controls (105±64 cells/ml vs. 78±22 cells/ml, $P<0.001$). IgE levels in patients were markedly elevated compared to controls (788±98 UI/ml vs. 204±122 UI/ml, $P<0.001$). IL-16 levels in patients were double of controls (12.8±3.9 pg/ml vs. 6.2±2.9 pg/ml, $P<0.01$). Logistic regression analysis indicated that elevated levels of IL-16, IgE, and eosinophils were significantly associated with an increased risk of severe COVID-19, with IL-16 showing a particularly strong association (odds ratio=1.7, $P<0.001$). Sensitivity values were 0.74, 0.48, and 0.85 for eosinophils, IgE, and IL-16, while specificity values were 0.66, 0.58, and 0.72.

Conclusions: Findings underscore probable implication of immune mediators in respect, more especially IL-6, as biomarkers for COVID-19 severity and diagnosis.

KEY WORDS: IgE, COVID-19, Eosinophil, Immune Mediators, IL-16

Pol Merkur Lek,2025;53(4):467-472 doi: 10.36740/Merkur202504105

INTRODUCTION

COVID-19, the disease caused by the SARS-CoV-2 virus, has emerged as one of the most formidable health challenges worldwide. Dysregulation of the immune response has been notable in severe COVID-19 disease, shown also by decreased lymphocyte counts especially T cells alongside elevated inflammatory cytokines. The imbalance includes profoundly reduced helper and regulatory T cells in those severe presentations necessary for strong humoral immune responses. This degree of immunosuppression thus argues a relationship between reduced functionality of lymphocytes and critical disease in the context of severe COVID-19 infections [1]. Alternatively, some patients show a vigorous T cell and B cell response, resulting in positive outcomes. The identification of distinct immunotypes associated with disease severity reveals that the immune response is heterogeneous, not the same for everyone. Variability in individual responses highlights the need for personalized treatment strategies that account for different immune profiles [2]. The pathogenic role of pro-inflammatory cytokines in COVID-19 has been underlined by several studies. Indeed, the virus induces an overwhelming release of such cytokines that fuel acute lung inflammation and, in turn, possible tissue pathologies. Indeed, specific targeting of cytokines like IL-1β and IL-6 might provide therapeutic benefit by attenuating this inflammatory response but not compromising the ability of the immune system to clear the virus [3]. IgE is mainly known for its involvement in allergic reactions and asthma. Nevertheless, its prospective use in COVID-19 diagnosis is still being explored. Though not the major point of interest, the presence of IgE in the patient can help elucidate the immune response – which, in the light of respiratory diseases, can be quite important. Furthermore, the interplay between IgE and other immune mediators overall could give insight into the immune landscape in the setting of COVID-19. New studies should be focused on the involvement of IgE in the severity of COVID-19 especially among patients, to determine whether or not there is any pattern among those with pre-existing allergic conditions [4]. The most studied category is eosinophilic inflammation, which relies on a type 2 (T2) inflammation. Eosinophils provide an immune response whereby their role is particularly relevant to allergic reactions and parasitic infections. Little is known about

their possible impact on COVID-19 pathology. A study of immune profiles in COVID-19 patients might shed light on the trends of eosinophil counts and their association with disease severity. Changes in eosinophil levels might associate with worse clinical outcomes and, therefore, might serve as a diagnostic indicator. An assessment of eosinophil numbers together with immune mediators, including IL-16 and IgE, may further improve the understanding of the immune response in COVID-19 infection. Also, more longitudinal studies are needed to determine the relationship between the levels of this cell type and the disease's course [5]. Proteins sharing a family resemblance are a 155-amino acid protein referred to as IL-16, which is typically secreted in humans [6]. Cytokines of IL-16, those such chemokine's and cytokines responsible for stimulating the epithelial cells to produce the site of inflammation for attraction of neutrophils, are most often associated with neuthrophillic inflammations [7]. IL-16 is a pro-inflammatory cytokine that has been linked with several immune responses. Direct evidence for the involvement of IL-16 in COVID-19 is quite scanty; however, other related cytokines, such as IL-6, play crucial roles in the understanding of the pathology of the disease. For instance, elevated levels of IL-6 have been associated with the disease's severe outcomes in COVID-19 patients, which further supports that the monitoring of IL-6 might help to identify patients critically ill who might benefit from targeted therapies [8]. Moreover, such studies show that differences in IL-6 levels between mild and severe cases are significant and underscore its potential as a diagnostic marker for disease susceptibility [9]. With IL-16, therefore, the interrogation has to be placed together with other cytokines based on the association with cytokine storms and poor clinical outcomes. There are predictors for disease severity being elevated such as IL-6 and IL-10 levels [10], hence, it is likely that similar patterns might be seen with IL-16. Such an idea proposes direction for further investigation to prove the association between IL-16 and COVID-19 disease advancement, especially within the inflammatory responses in which it works. The COVID-19 pandemic stimulated a great deal of interest in searching for diagnostic markers capable of predicting severity as well as aiding in patients' advantageous outcomes against pathology caused by the SARS-CoV-2 virus. Among the latter, Interleukin-16 (IL-16), Immunoglobulin E (IgE), and eosinophils emerged as possible biomarkers [11]. In this respect, the present study aims to check the clinical applicability of some immune mediators (IL-16, IgE, and eosinophils) in the severity and diagnosis of COVID-19.

AIM

To evaluate clinical applicability of immune mediator's interleukin-16, immunoglobulin E along with eosinophil count in diagnosing COVID-19 and determining its severity.

MATERIALS AND METHODS

STUDY DESIGN AND SETTINGS

This cross-sectional case-control research carried out at Al-Najaf General Hospital / Najaf, Iraq from March 2024 to August 2024. One hundred twenty participants were included in this study, of which 60 were cases of COVID-19 and 60 were healthy control. Control was matched by age and sex to cases. The data on COVID-19 patients were collected in the respiratory outpatient clinic.

DATA COLLECTION

Demographic data, and smoking history were obtained by direct patient interviews. Paper hospital records were used to obtain data on laboratory investigations. Blood samples were collected for the measurement of serum levels of IgE, complete blood count (Eosinophil count), and IL-16. Conventional Laboratory Protocols were used.

BIOCHEMICAL ANALYSIS

Complete blood pictures (CBC) and IgE were analyzed at Al-Sadr medical city Educational Lab. Division in Najaf in Iraq using automated system SIEMENS ATELLICA (CE approved). On the other hand, serum IL-16 were measured vie ELISA technique in the private sector under supervision of a senior biochemist.

COVID-19

Adult patients, aged 18 years or older, were involved if they met the nucleic acid test for SARS-CoV-2 by RT-PCR, according to WHO guidelines as confirmed COVID-19 cases. This study included adult patients (18 years or older) with a clear outcome (either discharged alive or dead) with a disease duration between 5-20 days. Patients were given antipyretic drugs (paracetamol), vitamins D and C to boost immune system, in addition to antibiotics (azithromycin) to fight secondary bacterial infection. For the diagnosis of COVID-19 in all hospitalized patients, severity assessment was done by either oxygen saturation or perfusion evaluation with an arterial blood gas test and a computed tomography (CT) scan of the chest. Disease severity was characterized according to the guidelines as mild, moderate, or severe.

INCLUSION CRITERIA

Known cases of COPD aged 18 and above were included in this research. Healthy controls are subjects without the disease being studied but may have other conditions indirectly affecting outcome.

EXCLUSION CRITERIA

Patients with any concomitant pulmonary pathology, any type of chronic disease were excluded from the study.

STATISTICAL ANALYSIS

The SPSS software version 25.0 (SPSS) was used for all the appropriate statistical analyses. The normality test which was used to test who want to continuous data for Shapiro Wilk test. All normally distributed data are acted as mean±standard deviation. Independent t test was used to find out the statistical difference in the immune markers between patients' and control. ANOVA test was used to find out the statistical difference in the immune markers among patients' subgroups classified according to severity of COVID-19. A p-value less than 0.05 was considered to indicate a statistically significant difference.

ETHICS APPROVAL

The project in this study was approved by the ethical committee of the Medical College in the University of Kufa (No. 240 in 2024).

CONSENT TO PARTICIPATE

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

RESULTS

The levels of severity of COVID-19 cases are displayed in Figure 1. Patients are divided into three categories: Mild, Moderate, and Severe, and percentages are given for each. According to the findings, 35 COVID-19 cases (65%) were mild, 15 were moderate which accounts for 25%, and only 9 severe cases were there in the sample that is 10% of the total sample, Fig. 1.

Results showed that most people in both groups are between 35-44 years old (48.33% in COVID-19 and 53.33% in control). There is near parity of males and females in both groups, with males slightly more than females in the COVID-19 group and equal numbers in the control group (50% for both). The proportion of patients who are smokers is 41.67% among the COVID-19 group and 33.33% in the control group. This difference is, however, not statistically significant, fig. 1. Regarding immune markers, the eosinophil count is significantly higher in patients (105±64 cells/ml) than in the control group (78±22 cells/ml), P<0.001. IgE levels are markedly elevated in patients (788±98 UI/ml) compared to the control group (204±122 UI/ml), P<0.001 also. IL-16 levels in patients (12.8±3.9 pg/ml) are nearly double those in the control group (6.2±2.9 pg/ml), P<0.01, Table 1.

The levels of immune markers have been compared between patients' with COVID-19 and control healthy subjects, the eosinophil count is significantly higher in patients (105±64 cells/ml) compared to the control group (78±22 cells/ml) with a P-value of <0.001, indicating a strong statistical difference. IgE levels are markedly elevated in patients (788±98 UI/ml) compared to the control group (204±122 UI/ml), also with a highly significant P-value of <0.001. IL-16 levels in patients (12.8±3.9 pg/ml) are nearly double those in the control group (6.2±2.9 pg/ml), with a significant P-value of <0.01, Table 2. The authors have performed the univariate logistic regression analysis of the

Table 1. Baseline characteristics of patients and control and the statistical difference between the two groups

Characteristics		COVID-19 N = 60		Control N = 60		Chi Square (P-value)
		Freq.	%	Freq.	%	
Age (years)	25-34	11	18.33	13	21.67	1.02 (0.59)
	35-44	29	48.33	32	53.33	
	≥45	20	33.34	15	25	
Gender	Male	32	53.33	30	50	0.13 (0.71)
	Female	28	46.67	30	50	
Smoking	Yes	25	41.67	20	33.33	0.89 (0.34)
	No	35	58.33	40	66.67	

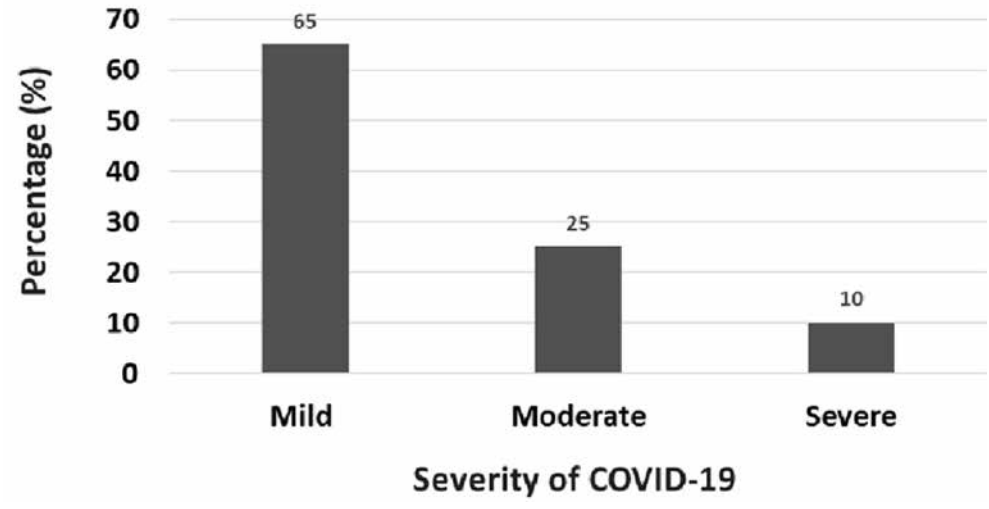

Fig. 1. Distribution of COPD control status in the cases group

Table 2. Baseline characteristics of patients and control and the statistical difference between the two groups

	Patients N = 60	Control N = 60	P-value
Eosinophil count (cells/ml)	105±64	78±22	<0.001
IgE (UI/ml)	788±98	204±122	<0.001
IL-16 (pg/ml)	12.8±3.9	6.2±2.9	<0.001

Table 3. Univariate logistic regression analysis of the association of IL-16, IgE, Eosinophil and the risk of severity of COVID-19

	OR	95% CI	P-value
Eosinophil count	1.2	1.03-1.6	<0.01
IgE	1.3	1.02-1.8	0.046
IL-16	1.5	1.11-1.16	<0.001

OR: odds ratio, CI: confidence interval

Table 4. IL-16 Cutoff point in different COPD control status

	Cutoff point	Sensitivity	Specificity	AUC[1]
Eosinophil	100	74%	66%	73%
IgE	350	48%	58%	48%
IL-16	10.2	85%	72%	82%

[1]*Area under the curve; cutoff point calculated using Youden index method*

association of IL-16, IgE, eosinophil and the risk of severity of COVID-19, Table 3. It shows that high serum levels of eosinophil count, IL-6 and IgE were associated with higher risk of severe COVID-19. Especially, high Il-16 level was associated with 50% more risk (OR=1.7, P-value <0.001). The receiver-operating characteristic (ROC) curve analysis of IgE, eosinophil and IL-6 was used in the diagnosis of COVID-19. The sensitivity ratios were 0.74, 0.48 and 0.85 for eosinophil, IgE and IL-6 respectively, while specificity ratios were 0.66, 0.58 and 0.72 for eosinophil, IgE and IL-6 respectively, Table 4.

DISCUSSION

Mild, moderate, and severe categorization of COVID-19 is fundamental for the management of a patient in a clinic and understanding of pathophysiology. It has been evidenced that severe COVID-19 is truly related to a poor prognosis for the patient. Therefore, the grading of the severity of COVID-19 into mild, moderate, and severe has clinically relevant ramifications in the management of a patient, therapeutic strategies, and public health responses. This has been reinforced by current evidence on post-acute COVID-19 syndrome that has highlighted long-term consequences of COVID-19 for individuals, regardless of initial disease severity [12]. The results presented by Amenta et al., as well as Wang et al., show that patients can experience chronic symptoms based on their initial classification, which necessarily implies that the classification of severity needs to consider long-term health outcomes. This provides support for the initiation of a more refined classificatory approach that can adequately include both chronic and acute manifestations of COVID-19 [13, 14]. With the COVID-19 pandemic, more studies on the immune response to SARS-CoV-2 are needed, most essentially finding reliable diagnostic markers that can predict disease severity and outcome. Potentially notable diagnostic markers include immune mediators, such as Interleukin-16 (IL-16), Immunoglobulin E (IgE), and eosinophils. IL-16 belongs to the chemokine family that plays a significant role in immune cell recruitment in normal immune responses [9]. Due to this fact, scarce direct evidence on monitoring IL-16 for diagnostics of COVID-19 exists. The relevance of IL-16 information is based on related studies on other cytokines. Significant amounts of evidence implicate these molecules in disease pathology, in particular IL-6, which has been associated with adverse outcomes in COVID-19 patients [10]. The levels of IL-6 are directly associated with an adverse clinical outcome; therefore, other cytokines such as IL-16 can be measured in a similar aspect of reflecting disease severity. The urgency of investigating IL-16 for

diagnostics is supported by the hyper inflammatory condition of COVID-19, known as a cytokine storm [15]. IgE is known to be mainly involved in allergic responses but it also has substantial functions in immunity against infections. Recent studies also identified, for the first time, the presence of IgG antibodies in COVID-19 patients indicative of its potential employment as a diagnostic marker (Isho et al., 2020) [16]. While the specific contributions of IgE to COVID-19 are yet to be thoroughly examined, the mere existence of the antibody response gives an idea of how the immune system interacts with the virus. The very presence of IgE might be indicative of an ongoing immune response, thereby suggesting further research regarding its potential utility as a marker for disease progression and severity; research area [17]. Eosinophils are white blood cells that play a rather major role in allergies and defense against some parasite infections. The role they play in viral infections, especially with COVID-19, is not clear. Some current results show a relationship between the level of eosinophils and the severity of the disease, where high levels might indicate a good forecast for the patient in terms of respiratory infections [11]. However, more research targeting this area specifically is needed for the diagnostic value of eosinophils in COVID-19 since much of the earlier work has focused mainly on other immune cells. Levels of markers have been associated with COVID-19 disease severity implying that monitoring these markers could aid in early disease detection and management [18]. In a recent exhaustive study by Arunachalam et al. on immune profiling in COVID-19 patients, distinct immunotypes were identified significantly associated with disease severity. Specific immune cell types and cytokine profiles can be used as biomarkers to differentiate mild, moderate, and severe cases [19]. It has established associations between serum cytokine, and chemokine levels and COVID-19 severity, thus providing insights into inflammatory responses concomitant with different levels of disease severity. To develop diagnostic tools and treatment strategies customized to the level of disease severity on the basis of these cytokine profiles would ensure a higher degree of accuracy in classification [20]. Integration of findings from numerous studies reveals that there is a complex relationship between immune mediators and COVID-19. For example, though IL-6 has come out as a strong predictor of disease severity, potential roles of IL-16, IgE, and eosinophils should not be undermined. The study puts great emphasis on the need for early predictors to present with COVID-19, and this includes widening the scope of immune mediators [21]. Equally important are sensitive diagnostic methods that combine imaging with immune marker detection for better patient care [22]. The COVID-19 pandemic has accelerated study on new biomarkers for early diagnosis and prognosis in disease. Although it is basically known to play a role in allergic reactions, there have been very recent studies regarding its candidacy in COVID-19. Ma et al. described the serum responses of IgA, IgM, and IgG in COVID-19 patients. This implies that while it might relate with IgE, sensitivity and specificity for diagnosis of COVID-19 is not known. Such non-specificity in IgE response should further outline more research to determine diagnostic usability especially in the context of COVID-19 against other respiratory infections [23, 24], among COVID-19, IL-6 has gained credibility as one of the top biomarkers especially for disease severity, Gao et al. Evidence further indicated that patients with elevated IL-6 levels were more likely to develop severe COVID-19, with a reported high sensitivity of 96.4% and specificity of 93.3% when combined with d-dimer testing. The positive and strong correlation between levels of IL-6 and the severity of the disease underlines its use as a potential diagnostic indicator. Also, IL-6 proved to meet one of its requirements as part of the COVID-19 diagnostic landscape, as Chen et al. found high levels of association between IL-6 and RNAaemia. All these findings point to the fact that IL-6 may indeed be a key factor in detecting patients at risk of severe outcomes, thus making it an important marker for clinicians.

CONCLUSIONS

In conclusion, the evaluation of IL-16, IgE, and eosinophils as diagnostic markers for COVID-19 presents a promising avenue for enhancing patient management and treatment strategies. While significant progress has been made in understanding the immune response to SARS-CoV-2, further research is essential to fully elucidate the potential roles of these immune mediators in diagnosing and predicting disease outcomes. In addition, IL-6 has emerged as a critical biomarker for diagnosing and prognosticating COVID-19, the roles of eosinophils and IgE require further exploration.

ABBREVIATIONS

CBC: Complete Blood Pictures

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Ali A. Al-Fahham
University of Kufa
299G+HPX, Kufa Street, Kufa, Najaf Governorate, Iraq
e-mail: aliaz.mahdi@uokufa.edu.iq

ORCID AND CONTRIBUTIONSHIP

Sarah Kassab Shandaway Al-Zamali: 0000-0002-4950-132X (B) (C)
Ruqaya Yahya Abd AL-Shaheed: 0009-0007-3442-2227 (C) (D)
Hawraa S. AL-Jobory: 0009-0002-3369-4996 (D) (E)
Ali A. Al-Fahham: 0000-0002-6316-6281 (A) (F)

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

RECEIVED: 22.12.2024
ACCEPTED: 15.05.2025

CREATIVE COMMONS 4.0

ORIGINAL ARTICLE

Prevention of pseudoexfoliation glaucoma in patients with age-related cataract in the background of pseudoexfoliation syndrome

Volodymyr O. Melnyk[1,2], Anastasiia O. Likhatska[2], Liudmyla I. Haliienko[1], Borys I. Palamar[1]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2]LLC «VISIOBUD CLINIC», KYIV, UKRAINE

ABSTRACT

Aim: To evaluate the possibility of using cataract phacoemulsification with simultaneous intraocular lens (IOL) implantation in patients with age-related cataract (ARC) combined with pseudoexfoliation syndrome (PES) as an algorithm for the pseudoexfoliation glaucoma (PEG) prevention.

Materials and Methods: A retrospective case-control study was conducted using data from medical records of 610 outpatients (813 eyes) with ARC aged from 49 to 79 years (average age 69 ± 3 years). Group 1 included 488 patients (625 eyes) with ARC and PES, and Group 2 (control) included 122 patients (188 eyes) without signs of PES. Patients in both groups underwent ultrasonic phacoemulsification and IOL implantation.

Results: Patients from Group 1 presented with less anterior chamber depth, a thicker lens, and higher intraocular pressure (IOP), as compared to Group 2. In patients with PES after cataract surgery, we observed a slight increase in IOP during the first week, followed by a significant decrease (by 3.1 mm Hg) during the next 3 months (vs. baseline; $p<0,001$). In patients without PES, a slow decrease in IOP (by 1,0 mm Hg) was observed during 3 months after surgery (vs. baseline; $p<0,001$). The cataract surgery favored an increase in anterior chamber depth by 45,2 % in patients with ARC and PES.

Conclusions: Ultrasonic cataract phacoemulsification with IOL implantation in patients with PES leads to a significant decrease and stabilization of IOP in the long-term postoperative period (3-month follow-up), and may be an alternative method for the prevention of PEG development.

KEY WORDS: prevention, glaucoma, cataract, pseudoexfoliation syndrome, phacoemulsification

Pol Merkur Lek,2025;53(4):473-477 doi: 10.36740/Merkur202504106

INTRODUCTION

Glaucoma is one of the most common diseases that lead to vision loss, affecting about 8 million people worldwide [1]. This disease is known to occur more often in the elderly, and the main symptoms of glaucoma are elevated intraocular pressure (IOP), optic atrophy, and narrowing of the visual field. Therefore, the basis of glaucoma prevention should be health control of older people, as well as monitoring and prevention of IOP increase in the early stages of the disease.

Glaucoma is associated with heredity, prolonged use of glucocorticosteroids, and the presence of concomitant diseases such as myopia, a history of eye injuries, hypertension, diabetes mellitus, and other chronic conditions. The occurrence of a systemic dystrophic disease, namely pseudoexfoliation syndrome (PES), in patients with age-related cataract (ARC) provokes the development of pseudoexfoliation glaucoma (PEG). This disease, which is characterised by age-related systemic microfibrillopathy, leads to predominant damage to eye tissues with gradual accumulation of exfoliative material on the iris and lens [2–6].

The average age of PES onset ranges from 60 to 70 years. The prevalence of the disease increases with age: in persons aged 50–60 years, PES occurs in 0,7%, and in those aged 80 and older – in 7,3% [4, 5, 7, 8]. The distribution of PES prevalence among men and women is the same. However, it is known that pseudoexfoliation without signs of glaucoma is more common in older women, which is associated with the longer life expectancy of women compared to men.

The exact cause of PES remains unknown. The influence of ultraviolet rays, dietary factors, tobacco smoking, stress, and other unfavourable factors is noted. Mutations in the LOX1 gene (locus 15q22), which encodes components of elastic fibres of the extracellular matrix, are of great importance. The accumulation of exfoliative material in PES is found not only in the tissues of the eyes but also in the skin, brain membranes, gallbladder, and visceral organs. Given the systemic nature of the lesion, PES is considered a risk factor for the development of various vascular diseases, including stroke and heart attack, so the provision of medical care may require the participation of other specialists [9].

Eye lesions are among the most studied localisations of the manifestation of the pathological process in PES. It has been established that PES predominantly affects both eyes, but clinical manifestations are often observed first in one eye and only later in the other eye [10].

PES creates an unfavourable background for the development of other eye diseases, the most important

of which is PEG [5, 8]. PEG is considered to be one of the most resistant to treatment and is the most common cause of blindness [7]. The frequency of PES detection in glaucoma is higher than in non-glaucoma patients [11].

PES often accompanies ARC: the frequency of combinations of these diseases ranges from 24 % to 70 % or more [5, 12]. The combination of ARC and PES is accompanied by changes in various structures of the eye, and morphometric changes in the anterior segment of the eye, such as a decrease in the depth of the anterior chamber and an increase in the thickness of the lens [7, 8].

Reducing IOP to a „target" level that minimizes the development and progression of glaucomatous optic neuropathy is the main goal of the prevention and treatment of any type of open-angle glaucoma, including PES [13]. Scientists have proven that ultrasonic phacoemulsification of ARC leads to a significant decrease in IOP by 1,5–2,5 mm Hg [14-17].

Successful implementation of glaucoma prevention requires a comprehensive, multisectoral approach. This approach suggests effective interaction between ophthalmologists, family doctors, specialists from other related fields, and public health professionals, with the participation of all involved sectors, non-governmental organizations, and the population.

AIM

The work was aimed at assessing the possibility of using cataract phacoemulsification with simultaneous intraocular lens (IOL) implantation in patients with ARC in combination with PES as an algorithm for the prevention of the development of PEG.

MATERIALS AND METHODS

A retrospective case-control study was conducted based on medical records of 610 outpatients with ARC who were treated at LLC "VISIOBUD Clinic" (Kyiv, Ukraine) during 2014–2024. The study was carried out from June 2023 to December 2024. The age range of patients was 49–79 years, and the average age was (mean ± standard deviation) 69 ± 3 years.

The study analysed the data from 813 eyes of 610 patients. Two observation groups were formed: the first group included 488 patients (625 eyes) with ARC in combination with PES, and the second (control) group included 122 patients (188 eyes) without signs of PES. Thus, the ARC and PES combination was observed in (rate ± standard error) 76,9 % ± 1,5 % of the eyes.

Medical records of patients with signs of hyperopia, myopia, and astigmatism of moderate and high degree were excluded from the study.

There were no typical signs of glaucomatous optic neuropathy according to computerised static perimetry and optical coherence tomography.

Patients in both groups underwent ultrasonic phacoemulsification with IOL implantation. All patients underwent assessment of morphometric parameters of the anterior segment of the eye (lens thickness before surgery, anterior chamber depth before and after surgery) in the preoperative and postoperative periods.

The Goldmann applanation tonometry method was used to determine the level of IOP in patients before surgery, and at 1 week, 1 month, and 3 months after surgery.

The operation was performed by a single surgeon using the same equipment. There were no complications during the operation, or in the early (up to seven days), late (up to three weeks), and long-term (three to twelve months) postoperative periods.

Statistical data processing was carried out using Statistica v. 14.0 (TIBCO Software Inc., USA) and EZR v. 1.68. The Shapiro–Wilk test was used to determine the normality of the quantitative data distribution. Quantitative data were presented as median and interquartile range. Qualitative data were presented as absolute and relative (%) frequency with a standard error.

The Mann-Whitney U test was used to compare the quantitative characteristics of two independent samples. The quantitative characteristics at different follow-up stages were compared using the Friedman test, followed by post hoc comparisons by means of the Wilcoxon signed-rank test (with Bonferroni correction).

Differences were considered statistically significant at $p < 0,05$ (with Bonferroni correction).

In this study, the authors adhered to the principles of the Council of Europe Convention on Human Rights and Biomedicine, the World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, and current Ukrainian regulatory documents. The study design was approved by the local bioethical committee. The retrospective nature of the study excluded the need for patients to complete informed consent forms.

RESULTS

The morphometric parameters of the anterior segment of the eye of patients of both groups in the preoperative period are given in Table 1.

According to the data obtained, before the operation, the depth of the anterior chamber of the eye in the patients of the first group (with ARC and concomitant PES) was on average 0,32 mm less than in patients of the non-PES control group ($p<0,001$); the thickness of the lens was 1,05 mm greater than in patients without PES ($p<0,001$) (Table 1).

IOP levels before and after surgery (ultrasonic phacoemulsification with IOL implantation in patients with ARC and concomitant PES, and patients with ARC without PES, are presented in Table 2.

Before surgical treatment, the average level of intraocular pressure (IOP) in patients with ARC combined with PES was higher than that in the control group by 1,7 mm Hg ($p < 0,001$) (Table 2).

At the 1-week postoperative follow-up, a slight increase in IOP was detected in patients of group 1; the increase was 0,4 mm Hg on average, or 2,2 % ($p < 0,001$). In the control group, a decrease of 0,3 mm Hg, or 1,8 %, was observed ($p<0,001$). This difference in pressure dynamics in the early postoperative period is expected but not clinically significant.

Table 1. The eye anterior segment morphometric parameters before the surgery in the studied groups of the eyes

Parameters	Group 1 (ARC+PES) n = 625	Group 2 (ARC) n = 188	p
Anterior chamber depth, mm	2,76 (2,49-3,13)	3,08 (2,89-3,33)	<0,001
Lens thickness, mm	4,70 (4,45-5,07)	3,65 (3,52-3,81)	<0,001

Table 2. IOP (mm Hg) before and after the surgery in the studied groups of the eyes

Study stage	Group 1 (ARC+PES) n = 625	Group 2 (ARC) n = 188	p'
Before surgery	17,5 (15,5-19,3)	15,8 (14,8-17,2)	<0,001
1 week after surgery	17,9 (16,2-20,4)	15,5 (14,3-16,9)	<0,001
1 month after surgery	15,0 (14,1-16,1)	14,2 (13,5-15,1)	<0,001
3 months after surgery	14,4 (12,8-16,5)	14,8 (14,0-15,7)	0,024
p''	p_{1-2}<0,001 p_{1-3}<0,001 p_{1-4}<0,001 p_{2-3}<0,001 p_{2-4}<0,001 p_{3-4}=0,001	p_{1-3}<0,001 p_{1-4}<0,001 p_{2-3}<0,001 p_{2-4}<0,001 p_{3-4}<0,001	-

Notes: p' – the significance of difference between groups 1 and 2; p'' – the significance of difference within the corresponding group at different study stages: p_{1-2} – between the stage before surgery and 1 week postoperatively; p_{1-3} – between the stage before surgery and 1 month postoperatively; p_{1-4} – between the stage before surgery and 3 months postoperatively; p_{2-3} – between 1 week and 1 month postoperatively; p_{2-4} – between 1 week and 3 months postoperatively; p_{3-4} – between 1 month and 3 months postoperatively

At the 1-month postoperative follow-up, a decrease in IOP was observed in patients of both groups: in group 1, the decrease was 2,5 mm Hg on average, or 14,3% (p<0,001); in the control group, it was 1,6 mm Hg, or 10,1% (p<0,001). At this stage of follow-up, the intergroup difference in IOP remained statistically significant.

In the remote postoperative period (3 months after surgery), the IOP level in patients with ARC and PES was 0,4 mm Hg less than in the control group without concomitant PES (p=0,024). However, at this stage of follow-up, the difference between the groups was clinically non-significant.

During the three-month follow-up period in group 1, a clinically insignificant increase in IOP was observed in the early postoperative phase. However, a subsequent stable decrease in IOP by 3,1 mm Hg, or 17,7% from baseline, was noted (p<0,001).

In the control group, a sustained overall reduction in IOP by 1,0 mm Hg (6,3%) was observed over the three-month follow-up period, which was statistically significant (p<0,001). Notably, a slight, clinically non-significant increase of 0,6 mm Hg was recorded at the three-month follow-up compared to the one-month measurement.

In 75 patients with ARC and PES (100 eyes), the depth of the anterior chamber of the eye in the long-term (3 months) postoperative period was evaluated. The preoperative depth of the anterior chamber ranged from 2,02 to 3,87 mm, with an average of 2,70 (2,49-3,12) mm. Compared with the preoperative data, the average anterior chamber depth in patients with ARC and PES (100 eyes) was 3,92 (3,87-4,07) mm, representing an increase of 1,22 mm (or 45,2% of the baseline value) (p<0,001).

DISCUSSION

The development of ARC in the vast majority of patients was accompanied by changes in the anterior segment of the eye. PES, as a concomitant pathology, was one of the most common background diseases of ARC. There is an opinion that PES, as a systemic dystrophic disease, served as a trigger for cataract and glaucoma [1].

PES occurred in up to 65 % of patients with glaucoma and 50 % of patients with cataract, and later, after cataract surgery, PES was the main risk factor for IOL dislocation [18, 19].

According to the study, during 2014-2024, 813 surgeries were performed in the clinic for patients with cataracts.

It was found that in the vast majority of cases (76,9 %±1,5 %), patients had a cataract against the background of concomitant PES.

The study of morphometric parameters of the anterior segment of the eye showed that patients with ARC and PES presented with less anterior chamber depth and higher lens thickness, as compared to their PES-free counterparts. After ultrasonic phacoemulsification of a cataract with IOL implantation in patients with PES, a significant increase in anterior chamber depth compared to preoperative values was detected. The study also demonstrated, that in the postoperative period, patients with PES showed a decrease in IOP within the first three months, which was typical and coincided with previous studies [16, 19, 20].

Prevention of glaucoma remained an urgent problem in the field of public health, given the rapid increase in its prevalence in Ukraine and the world and a significant causal link with vision loss. Promising areas of further scientific research should included: scientific substantiation of organization and management principles of preventive surgical treatment of patients with combined pathology: ARC and PES by ultrasonic phacoemulsification of cataract with IOL implantation to prevent the development of PEG; scientific justification, development and implementation of a program for monitoring and evaluating the management of prevention of PEG.

CONCLUSIONS

Prevention of the development of PEG is the main goal of diagnostic and therapeutic measures in patients with ARC, and syndrome, which requires the introduction of a systematic approach to its organization. PES is a typical concomitant pathology of ARC, which is confirmed by its detection in 76,9 %±1,5 % of patients examined in the study.

The development of a cataract in patients with concomitant PES is accompanied by morphometric changes in the anterior segment of the eye, characterized by a significantly more pronounced decrease in the depth of the anterior chamber of the eye and an increase in lens thickness compared to morphometric changes in the anterior segment of the eye in patients suffering from a cataract without PES.

Ultrasound phacoemulsification of cataracts with IOL implantation in patients with PES leads to a statistically significant decrease and stabilization of IOP in the long-term postoperative period (3 months follow-up) and can be an alternative method for preventing the development of PEG.

The improvement of PEG prevention in patients with ARC and PES requires further scientific justification, taking into account the degree of risk of PEG development and the effect of ultrasonic phacoemulsification on early and late reduction of IOP.

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The study was conducted within the framework of the scientific-research work funded by the Ministry of Health of Ukraine, in particular «Scientific substantiation of improving the organizational principles of the healthcare system in the conditions of modern transformational changes» (state registration number 0123U101432; registration date: 03.03.2023). The organization and implementation of the study did not require additional funding.

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Volodymyr O. Melnyk
Bogomolets National Medical University
13 Taras Shevchenko Ave., 01601 Kyiv, Ukraine
e-mail: volo_mel@ukr.net

ORCID AND CONTRIBUTIONSHIP
Volodymyr O. Melnyk: 0009-0001-4177-4702 A B C D
Anastasiia O. Likhatska: 0009-0006-1006-8799 B D
Liudmyla I. Haliienko: 0000-0003-3728-9445 B E F
Borys I. Palamar: 0000-0003-2510-0713 A B D E F

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

RECEIVED: 09.01.2025
ACCEPTED: 20.06.2025

CREATIVE COMMONS 4.0

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ORIGINAL ARTICLE

The screening and analysis of the response questionnaire in the care of temporomandibular disorders and psychoemotional state diagnosis in the Polish population

Justyna Grochala[1], Małgorzata Pihut[1], Jolanta E. Loster[2]

[1]DEPARTMENT OF PROSTHODONTICS AND ORTHODONTICS, INSTITUTE OF DENTISTRY, JAGIELLONIAN UNIVERSITY MEDICAL COLLEGE, CRACOW, POLAND

[2]PROFESSOR LOSTER'S ORTHODONTICS, JAGIELLONIAN UNIVERSITY MEDICAL COLLEGE, CRACOW, POLAND

ABSTRACT

Aim: Due to the increasing prevalence of temporomandibular disorders within the population, it is beneficial to implement effective diagnosis at the early stages of the disorder's manifestation. The consequence of the occurrence of temporomandibular disorders may be a dysfunction related to the psychoemotional state. One of the research objectives was to assess the prevalence of temporomandibular disorders in the examined group of patients within the Polish population. We aimed that a relationship between psychoemotional state and the occurrence of temporomandibular disorders can be established, which was also the subject of the research conducted.

Materials and Methods: Patients were examined and diagnosed according to the Polish version of the RDC/TMD questionnaire (Axes I and II).

Results: In the research, 135 subjects were enrolled, however 91 finished. The patients were aged 18-53. The prevalence of temporomandibular disorders in this research is 37.36% and is more frequent in women.

Conclusions: The assessment and treatment of temporomandibular disorders require a multidisciplinary approach that includes consideration of the psychoemotional status.

KEY WORDS: temporomandibular disorders (TMD), temporomandibular joint, psychoemotional state, research diagnostic criteria for temporomandibular disorders

Pol Merkur Lek,2025;53(4):478-484 doi: 10.36740/Merkur202504107

INTRODUCTION

Temporomandibular disorders (TMD) manifest multifactorial symptoms, such as orofacial pain, limited jaw-opening movements, and sounds in joints during daily activities, including opening and closing the mouth, eating, yawning, and singing [1]. The prevalence of TMD has been identified as a widespread problem as described in the literature, for example, by Dworkin [2], de Godoi Gonçalves et al. [3], Muthukrishnan et al. [4], Chandak [5], Wieckiewicz et al. [6], Osiewicz et al. [7] and Loster et al. [8]. There are various factors which might have an influence on TMD including parafunctional habits e.g. gum chewing, nail-biting, resting on the chin, teeth clenching, teeth grinding, reported neck pain [9].

It has been confirmed that psychosocial status, stressful life, tension in muscles, anxiety, and depression may lead to TMD [10-12]. The etiological factors responsible for TMD are associated with psychoemotional status [13]. Stress, anxiety, and depression should be taken into consideration during dentist examinations of patients with TMD. These aspects are particularly relevant for individuals with a painful form of TMD [14]. A universal questionnaire – The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) – was developed in 1992 by Samuel F Dworkin and Linda LeResche [2] to evaluate patients with TMD. The questionnaire has been translated into twenty-one languages, including Polish. Since then, the comparison and interpretation of clinical examinations can be conducted globally, especially considering that 10-20% of the general population experiences TMD symptoms [15-17]. The RDC/TMD questionnaire consists of Axis I- clinical physical examination forms and Axis II- biobehavioural questionnaires, which cover information about general health, pain, chronic pain, physical symptoms, mental and emotional state (including a tendency to depression), and questions from the demographic domain (Fig. 1).

In Axis I RDC/TMD, the possible diagnoses include three groups of clinical problems (muscle disorders- Group I, disk displacement- Group II, and arthralgia, osteoarthritis, or osteoarthrosis- Group III) – the diagnosis is established separately for the right and left TMJ (temporomandibular joint). In the Axis II RDC/TMD instructions, there is an algorithm to classify the participants into the following groups: involved pain-related impairment (Graded Chronic Pain Severity, from 0: no TMD pain in the prior 6 months, to IV: high disability- severely limiting), depression, and somatization (normal, moderate, severe).

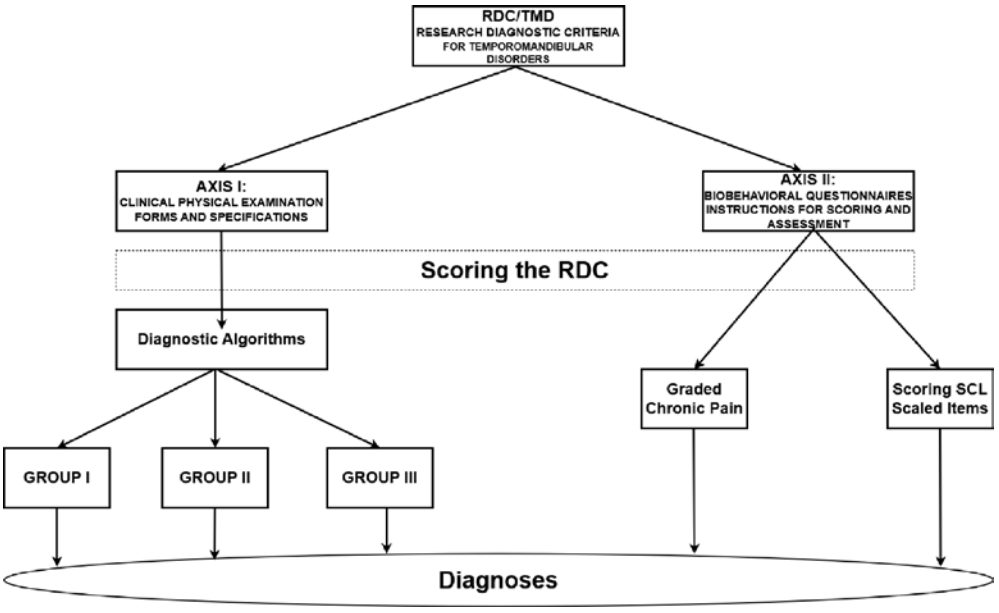

Fig. 1. The diagram illustrating the RDC/TMD questionnaire

Since 2023, the newer version of RDC/TMD in Polish [18], known as Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [19], has been available. During the study, the Polish version of DC/TMD was unavailable; however, research conducted by Finnish scientists shows that the data obtained from Axis II of the RDC/TMD questionnaire overlap with the results obtained from Axis II of the DC/TMD questionnaire [20]. Additionally, Lestari et al. confirmed that TMD diagnoses based on Axis I RDC/TMD are still classified in the same way as diagnoses based on Axis I DC/TMD [21]. Therefore, this indicates that the research results presented in this paper are still valid.

In Poland, Więckiewicz et al. observed a significant role of psychoemotional factors in the development of temporomandibular disorders in Polish students [6]. The studies were conducted between 2012 and 2014 at four universities in Wroclaw and revealed that patients' emotional and psychological states should also be evaluated in addition to assessing the temporomandibular joints and muscles.

The analysis conducted by Osiewicz et al. in Krakow has shown that 32.3% of dentists consider their knowledge of TMD good, while 39.3% state that it is sufficient. Among the participants, 64.2% indicated a lack of training in the study of TMD during their academic education. The research authors noticed it was the first study on the self-perceived dentists' knowledge of TMD in Central/East Europe [22]. Teachers have observed difficulties among students in studying and recognizing TMD, which inspired the presentation and teaching of the examination based on the standardized RDC/TMD questionnaire. For example, research conducted at the Dental Institute in Krakow has shown that the teaching of clinical examination of the masticatory system in fifth-year students, utilizing the RDC/TMD questionnaire, proved effective [23].

However, according to electronic health records at the Dental Institute in Krakow, the number of patients seeking examination and treatment for TMD assessment is constantly high. Therefore, a study was decided to estimate the prevalence of TMD among those presenting to the Dental Institute in Krakow.

In this paper, the RDC/TMD questionnaire Axis II was used to evaluate the psychoemotional status and Axis I was applied to assess masticatory disorders.

AIM

One of the research objectives was to assess the prevalence of TMD in the examined group of patients from the Dental Institute in Krakow. The relationship between psychoemotional status and the occurrence of masticatory disorders was also assessed.

MATERIALS AND METHODS

GENERAL INFORMATION

Among the patients examined (April 2019-June 2021) at the University Dental Clinic in Krakow, 135 individuals were recruited for the study. Every participant was informed about the aim of the study. All patients provided written consent for the clinical examination. The study was officially approved by the Krakow University Bioethics Committee (consent number 1072.6120.71.2019).

Some participants who attended the consultation did not report any symptoms or abnormalities. However, several individuals reported experiencing facial muscle pain, teeth grinding, jaw clenching, a limited range of jaw opening, and headaches. Additionally, some patients were referred by general practitioners or various dentists for assessment of the TMJ.

CRITERIA

The inclusion criteria included adults over 18 years of age who volunteered to participate in the study. The exclusion criteria included the occurrence of general diseases that made it impossible to continue the research (people with

trismus, active herpes, patients with systemic sclerosis), the withdrawal of consent to participate in the project, and people who did not complete the Axis II questionnaire.

THE COURSE OF THE STUDY

Patients participating in the clinical process were examined according to the Polish version of the RDC/TMD questionnaire (Axis I and Axis II).

The analysis included answers to questions regarding headaches and/or migraines during the last six months or pain in the face, jaw, temple, in front of the ear, or the ear in the past month.

The last step of the research was to give the diagnosis based on RDC/TMD guidelines.

RESULTS

The study included 135 patients; however, after applying the inclusion and exclusion criteria, 91 individuals were finally included in the analysis. The following flow chart shows the pathway to determine the final number of individuals qualified for further analysis (Fig. 2).

Among the research participants, 60 women (66.00% of all participants) and 31 men (34.00% of all participants) took part in the examination.

After reducing the inclusion criteria, the youngest participant was 18, while the oldest was 53.

An analysis of the questionnaire responses revealed that 46 women (50.55%) and 17 men (18.68%) reported pain in the face area, while the remaining subjects did not report any pain in the face area.

71% of all participants, including 48 women (52.75%) and 17 men (18.68%), reported headaches or migraines during the last six months. Headaches, migraines, and pain in the head and neck area were reported by 59% of respondents. The RDC/TDM questionnaire includes questions related to patient habits. The responses obtained from these questions have also been analyzed.

The current research showed that the examined participants had problems grinding teeth and clenching their jaws. Grinding teeth or clenching jaw while sleeping at night was applied to 36 women and 13 men, and 41 women and 16 men reported the habit during the day. From all responders, 41.00% noticed both grinding teeth and clenching jaw.

In parallel to the analysis of the participants' responses to the RDC/TMD questionnaire (Axis II), the data from the clinical examination in Axis I were analyzed. As illustrated in Fig. 1, the classification into groups I, II, and III was performed.

The data analysis has shown that 34 participants (37.36%) – 25 females and 8 males – can be assigned to more than one group.

A total of 25.27% of patients were diagnosed with muscle disorders (Group I), including 17 females and 6 males. Group II was diagnosed in 12 people: 9 female and 3 male. A Group III diagnosis occurred in 12 females and 3 males. Diagnoses I and II applied to 4 people, and I and III applied to 7.

One person received both II and III. Diagnosis I, II, and III applied to 2 patients.

More detailed information about the distribution of diagnoses of all participants is presented in Table 1.

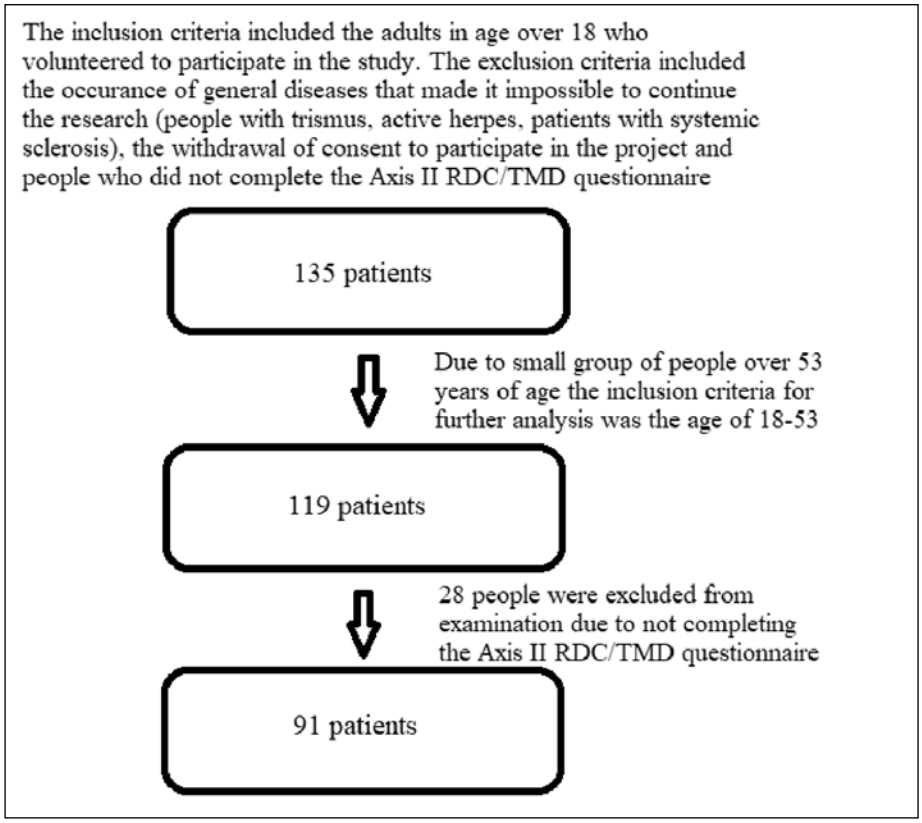

Fig. 2. The application of established criteria for inclusion and exclusion in the study

Table 1. RDC/TMD axis I diagnoses in the study group n=91 with sex distribution

RDC/TMD axis I	Participants	Frequency	Female	Male
I	23	25.27%	17	6
II	12	13.17%	9	3
III	15	16.48%	12	3
I+II	4	4.39%	3	1
I+III	7	7.69%	6	1
II+III	1	1.09%	1	0
I+II+III	2	2.2%	1	1
Total with RDC/TMD axis I diagnoses	34	37.36%	25	9
Total without axis I RDC/TMD diagnoses	57	62.64%	35	22

Table 2. GCPS, Depression and Somatisation based on RDC/TMD Axis II diagnoses in the group with axis I diagnoses

Graded Chronic Pain Scale(GCPS)	Participants with one or more diagnoses on Axis I	Frequency [%]	Women	Men
0: no disability	4	11.76%	2	2
I: low disability, low intensity	13	38.24%	9	4
II: low disability, high intensity	12	35.29%	10	2
III: high disability, moderately limiting	5	14.71%	4	1
IV: high disability, severely limiting	0	0.00%	0	0
Depression Symptoms Checklist	Norm		Moderate 1	Severe 2
Women	10		7	8
Men	5		3	1
SOMATISATION Symptoms Checklist	Norm		Moderate 1	Severe 2
Women	6		9	10
Men	4		2	3

Table 3. GCPS, Depression and Somatisation based on RDC/TMD Axis II diagnoses in the group without axis I diagnoses

Graded Chronic Pain Scale (GCPS)	Participants without diagnoses on Axis I	Frequency [%]	Women	Men
0: no disability	24	42.11%	12	12
I: low disability, low intensity	15	26.32%	10	5
II: low disability, high intensity	16	28.07%	12	4
III: high disability, moderately limiting	2	3.51%	1	1
IV: high disability, severely limiting	0	0.00%	0	0
Depression Symptoms Checklist	Norm	Moderate 1	Severe 2	
Women	19	8	8	
Men	18	4	0	
SOMATISATION Symptoms Checklist	Norm	Moderate 1	Severe 2	
Women	17	10	8	
Men	17	5	0	

Axis I diagnoses classify participants for group I, II, or III diagnoses (muscle disorders – Group I, disk displacement – Group II, and arthralgia, osteoarthritis, or osteoarthrosis – Group III), but the RDC/TMD Axis II diagnoses also enable the evaluation of Chronic Pain Grade Classification scores and provide information on depression and somatization seen in Table 2.

Participants who received a diagnosis at the RDC/TMD after the counted scores in Chronic Pain Grade Classification have shown that they suffer from a disability with different intensities (low, high, moderately limiting). Because dentists can only treat pain in limited ways, cooperation with relevant specialists in this field should be considered, as the problem seems to be widespread. Depression and somatization among participants with RDC/TMD diagnoses are also common. These observations demonstrate the multi-proneness problems that dentists encounter in their practice. Teams of different specialists should correlate the treatment of patients with TMD.

Table 3 presents the results of GCPS, Depression, and Somatization based on RDC/TMD Axis II diagnoses in the group without Axis I diagnoses.

The presented data show that among individuals without a diagnosis in RDC/TMD Axis I, the percentage distribution of individuals with dysfunction in GCPS, Depression, and Somatization is lower, but it still occurs.

DISCUSSION

Więckiewicz et al. concluded that the prevalence of TMD in their studied Polish student population is 54% with a mean age of 22.01±2.11 years [6]. 47.4% of all examined people with a mean age of 20.66±1.72 had TMD symptoms in the research conducted by Acharya et al. [24]. A similar frequency of TMD occurrence was confirmed by researchers from other research centers [25]. Systematic review and meta-analysis based on twenty-one articles conducted by Valesan show that the overall prevalence of temporomandibular joint disorders was approximately 31% for adults/elderly and 11% for children/adolescents [26].

In this paper, 34 participants had one or more diagnoses, 37.36% of the subjects. This study validates the presence of TMD in the population of individuals in Krakow and the surrounding regions. A previous study at the same research center by Loster et al. revealed that 26.5% of participants were diagnosed with one or more possible RDC/TMD axis I diagnoses (conducted between May 2011 and February 2013). Notably, there has been an increase in the number of individuals receiving a diagnosis. This issue remains pertinent, and practical solutions should be sought to reduce the frequency of TMD problems. It is essential to educate patients and raise awareness about the importance of eliminating parafunctional habits, e.g., gum chewing, pen or nail biting, grinding teeth, and clenching teeth, as in this research, 69% of participants reported grinding their teeth or clenching their jaw during the day. It is a common parafunctional habit that patients perform daily without paying attention or being aware of the problem [9, 27]. This leads to consolidation of habits, deepening joint problems and making it difficult to treat advanced problems. A detailed conversation to identify the problems that patients are experiencing, as well as gathering information about any abnormal daily habits, the location, and frequency of pain, e.g., headaches, the duration of symptoms, body posture, and reported muscle tension, is crucial in raising awareness of the problem and motivating change. The research shows that among participants, one symptom was headache or pain in the head or neck area, migraine, or co-occurrence. Headaches in TMD disorders affect many patients and are the reason for seeking help. The co-occurrence of headaches or migraines and pain in the face area occurred in 59% of the examined patients. Speciali et al. noticed that primary headaches (migraine, tension-type headache) and TMD are comorbid symptoms, and the relationship can be physiopathological [28]. The literature review confirms the relationship between headache and TMD [28-30]. The data available in the literature presents a widespread view of problems with TMD. Pihut et al. and other researchers noticed a more frequent occurrence of TMD in women than in men [28, 29, 31-33]. In the research, there is a predominance of women who came for TMJ assessment. The large group of females may be related to higher sensitivity to most pain modalities [34-36].

Florjański et al. [37] confirmed that a correlation exists between diagnoses from Axis I and the presence of chronic pain, depression, or somatization based on Axis II. This finding is also supported by Restrepo et al. [10] studies and Namvar et al. [38]. The assessment of chronic pain, depression, and somatization in patients without a diagnosis on Axis I highlights the need to evaluate the psychoemotional state of these individuals, as studies suggest the presence of issues in this area. The results from the literature review and the protocol examination of subjects suffering from TMD indicate that specialized treatment is necessary. In Axis II, among participants without a diagnosis in Axis I, there was only one woman and one man, which represents high disability, moderately limiting pain-related impairment, which is 3.51% of all individuals. On the depression scale, 21.05% of all participants had moderate results, while 14.03% had severe results. More detailed information is presented above in Table 3.

The problem of TMD patients is noticeable and analyzed by scientists in independent research centers. Patients with disorders still constitute a large group of people in dental offices. The psychoemotional state should be considered when evaluating TMD, as presented above and confirmed in the literature [39–41].

CONCLUSIONS

In the conducted study, TMD was diagnosed in 37%, with a higher prevalence among women. Among individuals without a diagnosis in Axis I, 42.11% showed no disability in the Graded Chronic Pain Scale, whereas among those with a diagnosis in Axis I, the percentage was 11.76%. Based on the literature review and the results obtained in this study, the occurrence of TMD and lowered mood suggest that a psychological examination should be conducted. Further studies should be conducted on a homogeneous group of patients, in collaboration with other specialists such as psychologists.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Justyna Grochala
Department of Prosthodontics and Orthodontics, Institute of Dentistry
Jagiellonian University Medical College, Cracow, Poland
e-mail: justyna.grochala@uj.edu.pl

ORCID AND CONTRIBUTIONSHIP
Justyna Grochala: 0000-0003-0561-9681 A B C D F
Małgorzata Pihut: 0000-0002-0239-4328 E F
Jolanta E. Loster: 0000-0002-8759-0810 A C E F

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

RECEIVED: 25.02.2025
ACCEPTED: 29.06.2025

CREATIVE COMMONS 4.0

ORIGINAL ARTICLE

Coronavirus disease 2019 (COVID-19) during pregnancy: Pathomorphological changes in the terminal villi of the placenta

Tetiana V. Savchuk[1], Ivan V. Leshchenko[1], Viktorya V. Vaslovych[2], Oksana H. Chernenko[2], Tetiana A. Malysheva[2]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2] STATE INSTITUTION «ROMODANOV NEUROSURGERY INSTITUTE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE», KYIV, UKRAINE

ABSTRACT

Aim: To investigate the pathomorphological changes in the terminal chorionic villi during COVID-19 in pregnant women.

Materials and Methods: A total of 123 placentas were studied in cases of live term births (groups I) and antenatal asphyxia (groups II). The subgroups were defined as follows: II.2 and I.2 (post-COVID interval of 1–4 weeks); I.1 and II.1 (5–16 weeks). Morphological and statistical research methods were applied.

Results: Spherical structures resembling viral particles were identified in the placenta. In 100 % of the observations, damage to the microcirculatory bed of terminal villi was detected, manifested by cytoplasmic edema of endothelial cells, disruption of cell membranes, nuclear apoptosis and placentitis. With increasing duration of the post-COVID interval, a gradual restoration of endothelial functional activity was observed, evidenced by an increase in laminar microvilli and vesicles, as well as widening of the vascular lumen; whereas in cases of antenatal asphyxia, obliteration of the vascular lumen and stromal fibrosis were noted. A reduction in endothelial cell cytoplasmic edema and stromal edema of terminal chorionic villi was also observed.

Conclusions: The morphogenesis of placental dysfunction in cases of antenatal fetal asphyxia associated with immature protective mechanisms involves endothelial dysfunction, impaired microcirculation, inflammatory infiltration, stromal edema of terminal villi with a reduction in vascular lumen, and subsequent fibrosis. The detection of viral particles with increasing post-COVID interval suggests persistence of SARS-CoV-2, the long-term effects of which on vascular function and its role in the development of placental insufficiency require further investigation.

KEY WORDS: SARS-CoV-2, pregnancy, placenta, pathology

Pol Merkur Lek,2025;53(4):485-494 doi: 10.36740/Merkur202504108

INTRODUCTION

Adequate maternal and fetal perfusion in the placenta is maintained through diffusion exchange across the endothelium, basement membrane, and syncytiotrophoblast cytoplasm – components of the vasculosyncytial membranes [1]. SARS-CoV-2, the causative agent of COVID-19, binds to ACE2 receptors [2, 3], activates endothelial cells, macrophages, and neutrophils, and disrupts microcirculation [4-6]. The birth of polymerase chain reaction (PCR)-negative newborns to COVID-19–positive mothers suggests effective placental defense mechanisms against vertical transmission in late gestation [7]. Nevertheless, cases of antenatal fetal death and placental dysfunction linked to maternal infection have been documented [8, 9]. The identification of irreversible changes in the structures of the vasculosyncytial membranes that contribute to the development of placental dysfunction prompted us to conduct this study.

AIM

The aim of the study was to investigate the pathomorphological changes in terminal chorionic villi during COVID-19 in pregnant women in the second and third trimesters of gestation.

MATERIALS AND METHODS

A total of 123 placentas from pregnant women with confirmed COVID-19 were examined. The mean gestational age in group I was (mean ± standard deviation) 40 ± 1 weeks (n=91), and in group II it was 33 ± 4 weeks (n=32). Group I included cases with live births, while Group II consisted of cases with antenatal asphyxia. Depending on the duration of the post-COVID interval (the time between maternal COVID-19 diagnosis and delivery), subgroups were formed. In subgroups I.1 (n=52) and II.1 (n=11), the post-COVID interval ranged from 5 to 16 weeks; in subgroups I.2 (n=39) and II.2 (n=21), it ranged from 1 to 4 weeks. The condition of newborns in Group I was assessed using the Apgar score, which evaluates heart rate, respiratory effort, muscle tone, reflex irritability, and skin coloration. Placental samples were collected at the Department of Pathological Anatomy of the National specialized children's hospital «OHMATDYT» Ministry of Health of Ukraine during 2020–2022. COVID-19 in pregnant women was confirmed by a positive PCR test for SARS-CoV-2 RNA. PCR testing of live newborns was negative. For comparison, placentas from physiological deliveries before the COVID-19 pandemic were analyzed. The mean gestational age in the control

group was 39 ± 1 weeks (n = 50). The following methods were used: macroscopic, microscopic, electron microscopy (EM), morphometric, and statistical analysis. Tissue sections were stained using standard histological techniques, and immunohistochemistry with monoclonal mouse anti-CD34 antibodies. To visualize full histological tissue sections, digital slides were analyzed using the Pannoramic DESK DW II scanner [10].

To assess quantitative differences in terminal villi (capillaries, stroma), histological images (×630, ×2700) were color-coded in Microsoft Paint (capillaries – black, background – green) and analyzed via ONLINE JPG TOOLS to calculate the color percentage, reflecting the area of the structure [11, 12].

The statistical data analysis was performed by the use of Statistica v. 14.0 (TIBCO Software Inc., USA), IBM SPSS Statistics v. 27.0 (Armonk, NY: IBM Corp., USA), MedStat v. 5.2 and EZR v. 1.68. Quantitative data were presented as median and interquartile range (lower and upper quartiles). Qualitative data were presented as absolute and relative (%) frequency with 95 % confidence intervals. The Kruskal-Wallis test was used to compare the quantitative characteristics of five independent samples, with the following *post hoc* comparisons between the study groups using the Mann-Whitney U test (considering the Bonferroni correction). The qualitative binary data between two independent samples were compared by the use of Fisher`s exact test; between four independent samples by the use of Marascuilo-Liakh-Gurianov procedure. The differences were considered statistically significant at $p < 0,05$ (considering the Bonferroni correction).

RESULTS

We studied the pathomorphological changes in the placenta of live-born infants (Group I) and in the placenta from cases of antenatal fetal asphyxia (Group II), where the mothers had COVID-19 during pregnancy (Table 1). Group II showed a lower gestational age compared with Group I and the control group. In Group I, the course of COVID-19 in the pregnant women was mild in 44 (48,3 %) cases, moderate in 39 (42,9%) cases, and severe (with pneumonia) in 8 (8,8 %) cases. At birth, 64 (70,3 %) newborns had Apgar scores of 8-9 points (normal condition). Twenty-one infants (23,1 %) had scores of 7-8 points, five (5,5 %) had scores of 6-7 points (mild distress), and one (1,1 %) newborn received a score of 3-4 points (severe distress). In Group II, 14 (43,8 %) women had a mild course of COVID-19; 12 (37,5 %) experienced moderate illness, and 6 (18,7%) had a severe form. The incidence of severe COVID-19 was slightly higher in Group II compared to Group I; however, no statistically significant difference was found between the groups. In Group I, no significant correlation was observed between the severity of COVID-19 in pregnant women and the condition of the fetus at birth.

Macroscopic examination of the placenta in the main study groups revealed circulatory disorders in 100% of cases during the acute period of COVID-19 (in subgroups I.2 and II.2), and in 92,3% and 63,6% in subgroups I.1 and II.1, respectively (Table 1): hyperemia, hemorrhages filling cystic cavities (Fig. 1A), and the presence of blood clots on the maternal surface of the placenta. The severity of microcirculatory disturbances decreased with the lengthening of the post-COVID interval. In the case of intrauterine fetal death, placentas in subgroup II.2 exhibited signs of withering and paleness (Fig. 1A), or alternatively, were soaked with dark blood (Fig. 1C, D). Infarctions, predominantly red, were present in subgroups I.2 and II.2. In subgroups I.1 and II.1, infarctions of both types were observed (Fig. 1A, C). The increase in their number was attributed to the organization of red infarcts and fibrinoid deposition in the intervillous space with the prolongation of the post-COVID interval.

Microscopic and EM analysis of the main groups revealed aggregated erythrocytes in the intervillous space and within the lumens of terminal villi blood vessels (Fig. 2D; Fig. 3C, D; Fig. 3D, E), which formed distinctive column-like structures (Fig. 3H). The cytoplasm of endothelial cells in subgroup I.2 was edematous, translucent, with a small number of cytoplasmic ultrastructures (Fig. 2C, D, E). Ruptures in cell membranes were observed (Fig. 2A). Within the vessel lumen, disrupted erythrocytes were detected (Fig. 2A). In one vessel from subgroup I.1, the marginal parts of endothelial cells appeared both electron-dense and translucent. (Fig. 2D, F). Thin-walled vessels with areas of irreversibly damaged endothelial membranes were observed, with ruptured membranes and large cytoplasmic vacuoles replacing destroyed organelles (Fig. 2B). Endothelial cells formed numerous cytoplasmic processes, which in turn created luminal microvilli (arrow) and micropinocytic vesicles. The number of these vesicles was more prominent in subgroup I.1 (Fig. 2C, D; Fig. 3D), whereas in subgroup I.2, only single processes were observed, and desquamated microvilli were seen within the vessel lumen (Fig. 2C). Electron-dense swollen, homogenized mitochondria were seen, along with expansion and splitting of the basal membrane. Apoptotic changes in the nuclei of endothelial cells were evident, with chromatin condensation and invaginations of the nuclear envelope (Fig. 3C).

Numerous acute hemorrhages (subgroups I.2, II.2) and infarctions (subgroups I.1, II.1) led to a reduction in the percentage of free intervillous space. A reduced number of terminal villi was observed in subgroups I.1, II.1, and II.2. In subgroups I.1 and II.1, this was explained by damage to stem villi (endothelial necrosis, vascular thrombosis, stromal fibrosis), which serve as the source for terminal villi formation. In subgroup II.2, the reduction was associated with placental immaturity due to low gestational age. In subgroup I.2, the number of terminal villi did not significantly differ from the control group, which can be explained by the fully developed chorion at the time of infection. Changes in the syncytiotrophoblast included nuclear chromatin condensation and nucleolar disorganization; in the cytoplasm, there was dilation of smooth endoplasmic reticulum cisternae and the formation of numerous vacuoles (Fig. 3E, F). The nuclear envelope of endothelial cells showed multiple protrusions. Changes in microvilli on the surface of the syncytiotrophoblast were noted as a decrease in their number, alteration in shape, shortening, and complete

Table 1. Gestational age, COVID-19 severity, and the pathomorphological changes in the placenta in pregnant women with COVID-19

Parameters		Study groups					p
		Live birth (Group I) (N=91)		Antenatal asphyxia (Group II) (N=32)		Control group (N`=50)	
		Subgroup I.1 (N`=52)	Subgroup I.2 (N`=39)	Subgroup II.1 (N`=11)	Subgroup II.2 (N`=21)		
Gestational age, weeks		40 (39-40)	40 (40-40)	36 (34-37)	31 (30-34)	40 (39-40)	p1-3<0,001 p1-4<0,001 p2-3<0,001 p2-4<0,001 p2-5=0,070 p3-5<0,001 p4-5<0,001
COVID-19 severity, n (%) [95 % CI]	Mild	44 (48,3) [38,1-58,7]		14 (43,8) [26,6-61,7]		-	0,685
	Moderate	39 (42,9) [32,8-53,2]		12 (37,5) [21,2-55,4]		-	0,679
	Severe	8 (8,8) [3,8-15,5]		6 (18,7) [7,0-34,5]		-	0,192
Morphological features							
Stasis, thrombosis, hemorrhage, n (%) [95 % CI]		48 (92,3) [83,4-98,0]	39 (100) [95,2-100]	7 (63,6) [30,7-90,6]	21 (100) [91,3-100]	-	p2-3=0,044
Infarctions, n (%) [95 % CI]		50 (96,2) [89,1-99,7]	13 (33,3) [19,2-49,2]	11 (100) [84,1-100]	21 (100) [91,3-100]	-	p1-2<0,001 p2-3<0,001 p2-4<0,001
Number of terminal villi*		17 (15-18)	26 (25-27)	8 (8-8)	5 (5-6)	26 (25-27)	p1-2<0,001 p1-3<0,001 p1-4<0,001 p1-5<0,001 p2-3<0,001 p2-4<0,001 p3-4<0,001 p3-5<0,001 p4-5<0,001
Stromal edema of terminal villi, n (%) [95 % CI]		50 (96,2) [89,1-99,7]	39 (100) [95,2-100]	10 (90,9) [64,1-100]	21 (100) [91,3-100]	-	0,264
Stromal edema of terminal villi, % of the stromal area		55 (53-56)	71 (67-73)	86 (78-89)	85 (84-87)	32 (30-35)	p1-2<0,001 p1-3<0,001 p1-4<0,001 p1-5<0,001 p2-3<0,001 p2-4<0,001 p2-5<0,001 p3-5<0,001 p4-5<0,001

Table 1. Cont.

Capillary lumen narrowing, % of lumen		46 (44-47)	29 (27-33)	14 (11-22)	15 (13-17)	68 (65-70)	p1-2<0,001 p1-3<0,001 p1-4<0,001 p1-5<0,001 p2-3<0,001 p2-4<0,001 p2-5<0,001 p3-5<0,001 p4-5<0,001
	Chorionamnionitis, n (%) [95 % CI]	47 (90,4) [86,7-96,9]	38 (97,4) [89,9-100]	3 (27,3) [4,5-59,9]	21 (100) [91,3-100]	-	p1-3=0,002 p2-3<0,001 p3-4<0,001
Placentitis	Intervillositis, n (%) [95 % CI]	4 (7,7) [2,0-16,6]	10 (25,6) [13,0-40,8]	11 (100) [84,1-100]	21 (100) [91,3-100]	-	p1-3<0,001 p1-4<0,001 p2-3<0,001 p2-4<0,001
	Basal deciduitis, n (%) [95 % CI]	52 (100) [96,3-100]	39 (100) [95,2-100]	8 (72,7) [40,1-95,5]	21 (100) [91,3-100]	-	<0,001
Capillary lumen narrowing, n (%) [95 % CI]		50 (96,2) [89,1-99,7]	39 (100) [95,2-100]	10 (90,9) [64,1-100]	21 (100) [91,3-100]	-	0,264

*Notes: p_{1-2} – statistical significance of difference between subgroups I.1 and I.2; p_{1-3} – statistical significance of difference between subgroups I.1 and II.1; p_{1-4} – statistical significance of difference between subgroups I.1 and II.2; p_{1-5} – statistical significance of difference between subgroup I.1 and control group; p_{2-3} – statistical significance of difference between subgroups I.2 and II.1; p_{2-4} – statistical significance of difference between subgroups I.2 and II.2; p_{2-5} – statistical significance of difference between subgroup I.2 and control group; p_{3-4} – statistical significance of difference between subgroups II.1 and II.2; p_{3-5} – statistical significance of difference between subgroup II.1 and control group; p_{4-5} – statistical significance of difference between subgroup II.2 and control group; * – number of terminal chorionic villi per field of view at 400× magnification*

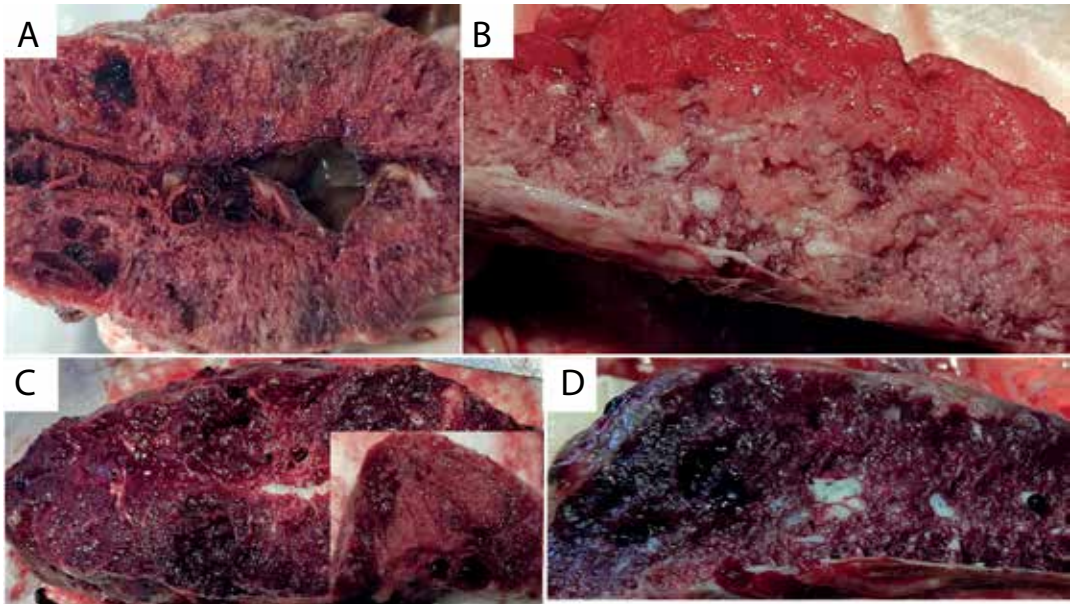

Fig. 1. Pathomorphological changes in the placenta in COVID-19-positive pregnant women. Macroscopic view. A, C – Placenta of a fetus with antenatal asphyxia. B, D – Placenta of a live-born infant at 40 weeks of gestation

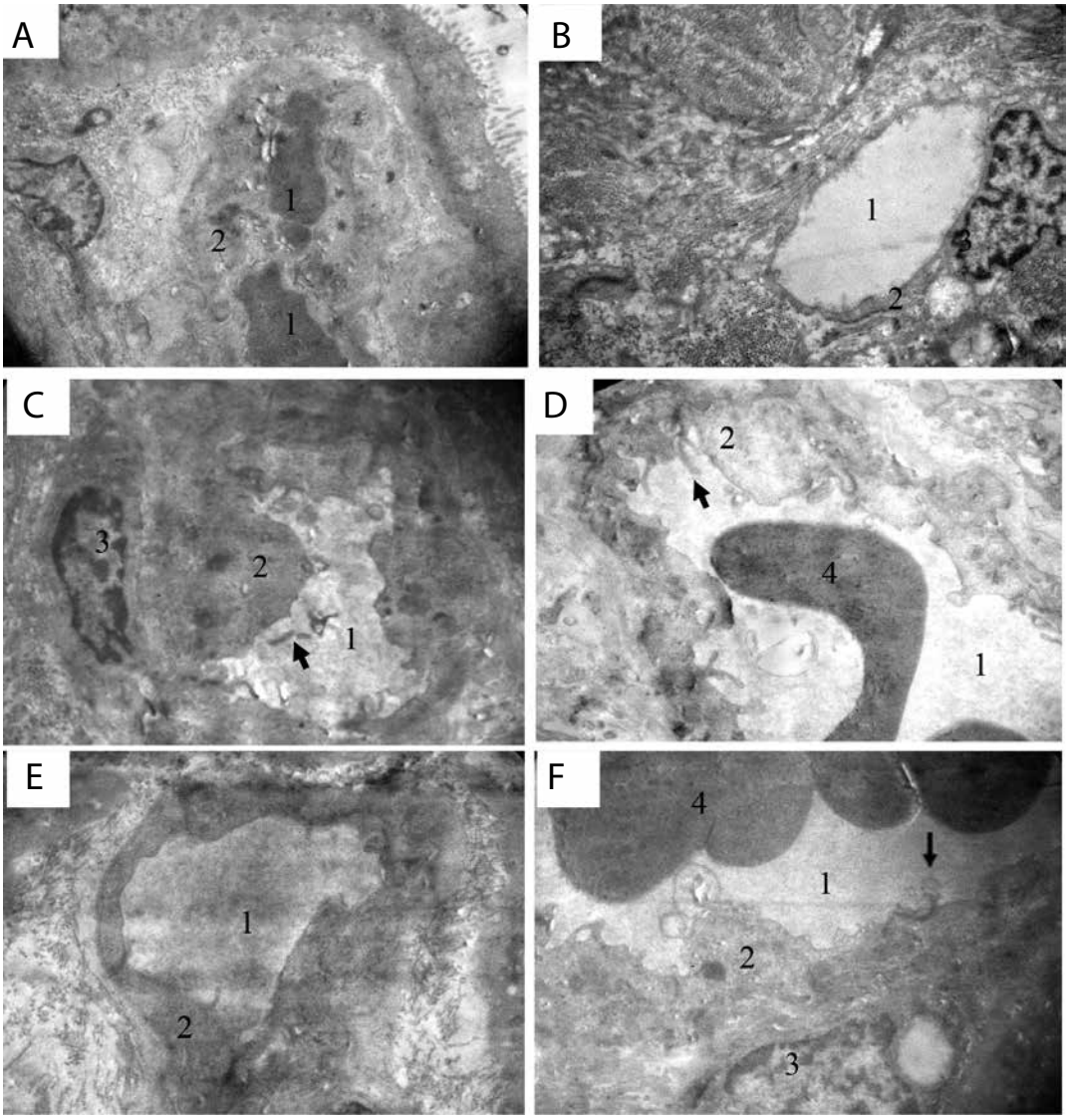

Fig. 2. Microscopic and EM changes in terminal villous vessels in pregnant women with COVID-19 (main groups). A, C, E – subgroup I.2; B, D, F – subgroup I.1. 1 – vessel lumen; 2 – endothelium; 3 – pericyte; 4 – erythrocyte; arrow – microvilli. A ×3000; B, C ×6000; D, E, F ×10000

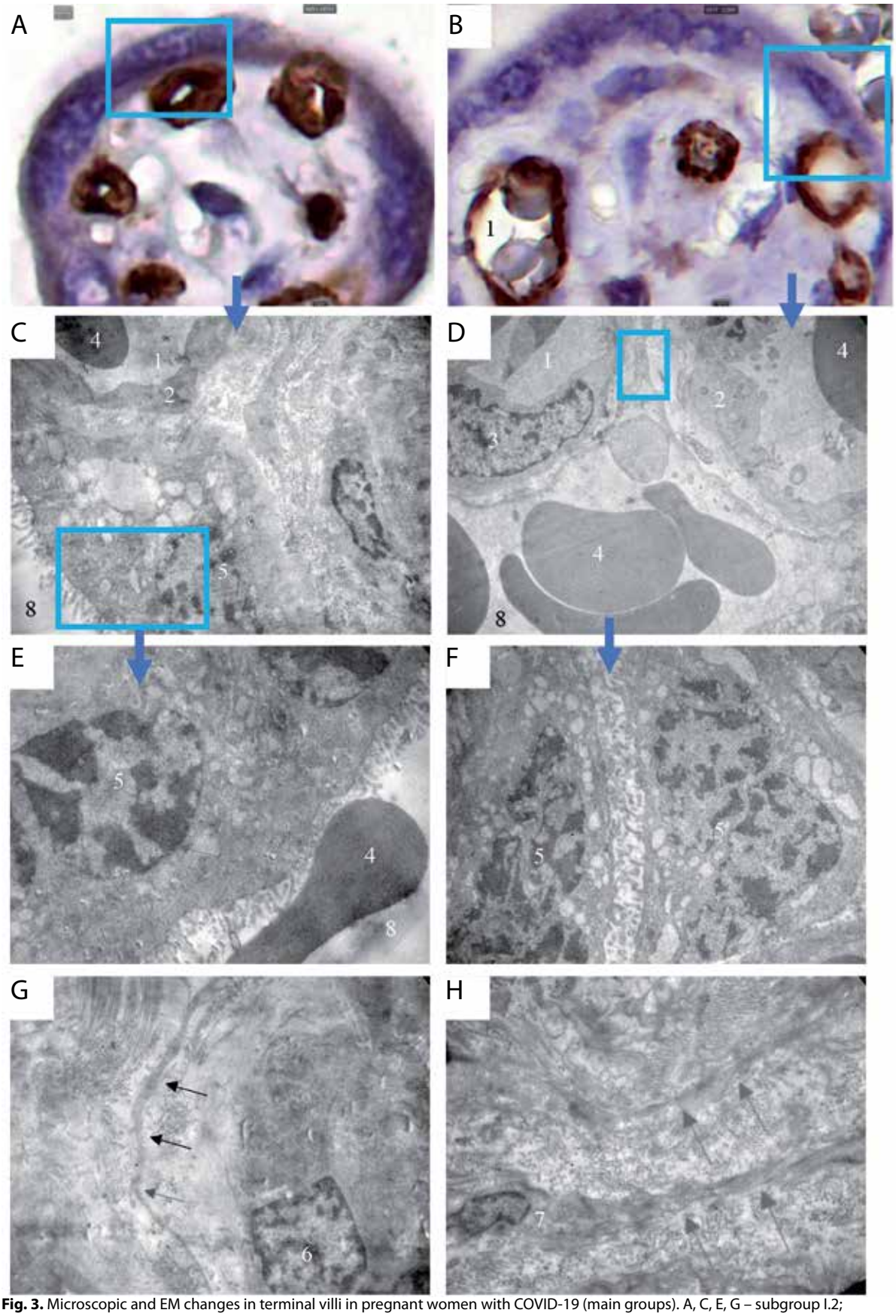

Fig. 3. Microscopic and EM changes in terminal villi in pregnant women with COVID-19 (main groups). A, C, E, G – subgroup I.2; B, D, F, H – subgroup I.1. 1 – vessel lumen; 2 – endothelium; 3 – endothelial cell nucleus; 4 – erythrocyte; 5 – syncytiotrophoblast nucleus; 6 – fibroblast; 7 – telocyte; arrows – telopodes. 8 – intervillous space. A, B – expression of monoclonal anti-CD34 antibodies in endothelial cells of villous arterioles, ×2700. C–H – EM. C, D ×3000; F ×10000; G, E, H ×6000. Blue arrows indicate enlarged views of the structures shown in the squares

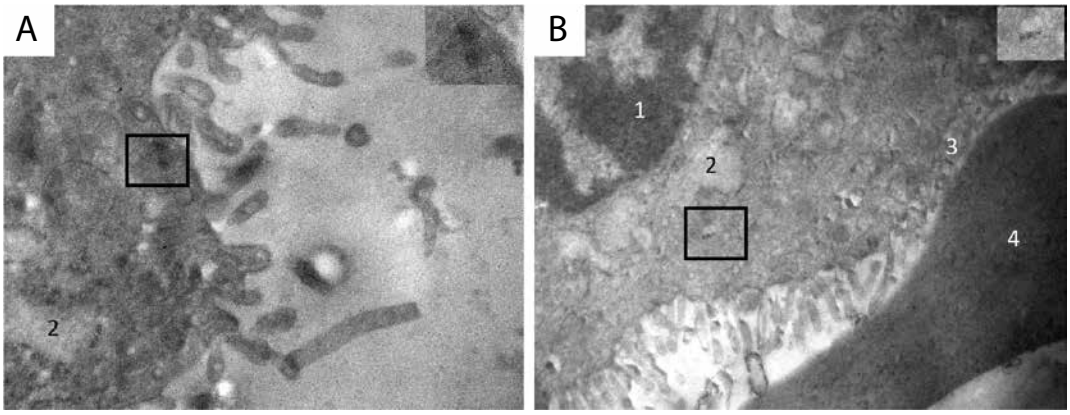

Fig. 4. Ultrastructural changes in the terminal villus of the placenta during the acute phase of COVID-19 in a pregnant woman. 1 – apoptosis of the syncytiotrophoblast nucleus; 2 – enlarged vacuoles in the cytoplasm of the syncytiotrophoblast; 3 – atrophy of microvilli at the site of contact with an erythrocyte; 4 – erythrocyte. Viral particles in the cytoplasm of the syncytiotrophoblast (structures within the black square are shown in the inset), ×10000

loss in areas of hemorrhage, fibrin deposition, or close apposition of terminal villi (Fig. 3D, E, F).

In the terminal villi of the main groups, structures resembling virus-like particles of spherical shape with an osmiophilic membrane were present and were detected near the cell membranes of stromal fibroblasts or syncytiotrophoblasts (Fig. 4A, B).

In the stroma of terminal chorionic villi in mostly all the cases of maternal COVID-19, edema was observed (Fig. 3A, B; Fig. 5B, D), which led to an increased percentage of stromal area in the subgroups. In addition, the studied subgroups were almost entirely represented by the cases of terminal villi capillary lumen narrowing, being the most pronounced in Group II. With an increasing post-COVID interval, a decrease in stromal edema of terminal villi (% of the stromal area) was observed in the subgroup I.1, as compared to the subgroups I.2, II.1 and II.2. This indicated a reduction in edema and was accompanied by restoration of the vascular lumen, as evidenced by an increase in the capillary lumen (Fig. 5A, C). A reduced number of terminal villi (hypoplasia) was noted in subgroups II.1 and II.2 (Table 1). In subgroup II.1, the central localization of capillaries within the chorionic villi was particularly notable (Fig. 5C), which is characteristic of damage to the immature placenta caused by SARS-CoV-2 and may contribute to delayed villous maturation [12].

Electron microscopy of the stromal compartment revealed an increase in collagen fiber content in subgroup I.1 (Fig. 3H) compared to I.2 (Fig. 3G). Fibrin deposits, mucoid and fibrinoid alterations of collagen fibers were observed, manifested by disruption of their compactness and loss of transverse striation, homogenization, and subsequent degradation (Fig. 3G, H).

The amniotic membranes in the main groups appeared thickened and yellowish (Fig. 1B), with microscopic examination revealing chorioamnionitis. It was observed in 90,4% of subgroup I.1, 97,4% of subgroup I.2, 27,3% of subgroup II.1, and 100% of subgroup II.2. Basal deciduitis was observed in 100% of subgroups I.1, I.2 and II.2, and 72,7% of subgroup II.1. Intervillositis was found in 25,6% of subgroup I.2, and in 100% of cases with antenatal fetal asphyxia during the acute phase of COVID-19 (Table 1).

DISCUSSION

Cases of COVID-19 in pregnant women resulting in live births and intrauterine fetal death were analyzed. The condition of the fetus at birth was found to be dependent on the severity of placental pathological changes caused by SARS-CoV-2 [13, 14]. No statistically significant correlation was found between the severity of COVID-19 in pregnant women and the fetal condition at birth [15], which can be attributed to the absence of a consistent association between the maternal clinical status and the placental pathological changes induced by the infection.

Our study focused on morphological changes in components forming the vasculosyncytial membranes: endothelium, stroma, and syncytiotrophoblast. In 100% of our cases, during the acute phase of COVID-19 in pregnant women, microcirculatory damage in the terminal villi was observed, manifested by endothelial cell cytoplasmic edema, membrane rupture, and irreversible endothelial damage. Edema and microvilli desquamation caused by SARS-CoV-2 were signs of endothelial dysfunction [4]. With an increase in the post-COVID interval, restoration of the functional activity of the endothelium was observed (subgroup I.1), as evidenced by an increase in the number of microvilli and micropinocytic vesicles on the luminal surface of endothelial cells. Direct viral action on endothelial cells (aponecrosis) or cytokine-mediated effects triggered by SARS-CoV-2 can lead to a preeclampsia-like syndrome in COVID-19-positive pregnant women [15]. According to researchers, apoptotic changes in the nuclei and cytoplasm of endothelial cells and circulatory disturbances impair fetal perfusion [16]. During the acute phase, vascular lumens were obstructed with destroyed erythrocytes, resulting in a reduced number of vessels in the villi (subgroup II.1). In subgroup I.1, gradual restoration of vessel lumen and an increase in their percentage was noted. As the post-COVID interval increased, a reduction in

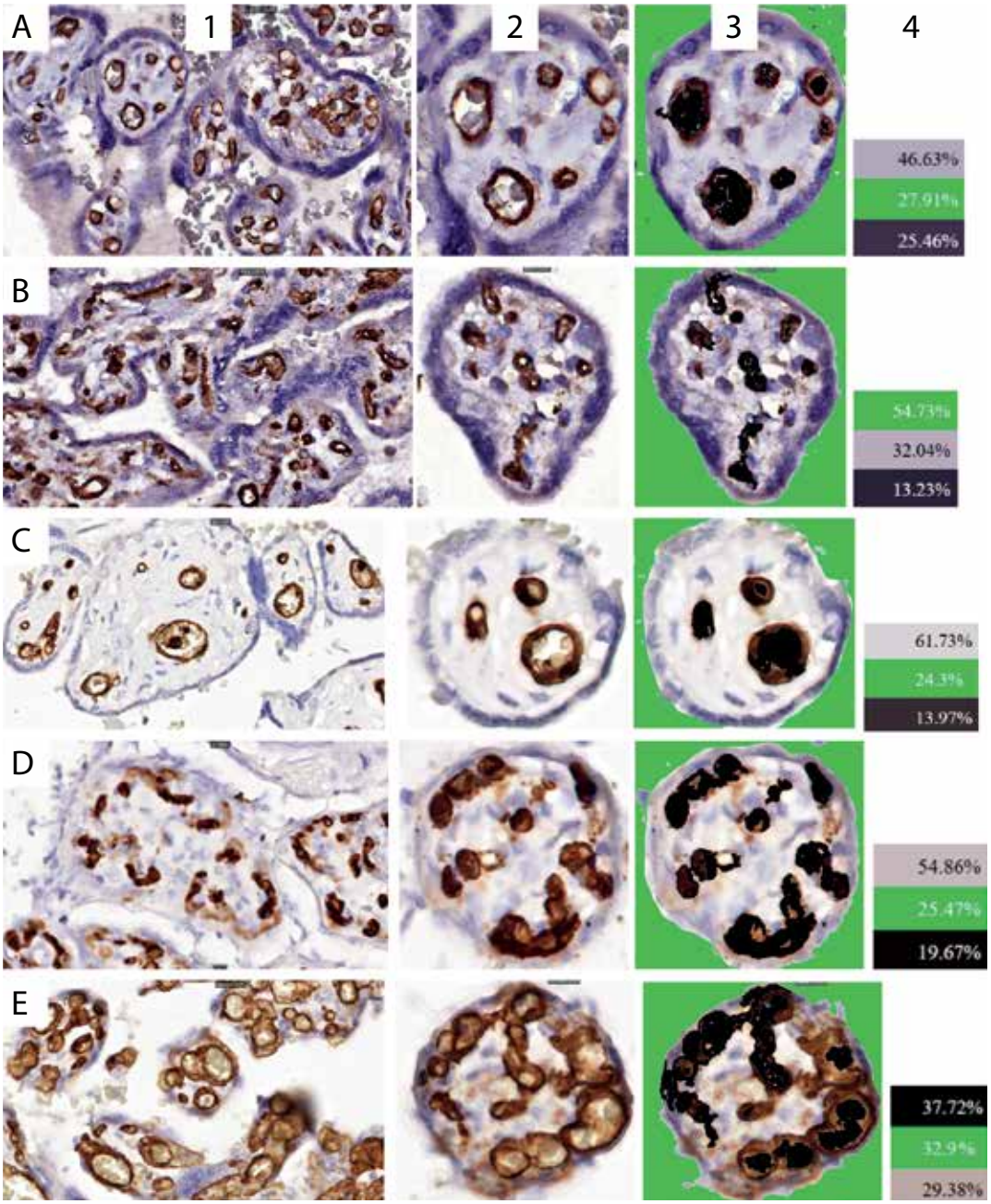

Fig. 5. Microscopic structural changes in the placenta during COVID-19 – 1. Representative placentas: A – subgroup I.1; B – subgroup I.2; C – subgroup II.1; D – subgroup II.2 and in the comparison group – E. Expression of monoclonal antibodies against CD34 in the endothelium of villous arterioles, ×630. 2 (A–E): Terminal villi, ×1200 – quantitative assessment of vascular and stromal percentages in histological sections of terminal villi. 3 (A–E): Lumen of vessels (black) and background surrounding the villi (green) colored using Microsoft Paint. 4 (A–E): the percentages of dominant colors in the images were determined using the ONLINE JPG TOOLS service, with each color corresponding to the proportional area of the analyzed structures: vessels (black), stroma (gray), and background (green)

cytoplasmic edema of endothelial cells and stromal edema in the terminal chorionic villi was observed. However, despite these improvements, stromal edema remained until delivery, contributing to thickening of the vasculosyncytial membrane compared to the control group [16].

Edema led to increased thickness of the vasculosyncytial membranes (central location of vessels), which caused malperfusion [11, 12]. The thickening of the vasculosyncytial membranes contributes to pathological endothelial activation, and the substances they produce lead to impaired microcirculation in the vascular lumen, vasoconstriction, stromal edema, hypoxia, and fibroblast activation, ultimately resulting in fibrosis [4]. The presence of apoptotic syncytiotrophoblasts, endothelial cells indicate an energy deficit caused by cytokine storm and tissue hypoxia, which activates fibroblasts.

Viral particles were detected by EM both in the acute phase of COVID-19 and in cases from subgroup I.1. Spherical particles

were localized in the villous stroma and in the cytoplasm of the syncytiotrophoblast. Our data align with other researchers who have reported extracellular viral particles [3]. Although placental pathological changes such as the presence of viral particles, placentitis, and malperfusion were observed during late gestation in COVID-19 cases, neonates were born PCR-negative and without clinical signs of hypoxia, even when delivered by PCR-positive mothers [13]. This is associated with protective mechanisms against vertical transmission of the virus [2, 3]. Placentitis of varying degrees of severity was detected in placentas from the main groups. The intensity of inflammatory manifestations declined with increasing post-COVID interval duration. Generalized intervillositis was observed predominantly in subgroup II.2, which was explained by the immaturity of the placental protective mechanisms and was the cause of antenatal fetal death [12].

CONCLUSIONS

The morphogenesis of placental dysfunction in cases of antenatal fetal asphyxia associated with immature protective mechanisms involves endothelial dysfunction, impaired microcirculation, inflammatory infiltration, stromal edema of terminal villi with a reduction in vascular lumen, and subsequent fibrosis.

In the placentas of live-born infants, an increasing post-COVID interval was associated with restoration of the vascular lumen in the terminal chorionic villi and a reduction in the severity of placentitis (subgroup I.1).

The presence of viral particles with an increasing post-COVID interval indicates SARS-CoV-2 persistence, the prolonged impact of which on vascular function and its role in the development of placental insufficiency requires further investigation.

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The work is a fragment of scientific research work of the Department of Pathological Anatomy, Bogomolets National medical university, Kyiv, Ukraine: "Morphogenesis Research and Optimization of Morphological Diagnostics of the Most Prevalent Socially Significant Diseases"" (registration number 0124U000022). Planned duration of the research project: 2024 to 2026."

The study was approved by the local bioethical committee of the Bohomolets National Medical University (protocol No 144 of 29.03.2021), and was carried out in accordance with the principles outlined in the Declaration of Helsinki. All participants provided written informed consent.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR:
Tetiana V. Savchuk
Department of Pathological Anatomy
Bohomolets National Medical University
13 T. Shevchenko Blvd., 01601 Kyiv, Ukraine
e-mail: t.savchuk@nmu.ua

ORCID AND CONTRIBUTIONSHIP

Tetiana V. Savchuk: 0000-0002-7218-0253 A B C D E F
Ivan V. Leshchenko: 0000-0001-8239-256X A B C
Viktoriya V. Vaslovych: 0000-0002-7503-4547 A D
Oksana H. Chernenko: 0000-0001-6292-8339 A B
Tetyana A. Malysheva: 0000-0003-4071-8327 D E F

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

RECEIVED: 14.01.2025
ACCEPTED: 27.06.2025

CREATIVE COMMONS 4.0

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ORIGINAL ARTICLE

Analysis of the work of the inpatient military hospital during the Russian-Ukrainian war

Oleksandr M. Korneta, Iryna A. Holovanova, Maksym V. Khorosh
POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

Aim: The aim of this work is to analyze the provision of medical care to military personnel on the example of the activities of the Poltava Military Hospital (Poltava, Ukraine) for the period 2021-2023.

Materials and Methods: The design of our study was descriptive. During the research, the reporting and accounting documentation of the Poltava Military Hospital for the relevant years was used. Descriptive statistics methods were used to analyze the main indicators of the hospital's activity: growth rates and growth rates were calculated to describe changes in the main indicators.

Results: The average number of staffed beds in the hospital as a whole is growing. Thus, compared to 2021, in 2023, this figure increased by 200% (100% growth increment rate). The bed utilization, we can note that in 2022, the utilization of both staffed beds (67.29%) and actually deployed beds (47.93%) was inefficient, and during the war it reached a sufficient level – 89.27% and 63.84.8%, respectively, bed occupancy rates in all hospital departments were 7.7-7.3.

Conclusions: The ultimate impact of the ongoing war in Ukraine on the organization of medical care for injured servicemen and women remains uncertain, and we plan to explore this issue in our next work.

KEY WORDS: anti-terrorist operation, Joint Forces operation, medical care, combatants

Pol Merkur Lek,2025;53(4):495-501 doi: 10.36740/Merkur202504109

INTRODUCTION

During the anti-terrorist operation and the Joint Forces operation (ATO/JFO), the medical service of the Armed Forces of Ukraine went through a difficult path of combat formation, acquired the necessary capabilities for medical support of troops (forces) in combat conditions and providing medical aid to the wounded, injured, traumatized and sick servicemen [1]. At the same time, an assessment of the state of the medical service of the Armed Forces of Ukraine before the beginning of the anti-terrorist operation, as well as an analysis of the state of the medical support system of the Armed Forces of Ukraine at the beginning of its implementation, give grounds for asserting that the military medical service was not fully ready to perform its assigned tasks in combat conditions, did not have the necessary regulatory framework, organizational structure and modern complete and time-table equipment [2]. Theoretical developments regarding the medical support of the Armed Forces of Ukraine did not correspond to the nature of the use of troops during the anti-terrorist operation, which had the characteristics of a hybrid war and included open combat operations of varying intensity, sabotage and intelligence operations, separatism, information warfare and economic confrontation at the regional and international levels [3]. A number of documents important for the national security of the state, including the Military Doctrine of Ukraine, the Concept of the Development of the Security and Defense Sector of Ukraine, and the Strategic Defense Bulletin of Ukraine, were developed and put into effect during the time of the ATO/JFO, which became the prerequisite and basis for the development of the Program for the Development of the Armed Forces of Ukraine for the period up to 2020 with the relevant section on the development of their medical care system for the specified period. In the new edition of the Military Doctrine of Ukraine, it is determined that the main role in ensuring military security, state sovereignty and territorial integrity of the state belongs to the Armed Forces of Ukraine [4]. The priority task for the Armed Forces of Ukraine is to achieve full compatibility with the relevant forces of NATO member states by 2020, and one of the directions of their reform and development is the modernization of the military medical support system with maximum integration of it with the civilian health care system [5-7].

These tasks became especially relevant during the full-scale invasion of Russia in February 2022. In Ukraine, Russian forces used modern man-portable anti-tank guided missiles with an advanced dual cumulative charge or thermobaric warheads, or the barrage of thermobaric rocket artillery. This thermobaric weapon inflicts blunt and penetrating wounds, amputation of limbs, and extensive thermal damage [8].

Russia's use of incendiary munitions results in significant deep burns, organophosphate poisoning, and other toxic effects from vapors associated with burning substances [9]. Caring for the burn victims imposes a significant logistical and medical burden due to the complexity of care and intensive resuscitation. This emphasizes the need to plan for significant thermal/burn injuries in future combat [10, 11].

In this regard, the burden on the healthcare system in Ukraine has increased. Assistance in the inpatient military hospital, where wounded soldiers are admitted, is of great importance today. In addition to injuries, diseases of internal organs, nervous system, and skin occur.

AIM

The aim of this work is to analyze the indicators of the provision of medical care to military personnel on the example of the activities of the Poltava Military Hospital (Poltava, Ukraine) for the period 2021-2023.

MATERIALS AND METHODS

The design of our study was descriptive. During the research, the reporting and accounting documentation of the Poltava Military Hospital for the relevant years was used. Descriptive statistics methods were used to analyze the main indicators of the hospital's activity: growth rates and growth increment rate were calculated to describe changes in the main indicators. Generally accepted methods were used for statistical processing, calculations were carried out using MS Excel 2016.

RESULTS

Medical care for military personnel in Poltava region is provided in inpatient settings in all healthcare facilities in Poltava region. In Poltava region, rehabilitation care for the military is provided in 19 inpatient medical facilities and outpatient care in 22. All these medical institutions have signed contracts with the National Health Service of Ukraine [12].

When a serviceman is injured, he is sent to a military medical institution, if there is none nearby, he is sent to a civilian medical institution.

Even during the ATO, two main evacuation routes were formed with the stages of medical evacuation (levels of medical care) deployed on them: one – mainly from Luhansk region to Kharkiv; the other – mainly from Donetsk region to Dnipro [13]. During a full-scale invasion, soldiers with injuries, wounds, and diseases are sent to military hospitals: from the Chernihiv direction of hostilities to Kyiv, from the Sumy, Luhansk, and Kharkiv directions to Kharkiv, partially to Poltava, from the Donetsk direction to Dnipro and Zaporizhzhia, from the Mykolaiv and Kherson directions to Odesa and Mykolaiv.

Thus, inpatient medical care is provided to servicemen after evacuation in the Kharkiv and Sumy directions at the Poltava Military Hospital. The hospital's departments are organized in such a way that they can meet different health needs of the soldiers. If there are wounds or traumas, this is the surgical and traumatology department. Neurological diseases are also taken into account, so there is a neurological department, internal diseases – a therapeutic department, and skin diseases – a dermatovenereological department.

As shown in Table 1, the average number of staffed beds in the hospital as a whole is growing. Thus, compared to 2021, in 2023, this figure increased by 200% (100% growth increment rate). Separately, by department, the situation was as follows (Tables 2-3.): the average number of staff beds in surgery increased by 160% (60% growth increment rate), in traumatology by 250% (150% growth increment rate), in the infectious diseases department by 300% (200% growth increment rate), in therapy by 183.33% (83.33% growth increment rate), in neurology by 166.7% (66.7% growth increment rate), and in dermatology by 200% (100% growth increment rate). Similar changes occurred in the average number of beds actually deployed. In general, the number of patients treated during the war increased by 162.7% (62.7% growth increment rate) compared to 2021, due to such departments as surgery – by 58.8% (158.85% growth increment rate), traumatology – by 290.1% (190.1% growth increment rate), therapy – 154.45% (54.45% growth increment rate), neurology – by 183.45% (83.45% growth increment rate). And only in the infectious diseases department we see a decrease in the number of treated patients by 55.56% (growth increment rate – -44.44%).

If we look at bed utilization, we can note that in 2022, the utilization of both staffed beds (67.29%) and actually deployed beds (47.93%) was inefficient, and during the war it reached a sufficient level – 89.27% and 63.84.8%, respectively. This increase is mainly due to the surgical and trauma departments, where it reaches 110.46/76.45% and 197.2/81.08% for staffed beds, respectively, and 78.99/54.46% and 141/57.75% for actually deployed beds.

The bed idle time is the time from the moment a bed is vacated by discharged patients until it is occupied by newly admitted patients. The average downtime required to prepare a bed for the next patient is assumed to be at the minimum required level, namely two days of downtime for beds for patients with, for example, tuberculosis and infectious diseases (adults).

As shown in Table 1, bed occupancy rates in all hospital departments were 7.7-7.3. The highest bed occupancy is observed in the Infectious Diseases and Therapeutic Departments, reaching 68.8 and 11.6 percent respectively in 2023. At the same time, it is the lowest in the traumatology and dermatology departments – -4.4 and 1, respectively (Table 2, Table 3). Nevertheless, this indicator still exceeds the standard of downtime.

The dynamics of the average bed occupancy rate shows that in 2022 and in 2023 this indicator decreased to -1.98% (growth increment rate – 98.02%).

Accordingly, the same fluctuations (decrease) can be noted when analyzing the bed turnover rate, which grew by -26.12% (73.88% growth increment rate) mainly due to the infectious diseases and therapeutic departments. At the same time, the traumatology department grew by 15.9% and the neurology department by 10.15%. Overall, these data

Table 1. Dynamics of performance indicators of inpatient medical care for servicemen in the hospital in all departments for 2021-2023

	Poltava Military Hospital				
	2021	2022	2023	Growth rate (by 2021)	Growth increment rate (by 2021)
Average number of staff beds	100	150	200	200,00	100,00
Average number of beds actually deployed	100	150	200	200,00	100,00
Number of patients treated	2228	3692	3625	162,70	62,70
Loading of regular beds	-	67,29%	89,27%	132,66*	32,66*
Loading of actually deployed beds	-	47,93%	63,84%	133,19*	33,19*
Downtime of the bed	69,8	7,7	7,3	10,46	-89,54
Average number of occupied beds	-	10,1	9,9	98,02*	-1,98*
Average bed day	-	7,1	12,9	181,69*	81,69*
Bed turnover	-	24,5	18,1	73,88*	-26,12*
Average number of days of bed occupancy	-	175	233	133,14*	33,14*

** - indicators relative to 2022*

Table 2. Dynamics of performance indicators of inpatient medical care for servicemen in the surgical and trauma departments in 2021-2023

	2021	2022	2023	Growth rate (by 2021)	Growth increment rate (by 2021)
Surgical department					
Average number of staff beds	25	33	40	160,00	60,00
Average number of beds actually deployed	25	33	40	160,00	60,00
Number of patients treated	627	1003	996	158,85	58,85
Loading of regular beds	54,30%	76,45%	110,46%	203,43	103,43
Loading of actually deployed beds	49,10%	54,46%	78,99%	160,88	60,88
Downtime of the bed	7,4	5,4	3,1	41,89	-58,11
Average number of occupied beds	12,3	2,7	2,7	21,95	-78,05
Average bed day	7,1	6,5	11,6	163,38	63,38
Bed turnover	25,1	30,8	24,9	99,20	-0,80
Average number of days of bed occupancy	179,2	198,8	288,3	160,88	60,88
Trauma department					
Average number of staff beds	10	18	25	250,00	150,00
Average number of beds actually deployed	10	18	25	250,00	150,00
Number of patients treated	294	462	853	290,14	190,14
Loading of regular beds	69,10%	81,08%	197,20%	285,38	185,38
Loading of actually deployed beds	62,50%	57,75%	141,01%	225,62	125,62
Downtime of the bed	5	5,9	-4,4	-88,00	-188,00
Average number of occupied beds	6,2	1,3	2,3	37,10	-62,90
Average bed day	7,8	8	15,1	193,59	93,59
Bed turnover	29,4	26,3	34,1	115,99	15,99
Average number of days of bed occupancy	228,1	210,8	514,7	225,65	125,65

Table 3. Dynamics of performance indicators of inpatient medical care for servicemen in the infectious, therapeutic, neurological, and dermatological departments of the units in 2021-2023

	2021	2022	2023	Growth rate (by 2021)	Growth increment rate (by 2021)
Infectious department					
Average number of staff beds	15	30	45	300,00	200,00
Average number of beds actually deployed	15	30	45	300,00	200,00
Number of patients treated	396	395	220	55,56	-44,44
Loading of regular beds	86,10%	34,46%	11,03%	12,81	-87,19
Loading of actually deployed beds	77,90%	24,55%	7,88%	10,12	-89,88
Downtime of the bed	3,1	21	68,8	2219,35	2119,35
Average number of occupied beds	11,7	1,1	0,6	5,13	-94,87
Average bed day	10,8	6,8	5,9	54,63	-45,37
Bed turnover	26,4	13,1	4,9	18,56	-81,44
Average number of days of bed occupancy	284,3	89,6	28,8	10,13	-89,87
Therapeutic department					
Average number of staff beds	30	43	55	183,33	83,33
Average number of beds actually deployed	30	43	55	183,33	83,33
Number of patients treated	551	886	851	154,45	54,45
Loading of regular beds	56,50%	56,59%	71,06%	125,77	25,77
Loading of actually deployed beds	51,10%	40,31%	50,81%	99,43	-0,57
Downtime of the bed	9,7	10,5	11,6	119,59	19,59
Average number of occupied beds	15,5	2,4	2,3	14,84	-85,16
Average bed day	10,4	7,1	12	115,38	15,38
Bed turnover	18,4	20,8	15,5	84,24	-15,76
Average number of days of bed occupancy	186,6	147,1	185,5	99,41	-0,59
Nneurological department					
Average number of staff beds	15	20	25	166,67	66,67
Average number of beds actually deployed	15	20	25	166,67	66,67
Number of patients treated	296	871	543	183,45	83,45
Loading of regular beds	69,10%	119,27%	110,74%	160,26	60,26
Loading of actually deployed beds	62,40%	84,96%	79,19%	126,91	26,91
Downtime of the bed	0,9	1,3	3,5	388,89	288,89
Average number of occupied beds	9,4	2,4	1,5	15,96	-84,04
Average bed day	11,3	7,1	13,3	117,70	17,70
Bed turnover	19,7	43,5	21,7	110,15	10,15
Average number of days of bed occupancy	221,9	310,1	289	130,24	30,24
Dermatological department					
Average number of staff beds	5	8	10	200,00	100,00
Average number of beds actually deployed	5	8	10	200,00	100,00
Number of patients treated	10	65	162	1620,00	1520,00
Loading of regular beds	7,30%	45,67%	133,33%	1826,44	1726,44
Loading of actually deployed beds	1,80%	32,53%	95,34%	5296,67	5196,67
Downtime of the bed	43,7	28,5	1	2,29	-97,71

Table 3. Cont.

Average number of occupied beds	0,3	0,2	0,4	133,33	33,33
Average bed day	11,3	13,7	21,5	190,27	90,27
Bed turnover	2,4	8,6	16,2	675,00	575,00
Average number of days of bed occupancy	22,6	118,7	348	1539,82	1439,82

indicate an increase in both the number of patients and the average length of stay of a patient in an inpatient bed for injured military personnel in 2023. Thus, as shown in Table 1, the average length of stay increased by 181.7% (81.7% growth increment rate) due to the surgical department – 11.6 in 2023 (63.38% growth increment rate), trauma department – 15.5 (93.59% growth increment rate), neurological department – 13.3 (17.7% growth increment rate), but the highest rate was in the dermatovenereology department – 21.5 (90.27% growth increment rate) (Table 2, Table 3).

DISCUSSION

The military operations taking place on the territory of Ukraine involve the loss of human potential, which imposes an additional burden on the healthcare system. In accordance with the Order of the Ministry of Health of Ukraine „On the provision of medical care under martial law to servicemen participating in the Joint Forces Operation" of 25.02.2022 No. 379, medical care is provided to all injured and wounded around the clock without fail, and the injured and wounded are hospitalized in the nearest health care facilities that are able to provide care in accordance with the profile of the injury [14]. The level of medical care in the military hospital in Poltava increased significantly during the war, and the need for material and technical conditions for treating soldiers increased, to which the administration of the institution responded in a timely manner. When analyzing the hospital's inpatient department, an increase in the number of both staffed and deployed beds in all departments was noted, which suggests that the need for beds was fully met within the space available in the institution. The bed utilization rate has increased to 89.27%, with the largest contribution to this indicator coming from the surgical and trauma departments. Such figures may indicate that specialized surgical and trauma beds were placed in other departments. That is, the burden on the hospital is increasing, including in terms of qualified medical staff material and technical resources, and space for surgical beds. All of this requires optimization and reorientation of medical care with an emphasis on surgical and trauma care [15].

The value of „bed downtime" for a military hospital is too high and requires an analysis of the material and technical base, the level of staff qualifications, and timely management decisions that lead to optimization of the institution's operations.

At the same time, the dynamics of the average bed occupancy rate is decreasing, which may indicate insufficient selection of patients for inpatient treatment, or that serious patients were transferred to higher-level HCFs: regional and state. In addition, according to the current legislation, servicemen could undergo treatment or rehabilitation abroad [16-18]. The growth of such an indicator as „bed turnover", especially in the trauma and neurological departments, indicates a significant movement of patients in these profiles, and it is possible that beds in other departments that were less busy were used. In general, these data show an increase in the number of patients and the average length of stay of a patient in an inpatient care bed for injured military personnel in 2023, which indicates the severity of the process.

Thus, our data shows an increase in the number of patients, which indicates an increase in the number of cases of military personnel seeking medical care, while at the same time there is an insufficient number of beds to meet this need for surgical trauma care [19].

In the Ukrainian conflict, Russia has used specially manufactured munitions on an industrial scale and has used rocket and artillery fire on a regular basis. This increase in firepower has led to an increase in injuries. Statistics provided by Ukrainian doctors show that more than 70% of all Ukrainian combat casualties were caused by artillery and rocket fire from Russian forces, resulting in significant polytrauma to several organ systems [20]. In comparison, in most recent conflicts, soldiers who sustained chest and abdominal injuries could have survived if the associated injuries to their limbs and other body parts had been limited.

Common mechanisms of injury include multiple high-velocity wounds, barotrauma and blunt force trauma from being thrown during an explosion, as well as traumatic brain injury [21].

It is estimated that between 5% and 10% of Ukrainian soldiers deployed in theater will be wounded or killed in action. Thus, in general, medical evacuation planning, prolonged field care, and other interventions planned by medical personnel will have to account for massive polytrauma, significantly more patients at a time, and the resources required per patient will be significantly greater [22].

UKRSOF surgeons have reported receiving multiple patients at the same time with multiple potentially fatal injuries. Patients often require several emergency interventions to control the damage before doctors can begin to treat the next patient [23]. During a 3-week period with constant artillery fire, one Ukrainian surgeon treated

over 200 patients, of whom 36 underwent laparotomy and 20 underwent thoracotomy. Penetrating wounds to the abdomen and chest occurred laterally to the body armor plates in approximately 60% of cases and below the body armor plates in 30% of cases. An estimated 10% had either material penetrating the body armor plates or were not wearing body armor. Traumatic penetrating wounds to the skull were almost always fatal and were treated in a wait-and- see manner. The need for specialized medical care is growing to treat soldiers with spinal and peripheral nervous system injuries. This war has hit a country whose healthcare system is still far from Western standards due to insufficient public funding, overcentralization, and generally outdated equipment [24]. For example, there is a large shortage of operating microscopes, which are necessary for surgical treatment of peripheral nerve injuries [25].

One surgery department at Poltava Military Hospital cannot meet all the needs of patients with penetrating wounds of the chest, abdomen, spine, and skull.

According to the researchers, who showed an insufficient logistical component in the provision of neurosurgical care, namely, that neurosurgeons were forced to perform operations outside their neurosurgical spectrum. This fact indirectly reflects the shortage of Ukrainian medical personnel, as well as the growing burden on patients caused by the hostilities.

CONCLUSIONS

We understand the limitations of this article, which covers the work of only one hospital in Ukraine, but its example can be used to trace the main problems in the organization of inpatient medical care – lack of staff, poor material and technical support. This paper mainly focuses on the needs of a military hospital through the analysis of its inpatient care activities, which are documented in this study. The ultimate impact of the ongoing war in Ukraine on the organization of medical care for injured servicemen and women remains uncertain, and we plan to explore this issue in our next work.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Maksym V. Khorosh
Poltava State Medical University
24 Shevchenko St., 36000 Poltava, Ukraine
e-mail: indarion0@gmail.com

ORCID AND CONTRIBUTIONSHIP

Oleksandr M. Korneta: 0000-0001-7924-1947 B C D
Iryna A. Holovanova: 0000-0002-8114-8319 A E F
Maksym V. Khorosh: 0000-0002-2083-1333 C D

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

RECEIVED: 30.10.2024
ACCEPTED: 22.05.2025

CREATIVE COMMONS 4.0

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ORIGINAL ARTICLE

Rational nutrition as a factor of healthy lifestyle and prevention of chronic non-communicable diseases

Grygoriy P. Griban[1], Olha S. Zablotska[2], Olena O. Mitova[3], Soslan G. Adyrkhaiev[4], Ludmyla V. Adyrkhaieva[4], Yuliia V. Paryshkura[5], Alimia M. Osmanova[4]

[1]ZHYTOMYR IVAN FRANKO STATE UNIVERSITY, ZHYTOMYR, UKRAINE
[2]ZHYTOMYR MEDICAL INSTITUTE OF ZHYTOMYR REGIONAL COUNCIL, ZHYTOMYR, UKRAINE
[3]PRYDNIPROVSK STATE ACADEMY OF PHYSICAL CULTURE AND SPORT, DNIPRO, UKRAINE
[4]VOLODYMYR DAHL EAST UKRAINIAN NATIONAL UNIVERSITY, KYIV, UKRAINE
[5]STATE UNIVERSITY OF TRADE AND ECONOMICS, KYIV, UKRAINE

ABSTRACT

Aim: The aim is to conduct medical and sociological research on public awareness of the impact of rational nutrition on promoting human health and preventing chronic non-communicable diseases.

Materials and Methods: The research was conducted in 2022-2024 and involved 214 respondents of different ages and genders who were patients of outpatient clinics in Zhytomyr (Ukraine). Research methods included theoretical analysis of literary sources, medical and sociological (questionnaire), mathematical and statistical, system analysis, and logical generalization.

Results: It has been found that less than a third of the surveyed population (31.0 %) is in good health; 26.0 % report chronic diseases of the cardiovascular, excretory, hepatobiliary, and endocrine systems; 12.1 % of the respondents each suffer from diabetes and obesity. Despite this, only 18.0 % of the respondents adhere to healthy eating habits, and more than half abuse junk food and violate their diet. It has also been found that 79.0 % of the respondents do not have sufficient information about healthy eating; 93.0 % expressed a desire to improve their knowledge of the basics of healthy eating.

Conclusions: It has been found that rational nutrition is the most important factor in the body's vital activity, which ensures human health and working capacity, the ability to withstand adverse environmental influences, and determines the quality and duration of life. The article substantiates a set of measures for organizing public health professionals' outreach and awareness-raising activities to promote public health and prevent chronic non-communicable diseases through dietary nutrition.

KEY WORDS: rational nutrition, nutrition quality, health, healthy lifestyle, prevention of chronic non-communicable diseases

Pol Merkur Lek,2025;53(4):502-508 doi: 10.36740/Merkur202504110

INTRODUCTION

Maintaining public health is one of the most important tasks of society. The health phenomenon is influenced by socio-economic, socio-biological, environmental, natural and climatic, and organizational and medical factors. The state of health mainly (by 50-60 %) depends on a person's lifestyle, including their diet [1]. Healthy, i.e., balanced nutrition, improves human health, increases working capacity, and extends life expectancy. An imbalance in the chemical composition of the diet triggers the mechanisms of developing non-communicable diseases. Dietary nutrition is used to prevent chronic non-communicable disease exacerbation. Correction of food components in the diet positively affects the condition of individual organs, their systems, and human health in general [2].

The problem of nutrition and its impact on public health remains one of the priorities in forming and implementing international projects of the World Health Organization (WHO). Studies [3] show a deterioration in the quality of nutrition of the Ukrainian population, manifested in a decrease in the consumption of valuable food products such as meat, milk, and vegetable fats. Such an imbalance in the intake of nutrients weakens the human body, causing the corresponding diseases associated with impaired metabolism of proteins, lipids, and carbohydrates.

According to scientists [4], the issues of "nutrition and health" and "nutrition and disease" are closely related. An unhealthy diet is the main cause of overweight, hypertension, and other diseases. At the same time, food consumption is a necessity and one of the greatest pleasures for most people. People eat food not only to satisfy hunger but also to enjoy it. At the same time, food is a carrier and source of many pharmacologically and biologically active substances with a significant therapeutic and health-promoting effect [5]. Therefore, studying the awareness of the population of Ukraine about the impact of rational nutrition on improving human health, as well as the prevention of chronic non-communicable diseases, is relevant and timely.

AIM

The aim is to conduct medical and sociological research on public awareness of the impact of rational nutrition on promoting human health and preventing chronic non-communicable diseases.

MATERIALS AND METHODS

The research was conducted in 2022-2024 at Zhytomyr Medical Institute of Zhytomyr Regional Council and Zhytomyr Ivan Franko State University. The research involved 214 respondents of different ages and genders. All respondents were patients of outpatient clinics in Zhytomyr (Ukraine).

Research methods: theoretical analysis of literature sources on the topic of the research (16 literature sources from various world scientometric databases were processed); medical and sociological (questionnaire) – to determine the population's adherence to the principles of healthy eating, as well as to understand its importance for the prevention of chronic non-communicable diseases; mathematical and statistical – to process and analyze the results of the research; system analysis and logical generalization – to substantiate the content of outreach and awareness-raising activities of public health professionals on the prevention of chronic non-communicable diseases among the population through rational nutrition.

The survey was conducted using the author's questionnaire, which contains 20 questions and consists of three sections: socio-demographic information, respondent's consent to participate in the research, and the section with targeted questions. The questionnaire was anonymous without any references to the authors of the article in the answers. The results were used for scientific purposes only. Questionnaire was assessed by the experts in this field (3 professors and 3 associate professors) and was approved by the Academic Council of Zhytomyr Ivan Franko State University (Protocol No. 2 dated 12.09.2022).

Data collection, processing, and analysis of the research results were performed on a personal computer using MS Excel, a software package that allows the use of statistical data processing methods. Consent to voluntary participation in the survey was obtained from all the respondents involved in the study. This research followed the regulations of the World Medical Association Declaration of Helsinki – ethical principles for medical research involving human subjects.

RESULTS

The analysis of socio-demographic characteristics of the respondents showed that 176 (82 %) women and 38 (18 %) men of the following age groups took part in the questionnaire survey: 18-29 years old – 17.0 %, 30-39 years old – 19.0 %, 40-49 years old – 28.0 %, 50-59 years old – 15.0 %, 60-69 years old – 18.0 %, over 70 years old – 3.0 %. The distribution of answers to the question "Do you follow a balanced and rational diet?" presented in Fig. 1 shows that only a small proportion of the respondents specifically follow nutrition rules and monitor their diet (18.2 %). The overwhelming majority of the respondents (59.8 %) stated that they do not follow the rules of healthy (rational) eating.

It was found that almost half (47.3 %) of the respondents assessed their health as "satisfactory," 31.0 % as "good," and 6.0 % as "very poor." This percentage may be because the survey was conducted in outpatient clinics, where patients usually seek medical care for existing illnesses. It was found that 56.0 % of the respondents drink alcohol several times a month, 18.0 % – several times a year, and 20.0 % – do not drink at all. It should be noted that according to research by scientists, repeated or frequent alcohol consumption leads to functional disorders, which in turn gradually turn into organic disorders. Serious illnesses such as gastritis, hepatitis, liver cirrhosis, pancreatitis, chronic lung disease, etc. develop.

The analysis of the question about the presence of chronic diseases showed that 26.0 % of the respondents indicated

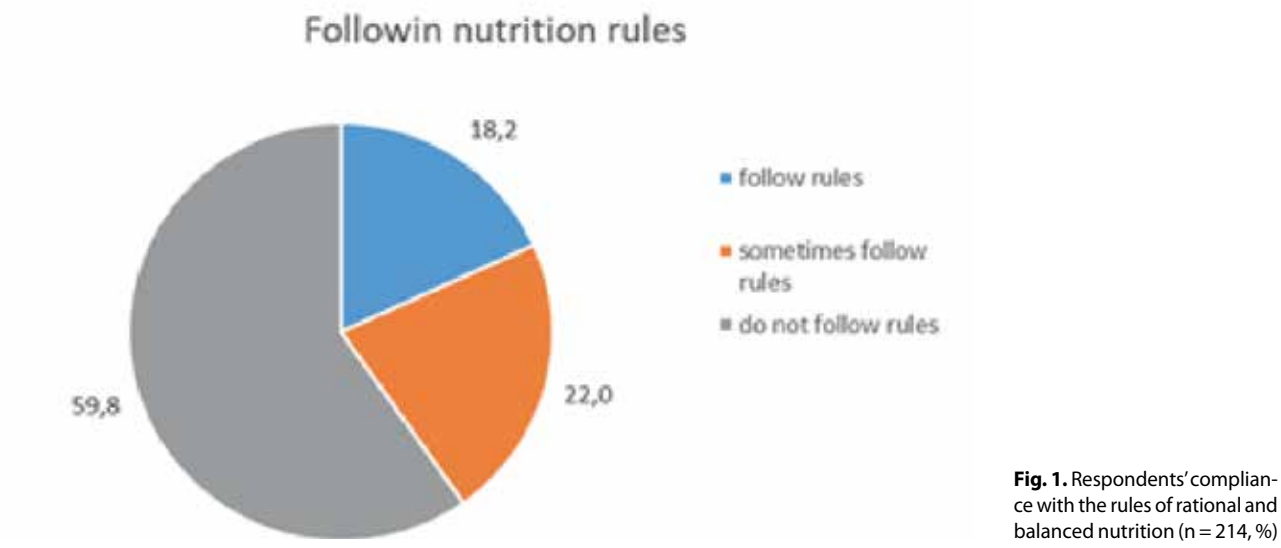

Fig. 1. Respondents' compliance with the rules of rational and balanced nutrition (n = 214, %)

that they had chronic diseases of various kinds. Among these respondents, only 80.0 % are under constant supervision of a family doctor or other specialist. When specifying chronic diseases, it was found that the majority of the respondents have cardiovascular diseases – 20.7 %, diabetes mellitus, and obesity – 12.1 % each, gallbladder and biliary tract diseases – 10,3 %, liver and kidney diseases – 8.6 % and 5.2 %, respectively, urolithiasis – 6.9 %, atherosclerosis, and gout – 5.2 %, and the smallest proportions were gastrointestinal diseases, tuberculosis and lactose deficiency – 3.4 % each.

At the same time, 78.0 % of the respondents consume excessive amounts of sour and pickled food and canned food; 71.5% eat sugar and sweets; 52.8 % eat fatty, smoked, and fried food; 45.3% eat bakery products, and 22.9% eat fast food. The proportion of responses about food abuse in the respondents' diets is presented in Table 1.

The questionnaire survey results also show that almost 100 % of the respondents have health complaints of various kinds. Thus, more than a third of the respondents (38.0 %) say they suffer from frequent headaches, 30.0 % say they are often tired, and 22.0 % have difficulty concentrating. The smallest number of the respondents (10.0 %) report periodic abdominal pain, and when specifying the causes of pain, they mention overeating, irregular eating, or eating out. Answering the question "Do you control your blood glucose level?" more than half (53.3 %) indicated that they "systematically" take blood tests to control their glucose level. More than a third of the respondents (36.0 %) said they check their glucose levels only when directed or recommended by their doctors. Only 20.0 % of the respondents have undergone lipid testing. Among the respondents who had undergone lipid testing, a quarter of them reported elevated blood cholesterol levels (26.0 %), which is the main reason for the risk of developing many cardiovascular diseases that can be life-threatening. Elevated levels of urea and creatinine are an indicator of protein metabolism disorders. The distribution of the respondents' answers to the question "Do you check your urea and creatinine levels?" shows that only 10.0 % of the respondents systematically perform such tests.

Lack of time, long hours at work or school, lack of sleep, excessive workload, financial means, etc., often make it impossible to prepare meals and have regular and balanced meals, which leads to snacks between meals, fast food consumption, or eating out. Our research shows that most of the respondents neglect the rules of eating, most of whom eat only twice a day. The analysis of the respondents' answers reveals that only half of the respondents have breakfast in the morning before going to work or school (53.0 %). Regarding the time of breakfast, the following distribution of answers was obtained. Thus, most respondents – 85.0 %) have breakfast from 6.00 to 9.00, i.e., immediately before going to work or school, and a sixth (14.0 %) have breakfast after 9.00. As a rule, it is a quick snack or breakfast in a public catering establishment. Younger respondents stated that they neglected breakfast due to lack of time and noted that they overwhelmingly preferred coffee or tea to a full meal. A significant number of the respondents reported frequent headaches and rapid fatigue from daily activities. Every person's body consumes a lot of energy that needs replenishment. Each meal should provide a certain amount of nutrients, vitamins, and minerals. Nutritionists believe 35-40 % of the daily diet should be spent on lunch. However, a fifth of the respondents (20.0 %) state that they do not eat lunch due to lack of time and heavy work or study loads. It was found that 41.0 % of the respondents eat food they take from home or prepare themselves for lunch; 26.0 % buy food in stores or at street stalls; 13.0 % have lunch in public catering establishments. Thus, a significant portion of the respondents neglect the rules of rational nutrition and the regularity of meals.

There are frequent discussions about the importance and usefulness of evening meals. Nutritionists have different opinions on this matter, but they unanimously say that the human body not only rests but also recovers at night. Human skin and muscles are restored, and hair and nails grow. Therefore, the main task of dinner is to replenish the human body with amino acids. When asked, "Do you usually eat dinner?" most respondents answered in the affirmative. The majority of the respondents eat dinner

Table 1. Proportion of responses about food abuse in the respondents' diet

Products	Yes		No	
	Number of responses	Proportion	Number of responses	Proportion
Salt	39	18.2%	175	81.8%
Hot sauces and spices	21	9.8%	193	90.2%
Sour foods, pickled foods, canned foods	167	78.0%	47	22.0%
Fatty, smoked, fried foods	113	52.8%	101	47.2%
Sugar and sweets	153	71.5%	61	28.5%
Dairy products	107	50.0%	107	50.0%
Bakery products	97	45.3%	117	54.7%
Fast food	49	22.9%	165	77.1%

from 18.00 to 21.00; 18.0 % do not eat dinner. Almost a tenth of the respondents state that they do not observe the time intervals for eating, and the dinner hours are often late – between 21.00 and 24.00. Most respondents say they usually eat dinner at home – 82.0 %; 11.0 % – dine in public catering establishments; 7.0 % – at work or school. To the question "What do you usually eat between main meals?" the distribution of answers was as follows: baked goods (buns, pies, cookies, muffins, cakes, pancakes) and sweets (candies, chocolate, chocolate bars, waffles) accounted for the largest share – 24.3 % and 17.1 % respectively; tea or coffee – 16.4 %, sandwiches with cheese or sausage – 16.4 %; seasonal fruits (apple, pear, strawberry, cherry, orange, banana) – 13.8 %; fruit juices or compote showed a small share – 5.9 %; potato chips, crackers, dry noodles – 3.3 %; energy drinks – 2.6 %; sweet carbonated drinks – 1.3 %. At the same time, 76.0 % of the respondents state that they have skipped meals due to lack of time. The results of the analysis of answers to the question "Please indicate how often you eat different foods" are presented in Table 2.

The analysis of the answers presented in Table 2 shows that the respondents' diets are rather unbalanced. Thus, only a quarter of the respondents (26.6 %) eat fish and seafood 2-3 times a month; 43.5 % eat vegetables and fruits 2-3 times a week; 21.5 % eat sweets (candy, chocolate) daily; chips, snacks, and sweet carbonated drinks – 8.4 %.

To the question, "How often do you undergo preventive examinations?" 71.0 % of the respondents answered "I don't," indicating that doctor visits are chaotic. 18.0 % of the respondents had undergone preventive examinations at school. The smallest number of the respondents (11.0 %) undergo preventive examinations once a year.

The distribution of answers to the question "Please indicate if you have the following health problems?" is presented in Table 3

As can be seen from Table 3, the following health problems were reported by the respondents: "frequent headaches" – 88.3 %, "severe hair loss" – 83.2 %, "poor sleeping" – 79.9 %, "brittle nails and hair" – 71.0 %, "joint pain" – 69.6 %, "heart pain" – 53.3 %, "tachycardia" – 54.7 %. The survey also showed that the respondents have insufficient knowledge and information about the impact of nutrition on improving people's health. One-third of the respondents (32.0 %) mistakenly believe that diets harm health rather than improve it. At the same time, 93.0 % of the respondents would like to receive information about rational nutrition.

DISCUSSION

Preserving and promoting public health has always been one of the most important issues in society [6]. In modern Ukraine, there is a steady deterioration in the population's health, which has generally reached the threat level. This situation is due to a decline in the population's quality of life in general and unhealthy eating behavior in particular. Therefore, the issue of preserving public health has recently become a priority area of research in the public health system.

According to WHO experts [7], the importance of lifestyle as a factor in promoting health is up to 60 %, followed by genetic predisposition (up to 20 %), ecology (up to 20 %), and the effectiveness of the health care system in the country (up to 10 %). Among a person's lifestyle components, nutrition is perhaps the most important. Physiologists argue that nutrition replenishes the human body with nutrients and energy, which enables it to function normally and maintain a sufficient level of health [8]. According to scientists [9], a healthy diet should meet the body's needs for nutrients and energy and prevent various non-communicable diseases.

A balanced diet is a way of eating that contains an optimal ratio of food quantity and quality and biologically active compounds. Particular importance is attached to the balance of essential substances that cannot be synthesized in the body on their own and/or are synthesized in minimal amounts, not fast enough. The main crucial components of food include vitamins, unsaturated fatty acids, and micro- and macro-elements [10].

The analysis of nutritional adequacy is characterized by the ratio of the amount of food substances absorbed by the body to their total amount. The adequacy of nutrition depends on the quality of the food and the state of human health necessary for food absorption. Animal products are

Table 2. Proportion of answers about the frequency of consumption of different products

Products	Every day		Once a week		2-3 times a week		2-3 times a month		Once a month		Other	
Vegetables and fruits	53	24.8%	32	15.0%	93	43.5%	29	13.6%	7	3.3%	-	-
Sea fish and seafood	12	5.6%	39	18.2%	24	11.2%	57	26.6%	79	36.9%	3	1.4%
Meat and meat products	74	34.6%	32	15.0%	28	13.1%	19	8.9%	47	22.0%	14	6.5%
Dairy products	36	16.8%	32	15.0%	56	26.2%	19	8.9%	53	24.8%	18	8.4%
Ketchup, sauces	31	14.5%	32	15.0%	72	33.6%	42	19.6%	37	17.3%	-	-
Sweets	46	21.5%	32	15.0%	88	41.1%	19	8.9%	29	13.6%	-	-
Chips, snacks, sweet drinks	18	8.4%	32	15.0%	42	19.6%	51	23.8%	50	23.4%	21	9.8%

Table 3. The ratio of respondents' answers regarding the presence or absence of health problems

Health problems	Yes		No	
Quick tiredness from physical activity	78	36.4%	136	63.6%
Shortness of breath	34	15.9%	180	84.1%
Brittle nails and hair	152	71.0%	62	29.0%
Severe hair loss	178	83.2%	36	16.8%
Lips often crack	98	45.8%	116	54.2%
Poor sleeping	171	79.9%	43	20.1%
Frequent headaches	189	88.3%	25	11.7%
Bruises often appear, and wounds take a long time to heal	23	10.7%	191	89.3%
Constant stomach pain	29	13.6%	185	86.4%
Constant pain in the right side under the rib	42	19.6%	172	80.4%
Frequent nighttime toileting	36	16.8%	178	83.2%
Joint pain	149	69.6%	65	30.4%
Heart pain	114	53.3%	100	46.7%
Tachycardia	117	54.7%	97	45.3%
Dry mouth	52	24.3%	162	75.7%
Persistent coughing	41	19.2%	173	80.8%
Bloating after eating dairy foods	62	29.0%	152	71.0%

best absorbed (95 %), while vegetable products are absorbed worse (80 %). Mixed food is absorbed by 82-90 % [11]. Various factors, such as proper cooking and temperature, influence the digestibility of food. The optimal temperature for food digestibility is 50°C for the first and second courses.

Another essential factor in digestibility is the culture of food consumption. When eating, you should not do other things; eat food on the go and chew it well. Creating a pleasant atmosphere in eating places and eating habits are also important factors. It is recommended that meals be taken simultaneously, which contributes to the systemic functioning of the digestive glands and, as a result, better absorption of food. Correct observance of the quantity and quality of food consumed prevents overloading of the digestive system and contributes to overall health [12]. An eating regimen is the consumption of food at a set time and the optimal distribution of meals throughout the day. It depends on the nature of work, production and living conditions, individual habits, age, local traditions, etc. The most traditional and widespread diet is the one that divides the daily ration into three meals according to the energy value of the food. Breakfast accounts for 30 % of energy expenditure, lunch 45 %, and dinner 25 % [13]. Recently, nutritionists have been advising to eat four meals a day. With four meals a day, the daytime area is redistributed as follows: the first breakfast accounts for 15 % of the daily energy intake, the second breakfast – 25 %, lunch accounts for 35 %, and dinner accounts for 25 %. For rational and balanced nutrition, the time intervals between meals should not exceed 6 hours.

According to experts [14], the basic principles of a healthy diet include daily consumption of a variety of vegetables and fruits; consumption of whole grain products; reduced consumption of red meat; increased consumption of lean proteins of plant origin, as well as fish and poultry; limited consumption of sweetened beverages and foods with added sugar. These nutritional models contain general recommendations that can improve health. Still, each person's choice of a specific model should be individual, considering age, working conditions, climatic and geographical features, traditions, etc. [15].

As doctors and nutritionists explain, healthy eating is based on three basic principles: variety, balance, and moderation. These principles should be followed in your diet at all times. The principle of variety – the food we eat should be varied. Consuming the same food leads to addiction, and food begins to seem tasteless. This limits the body's ability to receive the full range of nutrients and vitamins from eating various foods. Addiction leads to the fact that the body is not fully satiated, and therefore, food consumption increases, causing weight gain. That's why you should combine different foods in your diet. The principle of balance – at each main meal, the body should receive a rational proportion of proteins, fats, carbohydrates, water, fiber, vitamins, and minerals. The principle of moderation is that the amount of food we consume should fully cover our energy expenditure but not exceed it [16].

Summarizing the results of the research on the essence of rational nutrition and its impact on public health promotion, we propose the following areas of outreach and awareness-raising activities for public health professionals:

1. To use the Internet platform of the Public Health Center of Ukraine and regional centers for disease control and prevention of the Ministry of Health of the country to post educational materials on dietary nutrition for different groups by age, existing diseases, degree of energy expenditure, children and pregnant women.
2. To conduct outreach activities of specialists of the regional Centers for Disease Control and Prevention of the Ministry of Health of Ukraine in territorial communities (educational institutions, enterprises, etc.) to promote healthy eating, including dietary nutrition, to prevent chronic non-communicable diseases.
3. To disseminate and systematically update information about dietary menus to prevent and treat various diseases in popular social networks (YouTube, WhatsApp, Facebook, TikTok, etc.).
4. To create and distribute short videos about healthy eating in the media aimed at children and youth, using animation, modern music, etc., promoting various foods, daily consumption of vegetables, fruits, and dairy products, and limiting fat, salt, and sugar.

Thus, proper nutrition is a simple and sure way to stay healthy. One of the causes of many diseases is the consumption of unhealthy food and an improper drinking regimen. A balanced diet is an essential component of a healthy life. It helps maintain normal health, control weight, and reduce the risk of developing various pathologies. Unhealthy diets can lead to chronic diseases that can have serious consequences.

CONCLUSIONS

It has been found that healthy nutrition is the most important factor in the body's vital activity, which ensures human health and working capacity, the ability to withstand adverse environmental influences, and determines the quality and duration of life. It has been established that today, there is no single model of nutrition and no strict, legally enshrined rules for preparing a food ration. The basic principles of healthy eating are variety, balance, and moderation.

The survey found that less than a third of the population (31.0 %) is in good health; 26.0 % report chronic diseases of the cardiovascular, excretory, hepatobiliary, and endocrine systems; 12.1 % of the respondents each have diabetes and obesity. Despite this, only 18.0 % of the respondents adhere to healthy eating habits; more than half of them abuse "junk" food (smoked, fried, pickled, salty, sweet, etc.), violate dietary regimens, eat excessive amounts of food, and eat for the night.

Only 11.0 % of the respondents regularly monitor their health during systematic preventive examinations; 37.0 % limit their food intake to reduce body weight; and 53.3 % constantly monitor their blood glucose levels. It has also been found that 79.0 % of the respondents do not have sufficient information about healthy eating and identify it with weight loss diets; 32.0 % of the respondents believe that diets are harmful to health; only 3.0 % of the respondents know about the essence of diets and their purpose; 93.0 % of the respondents expressed a desire to improve their knowledge of the basics of healthy eating. Given the low public awareness of dietary nutrition as a factor in promoting health and preventing chronic non-communicable diseases, a set of preventive measures to promote public health and organize outreach and awareness-raising activities of public health professionals in this area has been justified.

PROSPECTS FOR FURTHER RESEARCH

A study of the impact of dietary nutrition on the dynamics of somatic health indicators in patients with various diseases is planned.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Grygoriy P. Griban
Zhytomyr Ivan Franko State University
40 Velyka Berdychivska St., 10008 Zhytomyr, Ukraine
e-mail: gribang@ukr.net

ORCID AND CONTRIBUTIONSHIP

Grygoriy P. Griban: 0000-0002-9049-1485 A
Olha S. Zablotska: 0000-0002-0850-5754 B
Olena O. Mitova: 0009-0003-2306-5464 D
Soslan G. Adyrkhaiev: 0000-0001-7083-8499 E
Ludmyla V. Adyrkhaieva: 0000-0002-1102-170X E
Yuliia V. Paryshkura: 0000-0002-8777-1726 D
Alimia M. Osmanova: 0000-0002-7180-8176 F

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

RECEIVED: 16.09.2024
ACCEPTED: 18.03.2025

CREATIVE COMMONS 4.0

ORIGINAL ARTICLE

Morphological features of the great saphenous vein in patients with chronic venous disease of the lower extremities undergoing the most common endovenous treatment techniques

Olena O. Dyadyk[1], Valentyn A. Khodos[1], Hlib O. Melnychuk[1], Mykhailo S. Myroshnychenko[2], Kateryna I. Popova[3]

[1]SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE
[2]KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE
[3]KHARKIV CLINICAL HOSPITAL ON RAILWAY TRANSPORT No. 1 «HEALTH CARE CENTER» OF JOINT-STOCK COMPANY «UKRAINIAN RAILWAYS», KHARKIV, UKRAINE

ABSTRACT

Aim: The purpose was to identify the morphological features of the great saphenous vein in patients with chronic venous disease of the lower extremities undergoing treatment with endovenous high-frequency electric welding in automatic mode, endovenous laser ablation, and ultrasound-guided microfoam sclerotherapy.

Materials and Methods: The material for the comprehensive morphological study consisted of fragments of the great saphenous vein obtained from 32 patients with chronic venous disease of the lower extremities. The material was divided into three groups according to the endovenous treatment techniques applied. Group 1 included vein fragments from 12 patients who underwent endovenous high-frequency electric welding in automatic mode. Group 2 comprised material from 9 patients treated with endovenous laser ablation. Group 3 included material from 11 patients who underwent ultrasound-guided microfoam sclerotherapy using a 3% polidocanol solution. Histological and immunohistochemical research methods were used.

Results: The great saphenous vein in patients with chronic venous disease of the lower extremities undergoing treatment with endovenous high-frequency electric welding in automatic mode and endovenous laser ablation was characterized by similarly pronounced diffuse alterative and desquamative changes in endothelial cells, disruption of the structural organization of the venous wall layers accompanied by edema, and alterative changes in both muscular and connective tissue fibers. In cases where ultrasound-guided microfoam sclerotherapy was applied, the great saphenous vein showed focal alterative and desquamative changes in endothelial cells, preservation of the layered structure, edematous changes in the media and adventitia, focal areas of dysmucoidosis, and regions of angiomatosis.

Conclusions: The severity of structural changes in the great saphenous vein in patients with chronic venous disease of the lower extremities following ultrasound-guided microfoam sclerotherapy was significantly lower compared to endovenous high-frequency electric welding in automatic mode and endovenous laser ablation, resulting in less favorable conditions for the qualitative development of the fibrous process.

KEY WORDS: morphology, great saphenous vein, chronic venous disease of the lower extremities, endovenous high-frequency electric welding in automatic mode, endovenous laser ablation, ultrasound-guided microfoam sclerotherapy

Pol Merkur Lek,2025;53(4):509-514 doi: 10.36740/Merkur202504111

INTRODUCTION

Chronic venous disease of the lower extremities is a common condition, with an estimated global prevalence ranging from 62.5% to 83.6% [1]. It is a polyetiological disease involving genetic, proteomic, and cellular mechanisms that lead to alterations in the morphofunctional state of the venous wall [2]. From a mechanical standpoint, chronic venous disease may be associated with venous outflow obstruction, reflux, or a combination of both [3].

Chronic venous disease presents with a broad clinical spectrum, ranging from heaviness, pain, nocturnal cramps, itching, telangiectasias, varicosities, and edema to skin hyperpigmentation, lipodermatosclerosis, and venous ulceration. This condition may significantly impair a patient's ability to engage in occupational and social activities, thereby reducing quality of life and contributing to economic decline [4, 5].

The 21st century has witnessed revolutionary advances in the treatment of patients with chronic venous disease of the lower extremities, owing to the expansion of therapeutic interventions [6]. One of the novel approaches to eliminating vertical reflux in the great and small saphenous veins in the treatment of chronic venous disease of the lower extremities is endovenous laser ablation [7, 8]. The outcome of treatment is influenced by the choice of laser wavelength, the type of optical fiber, and the amount of energy to be delivered, which must be carefully determined [7]. According to various authors, when the above-mentioned parameters are optimally

aligned, stable vein occlusion can be achieved in 94.3% to 99.2% of cases during a follow-up period of 12 months or more [8, 9]. Among the complications of endovenous laser ablation, researchers report pain along the treated vein (21.1%), hyperpigmentation (9.8%), thrombophlebitis (5%), and paresthesia (2.5-7.3%) [7, 9].

Another endovenous technique is ultrasound-guided microfoam sclerotherapy [10, 11]. According to various authors, the reported success rates following the use of this treatment method range from 63.6% to 95% during a follow-up period of 12 months or longer [10-12].

In recent years, a novel method known as high-frequency electric welding has been introduced as an endovenous technique that involves targeted thermal fusion of the venous wall using high-frequency current and includes automatic adjustment of energy parameters to ensure effective and safe vein closure [13-16].

Our review of the available literature has revealed the presence of numerous unresolved issues related to the use of the aforementioned endovenous techniques, as well as the lack of morphological justification for their clinical effectiveness. This fact underscores the relevance of conducting the present study.

AIM

The purpose was to identify the morphological features of the great saphenous vein in patients with chronic venous disease of the lower extremities undergoing treatment with endovenous high-frequency electric welding in automatic mode, endovenous laser ablation, and ultrasound-guided microfoam sclerotherapy.

MATERIALS AND METHODS

The material for the comprehensive morphological study consisted of fragments of the great saphenous vein obtained from 32 patients with chronic venous disease of the lower extremities. The material was divided into three groups according to the endovenous treatment techniques applied. Group 1 included vein fragments from 12 patients who underwent endovenous high-frequency electric welding in automatic mode. Group 2 comprised material from 9 patients treated with endovenous laser ablation. Group 3 included material from 11 patients who underwent ultrasound-guided microfoam sclerotherapy using a 3% polidocanol solution.

The surgical specimens were fixed in 10% neutral buffered formalin (pH 7.4) for 24-36 hours. After fixation, tissue processing was performed using the Excelsior AS apparatus (Thermo Fisher Scientific, UK). Embedding in paraffin blocks was done on a HistoStar apparatus (Thermo Fisher Scientific, United Kingdom). Serial sections 2-3 μm thick were prepared from paraffin blocks using the HM 325 rotary microtome (Thermo Shandon, UK). Histological slides were stained with hematoxylin and eosin, picrofuchsin according to van Gieson.

During immunohistochemical analysis, tissue sections were mounted on Super Frost Plus adhesive slides (Menzel, Germany). Heat-induced epitope retrieval was performed using citrate buffer (pH 6) and EDTA buffer (pH 8). Detection was carried out with the Vitro Master Polymer Plus Detection System (Peroxidase) including the DAB Quanto chromogen (Master Diagnostica, Spain). Mouse monoclonal antibodies against CD34 (clone QB-End/10) and alpha-smooth muscle actin (α-SMA) (clone 1A4 (asm-1), as well as rabbit monoclonal antibody against vimentin Ab-2 (clone SP20), were used.

Immunohistochemical reactions using monoclonal antibodies against CD34, α-SMA, and vimentin were evaluated based on the intensity and extent of marker expression. The intensity of expression was assessed using a semi-quantitative scoring system, where 0 indicated no staining, 1 indicated weak («+») staining intensity, 2 indicated moderate («++») intensity, and 3 indicated strong («+++») intensity. The prevalence of expression was analyzed by calculating the ratio of the area of positively stained cells/tissues to the total tissue area within the visual field (in 5 fields of view at ×200 magnification in each case) with subsequent conversion into the scores (0 – no staining, 1 – staining covering less than one-third of the tissue section, 2 – staining covering one-third to two-thirds of the section, 3 – staining covering more than two-thirds of the section).

Microscopic examination and photo archiving were performed using ZEISS light-optical microscope (Germany) equipped with the AxioImager.A2 data processing system at objective magnifications of 5×, 10×, 20×, and 40×, with a 1.5× binocular tube and 10× eyepieces, and an ERc 5s camera. Additionally, a ZEISS Primo Star microscope (Germany) equipped with an Axiocam 105 color camera was used.

RESULTS

In Group 1, the endothelium, media, and adventitia of the venous wall exhibited edema, dysmucoidosis, disrupted architectonics, and alterative changes. These changes were manifested by homogenization of collagen fibers and smooth muscle structures (Fig. 1). At the same time, preservation of perivascular structures and marked hyperemia of small-caliber vessels were observed.

In all cases, immunohistochemical staining with monoclonal antibody against CD34 revealed pronounced endothelial damage, with a complete absence of expression in endothelial cells («–», score 0). In some vessels, positive CD34 expression was observed in the perivascular structures, indicating that the automatically regulated energy parameters acted selectively within the boundaries of the venous wall tissue (Fig. 2).

Immunohistochemical reaction with monoclonal antibody against α-SMA revealed uneven expression in smooth muscle structures of the media and in some adventitial cells. Positive expression was observed only in 2 cases (16.7%) and corresponded to «++» (score 2) (Fig. 3). Morphologically, the smooth muscle cells were predominantly elongated in shape and arranged parallel to the orientation of the venous wall layers.

In immunohistochemical reaction with monoclonal antibody against vimentin, only one case (8.3%) showed moderately pronounced positive staining («+», score 1)

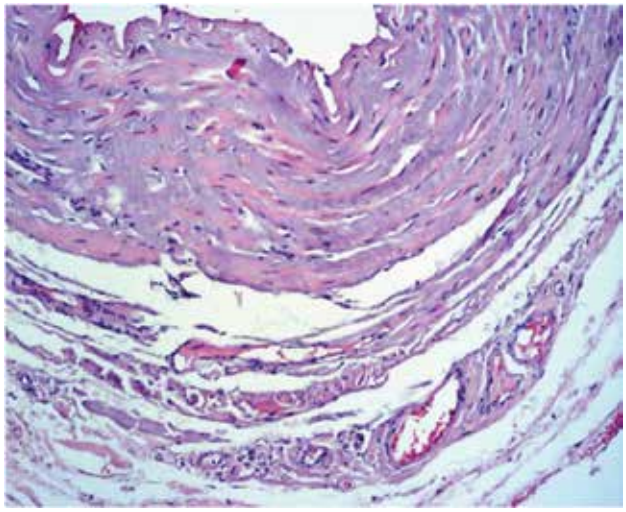

Fig. 1. Group 1. Uneven disruption of the architectonics in all layers of the venous wall, edema, dysmucoidosis, endothelial damage, and homogenization of collagen fibers in the intimal and medial layers. Hematoxylin and eosin staining, ×100.

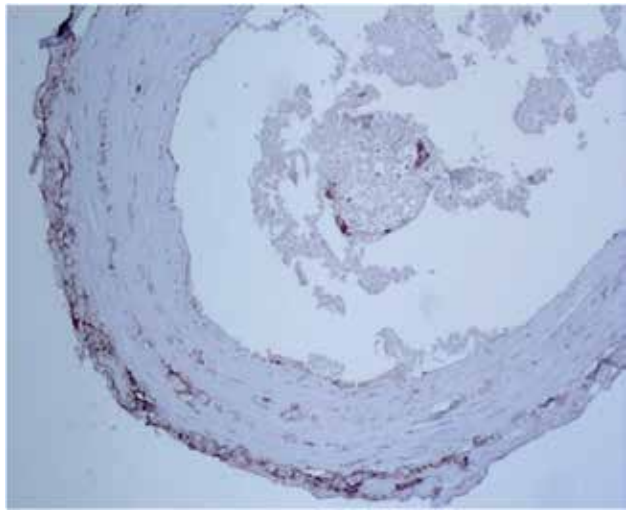

Fig. 2. Group 1. Absence of CD34 expression in the endothelium of the venous wall; positive expression in vessels of the perivascular structures. Immunohistochemical reaction with monoclonal antibody against CD34, ×50.

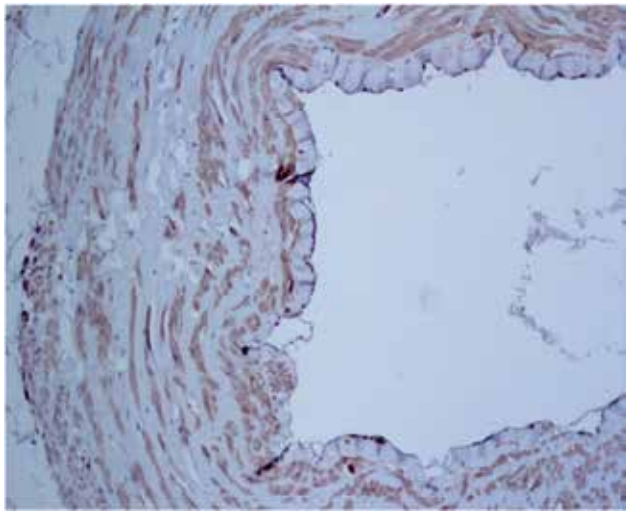

Fig. 3. Group 1. Positive α-SMA expression in some smooth muscle cells of the medial layer and in a portion of adventitial cells in the vessel wall, in perivascular structures. Immunohistochemical reaction with monoclonal antibody against α-SMA, ×100.

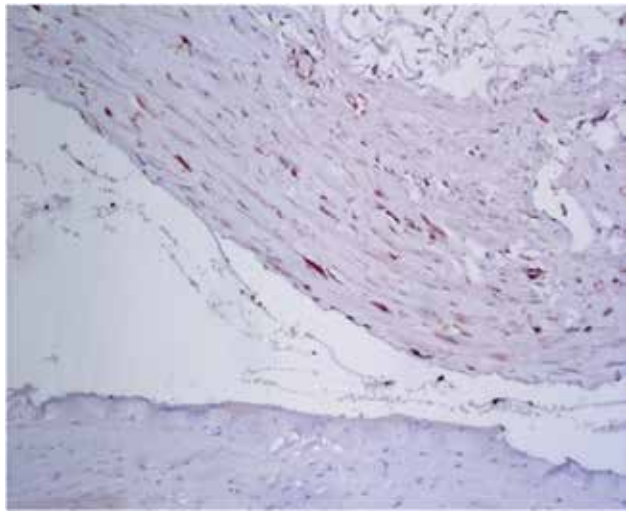

Fig. 4. Group 1. Positive moderately pronounced expression of vimentin by fibroblastic cells in all layers of the vein wall. Immunohistochemical reaction with monoclonal antibody against vimentin, ×100.

of the indicated antibody by fibroblastic cells in the vein wall (Fig. 4).

In Group 2, edema, disruption of the wall architectonics, alterative changes, homogenization of all layers, dysmucoidosis, endothelial damage, and fibrous tissue proliferation were observed in the areas affected by laser ablation (Fig. 5).

Immunohistochemical reaction with monoclonal antibody against CD34 showed a complete absence of expression («–», score 0) in all cases. Immunohistochemical reaction with monoclonal antibody against α-SMA revealed moderate expression («++», score 2) in 2 cases (22.2%). Vimentin expression was detected as weak («+», score 1) in 3 cases (33.3%). Additionally, we observed that during immunohistochemical reaction with monoclonal antibody against α-SMA, smooth muscle cells appeared fragmented, mostly lacked an elongated shape, and were often arranged perpendicularly to the orientation of the venous wall layers (Fig. 6).

In group 3, in all studied cases, the vein wall retained its layering. The changes were registered mainly in the endothelium. The latter were manifested by focal dystrophic-necrotic and desquamative changes. In the media and adventitia, edema, focal areas of dysmucoidosis, intact

smooth muscle cells and collagen fibers, as well as regions of angiomatosis, were identified (Fig. 7). Fragments of thrombotic masses were observed in the vein lumen.

Immunohistochemical reaction with monoclonal antibody against CD34 revealed positive, uneven expression of this marker by vascular endothelial cells in 4 cases (36.4%), with an intensity score of «+» (score 1) (Fig. 8).

Immunohistochemical reaction with monoclonal antibody against α-SMA revealed moderately positive expression («++», score 2) of this marker by smooth muscle cells in 6 cases (54.5%). The expression pattern of α-SMA indicated damage to a portion of smooth muscle cells, manifested as their homogenization, predominantly in the medial layer of the venous wall. Immunohistochemical reaction with monoclonal antibody against vimentin showed in 6 cases (54.5%) weakly positive expression («+», score 1) of this marker by single cells of the fibroblastic series.

DISCUSSION

The authors conducted a comprehensive morphological study of great saphenous vein fragments obtained from patients with chronic venous disease of the lower extremities who underwent treatment with the most commonly used endovenous techniques, including high-frequency electric welding in automatic mode, endovenous laser ablation, and ultrasound-guided microfoam sclerotherapy.

During microscope slides examination in cases treated with endovenous high-frequency electric welding in automatic

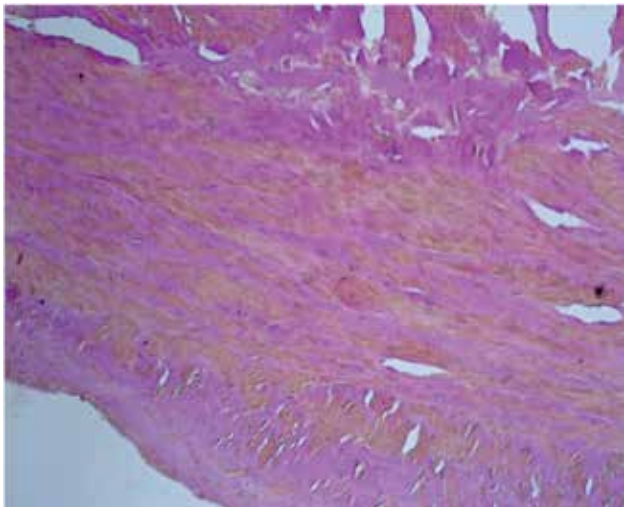

Fig. 5. Group 2. Destruction of layers structures, complete homogenization. Staining with picrofuchsin according to van Gieson, ×100.

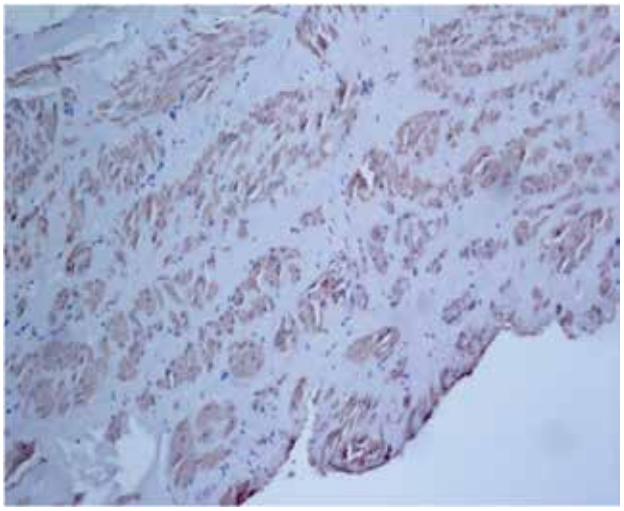

Fig. 6. Group 2. Moderately positive expression of α-SMA by some fragmented smooth muscle cells. Immunohistochemical reaction with monoclonal antibody against α-SMA, ×100.

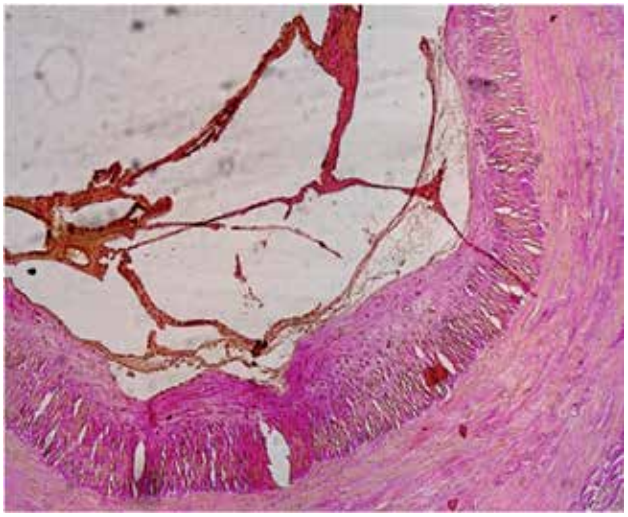

Fig. 7. Group 3. Preserved layered structure of the venous wall, partially intact endothelium, and thrombus fragments in the vessel lumen. Hematoxylin and eosin staining, ×50.

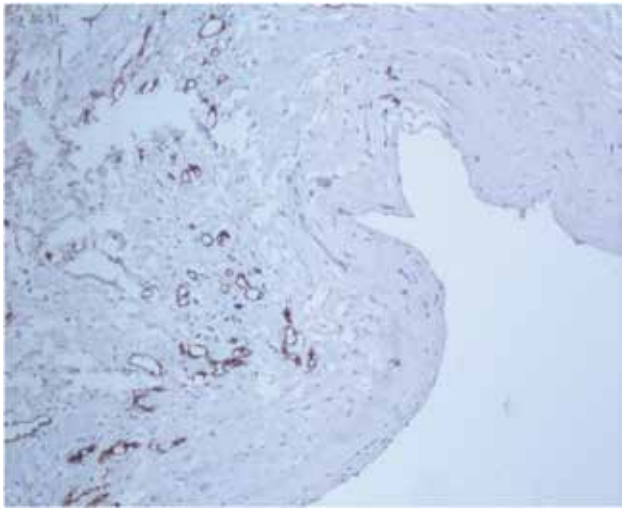

Fig. 8. Group 3. Positive CD34 expression in venous endothelial cells and in vessels of the perivascular structures. Immunohistochemical reaction with monoclonal antibody against CD34, ×50.

mode and endovenous laser ablation, the authors identified similarly pronounced and uniform structural changes across all layers of the venous wall. The endothelial layer was characterized predominantly by diffuse dystrophic and necrotic changes. Damaged endothelial cells were detached from the basement membrane and displaced into the vascular lumen. The dystrophic-necrotic and desquamative changes in endothelial cells resulted in a negative immunohistochemical reaction with monoclonal antibody against CD34 in all cases. The observed morphological disruption of endothelial integrity, as noted by the authors, indicates the presence of endothelial dysfunction. According to numerous studies, endothelial dysfunction is considered a key factor in the pathogenesis and progression of chronic venous disease of the lower extremities [17].

In cases where endovenous high-frequency electric welding in automatic mode and endovenous laser ablation were applied, the authors observed equally pronounced violations of the architectonics of the layers, edematous changes, and alterative changes in muscle and connective tissue fibers. These alterations, as revealed by immunohistochemical analysis, were manifested by decreased expression of vimentin and α-SMA. The identified changes in the wall of the great saphenous vein will subsequently lead to fibrous transformation of the vein.

The morphological changes in the venous wall observed by the authors in this study following the use of endovenous high-frequency electric welding in automatic mode were consistent with previously reported findings in the literature [1-3].

In patients with chronic venous disease of the lower extremities who underwent ultrasound-guided microfoam sclerotherapy, focal alterative and desquamative changes in endothelial cells of the great saphenous vein were observed, accompanied by reduced CD34 expression by these cells. In the media and adventitia, the layered structure was preserved with edema, focal areas of dysmucoidosis, regions of angiomatosis, and decreased expression of vimentin and α-SMA.

A subsequent comparative analysis conducted by the authors demonstrated that the severity of structural changes in the venous wall layers following ultrasound-guided microfoam sclerotherapy was significantly lower compared to endovenous high-frequency electric welding in automatic mode and endovenous laser ablation, which to a lesser extent provides conditions for the qualitative development of the fibrotic process. This difference indicates the effectiveness of the effects of endovenous high-frequency electric welding in automatic mode and endovenous laser ablation.

CONCLUSIONS

The great saphenous vein in patients with chronic venous disease of the lower extremities undergoing treatment with endovenous high-frequency electric welding in automatic mode and endovenous laser ablation was characterized by similarly pronounced diffuse alterative and desquamative changes in endothelial cells, disruption of the structural organization of the venous wall layers accompanied by edema, and alterative changes in both muscular and connective tissue fibers. In cases where ultrasound-guided microfoam sclerotherapy was applied, the great saphenous vein showed focal alterative and desquamative changes in endothelial cells, preservation of the layered structure, edematous changes in the media and adventitia, focal areas of dysmucoidosis, and regions of angiomatosis. The severity of structural changes in the venous wall following ultrasound-guided microfoam sclerotherapy was significantly lower compared to endovenous high-frequency electric welding in automatic mode and endovenous laser ablation, resulting in less favorable conditions for the qualitative development of the fibrous process.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Mykhailo S. Myroshnychenko
Department of General and Clinical Pathological Physiology
named after D.O. Alpern, Kharkiv National Medical University,
4 Nauky Avenue, Kharkiv, 61022, Ukraine
e-mail: msmyroshnychenko@ukr.net

ORCID AND CONTRIBUTIONSHIP

Olena O. Dyadyk: 0000-0002-9912-4286 E
Valentyn A. Khodos: 0000-0003-0150-3868 A
Hlib O. Melnychuk: 0009-0006-6498-7758 C D
Mykhailo S. Myroshnychenko: 0000-0002-6920-8374 F
Kateryna I. Popova: 0009-0007-2049-9151 B

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

RECEIVED: 10.01.2025
ACCEPTED: 22.06.2025

CREATIVE COMMONS 4.0

REVIEW ARTICLE

Pedeutology of the profession of an academic teacher in the field of medical studies

Tadeusz Pietras[1,2], Karol Batko[3], Aleksander Stefanik[3], Kasper Sipowicz[2], Anna Mosiołek[4], Ignacy Stefańczyk[5], Magdalena Dutch-Wicherek[2]

[1]DEPARTMENT OF CLINICAL PHARMACOLOGY, DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY, MEDICAL UNIVERSITY OF LODZ, LODZ, POLAND
[2]NATIONAL INSTITUTE OF GERIATRICS, RHEUMATOLOGY AND REHABILITATION, WARSAW, POLAND
[3]STUDENT SCIENTIFIC CLUB AT THE DEPARTMENT OF CLINICAL PHARMACOLOGY, DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY, MEDICAL UNIVERSITY OF LODZ, LODZ, POLAND
[4]DEPARTMENT OF INTERDISCIPLINARY DISABILITY STUDIES, THE MARIA GRZEGORZEWSKA UNIVERSITY IN WARSAW, WARSAW, POLAND
[5]BABINSKI PSYCHIATRIC HOSPITAL, LODZ, POLAND

ABSTRACT

The aim of the paper is to reflect on the importance of the teacher of the medical profession in graduate and postgraduate education. The objective of the analysis was a narrative reflection on the profession of a teacher of medical professionals based on the principles of medical education and specialization programs applicable in Poland. The core curriculum for teaching in the field of medicine was analysed in detail, including also the insufficiently developed principles of selection and education of academic and vocational teachers. It has been demonstrated that there is no uniform concept of teaching competences for teachers of the medical profession in Poland. Academic teachers are usually recruited by medical universities based on their education and declaration of scientific work. Much less attention is paid to the development of their teaching competences. The current medical study programs are increasingly focused on practical skills. However, the limitation of theoretical subjects sometimes fails to provide sufficient knowledge to ensure the proper and in-depth education of medical students. Teaching future doctors requires reasonable care and reflection on the structure of the curricula, specialization programs, as well as on appropriate preparation of the teachers.

KEY WORDS: intellectual disability; learning of psychiatry; medical student

Pol Merkur Lek,2025;53(4):515-521 doi: 10.36740/Merkur202504112

INTRODUCTION

The education of a future doctor requires many years of work within the framework of graduate studies in the field of medicine, during internship and in the course of specialization. The prerequisite for the education of medical personnel is to have an appropriate staff of teachers teaching the medical profession. In the medical education of doctors, considerable attention is paid to the very process of teaching and upbringing, the study programs, teaching methods, and the application of modern techniques supporting the teaching process. Much less attention is paid to the education of teachers - the mentors of these doctors, as well as to the social, psychological and pedagogical context of practicing the profession of a medical teacher educating medical students and doctors. In the profession of a doctor, education takes much longer than in other professions, so the training of the teaching staff requires strategic thinking in terms of a long-time horizon and taking into account modern knowledge in the field of didactics at the academic level.

Pedeutology is a subdiscipline of pedagogy dealing with the profession of a teacher and educator [1, 2]. This term is not used in English-language literature. It is replaced by the concept of the science of teacher education [3].

Teacher's deontology, which means a pedagogical subdiscipline dealing with the duties of a teacher, and teacher axiology, which is defined as the science of teacher values (e.g. concerning the ethics of the teaching profession) are closely related to pedeutology. Teacher deontology and axiology are subdisciplines of broadly understood pedeutology [1-3].

Many papers and books on the profession of primary and secondary education teachers have been written in Polish literature. However, there is a lack of scientific reflection on the professional work of academic teachers, including those who are physicians – medical practitioners teaching both

students of medical faculties as part of graduate training and young doctors in the postgraduate and specialization programs. What is the identity of this professional group practicing the professions of a doctor, teacher and educator, and often also a research worker? Are these people prepared to perform all three professional roles at the same time? Are these roles complementary to one another and mutually reinforcing, or, on the contrary, does the contradiction of these roles result in a worse quality of work? What is the professional identity of doctors – academic teachers, do they feel like doctors or like educators in their own self, or is there some kind of internal balance integrating both these social roles? There is also the identity of a scientist, a researcher, a scholar in some of these doctors-teachers. Can these different social roles be reconciled, do they reinforce one another, or is each of them an obstacle to the reliable performance of the other ones? How to teach doctors how they should teach medicine correctly, how to develop the soft skills useful in the profession of a teacher of the medical profession?

AIM

The aim of the paper is to reflect on the profession of an academic teacher who is a practicing physician, teaches medical students and is a researcher. This reflection is extremely necessary at present, because young doctors are not interested in an academic career, the medical school staff is aging, and new medical schools not fully prepared to teach and educate future doctors are being established.

MATERIAL AND METHODS

We attempt to present the problem in the axiological and cognitive aspects, trying not to refer to legislative solutions, which often change in Poland with the change of the government team. In this paper, we have focused on the principles rather than specific solutions, although this chapter is somewhat simplified. The article was written by two medical educators participating in the process of creating study programs (Anna Mosiołek, Tadeusz Pietras), an experienced non-medical educator (Kasper Sipowicz), a representative of a scientific and research institute (Magdalena Dutch-Wicherek) and students of the medical faculty (Karol Batko, Aleksander Stefanik), as well as a resident (Ignacy Stefańczyk). In the publication, we have limited ourselves only to the issues of educating doctors teaching medicine. The problem of educating teachers for the faculties of medicine and dentistry, nursing, veterinary medicine, physiotherapy, emergency medical services, pharmacy and laboratory diagnostics was not raised, as we are not representatives of these professions. Some aspects of higher education discussed in this article are universal and apply to all medical faculties. However, there are also significant curriculum differences between these faculties, and individual medical professions require slightly different knowledge, skills and social competences than those necessary in the doctor's profession.

REVIEW AND DISCUSSION

STRUCTURE OF MEDICAL STUDIES IN POLAND

Medical studies in Poland last six years [4]. The curriculum is implemented over five years, the teaching of the sixth year is practical in character, preparing students for postgraduate internships. The first two years are the so-called preclinical part, where subjects that discuss the structure and function of a healthy human body are taught, as well as the biopsychosocial aspects of human functioning in the social and ecological environment. The program includes subjects such as biophysics, biochemistry, histology, anatomy, physiology, biology, microbiology, immunology, psychology [4]. In the third year of studies, subjects that discuss the biological and psychosocial aspects of diseases are taught: pathology (which includes pathophysiology, pathomorphology, laboratory diagnostics) and pharmacology. Teaching clinical medicine at the bedside and in medical simulation centers also begins in the third year. Such training lasts until the end of the sixth year and in the practical activity of a young doctor, as well as during the postgraduate internship, ending with the Final Medical Examination. There are various, usually minor, deviations from the presented scheme at different universities (e.g. physiology is taught together with pathophysiology, or microbiology classes are held in the third year), but this curriculum structure is in force approximately in medical faculties all over the world [4]. Completing medical studies at the university level guarantees knowledge and skills in several areas. The first of these are basic sciences, on which medical knowledge is built, including the structure and function of the human body, the ecological and social environment of humans. The second area includes knowledge, skills and social competences in the field of pathologies of the structure and function of the human body and pathologies resulting from the negative impact of the biological and social environment on people. The third area comprises knowledge, skills and social competences from the individual subdisciplines of medicine, which are also medical specializations defined by law. In particular, teaching considers the prevention and treatment of the most common diseases that a physician encounters in emergency medicine, family medicine, internal medicine (along with other non-surgical specialties), mental and behavioral disorders and surgical disciplines. Another area includes the so-called soft and generic skills, such as the ability to establish and maintain a therapeutic relationship, the ability to coexist with other doctors and representatives of other medical professions, and appropriate legal culture. The last area is the development of the ability to interpret critically the results of scientific research and to obtain basic knowledge of the methodology of conducting research in medicine and related sciences [4]. In the countries where two-cycle medical studies are obligatory, only the graduates of master studies have the right to practice medicine [4] The clinical part of medical studies takes place at the patient's bedside, so in the field of medicine teaching involves attempts of the students to solve a clinical problem under the supervision of a teacher, reproduction of the

doctor's clinical thinking, or observation – participation in the performance of medical procedures. Practical skills are consolidated during summer internships in health care facilities and during postgraduate internships.

Preclinical and general subjects are often not taught by doctors. On the one hand, it broadens the horizons of future doctors, on the other hand, it can give the wrong perspective of a particular subject from the point of view of medicine as a whole. For example, too much concentration of chemists teaching biochemistry on chemical formulas and terminology does not provide the prospect crucial for medicine of linking metabolic pathways in health and disease. Due to the lack of doctors willing to teach preclinical subjects, it happens that these subjects are taught by biologists, chemists or physicists. Teaching biophysics or biochemistry by a physicist is still somehow understandable, but teaching human anatomy by biologists raises some concern.

The Regulation of the Minister of Education and Science of October 6th, 2023, divides subjects in the field of medicine into nine following groups:

A. Morphological sciences 270 hours (20 ECTS credits)
B. Scientific basis of medicine 465 hours (35 ECTS credits)
C. Preclinical Sciences 525 (40 ECTS credits)
D. Behavioral and social sciences with elements of professionalism and communication, including the idea of humanism in medicine 240 hours (18 ECTS credits)
E. Non-surgical clinical sciences 1120 hours (70 ECTS credits)
F. Surgical clinical sciences 940 hours (55 ECTS credits)
G. Legal and organizational aspects of medicine 90 hours (6 ECTS credits)
H. Practical clinical teaching in the sixth year of study 900 hours (60 ECTS credits)
I. Internships 600 hours (20 ECTS credits).

In total, it gives 5150 hours and 324 ECTS credit points.

The choice of medical specialization depends on the result of the State Medical Examination and the interests of a young doctor. The score obtained in the Final Medical Examination determines the priority of choosing a specialization placement in the preferred medical specialization. This choice is determined by the interests of individual residents, the state policy regulated by the allocation of specialization places and the number of points scored in the Final Medical Examination. According to the directive of the European Parliament and the Council, studies in the field of medicine should last at least six years and include 5500 hours of tutorials at a university or under the supervision of a university. The detailed conditions of admission to studies and characteristics of the course of studies in various European countries were presented in by Stryjski and Stryjski in their article [4]. Therefore, there is no need to characterize the curricula in different countries in detail.

PEDEUTOLOGY OF THE PROFESSION OF AN ACADEMIC TEACHER IN THE FIELD OF MEDICINE

In Poland, there is still a shortage of doctors in relation to the number of inhabitants [5]. The above condition requires intensive and extensive education of students in the field of medicine. Preclinical subjects are taught by doctors or specialists with other education adequate to the teaching of the subject (biologists, psychologists, chemists, physicists). Universities prefer these subjects to be taught by doctors, because they have a practical perspective on understanding the theoretical subject. Clinical subjects can be taught only by people who have completed medical studies and a specialization corresponding to the subject being taught. Academic degrees and titles determine the academic position of a teacher. A physician employed on a research and teaching position or a teaching position may hold the following positions: professor (a person with the title of professor), university professor (a person with the title of professor or a person with a postdoctoral degree), assistant professor (a person with a postdoctoral degree, a person with a doctoral degree) and an assistant (a person with a doctoral degree, a person with a professional title of medical doctor) [6]. Persons who are research and teaching employees are obliged to conduct scientific research.

The choice of the medical profession results primarily from the interest in medicine with a parallel motivation to help people. This motivation is autotelic and prosocial in character. Some people still want to study medicine for the sake of science and prestige. The prestige of the profession and the indirectly related lifestyle is an example of socially acceptable, external, instrumental motivation. Hardly anyone assumes that by choosing to study at the faculty of medicine they will also become teachers and educators in the future [7]. Secondary school graduates who want to teach and educate in their professional work usually choose pedagogical or university studies, where it is possible to obtain pedagogical training to teach in elementary or secondary schools. The research of Polish authors has demonstrated that the most common motivation to choose medicine as a field of study turned out to be the desire to help others. This indicates the prosocial motivation of the surveyed students and is a phenomenon favorable for the formation of appropriate ethical attitudes. In the next place, the respondents indicated the prestige of the medical profession, sometimes the desire to take up scientific research. Rarely did they admit in their answers that their choice was influenced by family tradition or expectations of the family. Students currently follow their own path in life, regardless of the opinions of their family and friends [7]. Professional prestige and finances result from instrumental (external) motivation. A balance between autotelic and instrumental motivation to practice a profession is a prerequisite for professional satisfaction and prevents burnout. It is interesting that among students of physiotherapy, dietetics, emergency medicine and nursing, the most frequently indicated motive for taking up medical studies, regardless of the field of education, was interest in the medical profession and the desire to help others. Thus, the motivation for choosing medical professions other than the profession of doctor was similar to the motivation for choosing a medical field of study [8].

During medical studies, no subjects preparing for the work of a teacher or academic teacher are taught. Students do not learn general pedagogy, didactics, teaching methodology, pedeutology, theory of assessing learning results, developmental psychology, educational pedagogy, axiology of teaching and education, and other subjects that give both pedagogical qualifications (to work in educational institutions) and prepare doctors to teach at graduate and postgraduate levels. People who remain at universities in clinical or theoretical departments must be aware that a large part of their professional activity will be teaching and forming future doctors in the context of their knowledge, soft skills and values recognized by medicine [9,10]. Such axiological didactics in the field of medicine can be considered a broader process than teaching and education. It is rather a formation where proper ethical attitudes, interiorization of the norms of the medical community, sensitivity to suffering, empathy, tolerance and acceptance of otherness are as important as hard skills, i.e. knowledge [9-11]. The question of how to teach medicine is a fundamental question about the metatheory of the theory of academic teaching of medicine [12].

Young assistants usually acquire the ability to teach students intuitively, through their own experience and observations of others. Learning by doing has an important practical dimension, but if not directed by professionals in didactics and teaching methodology, it may proceed in an erroneous way, inconsistent with modern standards. On the other hand, education in action is the most effective method of learning, giving practical skills and forcing to expand knowledge that is useful in this activity [1]. Therefore, it would be good to provide the willing students with a module preparing them to work as teachers at every level, from primary education, through secondary education, to academic teaching. Employment at an academic level school should be conditional on completion of such a course provided within the framework of graduate education, or after employment at a higher education institution in the form of post-graduate studies.

Let us think about what this training of a doctor is all about and what attributes should one have in order to participate in it as a master? All teaching and upbringing are normative in character, and these norms are obligatory in nature. It means that a young doctor is formed to a specific ideal model to which he or she should conform as closely as possible [13, 14]. This model is always entangled in ideology and politics, as has been pointed out by the postmodernists. They believe that science, culture and the legal system in modern civilization are the tools of power and domination of patriarchal and heteronomous men over women and minorities [15]. Medicine is also subject to political subsumption to the state, although not to the same extent as education [16]. However, already the teaching of medicine gives the temptation to subordinate to various ideologies and political inclinations. Medical professionals teaching in the field of medicine, who are also the elite of the medical community, must, in the interest of the state, shape the desired worldview and ethical attitudes. Attempts to limit the autonomy of universities (including medical universities), the appointment of directors of scientific and research institutes by the minister (and not by election), the recently introduced change in the method of appointing the director of the Medical Centre for Postgraduate Education from elected to imposed by the Minister of Health are examples of „manual control" of medical education. This disturbing trend of centralization of decisions concerning the choice of a leader in research and teaching is worrying, because it is evolving towards a single, authoritarian, strongly anchored ideologically and infallible model of education. Such a system was in force during the existence of real socialism in the People's Republic of Poland.

The next question concerns the determination of what temperamental and personality variables are useful in practicing the profession of a doctor and an academic teacher in the field of medicine at the same time. Common stereotypes of attribution of such skills include empathy, a positive attitude towards people, a sense of mission in educating medical staff, a sense of satisfaction with the fact of forming new doctors, a sense of justice, and consistency in pursuing goals [17]. A teacher of doctors should have authority both as a source of medical knowledge and as a role model with a charismatic personality inspiring young people to learn. This authority is necessary to be able to model appropriate medical behaviors [17]. Despite the verging certainty of the above statements, there is little empirical research in psychology to confirm these claims. Most of them are probably true, but there are no large meta-analyses verifying them [18,19]. From a logical point of view, a teacher of the medical profession should meet the criteria of a good educator, a good doctor and a good scientist at the same time. There is abundant literature concerning each of these professional predispositions, but there is a lack of research on people who simultaneously practice the profession of a doctor, an academic teacher forming future doctors, and a researcher. Research on the personality structure in the Big Five model conducted in 2021 on medical students and teachers showed that high openness to experiences, agreeableness and conscientiousness, with low neuroticism, are conducive to professional success in the work of a doctor and academic teacher at the same time [20]. Other studies pointed out a different profile of personality structure and learning goals depending on the specialization performed by the physician-educator. Each subdiscipline of medicine has been culturally assigned a certain script and cognitive scheme of the image of a specialist. Young doctors choose their specialization often guided by these stereotypes, which functions as a self-fulfilling prophecy confirming the truth of this stereotype. This also translates into various preferred forms of teaching young doctors by their teachers-specialists [21]. Therefore, internal medicine is taught by internal medicine specialists differently than, for example, surgery by surgeons [21].

The question should be asked whether there is a professional identity of a doctor-teacher-scientist. Identity gives a sense of continuity of being oneself as a teacher and enables constant discovery of one's true self. This search for

one's own professional self allows an academic teacher of medicine to find himself in the educational reality of the university and in the medical profession. Self-reflection allows one to find one's place in both professions at the same time in the existing educational reality of higher education and health care. The self-reflection of the teacher-physician is based on critical thinking and on appealing to the creative imagination that allows him/her to be both a subject in the process of educating future doctors and a subject in the practice of medical profession [22, 23]. The individual choice of each physician-teacher of medicine is a double or triple identity (the identity of the doctor and the identity of the teacher, as well as the identity of the researcher) in relation to the sense of separate identity as a doctor-academic teacher of medicine.

Each professional community enjoying public trust develops its own ethos. Ethos is a social and mental symbol of teaching, medical and scientific professional identity. It is still a point of reference for moral behaviors attributed to these two professional groups, which is a point of reference for many people. Especially for medical students, the role model of their teachers determines their entire professional life following graduation. Students are both highly sensitive to formation processes and largely susceptible to them. The formation of medical adepts during the education process involves not only the transfer of professional knowledge, but first the development of an appropriate quality of the doctor-patient relationship, considering the subjectivity of both sides of the interaction. Modeling the proper doctor-patient relationship in students should take place in three dimensions: observation of the teachers' conversations with patients in a hospital or outpatient clinic, observation of the teacher-student relationship (which is a certain equivalent of the doctor-patient relationship), and the transfer of theoretical knowledge in the field of interpersonal communication [22, 23]. Modeling should also include the relationships between doctors and between doctors and other medical personnel. It should be remembered that the doctor's relationship with the social environment is considerably influenced by the cultural resources of students, which are quite diverse. People with good results in high school examinations are admitted to medical studies, but nobody checks the temperamental and personality predispositions or cultural resources necessary for the profession [24]. These considerations concern the sociological understanding of the social role of the doctor. However, this concept also occupies an important place in the scientific field of social psychology. The social role of a doctor is understood as:

- the sum of requirements relating to the doctor's social position;
- the way in which a particular individual understands the requirements and expectations resulting from the doctor's social position;
- the actual actions of the individual in relation to the social position [25].

The profession of a doctor is a profession of social trust, which is a factor taking part in the personal formation of a human being. Practicing the profession of a doctor refers not only to the moral and ethical aspect, but also to the overall developmental area of the individual. Trust means a form of relationship that is full of understanding between people in various forms of mutual interpersonal interactions [25]. Teachers of the medical profession should develop and reinforce this sense of mission but warn against the domination of medicine and doctors over other aspects of functioning. The profession of medical teacher enjoys double social trust – both as a teacher and as a doctor. Preparing a person to play both these roles at the same time is a difficult task that requires interiorization and internal integration of many norms from various areas of human professional activity [25].

A teacher of the medical profession should be particularly sensitive to the process of reification (objectification) of patients and the reification of students. Terminology is used to reify the patient as a so-called case, using statistical and epidemiological data, in which the subjectivity and uniqueness of each person's existence is lost [25, 26]. The issue of reification is complex, because comprises various factors such as burnout, work overload, excessive technicalization of medicine, or the „imperialism" of medicine in relation to other aspects of human activity, which is emphasized by postmodernists. A phenomenon unfavorable for both students and their teachers is, for instance, the possibility of recording a lecture by a lecturer. Listening to such a lecture, the student loses sight of the personal character of the master-student relationship. Such a lecture is a technical transfer of knowledge, and it could just as well be recorded by a bot created by artificial intelligence instead of an academic teacher. Unfortunately, the COVID pandemic has intensified the tendency towards remote and impersonal teaching of medicine [27].

Medical teachers should be sensitized to teach basic principles and values, independent of technological progress. Medical knowledge and its technical instrumentation are changing at a dizzying pace, and it is not possible to teach students about all the directions of changes in medical progress and paradigmatic changes in medicine. Teaching medicine must therefore be euthyphronic in character, i.e. using common sense, considering scientific and technical innovations as well as the tradition of medicine [28]. Tradition is learned through learning the history of medicine and a sense of belonging to the academic community of doctors with a specific tradition, sometimes constituting the so-called school [29, 30]. (Tadeusz Pietras comes from a school created by the students of Professor Jan Stopczyk and Jerzy Rożniecki). An example of such schools are also the students and successors of Professor Witold Orłowski or Professors Edward and Andrzej Szczeklik.

CONCLUSIONS

The profession of an academic teacher in the field of medicine is uniquely complex, thus requiring the integration of medical expertise, pedagogical competence and scientific engagement. Despite the growing emphasis on practical competencies in medical education, the systemic neglect of formal pedagogical training for physician-teachers poses a significant challenge. Academic teachers are

often unprepared to fulfil their educational role, having been recruited primarily based on clinical and research credentials, rather than teaching proficiency.

This creates a structural imbalance where the formation of future physicians relies heavily on the intuitive and informal teaching methods of their mentors, rather than on evidence – based didactic strategies. Given the normative and formative nature of teaching medicine – where ethical attitudes, professional identity, and interpersonal values are shaped as much as clinical skills – there is an urgent need to institutionalize pedagogical training within both undergraduate and postgraduate medical curricula

Moreover, the dual or even triple identity of doctor-teacher-scientist demands self-reflection and internal integration, which should be supported by academic structures fostering professional development in all three domains. Research shows that certain personality traits – such as openness, conscientiousness, and low neuroticism - favour success in combining these roles.

To ensure high standards of medical education, it is essential to strengthen the ethos of the teaching profession in medicine, resist the instrumental reification of students and patients, and protect the autonomy of academic institutions from ideological or political influence. Medical education must remain euthyphronic – grounded in both scientific innovation and the humanistic tradition of medicine - so that teachers not only impart knowledge but also model values that define the medical vocation.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Tadeusz Pietras
Department of Clinical Pharmacology,
Medical University of Lodz, Lodz, Poland
e-mail: tadeusz.pietras@umed.lodz.pl

ORCID AND CONTRIBUTIONSHIP

Tadeusz Pietras: 0000-0003-1771-3819 A B D E F
Karol Batko: 0009-0000-9949-508X B D E
Aleksander Stefanik: 0009-0004-3013-9385 B D E
Kasper Sipowicz: 0000-0001-7384-2899 B D E F
Anna Mosiołek: 0000-0001-6999-2309 A B D E F
Ignacy Stefańczyk: 0009-0007-5743-8790 B D E
Magdalena Dutch-Wicherek: 0000-0001-6560-0398 A B D E F

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

RECEIVED: 20.03.2025
ACCEPTED: 30.06.2025

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REVIEW ARTICLE

Practical application of motivation theories for engaging and retaining medical staff

Angelika O. Keretsman, Valeriya V. Brych, Emiliia M. Shykula
UZHHOROD NATIONAL UNIVERSITY, UZHHOROD, UKRAINE

ABSTRACT

Aim: To provide a scientific rationale for various approaches to the practical application of individual motivation theories in order to develop a motivated medical workforce as the foundation for strengthening healthcare systems

Materials and Methods: Based on comparative analysis, as well as systematic and analytical approaches to understanding selected motivation theories – namely Maslow's Hierarchy of Needs, Herzberg's Two-Factor Theory, Adams's Equity Theory, Vroom's Expectancy Theory, and Deci and Ryan's Self-Determination Theory – the authors propose integrating these theories into managerial strategies.

Conclusions: A well-functioning healthcare workforce system requires not only a sufficient number of professionals but also effective motivation strategies based on various theories, such as those by Maslow, Herzberg, and Vroom, to enhance job satisfaction and retention. Understanding and applying these theories help managers create optimal working conditions, reduce turnover, improve service quality, and strengthen the healthcare system's overall efficiency and reputation.

KEY WORDS: medical professionals, engagement and retention, motivation theories, practical application

Pol Merkur Lek,2025;53(4):522-528 doi: 10.36740/Merkur202504113

INTRODUCTION

In the 21st century, human resources for health (HRH) play a decisive role in addressing challenges related to demographic, epidemiological, and technological changes, as well as those arising from conflicts and natural or man-made disasters. Healthcare professionals stand on the front lines of tackling these issues, mitigating the influence of social determinants of health, delivering integrated medical services, and preventing diseases. World Health Organization (WHO) strategic documents increasingly emphasize that the planning of investments specifically in healthcare human resources is a key factor in strengthening any national healthcare system (HCS) worldwide [1, 2].

At the international level, there are frequent calls for the necessity of having national strategies for developing and strengthening HRH, as the future well-being of people of all ages largely depends on these professionals' activities – specifically, their alignment with population needs, as well as the acceptability and quality of the services they provide [3]. Furthermore, as highlighted in WHO's main strategic documents, an effective and accessible healthcare system can only be fully achieved by having stable human resources who possess the knowledge, skills, values, ethics, and appropriate conduct needed to address existing, emerging, and new health challenges [4]. In light of this, the low level of motivation among healthcare professionals has become a critical challenge for the HCS in most countries. According to data from the ministries of health in many European countries, low motivation among healthcare professionals is the second most significant HRH issue after staff shortages [5, 6]. Simultaneously, the global problem of healthcare worker migration remains unresolved [7-10], including in Ukraine, where the intention to leave work is exacerbated by the war – one of the principal demotivating factors [11-13].

In the context of a growing shortage of healthcare workers, effective mechanisms for attracting and retaining young specialists are especially important. Therefore, the study and scientific substantiation of new motivational strategies – the focus of our research – will not only increase healthcare worker retention but also foster the overall development of the healthcare system and improve the quality of medical services as a whole.

AIM

To provide a scientific rationale for various approaches to the practical application of specific motivation theories with the aim of forming a motivated medical workforce as the basis for strengthening human resources for health (HRH).

MATERIALS AND METHODS

A comparative analysis of motivation theories was conducted, along with the use of systems analysis and a systems approach to achieve the stated objectives.

REVIEW AND DISCUSSION

The quality of medical services is directly dependent on the professionalism and motivation of healthcare

professionals. However, under current conditions, many medical institutions face challenges in attracting and retaining qualified personnel [14]. High professional workloads, emotional burnout, and insufficient levels of both material and non-material incentives contribute to staffing shortages and high turnover [15].

Motivation has always mattered for businesses, and in today's market-driven reality, healthcare systems are no exception. Motivated employees work more effectively, are more productive, and are more engaged in carrying out their work. In view of this, one of the most important tasks for modern managers and HR professionals is to create working conditions in which employees feel motivated and efficient.

Essentially, motivation stems from the satisfaction derived from the job itself and the desire to achieve certain goals (for example, earning more money, getting promoted, or gaining societal recognition). In other words, motivation dictates human behavior. Although it is widely acknowledged that an individual's job performance results from their abilities – acquired through knowledge, skills, and experience – even a talented employee who feels deprived of motivation is unlikely to perform well. Meanwhile, a well-motivated employee can often accomplish much more than expected. In other words, employees' specific wants drive them to do certain things, defining their behavior, and these desires correspond to certain needs – namely, satisfying them (including the satisfaction derived from the work itself). This can subsequently change what needs and wants are primary in the course of completing one's work [14, 16]. At a basic level, employee behavior can be explained by the idea that we do something (e.g., go to work) in order to get what we want (money or money to buy something specific) and avoid what we don't want (e.g., doing extra work, spending our own funds on professional development, etc.).

Based on the above, in order to create a competitive and successful healthcare facility, a good manager or HR professional involved in recruiting and hiring medical personnel in today's environment must find answers to the obvious questions: "Why exactly do employees want what they want, and why do they not want what they don't want?"

Understanding certain approaches in motivation theories – namely, content theories and process theories – can help answer such critical questions. Early content theories may provide an answer to "what?" motivates employees, while process theories focus on "how?" to motivate individual behavior. These are commonly understood as need-based theories because they attempt to identify and categorize employee needs, linking the emergence of motivation specifically to satisfying those needs. At the same time, content theories alone cannot fully explain what motivates or demotivates an employee, given the vast array of complex factors affecting each individual in specific workplace conditions. Consequently, although they have made the greatest contribution to the practice of management (e.g., Maslow's Hierarchy of Needs, McClelland's Theory of Needs, Herzberg's Two-Factor Theory, and others), content theories are the least accepted among scholars and, in our view, remain underappreciated.

Process theories focus on identifying the origins of motivation and the tools and methods for maintaining it (Skinner's Theory, Vroom's Expectancy Theory, Adams's Equity Theory, Locke's Goal-Setting Theory, etc.) [17].

No single motivation theory explains the absence of employee motivation or every aspect of people's motives. However, their theoretical underpinnings can serve as the basis for developing motivational techniques in contemporary conditions. According to Abraham Maslow's perspectives [18], satisfying the psychological needs of healthcare workers can be achieved through:

- Ensuring competitive salaries, a convenient work schedule shaped by the employees themselves, and comfortable working conditions (such as rest areas at the workplace, the availability of quality meals) to meet physiological needs;
- Guaranteeing official employment with transparent wage payments, insurance (health, life, potential professional errors!), safe working conditions (including bomb shelters – particularly crucial amid ongoing hostilities in Ukraine), and compensation in cases of occupational diseases (the option for healthcare providers to receive sick leave and sanatorium-resort treatment and rest) to address safety needs;
- Building a friendly team within the healthcare facility, encouraging senior or more experienced physicians to mentor young or new colleagues, organizing corporate events demonstrating management's concern for its subordinates, and promoting open communication between managers and employees in order to "hear their voices," "hear their needs," and prevent internal conflicts, all to fulfill social needs;
- Introducing fair bonus payments and commendations as rewards, recognizing high-quality work, and publicly acknowledging individual employees' achievements to meet the need for recognition;
- Providing opportunities for continuous professional education paid for by the employer, pathways for career advancement within a particular medical institution, or facilitating career progression into regional or state authorities; engaging staff in medical research or professional communities; and collaborating with higher medical education institutions (HEIs) to meet the need for self-actualization.

A practical application of Maslow's motivational concepts, structured by the hierarchy of needs, when working with medical university graduates may include:

– Physiological needs: guarantee graduates a stable starting salary during their internship, correlated with their professional achievements, as well as provide access to dormitories or housing assistance – especially when placed in a different city or region.
– Safety needs: official employment with transparent competition among young specialists, medical insurance, and legal protection from professional errors; offering a social benefits package with various perks.

– Social needs: organize mentorship and orientation programs during the first year of work in a healthcare facility.
– Esteem needs: the employer pays for the internship training of graduates through scholarships for top students, or bonuses for excellent performance or successful completion of specific critical tasks.
– Self-actualization: provide financial support for international internships (enabling participation funded by the employer), and opportunities for engagement in scientific activities.

For example, a medical facility might offer young physicians a one-time starting bonus, mentorship, and potential career advancement. Meeting these fundamental workplace needs helps employees move higher up the hierarchy, thus becoming more efficient, creative, and innovative. Meanwhile, managers and HR personnel must bear in mind that employees are motivated differently and move through the hierarchy at varying speeds; therefore, the set of motivational incentives must be tailored individually to each worker.

Applying Fredrick Herzberg's Two-Factor Theory [19], which is based on meeting hygiene and motivation factors, might entail the following practical actions for shaping healthcare worker motivation:

- Enhancing hygiene factors (salary levels, working conditions, and job stability) to eliminate employees' dissatisfaction;
- Implementing motivational components (delegating interesting tasks that align with an individual's professional interests, publicly recognizing achievements, defining clear responsibilities for each worker, supporting and fostering career growth, offering opportunities for job rotation, and involving employees in various projects to prevent monotonous work and loss of interest) to boost job satisfaction.

For young specialists, a practical approach to implementing this theory can be used to minimize dissatisfaction and encourage them to choose a particular healthcare facility as their prospective workplace by guaranteeing competitive salaries for recent graduates compared to other medical professionals, setting a manageable workload and flexible work schedule for combining work with continued education, providing comfortable working conditions (an appropriately equipped personal workspace), and offering housing (conveniently located dormitories with reduced costs), thereby minimizing the adverse impact of hygiene factors on graduates' motivation.

Motivational factors (growth incentives) can be applied to graduates through broad informational campaigns by certain healthcare facilities from specific regions, clearly communicating their career growth opportunities as early as the professional development stage via partnerships with higher education institutions. For young specialists already working, recognition can be encouraged by introducing a "Best Young Doctor" status, creating a rating system of achievements that offers incentives, etc. For instance, a medical facility might establish a ranking system for young physicians that comes with bonuses and faster promotions. Ultimately, such practical measures will significantly facilitate the recruitment of young people into a specific healthcare facility and the healthcare system as a whole.

Managers implementing practical techniques based on the two-factor motivation theory must remember that true motivators are factors that directly encourage employees to work more. Hygiene factors alone cannot motivate employees to put in extra effort. It is crucial to understand that motivators mainly concern the nature of the work itself: how interesting the tasks are and how many opportunities those tasks provide for additional responsibility, recognition, and career advancement. Hygiene factors, by contrast, serve as the backdrop for work performance: an employee will agree to work in a healthcare facility with good hygiene conditions only if the facility provides a reasonable salary and safe working conditions; however, these factors on their own will not compel the employee to perform tasks more diligently. Therefore, in the process of delegating tasks, a democratic management approach should be used. This improves the nature and content of the actual work by employing practical methods such as expanding job duties and giving employees more diverse tasks (not necessarily more complex) that make work more interesting without increasing the workload. At the same time, teamwork involves tackling a broader range of more challenging tasks in a given project, whose successful completion leads to a greater sense of accomplishment, especially if expanding employees' rights and responsibilities allows them to make their own decisions about their work lives.

Vroom's Expectancy Theory [20] can be put into practice through the following techniques:

- Show staff the connection between effort and reward. For instance, high-quality work = receiving various bonuses – both material (coupons for specific products or services) and non-material (additional days off, paid vacations, etc.) – or career advancement.
- Provide opportunities for professional development funded by the employer or clearly outline career growth prospects for employees who invest in their own professional development.
- Implement a fair performance-based evaluation system to stimulate results.
- For young specialists and recent graduates, Vroom's Expectancy Theory can be applied by:
- Establishing a clear system: "If you study and work diligently, you will receive good conditions."
- Setting targets such that upon reaching certain performance benchmarks, "We guarantee stable career growth in our medical facility, including expanded responsibilities and the opportunity to make certain management decisions."
- Offering support programs for top university graduates (grants, tuition coverage, etc.).

For example, a young physician might know that after one year of successful work, they will receive a promotion and additional pay for their specialization.

This theory combines the perceptual aspects of Equity Theory with the behavioral aspects of other theories. It is

based on the assumption that a person's behavior stems from a conscious choice among various alternative actions. The behavior an employee chooses will always be the one that maximizes satisfaction and minimizes negative emotions. Hence, a manager must remember that each employee will ask: "What are the chances I'll be rewarded if I do a good job?" (external motivational factors) and, on a personal level: "What exactly do I want in return if I can accomplish this well?"

In practice, Expectancy Theory can help managers understand how individual team members choose from different behavioral options in the workplace. Its greatest advantage is clarifying that performance must be directly linked to reward (and the method for choosing that reward must be transparent, well-deserved, and desirable!). This motivation theory can yield a highly motivated workforce and high-performing teams that will elevate a healthcare facility's reputation. It is important to note that patients often "follow the doctor's name" in seeking particular medical services, especially in today's environment of social media and other information resources.

John Stacey Adams's Equity Theory [21], in practical terms, involves regularly analyzing market-level salaries to avoid employees feeling underpaid, ensuring transparent criteria for promotions and bonuses, setting equitable workloads, and introducing a system of internal feedback from staff to account for their needs and preferences.

For young professionals, this entails a transparent salary and bonus system (so that recent graduates do not feel unfairly treated compared to senior physicians), guaranteed equal access to career opportunities and training, and the assessment of young specialists based on objective criteria that consider their experience. An example would be a hospital that introduces a merit-based recruitment rating system tied to academic performance and openly administers bonuses and performance evaluations without favoritism.

McClelland's Theory [22] involves identifying practical ways to influence motivation by first categorizing employees according to their predominant needs (achievement, power, affiliation). Its application could include:

- For those driven by achievement: Provide opportunities to tackle complex tasks and set ambitious goals.
- For those driven by power: Consider offering managerial positions in the healthcare facility or involving them in managerial decision-making.
- For those driven by affiliation: Create a strong corporate culture, team-building activities, and ensure collegial support.
- For young specialists:
- Achievement-oriented: Fast-track professional development programs (internship + education + exposure to complex cases).
- Power-oriented: Leadership courses, opportunities to become department heads quickly.

Affiliation-oriented: Establish medical communities and involve young doctors in team projects.

For example, student leaders might be allowed to manage hospital projects even before graduation.

Understanding the basic tenets of McClelland's "Learned Needs" Theory enables a manager to focus on meeting existing employee needs rather than creating or cultivating them – an approach that fundamentally differs from Maslow's. From a practical managerial perspective, an employee's need for achievement is evidenced by the drive to demonstrate their competence or expertise; affiliation may be expressed in an emotional need for belonging, acceptance, or interpersonal closeness; and power relates to the desire to control their own work or that of others. Managers should remember that all people possess these three needs in some form, regardless of age, gender, race, or cultural background. They are shaped by life experience, not innate traits. Thus, although certain individuals might desire power, not everyone wants to be powerful at any cost, and conversely, even the shy or introverted also wish to receive recognition.

Therefore, for successful employee motivation, a manager must first determine each team member's key needs based on their psychological profile. A new manager unfamiliar with the team might conduct a survey asking employees to rate how important each need is to them personally. Such information can help identify the core motivators that drive each employee and ultimately maximize productivity. With this data, a manager can tailor their leadership style and approach to each member of the healthcare facility team. By adjusting feedback methods, goals, and leadership styles – and the manner in which employees are motivated – one can ensure high performance from a well-motivated workforce.

Self-Determination Theory (SDT) by Edward Deci and Richard Ryan [23] posits that a person is motivated not only by external factors (money, rewards) but also by internal ones, such as enjoyment of the activity itself and personal growth. Thus, one must acknowledge that an employee can be motivated by:

- Intrinsic motivation – the individual engages in an activity out of personal interest, satisfaction, or a desire to develop (for example, a doctor learns new treatment methods because they find them fascinating).
- Extrinsic motivation – the individual's actions are driven by rewards or punishments (for example, a doctor works overtime for a bonus or to catch up on paperwork).

In addition, amotivation (lack of motivation or lack of meaning in one's work) may occur when tasks are done solely out of obligation.

According to this theory, three basic psychological needs exist:

1. Autonomy – the desire to control one's own life and make personal decisions (e.g., doctors who can influence their own schedules typically feel greater job satisfaction).
2. Competence – a sense of skill mastery and professional growth (e.g., opportunities for training, advanced learning).
3. Relatedness (Affiliation) – the need to feel supported and significant within a team (e.g., a healthy team spirit, trust among colleagues, healthy competition).

Motivation is viewed along a continuum: from amotivation (lack of interest) – through extrinsic motivation (external rewards and incentives) – to intrinsic motivation (acting for enjoyment and personal development).

Practical applications in healthcare workforce management:

1. Allow physicians and medical staff to participate in decision-making, influence their schedules, and choose their work methods (autonomy).
2. Provide training, workshops, and career advancement opportunities (competence).
3. Foster a supportive environment through team collaboration and mentoring; develop a positive organizational culture so that staff feel engaged, valued, and needed (relatedness).
4. Use not only financial incentives but also emotional recognition and opportunities for self-actualization.

Thus, this theory emphasizes the importance of intrinsic motivation and creating conditions for employees to achieve self-actualization. Practical steps based on this theory – such as flexible work schedules to avoid burnout, continuous professional education (training, conferences, educational grants), fair evaluations and rewards (clear KPIs, bonuses, promotions), emotional support (psychological counseling, coaching), and involving staff in management decisions (engaging them in strategic planning) – can help maintain an appropriately motivated healthcare workforce.

To evaluate the validity of the proposed practical aspects of applying motivation theories for healthcare workers, we conducted a survey of 20 experts, including 5 university faculty in the healthcare field, 5 healthcare administrators holding the highest certification in "Healthcare Organization and Management," and 10 physicians at healthcare facilities (2 heads of general practice/family medicine clinics, 5 heads of cluster-level departments, and 3 heads of supra-cluster departments). They were given a questionnaire containing 10 statements rated on a 5-point scale (minimum 0, maximum 5 points each).

According to the results of these expert evaluations, the practical application of understanding healthcare worker motivation theories for attracting and retaining medical personnel was rated highly at 4.7±0.15 points. Most surveyed experts (85-95%) gave the recommended measures a high rating (Table 1).

Motivation theories provide insights into what drives an employee to work more effectively and efficiently. Their understanding equips managers with tools for motivating staff and aids in making optimal managerial decisions – innovative and adaptable to today's complex and changing working conditions for healthcare professionals. It is therefore unsurprising that employee motivation is of paramount importance in the fields of human resource management and organizational behavior.

By examining how tasks are carried out and work is performed overall – along with an individual's position and importance within these processes through the lens of motivation or lack thereof – different motivation theories offer a range of perspectives. Based on their insights, we can identify and formulate certain points relevant for practical use in improving human resource management processes in healthcare, both within individual medical facilities and the healthcare sector as a whole [24]. As noted in modern personnel management research [25, 26], a well-motivated team can deliver the following benefits:

- High productivity
- Lower absenteeism
- Reduced staff turnover
- Enhanced reputation and credibility for the organization
- Improved product and customer service quality

In the healthcare system, using effective motivational strategies for medical professionals can achieve the following:

Table 1. Experts' evaluation of the proposed practical recommendations for applying the understanding of healthcare worker motivation theories to attract and retain medical personnel

Criteria for expert evaluation	Distribution by ratings					
	4 i 5 points		3 points		1 i 2 points	
	Abs.	%± Δ%	Abs.	%± Δ%	Abs.	%± Δ%
Relevance of understanding motivation theories for optimizing approaches to motivating medical personnel	18	85,8±1,7	2	14,18±1,2	0	0
Justification of practical approaches based on specific recommendations derived from understanding individual motivation theories	19	95,09±1,6	1	4,91±0,6	0	0
Appropriateness of implementing the proposed practical approaches grounded in motivation theories	20	100	0	0	0	0
Innovativeness of the proposed practical approaches	17	85,06±1,3	3	14,94±1,1	0	0
Average value, %	91,4±1,6		8,5±0,9			
Average score (points)	4,7±0,15					

- Highly productive, motivated employees save time for themselves and, most importantly, for patients – an advantage for a healthcare facility (HCF) in the medical services market. This can even lower service costs through increased patient coverage, particularly in the private sector.
- Employees who are motivated and satisfied with their work are less influenced by external or internal factors that might lead them to neglect their duties by not reporting to work or refusing additional training.
- Motivated staff are less susceptible to leaving a specific healthcare facility (thereby reducing turnover) or the country (the "brain drain" phenomenon due to migration), or exiting the healthcare field entirely in search of better working conditions.
- Having a motivated healthcare workforce lowers the employer's costs for recruitment and training, especially relevant in a financially constrained environment (particularly in the public sector).
- Satisfied medical staff foster a strong employer reputation for the HCF, making it easier to attract top talent and even enhancing the stature of the entire national healthcare system. This leads to higher quality healthcare and better customer service, potentially elevating the country to reference-standard levels in medical service provision.

CONCLUSIONS

1. Strategic documents and the main WHO recommendations for building a sustainable healthcare workforce system – also at the national level – encompass not only having a sufficient number of medical specialists per the population served but also ensuring that these professionals possess the necessary motivation.
2. A lack of knowledge about motivation theories can lead managers, administrators, and policymakers to mistakenly believe that monetary incentives alone can motivate healthcare personnel. In contrast, understanding specific motivation theories can help leaders and stakeholders identify and choose the most effective motivational stimuli, which will facilitate the attraction and retention of medical professionals in the healthcare system, raising it to a qualitatively higher level of service provision.
3. Key practical points of various motivation theories:
   - Maslow's theory → Helps create comfortable conditions for both recent graduates and employees.
   - Herzberg's theory → Motivates through career advancement and development.
   - Vroom's theory → Establishes a clear link between "effort = reward."
   - Adams's theory → Ensures fairness in salaries and promotions.
   - McClelland's theory → Enables individualized approaches for different types of young and long-serving physicians.
   - Self-determination theory → Creates conditions for professional self-actualization.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Angelika O. Keretsman
Uzhhorod National University
1 Narodna Square, 88000 Uzhhorod, Ukraine
e-mail: angelika.keretsman@uzhnu.edu.ua

ORCID AND CONTRIBUTIONSHIP
Angelika O. Keretsman: 0000-0002-8902-2227 A B D
Valeriya V. Brych: 0000-0003-3741-6002 B E
Emiliia M. Shykula: 0009-0008-3288-9728 B D

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

RECEIVED: 17.02.2025
ACCEPTED: 28.06.2025

CREATIVE COMMONS 4.0

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REVIEW ARTICLE

Protection of the rights of drug addicts and the right to a fair trial: Practice of the European Court of Human Rights

Oleksandr M. Shevchuk, Oleksandr M. Drozdov, Oleksandra V. Babaieva, Inna L. Bespalko, Alisa V. Panova

YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

Aim: To identify violations of the rights of persons who use psychoactive substances through the analysis of decisions of the European Court of Human Rights within the framework of the implementation of the right to a fair trial in cases related to illicit drug trafficking, and to propose directions for reducing their negative impact on public health.

Materials and Methods: The methodological basis of the article is a set of methods and techniques of scientific knowledge.

Conclusions: Respect for the rights of persons who use psychoactive substances, including their full exercise of the right to a fair trial, remains a key element of the rule of law, particularly in the context of protecting their lives and public health, and is an obligation of the state.

KEY WORDS: human rights, drug-related crime, public health

Pol Merkur Lek,2025;53(4):529-533 doi: 10.36740/Merkur202504114

INTRODUCTION

The Constitution of Ukraine stipulates that "a person, his life and health, honor and dignity, inviolability and security are recognized in Ukraine as the highest social value" (Article 3), and according to Article 27, the protection of human life is the duty of the state. One of the fundamental rights of every person, which is a component of the principle of the rule of law, is considered a fundamental legal value of a democratic society and is enshrined in Article 6 of the European Convention on Human Rights [1]. The above also applies to the right to a fair trial in the area of drug trafficking.

The impact of illicit drugs on human health is a global problem [2], and a pressing issue in EU Member States is the implementation of effective measures to combat illicit drug trafficking [3, 4], eliminate the threats posed by illicit drugs, and mitigate their consequences for public health. According to the UN, the number of people using illicit drugs increased from 240 million in 2011 to 296 million in 2021, indicating a 23% increase over the decade [5]. The World Drug Report 2024 also indicated that one in 18 people in the world had used illicit drugs at least once, a 20 percent increase from 2022 [6]. Therefore, it is becoming increasingly relevant to study the problems of implementing the rights of persons who use psychoactive substances, including the right to a fair trial [7], since such court cases are often accompanied by an increased risk of abuse by state and law enforcement agencies, and violations of the rights of drug-dependent persons to medical care.

AIM

The aim is to study the problems of implementing the right of persons who use psychoactive substances to a fair trial, to provide a classification of the structural elements of this right, and to offer their detailed characteristics, taking into account Article 6 of the European Convention on Human Rights and the case law of the European Court of Human Rights.

MATERIALS AND METHODS

The methodological basis of the article is a set of methods and techniques of scientific inquiry. Methods of theoretical analysis, system-analytical and comparative-legal approaches, made it possible to characterise the problems of protecting the rights of persons who use psychoactive substances within the framework of the implementation of the right to a fair trial. The comparative-legal method was applied to identify trends and compare approaches in various cases of the European Court of Human Rights (ECtHR). The norms of the European Convention on Human Rights regarding the realisation of the right to a fair trial for persons who use psychoactive substances were analysed using the formal-logical method: the content of basic concepts was clarified, and problematic issues were systematised to draw conclusions within the framework of the research task. The systems analysis method enabled the identification of key issues in protecting the rights of persons who use psychoactive substances in the context of ensuring their right to a fair trial.

REVIEW AND DISCUSSION

After the ratification of the Single Convention on Narcotic Drugs of 1961, the UN Convention on Psychotropic Substances of 1971, and the UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, their provisions became generally binding on Ukraine, including the obligation to pay special attention to and take all possible measures aimed at preventing the abuse of narcotic drugs and psychotropic substances.

The Ministry of Health of Ukraine in the field of drug trafficking and countering their illicit trafficking, in particular, coordinates, within its powers, the implementation of obligations stipulated by international treaties [8], identifies conditions and causes that lead to the illegal circulation of narcotic drugs, organizes measures to eliminate them, conducts constant monitoring of the state of combating crimes in the field of narcotic drug trafficking, approves the procedure for identifying and registering persons who illegally use psychoactive substances [8]. The Ministry of Health of Ukraine is one of the leading executive bodies that coordinates the activities of other bodies in the field of combating illicit drug trafficking [9].

Particular attention should be paid to Article 6 of the European Convention on Human Rights, which enshrines the right to a fair trial. It provides for the opportunity for everyone to have their violated rights restored through a fair and public hearing by an independent and impartial tribunal established by law, within a reasonable time [1]. The provisions of the Law of Ukraine dated 12 February 2015, No. 192-VIII, are aimed at the legal regulation of the national legal system in accordance with the requirements of the European Convention on Human Rights and the Constitution of Ukraine [10].

When analysing the practice of the European Court of Human Rights in cases related to drug trafficking, it should be emphasised that the role of the Court is not to assess the admissibility of specific types of evidence, the subject of which are narcotic drugs or psychotropic substances – particularly when such evidence was obtained illegally from the perspective of national law – nor to determine the applicant's guilt or innocence.

The main question in analysing the practice of the ECtHR that needs to be clarified in court cases related to drug trafficking is whether the judicial proceedings in the area under study were fair overall. It is necessary to take into account the manner in which the evidence (the subject of which is drugs) was obtained. These circumstances also affect the examination of the category of "illegality", as well as the nature of the violations identified in this area.

Scholars do not deny that the right to a fair trial is a complex concept consisting of a set of elements [11]. Article 6(1) of the European Convention on Human Rights [1] does not list these elements explicitly, but they have been developed through the case law of the ECtHR. It is possible to identify the main components of the right to a fair trial in cases related to drug trafficking (Table 1) [1].

Let us consider individual components of the human right under study. An example is the violation of the right to a fair trial in cases related to illegal drug trafficking. Thus, in the case of Teixeira de Castro v. Portugal [12], the facts showed that the applicant had never had a criminal record and had not been held criminally liable; moreover, the police became aware of him only through the mediation of other persons. There was also no reason to claim that the applicant was predisposed to committing a drug-related crime. In other words, the police did not investigate the applicant's criminal activities in a passive manner but, on the contrary, through their influence, incited him to commit a drug-related offence. The Court therefore concluded that there had been a violation of Article 6 § 1 of the European Convention on Human Rights – namely, an interference with the applicant's right to a fair trial – since the police officers had not limited themselves to passive observation but had provoked the commission of a crime.

Similarly, in the case of Vanyan v. Russia, the ECtHR drew attention to the risks associated with the use of anonymous informants and undercover agents. It emphasised that their activities should be subject to strict control to avoid violations of the right to a fair trial [13].

Another example of a violation of Article 6 of the European Convention on Human Rights in drug trafficking cases, namely the restriction of access to a lawyer at the initial stages of the proceedings, is the case of «A.V. v. Ukraine» [14], according to which the applicant was detained for violating the rules of drug trafficking. At the same time, the latter complained that his right of access to a lawyer had been restricted at the initial stage of the proceedings (Article 6 § 1 and § 3 (c) of the Convention) [1].

Table 1. The constituent elements of the rights of people who use psychoactive substances to a fair trial

Element
The right to have the case considered by a court
The fairness of the case
The openness of the trial and the publicity of the decision
Compliance with a reasonable time limit for considering the case
The independence and impartiality of the court
The court considers the case under the requirements of the law

The Court emphasised that Article 6 § 1 of the European Convention on Human Rights generally requires that access to a lawyer be granted from the first questioning of a suspect by law enforcement authorities, except where it is apparent from the particular circumstances of the case that there are compelling reasons for restricting such a right. However, even if, in exceptional cases, the reasons given may justify a denial of access to a lawyer, such a restriction must not, in any event, unlawfully infringe the accused's rights under Article 6 of the Convention [1]. It has been held that the right to a defence would be irreparably violated if a person, during questioning in the absence of a lawyer, made a confession which would subsequently be used to convict him [14].

Let us cite another case. Thus, in the case of Malininas v. Lithuania, the European Court of Human Rights focused on the principle of proportionality, noting that the initiative of law enforcement officers, which directly led to the commission of a drug crime, is a violation of this principle. The ECtHR has stated that law enforcement intervention should be passive and not create artificial conditions for drug-related crime [15]. Excessive state interference in the personal sphere without a proper legal basis undermines the legitimacy of the judicial process.

In the case of Bannikova v. Russia, the Court emphasised the inadmissibility of using evidence obtained as a result of police provocation, stating that such actions undermine the fairness of the trial. The European Court of Human Rights has noted that even within the framework of the fight against drug crime, where the interests of public safety are of paramount importance, these interests cannot justify the violation of an individual's rights by inciting him to commit a crime. Such actions, according to the position of the European Court of Human Rights, are incompatible with the right to a fair trial [16].

In the case of Ramanauskas v. Lithuania, the European Court of Human Rights confirmed that the actions of law enforcement officers who provoke a person to commit a crime violate Article 6 of the Convention [1]. The Court emphasised that law enforcement agencies must adhere to high standards of reasonableness and proportionality, and respect individual rights [17]. At the same time, violations should be considered in the context of „planted evidence" within the framework of an artificially created situation by law enforcement officers regarding a person suspected of committing a drug crime, to further detain him [17].

In this case, as an example, we can cite the case of *Kobiashvili v. Georgia*, where the applicant complained that the criminal proceedings initiated against him were unlawful, as his conviction was based on "fake" evidence [18]. According to the official version of events, when the applicant and his friends were heading to a billiard room, the latter was stopped by two police officers and searched without a court warrant. Therefore, a report on a personal search was drawn up at the police station, which stated that there were reasonable grounds to believe that the suspect might commit a crime, namely, destroy evidence (the narcotic substance – heroin). However, the applicant alleged that no search had been carried out on him either before or after his arrest, and that the substance allegedly found on him had been planted by police officers [18]. The ECtHR stated that the totality of the procedural irregularities committed during the personal search of the applicant, together with the contradictory and inconsistent evidence concerning the factual circumstances of the search, as well as the inadequate judicial review both before and during the trial, had rendered the proceedings as a whole unfair.

The main purpose of political, civil, socio-economic and cultural rights is to protect the dignity of all people. Human rights are a means of realizing human dignity [19]. For example, in the Netherlands and the USA, the right to a fair trial for people who use psychoactive substances is under serious pressure. The Netherlands and the United States have adapted their fight against drug-related crime to the limitations of criminal law, but scholars point out that the legal protection of such individuals has not yet adapted to this state policy. In some cases, it is better to apply administrative and private law measures [20]. However, experts estimate that around half a million people worldwide are detained for the purpose of "drug treatment", many held for months or years without criminal charges or the opportunity to challenge the legality of their detention. That is, the protection of human rights, effective drug policies, and the application of the principles of medical ethics remain acute problems [21]. In particular, Portugal decriminalized the public and private use, acquisition, and possession of all drugs in 2000. Therefore, it is urgent in this country to adopt a state drug policy approach focused on public health rather than public order priorities [22]. National legislation does not disclose the content of the right to a fair trial in cases related to illegal drug trafficking in a specific legal norm, but it embodies and enshrines its individual components in various regulatory legal acts. In particular, in Article 7 of the Law of Ukraine "On the Judicial System and the Status of Judges", fair and impartial consideration of cases within reasonable time limits established by law is a component of the right to judicial protection [23].

In scientific works, there is no unified understanding of the content of the „right to a fair trial," and there is no unified scientific approach to identifying its constituent elements. Some scholars believe that the right to a fair trial consists of four main aspects (substantive, institutional, material, procedural), which organically complement each other [24]. Other scholars supplement this component with the "right to a fair trial" as a security (preliminary) element that guarantees the possibility of effective implementation of this right [25]. Regarding the content of the category „right to a fair trial," the interpretation of this term in scientific works is considered in a broad and narrow sense [26, 27]. In the first case, such a right is understood as enshrined in paragraph 1 of Article 6 of the European Convention on Human Rights and is often identified with the right of access to a court [11], in compliance with the requirements set out in Article 6 of this Convention [1]. In a narrow sense,

the studied right to a fair trial covers only a "fair" judicial procedure, as well as the requirements of independence and impartiality of the court, publicity, and reasonableness of the term of the trial [28].

CONCLUSIONS

Respect for the rights of people who use psychoactive substances, including their right to a fair trial, must remain a key element of the rule of law, within the framework of protecting their lives and public health, and is an obligation of the state. In today's environment of effective measures to combat illicit drug trafficking, health authorities should play a special role. The position of the European Court of Human Rights in cases concerning illicit drug trafficking clearly outlines the need to respect the rights of persons who use psychoactive substances using the principles of legality, proportionality and necessity in both the law-making and law-enforcement activities of the state.

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The work is a fragment of 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).

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Oleksandr M. Shevchuk
Yaroslav Mudryi National Law University,
77 Hryhorii Skovoroda, 61024 Kharkiv, Ukraine
e-mail: oleksandr-shevchuk@ukr.net

ORCID AND CONTRIBUTIONSHIP
Oleksandr M. Shevchuk: 0000-0003-4864-7316 B D
Oleksandr M. Drozdov: 0000-0003-1364-1272 A E
Oleksandra V. Babaieva: 0000-0001-5427-1955 D
Inna L. Bespalko: 0000-0001-7161-1720 F
Alisa V. Panova: 0000-0001-5833-7229 B

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

RECEIVED: 04.02.2025
ACCEPTED: 27.06.2025

CREATIVE COMMONS 4.0

REVIEW ARTICLE

The national health service of Ukraine as a purchaser of medical services and medicines under the medical guarantees programme during martial law

Anatoly M. Strelchenko[1], Yuriy M. Siryi[1], Liudmyla O. Mostepaniuk[1], Oksana Yu Khablo[1], Anatolii G. Krut[2]

[1]NATIONAL ACADEMY OF INTERNAL AFFAIRS, KYIV, UKRAINE
[2]SHUPIK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: To analyse the effectiveness of the National Health Service of Ukraine, which performs the functions of a purchaser of medical services and medicines under the Medical Guarantees Programme during wartime, as well as to identify and characterise the key challenges it faces and to propose effective solutions based on statistical data and comparative analysis concerning the provision of high-quality and effective medical care to the population, along with suggesting the development of promising directions for improving the performance of the National Health Service.

Materials and Methods: Retrospective, analytical, and modelling methods were used to assess the main processes related to the activities of the National Health Service of Ukraine as a key actor in the financing of medical services within the healthcare system under martial law conditions in Ukraine. Through the use of synthesis and modelling methods, recommendations for the further reform of the National Health Service were developed, along with proposals for the development of promising directions to enhance the effectiveness of its activities.

Conclusions: The study confirmed the need to define the directions for enhancing the effectiveness of the National Health Service of Ukraine as a purchaser of medical services and medicines under the Medical Guarantees Programme during martial law. One such direction is the improvement of logistics under wartime conditions and its restoration in the post-war period, which can be outlined as follows: (a) ensuring the active digitalisation of logistics processes; (b) decentralising warehouses; (c) creating mobile medical units; (d) providing personnel training; and (e) preparing appropriate legislative regulation.

KEY WORDS: governance entity, digital evidence, medical confidentiality

Pol Merkur Lek,2025;53(4):534-539 doi: 10.36740/Merkur202504115

INTRODUCTION

Under the challenging conditions caused by the full-scale war in Ukraine, ongoing since February 2022, the effective management of financial flows and contracting of medical services has become a key element in maintaining the functioning of the healthcare system. The central authority responsible for financing the healthcare sector within the Medical Guarantees Programme (MGP) is the National Health Service of Ukraine (NHSU). Its role as a purchaser of medical services and medicines has gained particular significance during martial law, as the accessibility and quality of medical care for millions of citizens depend on its ability to respond swiftly to emerging challenges.

The main tool for implementing state policy in the healthcare sector is the Medical Guarantees Programme, which ensures state-guaranteed funding for the provision of a defined volume of medical care. The NHSU acts as the sole national purchaser by concluding contracts with both public and private healthcare institutions that meet the service provision requirements. In 2022, despite daily challenges such as shelling, population displacement, and the destruction of medical infrastructure, the NHSU transferred UAH 145,6 billion to healthcare institutions, ensuring the uninterrupted provision of care [1, 2].

A distinctive feature of the NHSU's operations during wartime has been the shift in focus from planned medical care to emergency, primary, palliative care, and rehabilitation. Priorities have included saving lives, providing medicines to internally displaced persons, and treating military personnel and those affected by hostilities. To this end, in 2023, the Medical Guarantees Programme was expanded with new service packages, including medical examinations for mobilised individuals, psychological support, and enhanced rehabilitation. In 2023, UAH 132 billion was allocated for these purposes, including UAH 97,4 billion for specialised medical care [1, 2].

AIM

This study involves a comprehensive analysis of the effectiveness of the National Health Service of Ukraine in its role as the main purchaser of medical services and medicines under the Medical Guarantees Programme during wartime. It also aims to identify and characterise the key challenges in its operations and to propose effective solutions based on statistical data and comparative analysis concerning

the provision of high-quality and effective medical care to the population during armed conflict. Additionally, the study proposes the development of promising directions to improve the effectiveness of the National Health Service both during and after the war.

MATERIALS AND METHODS

To achieve the defined goal and objectives, a set of general scientific and specialised methods was used, including: the abstract-logical method applied during the analysis of scientific sources and the review of the legal framework, particularly the main Regulation "On the National Health Service of Ukraine" and other normative legal acts in force during the war; the structural-functional and systemic methods employed in the comprehensive study of the functioning of a public administration entity such as the National Health Service of Ukraine; the historical method used to examine the historical retrospective, genesis of the creation, and functioning of the National Health Service in Ukraine during the reform period and the wartime; analogy and comparison methods applied when assessing the feasibility of implementing best practices in healthcare reform during the establishment of the National Health Service of Ukraine.

Using synthesis and modelling methods, recommendations were developed for the further reform of Ukraine's healthcare sector, including the National Health Service, under martial law and in the post-war period, as well as proposals for the development of promising directions to enhance the effectiveness of the National Health Service's activities during and after the war.

REVIEW AND DISCUSSION

In the context of the full-scale war ongoing in Ukraine since 2022, the healthcare system has faced significant challenges, as this sector is vital for ensuring the country's national security and defence. Healthcare remains under constant strain across all regions during the period of armed conflict. However, thanks to effective management and adaptation to new conditions, the National Health Service of Ukraine (NHSU) continues to fulfil its key role as the purchaser of medical services and medicines under the Medical Guarantees Programme at an adequate level.

In 2022, despite daily challenges related to the war, the NHSU transferred UAH 145,6 billion to healthcare institutions. The largest amount of funding – UAH 24,6 billion – was allocated to primary healthcare. Overall, more than 32 million Ukrainians had signed declarations with family doctors in 2022. Meanwhile, under the reimbursement programme, which includes 435 medicinal products, the NHSU paid pharmacies over UAH 2,35 billion [3, 4].

In 2023, the National Health Service of Ukraine (NHSU) paid healthcare providers over UAH 132 billion under the Medical Guarantees Programme. Specifically, UAH 97,464 billion was allocated for specialised medical care; UAH 23,380 billion for primary healthcare; and UAH 11,155 billion for emergency medical care. For 2024, nearly UAH 159 billion is planned to be allocated for the programme, which is UAH 16 billion more than last year. This includes UAH 5,2 billion for medicine reimbursement [3, 4].

The Medical Guarantees Programme in 2023 expanded with new service packages tailored to the needs of Ukrainians arising from the war. In particular, the package "Medical examination of individuals organised by territorial recruitment and social support centres" was added. Psychological support services through family doctors were fully implemented to preserve the mental health of Ukrainians. Rehabilitation packages were improved, with a clear distinction made between outpatient and inpatient rehabilitation medical care [4, 5].

The largest number of patients received care within the following packages: prevention, diagnostics, monitoring, and treatment in outpatient settings – over 13,9 million; inpatient care for adults and children without surgical operations – over 2,5 million; surgical operations for adults and children in inpatient settings – over 1.1 million; dental care for adults and children – over 1,8 million; readiness and provision of medical care to the population residing in areas of active combat – 1,062 million [4, 5].

In 2023, the National Health Service of Ukraine (NHSU) paid healthcare providers over UAH 132 billion under the Medical Guarantees Programme. Specifically, UAH 97,464 billion was allocated for specialised medical care; UAH 23,380 billion for primary healthcare; and UAH 11,155 billion for emergency medical care.

For 2024, nearly UAH 159 billion is planned for the programme, which is UAH 16 billion more than last year. This includes UAH 5,2 billion for medicine reimbursement. In 2024, the Medical Guarantees Programme will focus on restoring health and human potential [4, 5].

Thus, even under martial law conditions, the National Health Service of Ukraine (NHSU) continues to effectively perform its functions, ensuring citizens' access to quality and free medical care. The adaptation of programmes and the implementation of new technologies demonstrate the flexibility and resilience of Ukraine's healthcare system.

A crucial factor in this effectiveness has been the use of the electronic health system (e-Health), which provides real-time accounting, service delivery control, and access to medical data. It is precisely e-Health that has allowed the preservation of patients' medical histories amid constant population displacement, the continued issuance of electronic prescriptions for medicines, and the reimbursement of pharmaceuticals. For example, in 2022, under the "Affordable Medicines" programme, over UAH 2,35 billion was reimbursed for the cost of medicines [4-6].

The mentioned amounts of funds allocated by the state to the healthcare sector create risks of their unlawful use. However, the digitalisation of medical services prevents abuses of granted powers and, in case of a criminal offence, allows for the prompt and comprehensive establishment of the circumstances of the act and the

collection of sufficient evidence. Indeed, information that has evidentiary value is recorded in digital form and stored for a long period. At the same time, information about a patient's health that becomes known to the doctor holds the status of medical confidentiality. This determines the specifics of evidence collection in such criminal proceedings [7-9].

Last year, funding for the Medical Guarantees Programme increased to UAH 158,7 billion. This growth indicates the strategic importance of the healthcare system even during wartime. The NHSU plans to introduce new service packages, improve the remuneration system for medical workers, and strengthen quality control over services [2, 4, 5].

During the wartime period, financial management within the activities of the National Health Service of Ukraine (NHSU) underwent significant changes. According to official data, in 2022 the NHSU budget decreased by 18% in real terms due to the reallocation of funds to defence needs. However, by the end of 2023, thanks to international support, 85% of the pre-war funding was restored. In particular, the EU allocated €300 million specifically to support the Medical Guarantees Programme, which helped to compensate for the main losses [2, 4, 5].

An important factor in the effective operation of the NHSU is also staffing, which faces challenges such as a shortage of logistics specialists (more than 25% of specialists have left), and an increased risk for couriers in frontline zones, among others. In 2023, 75% of medications were delivered via alternative land routes from Poland and Romania, whereas in 2021 this figure did not exceed 15%. Strategic reserves of critically important drugs were created to cover 4–6 months of demand [2, 4, 5].

Human resources in the provision of medical care during the state of war face several critical challenges, significantly influenced by the demographic situation, which was exacerbated by the mobilisation of a large number of medical professionals [2, 4-6].

An important issue negatively affecting the healthcare system during the wartime period is the uneven distribution of medical specialists across regions of Ukraine: 65% of doctors and 45% of nursing staff are concentrated in the western regions, resulting in a shortage of specialists in frontline areas (only 35% of the required personnel).

The quality of medical care is also negatively affected by the increased workload on medical personnel. In particular, the average number of patients per doctor has risen from 25 to 40 per day, and 78% of medical staff work overtime [2, 7-9].

Equally important is the issue of emotional burnout: according to a survey of medical workers, 63% exhibit signs of professional burnout [8], along with a 45% increase in psychosomatic illnesses among medical staff due to constant psychological stress [4-6].

According to surveys, 12% of medical workers employed under contracts with the NHSU were mobilised into the Armed Forces of Ukraine, and another 8% left the country. This has led to a 1,5-2 times increase in workload for the remaining doctors. In response, the NHSU introduced a system of financial incentives for doctors in frontline regions, where salary bonuses reached over 70% [2-4].

An important area of international cooperation is the development and implementation of modern treatment and rehabilitation protocols in accordance with NATO and EU standards. For example, with the support of NATO and the EU4Health project, the NHSU integrated the International Classification of Functioning, Disability and Health (ICF) into its rehabilitation policy, which enabled the assessment of patients' conditions based on uniform criteria across all medical institutions in Ukraine [10-15]. Equally important is cooperation with the International Committee of the Red Cross, which assists in restoring medical infrastructure in de-occupied areas by providing healthcare facilities with necessary equipment and medications [16-18].

For effective management of medical supplies during wartime and the post-war period, it is necessary to implement comprehensive strategies that take into account the specifics of crises. The main directions for improvement are outlined below: a) Creation of strategic reserves of medicines. In emergencies, it is critically important to have pre-formed stockpiles of medicines. This ensures uninterrupted supply of medications even when logistical chains are disrupted. Research emphasises the necessity of establishing reserves based on pharmacies of all ownership types to reduce risks in ensuring the population's access to medicines; b) Implementation of digital inventory management systems. The digitalisation of accounting and control processes for medical supplies contributes to increased transparency and efficiency in management. The use of electronic systems allows for real-time tracking of medicine availability, demand planning, and avoidance of surpluses or shortages. This is especially relevant in wartime conditions where rapid decision-making is crucial; c) Optimisation of supply logistics chains. Military actions often disrupt traditional routes for delivering medical goods. Therefore, it is necessary to develop alternative logistical solutions, including the use of mobile pharmacies, field warehouses, and flexible delivery schemes. This ensures continuous supply of medicines even in the most challenging conditions; d) International cooperation and resource sharing. Collaboration with international organisations and partners enables the mobilisation of additional resources and expertise to improve medical supply management; e) Training and capacity building of personnel. Qualified personnel are a key element in effective management of medical supplies. It is necessary to provide continuous training and professional development for specialists in logistics and inventory management, especially in crisis situations; f) Use of analytical and forecasting tools. The application of modern analytical methods, such as demand forecasting models, allows for more accurate planning of medicine needs. For example, integrating demand forecasting strategies for blood components helps reduce stock levels and order frequency, thereby lowering the risk

of shortages; g) Adaptation to changes in demand and market conditions. Flexibility in inventory management enables rapid response to changes in demand and market conditions. Strategies such as Just-In-Time (JIT) can be effective provided there are stable logistics chains and predictable demand [19-25].

Medical workers in wartime experience significant psychological stress, which can lead to emotional burnout, anxiety disorders, and post-traumatic stress disorder (PTSD). To ensure their mental health, it is necessary to implement comprehensive support measures, including:

a) Implementation of psychological support programmes that include training sessions, support groups, and coaching, which are effective means of reducing emotional burnout among medical personnel. These programmes contribute to increased stress resilience, improved team communication, and restoration of motivation;
b) Development of national protocols for psychological rehabilitation;
c) Application of mindfulness techniques. The introduction of mindfulness practices, such as meditation and awareness exercises, helps medical workers reduce stress levels and maintain mental health in wartime conditions;
d) Prevention of psychotrauma, which should be targeted at society as a whole. This aims to provide psychological prevention of psychotrauma for military personnel, medical staff working in combat zones, and citizens in need, to prevent the development of PTSD;
e) Use of digital technologies. Interactive technologies and artificial intelligence can be utilised to provide psychological support to medical workers, ensuring access to consultations and resources at any time.

Thus, during martial law, the National Health Service of Ukraine has become not only a guarantor of the continuity of medical services but also a key reformer of the healthcare system. Its activities exemplify how a state institution can ensure efficiency, transparency, and adaptability under the most challenging conditions. Thanks to the Medical Guarantees Programme and the work of the NHSU, millions of Ukrainians continue to receive necessary care, which directly impacts the preservation of life and health of the population [23-25].

CONCLUSIONS

Based on the analysis of the activities of the National Health Service of Ukraine (NHSU) as the purchaser of medical services and pharmaceuticals under the Medical Guarantees Programme during wartime and the post-war period, a series of measures should be implemented to improve the quality and efficiency of this activity through the development of relevant improvement directions, in particular: a) Ensuring active digitalisation of logistics processes by implementing a unified digital registry of the needs of medical institutions, electronic monitoring of medication movement, their stock levels, and expiry dates. Integration with the e-Health system should include supply accounting functions; b) Decentralising warehouses by establishing a network of regional mini-warehouses located outside combat zones, which will reduce logistics distance and increase system flexibility in emergencies; c) Creating mobile medical units by improving logistics for delivering equipment, medicines, and personnel to mobile medical points, especially in frontline territories. To achieve this, partnerships should be developed with international organisations (such as the International Olympic Committee, WHO) that have experience in emergency response; d) Providing personnel training by forming specialised logistics teams working in healthcare, enabling faster response to changing situations, optimising delivery routes, and managing inventories more efficiently; e) Preparing legislative regulation by reviewing current laws that restrict the rapid movement of medical cargo during a state of emergency. This includes simplifying customs procedures, certification, and expediting approvals. Thus, the logistics system in healthcare under wartime conditions is a critically important component of national security. The problems revealed by the war can only be overcome through a systematic approach, integration of digital technologies, interagency cooperation, and support from international partners. Effective logistics is not only a guarantee of saving lives but also of restoring citizens' trust in the healthcare system.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Anatoly M. Strelchenko
National Academy of Internal Affairs
1 Solomjanska Square, 03035 Kyiv, Ukraine
e-mail: strel1977@ukr.net

ORCID AND CONTRIBUTIONSHIP
Anatoly M. Strelchenko: 0009-0009-4535-3647 A B D F
Yuriy M. Siryi: 0009-0006-4203-9525X B
Liudmyla O. Mostepaniuk: 0000-0003-2894-0654 A F
Oksana Yu. Khablo: 0000-0003-3923-275X B F
Anatolii G. Krut: 0000-0001-6503-3952 E F

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

RECEIVED: 07.02.2025
ACCEPTED: 25.06.2025

CREATIVE COMMONS 4.0

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REVIEW ARTICLE

Edwards syndrome: Neurocognitive and linguistic profile, diagnosis, overlaps and treatment

Dimitra V. Katsarou[1], Alexandros Argyriadis[2], Maria Sofologi[3], Agathi Argyriadi[4], Georgios A. Kougioumtzis[5], Kalliopi Megari[6], Evangelos Mantsos[7], Maria Theodoratou[8]

[1]UNIVERSITY OF THE AEGEAN, MITILINI, GREECE
[2]HELLENIC MEDITERRANEAN UNIVERSITY, CHANIA, GREECE
[3]UNIVERSITY OF IOANNINA, IOANNINA, GREECE
[4]FREDERICK UNIVERSITY, NICOSIA, CYPRUS
[5]NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, ATHENS, GREECE
[6]UNIVERSITY OF YORK, EUROPE CAMPUS, THESSALONIKI, GREECE
[7]UNIVERSITY OF WESTERN MACEDONIA, KOZANI, GREECE
[8]NEAPOLIS UNIVERSITY, NEAPOLIS, CYPRUS

ABSTRACT

Aim: To provide a comprehensive understanding of the profound developmental and medical challenges associated with this condition.

Materials and Methods: This study employed a narrative review methodology, drawing upon a wide range of peer-reviewed scientific literature, clinical guidelines, and case studies. The reviewed materials were selected based on their relevance to the neurocognitive, linguistic, diagnostic, and therapeutic aspects of Edwards syndrome. Databases such as PubMed, Scopus, and Google Scholar were used, with key terms including „Edwards syndrome," „trisomy 18," „developmental delays," „prenatal diagnosis," and „palliative care." Comparative analysis was conducted to explore clinical overlaps with related syndromes such as trisomy 13 and Turner syndrome.

Conclusions: Edwards syndrome presents significant challenges, requiring early diagnosis and multidisciplinary care to improve quality of life. Comprehensive understanding and tailored interventions can foster better outcomes and enhance family support systems.

KEY WORDS: Edwards syndrome, trisomy 18, neurocognitive profile, linguistic impairment, prenatal diagnosis, therapeutic interventions, developmental delays

Pol Merkur Lek,2025;53(4):540-545 doi: 10.36740/Merkur202504116

INTRODUCTION

Genetic syndromes refer to a range of disorders caused by abnormalities in an individual's DNA, which can result from mutations, chromosomal changes, or inherited gene defects. These syndromes often affect multiple body systems, leading to diverse clinical manifestations that can range from mild to severe. Advances in genetic research have made it easier to diagnose and understand these conditions, enabling more personalized treatment and management approaches [1,2].

Edward's syndrome, also known as trisomy 18, is a genetic disorder caused by the presence of an extra 18th chromosome. This condition significantly affects multiple organ systems and is associated with a range of severe developmental and health challenges. The syndrome is characterized by features such as low birth weight, microcephaly, a distinctive facial appearance, and congenital anomalies in the heart, kidneys, and other organs [3].

The incidence of Edward's syndrome is approximately 1 in 5,000 live births, although the majority of affected pregnancies result in miscarriage or stillbirth [4]. The survival rate for infants born with trisomy 18 is low, with many not surviving past their first year of life; however, some individuals may live into their teenage years or beyond, albeit with significant medical complications [5]. Diagnosis typically occurs during prenatal screening or postnatally through karyotyping, which confirms the presence of the extra chromosome [6]. Management of Edward's syndrome focuses on supportive care and addressing specific health issues, as there is currently no cure for the condition [7].

Children born with Edward's syndrome face a range of significant somatic problems due to the extra copy of chromosome 18. These issues affect multiple organ systems, resulting in profound developmental and functional challenges. Cardiovascular abnormalities are among the most common somatic problems. Approximately 90% of individuals with trisomy 18 have congenital heart defects, including ventricular septal defects (VSD), atrial septal defects (ASD), and patent ductus arteriosus (PDA) [8]. These conditions can lead to heart failure, poor circulation, and

increased risk of infections. Respiratory issues are also prevalent, with many infants experiencing weak muscle tone (hypotonia) that compromises their ability to breathe and swallow effectively. This often results in chronic respiratory infections, feeding difficulties, and failure to thrive [9].

Another major concern is gastrointestinal problems, particularly malformations such as omphalocele (where organs protrude from the abdomen) and esophageal atresia (a blockage of the esophagus). These complications further hinder feeding and nutrition, necessitating medical intervention [10]. Neurological impairments are significant, with microcephaly (abnormally small head) being a common feature. These neurological deficits contribute to profound intellectual disabilities and developmental delays. Seizures and apneic episodes are also frequently observed, complicating the overall management of the condition [11]. Musculoskeletal abnormalities, such as arthrogryposis (joint contractures) and rocker-bottom feet, limit mobility and function, adding to the physical challenges experienced by individuals with Edward's syndrome [10].

AIM

To provide a comprehensive understanding of the profound developmental and medical challenges associated with this condition.

MATERIALS AND METHODS

This study employed a narrative review methodology, drawing upon a wide range of peer-reviewed scientific literature, clinical guidelines, and case studies. The reviewed materials were selected based on their relevance to the neurocognitive, linguistic, diagnostic, and therapeutic aspects of Edwards syndrome. Databases such as PubMed, Scopus, and Google Scholar were used, with key terms including „Edwards syndrome,"„trisomy 18,"„developmental delays," „prenatal diagnosis," and „palliative care." Comparative analysis was conducted to explore clinical overlaps with related syndromes such as trisomy 13 and Turner syndrome.

REVIEW AND DISCUSSION

The neurocognitive profile of individuals with Edward's syndrome is marked by significant developmental delays and intellectual disabilities, which stem from the extensive neurological impairments caused by the extra chromosome 18. These children generally have severe global developmental delays, affecting cognitive, motor, and language skills. Intellectual disability in Edward's syndrome is typically profound, with most affected children demonstrating very limited cognitive function. Studies show that the majority of individuals with trisomy 18 function at a developmental level equivalent to less than one year of age, even if they survive beyond infancy [12]. This profound intellectual impairment affects learning, problem-solving, and memory.

Motor development is also significantly delayed. Children with Edward's syndrome typically have severe hypotonia (low muscle tone), leading to challenges in motor milestones such as sitting, crawling, or walking. Those who live into later childhood may achieve some basic motor skills but often remain dependent on caregivers for mobility and daily care [13].

Language development in children with Edward's syndrome is profoundly impaired due to the significant intellectual disabilities and neurological deficits associated with the condition. Most children with trisomy 18 experience severe delays in communication, with many having little to no verbal communication ability. Children with trisomy 18 typically have minimal verbal language development. The vast majority do not develop functional speech, and if they do, their vocabulary is extremely limited. Research indicates that most children do not progress beyond simple sounds or vocalizations [14]. This lack of verbal communication is linked to extensive neurological impairments and motor difficulties affecting oral coordination and speech production [10, 14]. Despite these severe limitations, some parents report that their children can show social awareness and respond to their environment through non-verbal cues, such as eye contact or facial expressions, indicating some degree of emotional and sensory awareness [15].

While verbal communication is severely limited, some children with trisomy 18 may develop basic non-verbal communication skills. These include the use of gestures, facial expressions, or eye contact to convey simple needs or emotions. Caregivers and therapists often focus on encouraging these non-verbal forms of interaction to help the child engage with their environment [14]. For instance, some children can use eye-gaze systems or basic sign language to make choices or express preferences.

Receptive language, or the ability to understand spoken language, is also severely delayed in children with trisomy 18. Although they may recognize familiar voices or sounds, their ability to comprehend and follow verbal instructions is minimal due to their cognitive limitations [16]. However, some children may show limited recognition of caregivers' voices or respond to comforting tones, suggesting some level of basic auditory processing [11].

The neurological abnormalities contributing to these deficits include microcephaly, abnormal brain structure, and reduced cortical development, which are consistently observed in neuroimaging studies of trisomy 18 patients [17]. Memory deficits in individuals with Edward's syndrome (trisomy 18) are profound, reflecting the extensive neurodevelopmental abnormalities associated with the condition. Due to the severe intellectual disabilities and global developmental delays, both short-term and long-term memory functions are significantly impaired.

Short-term memory, which involves the ability to retain and manipulate information over brief periods, is extremely limited in individuals with trisomy 18. This is largely due to the structural brain abnormalities, such as microcephaly and reduced cortical development, which affect the brain regions responsible for processing and retaining new information [11]. These neurological deficits hinder the child's ability to engage in basic cognitive tasks, such as recognizing objects, and people, or responding consistently to stimuli.

Long-term memory deficits are similarly profound. The limited cognitive development observed in trisomy 18

means that affected individuals often do not form long-term memories or retain learned behaviors over time. Even in cases where children survive beyond infancy, there is little evidence to suggest significant long-term memory retention. Their ability to recall information, and events, or develop learned skills remains very minimal [14]. This makes educational and therapeutic interventions focused on cognitive and memory improvement particularly challenging, as the neural capacity to store and retrieve information is severely restricted. In general, the overall neurological impairment seen in Edward's syndrome, including abnormalities in brain structure and function, contributes to a severely compromised memory profile, which impacts both daily life functioning and learning potential [16].

Diagnosis of Edward's syndrome can occur during both the prenatal and postnatal periods, using a combination of screening and confirmatory tests. Prenatal screening for Edward's syndrome is often offered to expectant mothers, especially those at higher risk, such as women of advanced maternal age. Screening tests include ultrasound imaging and maternal serum markers, which can indicate an increased likelihood of trisomy 18. Ultrasound can detect physical anomalies characteristic of Edward's syndrome, such as growth retardation, heart defects, and limb deformities, which may prompt further investigation [18].

Non-invasive prenatal testing (NIPT), which analyzes fetal DNA in the mother's blood, has become increasingly popular for screening trisomies, including trisomy 18, due to its high sensitivity and specificity [19]. While NIPT is not diagnostic, a positive result would lead to confirmatory testing. The definitive prenatal diagnosis of trisomy 18 is made via karyotyping, typically following invasive procedures such as amniocentesis or chorionic villus sampling (CVS). These procedures allow for the collection of fetal cells, which can then be analyzed to detect the presence of an extra 18th chromosome [20].

If Edward's syndrome is not detected prenatally, the diagnosis is usually made shortly after birth based on the infant's characteristic physical features, including microcephaly, low birth weight, clenched fists, and other congenital anomalies [16]. Confirmation is achieved through postnatal karyotyping, which remains the gold standard for diagnosing trisomy 18 [11]. This test can identify the presence of an additional chromosome 18 in the cells, confirming the diagnosis.

Edward's syndrome shares clinical and genetic features with other chromosomal disorders, leading to potential overlaps in diagnosis and presentation. These overlaps can make early identification and differentiation from other conditions more challenging.

Trisomy 13, also known as Patau syndrome, is another autosomal trisomy that shares multiple clinical features with trisomy 18. Both conditions present with severe developmental delays, growth retardation, and congenital malformations. Common overlaps include congenital heart defects, such as ventricular septal defects, and craniofacial anomalies, such as cleft palate and microphthalmia [21]. However, trisomy 13 is more likely to involve midline defects, such as holoprosencephaly (failure of the brain to divide into two hemispheres), which is less common in Edward's syndrome [16].

Turner syndrome, a sex chromosome disorder resulting from the partial or complete absence of one X chromosome in females, can also present with some overlapping physical features. These include growth retardation, congenital heart defects (such as coarctation of the aorta), and limb anomalies. However, Turner syndrome typically lacks the severe intellectual disability seen in trisomy 18 and does not involve the same extensive multi-organ malformations [22].

Certain rare genetic syndromes, such as Smith-Lemli-Opitz syndrome and Cornelia de Lange syndrome, can exhibit similar features to trisomy 18, such as growth restriction, limb abnormalities, and developmental delays. However, these syndromes are caused by different genetic mechanisms, such as mutations in specific genes, rather than a chromosomal trisomy, which helps differentiate them from Edward's syndrome [11].

During prenatal screening, Edward's syndrome can sometimes be confused with other aneuploidies, particularly Down syndrome (trisomy 21). Both can present with abnormal ultrasound findings and increased nuchal translucency. However, Edward's syndrome is more strongly associated with severe intrauterine growth restriction, abnormal limb positioning, and a higher likelihood of fetal loss during pregnancy [19].

Therapies for individuals with Edward's syndrome are largely focused on supportive and palliative care, aimed at improving quality of life rather than curative interventions, given the severity of the condition and the low life expectancy. Due to the complex medical needs and poor prognosis, palliative care is often prioritized for children with trisomy 18. This approach focuses on providing comfort, managing symptoms, and supporting the family. Key elements include pain management, addressing feeding difficulties, and managing respiratory complications [23]. Palliative care teams often work closely with families to create care plans that respect the child's quality of life and parental wishes, particularly in cases of severe congenital malformations that may not be surgically treated.

In some cases, surgical interventions may be considered, particularly for congenital heart defects like ventricular septal defects (VSD) or patent ductus arteriosus (PDA), which are common in trisomy 18 [24]. However, decisions about surgery are complex, as the risks are high and survival rates are often low. Some centers may opt for limited interventions if the child's condition is stable enough and surgery could significantly improve quality of life, though many parents and healthcare teams opt against aggressive treatments given the prognosis.

Feeding difficulties, often due to weak muscle tone and gastrointestinal malformations, are common in children with Edward's syndrome. As a result, nutritional therapy becomes an essential aspect of care. Many children require gastrostomy tube (G-tube) placement to ensure adequate nutrition and hydration [11]. Nutritional support aims to

prevent malnutrition and failure to thrive, but it is typically part of a broader supportive care approach rather than an effort to prolong life indefinitely.

For children who survive into infancy and beyond, physical and occupational therapy can help maximize their functional abilities, even though developmental milestones are severely delayed. These therapies focus on improving muscle tone, facilitating mobility, and enabling the child to engage with their environment to the best of their ability. Though significant developmental progress is rare, these therapies can enhance the quality of life by promoting comfort and limited independence [14].

Many children with trisomy 18 suffer from chronic respiratory issues due to weak chest muscles, frequent infections, and abnormal airway anatomy. Respiratory therapy can include interventions such as oxygen supplementation, suctioning of airway secretions, and, in some cases, the use of continuous positive airway pressure (CPAP) or mechanical ventilation [25]. Decisions about long-term ventilation are often guided by considerations of quality of life and the family's wishes.

Given these challenges, speech and language therapy is an important component of care for children with trisomy 18. Therapists typically focus on improving communication through alternative methods, such as augmentative and alternative communication (AAC) systems. These systems can include picture boards, communication devices, or simple sign language, which help children express basic needs and engage with their caregivers, even when verbal communication is not possible [14].

Educational interventions for children with Edward's syndrome are typically focused on individualized and highly supportive strategies that address the profound developmental delays and intellectual disabilities associated with the condition. Given the significant cognitive and physical impairments, educational goals are generally tailored to improve the child's quality of life, encourage sensory engagement, and support limited communication and mobility skills.

Children with trisomy 18 who survive into later infancy and childhood often qualify for Individualized Education Programs (IEPs) under special education services. IEPs are designed to meet the unique educational needs of each child by setting personalized goals, which may include improving motor skills, communication, and social interaction. These programs are developed in collaboration with a multidisciplinary team, including special education teachers, physical therapists, and speech therapists, to ensure the child receives appropriate support [16].

Given the profound intellectual and developmental delays, many educational interventions focus on sensory stimulation. Activities that involve touch, sound, and visual stimuli are used to engage children with trisomy 18, promoting interaction with their environment. Sensory-based learning strategies can help improve the child's responsiveness to external cues and foster a sense of connection with caregivers and educators [22]. These interventions can include activities such as exposure to soft textures, gentle music, and bright colors, which help stimulate the child's limited cognitive abilities.

Since most children with trisomy 18 have little to no verbal communication, augmentative and alternative communication (AAC) devices or systems may be introduced to help them express basic needs. This can include the use of picture boards, gestures, or assistive communication devices tailored to the child's capabilities. Although the cognitive limitations may prevent mastery of complex communication, some children can learn to use simplified systems to indicate choices or preferences, improving their interaction with others [15].

Physical and occupational therapy play a crucial role within educational settings for children with Edward's syndrome. Physical therapy focuses on improving gross motor skills, such as head control and sitting, while occupational therapy helps children develop fine motor skills and assists them with activities of daily living. These therapies are often integrated into the educational environment, helping children improve their mobility, posture, and functional use of their hands [14].

Early intervention services, typically provided before the age of three, are particularly important for children with trisomy 18. These programs offer specialized therapies designed to address developmental delays as early as possible, which may include speech therapy, feeding therapy, and physical therapy [16]. The goal of early intervention is to maximize the child's developmental potential and provide the family with resources and strategies for supporting their child's needs.

Educational interventions for children with trisomy 18 often emphasize quality of life rather than traditional academic achievement. These programs aim to create a positive and stimulating environment where the child can experience social interaction, sensory exploration, and the satisfaction of meeting individualized goals, even if those goals are not on par with typical developmental milestones [14].

The clinical presentation of Edwards syndrome (trisomy 18) embodies the intersection of profound genetic complexity and human developmental vulnerability. Children with this condition face extensive neurocognitive and physiological impairments from birth, often resulting in brief life expectancy and significant challenges to both care provision and ethical decision-making. This discussion explores the implications of these realities, not only from a biomedical standpoint but also through developmental, familial, and societal lenses.

At the heart of the Edwards syndrome profile lies severe global developmental delay. The presence of an extra chromosome 18 disrupts the architecture and connectivity of the developing brain, as seen in consistent findings of microcephaly, cerebellar hypoplasia, and cortical underdevelopment. These neurological anomalies manifest as extreme intellectual disability, absent or minimal verbal language, and very limited motor achievements. While these deficits might suggest a uniformly „non-responsive" child, qualitative studies and parental reports challenge this assumption. Some children demonstrate relational

awareness – such as responding to voice, touch, or gaze – which, although subtle, reflects a retained capacity for sensory-emotional engagement. These insights call for a redefinition of developmental progress in trisomy 18, one that values relational and sensory interactions as meaningful developmental outcomes in their own right.

The linguistic profile of children with Edwards syndrome is shaped by both neurological and anatomical limitations. Most never develop functional speech. Nevertheless, the potential for non-verbal communication should not be underestimated. The use of augmentative and alternative communication (AAC) systems, such as eye gaze technologies or picture boards, has shown promise in enhancing expressive capabilities, even minimally. Such tools challenge the assumption that lack of speech equals lack of understanding. As language is a key conduit for human dignity and autonomy, investing in AAC and training caregivers to interpret non-verbal cues can transform the child's relational environment, facilitating not only communication but also participation and emotional reciprocity.

While prenatal screening and diagnostic advancements (such as NIPT and karyotyping) have greatly enhanced early detection, they also raise complex ethical questions. Parents are often presented with a diagnosis of trisomy 18 accompanied by bleak survival statistics, which may pressure them toward pregnancy termination. Yet, survival beyond infancy, although rare, is possible and accompanied by a wide range of functioning. This variability underscores the ethical tension between clinical prognostication and the uniqueness of individual developmental trajectories. Counseling must therefore be non-directive, grounded in evidence, and sensitive to parental values, ensuring that families are supported, not steered, in their decision-making process.

Historically, a diagnosis of trisomy 18 often led to the withholding of active treatment. However, recent shifts in pediatric ethics advocate for individualized assessments over categorical judgments. Children with Edwards syndrome can benefit from supportive interventions that emphasize comfort, engagement, and dignity. Physical and occupational therapies can alleviate musculoskeletal discomfort and enhance mobility, even in small ways. Early intervention services and sensory-stimulating educational environments support not cognitive recovery, but quality of life, caregiver bonding, and developmental enrichment.

Educational strategies, although highly adapted, play a crucial role in shaping the child's day-to-day experiences. Activities that promote sensory awareness, social interaction, and basic choice-making are valuable for both the child and the caregivers. Individualized Education Programs (IEPs) tailored to children with profound disabilities are not about meeting standard milestones but about achieving personalized, meaningful moments of connection and autonomy.

Perhaps most importantly, the discussion must include the psychosocial and emotional dimensions of caregiving. Families of children with Edwards syndrome often navigate complex medical systems, societal stigma, and ambiguous futures. Yet, many also report deep emotional bonds, resilience, and meaning-making in their caregiving role. Professionals should acknowledge this emotional terrain, offering consistent support services, peer connections, and respite care. Multidisciplinary teams – comprising geneticists, neonatologists, therapists, educators, and psychologists – are essential in providing holistic care that respects the child's life while supporting the family's evolving needs.

CONCLUSIONS

In conclusion, Edward's syndrome represents a complex interplay of genetic factors that profoundly impact individuals and their families. As our understanding of these disorders continues to evolve through advancements in genetic research and technology, we are witnessing a shift towards more effective diagnosis, treatment, and support strategies. Increased awareness and education about genetic syndromes not only foster empathy and inclusion but also empower affected individuals and their families to advocate for their needs. The future holds promise, with ongoing research paving the way for potential therapies that target the underlying genetic causes of these syndromes. By continuing to expand our knowledge and resources, we can enhance the quality of life for those living with genetic conditions and move closer to a world where all individuals are recognized for their unique contributions, regardless of their genetic makeup.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Alexandros Argyriadis
Hellenic Mediterranean University
G, Romanou 3, Chania 731 33, Greece
e-mail: hsc.arg@frederick.ac.cy

ORCID AND CONTRIBUTIONSHIP
Dimitra V. Katsarou: 0000-0001-8690-0314 (A) (B) (D) (E) (F)
Alexandros Argyriadis: 0000-0001-5754-4787 (D) (E)
Maria Sofologi: 0000-0003-0380-2220 (E)
Agathi Argyriadi: 0000-0003-3935-0414 (D) (E)
Georgios A. Kougioumtzis: 0000-0002-2362-2094 (B)
Kalliopi Megari: 0000-0002-5861-7199 (B) (E)
Evangelos Mantsos: 0009-0002-8490-2660 (A)
Maria Theodoratou: 0000-0003-4200-4643 (D) (E)

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

RECEIVED: 19.11.2024
ACCEPTED: 04.07.2025

CREATIVE COMMONS 4.0

REVIEW ARTICLE

Human papillomavirus: problems and prospects for women's reproductive health (systematic review)

Oleksandr Y. Hrynevych
LLC „ECOFARM", KYIV, UKRAINE

ABSTRACT

Aim: To consider the specific activity of drops and suppositories of PROTEFLAZID® at the stage of preclinical study, to assess the effectiveness and safety of use in clinical practice in papillomavirus-associated diseases of the female reproductive system.

Materials and Methods: Analysis of scientific publications on the treatment of palilomavirus infection with PROTEFLAZID® in women over the past decade.

Results: Medicines have a direct antiviral effect on papillomaviruses. Clinical trials have shown that the drugs are safe and effective agents for the treatment of papillomavirus-associated CIN1 and CIN2 in the mode of simultaneous systemic and topical use. The proposed scheme is a promising method of treating class I-II neoplasias in women of reproductive age, as it avoids cervical damage, early and late complications and preserves female reproductive function.

Conclusions: PROTEFLAZID® (drops and suppositories) are safe and effective etiopathogenetic drugs for the systemic and topical treatment of papillomavirus-associated diseases in women. Medicines demonstrate the potential for the prevention of cervical cancer, as they allow organ-preserving treatment in women of reproductive age as a guarantee of future motherhood.

KEY WORDS: papillomaviruses, dysplasia, prevention, treatment, PROTEFLAZID®

Pol Merkur Lek,2025;53(4):546-554 doi: 10.36740/Merkur202504117

INTRODUCTION

Cervix disorders are of particular importance both in the clinical practice of obstetricians and gynaecologists and in the healthcare sector in general. Their incidence is exceptionally high and does not tend to decrease. Early detection and proper treatment of both pre-existing conditions and precancerous cervix disorders can prevent the onset of cervical cancer (CC). Hence, the issue of early diagnosis and treatment of cervix disorders from the perspective of women's reproductive health is crucial, as the absence of symptoms of the condition facilitates its progression.

Multiple investigations by morphologists, oncologists, gynaecologists and immunologists indicate that DNA-containing viruses, namely human papillomaviruses (HPV), are an etiological factor for CC.

The production of intact viral particles characterises the non-integrated form of infection. This is when HPV infection is asymptomatic and extremely pathogenic.

In patients with pre-existing cervix disorders (diseases), HPV infection is common. Therefore, the issue of HPV infection warrants particular attention, given the presence of a viral factor (HPV) that puts such patients at increased risk of CC.

HPV can be classified as a disease that affects the nation's demographics, as the infection is sexually transmitted. In pregnancy, latent HPV becomes active due to changes in the immune system and accelerates the tumour transformation of the cervical epithelium. Infection during pregnancy and childbirth is also possible. Typically, young women and men aged 20-30 years are affected, who consult an oncologist with an advanced disease, since the disease progression to malignancy is slow and almost unnoticeable to patients.

Genital HPV infection is one of the most common sexually transmitted infections [1-33]. Viral infections play a prominent role among reproductive system diseases due to the global deterioration of the population's immune status [34-42]. HPV is a DNA-containing viruse of the family Rapovaviridae and has a tropism for squamous cell carcinoma [35, 38, 39, 41]. Current data indicate that HPV is a conditional pathogen, as evidenced by its diagnosis in 10-30% of women without reproductive system diseases [2, 7, 15, 17]. Spontaneous regression of the virus is possible within 1-2 years (in the case of non-oncogenic types), and in cases of highly oncogenic types, the infection often acquires a persistent character [1]. HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 are considered to be the most highly carcinogenic types [35, 38, 39], which account for 71.5% of cervical cancer cases in Europe [33,38,39,42]. Viral infection was shown to remain latent for several years; however, its presence increases the risk of developing cancer by an average of 300 times; 99.7% of cervical squamous cell carcinoma cases contain human papillomavirus DNA [15, 39, 42]. The pathogenetic foundation of HPV-induced cancer is the integration of viral DNA into the chromosomes of infected cells, active synthesis of viral oncoproteins E_6 and E_7, and disruption of the normal process of apoptosis and cell differentiation [15, 35, 38, 42]. HPV leads to chronic

inflammation of the cervix (HPV-associated cervicitis) in 5-15% of patients [1, 4, 12, 26, 27, 32].

Cervical cancer ranks seventh among the most common types of cancer among women in the European region. Its share in the total cancer incidence is about 3.8% [20], and it is the second most common cancer among women worldwide [9]. Most cases of cervical cancer come from less developed regions-low- and middle-income countries, and less often from high-income countries where monitoring programmes are in place [9, 10, 20, 30].

According to the National Cancer Registry, CC ranks as the fifth most common cancer among Ukrainian women. Currently, Ukraine records 20 cases of CC per 100,000 women [22]. For many years, CC has been proven to be preceded by precancerous lesions-cervical intraepithelial neoplasias (CINs). CINs are most often localised in the cervical epithelial transformation area and are associated with persistent HPV infection.

In Poland (as of 2018), the female population (over 15 years of age) was 17.1 million, with 14.4% of them carrying HPV with normal cytology, which amounted to 2.46 million people. The total number of infected women reached 4.92 million. The estimated number of women with persistent HPV infection who may develop cervical cancer ranges from 246,000 to 492,000 [29]. This cohort of the Polish female population needs timely etiopathogenetic treatment to preserve reproductive function and health, just like women in other countries.

Annually, more than 30 million new cases of mild cervical squamous epithelium dysplasia are diagnosed worldwide, with more than 10 million cases of moderate and severe dysplasia [37]. Regrettably, Ukraine does not record the incidence of cervical precancer in the Cancer Registry. Hence, the data are somewhat contradictory, as the incidence of cervix disorders is recorded based on the published data and ranges from 18 to 43%. Intraepithelial cervical lesions are essentially stages of cervical carcinogenesis. Timely diagnosis and treatment of CIN is a prevention of invasive CC.

To date, numerous studies showed that cervical epithelial dysplasia and cervical cancer develop in the context of CIN [11, 19, 36].

HPV infection is the major and key risk factor for CC. An HPV serotype is detected in 99.7% of CC cases [1]. The epithelial layers of the skin and mucous membranes represent the target cells for this virus. The ultimate result of the transformative effect of HPV is CIN, whose progression leads to CC [3].

Certain types of HPV, high-risk (HR) HPVs, have an increased ability to transform the cervical epithelium with subsequent malignancy. HPV 16 is the most prevalent type globally, found in almost 50% of CC patients, followed by HPV 18 in 15% of CC patients, and HPV 31 and 45 in 10% of CC patients [18, 23, 34].

In Ukraine, HPV 16 is also the most common type, regardless of the patient's age. An epidemiological feature of HPV infection in Ukraine is the high incidence of HPV 53, 31, 33, and 68; HPV 18 ranks only 9th. The risk of HPV persistence and progression of cervical epithelial dysplasia rises when several high viral load HPV types come up simultaneously. Both high- and low-risk HPV types or their combination can be the etiological factor in the development of CIN1 and CIN2 [11, 25].

The national and international literature provides a wealth of information that HPV infection occurs at the level of immature cells of the epithelium of the skin and mucous membranes (basal layer). As the cells move towards the epithelial surface, they differentiate. HPV actively replicates in differentiated cells. The passage of one infected cell from the basal layer to the surface layer can take up to 3 months. This fact determines the need for long-term HPV therapy for at least 3 months [11].

Subsequently, as HPV progresses, a decrease in immune defence and impaired apoptosis play a crucial role.

The immune system's inability to cope with the virus results in long-term HPV persistence in the cervical epithelium. The virus DNA integrates into the epithelial cell DNA. It starts the synthesis of the so-called oncoproteins E_6 and E_7. HPV oncoproteins E_6 and E_7 bind to cellular proteins that suppress the formation of malignant cells (p53 and pRB). This blocks the apoptosis (self-destruction) of the infected cell and blocks the control of proliferation. Consequently, the altered cells divide uncontrollably and intensively, forming a clone of tumour cells.

Importantly, HPV infection of epithelial cells is a prerequisite but insufficient factor for cancer development. The following are also essential to develop irreversible neoplasia: active expression of the E_6 and E_7 genes and high-risk HPV types; induction of metabolic mechanisms for the conversion of estradiol to 16-OH; and induction of multiple chromosomal DNA damage in the infected cell, which completes the degeneration process [41].

Unfortunately, irrespective of the current knowledge of precancerous cervical lesions and their diagnosis and treatment, the incidence of invasive CC is more than 500,000 women a year worldwide, with 274,000 dying from the disease [10]. In Ukraine, 58,419 women were registered with healthcare facilities with CC diagnoses in 2022-2023 [22].

Such statistics compel doctors to improve approaches for optimising the management and treatment of HPV infection and CIN, avoiding overdiagnosis and unnecessary invasive interventions in young women that can interfere with their reproductive function; this is critical in the context of the global demographic crisis, and especially in Ukraine and Poland.

Although proven effective, invasive interventions are traumatic and can disrupt a patient's reproductive plans. At the same time, long-term monitoring and watchful waiting strategies may be dangerous due to the risk of further progression. Therefore, the search for a conservative and safe treatment for HPV infection and CIN1 and CIN2 is still relevant.

Currently, using Ukrainian-made medicinal products PROTEFLAZID® (drops) and PROTEFLAZID® (suppositories) (SMC ECOPHARM LTD) is a promising treatment for HPV-associated CIN1 and CIN2 (mild-to-moderate). The medicinal products have a direct antiviral effect on DNA viruses, which include HPV. The active substances of these antivirals are

the flavonoids apigenin, tricine, and luteolin, obtained from *Herba Deschampsia caespitosa L.* and *Herba Calamagrostis epigeios L.* Flavonoids inhibit DNA polymerases (specific enzymes of papillomaviruses) in cells infected with the virus. These enzymes inhibition leads to the cessation of viral DNA replication, thereby preventing its reproduction.

PROTEFLAZID® (drops) has a specific direct antiviral effect on HPV. This was proven in studies of the specific antiviral activity of PROTEFLAZID® (drops) against HPV in *in vitro* experiments conducted at State Institution „L.V. Gromashevsky Institute of Epidemiology and Infectious Diseases of the National Academy of Medical Sciences of Ukraine" (Kyiv, Ukraine) [24].

An HPV culture model established the specific activity of the active substance of PROTEFLAZID® (drops) in HPV infection at the non-clinical stage of research. The HPV-producing cell culture was obtained by transfection of DNA isolated from infected human cells in suspension cultures of MT 4 cells (suspension culture of human lymphoblastoid cells) and transfected Baby Hamster Kidney fibroblasts (BHK cells). HPV testing was performed by PCR for virus cytopathic action and cytological characteristics such as mitotic index and abnormal mitoses. The HPV isolates were tested with primers for HPV 16, 18, 31, 33, 35, 39, 45, 52, 58, 59, and 67. PROTEFLAZID® (drops) was found to exert a cytopathic effect in the culture of transfected BHK cells, characterised by the formation of transformation foci. *In vitro* experiments established the ability of PROTEFLAZID® (drops) to inhibit HPV reproduction in cell culture by 2 lg ID_{50} [24]. Cytological studies confirmed that following exposure to PROTEFLAZID® (drops), the level of abnormal mitosis in HPV-infected cells was the same as in uninfected cells. PROTEFLAZID® (drops) substantially reduces mitotic activity and the level of abnormal forms of mitosis in HPV-infected cells. These results point to a high degree of inhibition of the proliferative and destructive effects of HPV on cells, which is essential for the clinical efficacy of the specific effect of PROTEFLAZID® against oncogenic HPV. PROTEFLAZID® also inhibits the synthesis of virus-specific enzymes: Thymidine kinase, DNA and RNA polymerases, and reverse transcriptase in virus-infected cells, which is especially important in viral mix infection. The inhibition of cell transformation involves three mechanisms: Inhibition of cell proliferation, induction of cell differentiation, and induction of cell apoptosis. PROTEFLAZID® stimulates apoptosis and, therefore, can inhibit HPV reproduction and cell proliferation. In infected cells, PROTEFLAZID® is capable of inhibiting viral DNA and RNA polymerases. This mechanism was revealed when PROTEFLAZID® (drops) was evaluated in model systems: Transcriptional (DNA-dependent RNA polymerase of bacteriophage T7) and replicative (Taq DNA polymerase) [24].

The above non-clinical studies suggest that PROTEFLAZID® (drops) has specific antiviral activity against DNA-containing HPV.

Furthermore, PROTEFLAZID® (drops) induces the synthesis of endogenous alpha- and gamma-IFNs, which is one mechanism of antiviral action and is confirmed by the detected levels of IFN-alpha and RNase L gene expression. As such, the medicinal product also enhances the body's nonspecific resistance to viral and bacterial infections. PROTEFLAZID® (drops) induces the synthesis of interferons to physiologically active levels without developing refractoriness, whereby immune cells cannot respond to repeated (multiple) inductor administration by producing interferons. Refractoriness leads to the failure of the first line of antiviral protection and, as a result, to developing any infectious complications. Hence, the medicinal product can be used for a long time (vital in treating HPV infection) without risk of immune system depletion. PROTEFLAZID® (drops) stimulates tissue macrophages (increasing their capture, absorption, and digestive capacity), representing an important part of the body's non-specific defence against infectious agents. It can restore the levels of local immunity in both early and late immune responses in the treatment of HPV infection, affecting both early and late immune responses.

PROTEFLAZID® (suppositories) normalises local immunity factors: Secretory IgA, lysozyme, complement component C_3. This results in restoration of the barrier function of the vaginal and cervical mucosa. In addition, the medicinal product helps to resolve dysbiotic disorders of the vaginal microflora, restores the normal vaginal biotope, and accelerates the regeneration of the cervical mucosa epithelium. This is a vital aspect for treating and preventing disease recurrence, given that HPV penetration into the basal cells, where infection occurs, depends on the disruption of the epithelium's integrity and barrier function.

Moreover, PROTEFLAZID® (drops) affects an important mechanism of progression of the HPV infection - the disruption of apoptosis. The medicinal product potentiates the effect of apoptosis-inducing substances and activates caspase 9, thereby promoting the clearance of virus-affected cells and primary prevention of chronic diseases in the context of latent viral infections.

PROTEFLAZID® (drops and suppositories) has a direct antiviral effect on HPV and mechanisms of influence on key processes of HPV progression (which can lead to tumour transformation of the cervical epithelium), the possibility of prolonged use (three months or more) with no development of immune system refractoriness allows us to consider the use of PROTEFLAZID® (drops and suppositories) in the treatment of patients with diagnosed HPV infection complicated by mild-to-moderate cervical epithelial neoplasia as an etiopathogenetic treatment of HPV infection and secondary prevention of CC.

Currently, PROTEFLAZID® is available in two pharmaceutical forms: Oral drops and vaginal suppositories. The availability of two forms provides for concurrent systemic and topical use and improves the effectiveness and efficacy of HPV therapy.

AIM

To review the specific activity of PROTEFLAZID® Drops and Suppositories at the stage of non-clinical study, and to assess the efficacy and safety of its use in clinical practice in HPV-associated female reproductive system diseases.

MATERIALS AND METHODS

Analysis of scientific publications on the treatment of palilomavirus infection with PROTEFLAZID® in women over the past decade.

REVIEW AND DISCUSSION

In 2015, Ukrainian scientists published a systematic review of the literature accompanying the analysis of the first scientific publications on the experience gained to date in the use of medicinal products PROTEFLAZID® in clinical settings in the treatment of HPV-associated diseases[12]. The review of the literature on non-clinical studies revealed that the active substance of PROTEFLAZID® (drops) had direct antiviral action against DNA-containing human papillomaviruses. In addition, PROTEFLAZID® (drops) induces the synthesis of alpha- and gamma-interferons, which contributes significantly to the medicinal product's indirect antiviral effect.

A systematic review of the literature on the clinical use of PROTEFLAZID® (drops) confirmed the medicinal product's antiviral activity against HPV. This is consistent with the results of non-clinical studies and confirms the product's efficacy in HPV-associated diseases in women (including those in pregnancy) and men of reproductive potential. A strong clinical effect was achieved in more than 1500 patients treated with PROTEFLAZID® (drops). The absence of adverse events confirmed the safety. The information is based on the results of independent clinical observations with coincidental positive effects of the treatment.

Summing up, the authors emphasised that the studies prove that the active substance of PROTEFLAZID® has a polypharmacological effect, in particular: Antiviral, immunocorrective, antioxidant, and apoptosis-modulating, which contributes to a stable therapeutic effect, HPV eradication, elimination of vaginal microflora dysbiosis, restoration of normal vaginal flora, reduction of the incidence of recurrence and HPV infection, as well as normalisation of the cervical epithelium, reduction of the proliferative activity of neoplasms, which allows the use of organ-preserving treatment in the reproductive population as a guarantee of future parenthood [12].

PROTEFLAZID® (vaginal tampons impregnated with drops) as a topical, intravaginal treatment normalises cytology and promotes the transition of cervical intraepithelial neoplasia of class CIN2 (moderate dysplasia) to class CIN1 (mild dysplasia), reducing the severity of signs of cervical epithelial dysplasia and contributing to a significant reduction in HPV DNA viral load compared to baseline. PROTEFLAZID® (vaginal tampons impregnated with drops) in the treatment of HPV-associated diseases helps to normalise clinical and laboratory parameters and eliminate HPV by more than 3.6 lg in 80% of patients, as confirmed by PCR.

The efficacy of PROTEFLAZID® (vaginal tampons impregnated with drops) was proven at the stage of preconception preparation of infected women for pregnancy and reduction of the frequency of perinatal complications of the gestational period. No significant adverse events were reported during long-term use of the medicinal product in pregnant women [12].

In a clinical trial [7] on the use of PROTEFLAZID® (drops) and PROTEFLAZID® (vaginal tampons impregnated with drops) in the treatment of genital HPV infection in women with systemic and vaginal administration to treat benign and precancerous cervical lesions, the authors concluded the efficacy of PROTEFLAZID® (vaginal tampons impregnated with drops) and PROTEFLAZID® (drops). The standard of care is inferior in terms of virostatic and anti-relapse effects to combination treatment with PROTEFLAZID®. Given that PROTEFLAZID® reduces the viral load in HPV infection by 3.0 lg D_{50} and increases the number of antigen-presenting cells, using these medicinal products as part of combination therapy in all patients with HPV infection is clearly warranted.

A study on the comparative efficacy and safety of PROTEFLAZID® Suppositories and Drops (vaginal tampons impregnated with drops) in patients with HPV-associated cervical epithelial dysplasia [14] showed that PROTEFLAZID® (suppositories) is highly effective and not inferior in therapeutic efficacy to PROTEFLAZID® (vaginal tampons impregnated with drops) when used in patients with HPV-associated cervical epithelial dysplasia (CED). After completing the treatment course with PROTEFLAZID® (suppositories), cytology or transition of cervical intraepithelial neoplasia was normalised from CIN2 to CIN1. Following treatment with PROTEFLAZID® (vaginal tampons impregnated with drops) and PROTEFLAZID® (suppositories), an 8-week follow-up confirmed a decrease in the severity of the signs of cervical intraepithelial neoplasia (leukoplakia, punctation, acetoblastic epithelium, mosaic, atypical transformation zone); improvement of cytological findings (decrease in leukocytosis, coilocytosis, dyskeratocytes); a significant increase in the level of local immunity (no significant differences between the groups in local immunity (sIgA, lysozyme and C3 complement component) at all evaluation time points); a significant decrease in the HPV DNA viral load, indicating a delayed antiviral effect of the medicinal products (no significant differences between the groups in the level of HPV viral load at all evaluation time points). Both pharmaceutical forms PROTEFLAZID® Suppositories and Drops (in the form of vaginal tampons impregnated with drops) proved to be well tolerated, but the suppositories have a more convenient dosing regimen, unlike the drops, which, at the same dosing frequency, required time to prepare the appropriate dilution and impregnate vaginal tampons. The authors recommended PROTEFLAZID® (suppositories) as an effective and safe antiviral treatment for HPV-associated female reproductive system diseases [14].

Given the high efficacy and safety of PROTEFLAZID® (drops and suppositories) in the treatment of HPV, the authors recommended using the medicinal products in routine clinical practice to treat women of reproductive potential [12].

A team of authors [13] conducted a meta-analysis of the results of long-term clinical trials to assess the efficacy of PROTEFLAZID® (drops and suppositories) in the treatment of HPV infection (the results of treatment in more than 1000

patients were analysed). The meta-analysis confirmed the high efficacy of PROTEFLAZID® (drops and suppositories) in the treatment of patients with HPV-associated urogenital and cervix disorders. The meta-analysis revealed the following: The likelihood of recurrence of condylomatous manifestations in the intervention group (treated with PROTEFLAZID® (drops and suppositories)) is 5.5 times lower than in the control group (not treated with PROTEFLAZID®); the likelihood of HPV detection (by PCR) in the intervention group is 6.7 times lower than in the control group; the likelihood of resolution (significant reduction) of HPV replication as determined by PCR in the intervention group is 4.7 times higher than in the control group. The medicinal products PROTEFLAZID® (drops and suppositories) promote the clearance of HPV from the body, preventing the recurrence of the disease and reducing the risk of virus-induced neoplastic lesions. PROTEFLAZID® (drops and suppositories) is recommended as an effective antiviral medication to treat HPV-associated cervix and urogenital disorders as an etiopathogenetic treatment in the acute period, during recovery and in persistent HPV infection [13].

In a study comparing the efficacy of different regimens of PROTEFLAZID® (drops and suppositories) in the treatment of mild-to-moderate cervical intraepithelial neoplasia associated with genital HPV infection, the team of authors found that treatment with PROTEFLAZID® (drops and suppositories) for HPV-associated CIN1 and CIN1 is etiologically and pathogenetically justified, given the direct antiviral effect of the medicinal product on HPV and the mechanisms of action on the transformation of cells affected by the virus [11]. Systemic use of PROTEFLAZID® (oral drops) to treat mild-to-moderate neoplasia improved the cervical epithelium in 60% of cases and eradicated HPV in 73.3% of patients. Topical use of PROTEFLAZID® (suppositories) in CIN1 and CIN2 normalised cytology or led to the transition of CIN2 to CIN1 in 63.3% of women; no HPV DNA was detected after treatment in 76.7% of cases. At the same time, 3 months of concurrent topical and systemic use of PROTEFLAZID® (drops and suppositories) to treat HPV-associated CIN1 and CIN2 resulted in regression of CIN1 to normal and CIN2 to CIN1 in 83.3% of patients; 90.0% of patients did not have HPV DNA detected after treatment. Clearly, this regimen of concurrent topical and systemic use of two pharmaceutical forms of PROTEFLAZID® (oral drops) and PROTEFLAZID® (suppositories, vaginal) provides the highest therapeutic efficacy [11].

The authors recommended PROTEFLAZID® (suppositories) and PROTEFLAZID® (drops) to be introduced into clinical practice as a safe and efficacious treatment for HPV-associated CIN1 and CIN2 as monotherapy, especially in the regimen of concurrent systemic and topical use of PROTEFLAZID® (drops + suppositories), ensuring the highest therapeutic efficacy. This regimen of concurrent use of two pharmaceutical forms of PROTEFLAZID® (drops and suppositories) is a promising approach to the treatment of HPV infection and CIN 1-2 in women of reproductive potential, as it helps to prevent cervical damage, early and late complications after invasive interventions and preserve female reproductive function [11].

In a study of the effect of PROTEFLAZID® (suppositories) on local immunity in disorders associated with human papillomaviruses, herpesviruses, or mixed genitourinary infections, a team of authors [31] revealed that PROTEFLAZID® (suppositories), when used to treat sexually transmitted diseases, significantly improves such local immunity parameters as sIgA, lysozyme, and complement component C_3 in cervical mucus. This improvement is sustained and persists for a long time after treatment. Furthermore, the medicinal product contributes to the correction of deregulated natural defence factors during exacerbation of mixed infections, when activation of the complement component C_3 may occur due to decreased sIgA and lysozyme levels. Following treatment with PROTEFLAZID® (suppositories), all three components of the natural defence response increased, and the ratios between them reached optimal values, which can provide the most significant anti-infective protection [31].

The relationship between macro- and microorganisms in vaginal homeostasis is complex. It is difficult to imagine that a single protective factor can prevent the onset and development of infection in the host. Only a complex of protective factors inherent in the body and in an active state can actually resist infection. In other words, 'aggregation' (in this case, combining components into a single system) and mobilisation of defence factors can actually resist the local spread of infection. This can explain the positive effect of PROTEFLAZID® (suppositories) when used topically to treat sexually transmitted diseases, when after a course of treatment with the medicinal product, the level of such key defence factors as sIgA, lysozyme, and complement component C_3 in cervical mucus increases significantly. Thus, the medicinal products PROTEFLAZID® (suppositories or vaginal tampons impregnated with drops) significantly and consistently improve the content and ratio of such major local immunity factors as sIgA, lysozyme, and complement component C_3, thus enhancing the anti-infective protection of cervical mucus in the female reproductive system as a whole, in the treatment of sexually transmitted diseases and infections caused by human papillomaviruses, herpes viruses, and mixed urogenital infections (herpes viruses + chlamydia) [31].

A study [5] on the clinical efficacy of PROTEFLAZID® Vaginal Suppositories for topical use in the treatment of HPV-associated mild-to-moderate cervical intraepithelial neoplasia showed that a tricyclic monotherapy (14 days for 3 months) has a positive effect on the cervix, according to the results of the PAP test based on liquid cytology – a decrease in the detection of low-grade squamous intraepithelial lesions (LSIS) from 80% to 8%, normalisation in 82% of cases; colonoscopic findings – 82% of women had normal findings after treatment; disappearance of proliferation markers p16 and Ki-67 in all cases; significant reduction of viral load by 1.8 times; morphologically confirmed regression of cervical intraepithelial neoplasia in 96% of cases. A positive effect of suppositories on the vaginal flora

was also reported, as evidenced by a 2.16-fold decrease in the number of leukocytes in the field of view and a 5.6-fold increase in the frequency of lactobacilli detection. Additionally, this treatment was well tolerated by patients, convenient, provided in outpatient settings, painless, and had virtually no side effects [5].

In a clinical paper dedicated to the study of ways to reduce diagnostic and therapeutic intervention in HPV-infected patients of reproductive potential found that after 3 months of treatment with PROTEFLAZID® systemically (drops) and topically (suppositories), regression of CIN was observed in 93% of patients [2]. A reduction in viral load of more than 2 Lg HPV/10^5 was recorded in all cases, which is a marker of the effectiveness of antiviral therapy. At 6 months post-treatment, 84% of patients and at 9 months, 88% of patients had complete HPV eradication or reduced viral load to clinically insignificant levels. The patients tolerated the therapy well, and mild vaginal itching in the first days of suppository administration did not require discontinuation. After treatment with PROTEFLAZID® (drops + suppositories), 93% of women did not require invasive interventions, which is essential given their reproductive plans.

Based on the data obtained, the authors recommended a treatment regimen that includes concurrent use of PROTEFLAZID® (suppositories for topical use) and PROTEFLAZID® (drop for systemic use) as an efficacious and safe way to treat patients with HPV-associated cervical intraepithelial neoplasia CIN1 and CIN2. The used treatment regimen enables practitioners to reduce unnecessary medical and invasive interventions in the treatment of patients with HPV-associated disorders. Successful treatment of CIN is the cornerstone of cervical cancer prevention in women of reproductive potential [2].

In the National Consensus (Ukraine) on the Management of HPV-Associated Cervical Intraepithelial Neoplasia [8], the leading experts of Ukraine stated that the most perspective direction in the treatment and secondary prevention of HPV infection is the use of direct antivirals (which include the active substance of PROTEFLAZID®), which are also immunomodulators, activate apoptosis and have an antiproliferative effect on cells [8].

The concurrent comprehensive systemic and topical use of the medicinal products PROTEFLAZID® can be used to successfully treat CIN1 and CIN2 without surgery. The use of medicinal products with direct antiviral action, such as PROTEFLAZID® (drops and suppositories), is necessary to provide anti-relapse therapy and help restore and strengthen the immune system, which is vital in HPV treatment.

An important consideration is the treatment of cervical intraepithelial neoplasia in pregnancy. However, the treatment of pregnant women has certain difficulties due to the impossibility of using many drug classes that are not approved or recommended for use in pregnant women. Yet, the medicinal products that combine direct antiviral action and immunomodulatory activity and are approved for use during gestation, such as PROTEFLAZID® (drops and suppositories), can not only improve the effectiveness of treatment of certain virus-induced disorders, but also reduce the incidence of obstetric and perinatal complications of pregnancy in such women [28].

A study on the results of clinical and molecular histological evaluations of the efficacy of the medicinal product PROTEFLAZID® is greatly relevant and is encouraging for further progress in the field of HPV infection treatment in women with cervical intraepithelial neoplasia [21]. His clinical and molecular morphological evaluations proved that concurrent use of PROTEFLAZID® (drops) and PROTEFLAZID® (suppositories) for 3 months in HPV-infected women without signs of cervical morphological damage contributed to HPV eradication in 86.7% of cases and in women with CIN1 caused by HPV – in 73.3% of cases. In addition, treatment contributed to the regression of cervical dysplasia in 76.7% of women. Treatment of HPV infection with PROTEFLAZID® in women with CIN1 leads to a steady regression of dysplastic lesions of the cervical epithelium, as all Pap tests and HPV tests were negative during 24 months of post-treatment follow-up in the treated women [21].

The results clearly indicate the need for antiviral treatment in women at the early stage of HPV infection, when cytology specimens show coilocytosis, i.e. before HPV can cause CIN1 or more severe dysplastic cervical lesions. Such treatment can be considered primary prevention of cervical cancer, as women without HPV infection were shown to have a shallow risk of developing cervical cancer.

Currently, the medicinal products PROTEFLAZID® (drops and suppositories) are among the most effective treatment options for HPV infection, used and recommended by healthcare professionals for HPV eradication in women with both cervical intraepithelial neoplasia and a positive HPV test with a normal Pap test [8].

Note: As of 30/09/2023, the cumulative sales volume of PROTEFLAZID® (drops, since marketing authorisation) and the number of sold vials (since 2006) in Ukraine and abroad (in vials) amounted to 5,629,300 vials. The cumulative sales volume of PROTEFLAZID® (suppositories) since its launch in Ukraine (2016) and abroad up to 01/03/2023 amounted to 414,306 packs No. 10. The cumulative pooled pharmacovigilance monitoring data from the local regulatory agency and available literature data indicate few reports of non-serious adverse events associated with both PROTEFLAZID® (drops) and PROTEFLAZID® (suppositories).

Given the current martial law regime and the challenging situation with clinical trials in Ukraine, the Company would be grateful to a foreign investor who would agree and/or directly participate in the further expansion of the trials mentioned above of PROTEFLAZID® (suppositories) and PROTEFLAZID® (drops) to treat HPV-associated disorders and prevent cervical cancer in women of reproductive potential in Poland or one of the European countries.

A clinical trial to investigate the combined effect of the investigational product PROTEFLAZID® (capsules; Phase II clinical trials of this pharmaceutical form were successfully completed in Ukraine) with systemic and topical use of PROTEFLAZID® (suppositories) to treat HPV-associated disorders in women of reproductive potential in one of the European countries could be of particular interest to potential European investors.

The active substance of PROTEFLAZID is of natural origin, highly active, and non-toxic (Category 5 toxicity). At present, Ecopharm manufactures the amount of the Active Pharmaceutical Ingredient that would be sufficient to treat HPV-associated disorders in women for the prevention of cervical cancer in one of the European countries, such as Poland or Germany.

Upon completion of clinical trials and marketing authorisation of the PROTEFLAZID® pharmaceutical forms (drops and suppositories) in a specific country, Ecopharm will be able to fully address the issue of treatment of HPV infection and cervical dysplasia (caused by HPV infection, CIN1 and CIN2), providing timely and effective prevention of cervical cancer in women of reproductive potential, which, in turn, is critical for non-invasive therapy and overcoming the challenges of the current demographic crisis.

CONCLUSIONS

PROTEFLAZID® (drops and suppositories) are safe and effective etiopathogenetic medications for systemic and local treatment of HPV-associated disorders in women. The medicinal products show potential for the prevention of cervical cancer, as they allow for organ-preserving treatment in women of reproductive potential as a pledge of future motherhood.

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CONFLICT OF INTEREST
Oleksandr Y. Hrynevych is an employee of ECOFARM – the company that produces the PROTEFLAZID

CORRESPONDING AUTHOR
Oleksandr Y. Hrynevych
ECOFARM
136 B Naberezhno-Korchuvatska, 03045, Kyiv, Ukraine
e-mail: o.hrynevych@ecopharm.ua

ORCID AND CONTRIBUTIONSHIP
Oleksandr Y. Hrynevych: 0000-0001-6542-8102 A B D E F

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

RECEIVED: 06.12.2024
ACCEPTED: 04.07.2025

CREATIVE COMMONS 4.0

REVIEW ARTICLE

Iodine deficiency and iodine supplementation in pregnancy and lactation. A literature review

Wiktoria Józefowicz[1], Julia Stawińska-Dudek[2], Damian Machaj[1], Jakub Dudek[1], Martyna Brzoza[3], Milena Orzeł[1], Bartłomiej Orzeł[1], Ali Aboud[4], Barbara Buras[5]

[1]MEDICAL UNIVERSITY NAMED AFTER THE SILESIAN PIASTS IN WROCLAW, WROCLAW, POLAND
[2]ORTHO.PL DENTAL AND ORTHODONTIC CENTRE, WROCLAW, POLAND
[3]CENTRAL CLINICAL HOSPITAL OF THE MEDICAL UNIVERSITY OF LODZ, LODZ, POLAND
[4]MEDICAL INNOVATION CENTRE, WROCLAW, POLAND
[5]AMERIDENT NON-PUBLIC HEALTH CARE INSTITUTION CIVIL LAW PARTNERSHIP MARIA AND LAZARZ LEGIEN, BIELSKO-BIALA, POLAND

ABSTRACT

Aim: Iodine is an essential nutrient for the synthesis of thyroid hormones. It has a huge impact on the normal brain development of the foetus and the health of the pregnant woman. During pregnancy and lactation, the need for iodine increases significantly. This review aims to summarize the role of iodine supplementation in addressing these elevated demands and preventing associated health risks.

Materials and Methods: The review is based on the thorough analysis of the materials selected from "PubMed" and "Google Scholar" scientific databases using the following key words: iodine; pregnant; lactation; supplementation. These key words were chosen based on their relevance to the matter of the article.

Conclusions: Iodine supplementation is essential for optimal maternal and foetal health. However, comprehensive strategies are needed to address iodine deficiency, including public education on iodine-rich diets, policy initiatives on salt iodisation and minimising exposure to harmful chemicals in the environment. These measures can affect the health of pregnant and lactating women and their children. Moreover, the paper discusses the potential implications of excessive iodine intake, which may lead to thyroid dysfunction.

This review underlines the crucial role of interdisciplinary collaboration in ensuring optimal maternal and neonatal health outcomes.

KEY WORDS: iodine; lactation; pregnancy; supplementation

Pol Merkur Lek,2025;53(4):555-560 doi: 10.36740/Merkur202504118

INTRODUCTION

Iodine is an essential element for the normal functioning of the thyroid gland [1]. Iodine in the body is mainly obtained from food. It is absorbed in the stomach and small intestine, from where it is transported to the thyroid gland [1]. Iodine is stored in the follicular cells, where chemical reactions produce the hormones thyroxine (T4) and triiodothyronine (T3) [1]. These hormones are responsible for the growth of the central nervous system and are involved in the regulation of metabolic processes in the body [2].

The demand for this element is higher during pregnancy and lactation due to increased production of T3 and T4 [3]. This is associated with iodine transfer to the foetus and increased urinary excretion of iodine [3]. The iodine requirement in pregnant women is 250µg/day and the recommended urinary iodine range is 150-249µg/day [4]. The consequences of iodine deficiency during pregnancy vary depending on the severity of the deficiency. In cases of mild to moderate iodine deficiency, cognitive problems may occur in children, although the evidence is not robust [5, 6]. In contrast, severe iodine deficiency in pregnant women is associated with obstetric complications, impaired neurological development or cretinism in children [7]. Therefore, maintaining adequate iodine levels through diet or supplementation is crucial to avoid deficiency of iodine. Effective management of iodine intake is particularly important in regions with endemic iodine deficiency, where food alone may not meet the increased requirements during pregnancy and lactation [8].

Iodine deficiency still remains a challenge in some populations. Widespread salt iodisation has significantly reduced the prevalence of iodine deficiency disorders, but awareness of iodine nutrition remains inadequate [9]. Both factors – lack of awareness and inadequate dietary intake of iodine are associated with insufficient levels in the body [9]. The influence of the environment should not be forgotten. It is common for people to be exposed to endocrine disrupting chemicals which further exacerbates the effects of iodine deficiency and poses additional risks to fetal development [10].

AIM

This article analyses current recommendations for iodine supplementation during pregnancy and lactation, and to evaluate the effectiveness and safety of these strategies. Special attention is given to the balance between deficiency and excessive intake, considering their respective impacts on maternal and fetal thyroid function.

MATERIALS AND METHODS

The review is based on the thorough analysis of the materials selected from "PubMed" and "Google Scholar" scientific databases using the following key words: iodine; pregnant; lactation; supplementation. These key words were chosen based on their relevance to the matter of the article.

REVIEW AND DISCUSSION

IODINE DEFICIENCY AND SUPPLEMENTATION IN PREGNANCY

Iodine deficiency can have negative consequences for both the developing foetus and the mother. Recent studies report a major role for supplementation in maintaining thyroid function and supporting fetal development [11, 12].

In a randomised, double-blind study conducted in Sweden, Manousou et al. (2021) [11] investigated the effects of daily iodine supplementation at a dose of 150 µg in pregnant women. To do so, they checked the median urinary iodine concentration (UIC), which, according to the WHO, is the best marker to assess iodine nutrition in pregnant women. This is due to the fact that more than 90% of dietary iodine is excreted in the urine [4]. The results showed that iodine supplementation improved the median UIC from 110 µg/L (before supplementation) to 139 µg/L in the second trimester and 136 µg/L in the third trimester in the intervention group, which was significantly higher than in the control group, which maintained values of 90 µg/L and 65 µg/L, respectively ($p < 0.001$). Supplementation also reduced median thyroglobulin (Tg) from 21 µg/L to 16 µg/L in the second trimester ($p = 0.010$) and to 22 µg/L in the third trimester ($p = 0.003$), indicating a beneficial effect on thyroid health. However, the reported results should be approached with caution, as the iodine tablet also contained iron and selenium [11]. These elements can affect thyroid metabolism and interfere with thyroglobulin results [13, 14].

However, no significant changes in neonatal thyroid hormone levels were observed, suggesting that supplementation corrects iodine status but may not affect markers of thyroid function [11].

Data on the efficacy and safety of iodine supplementation in pregnancy are inconclusive [5]. Therefore, recommendations for iodine supplementation cannot be safely given to pregnant women, despite mild deficiency in pregnant women [15].

Similar findings were presented in a cross-sectional study conducted in Portugal by Lopes et al. (2022) [12]. The researchers compared iodine levels in pregnant women before and after the implementation of national guidelines for iodine supplementation of at least 150 µg/day [12]. For this purpose, they used the median UIC, which is the most commonly used parameter to assess iodine levels in the population [16]. The authors focused on the area of Portugal, which is considered an iodine-deficient region. They considered data concerning pregnant women from 2006/2007 who were not taking iodine supplements in the currently recommended doses. For comparison, pregnant women in 2018/2019 were randomly selected to test the impact of the introduced 2013 guidelines on the use of iodine preparations. Women without thyroid disease were taken into account in the study. Pregnant women taking 200 µg of iodine daily showed an improvement in median UIC from 67.6 µg/L (2006/07, before the introduction of supplementation) to 106.8 µg/L (2018/19, after the introduction of supplementation). The percentage of pregnant women with severe iodine deficiency (UIC < 50 µg/L) decreased from 37.4% to 18.0% ($p = 0.0002$), and the percentage of women achieving sufficient levels (UIC ≥ 150 µg/L) increased from 9.9% to 20.7% ($p = 0.0069$).

Despite this, the median urinary iodine concentration remained below the World Health Organisation (WHO) recommended level of 150 µg/L for pregnant women, indicating that supplementation alone may not be sufficient to achieve optimal iodine levels in areas with severe deficiencies. This study suggests a potential need for broader measures, such as iodine supplementation before conception or widespread salt iodisation, to ensure sufficient iodine levels during pregnancy [12].

PUBLIC KNOWLEDGE AND ATTITUDES ON IODINE NUTRITION

The World Health Organization and Iodine Global Network recommend that iodine intake for pregnant and lactating women should be 250 µg/d due to a 50% increase in requirement compared to other women [4,17]. China also has its own recommendations issued in the 2017 Chinese Residents' Reference, Dietary Intake of Nutrients (Part 3: Trace Elements) where the recommended iodine intake for pregnant and breastfeeding women is 230 µg/d and 240 µg/d, respectively, and the tolerable upper intake level is 600 µg/d [18]. This is to prevent the occurrence of hypothyroidism in both mother and child and other complications resulting from iodine deficiency. Despite these indications, there are still uncertainties regarding iodine intake by pregnant women and during lactation [9].

Nie et al (2023) [9] conducted a study in different geographical regions of Xinjiang, China, on 1181 pregnant women and 504 lactating women. They wanted to test the extent to which knowledge of iodine requirements in these women is associated with adequate iodine intake. To this end, they arranged questions on the socio-demographic characteristics of the participants, dietary iodine intake and knowledge, attitude and behaviours about iodine. The region covered in the study was not chosen at random. Xinjiang is an iodine-deficient area in the environment and in the past has been considered a heavily endemic area for iodine deficiency disorders [9].

Previous studies have suggested that lack of knowledge of iodine and negative attitudes towards iodine may be a

risk factor for iodine deficiency in pregnant and lactating women [19-20]. A study in Xinjiang found that pregnant and lactating women had average knowledge of iodine, with adequate iodine intake in these women. However, there was considerable confusion about dietary sources of iodine and specific needs during pregnancy and lactation. Almost half of the pregnant and lactating women surveyed knew that high iodine content is found in foods such as eggs, dairy products and seafood. In addition, many participants were unclear about the role of iodised salt as a major source of iodine, despite its widespread availability. Pregnant women with higher education had significantly better knowledge of dietary sources of iodine than pregnant women without higher education [9].

The main sources of knowledge about meeting iodine requirements were information taken from medical professionals, social media platforms and also advertising material.

In the study participants, the median UIC of pregnant women was 179.27 µg/l and the median UIC in breastfeeding women was 192.81 µg/l. The median iodine intake for pregnant women was estimated at 407.16 µg/d and for breastfeeding women was estimated at 356.89 µg/d, which meets the criteria recommended by the Chinese Residents' Reference, Dietary Intake of Nutrients. A study by Nie et al. found, there was a positive correlation between iodine knowledge and dietary iodine intake among pregnant women [9]. Similar findings were found in 2015 by Combet et al [21] in the UK.

Of the 1,026 women, 87% said they would be willing to change their dietary behaviour to increase iodine intake if they received information on the importance of iodine during pregnancy [21].

The low level of awareness points to the need for educational programmes to increase knowledge of iodine sources, the risks of iodine deficiency and the importance of adequate supplementation, especially during pregnancy.

Further information on the role of healthcare providers in promoting iodine knowledge was provided by a study conducted in Germany by Buhling et al. (2022) [22]. In this study, gynaecologists' recommendations for dietary supplements during pregnancy, before conception and during lactation were analysed with a focus on iodine and other nutrients such as folic acid, vitamin D and omega-3 fatty acids.

The survey found that most doctors recommended supplementation with iodine and folic acid. In contrast, there was no consensus in recommendations for other nutrients due to limited evidence of their effectiveness. Iodine supplementation was recommended by more than three quarters of gynaecologists before conception, during pregnancy and during lactation.

In addition, only 30 per cent of gynaecologists believe that the rate of taking nutritional supplements before pregnancy is higher than 60 per cent, while less than 10 per cent believe that nutritional supplements are taken by the majority of patients (80-100 per cent) before pregnancy [22].

ENDOCRINE REGULATION AND THE COMBINED IMPACT OF IODINE DEFICIENCY AND ENDOCRINE DISRUPTORS ON FETAL BRAIN DEVELOPMENT

The most common cause of mild thyroid hormone deficiency in pregnant women is an insufficient intake of iodine in the diet [23], although it is not the only one. Researchers are increasingly investigating the negative impact of environmental pollution on the hormonal system, particularly on thyroid hormones [23,24]. Natural and synthetic endocrine-disrupting chemicals (EDCs) are widespread in the environment and therefore affect not only adults but also pregnant women and children. EDCs interfere with hormonal signaling pathways by binding to hormone receptors and modifying gene expression. Studies have shown that exposure to EDCs affects various processes in the brain, such as neurogenesis, neuronal differentiation and migration, as well as neuronal connectivity [23].

The literature review in this section explores the impact of iodine deficiency and exposure to EDCs, particularly on the regulatory pathways of thyroid hormones, which are critical for fetal neurodevelopment. It is essential to note that endocrine-disrupting substances can interfere not only with iodine uptake, but also with the synthesis, transport, and metabolism of thyroid hormones [10]. The liver, which plays a central role in converting thyroxine (T4) into the bioactive triiodothyronine (T3) and in thyroid hormone catabolism, must not be overlooked. In liver dysfunction (e.g., cholestasis, cirrhosis), deiodinase activity is altered, which may reduce the effectiveness of iodine supplementation alone and lead to suboptimal levels of circulating active hormones [25].

With the increase in global exposure to EDCs [23, 24], researchers have noted that with inadequate iodine supply, the effects of EDCs exposure may be worse on fetal brain development [26, 27]. The cumulative effects of iodine deficiency and EDCs exposure represent a new area of concern for fetal health. In a review by Grossklaus et al. (2023) [10] the effects of mild iodine deficiency and EDCs exposure on fetal brain development were investigated.

Exposure to certain EDCs, such as organochlorine pesticides, polychlorinated biphenyl compounds, has been shown to interfere with thyroid hormone function and brain development [26,28,29]. Iodine deficiency may promote these negative effects thus deregulate transcription and thyroid hormone-induced epigenetic effects on target genes [30]. The issue is all the more important given the inadequate supply of iodine [10].

Retrospective case-control and cohort and population studies provide clear evidence that fetal and neonatal brain development is exposed to the adverse effects of thyroid-disrupting chemicals [25,30]. It should be added that there has been a significant increase in neurodevelopmental disorders in recent years, including autism and ADHD [24, 32]. Furthermore, epidemiological evidence suggests that prenatal exposure to phthalates is associated with emotional and behavioural difficulties in children [33].

A study by Lumen et al (2013) [34] showed that a low iodine intake of 75 µg/day and a daily perchlorate dose of

4.2 µg/kg was sufficient to induce hypothyroxinaemia. On the other hand, an adequate iodine intake of 250 µg/day requires a higher daily perchlorate dose of approximately 34 µg/kg to induce hypothyroxinaemia [34].

A review by Grossklaus et al [10] highlighted that maternal exposure to EDCs may increase the risk of cognitive and behavioural disorders in the offspring, particularly in cases where maternal iodine levels are suboptimal [10].

The study highlights the importance of minimising exposure to EDCs and ensuring adequate iodine intake, particularly in early pregnancy, when fetal brain development is highly vulnerable to environmental influences. Therefore, there is a need to implement health initiatives that simultaneously promote adequate dietary iodine intake and reduce EDCs exposure to effectively protect the health of mothers and their developing fetuses [10].

On the other hand, even if maternal iodine intake is adequate, concurrent exposure to EDCs, maternal hormonal disorders, and impaired liver function may negate the expected increase in T3 and T4 levels, undermining the protective role of these hormones in fetal brain development. This highlights the need for a comprehensive assessment of endocrine health during pregnancy.

EFFECTS OF EXCESS AND DEFICIENT IODINE INTAKE

Studies have shown that both deficiency and excess iodine intake can have negative consequences for maternal thyroid status or for pregnancy outcomes [35, 36].

A comprehensive review by Croce et al. (2022) [35] summarised the results of randomised controlled trials on iodine supplementation and its impact on pregnancy outcomes.

Severe iodine deficiency during pregnancy leads to impaired thyroid hormone synthesis, which increases the risk of maternal goiter, affects growth retardation in the foetus and causes brain damage [37]. A study by Nazeri et al [38] showed that TSH in umbilical cord blood was significantly higher in infants of iodine-deficient mothers (UIC < 150 µg/L) compared to infants of mothers with adequate iodine levels, indicating an attempt to compensate for hormone metabolism.

With regard to the effects of brain development in populations with mild to moderate iodine deficiency, there are difficulties in drawing evident conclusions. The effects are more subtle than for severe iodine deficiency and depend on a number of factors, including the age of the child tested and the co-occurrence of other risk factors [35].

In contrast, a study by Levie et al (2019) [6] found that iodine deficiency in pregnancy can lower a child's verbal IQ, particularly if the deficiency occurs in the first 14 weeks of pregnancy.

On the other hand, excessive iodine intake (UIC > 500 µg/L) leads to an increase in TSH and may increase the risk of thyroid autoimmunity due to higher rates of TgAb (Anti-Thyroglobulin Antibodies) and TPO Ab (Anti-Thyroperoxidase Antibodies) [39].

Croce et al. [35] showed that there is a U-shaped relationship between iodine levels and health effects, so iodine intake should be carefully managed.

Sun et al. (2022) [36] compared thyroid function in pregnant women who had a median UIC of 100-149 µg/L with pregnant women whose median UIC was 150-249 µg/L. They found that the group of women with lower median urinary iodine concentration (MUIC) had a higher prevalence of goiter thyroid compared to the group with higher MUIC – 1.02% and 0.41%, respectively. On the other hand, the population with MUIC 100-149 µg/L had a lower rate of subclinical hypothyroidism (2.46%) than the group with MUIC 150-249 µg/L (5.38%) [36].

Additionally, excess iodine (MUIC ≥250µg/L) has been shown to lead to an increase in TPO Ab and TgAb [36, which is consistent with the results presented by Wan et al (2020) [39].

CONCLUSIONS

Iodine is a key nutrient essential for the proper functioning of the thyroid gland, especially during pregnancy and lactation, when the need for this element increases by approximately 50% [4]. Iodine deficiency in pregnant women can lead to serious health consequences such as fetal brain damage, increased risk of pregnancy loss and infant mortality, neonatal hypothyroidism, cretinism, and neuropsychomotor retardation [7].

The findings highlight the benefits of iodine supplementation at a dose of 150 µg per day. A study in Sweden showed that supplementation improved median urinary iodine concentration in pregnant women, also reducing thyroglobulin (Tg) levels, demonstrating a beneficial effect on thyroid health [11]. Similar results were reported in Portugal, where the implementation of supplementation recommendations reduced the rate of severe iodine deficiency from 37.4% to 18.0% [12]. In regions with severe iodine deficiency, however, supplementation may not be sufficient, suggesting the need for additional measures such as widespread salt iodisation [12].

Attention should also be paid to the potential dangers of excess iodine (>500 µg per day), which can lead to the development of autoimmune thyroid disease and increased levels of TPO Ab and TgAb antibodies [39]. Therefore, it is important to maintain a balance in iodine supply to avoid the negative effects of both iodine deficiency and excess [35].

Research also points to the important role of education. Low levels of knowledge about the role of iodine and its sources in the diet remain a major concern. An example is the study by Nie et al. [9], which showed that many women in China had limited knowledge of dietary iodine intake, which increased the risk of deficiency [9]. Similar observations were made in the United Kingdom, where 87% of women said they would change their dietary habits if they were informed about the importance of iodine in pregnancy [21].

Increased global exposure to endocrine-disrupting chemicals, such as pesticides or phthalates, may increase the effects of iodine deficiency, negatively affecting fetal brain development [10, 30]. Retrospective studies suggest

that prenatal exposure to EDCs combined with iodine deficiency increases the risk of cognitive and behavioural disorders in children [10, 33].

In view of this information, awareness of iodine sources and the risk of iodine deficiency in pregnant and lactating women should be increased [9, 21]. At the same time, iodine supplementation should be promoted according to guidelines, while ensuring that its effectiveness is monitored [4, 11]. It is also important to apply strategies to minimise exposure to EDCs by introducing environmental regulations and conducting information campaigns to protect the health of mothers and their children [10, 33].

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Wiktoria Józefowicz
Medical University named after The Silesian Piasts In Wroclaw
Wroclaw, Poland
e-mail: wiktoria.jozefowicz10@gmail.com

ORCID AND CONTRIBUTIONSHIP

Wiktoria Józefowicz: 0009-0004-7530-1710 A B F
Julia Stawińska-Dudek: 0009-0008-1677-3741 E
Damian Machaj: 0009-0007-8299-0990 D
Jakub Dudek: 0009-0001-7111-887X B D
Martyna Brzoza: 0009-0004-8975-4462 A E
Milena Orzeł: 0009-0005-1303-2778 D
Bartłomiej Orzeł: 0009-0003-1442-6790 E F
Ali Aboud: 0009-0004-8485-9302 B D
Barbara Buras: 0009-0008-9914-507X B

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

RECEIVED: 18.04.2025
ACCEPTED: 19.07.2025

CREATIVE COMMONS 4.0

Wielka Księga Balneologii, Medycyny Fizykalnej i Uzdrowiskowej

Tom I Część ogólna

Tom II Część kliniczna

Pod redakcją:
prof. dr hab. n. med. Ireny Ponikowskiej
dr. hab. n. med. prof. nadzw. Jana Wiesława Kochańskiego

ponad 1300 stron

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