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as.shevchenko@knmu.edu.ua
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GENDER DIMORPHISM OF THE RELATIONSHIPS BETWEEN THE CRANIAL AND FACIAL SKULL SECTIONS IN MATURE HUMAN INDIVIDUALS

Sosonna L.O.

Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. To date, the range of individual anatomical variability of the cranial profile type in mature adults, depending on gender and skull structure type has not yet been adequately established.

Aim. To study gender-specific ratios of the cranial and facial parts of the skull in mature adults.

Materials and Methods. The materials of our study consisted of 115 skulls of mature adults of both sexes, including 35 dry bone specimens of whole or fragmented skulls. For each parameter, the following metrics were calculated: The following parameters were used in the statistical analysis: $\bar{x}$ (arithmetic mean), σ (standard deviation), and $m_{\bar{x}}$ (standard error of the mean).

Results. It was found that in men the skull length is $\bar{x}$=181.36 with σ=3.31 and $m_{\bar{x}}$=0.46, while in women it does not exceed $\bar{x}$=176.57 with σ=3.28 and $m_{\bar{x}}$=0.47; the skull width in men reaches $\bar{x}$=141.17 with σ=2.62 and $m_{\bar{x}}$=0.34, and in women, it does not exceed $\bar{x}$=134.94 with σ=2.50 and $m_{\bar{x}}$=0.33; the height parameter of the skull in men also reaches maximum values at the level of $\bar{x}$=141.38 with σ=3.75 and $m_{\bar{x}}$=0.52, while in women, it is somewhat lower at $\bar{x}$=137.24 with σ=3.15 and $m_{\bar{x}}$=0.55. In mature men, the upper facial width is $\bar{x}$=94.17 with σ=3.87 and $m_{\bar{x}}$=0.50, while in women, this parameter averages $\bar{x}$=90.71 with σ=4.05 and $m_{\bar{x}}$=0.54; the middle width in men reaches $\bar{x}$=128.93 with σ=1.53 and $m_{\bar{x}}$=0.20, while in women, it does not exceed $\bar{x}$=122.49 with σ=1.44 and $m_{\bar{x}}$=0.19; the maximum indicators of angular width are established in men, averaging $\bar{x}$=99.64 with σ=4.15 and $m_{\bar{x}}$=0.54, while in women, they do not exceed $\bar{x}$=92.27 with σ=3.78 and $m_{\bar{x}}$=0.51.

Conclusions. The study identified significant gender-specific differences in the cranial and facial dimensions of middle-aged individuals. Men demonstrated larger average values for skull length, width, and height, as well as upper face width, bizygomatic width, and angular width, compared to women. These findings highlight distinct morphological characteristics between genders.

Keywords: *computed tomography, cranial index, face width, face length, face height*.

Introduction

To date, the full range of individual anatomical variability in the cranial profile of mature adults, depending on gender and skull type, has not been adequately established. The bony structure of the human skull shows immense diversity in its sections, bones, apertures, and channels, with insufficiently studied variability ranges according to age, gender, and individual head shape.

Corresponding Author:
Sosonna Liliia Oleksandrivna – MD, Assistant of the Department of Human Anatomy, Clinical Anatomy and Operative Surgery, Kharkiv National Medical University, Ukraine.
Ukraine, 03039, Kharkiv, Nezalezhnosti ave., 12.
E-mail: lo.sosonna@knmu.edu.ua

Building on the classic works of renowned scientists [1; 2], new perspectives and morphological aspects are emerging to refine cranial metrics [3–5]. The goal of cranial metric research is to determine the position of the jaws relative to the plane of the anterior part of the skull base, identify facial types, and detect deviations from the average sizes characteristic of normal occlusion for the same type [6; 7].

With the rapid advancements in maxillofacial surgery, surgical and orthodontic dentistry, reconstructive surgery, and modern prosthetic methods, there is a growing need for more detailed cranio- and morphometric data. Such research is essential to justify and develop optimal diagnostic methods for treating individuals with craniofacial pathology. The study of cranial structures in the facial

and brain sections of individuals of different genders is particularly pressing.

The number of studies on gender-specific features of the facial and cranial sections, especially using computed tomography, remains insufficient despite the relevance of the topic. Currently, notable works by both domestic and foreign authors exist on this subject. The results of a pilot study by Milella M. et al. [8] are of interest, confirming sexual dimorphism in cranial structure, albeit on a small sample size.

A significant contribution to the field is the work by Toneva D. et al. [9], which shows that dimensions, rather than the form, of the facial skull exhibit the greatest variability by sex. Their study also demonstrated significant sexual dimorphism in the nasal region of the facial skull. Furthermore, these authors showed age-related variations in the structure of the lower jaw section of the skull. Their findings established sexual dimorphism in the structure of the mastoid process area [10].

Works by Ukrainian scientists are also well-recognized. The studies of Vovk Y.M. [11] regarding skull structure have become foundational to modern cranial metric studies and constitute a cornerstone of human anatomy research. The works of Speransky A.D. [12] and Sinelnikov R.D. [13] have retained their relevance, supplemented by results from studies using advanced diagnostic methods, particularly computed tomography [14].

Therefore, despite the importance of the topic, many questions about gender dimorphism in the structure of the facial and cranial skulls remain unanswered and require further investigation.

Considering all the above, the **aim** of our work is to study the gender-specific features of the relationships between the cranial and facial sections of the skull in mature adults.

Materials and Methods

The material for our study consisted of 115 skulls from mature adults of both genders. This included 35 dry bone specimens of complete or fragmented skulls from the museum collection of the Department of Human Anatomy, Clinical Anatomy, and Operative Surgery at Kharkiv National Medical University (KhNMU). Additionally, 80 human head Computed Tomography (CT) scan results, free of bone tissue pathology, were collected from diagnostic centers based on cooperation agreements with the Department of Human Anatomy, Clinical Anatomy, and Operative Surgery at the KhNMU. The distribution of the specimens by gender is presented in *Table 1*.

Table 1. The distribution of the specimens by gender

Material of the study	Person by gender	
	Male	Female
Complete skull bone specimens	8	7
Fragmented skull bone specimens	11	9
Computed tomography images	40	40
Total	59	56

Our research was carried out following the recommendations on "Compliance with ethical and legislative norms and requirements in conducting scientific morphological research". These conclusions indicate that the materials presented for examination are scientifically substantiated, the research methods described in the study were used in compliance with human rights according to the current legislation in Ukraine, meet international ethical requirements, and do not violate ethical standards in science and biomedical research.

For the study, mature adult representatives of both genders were selected: men aged 22 to 60 years; women aged 21 to 55 years (according to the classification of age periodization of human life recommended by the Ministry of Health of Ukraine (Letter No.08.01-22/2472 dated December 9, 2008)).

Moreover, the material for our research had an almost equal gender distribution: 59 male skulls and 56 female skulls, which allowed for the establishment of certain patterns and reliable differences among the parameters studied depending on gender.

Cranial metric studies of CT scan results were conducted using measurement blocks of computer programs used for tomogram analysis and 3D reconstructions. Licensed versions of such programs are always available on the tomograph and allow for the precise measurement of the bony structure of the head. In our cranial metric studies, the following programs were used:

1. Ez3D Plus 3D, version 1.2.0.5 (E-WOO Technology Co., South Korea) – the 3D imaging and analysis software for precise tomogram measurement and visualization;

2. DICOM Vidar Dicom Viewer version 4.2 (VIDAR Systems Corporation, USA) – a medical image viewer designed for detailed evaluation of DICOM-format files;

3. eFilmLite, version 3.4 (Merge Healthcare, USA) – the lightweight diagnostic imaging software for reviewing and analyzing medical images in the DICOM format.

All anatomical structures, being three-dimensional objects, have three main dimensions: length, width, and height, corresponding to the three basic anatomical planes (sagittal, frontal, and horizontal). For the entire skull, length is the distance between the glabella (gl) and opisthocranion (op) points; width is the dimension between the right and left euryon (eu) points; height is the measurement between the bregma (b) and basion (ba) points.

For the facial part of the skull, two height calculations can be distinguished: overall height, the dimension between the nasion (n) and gnathion (gn) points; upper part height, the distance from the nasion (n) to the prosthion (pr). For the width dimensions of the face, the most appropriate measurements are: upper face width, the distance between the right and left frontomalar-temporal points (fmt-fmt); zygomatic diameter, the distance between the right and left zygion (zy-zy) points; and mandibular width, the distance between the right and left gonion (go-go) points.

In our study, the statistical processing of the obtained results was carried out using the computer programs Statistica 13.5.0.17 (TIBCO, USA) for Excel 365 (Microsoft, USA). For each parameter obtained, calculations were performed for the arithmetic mean ($\bar{x}$), standard deviation (σ), and the error of the arithmetic mean ($m_{\bar{x}}$). All obtained and described indicator values were considered reliable at $p<0.05$, and Pearson correlation analysis was performed for a series of samples.

Results and Discussion

Our research established the characteristics of the profile cranio-metric features of the facial section of the skull. The diverse dimensions that address this question, combined with the close interaction between different sections of the skull, necessitate, first and foremost, the study of the existing relationships between the cranial and facial sections of the bony structure of the head. The existing range of indicators for the main linear dimensions of the skull has been established, with the results presented in *Table 2*.

For mature men, the skull length ranged from 169 mm to 192 mm, while for women, this parameter is within 162 mm to 187 mm. In turn, the skull width for men varied from 128 mm to 152 mm, and for women, it ranges from 122 mm to 144 mm. The skull height for men was between 129 mm and 151 mm, while for women, it was between 127 mm and 147 mm.

Table 2. The main linear dimensions of the skull (mm)

Size \ Gender	Male	Female
Skull length (g-op)	169–192	162–187
Skull width (eu-eu)	128–152	122–144
Skull height (b-ba)	129–51	127–147

Notes:

g-op – skull length (distance from the glabella to the opisthocranion);

eu-eu – skull width (maximum cranial breadth, measured between the most lateral points of the parietal bones);

b-ba – skull height (distance from the basion to the bregma).

Thus, there was a slight but clearly defined trend indicating that the main linear dimensions were generally larger in males. To confirm this observation, a statistical analysis of the obtained data was conducted, with the results presented in *Table 3*.

It was established that in men the skull length was $\bar{x}$=181.36 mm with σ=3.31 and $m_{\bar{x}}$=0.46, while in women it did not exceed $\bar{x}$=176.57 mm with σ=3.28 and $m_{\bar{x}}$=0.47. The skull width in men reached $\bar{x}$=141.17 mm with σ=2.62 and $m_{\bar{x}}$=0.34, and for women, it was not more than $\bar{x}$=134.94 mm with σ=2.50 and $m_{\bar{x}}$=0.33. The height parameter of the skull in males also reached maximum values at $\bar{x}$=141.38 mm with σ=3.75 and $m_{\bar{x}}$=0.52, while in females it was somewhat smaller at $\bar{x}$=137.24 mm with σ=3.15 and $m_{\bar{x}}$=0.55.

Analysis of the statistically substantiated data leads to the conclusion that the main linear parameters of the skull are clearly dependent on gender. The longitudinal and transverse parameters are significantly larger in men. with a difference in averages up to 5-6 mm, while the height parameter does not show such a significant difference, although it is still larger in men by more than 4 mm.

To visually demonstrate the observed features of the shapes and sizes, our study used comparisons of 3D models of skull structures built with tomographic computer programs used during examinations. For instance, the established difference in the main linear dimensions of the skull in mature adults depending on gender is illustrated in *Figure 1*.

Table 3. Statistical indicators of the skull size of a mature person

Size \ Statistical indicator	Male			Female		
	$\bar{x}$	σ	$m_{\bar{x}}$	$\bar{x}$	σ	$m_{\bar{x}}$
Skull length (g-op)	181.36	3.31	0.46	176.57	3.28	0.47
Skull width (eu-eu)	141.17	2.62	0.34	134.94	2.50	0.33
Skull height (b-ba)	141.38	3.75	0.52	137.24	3.15	0.55

Notes:
g-op – skull length (distance from the glabella to the opisthocranion);
eu-eu – skull width (maximum cranial breadth, measured between the most lateral points of the parietal bones);
b-ba – skull height (distance from the basion to the bregma);
$\bar{x}$ – arithmetic mean (average of the measurements);
σ – standard deviation (indicating the variability of the data);
$m_{\bar{x}}$ – standard error of the mean (representing the precision of the mean estimate).

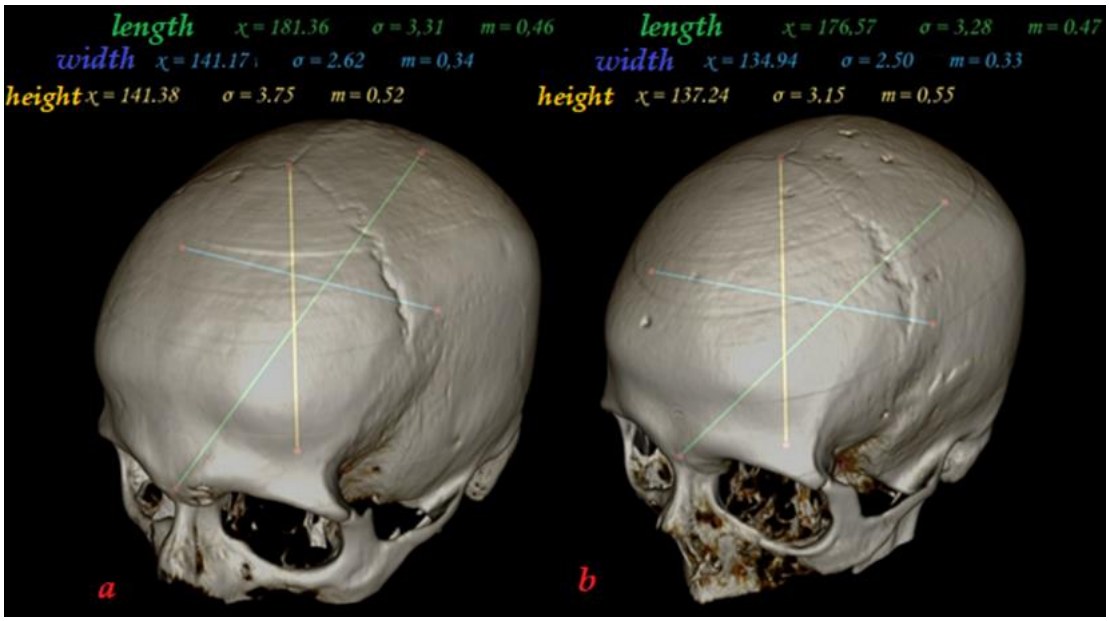

Fig. 1. Gender characteristics of the main linear dimensions of the skull of a mature person: *a* – male. *b* – female (CT No.1875-16; CT No.957-16)

Transverse dimensions play a significant role in understanding the relationships between different sections of the skull. For such a comparison the width of the skull (eu-eu) was taken from the cranial section. Three dimensions were taken from the facial section: upper facial width (fmt-fmt), middle or overall facial width (zy-zy), and lower mandibular width. also known in craniology as the gonial width (go-go). The number of transverse facial dimensions is due to the main objective of our study. The obtained range of these dimensions is presented in *Table 4*.

Table 4. Main transverse dimensions of the human skull in mature adults (mm)

Size \ Gender	Male	Female
eu-eu	128–152	122–144
fmt-fmt	85–102	81–97
zy-zy	110–142	104–135
go-go	87–113	84–102

According to our data, the upper facial width ranges from 85 mm to 102 mm in men, while in

women it ranges from 81 mm to 97 mm. The overall facial width also showed maximum values in men, ranging from 110 mm to 142 mm compared to the range of 104 mm to 135 mm in women.

The lower mandibular width in men varied from 87 mm to 113 mm, whereas in women, it ranged from 84 mm to 102 mm.

Compared to the previously described width of the cranial section, it can be asserted that the transverse dimensions of both sections tend to be larger in males. This thesis was confirmed by the results of the statistical analysis of the obtained data (*Table 5*). A visual representation of this established feature is presented in *Figure 2*.

Table 5. Statistical indicators of the transverse dimensions of the skull

Size \ Gender		Male	Female
eu-eu	$\bar{x}$	141.17	134.94
	σ	2.62	2.50
	$m_{\bar{x}}$	0.34	0.33
fmt-fmt	$\bar{x}$	94.17	90.71
	σ	3.87	4.05
	$m_{\bar{x}}$	0.50	0.54
zy-zy	$\bar{x}$	128.93	122.49
	σ	1.53	1.44
	$m_{\bar{x}}$	0.20	0.19
go-go	$\bar{x}$	99.64	92.27
	σ	4.15	3.78
	$m_{\bar{x}}$	0.54	0.51

Notes:
eu-eu – maximum cranial breadth (measured between the most lateral points of the parietal bones);
fmt-fmt – minimum frontal breadth (measured between the most lateral points of the frontal bones);
zy-zy – bizygomatic breadth (distance between the most lateral points of the zygomatic arches);
go-go – bigonial breadth (distance between the most lateral points of the mandibular angles);
$\bar{x}$ – arithmetic mean (average of the measurements);
σ – standard deviation (measure of data variability);
$m_{\bar{x}}$ – standard error of the mean (indicates the precision of the mean estimate).

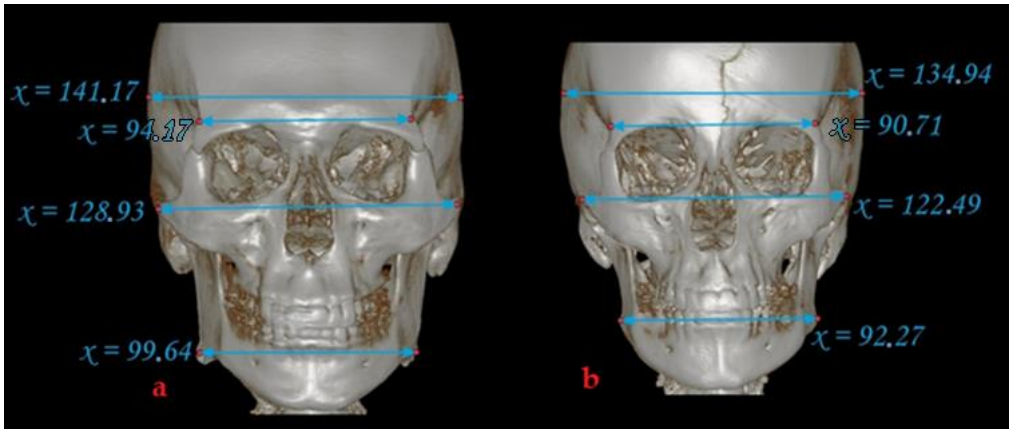

Fig. 2. Gender features of the main cross-sectional dimensions of a mature skull:
a – male, *b* – female (CT No.630700; CT No.650423)

It has been determined that in middle-aged men. the upper face width is $\bar{x}$=94.17 with σ=3.87 and $m_{\bar{x}}$=0.50, while in women this parameter has an average value of $\bar{x}$=90.71 with σ=4.05 and $m_{\bar{x}}$=0.54. The average width in men reaches $\bar{x}$=128.93 with σ=1.53 and $m_{\bar{x}}$=0.20, whereas in women it does not exceed $\bar{x}$=122.49 with σ=1.44 and $m_{\bar{x}}$=0.19. The maximum angular width indicators are found in males averaging $\bar{x}$=99.64 with σ=4.15 and $m_{\bar{x}}$=0.54, while in females they do not exceed $\bar{x}$=92.27 with σ=3.78 and $m_{\bar{x}}$=0.51. Similar trends were observed for the overall skull width.

Based on the obtained numerical characteristics it can be stated that regardless of the part of the skull. transverse dimensions are significantly dependent on gender, with all sizes in this direction predominantly larger in men, with average variations ranging from 4 to 7 mm.

Our research provides one of the first comprehensive studies of gender-specific differences in the relationship between the cranial and facial sections of the human skull in mature adults. We compared the findings obtained from dry bone specimens of whole or fragmented skulls from the museum collection of the Department of Human Anatomy, Clinical Anatomy, and Operative Surgery with those derived from CT scans. Previous studies have typically focused either on bone specimens [15] or on CT imaging results [16]. The unique value of combining these methods lies in the ability to compare the results and suggest that CT results might approach the accuracy of measurements obtained from native skull specimens.

Our findings suggest that CT scans can provide measurements of cranial structure that are nearly as accurate as those obtained from traditional bone specimens. With the widespread adoption of advanced diagnostic techniques and the integration of 3D modeling into routine medical practice, our study could serve as a foundational resource for developing 3D models of the human skull that account for gender-specific differences. Such 3D models could be valuable educational tools for teaching anatomy to students and interns. Additionally, 3D models that account for gender differences in skull structure could be used to prepare specialists (neurosurgeons, ophthalmologists, otolaryngologists, etc.) for surgical procedures, aiding in the selection of surgical approaches and planning of operational stages.

The identified gender dimorphism in cranial and facial structure can be beneficial for surgical planning in these areas. Furthermore, our research results could be valuable in forensic medicine for identifying individuals. Additionally, these findings not only enhance our understanding of human anatomy but also have potential applications in anthropology for refining knowledge about human origin, gender, and racial characteristics.

Conclusions

As a result of the conducted study, data were obtained on the gender-specific characteristics of the cranial and facial regions of the skull in middle-aged individuals. It was found that in men, the skull length is $\bar{x}$=181.36 with σ=3.31 and $m_{\bar{x}}$= =0.46, while in women, it does not exceed $\bar{x}$= =176.57 with σ=3.28 and $m_{\bar{x}}$=0.47. The skull width in men reaches $\bar{x}$=141.17 with σ=2.62 and $m_{\bar{x}}$=0.34, while in women, it is no more than $\bar{x}$= =134.94 with σ=2.50 and $m_{\bar{x}}$=0.33. The height parameter of the skull in men also reaches maximum values at $\bar{x}$=141.38 with σ=3.75 and $m_{\bar{x}}$=0.52, while in women, it is somewhat lower at $\bar{x}$=137.24 with σ=3.15 and $m_{\bar{x}}$=0.55.

In middle-aged men, the upper face width is $\bar{x}$=94.17 with σ=3.87 and $m_{\bar{x}}$=0.50, while in women, this parameter has an average value of $\bar{x}$= =90.71 with σ=4.05 and $m_{\bar{x}}$=0.54. The average width in men reaches $\bar{x}$=128.93 with σ=1.53 and $m_{\bar{x}}$=0.20, whereas in women it does not exceed $\bar{x}$=122.49 with σ=1.44 and $m_{\bar{x}}$=0.19. The maximum angular width indicators are found in males, averaging $\bar{x}$=99.64 with σ=4.15 and $m_{\bar{x}}$=0.54, while in females they do not exceed $\bar{x}$=92.27 with σ=3.78 and $m_{\bar{x}}$=0.51.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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THEORETICAL ANALYSIS OF THE INTESTINAL MICROBIOTA INFLUENCE ON COLORECTAL CANCER DEVELOPMENT

Tiuliukin I.O., Ivanchov P.V.

Bogomolets National Medical University, Kyiv, Ukraine

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ABSTRACT

Background. ColoRectal Cancer (CRC) is one of the most common malignant tumors: about a million new cases are diagnosed annually in the world. In Ukraine, the incidence of CRC is 20.5 per 100,000 population. The ratio of mortality and morbidity indicates significant shortcomings in the diagnosis, treatment and prevention of CRC.

Aim. To study theoretical scientific developments regarding the influence of intestinal microbiota on the development of colorectal cancer.

Materials and Methods. In the course of writing the scientific article, a number of modern literary sources and the latest data from scientific Web databases were studied of Science, Scopus, Google Scholar and PubMed, methods of systematic and comparative analysis of the specified problem were applied. Medical and statistical data of scientific publications on morbidity and treatment results in different countries of the world were studied.

Results. According to world statistics, CRC is the third most common in men (10.0% of the total number of malignant neoplasms) and the second most common in women (9.2%). Approximately 45.0% of CRC patients die despite treatment. A high percentage of emergency operations is recorded in elderly patients with chronic accompanying pathology, which is the cause of a large number of postoperative complications ([24.0–80.0] %) and mortality ([11.0–36.0] %). The incidence of CRC in Ukraine is the highest among a number of countries and indicates significant deficiencies in the diagnosis and treatment of patients, as well as in the prevention of this disease. Intestinal microbiota plays an important role in the development of colorectal cancer. Disruption of the functioning of the intestinal microbiota also leads to the development of a significant number of infectious, metabolic, oncological, neurological and endocrine diseases.

Conclusion. The analysis of literary sources and clinical studies of domestic and foreign authors allows us to assert that the microbiota, influencing the immune system, plays an important role in the induction and progression of colorectal cancer.

Keywords: *mortality, morbidity, treatment.*

Introduction

ColoRectal Cancer (CRC) is one of the most common malignant tumors: about a million new cases are diagnosed annually in the world. The highest incidence of CRC is recorded in Australia and New Zealand (44.8 per 100 thousand male and 32.3 per 100 thousand female population), the lowest – in West Africa (4.5 and 3.8 per 100 thousand population, respectively). Almost 55.0% of CRC cases occur in more developed regions of the world, however, in many countries, the lower prevalence of detected cancer may be due to the absence or incomplete coverage of the population by statistical observation. It is well known that there are significant differences between the shares of the population whose monitoring is reflected in cancer registries between high- and low-income countries [1–5].

For a long time, the occurrence of CRC was associated with a genetic predisposition, but later it was proven that in most cases, CRC occurs episodically and irregularly. Not only absorption of useful substances takes place in the intestines. It is also responsible for the formation of a normal immune response to stimuli. The normal state of the microbiota plays a major role in the stability of its work.

Corresponding Author:
Tiuliukin Illia – MD, senior laboratory assistant of the Department of Surgery No.3, Bogomolets National Medical University, Kyiv, Ukraine.
✉ Ukraine, 01601, Kyiv, Tarasa Shevchenka Blvd., 13.
E-mail: elia90ua@gmail.com

Microbiota is a term used to characterize the microbiocenosis of individual organs and systems of the human body.

Makkouk A. & Weiner G.J. (2014) examined the etiological factors of colorectal cancer. The authors report that in addition to genetic mutations and inflammation, the list of these factors includes epigenetic factors, nutritional changes, dysfunction of the immune system, and microbiota, that is, the population of microorganisms (bacteria, archaea, fungi, protozoa, and viruses) that inhabit all parts of our body [6].

According to Irrazabal T. et al. (2014) multiple effects of the intestinal microbiota are associated with the diversity of the composition of microorganisms. Since mutations of the genes of the cells of the colonic epithelium are an indispensable attribute of these effects, the microbiota is possibly associated with both the formation of genotoxic stress, which contributes to genetic and epigenetic changes of the intestinal epithelium, and the maintenance of the inflammatory state of the intestine, which together with oxidative and nitrosative stress leads to CRC [7].

Clark C.R. (2016) emphasizes that the microbiota is a community of all microorganisms that exist in a certain environment (on the skin, in the respiratory tract, intestines, etc.). In particular, the human intestinal microbiome contains a huge number of various bacteria, microscopic fungi and even viruses [8].

McDermott A.J. & Huffnagle G.B. (2013) in their research concluded that the gut microbiota is actively involved in morphogenesis, various metabolic processes and homeostasis maintenance. Observations on mice are especially revealing in this regard. Without microbiota, these animals are more sensitive to infections, they have a decrease in the vascularization of the intestinal wall, elongation of the villi of the intestinal epithelium due to atrophy of the crypts and a decrease in the rate of its renewal, a decrease in the enzymatic activity of digestion, the production of cytokines, the level of serum immunoglobulins and the number of intraepithelial lymphocytes, a decrease in the thickness of the muscle layer and the size of Peyer's patches [9].

Ha C. et al. (2014) state that colonization of the intestine of mice microbiota ensured the restoration of the mucosal immune system and induced the expression of various genes related to the absorption of nutrients, metabolism, angiogenesis, mucosal barrier function, and the intestinal nervous system. The microbiota in the intestines comes into contact with the second, after the brain, the largest pool of nerve cells in the body and with the pool of immune cells, influencing the formation of cognitive functions and the immune status of the body [10].

The above-mentioned studies conclude that the gut microbiota plays an important role in the development of infectious complications. Violation of its functioning leads to the development of a significant number of diseases (infectious, metabolic, autoimmune, oncological, neurological and endocrine), including colorectal cancer.

The **aim** of the study was to study the influence of intestinal microbiota on the development of colorectal cancer in patients.

Materials and Methods

Web databases of Science, Scopus, Google Scholar and PubMed were studied. During the development of the material, methods of systematic and comparative analysis were applied in relation to this problem.

Results and Discussion

Microbiota is a collection of microorganisms living in the human intestine. It consists of bacteria, fungi, protozoa, viruses and bacteriophages living in symbiotic relationships and having an epigenetic effect on the human body. This complex group of organisms has a significant metabolic potential, mainly due to its ability to decompose various substances. Hundreds of types of bacteria with different physiological and biochemical characteristics live in the lumen of the large intestine, in the mucus layer and on the surface of the epithelium.

Gill S.R. et al. (2006) state that the human gut microbiota is influenced by many factors, such as age, geographic location, dietary preferences and taste preferences, and physical activity. Microbiota constantly develops, grows and adapts depending on environmental factors and bacterial relationships [11].

Verdecchia A. (2007) emphasizes that the intestinal microbiota, which takes an active part in a wide range of physiological processes occurring in the large intestine, is of particular clinical interest. It is known that the intestinal microflora prevents the colonization of the large intestine by pathogenic microorganisms, stimulating the production of mucus and antimicrobial agents, strengthening the barrier between the intestinal tissues and its cavity, participating in the regulation of vital processes of intestinal cells [12].

According to Flint H.J. (2012), the composition of the human microbiota depends on a num-

ber of factors: the availability of nutrients, pH, the presence of oxygen, the influence of drugs (antibiotics), the secretion of bile acids and digestive enzymes, the integrity of the mucous membranes and the interaction with the host's immune system [13].

Ley R.E. (2006) proves that in situations where the bacterial balance in the large intestine is disturbed due to various external or internal factors, the number and variety of pathogenic bacteria increases, which in itself is the basis for the development of inflammatory changes in the intestinal wall. Thus, with disturbances in the functioning of the intestinal microflora, the risk of developing a significant number of diseases (infectious, metabolic, autoimmune, oncological, neurological, and endocrine), including colorectal cancer, increases [14].

Durban A. et al. (2011) emphasize that the microflora of the colon plays an important role in the development of infectious complications. A person exists in close contact with a huge number of microorganisms living on the skin, mucous membranes, in the oral cavity, urogenital and gastrointestinal tracts. Bacteria play a key role in many processes occurring in the colon, including fermentation of proteins and carbohydrates, transformation of bile acids and fats, metabolism of xenobiotic substances, stimulation of the immune system, and activation and disposal of mutagenic metabolites. The results of the vital activity of bacteria significantly affect the human body in many aspects - anatomical, physiological, biochemical and genetic [15].

Tkach S.M. et al. (2014) note that the microflora of the colon contributes to the development and regulation of the immune system (especially the local one), preventing the colonization of the colon by pathogenic agents [3].

According to Prakash S. et al. (2011), the intestinal microbiota stimulates the production of mucus and antimicrobial proteins, strengthening the barrier between the cavity and intestinal tissues, regulates the processes of intestinal cells (proliferation, growth, differentiation, survival and death), controls angiogenesis in the surrounding tissues [16].

Gagniere J. et al. (2016) claim that the species composition of the microbiota may vary depending on the age, lifestyle, diet and genotype of the subject. The microbiota is dominated by *Firmicutes phyla* ([30.0–50.0] %), *Bacteroidetes* (20.0–40.0 %) and *Actinobacteria* ([1.0–10.0] %). Strict anaerobes, including *Bacteroides, Eubacterium*, *Bifidobacterium, Peptostreptococci,* and *Atopobium,* constitute the main, and facultative anaerobes, such as *Lactobacilli, Enterococci, Streptococci,* and *Enterobacteriaceae,* a smaller (approximately 1000-fold) part of the microbiota of the large intestine, only 50.0% of the number of species, inhabiting the intestine [17].

Jandhyala S.M. et al. (2015) emphasize that the metabolic functions performed by the microbiota include anaerobic fermentation of carbohydrates with the formation of CO_2, H_2, CH_4, short-chain fatty acids, and such metabolites as phenolic compounds, amines, ammonia, nitroso compounds, and indoles. They can affect gene expression, proliferation and differentiation of the intestinal epithelium, mediate vitamin synthesis, ion absorption and mucus formation. Such a complex metabolic activity of the microbiota affects the obtaining of energy from the consumed food, regulates the storage of fat, and helps the absorption of substrates for both humans and the microbiota itself [18].

Wu N. et al al. (2013) conducted a comparative study of the microflora of the colon of patients with CRC and healthy people. The authors found no significant differences between samples for most bacteria, with the exception of *Fusobacteria*, which was found in greater numbers in the feces of patients with colon malignancies. Also, in the group of patients with CRC, an increased number of *Eubacteriaceae, Clostridiales, Staphylococcaceae* and *Enterococcaceae* bacteria was noted in comparison with the control group of healthy people [19].

Toprak N.U. et al. (2006) presented data in which EnteroToxigenic strains of *B. Fragilis* (ETBF) were isolated by the method of bacteriological cultivation of bacteria from feces of patients diagnosed with CRC. After that, using ethanol precipitation from cultivated colonies of *B. Fragilis* isolated DNA, with its subsequent analysis by polymerase chain reaction. According to the results of research, it was found that in patients with CRC, the percentage of detection of the ETBF strain is significantly higher than in the control group: 28.8% and 8.5%, respectively [20].

McCoy A.N. et al. (2013), found the connection of bacteria of the genus Fusobacterium with the development of KRR. When comparing groups of subjects, it was found that in the stool samples of patients with malignant neoplasm of the large intestine, Fusobacteria is present in a significantly greater number compared to patients with colon adenoma and healthy people [21].

Koropatkin N. et al. (2012) noted a decrease in bacterial diversity, an increase in the number of gram-negative bacteria of the genus *Fusobacterium* and *Porphyromonas*, which belong to pro-inflammatory bacteria in the colon of patients with CRC [22].

Boleij A. & Tjalsma H. (2012) published the results of a meta-analysis based on six independent studies (a total of 340 patients), demonstrating that in patients with a high bacterial load of *S. Gallolyticus* (biotype I) had a higher risk of developing colon cancer compared to patients who had increased growth of other *S. Bovi*. However, the main shortcoming of the presented results was that the researchers did not divide *S. Bovi* into biotypes. Thus, despite the fact that *S. Gallolyticus* infection, it can be, in its essence, an indicator of the development of colorectal cancer [23].

According to research by Klein R.S. et al. (1977) *Streptococcus gallolyticus* (formerly *S. Bovi biotype I*), is by definition a pathogenic microorganism for humans causing bacteremia, endocarditis and urinary tract infections and can provoke the development of colorectal cancer [24].

Conclusions

Thus, the analysis of literary sources and clinical studies of domestic and foreign authors allows us to state that the microbiota, influencing the immune system, plays an important role in the induction and progression of colorectal cancer. The influence of microbiota on cancer can be local, manifested at the level of the intestine itself, or systemic, realized first through an intact barrier, and then due to its violation. In turn, the immune and inflammatory responses to CRC are very complex and adapted to the stage of the cancer, the context of its microenvironment, and especially to the composition of the microbiota.

The scientific developments of scientists prove that with disturbances in the functioning of the intestinal microbiota, the risk of developing a significant number of diseases (infectious, metabolic, autoimmune, oncological, neurological and endocrine), including colorectal cancer, increases.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

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Consent for publication

All authors give their consent to publication.

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EARLY PHYSICAL REHABILITATION IN INTENSIVE CARE UNIT AND ITS IMPACT ON POST-COVID SYNDROME MANIFESTATIONS

Kovalenko V.

LLC "Treatment and Diagnostic Center "Dobrobut-Polyclinic", Kyiv, Ukraine
Bogomolets National Medical University, Kyiv, Ukraine

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ABSTRACT

Background. The COVID-19 pandemic has caused a global health crisis, notably through long COVID, which significantly affects the quality of life of patients' post-discharge from hospital care. Long COVID is characterized by prolonged symptoms such as fatigue, cognitive impairments, depression, and anxiety. Early physical rehabilitation is a crucial component of patient recovery; however, the optimal frequency and intensity of rehabilitation interventions remain unclear.

Aim. To evaluate the effects of various physical rehabilitation regimens on functional status, cognitive functions, psychosocial state, and manifestations of post-COVID syndrome in patients who underwent severe COVID-19.

Materials and Methods. 102 patients with confirmed COVID-19 requiring treatment in an Intensive Care Unit (ICU) were included in the study. They were divided into groups based on the number of rehabilitation sessions per day: Group I received one session, while Group II received two. Physical rehabilitation included changing the body position in bed, verticalization and breathing exercises. We assessed average values for physical functional status, cognitive functions, and psychosocial condition at discharge, along with post-COVID symptom severity 5–7 days after discharge.

Results. Increasing the number of rehabilitation sessions led to better psychosocial outcomes and reduced manifestations of post-COVID syndrome. However, in the short-term, increasing session frequency did not yield statistically significant improvements in cognitive functions or physical status.

Conclusions. Early physical rehabilitation in ICU is vital for reducing manifestations of post-COVID syndrome in severe COVID-19 patients. Enhanced physical activity not only improves mental health but also helps alleviate physical symptoms. Future research should focus on the long-term effects of rehabilitation and a holistic approach to supporting patient recovery.

Keywords: *mobilization of patients, early activation of patient, COVID-19, ICU.*

Introduction

The COVID-19 pandemic has caused a global health crisis, particularly due to high mortality rates and severe consequences, especially among patients with severe disease progression. Post-COVID syndrome (Long COVID) has emerged as a significant issue faced by patients following COVID-19, particularly those who required hospitalization in the Intensive Care Unit (ICU) [1; 2]. This syndrome is characterized by long-lasting symptoms, such as fatigue, muscle weakness, cognitive impairments (commonly referred to as "brain fog"), depression, anxiety, and other psycho-emotional problems, which considerably diminish the quality of life for patients [3–5].

Physical rehabilitation is a critical component of the recovery process that can positively impact patients' overall health. It not only aids in physical recovery but also supports psychological well-being, as regular activities enhance motivation for rehabilitation [6–8]. However, questions regarding the optimal frequency and intensity of rehabilitation interventions remain unresolved.

Corresponding Author:
Kovalenko Viacheslav – MD, PhD student of the Department of Surgery, Anesthesiology and Intensive Care, Institute of Postgraduate Education Bogomolets National Medical University, Kyiv, Ukraine; LLC "TDC "Dobrobut-Polyclinic", Kyiv, Ukraine.
✉ Ukraine, 04116, Kyiv, Moldovska str., 3.
E-mail: viacheslav.kovalenko04@gmail.com

The **aim** of this study was to evaluate the impact of different physical rehabilitation regimes on functional status, cognitive functions, psychoemotional state, and manifestations of post-COVID syndrome in patients who experienced a severe form of COVID-19.

Materials and Methods

The study included 102 patients who were hospitalized in the ICU with a confirmed diagnosis of COVID-19 and required mechanical ventilation or oxygen therapy due to Acute Respiratory Distress Syndrome (ARDS).

Inclusion criteria for the study were: age over 18 years; confirmed by Polymerase Chain Reaction (PCR) COVID-19; hospitalization in the ICU due to respiratory failure related to ARDS.

Exclusion criteria from the study included: pre-existing musculoskeletal disorders that limit mobility; neurological conditions that restrict mobility; presence of oncological diseases; patient death or transfer to another healthcare facility; refusal of the patient to participate in the study.

Two groups of patients were formed based on the number of rehabilitation sessions per day. Group 1 consisted of 51 patients who underwent 1 session per day, while Group 2 included 51 patients who had 2 sessions per day. It is important to note that a group of patients without rehabilitation was not formed for ethical reasons. The characteristics of the groups are presented in *Table 1*.

Physical rehabilitation sessions included: passive, active-passive, and active exercises, patient positioning in bed, sitting and standing verticalization, walking, and breathing exercises. The sessions were conducted by a physical therapist under the supervision of a nurse and an anesthesiologist. They began on the first day of hospitalization in the ICU, with each session lasting 15–20 minutes. During the session, the therapist aimed to achieve the highest possible intensity for the patient. Sessions were discontinued in the event of patient decompensation or if the patient refused to continue.

To assess physical functional status, the following scales were used:

1. Activity Measure for Post-Acute Care (AM-PAC) Activities of Daily Living (ADL) [9; 10]. This scale includes 6 parameters for assessing daily activities: the patient's ability to put on pants, bathe, use the toilet, put on a shirt, brush teeth, and eat. Each parameter can be scored on the scale from 1 to 4, where 1 indicates that the patient is unable to perform the task, 2 means significant assistance is required, 3 indicates minimal assistance, and 4 signifies that the task is performed independently. The maximum score on the scale is 24, while the minimum is 6.

2. Johns Hopkins: Highest Level of Mobility (JH-HLM) Scale [11]. This scale assesses patient mobility and consists of 8 levels of activity, ran-

Table 1. Comparative characteristics of the study groups

Characteristics, units (presentation)	Statistical data		Group (number of patients)	
	instrument	p value	1 (n=51)	2 (n=51)
Age, years (M±SD)	t-test	0.58	57.55±14.34	56.10±12.02
Sex (number, %):				
- males			35 (69)	34 (67)
- females			16 (31)	17 (33)
Body Mass Index, kg/m² (M±SD)	U-test	0.63	31.34±6.72	30.87±5.92
Comorbidities (number, %):				
- hypertension			31 (61)	33 (65)
- diabetes mellitus			22 (43)	15 (29)
- chronic kidney disease			13 (25)	8 (16)
- smoking			9 (18)	14 (27)
Severity of condition at admission:				
- computed tomography, % (M±SD)	U-test	0.63	51.33±19.80	46.62±19.0
- SpO_2, % (M±SD)	U-test	0.56	80.86±4.91	81.35±3.25
- respiratory rate, breaths per minute (M±SD)	t-test	0.09	24.20±1.51	23.69±1.52

Notes: (M±SD) – (Mean±Standard Deviation); SpO_2 – Oxygen saturation of hemoglobin as measured by pulse oximetry; U-test – Mann-Whitney U test; t-test – Student's t-test.

ging from the minimum level (1), where the patient is bed-bound, to the maximum level (8), where the patient is able to walk more than 100 meters.

To assess cognitive functions, the Mini-Mental State Examination (MMSE) scale [12; 13] was used. This standardized questionnaire consists of 22 questions and tasks, allowing for the evaluation of a patient's cognitive abilities in 5 dimensions: orientation in time and space, registration, attention and calculation, memory, and language. Scores range from 0 to 30 points, with a score of 27 or higher considered within the normal range. A key advantage of this questionnaire is its ease of use.

To assess mental status, the Hospital Anxiety and Depression Scale (HADS) [14] were used. This subjective method is designed for the screening of anxiety and depression in hospitalized patients. HADS is noted for its simplicity of application and analysis, as completing the questionnaire does not require significant time and does not pose complications for the patient. The scale consists of 14 statements divided into 2 subscales: subscale A for 'anxiety' and subscale D for 'depression.' Each statement in the questionnaire has 4 response options reflecting the severity of symptoms, ranging from 0 to 3.

To assess the severity of post-COVID symptoms, the Post-COVID-19 Functional Status (PCFS) scale [15] was used. The PCFS evaluation was conducted during the first visit to the physician or during a phone contact with the physician. The survey was performed, on average, 5–7 days after discharge from the hospital. A sample survey algorithm is presented in the *Figure.*

Results and Discussion

The physical functional status of patients is presented in *Tables 2* and *3*.

The assessment using the AM-PAC (ADL) scale showed a slight difference between the groups. The average score in Group 1 was 22.55± ±2.96, while in Group 2 it was 23.22±2.29. However, the difference between these groups was not statistically significant (p=0.24). The findings were similar for the JH-HLM scale. This indicates that an increase in the frequency of rehabilitation sessions does not have a significant impact on patient mobility levels and their ability to perform daily tasks in the short term.

Our results differ from the study by Mayer K.P. et al. (2024), which involved approximately 2000 COVID-19 patients and found that early initiation of physical rehabilitation in the ICU, along with increased session intensity, significantly improved the patients' physical condition at the time

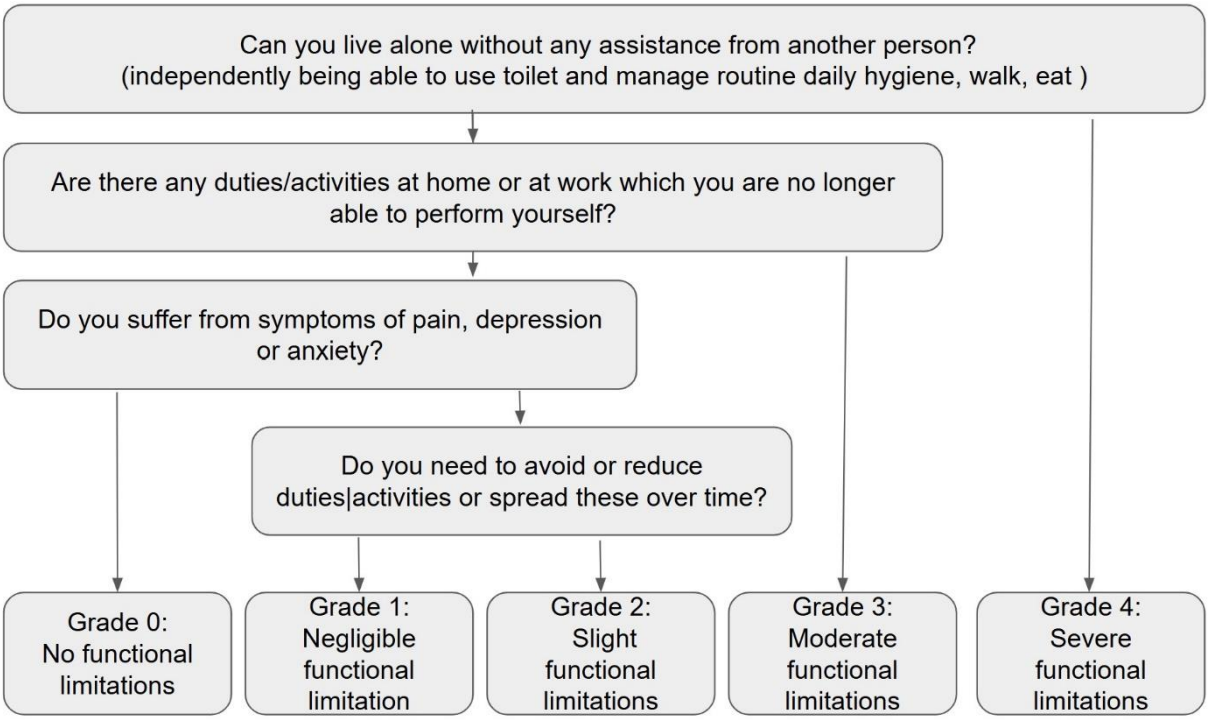

Fig. Post-COVID-19 Functional Status (PCFS) Tool [15].

Table 2. Physical functional status of patients in two groups at the time of hospital discharge

Characteristics, units (presentation)	Statistical data		Group (number of patients)	
	instrument	p value	1 (n=51)	2 (n=51)
AM-PAC (ADL) (M±SD)	U-test	0.24	22.55±2.96	23.22±2.29
JH-HLM (M±SD)	U-test	0.13	7.59±0.73	7.76±0.84

Notes: (M±SD) – (Mean±Standard Deviation); AM-PAC (ADL) – Activity Measure for Post-Acute Care (Activities of Daily Living); JH-HLM – Johns Hopkins: Highest Level of Mobility; U-test – Mann-Whitney U test.

Table 3. Cognitive and mental status of patients in two groups at the time of hospital discharge

Characteristics, units (presentation)	Statistical data		Group (number of patients)	
	instrument	p value	1 (n=51)	2 (n=51)
MMSE (M±SD)	U-test	0.24	26.45±4.37	27.35±3.58
HADS (A+D) (M±SD)	U-test	0.02	11.33±4.51	9.52±4.61

Notes: (M±SD) – (Mean±Standard Deviation); MMSE – Mini-Mental State Examination; HADS – Hospital Anxiety Depression Scale; U-test – Mann-Whitney U test.

of discharge [16]. According to other studies [17], the short-term effect of physical rehabilitation on functional status at discharge was negligible, while the long-term effect favored more intensive rehabilitation. This may indicate that the process of restoring physical activity requires more time and may depend on other factors, such as patients' baseline health status, the presence of comorbidities, or their previous level of physical activity.

Considering this, future studies should increase the sample size, measure and account for the intensity of each individual rehabilitation session, and extend the duration of patient follow-up.

Early physical rehabilitation is considered by researchers as one of the effective methods for improving cognitive functions in patients following their stay in the ICU [18]. The study conducted by Patel B.K. et al. (2023) found a positive effect of increasing the intensity of physical rehabilitation on cognitive functions, which became more pronounced over the long term [19].

In our study, the average MMSE score in Group 1 was [26.45±4.37] points, while in Group 2 it was [27.35±3.58] points. The difference in mean scores was not statistically significant. These results suggest that the recovery of cognitive functions after a severe form of COVID-19 may be a prolonged process and requires additional interventions beyond physical rehabilitation.

Regarding the mental component, patients who received two rehabilitation sessions per day exhibited a significant reduction in levels of anxiety and depression. The average score on the HADS (A+D) scale in Group 2 was 9.52±4.61, which is significantly lower than that in Group I, where the average score was 11.33±4.51 (p=0.02).

According to the literature [20], physical activity stimulates the production of endorphins (the 'happiness hormones'), which may contribute to reducing levels of anxiety and depression. Given the psycho-emotional consequences of COVID-19, intensive physical rehabilitation may be an important tool not only for physical but also for psychological recovery in patients.

One of the most significant findings of the study is the difference in PCFS scores, which assess the functional status of patients after discharge and serve as an important indicator of post-COVID syndrome manifestations. Patients who received two rehabilitation sessions per day had significantly better outcomes compared to those who underwent only one session (*Table 4*). The average score on the PCFS scale in Group 1 was 2.06±1.07, indicating a greater severity of post-COVID symptoms, such as weakness, pain, and fatigue, compared to Group 2, where the average score was 1.62±1.09. This highlights the potential of more intensive rehabilitation programs to reduce symptoms such as fatigue and weakness, which are common manifestations of post-COVID syndrome. The decline in physical strength and endurance may be related not only to the disease

Table 4. Manifestations of post-COVID syndrome in patients of both groups

Characteristics, units (presentation)	Statistical data		Group (number of patients)	
	instrument	p value	1 (n=51)	2 (n=51)
PCFS scale (M±SD)	U-test	0.02	2.06±1.07	1.62±1.09

Notes: (M±SD) – (Mean±Standard Deviation); PCFS – Post-COVID-19 Functional Status; U-test – Mann-Whitney U test.

itself but also to prolonged hospitalization; thus, maintaining a high level of physical activity plays a vital role in recovery.

It is important to note that one of the limitations of the study is its short time frame, as the assessment of results was conducted only at the time of discharge and a few days thereafter. There is a possibility that some effects, particularly in the cognitive domain, may manifest only after a longer period post-discharge.

Another significant limitation is the absence of a control group without rehabilitation. While this was justified by ethical considerations, it still restricts our conclusions regarding the absolute effectiveness of physical rehabilitation.

Future research should focus on examining the long-term effects of physical rehabilitation following severe COVID-19, specifically how changes in the intensity of physical exercises may influence patients' recovery in the long term. Studies should also take into account other aspects of recovery, such as social and psychological rehabilitation, which may contribute to the overall improvement in the quality of life for patients who have recovered from COVID-19.

Conclusion

The increase in the number of physical rehabilitation sessions for patients who have experienced severe COVID-19 demonstrates significant potential for reducing manifestations of post-COVID syndrome and improving patients' psycho-emotional state. Intensive rehabilitation programs may assist in alleviating symptoms such as fatigue and weakness, which are commonly observed in post-COVID patients. However, to achieve sustainable and long-lasting results, it is essential to consider other aspects of recovery, such as cognitive rehabilitation and social-psychological support, which play a crucial role in the recovery process following severe COVID-19.

DECLARATIONS:

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ERYPTOSIS CONTRIBUTES TO GESTATIONAL DIABETES MELLITUS IN MATERNAL OBESITY

Lazurenko V.V., Zhelezniakov O.Yu., Prokopiuk V.Yu.

Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. Obesity is considered to be a risk factor for Gestational Diabetes Mellitus (GDM), which is characterised by hyperglycaemia in pregnant women. Recent studies have demonstrated that glycated erythrocytes are more prone to eryptosis, a unique regulated cell death observed only in mature erythrocytes.

The **aim** of the current study was to analyse how eryptosis might contribute to GSM in maternal obesity.

Materials & Methods. Eryptosis parameters were assessed in pregnant women enrolled for the study: group 1 consisted of 12 obese pregnant women without the signs of GDM, 15 pregnant women without obesity but with GDM were included in group 2, 14 obese pregnant women with GDM were in group 3, group 4 (control) consisted of 15 pregnant women without the signs of obstetric and extragenital pathology. Phosphatidylserine externalisation was assessed by flow cytometry following Annexin V-FITC staining of circulating erythrocytes isolated from the pregnant women. Additionally, 2',7'-dichlorodihydrofluorescein diacetate (H2DCFDA) staining was used to analyse oxidative stress parameters in circulating erythrocytes.

Results. Groups 1, 2 and 3 of pregnant women showed a higher degree of ROS-dependent eryptosis compared to the control group (IV). There was no statistically significant difference ($p>0.05$) in the eryptosis of circulating erythrocytes between pregnant women of groups 1 and 2. However, the percentage of phosphatidylserine-dispersed erythrocytes in eryptosis and the level of ROS was statistically significantly higher in pregnant women of group 3 compared to pregnant women of groups 1 and 2.

Conclusions. GSM associated with maternal obesity is accompanied by accelerated ROS-dependent eryptosis. Enhanced eryptosis might act as an additional factor contributing to thrombosis and endothelial dysfunction in obese pregnant women with GDM.

Keywords: *pregnancy, phosphatidylserine, flow cytometry, Annexin, erythrocytes.*

Introduction

Gestational Diabetes Mellitus (GDM) is a condition associated with hyperglycaemia developing in pregnant women [1]. Compelling evidence suggests that obesity, together with high maternal age, is a significant risk factor for GDM development [2]. Since overweight and obesity have become a global health concern with a clear increasing trend, including among women [3], it is important to focus on the search for novel links between obesity and GDM that might be of predictive value. In the current study, it has been hypothesised that eryptosis defined as a caspase-independent, calcium-dependent regulated cell death modality of erythrocytes [4] might be such a link. Notably, accelerated eryptosis has been demonstrated to be observed in diabetes mellitus and its enhancement has been primarily attributed to oxidative stress-mediated damage to erythrocytes [5]. In general, glycated erythrocytes have been shown to be more prone to oxidative damage and eryptosis [6]. At the same time, enhanced eryptosis is accompanied by intensified clearance of eryptotic red blood cells primarily related to recognition of eryptosis-associated externalised phosphatidylserine molecules by macrophages with their subsequent uptake referred to as efferocytosis, which might result in anaemia [7]. Moreover, the eleva-

Corresponding Author:

Lazurenko Viktoriya V. – MD, DMedSc, Professor, Head of the Department of Obstetrics and Gynecology No.2, Kharkiv National Medical University, Ukraine.

✉ Ukraine, 61022, Kharkiv, Nauki Ave., 4, KhNMU.

E-mail: vv.lazurenko@knmu.edu.ua

ted number of phosphatidylserine-exposing eryptotic erythrocytes might be associated with enhanced blood clotting and damage to endothelial cells leading to endothelial dysfunction [8]. It should be emphasised that platelet and endothelial dysfunction is a common issue in GDM, which still remains poorly investigated [9]. Given the thrombosis- and endothelial dysfunction-promoting consequences of eryptosis and its contribution to erythrocyte damage in diabetes mellitus, its activation seems to be a possible factor that might be of huge importance in the pathogenesis of GDM.

Aim

This study was designed to analyse oxidative stress-mediated eryptosis in GDM and investigate its possible contribution to the emergence of GDM in maternal obesity.

Materials & Methods

Patients and their groups

56 pregnant women included in the study were divided into four groups: group 1 consisted of 12 obese pregnant women without signs of GDM, 15 pregnant women without obesity but with GDM were included in group 2, 14 obese pregnant women with GDM were in group 3, group 4 (control) consisted of 15 pregnant women without signs of obstetric and extragenital pathology. The examination of women took into account their age, weight, height, Body Mass Index (BMI), results of clinical and laboratory tests (clinical and biochemical blood tests including blood glucose, C-reactive protein, coagulogram, lipidogram), instrumental examination (ultrasound examination of the fetoplacental complex, cardiotocography).

Sample preparation

Eryptosis parameters were assessed in pregnant women enrolled for the study: group 1 consisted of 12 obese pregnant women without signs of GDM, 15 pregnant women without obesity but with GDM were in group 2, 14 obese pregnant women with GDM were in group 3, group 4 (control) consisted of 15 pregnant women without the signs of obstetric and extragenital pathology. The samples were collected in anticoagulant-containing (K2EDTA-containing) vacutainers and analysed within 2 h of collection to ensure reliable results. Fresh blood samples were used to prepare erythrocyte solution. Briefly, 5 µl of blood was aliquoted and added to a Ringer solution containing 125mM NaCl, 5mM KCl, 2mM $CaCl_2$, 2mM $MgCl_2$, 32mM HEPES, and 5mM glucose. The cells were centrifuged at 1500 g for 5 min. The cells were resuspended in the Ringer solution and the washing procedure was repeated twice to obtain erythrocyte suspensions for further staining [10; 11].

Detection of eryptosis by determining phosphatidylserine externalisation

The washed erythrocytes obtained from pregnant women were resuspended in 100 µl Annexin-binding buffer containing annexin V-FITC (BD Pharmingen™, FITC annexin V, Franklin Lakes, NJ, USA) for 30 min. This annexin-binding buffer contains calcium ions to ensure interactions of annexin V with the exposed phosphatidylserine molecules located on the surface of erythrocytes. After incubation, the cells were washed and resuspended in 100 µl Annexin-binding buffer [12]. The fluorescence was detected in the FL1 FITC channel (excitation 488 nm and emission 525 nm). The gating strategy included identification of the percentage of the erythrocytes with a high degree of translocated phosphatidylserine molecules indicating eryptotic cells.

Quantification of intracellular ROS levels in erythrocytes

In brief, 2',7'-dichlorodihydrofluorescein diacetate (H2DCFDA) supplied by Invitrogen™ (Waltham, MA, USA) was used to detect intracellular reactive oxygen species (ROS) levels characterising the state of the redox metabolism in erythrocytes. An aliquot of erythrocytes obtained as outlined above was stained with the stock solution of the dye in DMSO to obtain a final concentration of 10 µM. The cells were incubated for 30 min at 37°C in H2DCDA-containing phenol free medium. The fluorescence was detected in the FL1 FITC channel (excitation 488 nm and emission 525 nm). To quantify the data, the mean fluorescence intensity (MFI) was evaluated [11].

Data collection and post-acquisition analysis

A total of 100,000 events were collected per sample by a BD FACS Canto™ II flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). The doublets were excluded. The fluorescence was analysed in the population of single cells. FlowJo™ (v10, BD Biosciences, USA) software was used to process the raw data.

Statistical analysis

Comparative analysis was performed by carrying out the ANOVA test followed by the post-hoc Tukey test. The difference was considered statistically significant at $p<0.05$. Data are shown in Figures as mean and standard deviation (SD). Graph Pad Prism 5.0 software (USA) was used to provide statistical analysis.

Results

Patient's characteristics

The age of pregnant women ranged from 18 to 39 years. The mean age of obese women was (32.4±3.2) years, women with GDM – (34.7±3.6) years, obese and gestational diabetes mellitus – (33.5±2.9) years, and control group women – (27.3±2.8) years. The BMI in obese pregnant women was (37.2±3.5) kg/m^2, in gestational diabetes mellitus – (28.4±2.9) kg/m^2; in gestational diabetes mellitus with obesity – (35.4±3.6) kg/m^2, in the control group – (24.9±2.1) kg/m^2.

In this study, the eryptosis of circulating erythrocytes was judged primarily by the evaluation of phosphatidylserine externalisation. To quantify the degree of eryptosis, the percentage of cells expressing the high content of phosphatidylserine molecules on the cell surface was identified and compared. Since this parameter is considered a hallmark of eryptosis, it was selected as the most reliable available marker. Expectedly, maternal obesity, GDM and their combination were found to be associated with enhanced phosphatidylserine externalization compared to healthy non-obese pregnant females (*Figure 1*), which suggests acceleration of eryptosis.

Comparative analysis revealed that non-obese women with GDM and obese women not diagnosed with GDM had a negligible statistically insignificant difference (p>0.05) in the number of cells with significantly externalised phosphatidylserine molecules (*Figure 1*) indicating that the degree of eryptosis was comparable between the above-mentioned groups. Representative histograms reflecting eryptosis-characterising phosphatidylserine externalisation are available in *Figure 2*.

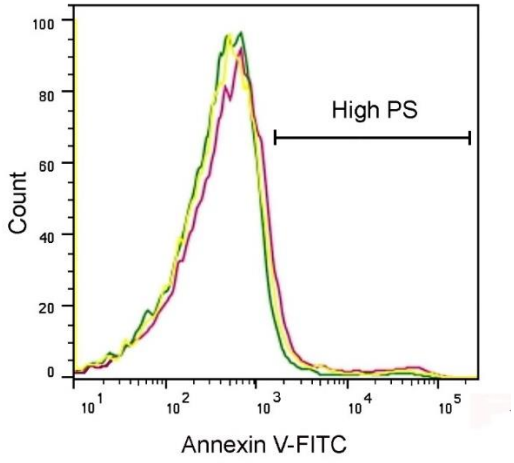

Fig. 2. Representative histograms demonstrate the population of the erythrocytes with the high degree of phosphatidylserine externalization (eryptotic cells) in obese pregnant women without GDM (green line), non-obese pregnant women with GDM (yellow line), and obese females with GDM (red line).

Note: GDM – gestational diabetes mellitus; PS – phosphatidylserine.

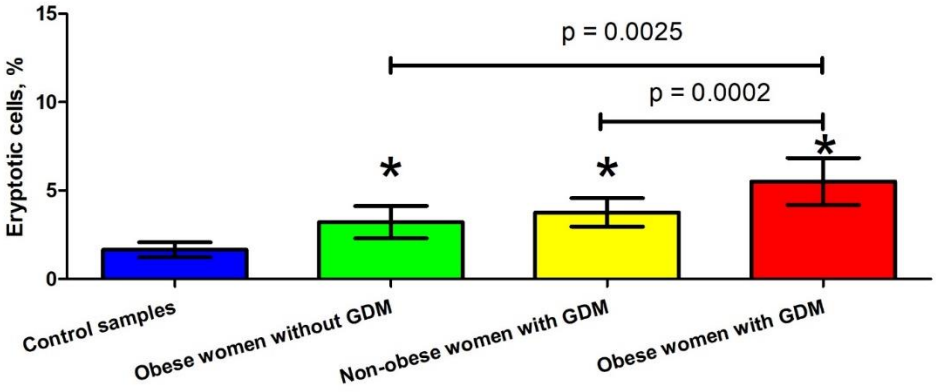

Fig. 1. Evaluation of eryptosis in circulating erythrocytes by assessing the percentage of cells with the high degree of phosphatidylserine externalization in healthy non-obese pregnant females (blue), obese pregnant females without GDM (green), non-obese pregnant women with GDM (yellow), and maternal obesity with GDM (red). ANOVA and Tukey tests, mean and standard deviation (SD).

Note: GDM – gestational diabetes mellitus;
* – indicates a statistical difference compared to the control samples (p<0.05).

On the contrary, GDM developed against a background of maternal obesity was found to be associated with accelerated eryptosis, evidenced by a statistically significant increase in the percentage of phosphatidylserine-expressing erythrocytes compared to both groups. Abundant evidence indicates that eryptosis is triggered by oxidative stress mediated by excessive production of ROS. Thus, our next step was to quantify ROS production in erythrocytes isolated from all three groups of pregnant women enrolled for the study. ROS quantification was performed by using the H2DCFDA staining. The data on the content of intraerythrocytic ROS were perfectly in line with the assessment of the phosphatidylserine externalisation. Maternal obesity, GDM and their combination resulted in elevation of intracellular ROS concentrations (*Figure 3*) compared to non-obese pregnant women with no GDM.

ROS levels were found to be comparable in non-obese women with GDM and non-GDM obese women. At the same time, obese pregnant women diagnosed with GDM had higher intracellular ROS levels, which was confirmed by higher values of the ROS-dependent fluorescence (Figure 3). Representative histograms demonstrating the ROS-dependent fluorescence in erythrocytes of pregnant women are shown in Figure 4.

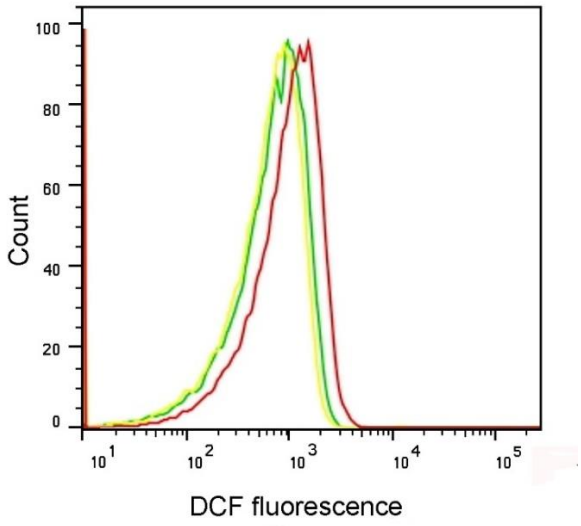

Fig. 4. Representative histograms reflect the intracellular ROS levels in circulating erythrocytes of obese pregnant women without GDM (green line), non-obese women with GDM (yellow line), and obese females with GDM (red line).

Note: DCF – dichlorofluorescein;
GDM – gestational diabetes mellitus;
ROS – reactive oxygen species.

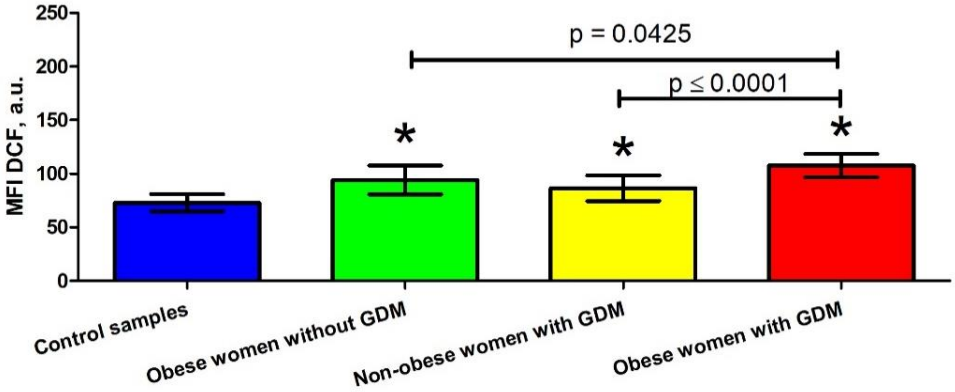

Fig. 3. Intracellular ROS levels in circulating erythrocytes of healthy non-obese pregnant females (blue), obese pregnant women without GDM (green), non-obese women with GDM (yellow), and obese females with GDM (red). ANOVA and Tukey tests, mean and standard deviation (SD).

Note: DCF – dichlorofluorescein;
GDM – gestational diabetes mellitus;
MFI – mean fluorescence intensity;
ROS – reactive oxygen species;
* – indicates a statistical difference compared to the control samples ($p<0.05$).

Discussion

In this study, eryptosis parameters were assessed in obese pregnant women without GDM, non-obese pregnant women with GDM, and obese pregnant females with GDM. We have hypothesized that eryptosis might be a factor influencing pathogenesis of GSM. In general, eryptosis is a controlled cell death of erythrocytes typically occurring in the injured or stressed cells to ensure their non-immunogenic clearance by phagocytic cells in the process called efferocytosis. Morphological changes characteristic of eryptosis are comparable to those observed in apoptosis and include cell shrinkage and membrane blebbing [13]. However, there are cell-specific signalling pathways making it unique in comparison with apoptosis [4]. A key role in eryptosis is played by Ca^{2+} signalling, which mediates structural changes typical for this cell death and phosphatidylserine externalization, a critical signal for macrophages that mediates clearance of eryptotic erythrocytes [7]. Phosphatidylserine externalization was used as a marker of eryptosis in this study and its analysis revealed that the obese pregnant women with GDM had enhanced eryptosis levels compared to other groups of the pregnant women investigated in this research. Notably, eryptosis can be enhanced when ROS get accumulated, ceramide is produced in the cells by sphingomyelinases or when prostaglandin E2 is overproduced [13]. As it turned out, phosphatidylserine externalization in the obese pregnant women with GDM is paralleled with ROS accumulation suggesting that eryptosis in this condition is ROS-dependent. Our findings are in line with other studies emphasizing the critical role of ROS in induction of eryptosis in hyperglycaemic conditions of diabetic patients [5]. Additionally, our study supports earlier remarks concerning the potential of evaluating eryptosis parameters in diagnostic purposes in diabetes mellitus [14].

Moreover, phosphatidylserine externalization revealed in the current study might contribute to pathological conditions associated with GDM in maternal obesity. Phosphatidylserine-expressing eryptotic erythrocytes interact with platelets and endothelial cells in a phosphatidylserine-dependent manner, which results in activation of platelet aggregation increasing blood coagulation and the development of endothelial dysfunction, respectively [8]. Notably, both obesity and GDM increased the risk of thromboembolic complication in pregnancy [15]. Similarly, endothelial dysfunction is common for maternal obesity and GDM [16]. Thus, our study sheds light on the new mechanism that might be involved in the development of thrombosis and endothelial dysfunction in GDM developed against a background of maternal obesity. It can be assumed therefore that eryptosis might be inhibited therapeutically in the obese pregnant women with GDM. However, more studies are necessary to clarify the diagnostic, prognostic and therapeutic potential of eryptosis in pregnant women.

Conclusions

Enhanced ROS-dependent eryptosis is revealed for maternal obesity, GDM, and their combination. Our findings indicate that maternal obesity with GDM is associated with enhanced eryptosis compared to maternal obesity with no GDM or GDM with no obesity suggesting that both conditions potentiate each other in promotion of eryptosis. Eryptosis in maternal obesity with GDM is dose-dependent. Eryptosis might contribute to thrombosis and endothelial dysfunction in maternal obesity with GDM.

DECLARATIONS:

Disclosure Statement

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Data Transparency

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BONE RESORPTION MARKER RANKL IN THE DIAGNOSIS AND TREATMENT OF PATIENTS WITH MAXILLARY SINUS CYSTS

Shkorbotun V.O., Nachesa Y.S.

Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine

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ABSTRACT

Background. RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) is a protein belonging to the tumor necrosis factor superfamily serving as a specific marker for osteoclast activation and osteolysis.

Aim. To determine RANKL levels in the homogenates of Maxillary Sinus Cysts (MSC) at the time of their removal, investigate the correlation of these indicators with the presence of pathology in the upper row of projection teeth in the respective patients, and refine the timing for potential dental implantation or sinus lifting after sinusotomy based on these findings.

Materials & Methods. The study included 25 patients aged 20–65 years who underwent surgical treatment for MSCs located on the inferior wall of the sinus. The research methods comprised general clinical, otorhinolaryngological, radiological, and pathohistological techniques and Enzyme-Linked ImmunoSorbent Assay (ELISA) for RANKL in the tissues of the removed cysts. Pathohistological examination revealed retention cysts in 11 patients and pseudocysts in 14 patients. The presence of dental pathology and active odontogenic processes at the time of cyst removal was established based on prospective clinical and radiological evaluations. The dynamics of mucoperiosteal defect regeneration in the MSC, considering RANKL levels, were assessed 3–6 months post-surgery.

Results. In the postoperative period, 8 (32%) out of 25 patients exhibited odontogenic alteration processes in the tissues of the maxilla adjacent to the cysts. The RANKL concentration in these patients was [80.65±34.22] pg/μg of protein, while in the other 17 patients without signs of bone damage, it was [33.10±4.35] pg/μg of protein ($p<0.05$). The threshold RANKL concentration distinguishing these groups in this study was 51.50 pg/μg of protein.

Conclusions. In patients with peri-apical bone changes in the maxilla in the projection area of the cysts (alveolar recess), the RANKL level in their homogenates is higher compared to patients without such pathology. Measuring RANKL levels in the homogenates of cysts removed during endonasal maxillary sinusotomy can serve as an additional indicator for planning postoperative dental treatment in these patients.

Keywords: *ENT-pathology, endoscopic rhinosurgery, histology, postoperative period, paranasal sinus x-ray, treatment.*

Introduction

Recent advancements in the management of Maxillary Sinus Cysts (MSC) include the introduction of highly informative imaging modalities and endoscopic surgical methods, leading to significant improvements in treatment outcomes [1]. However, a debate has emerged in recent years regarding the necessity of removing asymptomatic cysts, especially those smaller than 20 mm or 15 mm in diameter, in patients undergoing sinus lift procedures [2; 3]. This issue is particularly relevant for patients scheduled for dental implantation involving subantral bone augmentation. In these cases, the decision to remove a cyst is influenced not only by its size but also by its location. Research has shown that cysts directly above the planned augmentation site increase the risk of complications, such as Schneiderian membrane rupture during sinus lifting [4].

Corresponding Author:

Yaroslav Nachesa – MD, PhD student of the Department of Otorhinolaryngology, Shupyk National Healthcare University of Ukraine.

✉ Ukraine, 04112, Kyiv, Dorohozhytska str., 9.
E-mail: doctor.yaroslavnachesa@gmail.com

The cyst size remains a critical factor due to the potential for ostium blockage caused by cyst elevation during the sinus lift and the risk of reactive rhinosinusitis [4]. Nonetheless, the key determinant of successful surgical management of MSCs is the risk of recurrence [5].

Currently, endoscopic endonasal microdebrider-assisted maxillary sinusotomy, adhering to periosteum-preserving techniques, represents the gold standard for sinus surgery [6]. This minimally invasive approach allows for effective sanitation of the maxillary sinus while preserving the integrity of the periosteal layer of the mucoperiosteum.

A stable outcome in sinusotomy largely depends on the surgeon's ability to ensure complete sanitation of the tissues surrounding the cyst attachment site. This is particularly important for odontogenic cysts, as the absence of visible dental pathology does not always rule out inflammation in adjacent tissues of the maxilla. The completeness of bone tissue sanitation near the cyst is evaluated through imaging studies, primarily Computed Tomography (CT), and monitoring its postoperative dynamics [7]. However, awaiting positive CT changes often requires prolonged observation and follow-up scans, which may not be practical in clinical settings.

This highlights the need to identify inflammation markers in bone tissue at different stages of MSC management to detect localized inflammatory processes. One promising marker is the Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), which indicates bone destruction and could serve as a valuable diagnostic tool in these cases.

Aim

To enhance the effectiveness of treatment for patients with maxillary sinus cysts (MSCs) by developing a differentiated approach to determining the necessity for further sanitation of maxillary teeth adjacent to the cysts, based on the application of the RANKL immunoassay.

Materials and Methods

The study included 25 patients aged 20–65 who underwent surgical treatment for MSCs. The diagnosis was established through rhinological examinations, including endorhinoscopy and CT of the paranasal sinuses. General clinical investigations were also performed for all patients.

The cohort consisted of 11 women and 14 men, with an average age of [31±12.2] years. The examinations were conducted at the Department of Otorhinolaryngology of Shupyk National Healthcare University of Ukraine, the clinical facilities of Kyiv City Clinical Hospital No.9, and the Department of Fundamental and Applied Problems of Endocrinology at the "V.P. Komissarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine", where immunoassay analyses were performed.

This prospective study evaluated the dynamics of CT data obtained 3–6 months after endoscopic sinus surgery, correlating the findings with the levels of RANKL, a bone destruction marker, measured in tissue samples from cyst walls located on the floor of the maxillary sinus.

Inclusion criteria were the presence of cystic lesions of the maxillary sinuses in patients who required surgical treatment.

Exclusion criteria were radiological signs of facial bone resorption unrelated to sinus pathology, the presence of carious lesions of the mandibular teeth, skull fractures within the past 6 months, and a confirmed oncological diagnosis.

All patients underwent endoscopic endonasal maxillary sinusotomy with cyst removal. Radiological studies were performed using the NewTom GO CT scanner (Cefla Group, Italy), equipped with a "CANON/TOSHIBA D-067SB" tube (serial number 0D14854-J4241A3) (Canon/Toshiba, Japan). Measurement ranges were [155–172] mGy/cm ±10.00%, with an error margin of ±4.24%. The analysis focused on the condition of the mucoperiosteum of the maxillary sinus and the maxillary teeth in the region of the cyst (presence and extent of caries, apical changes, and periapical alterations in the bone adjacent to the cyst).

Histological examination of the removed cysts revealed that 11 cases (44.0%) were retention cysts, while 14 cases (56.0%) were lymphangiectatic cysts (pseudocysts).

RANKL levels in the fragments of cyst walls removed from the maxillary sinus were determined using Enzyme-Linked ImmunoSorbent Assay (ELISA). After weighing the biopsy material and adding phosphate buffer, homogenization was performed, followed by centrifugation of the homogenate to isolate the supernatant for analysis. The human TNFSF11 (RANKL) ELISA kit ("Abcam", UK) was used, employing a colorimetric method with sensitivity <10 pg/mL and a detection range of [78–5000] pg/mL [8].

All patients were informed about the study objectives, provided written informed consent for participation, and were allowed to withdraw at any stage. The study adhered to the ethical principles

of the Declaration of Helsinki, the Constitution of Ukraine, and national healthcare regulations.

Statistical analysis was performed using Statistica v.12.6 software (StatSoft, USA), employing non-parametric methods such as the Mann-Whitney U-test and Fisher's exact test. Qualitative variables were described using absolute and percentage values with 95% confidence intervals (CI). A p-value of <0.05 was considered statistically significant.

Results

The average RANKL level in the cyst walls of the studied patients was [56.07±29.72] pg/μg of protein. Among patients with true cysts, the level was [32.2±5.1] pg/μg of protein, while in individuals with pseudocysts, it was significantly higher, at [71.7±31.1] pg/μg of protein (p<0.05, Mann-Whitney U-test).

CT findings, considering the dental status of patients prior to endorhinosurgical intervention and cyst type, are presented in *Table 1*.

Analysis of Table 1 demonstrates that periapical bone changes in areas adjacent to the walls of removed cysts were significantly more frequent in patients with pseudocysts. Moreover, the proportion of patients with healthy teeth or superficial caries (not affecting deeper structures) was notably lower in this group. Additionally, endodontic treatment with root canal filling was more common among patients with pseudocysts (43%) than with retention cysts (18%), though this difference did not reach statistical significance.

Our prospective study focused on detecting odontogenic inflammation and analyzing CT dynamics in patients who underwent maxillary sinusotomy. The evaluation considered RANKL levels as markers of inflammation in bone tissue and residual inflammatory processes in maxillary structures. CT findings 3–6 months post-surgery were used to assess the mucoperiosteum regeneration and the state of the maxillary sinus in the areas of former cyst localization (*Table 2*).

Table 2 data indicate that no cyst recurrence was observed in patients, regardless of cyst type, suggesting the effectiveness of endoscopic surgical intervention. However, mucoperiosteal thickening at the cyst removal site was observed in 6 patients (42.8%) with pseudocysts and in 1 patient (9.1%) with a true cyst. In lymphangiectatic cyst cases, these changes were localized near the apices of the teeth, in the patient with a retention cyst, they were found in the lateral sections of the maxillary sinus, excluding odontogenic origin.

Signs of negative dynamics in bone tissue in the periapical areas of teeth adjacent to removed MSCs were identified in one patient, alongside mucoperiosteal thickening. In contrast, two patients after endodontic treatment before cyst removal

Table 1. Results of the study of maxillary structures in patients with maxillary sinus cysts based on computed tomography data

Radiological feature	Share of individuals with identified radiological signs						p*
	Patients with retention cysts (n=11)		Patients with lymphangiectatic cysts (n=14)		Total (n=25)		
	abs., n	% [95% CI]	abs., n	% [95% CI]	abs., n	% [95% CI]	
Absence of caries signs	5	45.5 [21.3–72.0]	1	7.1 [1.3–31.5]	6	24.0 [11.5–43.4]	≥0.05
Caries without pulp involvement	4	36.4 [15.2–64.6]	0	0.0 [0.0–13.0]	4	16.0 [6.4–34.7]	<0.05
Caries extending to the pulp	2	18.1 [5.1–47.7]	1	7.1 [1.3–31.5]	3	12.0 [4.2–30]	≥0.05
Periapical bone changes near maxillary teeth	0	0.0 [0.0–16.0]	8	57.2 [32.6–78.6]	8	32.0 [17.2–51.6]	<0.05
Edentulism in the area adjacent to the cyst	0	0.0 [0.0–16.0]	4	28.6 [11.7–54.6]	4	16.0 [6.4–34.7]	≥0.05
Endodontically treated teeth adjacent to the cyst	2	18.2 [5.1–47.7]	6	42.9 [21.4–67.4]	8	32.0 [17.2–51.6]	≥0.05

Note: for determine p* (1–2) the Fisher's exact test used.

Table 2. CT data of patients who underwent surgery for maxillary sinus cysts

Clinical signs considered	Share of individuals with identified clinical signs n (% [95% CI])		p***
	Patients with retention cysts (n=11)	Patients with lymphangiectatic cysts (n=14)	
Recurrence of the cyst	0 (0.0 [0.0–16.0])	0 (0.0 [0.0–13.0])	0.688
Thickening of the mucous membrane at the site of the intervention	1 (9.1 [1.6–37.7])	6 (42.8 [21.4–67.4])	0.090
Presence of exudate in the sinus cavity	0 (0.0 [0.0–16.0])	1 (7.1 [1.3–31.5])	0.366
Periapical decrease in bone density of the upper jaw	0 (0% [0.0–16.0])	8 (57.1% [32.6–78.6])*, **	0.003

Notes:
* – feature observed alongside thickened sinus mucosa;
** – in two patients, a reduction in periapical changes was noted, while in one case, the area of changes increased;
*** – to determine p the Fisher's exact test used.

demonstrated a reduction of periapical bone density loss. These two patients, exhibiting advanced caries with pulp involvement and periapical bone density reduction near the cyst-associated teeth, had elevated RANKL levels of 80.85 pg/μg and 73.88 pg/μg of protein, respectively. Subsequent dental evaluations confirmed the presence of inflammation in the roots of these teeth.

A total of 8 patients (32.0%) were identified with dental pathology associated with bone destruction in areas adjacent to the cysts. Analysis of RANKL levels in these patients revealed levels of 51.50 pg/μg or higher. *Figure 1* illustrates the relationship between dental pathology and RANKL levels in the homogenates of removed cyst walls.

Statistical analysis of Figure 1 data revealed that the mean RANKL level in cyst walls of patients with confirmed advanced dental pathology near the cyst site was [80.65±34.22] pg/μg of protein, significantly higher than the level in patients without such pathology, as determined by clinical and radiological assessments ([33.10±4.35] pg/μg of protein, $p<0.05$).

Discussion

The study data regarding CT characteristics in patients with MSCs can be explained by the peculiarities of their pathogenesis. It is well known that lymphangiectatic cysts are more often of odontogenic origin, which is supported by the higher frequency of dental pathology detected in this group.

However, it is not always possible to identify pathology based on CT findings during intervention. In 6 (42.8%) cases, inflammatory processes were detected only through mucosal thickening in the cyst removal area during follow-up. In all these cases, RANKL levels were elevated, and inflammation in the bone tissue was confirmed by dental evaluation and subsequent endodontic treatment. These findings corroborate the results of experimental studies by Daisuke Nishida et al. (2021), which indicated the significance of RANKL as a marker in osteolysis processes [9]. Furthermore, Natalia Asquino et al. (2021) emphasized the importance of investigating the RANKL system in patients with dental pathologies, particularly periodontitis, in their review [10].

A critical aspect of this study is determining the threshold RANKL level in MSC walls that indicates bone remodeling processes in adjacent maxillary areas. In our study, this threshold was established at 51.50 pg/μg of protein, which has significant practical implications.

Conclusions

1. Mean RANKL level in the cyst walls of patients with dental pathology was significantly higher than in those without deep tooth structure involvement, amounting to [80.65±34.22] pg/μg of protein and [33.10±4.35] pg/μg of protein, respectively.

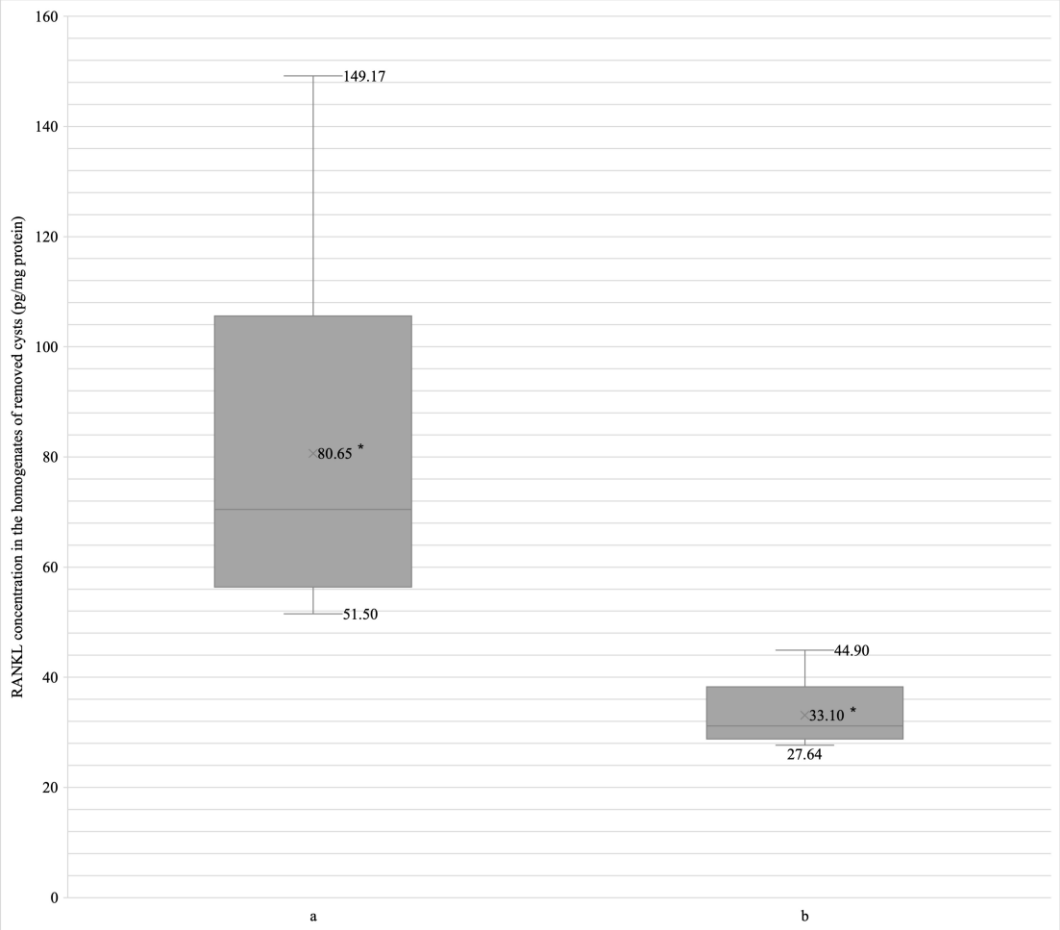

Fig. RANKL levels in cyst homogenates were relative to signs of active inflammation in the adjacent maxillary bone:
a – signs of a verified inflammation in the adjacent maxillary bone (n=8);
b – no signs of inflammation of the adjacent maxillary bone (n=17).

Notes: * – $p<0.05$; MB – maxillary bone.

2. The threshold RANKL level in the MSC wall indicative of bone destruction and remodeling processes in adjacent maxillary areas is 51.50 pg/µg of protein.

3. Measuring RANKL levels in cyst walls during their removal can be recommended as a laboratory method for identifying patients requiring sanitation of adjacent teeth.

Prospects for further research

Determining the significance of RANKL levels in the soft tissues adjacent to teeth requires further investigation in larger cohorts. This could potentially lead to the development of an algorithm for detecting hidden dental pathologies with osteolysis in patients with inflammatory MSC conditions.

Study limitations

This study is based on a limited sample size and a single pathological condition (MSC). Further research is needed to refine our understanding of the RANKL regulatory system in other nosological entities.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Data Transparency

The data can be requested from the authors.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

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JUSTIFICATION OF THE MODEL OF OPTIMIZED SYSTEM OF PROVIDING PALLIATIVE AND HOSPICE CARE TO THE POPULATION OF UKRAINE

Nesterenko V.G.[1], Burzyńska J.[2]

[1]Kharkiv National Medical University, Kharkiv, Ukraine
[2]Medical College of Rzeszów University, Rzeszów, Poland

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ABSTRACT

Background. National systems of Palliative and Hospice Care (PHC) are an important part of holistic systems of public health care. According to ratings (modified Wright M., Lynch T. and Clark D. country rating system, 2008/2011; Quality of Death Index, 2015), the PHC system of Ukraine is such that it does not have signs of systemic organization at the state level, provides low coverage of treatment and care of palliative patients (approximately 30% of the need) and the low quality of treatment (especially analgesia) of predominantly the majority (nearly 80%) of the covered patients.

Aim. To substantiate the model of the optimized PHC system of Ukraine on the basis of the generalized experience of countries with developed PHC systems and the results of own scientific research; evaluate the developed model.

Materials and Methods. System analysis and comparative methods were used in the study. To evaluate the developed model, a sociological method was used: a survey of specialists in the organization of health care and PHC was carried out. The results of the survey are evaluated on a quartile scale (Q_1–Q_4).

Results and Conclusions. A model of the optimized system of providing PHC to the population of Ukraine was developed, which outlines the subjects and objects of management, the goal, strategy, tactics, functions of the improved management system, directions, methods, measures, resources, and the system of scientific regulation. Scientific, legal, economic and administrative solutions are proposed to improve the existing order of PHC organization. According to the parameters of reasonableness and consistency, the model was recognized by experts as high-quality (the assessment is within Q_4[75–100]%). By parameters predictability, correlativeness and resistance to changes, as well as according to the general assessment, the model is recognized by experts as high-quality (the assessment is within Q_3[50–75]%). The evaluation of the developed model allows us to propose it for use in the organization of health care in the conditions of long-term reform of the health care system and the uncertainty of wartime.

Keywords: *health care system reform, qualimetry, expert assessment.*

Introduction

The health care system of Ukraine is in a state of long-term reform, which is characterized by researchers as inconsistent and inefficient, with irrational use of funds and a permanent shortage of medical personnel [1; 2]. Among the reasons for the shortcomings of the reform, the main ones are low spending on health care (up to 4% of the Gross Domestic Product, GDP, on average over the last decade from the state budget, with a low absolute GDP value), frequent changes in the strategy of the reform, and the lack of an honest assessment of the results. For comparison, EU spending on health care is higher thanks to a much higher average GDP [3].

National systems of providing Palliative and Hospice Care (PHC) are an important part of holistic systems of public health care. In Ukraine, the PHC system has undergone significant changes in

Corresponding Author:

Nesterenko Valentyna – MD, PhD in medicine, Docent, Assistant Professor of the Department of Public Health and Healthcare Management, Kharkiv National Medical University, Ukraine.

✉ Ukraine, 61022, Kharkiv, Nauki Ave., 4, KhNMU.

E-mail: vh.nesterenko@knmu.edu.ua

recent years, which was associated with a change in the system of financing palliative medical services for patients, adults, and children. The National Health Service of Ukraine offered hospital managers to order package financing for the treatment of palliative patients under the Medical Guarantee Program [4; 5]. Such financing corresponds to the principle "money follows the patient", which is an important part of the strategy of reforming the health care system in Ukraine in its latest stages (from 2014, and then from 2018) [6; 7] and meets the needs of palliative patients in building a patient-oriented medical care system [8].

Under this funding model, PHC were to be provided in hospitals (hospices, palliative care units and wards) and by outpatient teams until and including 2023. However, in 2024, the focus of funding was shifted to family doctors. That is, the financial powers actually began to change the procedure for providing palliative care in "hospices at home". The reasons and consequences of such changes will be analyzed later in this publication. But it can be immediately noted that such a change is a vivid illustration of the inconsistency of the PHC system reform.

In the comparative aspect of the success of countries in the development of national PHC systems, the modified rating of Wright M., Lynch T. and Clark D. (2008/2011) [5] and the Quality of Death Index (2015), which we investigated in the context of the possibility of legalizing euthanasia of palliative patients in Ukraine, are important [9; 10]. According to the first index, the PHC system of Ukraine is such that it does not have signs of system organization at the state level. The PHC system in its current state of existence ensures low coverage of treatment and care of palliative patients (approximately 30% of the need, including the number of beds – by 40.5%, with the practical absence of hospices at home) and the low quality of treatment (in particular, pain relief) of the vast majority (nearly 80%) of the covered patients [11–13].

Thus, a change in the strategy of organizing PHC in "hospices at home", the country low ratings in international indexes required a scientific assessment and revision of the existing model of the PHC delivery system.

The **aim** of the study was to substantiate the model of the optimized PHC system of Ukraine based on the generalized experience of countries with developed PHC systems and the results of own scientific research; and expert assessment of the developed model.

Materials and Methods

System analysis, comparative and sociological methods were used in the study. To evaluate the developed model of the optimized system of providing PHC in Ukraine, a questionnaire was developed in which 10 specialists from the organization of health care and PHC of Ukraine and Poland were asked to evaluate the proposed strategy, tactics, functions, directions, methods, measures (scientific, legal, economic and administrative decisions), resources of the improved PHC management system according to the criteria: 1) reasonableness; 2) sequences; 3) predictability, 4) correlation; and 5) resistance to change. All criteria were assigned the same qualitative weight (20.0%), which was also proposed to be evaluated as a research design criterion. At the beginning of the evaluation, the experts involved in the expert evaluation were asked to propose a different qualitative weight of the 5 evaluation criteria. But there were no comments on the proposed qualitative weight.

Each measure of improvement of the PHC provision model was proposed to be evaluated on a 10-point scale, the quartile distribution of which is presented in *Table 1*. A 10-point scale is the most intuitively acceptable for a quick assessment, which confirms the design of the Visual-Analog Pain Scale [14; 15]. The evaluation results are calculated in absolute values (number of points, average values with deviation, M±m) and in relative values (%) with rounding of results to tenths.

The research results were calculated according to the legend of the programmable cells of the program Excel 2019 (Microsoft, USA). The methods of intelligence statistics were used. The general design of the study was approved by the bioethics commission of Kharkiv National Medical University (Ukraine). Specialists were invited for the expert assessment, whose personal data are kept confidential (names of respondents are known only to researchers; for generalization and disclosure of information about the expert assessment, these names are replaced by numbers from 1 to 10).

Results and Discussion

To reform the PHC system in Ukraine, managerial influence on the subjects of the legislative and executive power of the state, state bodies managing medical aid to the population of Ukraine, professional public associations working

Table 1. Quartile distribution of assessments of measures to improve the model of providing palliative and hospice care

Quarter	Q_1[0–25]%	Q_2[25–50]%	Q_3[50–75]%	Q_4[75–100]%
Verbal evaluation of the proposed improvement	Unsatisfactory	Good	Qualitative	High quality
Number of points	1	2–4	5–7	8–10

in the field of palliative care to the population, as well as educational and scientific institutions that have the potential of training palliative medicine doctors and improving the qualifications of medical workers of other specialties who treat and care for palliative patients, adults and children. The influence on management subjects is envisaged to be indirect, through the announcement of the results of scientific research, the provision of the results of public opinion studies to the listed organizations, the attitude to the problems of palliative medicine of specialists who constantly or periodically provide assistance to palliative patients.

The objects of management are the management bodies of medical assistance to the population at the regional, city and district levels, medical education institutions in which specialists in the field of palliative medicine study and improve their qualifications, specialized palliative institutions (hospices), medical institutions of other or general profiles of treatment, as part of which include palliative departments and wards, homes for elderly people whose lives are coming to an end due to diseases and natural aging, family medicine clinics, medical institutions that created mobile teams and treatment of palliative patients at home, as well as the teams themselves, expert groups created to discuss PHC issues with the participation of scientists, public figures, medical and social workers, representatives of state authorities and local self-government.

Participation in scientific expertise and research in the field of PHC and its improvement in Ukraine is provided for in the model developed by us to determine the needs of the population for PHC, adults and children, taking into account the main palliative diagnosis, concomitant diseases, monitoring of satisfaction with PHC, in particular from the provided pathogenetic and symptomatic treatment, analgesia (including with the use of recently legalized cannabis preparations), palliative surgical interventions, secondary and tertiary prevention of complications and life-threatening conditions that can lead to premature death, and vice versa, from providing access to euthanasia, from psychological support of patients and their relatives (guardians, caregivers), from social support, spiritual support of religious palliative patients and their relatives. The National Health Service of Ukraine also conducted a scientific assessment on the effectiveness of PHC funding under the Medical Guarantees program. Using the sociological method, with the development of appropriate questionnaires and the invitation of respondents, the readiness of the population of Ukraine, patients, their relatives (caregivers), PHC specialists for public discussion of the need for legalization of euthanasia in Ukraine, the availability and quality of PHC was investigated.

In the scientific assessment, the comparative method was widely used with the study of the best foreign practices of building national PHC systems, legalizing cannabis and euthanasia for palliative patients [16–18]. In the issues of increasing the availability of adequate analgesia for palliative patients of Ukraine, emphasis was placed on the pathogenetic aspects of pain in the presence of various main palliative diagnoses [19–21]. In matters of assessing the current need for PHC and forecasting the need for the following years, scientific studies were conducted to improve forecasting methods, with a choice in favor of the creeping trend method with a constant smoothing segment [22; 23].

The main emphasis of this study was the determination of the purpose, strategy, tactics, functions, directions, methods, measures and resources of the optimized system of providing palliative and hospice care to the population of Ukraine, which is shown in the *Figure.*

The goal of developing an improved PHC model in Ukraine was to create a set of interrelated and consistent measures that had to be implemented in the conditions of uncertainty of wartime, as well as a long and inconsistent reform of the health care system. The strategic direction of the process of improving the existing PHC model was strict adherence to patient-oriented reform aimed at increasing the coverage of palliative patients and their close PHC, increasing the quality

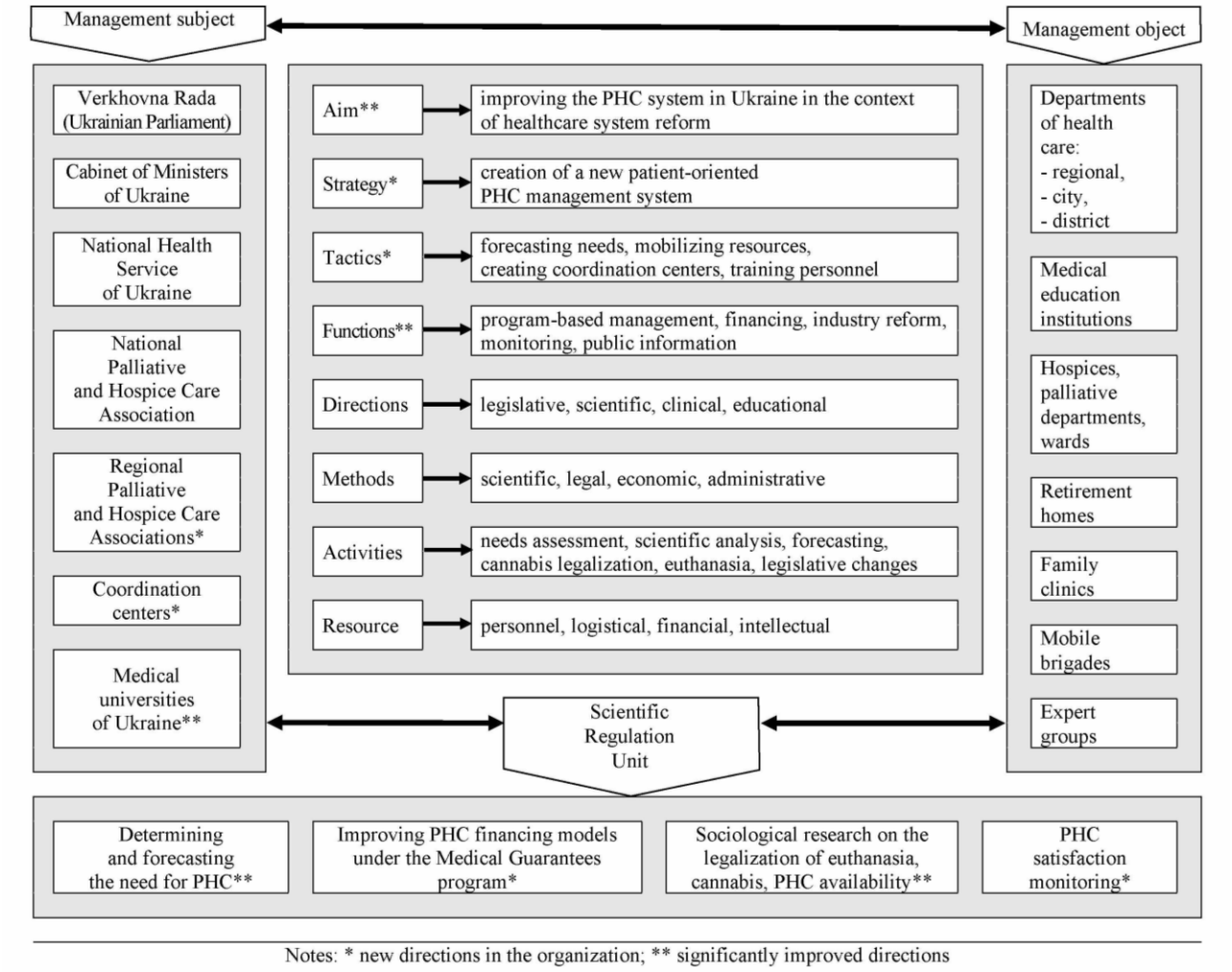

Fig. Functional and organizational model of the optimized system of providing palliative and hospice care to the population of Ukraine.

of PHC according to the criteria of satisfaction and the price/quality ratio of services.

We took into account the circumstances of the war in Ukraine, constant shelling and the danger of regions in close proximity to the borders of the aggressor country. Ensuring the safety of palliative patients in hospices and palliative departments/wards during the war is possible only by evacuating hospices in the eastern and central parts of Ukraine to the western regions [24]. Immobile or immobile palliative patients with serious illnesses are not able to quickly go to shelter during each successive shelling. It should also be taken into account that the warning about the threat does not always come, or comes already after the explosions.

PHC in Ukraine was complicated during the COVID-19 pandemic. This highly contagious disease increased mortality among all categories of patients. Patients with severe incurable diseases were at particular risk. The disease increased the costs of carrying out anti-epidemic measures in medical institutions, which was especially noticeable in hospices and palliative care units, in which a significant number of patients are immobile or have limited mobility and require the constant presence of a caregiver.

To improve the PHC system, we also propose [25; 26] to determine at the state level the list of palliative diseases (with diagnoses of the International Classification of Diseases-10 and the corresponding stages and severity of diseases, taking into account the main palliative diagnoses and comorbid pathology, by categories of adults and children). According to the list of these diagnoses, the need for PHC should be calculated, with appropriate funding of costs and provision of resources. In order to fully calculate the need for

PHC, it is necessary to resume the collection of medical and statistical information on such diseases as dementia in adults and severe and profound mental retardation in children. (Collection of these statistical data was discontinued in 2018). An important part of continuous and sufficient government funding of the PHC system should be scientifically based forecasting of PHC demand.

It is necessary to recognize and eliminate the shortage of personnel in hospices and palliative departments. For this, it is necessary to restore the record of bed days of palliative patients at the state level. This practice was stopped in connection with the rejection of Mykola Semashko's planned Soviet system of health care organization.

Providing hospices, palliative departments and wards, mobile teams treating palliative patients in home hospices with the necessary funding, qualified staff and other resources should lead to PHC coverage at the level of 90–95% of palliative patients. The goal of increasing patient and caregiver satisfaction with PHC should be 80% or more. To achieve such indicators, it is necessary to improve the legal framework of palliative medicine (with emphasis on the standards of treatment of chronic pain in all palliative diseases; increasing the availability of drugs for pain relief, especially narcotics). It is necessary to comply with the norm provided for by law on the introduction of the specialty "doctor of palliative medicine" to the official list of specialties of Ukraine, and to start the training of specialists of this profile at medical education institutions.

The experience of countries with developed PHC systems shows the expediency of creating regional PHC coordination centers, separated from medical institutions. Coordination centers should direct palliative patients to medical institutions that have received package financing of costs for palliative care from the National Health Service of Ukraine with the Medical Guarantees program. It is also necessary to abandon the obligation to treat palliative patients in "hospices at home" by family doctors. Because the reform of the primary link of medical care for the population in Ukraine provided for the principle: family doctors do not go to call patients at home. So, Art. 7 of Chapter II of the current "Procedure for providing primary medical care" provides [27] that Primary Medical Care (PMC) "is provided during a personal reception of the patient at the place of providing PMC. A doctor providing PMC can make a decision to provide individual PMD services at the patient's place of residence (stay) or using technical means of electronic communications in accordance with the mode of operation of the PMC provider". That is, the family doctor has the right to independently decide on the need to visit the patient at home, if he has the opportunity (for example, official transport or reimbursement of the cost of using other transport). But entrusting the family doctor with the duty of providing care for severely immobile palliative patients in "hospices at home" actually deprives the family doctor of the right to make such a choice. At the same time, if the family doctor has a service contract, he must visit a palliative patient at least once a week, in accordance with the standard of care for such patients [28].

The problem of insufficient influence of civil society on the decisions of legislators and executive authorities in matters of PHC planning and organization should be solved at the expense of state support for the development of the PHC national association (for example, [29]) with the mandatory creation of branches in all regions of Ukraine. Through the regional branches and the main organization, the Ministry of Health of Ukraine, the National Health Service of Ukraine, the centers of medical statistics of the Centers of Public Health, the Cabinet of Ministers of Ukraine and the committee of the Verkhovna Rada of Ukraine on Health Care should receive the generalized proposals of the members of the association, which should become all doctors of palliative medicine and, upon request, doctors of other specialties who regularly or periodically treat palliative patients. The functions of the association should be the analysis and formation of public opinion on the complex problems of PHC [30], protection of the rights of association members, influence on the decisions of the legislative and executive authorities in matters of development of the PHC system. In our research, we came to the conclusion that Ukrainian society needs the beginning of a broad public discussion about the possibility of legalizing euthanasia of palliative patients. The palliative care association and its communication with the mass media should be the main driving force in the issues of public dialogue about the possibility of such legalization.

The priorities of the National Health Service of Ukraine in matters of financing PHC programs should be package financing of mobile and stationary palliative care for adults and children, effective pain relief under medical guarantee programs, instead of financing palliative care at home, which is carried out by family doctors.

The standards and protocols of medical care for patients with chronic pain, a large part of which are palliative, need significant improvement. According to the generally recognized list of palliative diseases in the future, it is necessary to detail the list of drugs for pain relief (narcotic and non-narcotic analgesics, adjuvants) for various palliative diagnoses. The need for these drugs should be studied and reimbursed through the "Affordable Medicines" program at 100% with state funds. At the level of practical implementation of already existing norms of Ukrainian legislation, regulation of the turnover of legalized medical cannabis and its preparations should be accelerated.

Monitoring of the development of the national PHC system should be ongoing in the scientific plane: its personnel, material and technical, financial, intellectual resources, effectiveness of measures, scientific, legal, economic and administrative methods of managing the system. Centers of scientific analysis should be medical universities of Ukraine. We propose to return to the Soviet tradition of defining basic and supporting departments of medical universities of Ukraine. We propose to identify the Department of Public Health and Health Care Management of Kharkiv National Medical University (KhNMU) as the basic department in PHC issues, where the treatment and organization of medical care for palliative patients should be improved [31]. The possibility of practical implementation of such a solution is proved by our scientific research and the presence of a hospice of the university clinic of the KhNMU [32]. We propose to define the Department of Palliative and Hospice Medicine of Shupyk National Healthcare University of Ukraine [33], which can develop and continuously revise a typical curriculum in palliative medicine.

The principles, methods and measures proposed by us, in our opinion, can improve the provision of PHC to the population of Ukraine. To test this hypothesis, we conducted an expert evaluation of the developed model using a questionnaire developed by us. The results of the survey of 10 specialists in the field of palliative medicine and health care organization, evaluated on a quartile scale (Q_1–Q_4), are presented in *Table 2*.

Table 2. Results of expert assessment of principles, methods and measures for improving the PHC provision model in Ukraine

A proposed principle, method or measure	Quartile	Evaluation criterion: Justification	Consistency	Predictability	Correlation	Resistance to change	Overall assessment
		Evaluation result for individual criteria – (quartile): the number of responses within the quartile; for the overall assessment – (quartile): points (M±m) (Q_1 – 1 point; Q_2 – 2-4 points; Q_3 – 5-7 points; Q_4 – 8-10 points)					
Patient-oriented principle (all actions are aimed at increasing the satisfaction and quality of life of patients)	Q_1	–	–	2	–	–	1.0 ±0.0
	Q_2	–	1	2	2	–	2.7±0.7
	Q_3	1	3	–	–	4	6.2±0.4
	Q_4	9	6	–	5	6	9.4±0.5
Increasing the list of palliative diagnoses and enshrining them in the law for official recognition by the state	Q_1	–	–	–	–	–	–
	Q_2	–	1	–	–	–	3.0±0.0
	Q_3	–	1	2	3	1	6.3 ±0.6
	Q_4	10	8	8	7	9	8.9±0.5
Resumption of data collection of medical statistics on dementia in adults and mental retardation in children	Q_1	–	–	–	–	1	1.0±0.0
	Q_2	–	–	2	2	2	2.5±0.2
	Q_3	–	–	3	2	1	5.3±0.6
	Q_4	10	10	5	4	6	9.3±0.5
Continuous recalculation of the need for PHC among adults and children and forecasting of the need for the following periods	Q_1	–	1	–	–	1	1.0±0.0
	Q_2	–	2	1	–	–	3.1±0.4
	Q_3	2	–	5	3	1	6.1±0.3
	Q_4	8	7	4	4	8	9.0±0.5
Implementation of the order of the Ministry of Health of Ukraine to include a doctor of palliative medicine in the national list of specialists.	Q_1	–	–	3	–	–	1.0±0.0
	Q_2	–	–	2	2	–	3.5±0.2
	Q_3	–	1	–	2	–	6.0±0.3
	Q_4	10	9	5	6	10	8.9±0.6
Creation of a typical educational program in palliative medicine by the support department	Q_1	–	–	–	–	–	–
	Q_2	–	–	–	–	–	–
	Q_3	–	2	1		1	5.3±0.4
	Q_4	10	8	9	10	9	9.2±0.5

A proposed principle, method or measure	Quartile	Evaluation criterion: Justification	Consistency	Predictability	Correlation	Resistance to change	Overall assessment
		Evaluation result for individual criteria – (quartile): the number of responses within the quartile; for the overall assessment – (quartile): points (M±m) (Q_1 – 1 point; Q_2 – 2-4 points; Q_3 – 5-7 points; Q_4 – 8-10 points)					
Improvement of treatment protocols for chronic pain and palliative patients by the forces of the basic department	Q_1	–	–	–	–	–	–
	Q_2	1	–	–	1	–	3.5±0.2
	Q_3	1	1	1	2	2	6.2±0.4
	Q_4	8	9	9	7	8	9.0±0.7
Acceleration of the practical implementation of the legal norm of legalization of medical cannabis for palliative patients	Q_1	–	–	–	–	–	–
	Q_2	–	1	1	–	1	2.7±0.3
	Q_3	–	2	4	3	4	6.1±0.4
	Q_4	10	7	5	6	5	9.3±0.6
Development of the national and creation of a network of regional associations of palliative medicine	Q_1	–	–	–	–	–	–
	Q_2	–	–	–	2	2	4.0±0.0
	Q_3	3	1	–	1	2	5.9±0.6
	Q_4	7	9	10	7	6	9.4±0.5
Activation of a broad public and professional dialogue regarding the legalization of euthanasia	Q_1	2	1	–	–	1	1.0±0.0
	Q_2	1	1	1	2	2	3.3±0.2
	Q_3	1	2	3	1	2	6.1±0.3
	Q_4	6	6	6	7	5	8.6±0.4
Creation of regional and local PHC coordination centers, separate from hospitals	Q_1	–	–	–	–	–	–
	Q_2	1	2	2	–	–	2.4±0.3
	Q_3	1	–	1	3	4	9
	Q_4	8	8	7	7	6	8.1 ± 0.6
Returning the function of treating palliative patients in "hospices at home" to mobile teams from family doctors	Q_1	1	–	–	–	–	1.0 ±0.0
	Q_2	2	–	–	–	1	3.0 ±0.1
	Q_3	1	1	3	2	1	6.2±0.3
	Q_4	6	9	7	7	8	8.1±0.7
Evacuation of hospices from the east and center of Ukraine to the safer territories of the western regions of Ukraine during the war	Q_1	–	–	–	–	–	–
	Q_2	–	–	–	2	6	3.0±0.5
	Q_3	2	6	5	3	3	5.8±0.4
	Q_4	8	4	5	5	1	9.1±0.6
Reimbursement of 100% of drugs for pain relief for palliative patients under the "Affordable Medicines" program	Q_1	–	–	–	–	–	–
	Q_2	–	–	–	–	–	–
	Q_3	2	3	2	1	3	6.6±0.3
	Q_4	8	7	8	9	7	9.3±0.4
Continuous monitoring of satisfaction with PHC at the state level	Q_1	–	–	–	–	–	–
	Q_2	–	–	–	–	–	–
	Q_3	1	2	4	2	3	5.9±0.4
	Q_4	9	8	6	8	7	8.8±0.3
In total	Q_1	3	2	5	–	3	1.0±0.0
	Q_2	7	8	11	11	14	3.3±0.6
	Q_3	19	25	34	27	32	6.2±0.4
	Q_4	111	115	94	92	101	8.5±0.3

Notes: some questions were not answered by the experts. In this case, the number of points (M±m) was calculated as the average of the given answers.

The obtained results were evaluated taking into account the variance. Correction for dispersion allowed discarding the results with a range of [±(0.52÷0.34)] points. As a result of this assessment, the model was recognized by experts as high-quality based on the parameters of reasonableness and consistency (the assessment is within Q_4[75–100]%). According to the parameters of predictability, correlativeness and resistance to changes, as well as according to the general assessment, the model was recognized by experts as high-quality (the assessment is within Q_3[50–75]%).

Limitations of the study

Summarizing the average score for all proposals made only mathematical sense. The insufficient reliability of the results of the questionnaire according to certain criteria for medical research in the range of p=(0.14÷0.63) indicated the need

to increase the group of experts. The conducted generalization made it possible to determine the size of the minimum sample of experts of 23 people. We also noted the need for additional expert consultations regarding our proposed model: misunderstanding of certain aspects of scientific development made evaluation difficult and even led to the absence of evaluations according to certain criteria in part of the received questionnaires. Publication of research results with a detailed description of the developed model should partially solve the problem of insufficient understanding.

Prospects for future research consist in an additional survey of 15 experts, doctors, specialists in the field of palliative medicine and health care organizations with a generalization of the results of two stages of the survey (13 to achieve the minimum sample size with a reliable result of calculating points $p<0.05$ and 2 more to level the possible effect of dispersion).

Conclusions

The system of Palliative and Hospice Care (PCH) in Ukraine is characterized by the absence of signs of systemic organization at the state level, low coverage of the contingent of palliative patients and the quality of medical care and care according to the criteria of satisfaction of patients and their relatives (caregivers), as well as the price/quality ratio of services. Thus, the PHC system needs improvement in legislative, scientific, clinical and educational directions. We proposed a functional and organizational model of an optimized system of providing PHC to the population of Ukraine, based on the principle of patient orientation. The model provides for the expansion of the list of palliative diagnoses with the recognition of the new list at the state level, forecasting of the need for PHC, mobilization of resources and their rational use, creation of coordination centers for the treatment of palliative patients independent of medical institutions, training of staff for palliative medicine, expansion of the activities of the association of palliative medicine on all regions of Ukraine, activation of social and professional dialogue about the possibility of legalizing euthanasia of palliative patients, increasing reimbursement of medical means used in palliative medicine, especially for pain relief.

The model takes into account present-day challenges. We recognize that the war and the COVID-19 pandemic have added complexity to the process of organizing PHC in Ukraine, especially related to the safety of palliative patients in hospices and palliative departments in the front-line regions of Ukraine. But most of the problems in the development of the PHC system in Ukraine are not related to the war, and require ordinary organizational decisions and political will to improve regulatory and legal acts. Ukraine has sufficient scientific, administrative and political potential to accelerate the reform of this area of health care.

According to the parameters of reasonableness and consistency, the model is recognized by experts as high-quality (the assessment is within Q_4[75–100]%). By parameters predictability, correlativeness and resistance to changes, as well as according to the general assessment, the model is recognized by experts as high-quality (the assessment is within Q_3[50–75]%). The evaluation of the developed model allows us to propose it for use in the organization of health care in the conditions of long-term reform of the health care system and the uncertainty of wartime.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

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Consent for publication

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MOTIVATIONAL AND REGULATORY INSTRUMENTS OF VALEOLOGICAL EDUCATION

Shevchenko A.S.[1–3], ShevchenkoV.V.[3, 4], Shumskyi O.L.[5], Brown G.W.[6], Kucherenko S.M.[3], Kucherenko N.S.[3], Gavrylov E.V.[7]

[1]Kharkiv National Medical University, Kharkiv, Ukraine
[2]Kharkiv Regional Institute of Public Health Services, Kharkiv, Ukraine
[3]V.N. Karazin Kharkiv National University, Kharkiv, Ukraine
[4]National Technical University "Kharkiv Polytechnic Institute", Kharkiv, Ukraine
[5]Simon Kuznets Kharkiv National University of Economics, Kharkiv, Ukraine
[6]International Public Health Institute, Berlin, Germany
[7]Hameln-Pyrmont Adult Educational Center, Hameln, Germany

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ABSTRACT

Background. The competence-based approach is a condition for the implementation of higher education in Ukraine and the world. The list of competences that must be formed in university graduates includes health-saving. But there are obstacles to fulfilling the requirements of the standards in the form of imperfect practical pedagogical realization of competence formation.

Aim. To identify motivational and regulatory tools of non-medical education, the use of which is approved in the scientific-pedagogical environment, regulated by the legislation of Ukraine and effective in achieving the result of forming valeological competence, provided for by the standards of higher non-medical education of Ukraine.

Materials and Methods. The research was conducted using the system analysis method and the bibliosemantic method. The research is based on twenty years' experience in forming valeological competence in students of non-medical universities in the city of Kharkiv by means of teaching special valeological disciplines. The study does not describe these empirical studies, but only uses their findings.

Results and Discussion. As a result of the theoretical research, it has been established that the competence principle of education is not actually implemented in higher education, and in the course of forming valeological competence in particular. This happens because of the lack of mechanisms for evaluating personal components of competences. It is proposed to consider the student's main motivation in forming valeological competence as his/her desire to be healthy. Individual and organizational regulatory tools of valeological education are defined. They are as follows: typical curricula and textbooks for valeological education of students at non-medical universities, development of criteria for recalculating the evaluation of forming motivation and other personal components of competences for assessment in ECTS points.

Keywords: *valeological competence, health-saving competence, "Health Pedagogy", "Fundamentals of Medical Knowledge and Health-Saving", higher education standards, competences formation assessment.*

Introduction

The competence-based approach is generally accepted in European and Ukrainian education in the last two decades [1; 2]. Theoreticians of pedagogy and practitioners of business, finance and production understand competences almost equally. Thus, the International Board of Standards for Training, Performance and Instruction defines competence as "the ability of a person to perform activities, perform tasks or work in a qualified manner" [3].

The competence-based approach is appropriate both for primary education in schools and higher education institutions, and for lifelong learning [4–7].

Corresponding Author:
Shevchenko Alexander S. – MD, MM,E&P, Director of the Kharkiv Regional Institute of Public Health Services; 8, Rymarska str., Kharkiv, 61057, Ukraine.
E-mail: as.shevchenko@knmu.edu.ua

The competence-based approach is covered in detail in special pedagogical sources. During the practical application of theoretical pedagogical developments (for example, when setting educational standards), mechanical repetitions of definitions are often used and they are inconsistent with the content of the corresponding specialty standards [8–10]. This discords with the understanding of competency as the ability to perform variable practical tasks in life and career at a sufficient professional level, which is determined by cognitive abilities and skills, social interaction, motivation and will [11].

Competences, which are the subject of analysis and development, are divided by researchers into components, part of which corresponds to the cognitive component of the "knowledge–ability–skills" system, part – to the psychological component of motivation (applying competence in the practical sphere) and will (achieving the desired result from the application of competence) [12]. In the theoretical field, competences are well developed. But these studies continue, and the transfer of innovations into legislative practice is difficult, as evidenced by the imperfection of educational standards. At the next stage of practical implementation of higher education standards requirements, there are again difficulties in forming competences and assessing their formation. We will show these difficulties by the example of forming valeological competence in non-medical students [13].

At the level of generalization, the understanding of the competences of Ukrainian legislators is satisfactory. Thus, according to the Law of Ukraine "On Education" [14], "competence is a dynamic combination of knowledge, abilities, skills, ways of thinking, views, values, and other personal qualities that determine a person's ability to successfully socialize, conduct professional and/or further educational activities". According to the Law of Ukraine "On Higher Education" [15], "competence is the ability of a person to successfully socialize, study, and conduct professional activities, which arises on the basis of a dynamic combination of knowledge, abilities, skills, ways of thinking, views, values, and other personal qualities". The educational process requires the student in Ukraine to be fluent in the language of study, to be ready to study throughout his/her life, regardless of the study profile, to develop information and communication, cultural competences, innovativeness, financial literacy, environmental competence, civic and social competences, "related to ideas of democracy, justice, equality, human rights, well-being and a healthy lifestyle, with awareness of equal rights and opportunities". The law also provides for "other competences" defined by education standards. For example, competence in the field of natural sciences, engineering and technology, mathematical competence and others.

The National Qualification Framework of Ukraine [16] defines competence as "a dynamic combination of knowledge, abilities, skills, ways of thinking, views, values, and other personal qualities that determine a person's ability to successfully socialize, conduct professional and/or further educational activities". The Law of Ukraine "On Higher Education" defines competence as "a person's ability to successfully socialize, study, and conduct professional activities, which arises on the basis of a dynamic combination of knowledge, abilities, skills, ways of thinking, views, values, and other personal qualities". It is these definitions of competences that emphasize their key role in the preparation of a future specialist in the modern educational space, and cover all aspects necessary for forming competences. The provisions of these normative acts are the basis for a broad discussion of competences in the academic environment. Of course, the issues of motivation and practical application in pedagogical practice, especially in valeological education, require additional study. But in a generalized form there is everything necessary for the formation of competence.

The state of health of Ukrainian population indicates a low commitment of young people of university graduation age to a healthy lifestyle [17]. In our opinion, when applying the norms of the law on competence in the practical sphere of pedagogical activity, there are significant shortcomings that stand in the way of teaching young people safe models of behavior and a healthy lifestyle. So, for example, health-saving is a requirement of almost all standards of higher non-medical education. But institutions of higher non-medical education mostly do not have special valeological disciplines for the formation of valeological competence, and do not impose the duty of forming such competence on departments with related educational programs. If not, they set such a task to these departments, but do not control the result of forming valeological competence (health-saving competence) among graduates of non-medical universities [18]. In the absence of special valeological disciplines in a non-medical university, it is almost impossible to build an individual educa-

tional trajectory of valeological education [19] and there is no control of the content of health information through the filter of evidence-based medicine [20]. Therefore, at the level of practical implementing the requirements of higher education standards regarding the formation of valeological competence among graduates of non-medical universities, motivational tools for valeological self-education or regulatory management instruments should be applied. A similar practice exists in some known non-medical universities, but it is not generalized and translated into the field of pedagogical theory.

The **aim** of the study has been to determine the motivational and regulatory instruments of non-medical education, the use of which is approved in the scientific-pedagogical environment, regulated by the legislation of Ukraine and effective in achieving the result of forming valeological competence, provided for by the standards of higher non-medical education of Ukraine.

Materials and Methods

The research has been conducted using the system analysis method and the bibliosemantic method. The method of system analysis is applied according to the method of a large-scale step-by-step algorithm from the formulation of the problem to the final judgment, with the formation and verification of the preliminary judgment, with the feedback of the findings verification, but without the step of implementing the solution, which would involve empirical research. The bibliosemantic method was used to search for sources on PubMed, Google and Google Scholar, using relevant keywords in Ukrainian and English. The context of the study was higher non-medical education and the formation of valeological competence (health-saving competence) in graduates of non-medical universities. For medical higher education, in our opinion [21], there are other more complex mechanisms of health-saving competence formation, which is related to the topic of health in most academic disciplines of medical universities.

The study uses the conclusions regarding the development and introduction to educational programs of non-medical institutions of higher education in Kharkiv (V.N. Karazin Kharkiv National University and its institute – Ukrainian Engineering Pedagogics Academy, National Technical University "Kharkiv Polytechnic Institute") of valeological disciplines "Health Pedagogy" and "Fundamentals of Medical Knowledge and Health-Saving" during 2004–2024.

Results and Discussion

At the first stage of the research, we have additionally studied the competence approach in higher education, regardless of its direction, with an emphasis on the motivational component. We have found out that the competence-based approach is adopted in the educational systems of most countries. The definition of competency was found to be important, which is the ability to apply knowledge and action projects in practice and, at the same time, a tool for interpreting events that allows you to understand the situation, predict scenarios, plan and adjust your actions in accordance with the purpose of the activity [22]. It is obvious that a motivational component of competence is necessary to achieve the goal. Sushchenko O. et al. (2022) [23] propose to form professional competences in a university student in three stages:

1. to arouse interest in professional activity through conversations, discussions, role-playing games, cases;
2. to turn to the professional value orientation, which forms the image of an ideal specialist as the goal of the university student's education;
3. to form professional skills by solving situational tasks, cases, internships, and practical activities.

However, there are other opinions that university students do not need to be motivated to study disciplines [24]. According to Zhukova O.A., which we share, the student's motivation should be the need to successfully pass the exam in the discipline and get the right to study in the next course / get a diploma of higher education, as well as acquire competencies at a level that will allow the university graduate to be competitive in the labor market [25–27]. In the case of valeological education, the main motivator should be the desire to be healthy [28; 29].

Competence-based approach in education has been developed by many scientists from different countries of the world: Andreiev A., Boichuk Yu., Briukhanova N., Delor Zh., Druhanova O., Gutmacher W., Ivanenko L., Kasych A., Komyshan A., Kovalenko O., Kreig L., Kornilov A., Lokshyna O., Luhovyi V., Luniachek V., Lutaieva T., Mak-Klelland D., Mertens D., Nahorna N., Nalyvaiko O., Nekrashevych T., Ovcharuk O., Savchenko O., Shtefan L., Shvedova Ya., Sliusarenko O., Talanov Zh., Zhukova O., et al. The results of scientific developments are summarized in the reports of scientists and politicians (for example, "Key Competences in Europe" (Council of Europe, 1996), "Education. The Hidden Treasure" (Inter-

national Commission on Education for the 21st Century, 1993), etc.), program documents (for example, "New Ukrainian School" (Ministry of Education of Ukraine, 2016), "DeSeCo" (Switzerland, USA, Canada, 1998) and others) and models (for example, in Dietmar Kur's Heidelberg Model of Key Qualifications, Bloom's Taxonomy (1956) [30] etc.). Assessment competence formation success is based on the principles of gradual achievement of higher levels of competence, each of which includes all previous ones.

The relationship between competences and educational standards has been studied in detail in European and North American scientific sources. Thus, Münch R. (2012) [31] states that since competences are skills, and standards describe the level of achievement applied to knowledge and skills, these two concepts are often equated. At the same time, the definition of the content of competences lasts for years. Since there are no definitions of competences that clearly reflect their content, their components are described in the context of standards [32]. Through the lens of health-saving, such components are often considered to be the absence of bad habits, protection from adverse environmental influences, and sufficient physical activity. But there are lots of methodological errors in the comparison of program learning outcomes with the goals of competence formation in the theoretical sense. Instead of preserving mental health, they consider spiritual development to be a component of competence, instead of the need for a fully balanced diet, they consider giving up fast food and GMOs. In practical activities, the teacher does not have time to analyze the shortcomings of the standard, and simply performs it in accordance with the program learning outcomes, if he/she uses the standard at all. Therefore, there are often opinions [33] on the identity of the competence content from the scientific and formal (legal) points of view. The disadvantage of equating competence with the standard of education is the subordination of the competence content to the standard of education. It is this fact that makes it difficult to correct erroneous definitions in education standards. Also, in the education standards in the form of learning outcomes, they try to include those components of competence that are easy to model and measure [34; 35]. They do not include motivational and personal components.

In various scientific and legal sources, competences have different definitions, names, and belong to different classification groups. The standards of higher education of Ukraine [36] define the competencies that the student is supposed develop in accordance with the study specialty and educational level ("Bachelor" or "Master"). We have not found a definition of valeological competence in general and by components in any regulatory act. In scientific sources, the definition and content of valeological competence, or health-saving competence, depends on the perspective of the researcher, his/her education and teaching profile.

Let us immediately expand the issue of limiting the context of our research to non-medical students only. The formation of valeological competence should be distinguished from the competences of those obtaining higher medical education – diagnostic, therapeutic and prophylactic competences aimed at patients [37]. The issue of the content of valeological competence and the success of its formation among non-medical students is considered insufficiently studied [38]. Olle ten Cate (2017) believes [39] that valeological competence in students of higher medical education is necessarily formed in accordance with the content of programs of academic disciplines and ethical attitudes of the future doctor. But doctors also need health-saving. During their training, medical students often show contempt for their own health, which affects their credibility with patients when trying to promote a healthy lifestyle. Medical education provides all the necessary information to the student about the content of a healthy lifestyle and safe behavior, but the pace of learning, information overload and constant stress simply do not allow to follow a healthy lifestyle program. In addition, in our opinion, for the formation of valeological competence, medical students do not need a separate valeological discipline.

Not only medical education can be tense and stressful. The need to work while studying at university, studying during war and pandemics, the mismatch of the level of secondary education with the chosen higher education, the choice of other difficult specialties (for example, learning foreign languages) can also prevent a non-medical student from leading a healthy lifestyle. Therefore, the motivational component of competences in overloaded students will be difficult to form and will require the student's psychological adaptability.

The psychological component of competence can be measured only with the help of standard psychological surveys [40], which are not provided for by the European Credit Transfer and accumulation System (ECTS) system for evaluating

academic results. Instead, the components of cognitive competence ("knowledge–ability–skills") can be assessed with standard tools. In practical activities, the teacher does not have time to complete additional questionnaires, which can be used to assess the level of motivation, values, personal ability to achieve the results of practical activities using the developed competence. Also, teachers do not have instructions for converting the results of psychological tests into ECTS scores. Therefore, either forming these components of competences is evaluated "by eye" or is completely ignored, which violates the principle of competence training.

As well as the assessment of competence formation in the educational process, human activity in the social environment is often considered in four dimensions: affective-emotional, motivational, cognitive and volitional. The component of competence in human activity is interpretive, as it allows one to understand the situation, predict scenarios, plan and adjust one's actions in accordance with the goal of the activity. Motivation to action gives meaning to efforts spent on achieving a goal, strengthens a person's will. But the core of the activity corresponds to its cognitive content. Psychologists Kuhl J. & Heckhausen J. made a great contribution to the development of the cognitive function understanding [41; 42]. It was they who considered competence in relation to the motivation of activity and the desire to complete any project. To implement the action plan, the goal must have a certain value and subjective meaning. The performer must also possess the technical and practical skills and tools necessary to achieve the goal. Motivation is supported by the expectation of success. The operational abilities of the performer depend on the success of self-control (control of actions, attention, motivation, especially when the performer faces difficulties or failures) and self-regulation of his/her own emotions, thoughts and actions carried out under their influence. Therefore, in our opinion, motivation can be evaluated by changing the behavior model or quantitative increase in professionalism. The motivational and value component as a result of training can be improved to a large extent, even if the student started the formation of competence from a very low cognitive level (for example, due to low-quality secondary education).

Conversely, a small cognitive gain with a high cognitive result (when a student has a high-quality secondary education, makes little effort to study, but still gets a high result in ECTS scores) may indicate low motivation. Therefore, to evaluate individual learning outcomes, we suggest using qualitative models of competence formation [43] and including them in higher education standards along with a list of relevant programs' learning outcomes. The latter should describe the criteria for evaluating the formation of motivation and other personal components of competences. We suggest that the assessment of forming competences is carried out in parallel with the assessment of the academic success of training in ECTS points, or include the assessment of forming motivation in the general assessment of the ECTS, listed according to the clear criteria of the education standard. Individual success in the formation of competence should be monitored by the student and the teacher in real time, throughout the entire training. This approach will allow building individual educational trajectories.

Regulatory tools are also needed at the organizational level of valeological education. Among the measures of their use, we propose to include the creation of special valeological disciplines in the curricula of non-medical universities for forming valeological competence of graduates to meet the requirements of higher education standards. Regulatory tools in this case are typical curricula and textbooks of valeological education for non-medical universities, qualitative models for evaluating the formation of competences, and criteria for recalculating the evaluation of the formation of motivation and other personal components of competences for evaluation in ECTS points.

Conclusions

The competence-based approach is a prerequisite for modern higher education. The list of competencies is defined in the Standards of Higher Education of Ukraine. Their formation is an undeniable directive for teachers. But the Standards of Higher Education do not contain instructions for evaluating the formation of competencies. The practice of evaluating the academic success of students in ECTS consists in evaluating the cognitive components of competencies in the "knowledge–ability–skills" system. Assessment of personal components (motivation, etc.) is not carried out and is not recalculated into ECTS points, which violates the competency principle of education.

Based on our experience of developing and assessing the formation of valeological competence in non-medical students of Kharkiv universities during the 2004–2024, we claim that there are motivational and regulatory tools for the formation of this competence. The main motivation for forming

valeological competence is the understandable desire of every student to be healthy. An additional motivation is the need to successfully pass an exam or pass in the valeological discipline. Regulatory tools of valeological education are proposed by us at the individual and organizational levels. At the individual level, regulatory tools based on the compliance of the learning outcomes with the reference qualitative model will contribute to the constant monitoring of competence formation by the student and the teacher in real time and will allow building individual educational trajectories.

At the organizational level, the regulatory tools of valeological education are typical curricula and textbooks of valeological education for non-medical universities, qualitative models for evaluating the formation of competences, and criteria for recalculating the evaluation of forming motivation and other personal components of competences for evaluation in ECTS points.

Prospects for Future Research

These perspectives consist in the study of the tools for forming valeological competence, which is used to restore emotional balance and resolve conflicts, increase stress resistance, and prevent professional burnout of teachers and students.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

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VASYL YAKOVYCH DANYLEVSKYI'S LECTURE ON THE DOCTOR, THE PATIENT, AND THE SUCCESSES OF MEDICINE (1921): ANNOTATED TRANSLATION

Biletska O.M.[1], Korneyko I.V.[1], Markovska O.V.[1], Shevchenko A.S.[1, 2], Aleksanian K.A.[3, 4], Cherkova N.V.[5], Dushyk L.M.[5]

[1]Kharkiv National Medical University, Kharkiv, Ukraine
[2]Kharkiv Regional Institute of Public Health Services, Kharkiv, Ukraine
[3]Bogomolets National Medical University, Kyiv, Ukraine
[4]Municipal Non-Profit Enterprise City Clinical Hospital for Emergency Medical Services named after Prof. O.I. Meschaninov of Kharkiv City Council, Kharkiv, Ukraine
[5]V.N. Karazin Kharkiv National University, Kharkiv, Ukraine

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ABSTRACT

Unlike a mechanic, in front of a doctor there is a human being with all the manifestations of the feelings, with a painful soul, with aggravated egoistic intentions. The public easily forgives great failures and blunders of a quack but not a doctor. The doctor's duty is to forget about his personal troubles for the sake of his weak patient and to instill in him cheerfulness, spiritual fortitude, and optimistic expectations. In functional nervous disorders, the doctor can limit himself to psychotherapy only. A family doctor deserves greater respect and trust. A profound knowledge of all medicine is absolutely necessary for any specialized doctor. The doctor is obliged to serve public health – to supervise schools, factories, markets, railways, etc. The success of scientific medicine is not always known to the low-cultural public due to their insufficient popularization by the doctors. However, over the past 50 years, scientific medicine and medical practice have made tremendous progress: local and general anesthesia for operations, antisepsis and asepsis have been applied in surgery, organ transplant operations have been performed, vaccinations against cholera and bubonic plague in humans have been introduced, a new science – medical bacteriology has been founded, a successful fight against epidemic contagious diseases has been carried out, diagnostic reactions to typhoid fever, syphilis, Pasteur institutes have been established; fluoroscopy, chemotherapy are carried out, salvarsan has been invented to treat syphilis and relapsing fever; the therapeutic use of light rays and electrotherapy has begun; study of immunity, innate and acquired, anaphylaxis, study of immunity both innate and acquired, anaphylaxis, scientific psychiatry and psychotherapy is being developed, etc.

Keywords: *patient, social hygiene, superstitions, scientific discoveries*.

Medicus "in serviendo aliis consumor"
Nicolaes Tulp (1593–1674)

Introduction

Academy member Vasyl Yakovych Danylevskyi (1852–1939, *Fig.*) was an outstanding multifaceted scientist (biologist, physiologist, protozoologist), one of the founders of biophysics and physiotherapy, as well as one of the predecessors of psychoanalysis [1]. For many years he was delivering introductory lectures at the Faculty of Medicine of Kharkiv University and at the Medical Institute for Women organized under his leadership. These lectures were intended to prepare the medical students to mastering the profession. In 1921, Danylevskyi V.Ya. published the book "Doctor, His Vocation and Education. Introductory Readings" [2]. In the scientific journals of Kharkiv National Medical University, we have already presented the first two lectures from this book: the first one on science, the university and the choice of the faculty [3]; and the second one about health and disease [4]. In the third introductory lecture of Danylevskyi V.Ya. on the relationship between the doctor and the patient [5], the deontological position of the scientist runs like a golden thread. According to the evolutionary theory

Corresponding Author:
Biletska Olga – MD, DMedSc, Professor, professor of the Department of sports, physical and rehabilitation medicine, physical therapy and occupational therapy of the Kharkiv National Medical University, Ukraine.
Postal address: Ukraine, 61022, Kharkiv, Nauky Ave., 4, KhNMU.
E-mail: om.biletska@knmu.edu.ua

of Spencer G. [6] and his own works on personal and social psychohygiene, he explained to the students a natural decrease in the activity of "later life acquisitions of the human brain, and therefore less stable functions of mind and morality" in favor of survival. Thus, a talented teacher at the very beginning of the physiology course was forming a scientifically based tolerance to the "temporary predominance of primary, more strengthened feelings, inclinations and instincts, above all – in the form of an expressive increase in selfishness, rigidity and complexities of character, mood" in a sick person. That is, one of the most important adaptive reactions of the body was offered to the attention of the audience: a decrease in elated feelings, spiritual and intellectual activity under adverse conditions, for example, in diseases.

Fig. Vasyl Yakovych Danylevskyi, 1980

In the second part of the lecture, Danylevskyi V.Ya. fascinated the students with colossal scientific discoveries of medicine in the second half of the 19th century, which are still relevant today [7; 8]. Here it is appropriate to recall the world discoveries of this scientist, our great compatriot.

Even in his student years, Vasyl Danylevskyi received a gold medal for scientific work in the physiological laboratory of Professor Schelkov I.P. "On the decay of nitrogenous substances during muscular activity" (1872).

In his doctoral dissertation "Research on the physiology of the brain", Danylevskyi V.Ya. for the first time in the world, outlined the findings of the study on the electrical activity of the brain in dogs. He discovered spontaneous brain potentials, as well as their change due to various stimuli. Thus, Danylevskyi V.Ya. the first among domestic physiologists recorded an electroencephalogram in 1875 (independently of the English doctor Caton R., who in the same year presented the results on brain currents registration in rabbits and monkeys).

Danylevskyi V.Ya. was the first to reveal that heat production occurs in the muscles, which was described in the work "Thermophysiological studies of the muscles" (1879).

Danylevskyi V.Ya. was also behind the development of physiotherapy, studying the effect of remote electricity on the organisms, which was presented in his "Studies on the physiological process of electricity at a distance" (1900, 1901).

The discovery of Danylevskyi V.Ya., especially significant for the mankind, took place in the field of protozoology: it was the discovery of general patterns for malaria parasites of humans and birds, namely the relationship of the cyclic character of the disease and schizogony, the development of the parasites outside the peripheral blood (spleen, bone marrow), the existence of acute and latent forms of infection, the occurrence of relapses, etc. He developed the technique of capillary cultures, cultivation of blood parasites in an invertebrate host. Subsequently, the effect of thousands of antimalarial chemotherapeutic drugs was studied in similar experimental bird model. For his work in the field of protozoology, Danylevskyi V.Ya. received a prize of 2500 francs from the French Academy of Sciences "for the most useful work for French society" ("en prix dans le concours Montyon (Medecine et Chirurgie) de l'année 1889").

In the pre-revolutionary times, Vasyl Danylevskyi was also awarded a gold medal from the Imperial Society of Lovers of Natural Science (1891), a Small Prize named after von Baer K.E. from the Imperial Academy of Sciences (1894, 500 rubles), a prize named after Adam Chojnacki from the University of Warsaw (1900, 900 rubles), a prize named after surgeon Yunashev N.Z. from Imperial Military Medical Academy (1902, 3500 rubles).

After the October Revolution, Danylevskyi V.Ya. was engaged in development of issues of organizing labor and recreation for workers. In 2022 Vasyl Danylevskyi initiated the creation of Ukrainian Institute of Occupational Health, in which he worked as the head of the department of labor physiology. The following publications of the scientist featured physiology of work and rest: "Intelligent Entertainments and Their Scientific Substantiation" (1915), "Work and Rest" (1921), "Work

and Life" (1921), "Physiology of Work: Popular Essays" (1927).

In the same years, Vasyl Danylevskyi gained scientific interest in organ preparations, taking into account the well-known doctrine of Hippocrates about the "healing forces of the organism inherent in living beings". Thanks to his invention of the method of alcohol-water extraction of tissue preparations, for the first time in the world, it became possible to begin their widespread production (first Spermol, a testicular extraction from the testes of cattle). Within the period the 1920s–1930s, under the leadership of Danylevskyi V.Ya., his cherished dream of creating a large research center with a powerful department for production of organ preparations, in particular crystalline and synthetic, was realized. Among the wide range of drugs (more than 20 drugs in just the first 5 years of the institute existence), Danylevskyi V.Ya. paid much attention to the study of lecithin (according to his formulation, the institute produced Phosphren, a drug containing lecithin). In the 1930s, the social hygiene and prevention sector with the department of health education and the information and advisory bureau, where health issues were addressed, began to work as a part of the institute. As we can see from the lecture, it was also an old dream of the scientist. His idea of the unity of theory, clinical work and production ensured successful development of the Organ Therapy Institute, which was called the Institute of Endocrine Pathology Problems named after V.Ya. Danylevskyi. In 2026, Vasyl Danylevskyi was elected a member the Academy of Sciences of the Ukrainian SSR and was awarded the honored professor of the republic.

Lecture by Vasyl Yakovych Danylevskyi on the doctor, the patient and the successes of medicine (1921)

Having become acquainted with the general nature of pathological life, let us see now what the relationship between the doctor and the patient is, what image is characteristic of the patient in the contemporary society and what medicine can oppose to it.

If a mechanic has to repair a soulless, inanimate machine, his thought and attention are focused entirely on the essence of the damage and on the ways to fix it. <...> A doctor is in another position. <... > In front of him there is a living person with all his rights and feelings, with a painfully attuned soul, with elated selfish thoughts.

<... >In the past, adult patients placed themselves entirely at the disposal of the doctor. <...> Now newspaper articles, and especially advertising, skillfully support the interest and attention of the public to the issues of medicine, to new "true" methods of treatment, to "miraculous" new drugs. The public eagerly reads such printed works, without understanding if they are trustworthy, which is entirely dictated by purely commercial motives, and that sometimes it turns out to be quackery and is intended for gullible and uninformed readers.

<... >If the public so easily forgives even great failures and blunders to a healer or charlatan, it will not forgive them the doctor, especially the "famous" one.

Knowing such a critical mood of the patients, the inexperienced medical practitioners acquired a deep-minded appearance, an extremely doctrinal, authoritarian tone with the desire to fully maintain their prestige. But sooner or later the exposure will not pass... However, where patients are more cultured, there are fewer such doctors.

<... >The duty of a doctor requires him to forget about his personal moods and troubles for the good of his frail patient and inspire him with vivacity, mental stability, optimistic expectations... The patient must believe the doctor and respect him already through such self-denial for the sake of helping his neighbor. The patient must be sure that, in spite of personal worries and bad mood, the physician treats him as he would like to be treated if he fell ill with the same disease (Sydenham Th., 1624–1689).

Now you will understand the requirement of old teachers of medicine that doctors be practitioners-psychologists, so that in the treatment of the body they keep in mind the psyche of the patient. And this is necessary not only for the purposes of modern psychotherapy, but also, in addition to this special task, in order to recognize the patient's soul and direct it for the benefit of himself to eliminate mental obstacles of every kind. Ancient doctors knew about this. Love, hope, joy accelerate blood circulation, increase appetite and facilitate the treatment of diseases (A. von Haller, XVIII century). Hufeland Ch.W. argued that such a beneficial effect was characteristic of all elated emotions and feelings.

Hence it is clear why it is so important for medical education to teach psychology, and not only for the purposes of psychiatry and neuropathology, but also for the internist, gynecologist, school doctor, etc.

<...>in hysterical persons, hypochondriacs, with increased nervous unilaterally focused irritability, intense attention and imagination or, so to

speak, mental polarization can cause distinct disorders in the nervous system, autonomous and involuntary, that is, it can aggravate and generally modify existing disorders, for example, in innervation of the heart, blood vessels, glands, smooth muscles, internal secretion, etc.

<...>Where it is a question of functional (not organic!) nervous system disorders, the doctor can sometimes be limited to psychotherapy only.

<...>After all, the whims, intemperance, selfishness of an adult patient resemble the properties of childhood. Weakening of the mind directives and the higher "regulatory-restraint centers" degrade the adult psyche, in a sense weakening it to a state characteristic of an underdeveloped brain. All this is understandable for a doctor who knows that the higher functions of intelligence and restraining mechanisms of will, guided by the dictates of reason and morality, are later life acquisitions, and therefore the least stable, and the most vulnerable, for example, in diseases. Hence there is a temporary predominance of primary, more strengthened feelings, inclinations and instincts and, above all, in the form of an expressive increase in egoism, rigidity and inequality of character, mood.

<...>The struggle of the "Law against the Miracle" (in other words, education against prejudice and unconsciousness) should continue for many, many years before the kingdom of Reason and science comes, when knowledge and logic, not credulity, blind imitation and instincts, will direct and control human actions.

If in many healthy people superstitions so often motivate their behavior and actions, a sick person is subjected to this to a greater extent.

<...>His/her motives and criteria become dominant (feelings, passions, instincts), as is characteristic of the lower order psyche. For example, in children, savages. On the contrary, the higher the cultural and education level of a person, the stronger the active and powerful dispassionate imperatives of the objective mind, the more volitional acts obey them and the more inhibition and regulation of feelings and instincts occur. Such a mental system is a product of high progressive development. It requires a high organization of the telencephalon, and most importantly, its health. It guarantees impartiality and justice, which is so sharply contradicted by the stubbornness and prejudice of another patient who does not recognize anything outside his personal interests.

<...>Practicing doctors attach great importance to strengthening and encouraging influence of religious beliefs on the shattered psyche of patients. They serve only as a "moral anchor" in which spiritual life can be firmly held, weakened and disorganized by the disease. Recognizing such a psychotherapeutic effect, doctors are usually indifferent to the very content of beliefs, their form, and external manifestations.

<…>Strong mental unrest can undoubtedly greatly affect innervation and body functions (blood circulation, blood composition, lymph outflow, secretions, internal secretion glands, blood distribution in the body, absorption processes, digestion, internal breathing, tissue nutrition, etc.). This is confirmed by numerous physiological experiments on the influence of the telencephalon on the autonomic functions of the body, which our will cannot directly influence.

<...>Let me remind you the well-known fact that people who are distrustful, with an unstable nervous system, especially vasomotor, can have painful disorders in the form of vomiting, diarrhea, bloating, local edema, relaxation of sphincters, anesthesia and motor paralysis, weight loss, skin paresthesias, etc., under the influence of only one highly tuned idea or suggestion.

<... >There can be no doubt that in the vast majority of cases of real healing of patients by all sorts of healers, it is a matter of psychotherapeutic influence.

<... >it must be remembered that in many cases functional disorders, for example, some neuroses and psychoneuroses, can cause real organic persistent suffering. Sometimes one mental shock is enough for such a serious illness as, for example, motor paralysis, dumbness, etc., to disappear immediately and without a trace before the eyes of surprised others. We are talking about "psychogenic" disorders, when the primary damaging factor acts in the mental environment, and secondary symptoms can be bodily lesions. As for this occasion, modern doctors and clinicians who use psychotherapeutic methods of treatment have accumulated a huge casuistic material, which is scientifically substantiated.

<...>Perhaps the reasons for this socio-household anomaly include the fact that earlier, the respected institute of "home doctors" was much more common than now, which, through constant communication with the public, maintained respect for medicine in it. On the contrary, at present, apparently, due to the general rise in price of living on the one hand and the active specialization and multiplicity of representatives of medicine on the other hand, such communication is al-

most absent, and meetings with doctors have acquired the character of short-term, hasty contacts in which both interlocutors see each other for the first time, and often for the last time.

The "home doctor" used to be a "the friend of the family" which he visited not only at the time of someone's illness, but at other times. He was asked questions, he was consulted on hygiene, on family and household issues, as a kind loved one who has long known all family members. After all, he had to monitor their growth and life. He knew the "individuality" of everyone. Hence it is clear why such a doctor could incomparably easier and more correctly focus on treatment, prognosis and even diagnosis (especially in disorders of the nervous system, the influence of heredity, etc.).

<...>It must be added to all this that the home doctor, thanks to his tact and reasonable attitude, enjoyed great trust and respect. He kept at such a moral height with great dignity and with great benefit to the family. His position required him not only to know medical affairs, but also to be a person in the best sense of the word. He had to have high moral qualities, without which the position of a doctor, especially a home doctor, becomes very precarious: they are honesty and kindness, restraint and straightforwardness, truthfulness and compassion, absence of Pharisaic hypocrisy, false arrogance of a charlatan, understanding his own dignity. In medicine, he had to be almost an encyclopedist, to treat various diseases. In those old times, however, the medicine itself was less developed, not so wide, its therapeutic methods and means were simpler and more unvaried.

<...>Without a doubt in the essential fruitfulness of specialization in medicine, which enables a deeper and more thorough assimilation of the field, you still must firmly remember that no matter what your medical specialty is in the future, you should not ignore the states of the whole human body, its general diseases and deviations. "First – a doctor, and then – a specialist!"

This implies the necessity to conclude that for any specialist doctor a thorough knowledge of all medicine is necessary, and only on such a strong foundation can any specialties be further acquired. Life, however, proves that even great experts in their specialty can sometimes be backward in the general medicine. Even worse is the fact that they choose the future specialty on the student bench and this creates an obstacle for serious assimilation of other disciplines of the medical course.

<...>Until now, we have analyzed the cases that concerned only the individual interests of the patient. But he is a member of the community, the collective, and therefore it reflects social interests. Given this, the doctor has to guard not only individual health, but also public one. He must follow the interests of both personal happiness and social good – as far as his professional activity is concerned. Caring for the relief of a patient with an infectious disease, the doctor is obliged to take measures to isolate him for the safety of others.

This also includes supervision of the doctor for schools, factories, market places, railways, etc. All this drives the doctor out the individual conditions of life and health and adjusts him to many other issues of public improvement and wellbeing.

<... >outstanding success and studies that take place in purely theoretical science are very often unnoticed for the low-cultural public, because, I must admit, doctors so little and so rarely replenish people's knowledge with their popular lectures.

Meanwhile, especially in the recent 50 years, scientific medicine as a theory and medicine as *ars medicina* (from lat. – *medical art*), has made tremendous progress. Statistics of morbidity and mortality, especially from injuries in war and in general from contagious diseases, shows with evidence the huge progress of medicine, because a sharp drop in mortality does not depend on an increase in the general level of culture, but precisely on the improvement of medicine. In the Crimean campaign, the military died from diseases more than twice as many as were all killed and wounded. On the contrary, in the Japanese war, 30,000 people died from weapons, and only 1,200 from diseases.

<... >Using various methods (physical, chemical, physiological, microscopic, bacteriological), the doctor is now recognizes diseases incomparably easier than before.

<...>Regarding the progress of pharmacotherapy over the last period, it is impossible not to point out its major acquisitions in the form of a number of new drugs and methods of use. Examples include new salvarsan, salicylic acid and its many derivatives, iron and arsenic.

Organ preparations, which have appeared in the recent period, were prepared from various organs of animals, for instance Spermine, Adrenaline, Pituitrin, Thyroidin, etc. <...> The brilliant success of vaccinations in humans and domestic animals led to the fact that Pasteur institutions appeared in all countries of the world to combat infectious diseases (rabies, anthrax, malaria, yellow fever, sleeping sickness in humans, etc.).

<...>Major acquisitions of medicine in the recent years include a method to diagnose latent tuberculosis. Such diagnostic tests, performed on a large scale, indicated the spread of tuberculosis, which doctors did not suspect before this method of diagnosis. We should not forget that tuberculosis bacillus affects both the lungs and bones, glands and other organs.

At the same time, it is necessary to point out the success of the individual fight against tuberculosis diseases in the recent years, especially through social health care, aimed mainly at improving the soil, housing, water supply, food. The hope is put, in addition to personal events such as enhanced nutrition and proper lifestyle, in sanitary and hygienic measures on a large scale. At the same time, we must remember that the most dangerous for infection is the early childhood age, when the body still has little resistance to tuberculosis infection.

Strengthening the efforts and health care, raising the working capacity of the people, increasing the average life expectancy are the main tasks that life poses to medicine, which, according to natural laws, develops and becomes more complicated towards cultural progress.

<...>The most difficult task of health care, the continuous struggle against ignorance and backwardness, against "evil will", avarice and greed, selfishness and heartlessness falls on the share of public medicine, this newest branch of knowledge, which originated for the first time before our eyes in the second half of the last century... One of the means for this struggle is health education of the population, which requires at least the beginnings of general scientific education in all its mass.

The second weapon will be medical statistics, which now provides social medicine with such huge services as an objective reflection of its success and significance.

Sanitary legislation, created from the instructions of medical science, is the achievement of the new time. On the basis of health education of the inhabitants, it will turn out to be a powerful instrument of public and personal health, of course, depending on the general legal order and on the general cultural level.

We will confine ourselves here to a few indications of the remarkable results of its progress. These facts include the use of local and general anesthesia during operations, antiseptic method, asepsis, organ transplantation operations (cavitary, plastic), preventive vaccinations against cholera and bubonic plague in humans, new science medical bacteriology, discovery of pathogenic microbes for many diseases, successful fight against epidemic infectious diseases, diagnostic reactions to typhoid fever, syphilis, invention of therapeutic vaccines and serums, serodiagnosis, foundation of Pasteur institutes, fluoroscopy, chemotherapy, destruction of harmful microbes, invention of salvarsan to treat syphilis and relapsing fever, therapeutic use of light rays, scientific development of electrotherapy, close convergence of medicine with natural science...; the study of innate and acquired immunity, anaphylaxis; scientific development of psychiatry on an anatomical and physiological basis, scientific psychotherapy, including hypnosis... etc.

<...>Of course, in many ways medicine is still powerless: for example, it cannot fight confidently against cancer, as well as does not know what the essence of this terrible malignant neoplasm is.

<...>To study the conditions of aging, both external and internal, in special scientific institutes – the task that can provide a huge practical help to a person. After all, we must not forget that prolonging life or preserving strength for only a few years is a huge economic value for the population.

Whatever the gaps in our scientific and medical knowledge are, the progress is so great that this recent period of development of medicine is undoubtedly outstanding in its fruitfulness in the entire history of medicine.

Of course, everyday remnants can finally disappear only under the influence of the general educational upsurge and the associated social education. Hence it is clear why, in fulfillment of his broad professional tasks, the doctor should first of all be a representative of general scientific education, with a broad outlook, and not a simple specialist-craftsman.

<... >The prestige and huge merits of a scientifically educated doctor will become even more justified and understandable if we turn from the tasks of individual medicine to the program of public service. And this will be the topic of the next lecture.

Afterword

<...>It seemed necessary to remind the society of the scientific and moral height of the mission of the doctor and to warn against anything that could lead to the diminution of his social prestige. Of course, it would be both closer and easier for practicing professors and doctors, as more competent persons, to highlight these issues; but, perhaps, the real book of the physiologist will not be super-

fluous. They would be able to better demonstrate to the reader the importance and success of Medicine, they would dwell, for example, on the organization of medical care and sanitary and hygienic supervision, about which I say so little, on Dietary Therapy, which is completely lost here, on the protection of childhood and motherhood, on the fight against tuberculosis and alcoholism, insurance medical organizations, on the socio-economic side of medical activity, on health education. <... >medical and sanitary-hygienic practice usually lies outside our horizons; but still, at a time when the voices of practical physicians are heard so little, the reader may need our voice.

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