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Table of Contents

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THEORETICAL AND EXPERIMENTAL MEDICINE

THERAPY

OPHTALMOLOGY

DENTISTRY

INFECTIOUS DISEASES

EPIDEMIOLOGY & PUBLIC HEALTH

PATHOMORPHOSIS OF EYELID TUMOR PATHOLOGY IN DEMODECTIC INFECTION

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ABSTRACT

Background. Pathological changes in the tissues of the oculo-conjunctival region caused by the activity of the Demodex mite is represented by the development of inflammatory process. On detection of the parasite on eyelashes, the presence of the Demodex mite is diagnosed in half of adult patients seeking ophthalmic care. Pathomorphological descriptions of specific patterns associated with the presence of Demodex infection are practically absent. During pathological examination, in the vast majority of cases it is almost impossible to see the parasite in the test material. There are pathomorphological patterns associated with the presence of the mite as a commensal, not only on the eyelid surface or in the conjunctiva, but also in morphological structures formed against the background of pathological processes in this area.

Aim. To find out the morphological patterns reflecting the pathomorphosis of some tumor processes in the eyelid thickness caused by demodectic invasion, which have not been identified so far in ophthalmopathological studies.

Materials and Methods. We analyzed the archival material from the oculo-conjunctival region submitted to the ocular pathology laboratory within the period of 2020–2023. Surgical and biopsy specimens were processed by standard histologic methods.

Results. One of the pathognomonic patterns of demodecosis are calcifications with fragments of the dead mite and cysts. When a mite rapidly destroys tissue, it leaves the site until it dies without retaining its fragments. Post-demodecosis pathomorphosis in basal cell carcinoma of the eyelids complicates the pathomorphologic diagnosis of the biopsy.

Conclusions. Our results prove the presence of mites in tumor tissues and illustrate their influence on the development of the pathomorphological picture, which should be taken into account in the practical activity of a pathologist.

Keywords: *demodex mite, pathomorphology, ophthalmopathological examination, oculo-conjunctival region.*

Introduction

The idea of the role of Demodex mite in the development of ophthalmic pathology is still limited to the reactive inflammatory process of the eyelids and conjunctiva, usually associated with such clinical conditions as demodectic blepharitis, blepharoconjunctivitis, chalazion, episcleritis, and marginal keratitis. According to the experience of clinical and laboratory diagnosis aimed at detection of the parasite on the eyelashes, at least half of the adult population seeking ophthalmic care can be diagnosed with Demodex mite. Therefore, with such a prevalence of the parasite in the oculo-conjunctival region, it can be expected that the presence of Demodex in the adult population is not limited to an inflammatory response of the conjunctiva and eyelids [1; 2].

However, until recently in ophthalmopathology, all ideas about Demodex-induced morphological changes were limited to the picture of an acute or non-specific chronic inflammatory process. This is largely due to the fact that in ocular patho-

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logy, as in pathomorphology in general, there are virtually no descriptions of specific patterns associated with Demodex infection. This is largely due to the fact that, in contrast to clinical diagnosis during pathological examination, in the vast majority of cases it is almost impossible to see the parasite in biopsy or surgical material [1; 2].

At the same time, as our previous studies [1; 2] have shown, there are a number of pathological patterns associated with the presence of the mite as a commensal, not only on the eyelid surface or in the conjunctiva, but also in the morphological structures formed as a result of pathological processes in this area. The experience of veterinary pathology, where demodecosis is much more common, allows us to pay attention to seemingly insignificant details. It is this experience that has allowed us to link certain details in the histomorphological picture, which are usually ignored as insignificant artifacts, to demodectic infection.

The aim of our work is to find the morphologic patterns reflecting the pathomorphosis of some tumor processes in the eyelid thickness caused by demodectic infection, which have not been identified in ophthalmopathologic studies so far.

Materials and Methods

The clinical and morphologic analysis included cases of demodectic infection detected during histologic examination of clinical biopsy and surgical material received by the Laboratory of Ocular Pathology of Filatov Institute of Eye Diseases and Tissue Therapy of NAMS of Ukraine during the last four years (30 cases with demodex were found among 650 examined biopsies of patients with tumor diseases of the eyelids). The surgical and biopsy material was processed according to the generally accepted histologic methodology with the preparation of paraffin blocks. In each case, 8 to 12 serial hematoxylin-eosin-stained histologic sections were examined.

Results

Our understanding of the pathognomonic histomorphologic patterns of demodecosis was based on the experience of tissue examination of demodectic infections in veterinary medicine. It is in domestic animals that various manifestations of demodectic infection are most often detected, which, unlike in humans, often become the object of surgical intervention and, consequently, subsequent histologic examination. Thus, veterinary practice has allowed us to understand and evaluate the histomorphologic patterns that are pathognomonic for this parasitic infection, which we have noted in the study of a number of ophthalmic pathologic processes.

As a result of histomorphologic examination of surgical and biopsy material of the eyelids, the above patterns that are pathognomonic for demodicosis infection were detected in 30 cases, which is about 5% of the total number of studies for this period.

First of all, such patterns are cystic cavities, which are most often seen in direct contact with the skin appendages, especially the sebaceous glands. It is the destruction of the sebaceous glands that explains the appearance of these cysts (*Fig. 1*). However, the origin of such cavities is not obvious to the pathologist without appropriate experience.

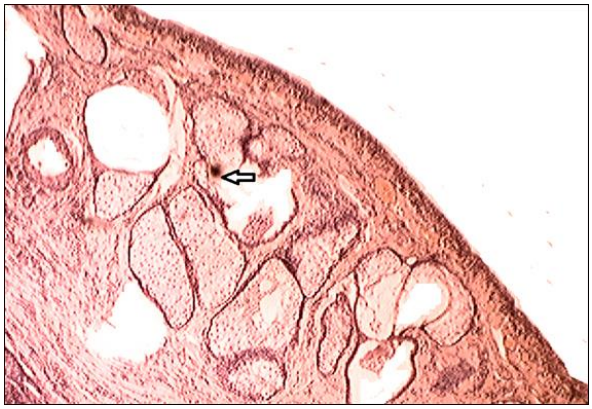

Fig. 1. Adenoma of the sebaceous gland near the lower lid margin with a large number of glands destroyed by the mite. *A calcified fragment of a dead mite is visible in one of the cavities (arrow). ×100*

Therefore, it is not surprising that such patterns are ignored, as well as many other artifacts caused by mechanical damage to histologic sections. For this reason, for a long time in ocular pathology, when examining biopsy and surgical material from eyelid tissues, no attention was paid to the characteristic patterns of demodecosis.

In veterinary practice demodectic infection is usually associated with acute, chronic or granulomatous inflammation, in which cystic cavities are usually found, as a result of the mite devouring the parenchyma of glands, mainly sebaceous glands.

An important pathognomonic pattern of demodecosis are foci of calcification, which, like the aforementioned cysts, are usually interpreted as trivial dystrophic calcifications (*Fig. 2*). Only a specific examination of these calcifications reveals their unusual nature due to the fact that they are based on fragments of a dead mite in the form of keratinous debris [3–7].

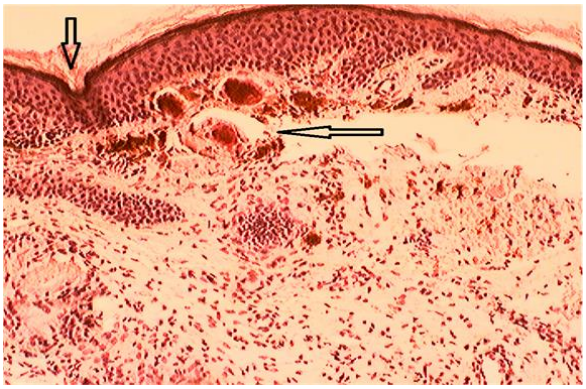

Fig. 2. Numerous foci of calcified mite fragments under the epidermis (horizontal arrow). *The upper part shows the presumed site of mite penetration through the epidermis (vertical arrow). ×100*

Cases in which pathomorphologic diagnosis revealed patterns that are pathognomonic for demodectic infection were usually clinically manifested as benign tumor processes: atheromas, sebaceous gland adenomas, fibrolipomas, nevi, xanthelasma. Fig. 2 shows the histomorphologic picture of a clinically diagnosed xanthelasma of the eyelid. However, it is very difficult to confirm this diagnosis on the basis of pathological examination, since most of the cell parenchyma of the tumor is destroyed, and mainly calcified fragments of the mite and its cavities are visible. Only the projection of the characteristic clinical manifestations of eyelid xanthelasma on the histomorphological picture, in which individual xanthoma cells are visible, allows to draw a conclusion about the post-demodecosis pathomorphosis of this tumor process. This pathomorphosis is most pronounced in adenomas of the sebaceous glands, which were often represented exclusively by cavities in the absence of glandular structures (*Fig. 3*).

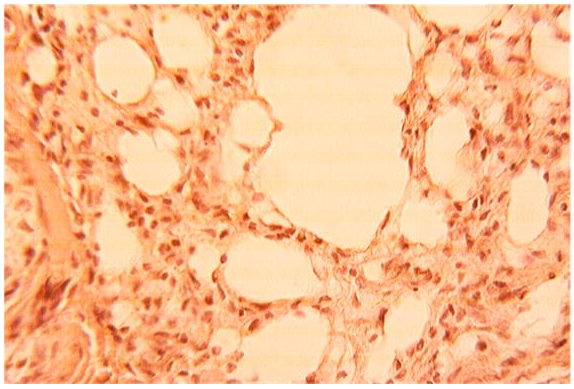

Fig. 3. Post-demodecosis pathomorphosis of a sebaceous adenoma with total destruction of the glands, leaving only cavities made by the mite. *×100*

As portrayed, concerning post-demodecosis pathomorphosis there are sometimes situations when the diagnosis of sebaceous adenoma is made without the adenomatous tissue itself, mainly on the basis of the previous clinical picture. Moreover, with such a total destruction of the tumor tissue, sometimes even fragments of the mite may not be detected. This is due to the fact that with a sufficiently rapid destruction of the cellular array available to the mite, it leaves the area before death without preserving its fragments.

This situation is more typical of sebaceous adenomas, which are usually small in size. In addition, it should be noted that after the death of a mite under normal conditions, almost complete destruction occurs within 2–3 hours, which can be observed directly on a native clinical diagnostic preparation. Therefore, it is not surprising that in most cases only small fragments of the mite body or calcium-impregnated microfragments, keratin debris, are found. The parts of the mite that have not undergone calcification are lost in the histologic specimen. Therefore, the absence of mite fragments cannot be considered a contraindication in the presence of other characteristic pathological patterns. However, even when such calcified fragments are preserved, they rarely contain elements of the parasite body. Only in one case we did find a head part that had the characteristic chelicerae of the parasite almost completely preserved (*Fig. 4*).

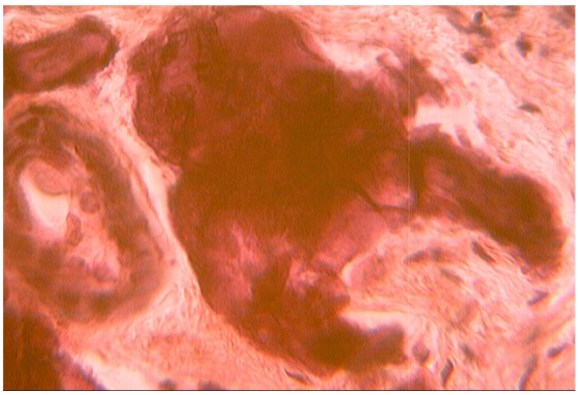

Fig. 4. A unique calcified fragment of the mite head with chelicerae preserved away from the epidermis. *×400*

It is interesting to note that in some cases, as a result of mite activity, the morphological picture of the pathological process changes so much that it can be difficult to diagnose. In this regard, the demodectic infection in basal cell carcinoma, which was detected in 10 cases on biopsy material, is of particular interest.

In most cases, the pathomorphosis taking place after demodecosis was limited to the formation of cysts in certain areas of the tumor with preservation of the typical pattern of basal cell carcinoma. In two cases, however, the changes were so pronounced that repeated review of the histopathologic specimens was required for correct verification of the tumor pathology (*Fig. 5*).

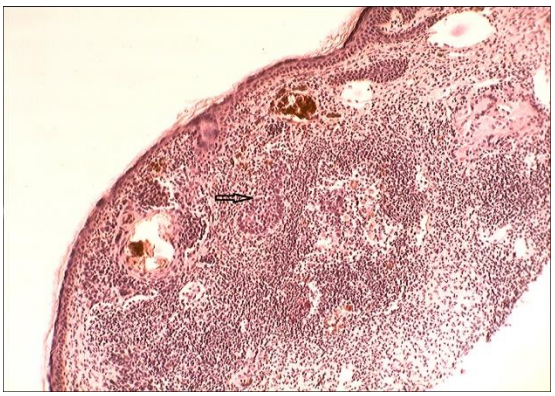

Fig. 5. The typical tumor pattern is severely disturbed: only a solid complex with a barely preserved palisade is visible (arrow). *Several cavities and areas of discharge can be seen beneath the epidermis due to the presence of Demodex, calcified fragments of which are also present near the epidermis. ×100*

The tumor was mostly represented by polymorphic cells situated randomly, without the tendency to form complexes characteristic of basal cell carcinoma, as can be seen in *Fig. 6*. This picture dominated the initial examination. It was not until 12 serial sections were examined that some of them showed the picture of Fig. 5, with only a single complex characteristic of basal cell carcinoma.

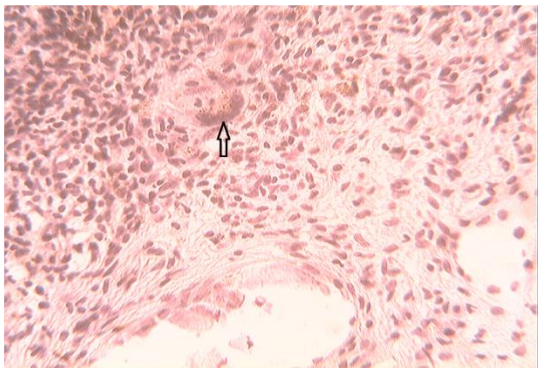

Fig. 6. Fragment of the previous tumor: cells are randomly distributed against a background of cavities, characteristic solid complexes are absent. *A calcified fragment of the parasite is seen in the upper part of the picture (arrow). ×200*

It should also be noted that the patient had two tumors removed with the same clinical diagnosis: basal cell carcinoma. The second tumor had a histomorphologic structure typical of basal cell carcinoma, which facilitated the targeted search and detection of the corresponding solid complexes in the other tumor.

It should be noted that malignant tumors of the eyelid skin are usually not completely removed, and after biopsy and diagnosis, local cryodestruction is performed, sometimes followed by radiotherapy. Therefore, the biopsy material is often small in volume and only some superficial layers of tumor tissue are present. Underestimating these circumstances can lead to difficulties in pathologic diagnosis, as illustrated by the case shown in Fig. 7.

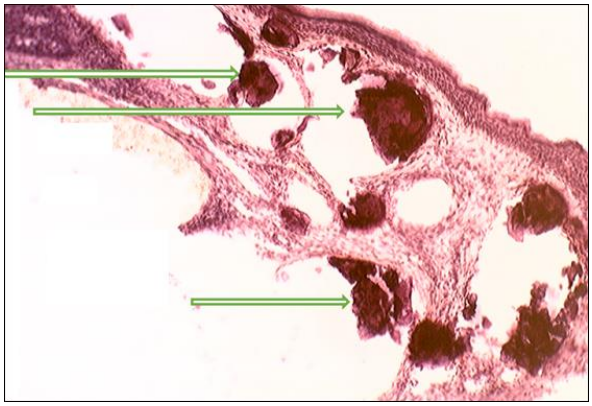

Fig. 7. Destruction of parenchyma by mites. *The biopsy shows numerous cavities that are passages of the Demodex mite with a large number of calcified parasite fragments (arrows). ×100*

The above picture in the biopsy seems to clearly indicate demodecosis. Despite the clinical diagnosis of basal cell carcinoma, no tumor elements were found in the 10 serial sections examined. However, when referring to the clinical data, it was noted that the tumor nodule at the lid margin measured 10×6 mm and macroscopically corresponded to a typical basal cell carcinoma, which was effectively cryodestructed after biopsy.

The analysis of these circumstances made it possible to realize that the examined biopsy, measuring of 2×0.5 mm, in this situation cannot reflect the entire structure of the pathological process. In addition, it is necessary to understand what cellular material was destroyed by the mite during the formation of a large number of cysts under the epidermis, especially since in this fragment there were no hair follicles with which sebaceous glands could be associated. Thus, the cysts

shown in the previous photo were most likely formed as a result of the mite's destruction of the tumor parenchyma. This was confirmed by the following observation.

On re-examining this biopsy material, special attention was paid to a small cluster of cells at the periphery of one of the cysts (Fig. 7, left part). Under high magnification, one of the sections showed a certain resemblance of the cells of this complex to basalioma (*Fig. 8*).

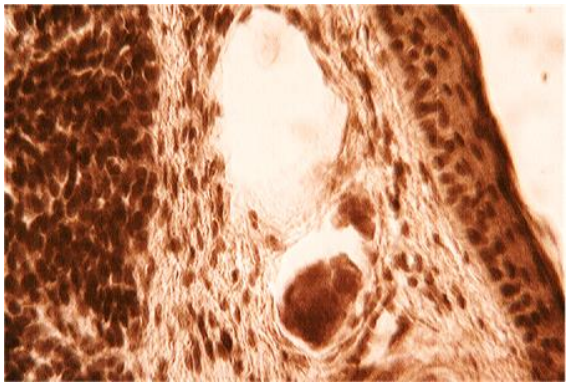

Fig. 8. A partially disrupted microcomplex at the periphery of a biopsy specimen of basal-like cells, but without a characteristic palisade. *×400*

Post-demodecosis pathomorphosis in basal cell carcinoma of the eyelids complicates the pathomorphologic diagnosis of the biopsy.

Conclusions

Based on the experience of studying biopsy material in veterinary medicine, in our study the attention was first drawn to the features of hypertrophic forms of chronic demodecosis, the morphologic manifestations of which had not been previously recorded in ocular pathology.

Subsequent observations performed in order to systematize a number of patterns that are pathognomonic for demodectic infection allowed, based on the study of biopsy and surgical material, to expand the understanding of pathological changes in eyelid tissues associated with the presence of Demodex mite and to draw attention to the pathomorphosis of some eyelid tumor processes.

In general, the current study should be considered as preliminary, since the concept of tumor pathomorphosis caused by the presence of the Demodex mite previously did not exist. At the same time, the examples presented by us not only prove the presence of the mite in the tumor tissue, but also show its significant influence on the pathomorphologic picture, which should be taken into account in diagnostic work.

DECLARATIONS:

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WHITE-COAT HYPERTENSION: WAYS OF OPTIMIZING THE PROVISION OF MEDICAL AID (literature review)

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ABSTRACT

Background. White-coat hypertension is a controversial issue of a modern cardiovascular medicine. It is a common condition in clinical practice, in which office blood pressure is elevated while out-of-office measurements (ambulatory or home) are normal.

The aim of this review is to address a number of issues related to white-coat hypertension, in particular, its definition, prevalence, etiology, symptoms, and consequences, emphasizing the need to improve diagnosis, management and prognosis of this disease.

Results. Recent studies demonstrate that white-coat hypertension is associated with cardiovascular risk factors, including the progression to sustained hypertension and the development of target organ damage. Timely and accurate diagnosis of white-coat hypertension is incredibly important as it allows postponing its conversion to sustained hypertension and prevents alterations of target organ structure and function. The need for improved patient-doctor interaction to enhance diagnosis and management of white-coat hypertension cannot be overstated. Other measures include exploring standardized measurements, improving communication and relationship establishing between physicians and patients, as well as investigating innovative interventions such as health education and telemedicine. The importance of the understanding of the emotional components contributing to white-coat hypertension are highlighted and strategies to improve patient outcomes through early diagnosis, reduced anxiety, and optimal healthcare experiences are proposed.

Conclusion. A comprehensive approach, encompassing standardized measurements, improved communication, and innovative interventions, is essential for effectively managing white coat hypertension.

Keywords: *blood pressure, cardiovascular risk, communication, healthcare, anxiety.*

Introduction

White-coat hypertension, also known as the "white-coat effect" or "white-coat syndrome", refers to the phenomenon where individuals exhibit elevated blood pressure readings specifically in a medical setting, despite having normal blood pressure in their daily lives. White-coat hypertension occurs in 15–30% of individuals with an elevated office blood pressure, and this condition is quite reproducible [1]. In the early 2000s, Thomas Pickering introduced the term "white-coat hypertension" to describe individuals not undergoing hypertension treatment, yet exhibiting elevated office blood pressure alongside normal daytime blood pressure recorded through ambulatory blood pressure monitoring. The condition is characterized by office measurements of 140/90 mmHg or higher, while ambulatory or home readings are normal [2]. Discrepancies in diagnostic criteria, as highlighted by different guidelines, contribute to challenges in accurate identification and management of white-coat hypertension. The consequences of misdiagnosis include the unwarranted use of antihypertensive medications, emphasizing the importance of standardized measurements. A balanced approach to diagnosis and treatment of white-coat hypertension is becoming increasingly important due to recent findings, which suggest that untreated white-coat hypertension is associated with an increased risk of cardiovascular events and cardiovascular mortality compared with normotensive patients [3].

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The aim of this review is to improve the understanding of white coat hypertension, focusing on accurate diagnosis and effective management. This will be done by considering recent scientific publications and accomplishments of international scientists published during the last decades.

Results and Discussion

White coat hypertension, first identified by Riva-Rocci in 1896, involves an immediate increase in blood pressure during a visit to the doctor. A follow-up study in 1983 using intra-arterial blood pressure monitoring confirmed that the increase in blood pressure and heart rate persisted throughout the visit. Microneurographic studies indicate an emotional "protective reaction" during communication with a doctor, which contributes to the emergence of "white coat" hypertension. Patients predisposed to this condition often report a negative medical experience in the past that leads to situational anxiety. Anticipation of high blood pressure readings and the peculiarities of perception of hypertension, whether accurate or not, may increase anxiety by influencing blood pressure responses during a visit to the doctor. Metabolic syndrome has also been linked to white coat hypertension, with associated risks for cardiovascular disease and diabetes. However, the limitations of anxiety measurement methods in previous studies require further research for a comprehensive understanding of this phenomenon [4].

Different measurements in medical offices and at home can lead to the fact that doctors mistakenly diagnose patients as hypertensive. The prevalence of white coat hypertension varies across studies due to different cut-offs for normal out-of-office blood pressure readings. While the 2013 European guidelines report a 13% prevalence, recent reviews suggest 30–40% of patients diagnosed with hypertension based on office measurements alone have normal out-of-office blood pressure [5; 6]. Ambulatory monitoring is crucial for accurate diagnosis, the suggested intervals for confirmation and ongoing monitoring should be maintained. Additionally, resistant hypertensive patients may present with white-coat hypertension, emphasizing the importance of cautious medical decisions based on comprehensive evaluations rather than isolated office readings.

Certain studies indicate that females, individuals over 50, and nonsmokers are more prone to white coat hypertension [7; 8]. However, some studies suggest that a patient's gender, if not influenced by variables such as stress, does not essentially determine the likelihood of developing white-coat hypertension. High levels of stress in women are more closely associated with white-coat hypertension than in men, which may be related to different responses to stress during clinic visits. The diagnosis of white coat hypertension tends to rise significantly with age, possibly attributed to age-related arterial stiffness. In addition, patients with white coat hypertension often exhibit lower office systolic blood pressure measurements [9].

Solving the problem of "white-coat" hypertension involves building a therapeutic relationship between physicians and patients. Effective communication, empathy, and trust can reduce patient anxiety during medical visits, potentially impacting white-coat hypertension. Physician-patient communication encompasses instrumental exchange (medical tasks) and affective communication (building a therapeutic relationship) [10; 11]. Nonverbal cues, such as warm demeanor and active listening, contribute significantly to patient outcomes. Empathy, involving understanding and reflecting patient feelings, is linked to improved patient adherence and satisfaction. Physician empathy can be enhanced through communication skills training. Trust, established through caring communication and shared decision-making, is crucial in reducing patient anxiety. Sufficient time during office visits is essential for addressing patient concerns, understanding perspectives, and fostering a positive physician-patient relationship.

The literature extensively addresses enhancing communication between medical providers and patients through training programs and courses [12]. Medical schools, residency programs, and advanced training courses are increasingly incorporating communication and interpersonal skills into their curricula. However, the effectiveness of such training remains somewhat limited, with improvements needed in methodological approaches for assessing the impact on health outcomes. Considering the emotional components of white-coat hypertension, studies focusing on emotional outcomes show promising results. Physician training programs that address patients' emotional concerns lead to reduced emotional distress, highlighting the potential impact on conditions like white-coat hypertension. Patient-focused training programs, encouraging participation through question asking or coaching before medical visits, proved to be beneficial [13]. Patients who prepare questions and receive information before visits report lower anxiety levels, suggesting a positive impact on overall well-being and treatment adherence.

Exploring future techniques to enhance the provider-patient relationship and reduce patient anxiety, interventions focusing on information provision and stress reduction before office visits have been considered. Past approaches involved waiting room interventions using health educators to improve communication about pain and increase patient-initiated communication, potentially reducing stress [14]. Telemedicine, including methods like email communication and video visits, presents an alternative to traditional communication, with evidence suggesting that patient-centered care and satisfaction can be maintained. In hypertension care, telemedicine has shown promise in improving accurate diagnoses, early intervention, medication adherence, blood pressure control, and overall health outcomes. While not specifically studied in patients with white coat hypertension, these findings could have positive implications for this group, potentially leading to improved health outcomes and reduced healthcare costs [15].

Conclusion

In conclusion, white-coat hypertension presents challenges in accurate diagnosis and management. Varying measurement criteria, emotional factors, and discrepancies in guidelines contribute to its complexity. Addressing this condition requires improved communication and relationship-building between physicians and patients. Training programs focusing on communication skills, empathy, and trust can mitigate patient anxiety. Nonverbal cues, patient-focused interventions, and potential telemedicine applications show promise. A comprehensive approach, encompassing standardized measurements, improved communication, and innovative interventions, is essential for effectively managing white coat hypertension. Understanding emotional components and exploring technological advancements can lead to more accurate diagnoses and better patient outcomes.

DECLARATIONS:

Disclosure Statement

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PLASMA AND PLATELETS AMINO ACIDS IN CORONARY ARTERY DISEASE AND ATRIAL FIBRILLATION PATIENTS – ARE THEY LINKED?

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ABSTRACT

Background. The impact of circulating amino acid levels and their combinations on the pathogenesis of ischemic heart disease and atrial fibrillation is a current issue, otherwise, the platelets amino acid spectrum is still under discussion, despite the known pathogenetic role of platelets in these disorders.

Aim. To compare changes in the plasma and platelets amino acid spectrum in patients with coronary artery disease and atrial fibrillation as well as to find their connections.

Materials & Methods. 300 patients were divided into 3 groups: I group – 149 patients with coronary artery disease without arrhythmias, II group – 124 patients with coronary artery disease and atrial fibrillation paroxysm, and the control group – 27 patients without coronary artery disease and arrhythmias. Plasma and platelet amino acid levels were detected by means of ion exchange liquid column chromatography.

Results & Conclusions. In platelets amino acid spectrum, a significant rise in leucine (12.63%), isoleucine (10.73%), and Fishers' ratio (6.37%); a decrease in threonine (23.05%), valine (30.83%) levels, glycine (32.21%), serine (5.06%), and glycine+serine sum (20.51%) in group 2 patients was found compared with group 1, $p<0.05$. In the plasma amino acids spectrum, a significant increase in glutamate, branched-chain amino acids, and Fishers' ratio and a decrease in glycine in group 2 patients was checked in comparison with group 1, $p<0.05$. Only 10 moderate strength correlations were revealed between the plasma and platelets amino acid spectrum of investigated patient's groups. These changes in platelets and plasma amino acids spectrum were not significantly congruent in patients with coronary artery disease and atrial fibrillation. Plasma and platelets amino acid spectrum should be analyzed separately in patients with coronary artery disease and atrial fibrillation for further studies and evaluation of new prognostic markers and pathogenetic clues to their development.

Keywords: *myocardial ischemia, heart rhythm violations, proteins, metabolomics.*

Abbreviations:

Coronary Artery Disease (CAD), Atrial Fibrillation (AF), CardioVascular (CV), InterLeukin (IL), Amino Acids (AAs), Platelet Count (PC), Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), Platelets-to-Leucocytes Ratio (PLR), Branched-Chain AAs (BCAA), Control Group (CG), Body Mass Index (BMI), Total Cholesterol (TC), Glomerular Filtration Rate (GFR), Myocardial Infarction (MI), aromatic AAs (AAAs), Sulfur Contains AA (SCAAs).

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Introduction

Coronary Artery Disease (CAD) and Atrial Fibrillation (AF) are known and widely spread CardioVascular (CV) pathology. Batta A. et al. notes that more than half of AF cases are accompanied by CAD [1]. Based on the world statistics, 16% to 28% Ukrainian population suffered from AF from 1990 to 2019 years. Moreover, data vary according to sociodemographic index quintiles – poverty leads to the worst AF prognosis and increases its quantity in the population [2]. CAD and AF are pathogenetically closely linked and have numerous similar risk factors, such as arterial hypertension, obesity, diabetes mellitus, dyslipidemia, inflammatory disease, etc. Besides, CAD is one of

the main and most important AF risk factors by itself [3; 4].

CAD and AF pathogenesis is undoubtedly closely linked with prothrombotic states. Platelet condition represents an important part of the hemostatic balance. Platelet activation is directly involved in thrombosis and inflammation processes, which are the known key factors in AF paroxysm development. Zhou P. et al. describes the importance of proinflammatory markers evaluation in prediction permanent AF development in CAD patients. They note that evaluation of InterLeukin-1 (IL-1), IL-6, IL-10 and C-reactive protein have the high predictive potential for evaluating the probability of permanent AF development [5]. Proinflammatory cytokines levels are closely linked with circulating nitrogen-contain Amino Acids (AAs) as arginine, glutamine etc. Arribas-Lopes E. et al. found that glutamine supplementation leads to significant rise of IL-6, which closely associated with increased morbidity and mortality [6]. Also, Zhang L. et al. notes that AF and CAD are characterized by a decrease in Platelet Count (PC) and a rise in Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), and Platelets-to-Leucocytes Ratio (PLR). Nowadays correction platelet characteristics in CAD and AF patients is an attractive substrate for AF paroxysm development prophylaxis in CAD patients [7; 8].

Metabolomic is a newer powerful tool for detection of global and cardiac-specific metabolism. It targets small molecule metabolites (sugars, nucleotides, AAs, and lipids). Proteomics is a crucial metabolomic part, which includes AAs exchange peculiarities in CV diseases [8]. The violations of AAs metabolism in CV patients are up-to-date and widely discussed in scientific society. A prevalence of studies describes circulating AAs values and their role in CV pathology pathogenesis [8; 9], but there is still a lack of data about platelets AAs composition in patients with CAD and AF.

Previous studies have shown several changes in the circulating AAs profile, which can be associated with AF development, but the obtained data are controversial. Also, She J. et al. mentioned that circulation AAs peculiarities are common for the majority of metabolic disorders, which are known as AF and CAD risk factors. The depth of metabolic disorders inherent in AF is shown by plasma AAs violations. Furthermore, therapeutic amino acids supplementation can be an attractive decision for AF paroxysm prevention and management [10]. On the other hand, Huang J. et al. described that AAs play an important role in platelet metabolism: calcium release, integrin activation, granular secretion, and shape changes [11]. For example, Branched-Chain AAs (BCAA) promote thrombosis risks [7]. Meanwhile, Bayron-Marrero Z. et al. noticed that the AAs composition of platelet receptors is crucial for CAD development and prognosis [12]. Thus, platelet proteome investigation is an up-to-date scientific problem [11]. Moreover, the changes in platelets and plasma AAs spectrum coinciding or mismatched are still unclear.

The aim of the study was to compare the changes in the plasma and platelets amino acids spectrum in patients with coronary artery disease and atrial fibrillation and to find their relations.

Materials & Methods

Mean characteristics of investigated groups are shown in *Table 1*.

Plasma and platelet AAs levels were investigated by ion exchange liquid column chromatography. Automatic amino acids analyzer T 339 (Mikrotehna, Czech Republic) was used. Blood sampling from patients was taken fasted from the cubital vein, before treatment. Citrated blood was centrifuged during 10 minutes with at a speed of 1500 revolutions per minute. For platelets collection the middle layer was selected by a Pasteur pipette, there plasma was saturated by platelets. This material was again centrifuged during 20 minutes with a speed of 3000 revolutions per minute. The upper supernatant liquid was collected by a Pasteur pipette, after the lower layer was washed by phosphate buffer solution with pH 6.2. Then washed platelets are resuspended in a buffer (pH 7.4). Twenty (20) AAs were identified in this study: arginine, lysine, alanine, ornithine, histidine, isoleucine, taurine, methionine, threonine, asparaginic acid, serine, proline, glutaminic acid, glycine, cysteine, tyrosine, valine, phenylalanine, leucine, glutamine. They include BCAAs – isoleucine, leucine, and valine; aromatic AAs (AAAs) – tyrosine and phenylalanine; Sulfur Contains AAs (SCAAs) – taurine, cysteine, and methionine [7]. All patients signed an informed consent to participate in the study.

The results were presented as mean ± standard error or for continuous variables. Pearson criterion checked variable distribution for normality. The data were compared using Wilcoxon signed-rank test or Student t-test with two critical regions by the type of distribution. Spearman's correlation analysis was used to explore their correlations [15]. MATLAB R2014a (MathWorks, Inc., USA, License No.271828) was used for calculations.

Table 1. The characteristics of investigated groups

Characteristic /group	Group 1	Group 2	Control group (CG)
Patients number	149	124	27
Patients' diagnosis (by the recent ESC guidelines [3; 4].)	CAD and without arrhythmias	AF paroxysm and CAD	without CAD and arrhythmias
Diagnosis conformation	coronary artery stenotic changes during invasive coronary angiography in history	12 leads electrocardiography at rest	exclusion by Holter ECG and history
Baseline characteristics	age, gender, Body Mass Index (BMI), Total Cholesterol (TC), total bilirubin, uric acid, Glomerular Filtration Rate (GFR), and Myocardial Infarction (MI), stroke, diabetes mellitus in history		
Exclusion criteria	reported malignancies, heart failure Class III to IV (by New York Heart Association [13]), thyroid pathology, chronic kidney disease (GFR <60 ml/min), valvular AF, irritable bowel syndrome, inflammatory bowel disease, vegetarians and vegans, pregnancy, usage of the probiotics and antibiotics for a three month before the study.		
Ethical improvement of the protocol	in the ethical commission of Kyiv City Clinical Hospital No.12 (No.8 on August 22, 2018). Informed consent was obtained from all subjects according to the Declaration of Helsinki [14].		
Study location	the cardiological and therapeutic departments of Kyiv City Clinical Hospital No.12 in 2018–2023 years		
Study laboratory	laboratory in Kyiv City Clinical Hospital No.12 (certificate # ІІТ – 257/21).		

The study was conducted according to the department scientific research project "Changes in protein, carbohydrate and lipid metabolism in patients with coronary heart disease and arterial hypertension with heart rhythm disorders, possibilities of drug correction" 2021–2023 (state registration number 0121U108875).

Results

All baseline characteristics were investigated in the observed patients. In groups 1 and 2, TC (32.64% and 43.06% respectively) and uric acid (22.66% and 30.53% respectively) levels were increased and GFR (by 26.16% and 19.38% respectively) was decreased in comparison with CG ($p<0.05$). In groups 1–2 included patients with stroke, or MI history, diabetes mellitus, obesity, such cases was not in CG. In both investigated groups no significant difference was found in the age and gender, total bilirubin, BMI, and smoking history ($p<0.05$). The data are shown in *Table 2*.

Platelet AAs spectrum was analyzed in investigated patients. Thus, in group 1 demonstrated a decrease in taurine (20.26%), serine (9.31%), and glycine (19.73%) and an increase in isoleucine (12.41%) level versus the CG ($p<0.05$). And group 2 showed decline in threonine (29.37%), taurine (19.84%), glycine (45.59%), serine (13.90%), and valine (27.87%), and a rise in leucine (10.20%), isoleucine (24.47%) levels versus the CG ($p<0.05$). In group 2, a decrease in serine (5.06%), threonine (23.05%), valine (30.83%), glycine (32.21%), and an increase in leucine (12.63%), and isoleucine (10.73%) levels were observed versus group 1 ($p<0.05$). The data are shown in *Fig. 1*.

The platelets AAs combinations were detected for a deeper understanding of propionic violations in investigated groups. In group 2 patients, an increase in AAAs (13.58%), BCAAs (10.34%), Fishers' ratio (26.50%), and a significant decrease in SCAAs (19.25%) and glycine+serine sum (32.91%) versus the CG ($p<0.05$) were found. In group 1 patients a significant increase in BCAAs (7.28%), Fishers' ratio (18.93%), and a decrease in SCAAs (19.52%) and glycine+serine sum (15.60%) ver-sus the CG, $p<0.05$ were revealed. In group 2 patients an increase in Fishers' ratio (6.37%) and a significant decrease in glycine+serine sum (20.51%) versus group 1 ($p<0.05$) were present. The data are presented in *Fig. 2*.

Table 2. The baseline characteristics of the study groups, mean ± standard error

Characteristic /group	Group 1	Group 2	CG
Age (years)	67.71±3.90	67.96±0.94	56.25±2.18
Men (%)	48.99	47.97	48.15
Smoking (%)	51.01	41.46	40.74
History of myocardial infarction (%)	30.87^{+}	26.02$^{\#}$	0
History of stroke (%)	8.72^{+}	8.13$^{\#}$	0
Diabetes mellitus (%)	18.12^{+}	14.63$^{\#}$	0
Obesity (%)	8.84^{+}	12.0$^{\#}$	0
BMI (kg/m^2)	27.02±0.33	26.93±0.43	27.12±2.10
Total bilirubin (mmol/l)	11.3±0.09	12.4±0.08	11.7±0.11
Uric acid (mmol/l)	380.5±28.16^{+}	404.9±36.11$^{\#}$	310.2±29.12
GFR (ml/min)	62.03±2.31^{+}	67.73±1.98$^{\#}$	84.01±5.48
TC (mmol/l)	5.73±0.37^{+}	6.18±0.31$^{\#}$	4.32±0.21

Notes: $^{+}$ – (p<0.05) I group – CG; $^{\#}$ – (p<0.05) II group – CG; * – (p<0.05) I–II groups.

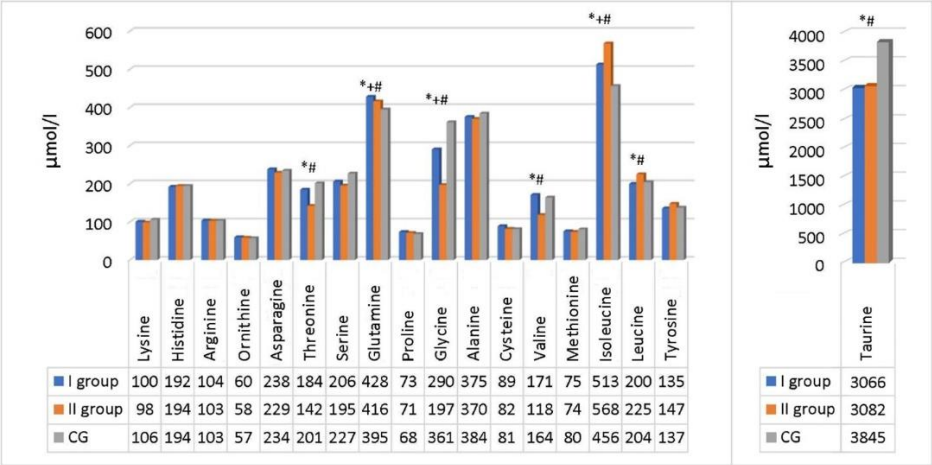

Fig. 1. Platelets amino acids profile in investigated groups, µmol/l.

Notes: $^{+}$ – (p<0.05) I group – CG; $^{\#}$ – (p<0.05) II group – CG; * – (p<0.05) I–II groups, CG – control group.

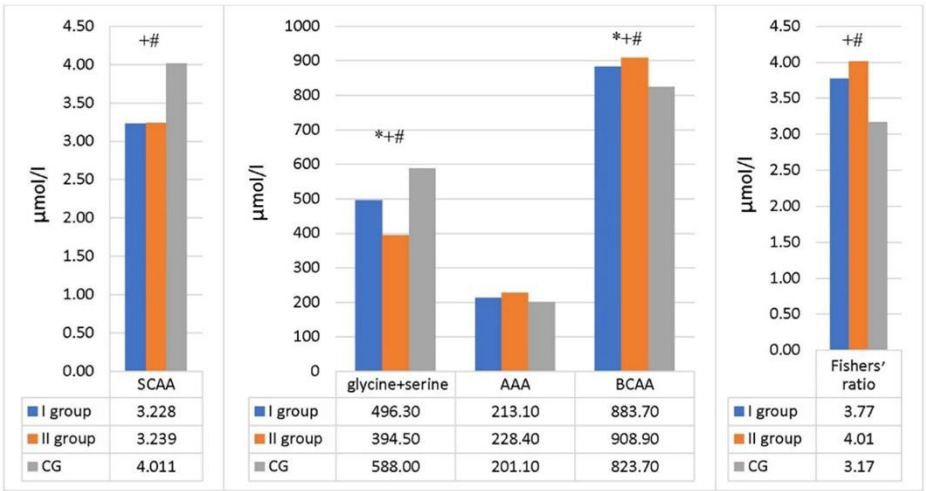

Fig. 2. Platelets amino acids combinations in investigated groups, µmol/l

Notes: $^{+}$ – (p<0.05) I group – CG; $^{\#}$ – (p<0.05) II group – CG; * – (p<0.05) I–II groups; CG – control group; BCAA – branched chain amino acids; AAA – aromatic amino acids; SCAA – sulfur contain amino acids.

The plasma AAs spectrum was analyzed in investigated groups. In group 1 patients a significant decrease in glycine, valine, and alanine levels was detected versus the CG ($p<0.05$). In group 2 patients an increase in glutamate, and a significant decrease in glycine, valine, alanine, serine, and glutamine levels were revealed compared with the CG ($p<0.05$). In group 2, a rise in glutamate and a significant depletion in glycine levels were detected versus group 1, $p<0.05$.

The data are presented in *Fig. 3* and *Table 3*.

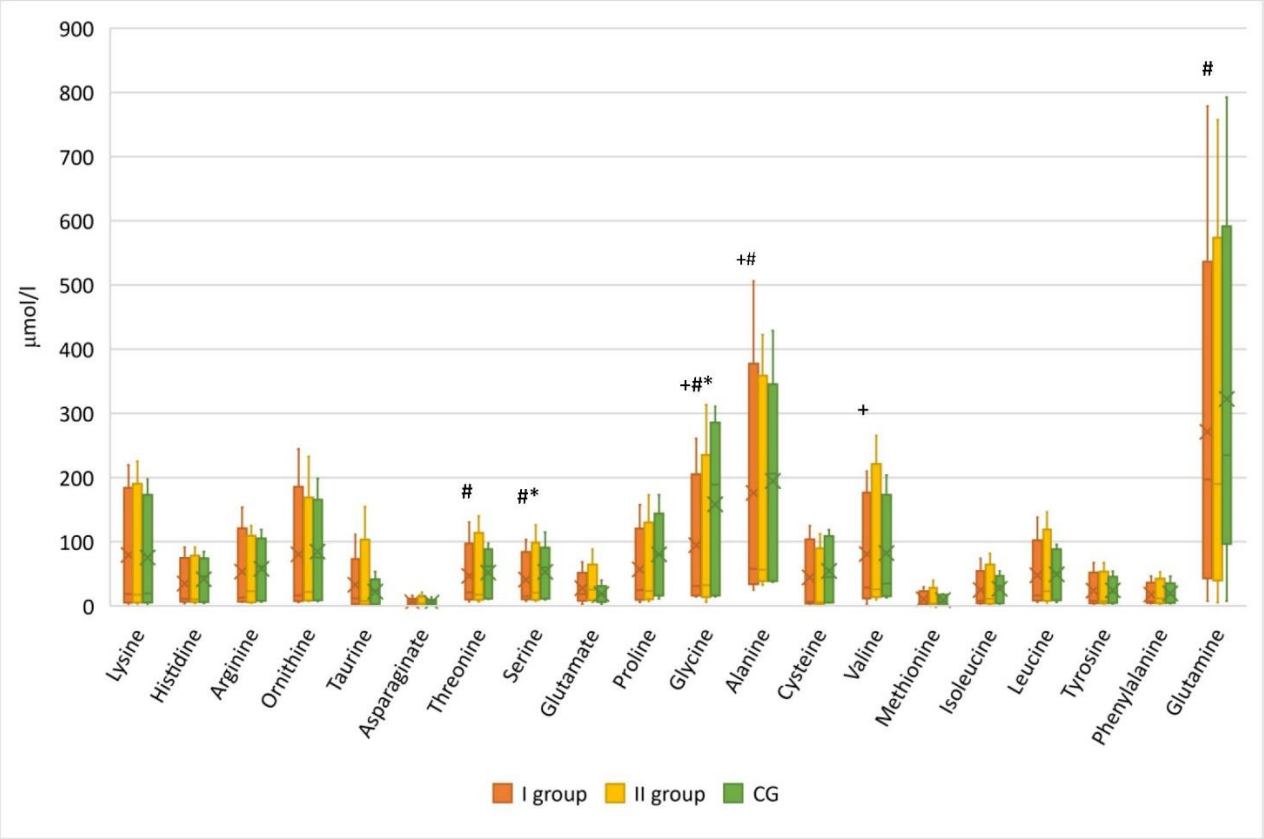

Fig. 3. Plasma amino acids spectrum in investigated groups, µmol/l

Notes: $^{+}$ – ($p<0.05$) I group – CG; $^{\#}$ – ($p<0.05$) II group – CG; * – ($p<0.05$) I–II groups; CG – control group.

Table 3. Plasma amino acids spectrum in investigated groups, µmol/l

Characteristic /group	Group 1	Group 2	CG	$p_{G1–G2}$	$p_{G2–CG}$	$p_{G1–CG}$
Lysine	25.35 [19.44; 133.33]	29.84 [19.36; 112.24]	91.83 [17.18; 181.32]	p>0.05	p>0.05	p>0.05
Histidine	11.52 [9.48; 53.04]	10.32 [9,60; 46.48]	46.49 [5.56; 63.38]	p>0.05	p>0.05	p>0.05
Arginine	13.13 [8.57; 87.5]	22.96 [9.12; 79.55]	62.09 [6.63; 119.32]	p>0.05	p>0.05	p>0.05
Ornithine	16.04 [10.01; 122.22]	22.09 [11.78; 88.00]	75.59 [7.85; 179.89]	p>0.05	p>0.05	p>0.05

Characteristic /group	Group 1	Group 2	CG	$p_{G1–G2}$	$p_{G2–CG}$	$p_{G1–CG}$
Taurine	12.04 [4.80; 29.41]	7.87 [4.30; 45.29]	23.97 [3.28; 53.37]	p>0.05	p>0.05	p>0.05
Asparaginate	4.82 [1.42; 6.08]	3.95 [1.83; 4.39]	4.43 [0.79; 9.39]	p>0.05	p>0.05	p>0.05
Threonine	21.19 [12.87; 63.22]	17.65 [14.23; 69.54]	61.82 [10.97; 91.46]	p>0.05	p>0.05	p>0.05
Serine	15.08 [13.70; 52.17]	20.64 [13.49; 29.37]	60.18 [11.51; 103.45]	p>0.05	p<0.05	p>0.05
Glutamate	18.67 [15.64; 29.41]	25.23 [21.51; 36.76]	17.57 [7.34; 20.15]	p<0.05	p<0.05	p>0.05
Proline	25.00 [16,33; 63.46]	23.33 [16.67; 82.50]	80.23 [13.33; 115.38]	p>0.05	p>0.05	p>0.05
Glycine	31.18 [20.95; 147.90]	28.04 [21.50; 44.82]	189.00 [56.56; 281.40]	p<0.05	p<0.05	p<0.05
Alanine	57.86 [45.64; 145.29]	56.25 [48.31; 131.65]	206.28 [40.47; 345.24]	p>0.05	p<0.05	p<0.05
Cysteine	6.52 [5.32; 78.95]	5.69 [5.21; 39.47]	44.83 [5.32; 88.45]	p>0.05	p>0.05	p>0.05
Valine	28.56 [22.44; 142.86]	25.89 [19.48; 137.50]	34.87 [13.97; 82.86]	p>0.05	p>0.05	p<0.05
Methionine	2.71 [2.07; 9.18]	3.97 [2.64; 11.09]	6.03 [2.37; 16.13]	p>0.05	p>0.05	p>0.05
Isoleucine	8.33 [5.78; 31.50]	11.02 [6.86; 36.17]	31.38 [5.34; 46.88]	p>0.05	p>0.05	p>0.05
Leucine	16.35 [12.70; 61.54]	23.07 [12.90; 63.46]	51.87 [12.90; 92.31]	p>0.05	p>0.05	p>0.05
Tyrosine	8.01 [5.84; 35.71]	7.69 [5.96; 15.07]	21.10 [9.57; 44.12]	p>0.05	p>0.05	p>0.05
Phenylalanine	6.79 [6.08; 23.53]	12.14 [6.69; 24.12]	17.64 [5.56; 29.41]	p>0.05	p>0.05	p>0.05
Glutamine	78.22 [57.14; 337.26]	74.01 [51.19; 164.44]	234.79 [96.18; 398.53]	p>0.05	p<0.05	p>0.05

Also, plasma AAs were combined according to their biochemical properties and exchange and these results were compared in investigated groups. In group 2, a rise in BCAAs and Fishers' ratio was found versus group 2 (p<0.05). In group 2, a significant rise in BCAAs and Fishers' ratio and a decrease in glycine+serine sum was found versus the CG (p<0.05). In group 1, a rise in Fishers' ratio and a decrease in glycine+serine sum was present versus the CG, p<0.05.

The data are presented in *Fig. 4* and *Table 4*.

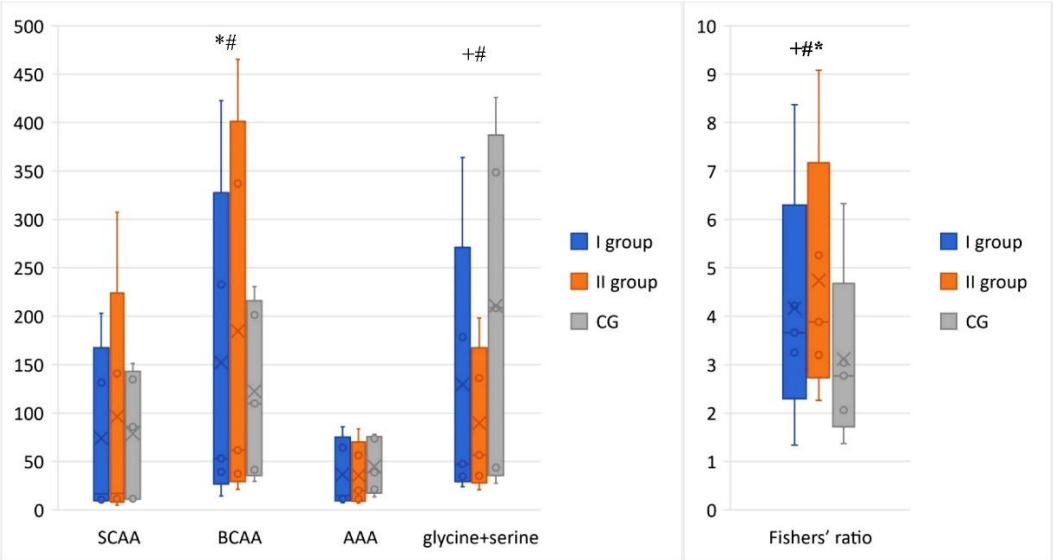

Fig. 4. Plasma amino acid combinations in investigated groups, μmol/l

Notes: $^{+}$ – ($p<0.05$) I group – CG; $^{\#}$ – ($p<0.05$) II group – CG; * – ($p<0.05$) I–II groups; CG – control group; BCAA – branched chain amino acids; AAA – aromatic amino acids; SCAA – sulfur contain amino acids.

Table 4. Plasma amino acid combinations in investigated groups, μmol/l

Characteristic/group	Group 1	Group 2	CG	$p_{G1–G2}$	$p_{G2–CG}$	$p_{G1–CG}$
SCAA	16.6 [11.29; 124.88]	17.19 [11.80; 133.10]	85.76 [10.73; 139.83]	p>0.05	p>0.05	p>0.05
BCAA	52.84 [40.73; 214.77]	61.55 [54.41; 260.92]	109.88 [38.63; 215.67]	p<0.05	p<0.05	p>0.05
AAA	14.54 [11.40; 60.29]	19.85 [11.69; 47.63]	38.74 [14.30; 77.63]	p>0.05	p>0.05	p>0.05
Fishers' ratio	3.66 [3.31; 4.04]	3.88 [3.29; 4.52]	2.77 [1.97; 3.14]	p<0.05	p<0.05	p<0.05
glycine+serine	47.40 [34.78; 188.10]	56.55 [39.73; 95.82]	208.52 [28.07; 363.95]	p>0.05	p<0.05	p<0.05

The correlation analysis between plasma and platelet AAs spectrum was done in the study. The biggest number of correlations was checked between the plasma AAs spectrum and asparagine acid (total number = 3). The largest amount of correlations was found between platelet AAs spectrum and glutamic acid (total number = 3). The data are presented in *Fig. 5*.

In sum, in this study the plasma and platelet AAs spectrum and their combinations were revealed and compared in group 1 (patients with CAD and without arrhythmias), group 2 (patients with CAD and AF), and control group (patients without CAD and AF). The correlation analysis between plasma and platelets AAs spectrum was performed to reveal their associations.

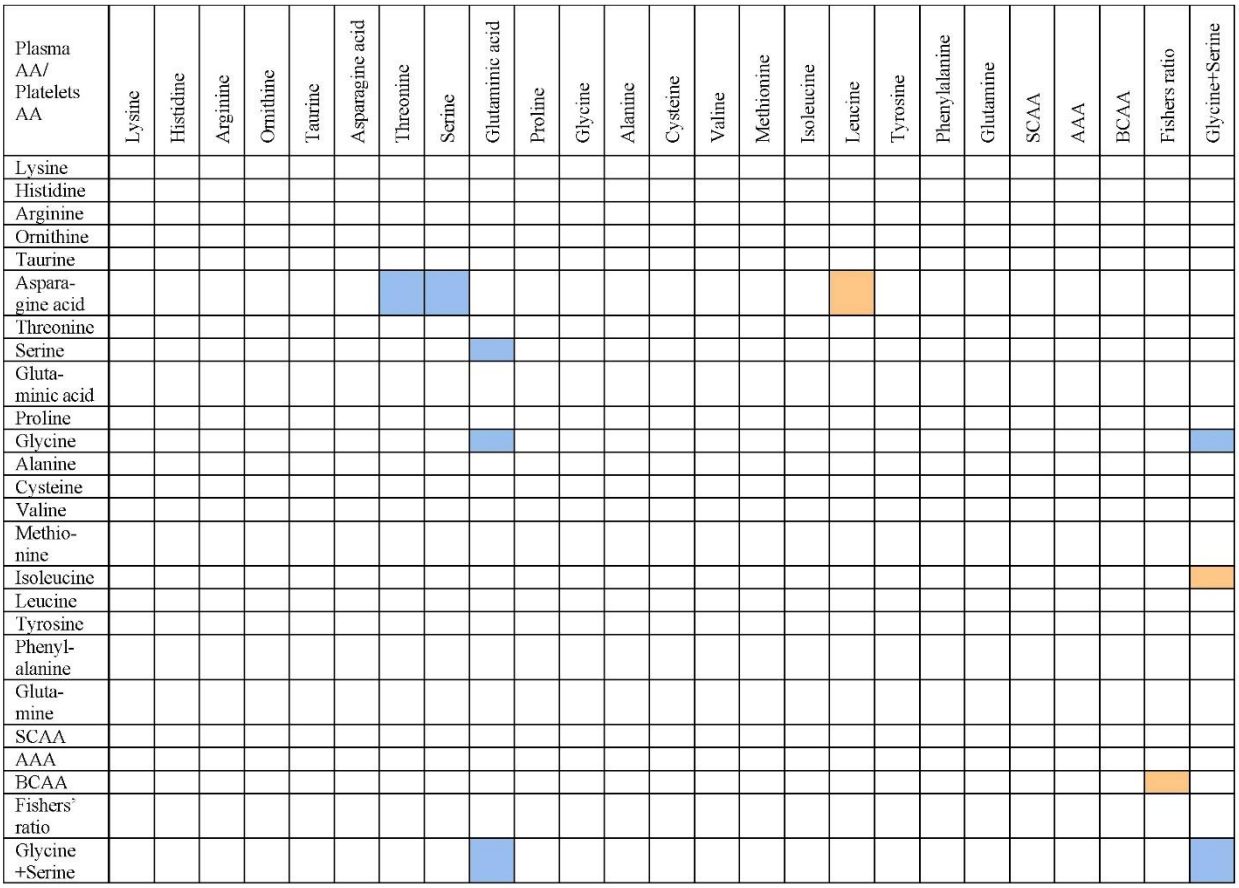

Fig. 5. Correlation matrices between plasma and platelet amino acids spectrum, $p<0.05$

Notes: – moderate negative correlations; – moderate positive correlations;
BCAA – branched chain amino acids; AAA – aromatic amino acids; SCAA – sulfur contain amino acids.

Discussion

Evaluation of plasma AAs features in patients with CV pathology is widely used. Several studies describe changes in plasma AAs profile in patients with arterial hypertension [16], coronary artery disease, heart failure [17], atrial fibrillation [8], etc. According to the obtained data patients with CAD and AF paroxysm were characterized by BCAAs, AAAs, glycine, serine, and threonine exchange violations in comparison with CAD and without arrhythmias group, what can imply their role in AF paroxysm development. Also, Fisher's ratio was increased in CAD patients with and without AF congruently.

These data are matched with the literature overview. According to Zhang L. et al. study, AF paroxysm is closely appropriate with glycine, serine, and threonine exchange [8]. Chu C. et al. noticed that their metabolism in cardiomyocytes is closely linked, and they can be a precursor of each other. Glycine metabolism is indirectly closely developed with the one-carbon metabolism pathway, which provides homocysteine regulation, DNA methylation, generation of methyl donors, and other components of antioxidative action. Glycine is also improving nitric oxide synthesis, thereby increasing central arterial pressure and arterial stiffens. According to several studies, it has anti-inflammatory and antilipidemic properties, thereby preventing atherosclerosis development [18; 19]. Cifuentes F. et al. described that, glycine depletion is associated with autonomic dysregulation, thereby an increase in sympathetic activity and cardiac autonomic remodeling formation [20]. Furthermore, the glycine, serine, and threonine metabolism pathway play a crucial role in energy regulation [18]. According to Gao X. et al. data, serine regulates mitochondrial activity, thereby cell formation and proliferation. Mitochondrial serine metabolism is thought to be considered for

cellular NADPH production. Precisely serine exchange is closely linked with lipids and indirectly with glucose exchange. Nucleotide synthesis, redox balance, and alteration of sphingolipids metabolism are intricately, but tightly connected with serine level [21]. In the Mesubi O. et al. animal experiment, serine-threonine protein kinases are abundant in the myocardium thereby linked with membrane excitability, calcium homeostasis, matrix remodeling, apoptosis, which are the basis for atrial remodeling and AF paroxysm development [22]. Tang Q. et al. noticed that serine and threonine in intestinal barrier permeability conduction and mucin production, are the crucial part of microbial endotoxemia development [23]. According to Gawalko M. et al. overview, gut microbiota, and its metabolites, which include AAs, play an important role in AF pathogenesis and are a remarkable part of most metabolomic studies [24]. Gut microbiota and AAs exchange relations are interesting and up-to-date scientific topic, which can be useful in the search of a new AF paroxysm prevention and management therapeutic strategies [25]. This study presents deeper insight into relations between platelets and plasma amino acids, but their links with gut microbiota composition are also interesting scientific question.

Also, BCAAs plasma levels and Fisher's ratio were increased in patients with CAD and AF. According to Karadeniz A. et al., increase of BCAAs concentrations regulates the mTOR signaling pathway, which is a central regulator of cellular metabolism, that improves insulin resistance and provokes low-grade chronic inflammation. Redundant BCAAs is addicted to atrial accumulation, which aggravates tissue fibrosis and mitochondrial oxidation. Moreover, BCAAs improved platelet activity, leading to their activation and degranulation by promoting thrombomodulin-3 propionylation [26]. Yang S. et al. mentioned that it is no wonder that glycine, serine, threonine, and BCAAs metabolism disruption are associated with life-threatening ventricular arrhythmias [27]. In Zhang J. et al. animal experiments, a rise of circulating BCAAs (mostly leucine and isoleucine) is associated with hypertriglyceridemia, thereby CV pathology via the mTOR/SREBP-1/betatrophin pathway. Moreover, BCAAs increase indirectly associated with diabetes mellites and fatty liver. Interesting, circulating BCAAs levels can be successfully reduced by metformin supplementation [28]. AAAs are involved in inflammatory processes by their impact on T lymphocytes and macrophage function. Tyrosine plays an important role in nitric oxide production. Phenylalanine is a precursor of adrenaline, noradrenaline, and thyroid hormones. Undoubtedly, all described mechanisms take part in CVD development [18]. Fishers' ratio is a known marker of CV events. It is calculated as BCAAs/AAAs circulating values. Thus, an increase in BCAAs and a decrease in AAAs are the important characteristic of investigated patients [8].

Despite this, the plasma AAs spectrum is characterized by high variability. It depends on the numerosity of external and internal factors, such as age, gender, diet, physical activity [29], coexistent diseases, mental state, stress [30], etc. This can be a limitation for further plasma AAs investigations. Moreover, the plasma and serum AA spectrum can be different, which needs further investigation and what can be the cause of misunderstanding in circulating AAs values analysis.

The evidence points out that the role of platelets in AF paroxysm pathogenesis is increasing. Platelets AAs composition is corelated with transthoracic echocardiography indexes. Left atrium characteristics are directly related with leucine level and inversely with alanine and serine levels. At the same time, left ventricular indices correlated with serine, threonine, alanine, arginine, and isoleucine levels, what proved the role of such platelet's changes in prothrombotic state development [31]. Huang J. et al. noticed that the platelet activation process is connected with its unique proteomic changes [32], which can be not congruent with cardiomyocytes and plasma features. In the Song Y. et al. experimental study it was suggested that AAAs derivates can activate platelets and mediate thrombosis via adrenergic receptor activation. Their production is connected with gut microbiota composition via a rise of pathogenic strains, such as Streptococcus spp., Enterococcus spp., and Ruminococcus spp., which can induce AF via an increase of trimethylamine-N-oxide, indole sulfate, and primary bile acids circulation [33]. The topic of thrombosis-associated metabolomics is understudied, and has a big potential for new biomarkers identification. Extracellular glycine is characterized by antithrombotic properties via CD8+ T-cell activation, which interacts with extracellular toxicity and thrombogenesis [34]. Huang K. et al. noticed that the prothrombotic state is closely linked with metabolic disorders, via gut microbiota metabolites that include AAs profile by itself and their derivates, such as trimethylamine-N-oxide, etc. several gut microbiota metabolites potentiating cytosolic phospholipase

A2 activation and platelets hyperresponsiveness, via inhibition of integrin α2β1. Thus, gut microbiota condition and its metabolites, including AA profile and its derivates are attractive potential therapeutic targets for thrombosis prevention [35].

Therefore, plasma and platelets AAs spectrum both are an important characteristic of human health, forming AF and CAD pathogenesis at different points, which can provide a further prognosis of pathological process development and can be the target for secondary prophylaxis and treatment.

Presented study is mostly explained the obtained peculiarities in platelets and plasma AAs changes and their links during AF paroxysm in CAD patients. The limitations are the lack of previous studies in this area and variability of plasma AAs spectrum.

Conclusions

In this study plasma and platelet amino acids spectrum features in patients with coronary artery disease and atrial fibrillation were analyzed and compared, but reliable relationships were not found. In platelets amino acids spectrum, a significant decrease in serine (5.06%), threonine (23.05%), valine (30.83%), glycine (32.21%) levels, and glycine+serine sum (20.51%) and an increase in leucine (12.63%), isoleucine (10.73%), and Fishers' ratio (6.37%) in patients with coronary artery disease and atrial fibrillation was found compared with patients with coronary artery disease and without atrial fibrillation, $p<0.05$. In the plasma amino acids spectrum, a significant increase in glutamate, branched chain amino acids, and Fishers' ratio and a decrease in glycine in patients with coronary artery disease and atrial fibrillation was checked compared with patients with coronary artery disease and without atrial fibrillation, $p<0.05$. Ten (10) moderate strength correlations were revealed between plasma and platelets amino acids spectrum of investigated patient's groups. Therefore, according to the obtained data, the changes in platelets and plasma amino acids spectrum are not congruent. But they give us insight, which amino acids metabolism violation can lead to atrial fibrillation paroxysm formation in coronary artery disease patients. The obtained data are important for understanding the mechanism of action therapeutical amino acids administration in patients with coronary artery disease and atrial fibrillation. Besides, these results can help to choose the best amino acid or its combination for investigated pathologies and comorbidities.

The comparison of cardiomyocyte and platelet, plasma, and leucocyte amino acid profiles in patients with atrial fibrillation and coronary artery disease will be an interesting item for a deeper understanding of their pathophysiology.

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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UVEITIS COMPLICATED BY PHTHISIS BULBI: HEMODYNAMIC PARAMETERS IN THE PREDICTION OF ANTERIOR-POSTERIOR EYE SIZE REDUCTION

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ABSTRACT

Background. Phthisis bulbi is a serious complication of uveitis, causing vision loss and esthetic defects. Hemodynamic disorders can play an important role in the formation of this complication as a result of uveitis. We did not find data on predicting the progression of phthisis bulbi with a reduction in anterior-posterior size in the available literature.

Aim. To analyze the possibility of predicting the reduction in the anterior-posterior size of the eye with uveitis, complicated by phthisis bulbi, based on hemodynamic parameters

Materials and Methods. 33 patients aged 5–84 years, of them 19 male and 14 female patients, with unilateral endogenous uveitis, complicated by phthisis bulbi, were examined. 15 patients with uveitis complicated by phthisis bulbi, who had not received any treatment during this time, were examined in dynamics (for at least 1 year). All patients underwent Doppler ultrasound examination of the ophthalmic artery and short posterior ciliary arteries. In addition, all patients underwent biomicroscopic and tonometric examinations, ultrasound biomicroscopy, rheoophthalmography of eyeballs, A-scan and B-scan ultrasonography. The results of the examination of eyes with uveitis complicated by phthisis bulbi were compared with the results of the examination of paired (healthy) eyes of the same patients.

Results. We have developed a multiple regression model that allows us to predict a reduction in the anterior-posterior size of the eye with phthisis bulbi due to uveitis. The dynamics of the disease in 15 patients not taking any treatment for uveitis, has been monitored for more than a year. The prediction of phthisis bulbi progression was confirmed in 13 patients, which amounts to 86.7% ($p<0.05$).

Conclusions. We have proposed a model that allows predicting the progressive or stationary course of phthisis bulbi due to uveitis based on hemodynamic parameters.

Keywords: *infectious uveitis, noninfectious uveitis, phthisis bulbi hemodynamic disorders, anterior-posterior size of the eyeball.*

INTRODUCTION

Uveitis is an inflammatory disease of the uveal tract, in the pathogenesis of which the leading role is played by immunologic disorders [1–7]. Most uveitis (56.0% to 86.3%) causes complications [8–13]. Phthisis bulbi is one such serious complication of uveitis, causing vision loss and cosmetic defects.

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The frequency of phthisis bulbi among all eye diseases according to the data of the tertiary center is 0.4% [14], and among patients with uveitis – 1.6% [15]. At the same time, among uveitis leading to significant visual impairment (0.1 or less) the frequency of phthisis bulbi is 19.0% [15].

Among patients blinded due to disease or injury, phthisis bulbi is diagnosed in 4.0–19.0% of cases [16–20].

Uveitis is the cause of 13.9–28.0% of phthisis bulbi [14; 15]; another 21.5–23.0% of cases are caused by infectious diseases [14; 15], and another 17.0% of patients are diagnosed with sympathetic ophthalmia [15].

In general, the proportion of phthisis bulbi as a cause of eyeball removal according to various

authors ranges from 11.7% to 27.0% [21–24]. After penetrating wounds, the proportion of phthisis bulbi as a cause of eyeball removal is 6.1–45.2% [25–27]. At the same time, according to Kaliki S. et al. (2019), phthisis bulbi and atrophy were an indication for enucleation in patients of working age (20–60 years) in 39.0% of cases [28].

The main factors in the pathogenesis of phthisis bulbi, according to researchers, are hypotonia, blood-ophthalmic barrier disorders and inflammation [29].

Hemodynamic disorders can play an important role in formation of this complication as a result of uveitis. It has been shown that ischemia of the anterior segment of the eye is a factor in the development of phthisis bulbi [30].

Researchers have studied the factors contributing to the development of phthisis bulbi after penetrating wounds [25]. We did not find any data on predicting the progression of phthisis bulbi with a reduction in anterior-posterior size in the available literature.

The aim of this work was to analyze the possibility of predicting the reduction in the anterior-posterior size of the eye with uveitis, complicated by phthisis bulbi, based on hemodynamic parameters.

Materials and Methods

33 patients with unilateral endogenous uveitis, complicated by phthisis bulbi, of them 19 male and 14 female patients, aged 5–84 years were examined. 15 patients with uveitis complicated by phthisis bulbi, who had not received any treatment during this time, were examined in dynamics (for at least 1 year).

All patients underwent Doppler ultrasound examination of the ophthalmic artery and short posterior ciliary arteries. Using this method, the maximum blood flow Velocity (V_{max}), minimum blood flow velocity, and Resistance index (R_i) are determined (compared with fellow eye and healthy subjects).

Becides, all of them were examined by rheoophthalmography of eyeballs (using the "Reo-Com" device). Using this method, the rheoophthalmography ratio, pulse volume blood flow, and minute volume blood flow were determined.

The Anterior-Posterior Size (APS) of the eyeball was determined by A-scan ultrasonography. In addition, all the patients underwent biomicroscopic and tonometric examinations, ultrasound biomicroscopy, and B-scan ultrasonography.

The results of the examination of eyes with uveitis complicated by phthisis bulbi were compared with the results of the examination of paired (healthy) eyes of the same patients.

Informed consent to participate in the study was obtained from all patients.

Results

We selected prognostically significant parameters, which can be used to determine the progression of phthisis bulbi in patients' eyes with uveitis.

Statistical processing of blood flow indices during Doppler ultrasound examination of the ocular artery, short posterior ciliary arteries (compared to the paired eye) was performed, such as:

- maximum blood flow velocity,
- minimum blood flow velocity,
- resistance index.

Statistical processing of rheophthalmologic parameters of blood flow (in comparison with the paired eye) was also performed:

- rheoophthalmography ratio,
- pulse volume blood flow,
- minute volume blood flow.

To build a multiple regression model, it is necessary to get rid of the effect of multicollinearity, i.e. to remove interdependent variables from the list of predictors. To do this, we first analyzed the correlations within the list of predictors, and then built and examined a linear multiple regression model.

According to the Pearson's correlation matrix, we determined relevant correlations that characterize the strong interdependence of predictors in the list of variables.

The results were confirmed by considering Spearman's correlations.

After that, regression results were calculated for the variable "anterior-posterior size in comparison with the paired eye".

It is shown that the obtained coefficients are insignificant, which indicates that simple linear regression is not applicable to describe these parameters.

Therefore, we applied a piecewise linear model. We used the quasi-Newtonian method of error minimization. The loss function was estimated by the least squares method.

Numerical test of independence of the residuals was performed using the Durbin-Watson test.

Several methods were applied to the multiple linear regression model: Standard with simultaneous inclusion of all variables in the model, Backward stepwise with exclusion and Forward stepwise with inclusion.

The presented model is the most statistically valid representation of the data and allows predic-

ting the development of anterior-posterior size change compared to the paired eye in uveitis.

The most significant of the analyzed hemodynamic parameters in progression of phthisis bulbi in patients with uveitis were minute volume blood flow, maximum blood flow velocity in the short posterior ciliary arteries and resistance index in the short posterior ciliary arteries.

Using these data, we developed a multiple regression model, which provides the possibility to predict the reduction in the APS of an eye with phthisis bulbi as a result of uveitis in comparison with the fellow eye. This mathematical model is described by the following equation:

$$y=A+0.00354\times x_1+0.015\times x_2+4.674\times x_3 \quad (1),$$

where:

y – is the estimated amount of reduction in the APS of the eye;

A – is a constant which presented formula represents the "initial" average reduction in the APS of the eye with phthisis bulbi due to uveitis, in the group of patients examined by us. It's equal to 4.64;

x_1 – is the disparity between the minute volume blood flow of fellow and diseased eyes

x_2 – is the disparity between maximum blood flow velocity in the short posterior ciliary arteries of fellow and diseased eye;

x_3 – is the disparity between resistance index in the short posterior ciliary arteries of fellow and diseased eyes.

The coefficient (k) represents progression of phthisis bulbi due to uveitis (in terms of the APS reduction compared to the paired eye) and is calculated by formula:

$$k=y/A \quad (1),$$

where:

y – is the estimated amount of reduction in the APS of the eye with phthisis bulbi due to uveitis (determined by the formula, mentioned above);

A – is a constant calculated from the average reduction in APS of the eye with phthisis bulbi due to uveitis in the cases under investigation (4.64).

If the value of the coefficient k=2.0 or more, we can predict a progressive course of phthisis bulbi (with a reduction in the APS of the eye by more than 1 mm per year), and if the value of the coefficient k is less than 2.0, a stable course of the disease is predicted (with a change in the APS of the eye by no more than 1 mm per year).

The dynamics of the disease in 15 patients with uveitis, complicated by phthisis bulbi has been monitored for more than a year. The prediction of phthisis bulbi progression was confirmed in 13 patients, which amounts to 86.7% ($p<0.05$). Patients did not receive treatment during the observation period.

The obtained data is illustrated by the following cases:

Case No.1.

A 61-year old patient was on inpatient treatment in the adult ophthalmologic department of Kharkiv Regional Clinical Hospital with the diagnosis of chronic recurrent uveitis in acute stage, phthisis bulbi OD. His examination results:

APS OD=20 mm,
OS=26 mm;
minute volume blood flow OD=543 mm³/min,
OS=2031 mm³/min;
V_{max} in short posterior ciliary arteries
OD=8 cm/s,
OS=13 cm/s;
R_i in short posterior ciliary arteries OD=0.57,
OS=0.60.

According to the proposed model, we calculated the reduction in APS of the eye in patient K.

Regression equation (1):

$y=4.64+0.00354\times x_1+0.015\times x_2+4.674\times x_3$

$y=4.64+0.00354\times 1488+0.015\times 5+4.674\times 0.03=$
$=10.12$ mm

$k=10.12/4.64=2.19$

Thus, the coefficient k=2,19 and k>2, which predicts a progressive course of phthisis bulbi of the eye in the patient.

The patient was offered a course of conservative therapy. However, due to family circumstances, the patient refused treatment.

This patient was examined a year later. Measurement of the eye APS was performed, and the following parameters were obtained:

OD APS=16.6 mm, OS APS=26.0 mm. Thus, the eye with phthisis bulbi decreased in size by 3.4 mm per year, which confirms the correctness of the prognosis.

Case No.2.

A 35-year-old patient was treated as an inpatient in the adult ophthalmologic department of Kharkiv Regional Clinical Hospital with the diagnosis of chronic recurrent uveitis in the acute stage, phthisis bulbi OD. His examination results:

APS OD=20.1 mm, OS=24.2 mm;
minute volume blood flow
OD=850.1 mm³/min,
OS=808 mm³/min;

V_{max} in short posterior ciliary arteries
OD=9.9 cm/s,
OS=14.7 cm/s;
R_i in short posterior ciliary arteries OD=0.69,
OS=0.69.

According to the proposed model, we calculated the reduction in APS of the eye in patient L.

Regression equation (1):

$y=4.64+0.00354\times x_1+0.015\times x_2+4.674\times x_3$

$y=4.64+0.00354\times(-42.1)+0.015\times 4.6+$
$+4.674\times 0=4.56$ mm

$k=4.56/4.64=0.98$

Thus, the coefficient k=0.98 and k<2, which predicts a stationary course of phthisis bulbi of the eye in this patient.

The patient was examined one year later. The eye APS was measured, and the following parameters were obtained: OD APS=20.0 mm, OS APS=24.2 mm.

The eye with phthisis bulbi decreased only by 0.1 mm during the year, which confirms the correctness of the prognosis.

Discussion

In terms of discussion of the obtained results, it should be noted that the pathogenetic factors of the occurrence of phthisis bulbi according to the researchers are hypotony, deranged blood-ocular barriers, and inflammation [29].

Coskun M. et al. [25], studying the factors that influence the development of phthisis bulbi after penetrating ocular wounds, concluded that the significant factors are the anatomical localization and size of the wound, concomitant pathologies of the anterior or posterior segment of the eye, as well as endophthalmitis due to trauma. However, those results cannot be extrapolated to patients with uveitis.

The development of phthisis bulbi due to severe ischemia of the anterior segment of the eye of various etiologies described in the literature [30; 31] indicates an important role of hemodynamic disorders in the pathogenesis of phthisis bulbi and indirectly corresponds with our results.

In the literature, we did not find a description of prediction models for progression of phthisis bulbi due to uveitis and reduction in APS.

Si S. et al. (2023) proposed a prognostic model for the development of phthisis bulbi after cosmetic injection of hyaluronic acid [30], based on the determination of the severity of anterior segment ischemia. According to the authors, anterior segment ischemia occurs as a complication of hyaluronic acid injection due to thrombosis of the terminal branches of the ocular artery. A prognostic model [30] can predict the long-term prognosis and the likelihood of subsequent development of phthisis bulbi through several dynamic assessments over a 6-month period. The authors state that patients with ophthalmoplegia at 1-month follow-up and persistent hypotony for 6 months are extremely likely to develop phthisis bulbi.

Our model allows predicting the progressive or stationary course of phthisis bulbi due to uveitis based on the ratio of minute volume blood flow, maximum blood flow velocity in the short posterior ciliary arteries and resistance index in the short posterior ciliary arteries of fellow and diseased eyes with the probability of correct prognosis 86.7%.

Limitations

We did not study the accuracy of the prediction in patients who underwent conservative treatment or surgical intervention.

The mathematical model was developed on the basis of 33 patients and shows a fairly high frequency of correct prognosis (86.7%), however, the constant A can be refined with an increase in the number of patients.

In this way, we have developed a mathematical model that provides the possibility to predict the reduction in the anterior-posterior size of the eye with uveitis, complicated by phthisis bulbi.

Conclusions

We have proposed a model that allows predicting the progressive or stationary course of phthisis bulbi due to uveitis based on hemodynamic parameters.

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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CHARACTERISTICS OF CARIOUS LESIONS OF PERMANENT TEETH IN 12-YEAR-OLD CHILDREN

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ABSTRACT

Background. The article deals with the characteristics of the condition of hard tissues of permanent teeth in children depending on the region of residence.

Aim. To characterize the condition of the hard tissues of the teeth in 12-year-old children living in different districts of Bukovyna.

Materials & Methods. 298 12-year-old children were examined in 13 schools in Chernivtsi region (78 children from Vyzhnytsky district, 74 from Chernivtsi, 146 from Dnistrovsky). The prevalence, intensity of caries, the index of the international caries detection and evaluation system were determined.

Results & Conclusions. The incidence of caries in 12-year-old children was high in all regions: 88.46% in Vyzhnytsia, 84.50% in Dniestr and 84.89% in Chernivtsi districts. The highest caries intensity values were found in children of the Vyzhnytsia District (3.39±0.21) affected teeth, the lowest – in the examined children of the Dniester District – (2.88±0.28). In the structure of the "DMF" index (Decay-Missing-Filled), the "D" component prevailed in all regions. It is worth noting that the extracted teeth were from 0.34% to 1.76%. In all regions, the average level of intensity prevailed, but the share of children with a high level was also high, from 24.32% to 38.46%. The carious process is characterized not only by simultaneous carious lesions of different groups of teeth, but even several surfaces of one tooth. Half of all carious cavities (52.88%) were diagnosed on the chewing surface of the lateral teeth, 24.00% – on the contact surfaces of all groups of teeth, 14.49% – on the vestibular surface of the incisors, and 7.02% – on the oral surface of the lateral teeth incisors. As for the depth of the lesion, 53.56% of carious cavities were located on the enamel surface, 26.95% – in the thickness of the enamel, 19.47% part – within the medium-deep layers of dentin. The high prevalence of caries in children of Bukovyna region indicates the need to study the regional risk factors for the development of caries.

Keywords: *children, caries, prevalence, intensity, localization of caries, depth of damage*.

INTRODUCTION

Caries is the most common dental disease in children and adults [1]. In Ukraine, the incidence is high, but the indicators vary depending on the region [2–6]. After all, development of caries is influenced by various factors, including climatic and geographical conditions. We conducted epidemiological studies in 13 schools of different districts of Chernivtsi region. This nosology is diagnosed in 84.89% of 12-year-old children. We noted that the frequency of carious lesions in children changed not only with age, but also depending on the location. The need to develop and carry out regionally adapted preventive measures in order to increase the resistance of enamel leads to the need to study the characteristics of the state of the hard tissues of teeth in children of different age groups, compare the dynamics and determine the factors that contribute to the development of caries.

The aim of the study was to characterize the condition of the hard tissues of the teeth in 12-year-old children living in different districts of Bukovyna.

Materials and Methods

To achieve the goal of the study, we examined 298 children aged 12 in 13 schools in the Bukovyna region. The following groups were selected:

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1 – 78 children in Vyzhnytsia, 2 – 74 children in Chernivtsi, and 3 – 146 children in Dnister districts. The prevalence, intensity of caries of temporary teeth, level of intensity, index of the International Caries Detection and Assessment System – The International Caries Detection and Assessment System (ICDAS1-6) in different regions of Bukovyna were analyzed. The prevalence of caries was estimated by the number of children affected by caries, as a percentage of the total number of examined. The interpretation of the results was carried out according to the WHO nomenclature, where the value from 0% to 30% is considered as low prevalence, from 31% to 80 % – medium, from 81% to 100% – high prevalence of dental caries. The intensity of caries of permanent teeth was assessed in each child according to the "DMF" index, where "D" is a tooth affected by caries, "F" is a sealed tooth, and "M" is a tooth removed due to caries complications. For this age group, WHO (WHO EURO, 1999) recommends evaluating the level of "DMF" according to the following criteria: (0–0.50) – very low; (0.51–1.50) – low; (1.51–3.00) – average; (3.01–6.50) is high and (6.51–10.00) is very high. Dental caries was assessed according to the International Caries Definition and Assessment System – ICDAS. The ICDAS II (1–6) criteria were used to compare caries incidence rates [4; 7].

The degree of probability of the obtained results was statistically evaluated in the case of normality of the distribution of both samples using the Student-Fisher test, in other cases – the U-Wilkson test for independent samples and the T-Wilkson test for dependent samples.

Results and Discussion

The largest number of caries lesions of permanent teeth (88.46%) is in Vyzhnytsia district, the least (84.50%) – in Dnister (*Fig.*).

We noted an increase in the values of the structural elements of the intensity index in children with age, namely the "D" component in 12-year-olds increased to (1.96±0.39) and the "F" component to (1.05±0.37) (*Table 1*). The ratio between these indicators remains the same as in the previous age period – the predominance of the number of carious teeth over filled ones. However, their share varies depending on the region: 53.98% of carious teeth and 44.24% filled teeth in Vyzhnyt–sia district, respectively 74.31% and 25.35% in Dnister and 66.55% and 32.06% in Chernivtsi districts.

As for component "D", on average, in children of this age, its value is (1.93±0.30) of cariously affected teeth. Among them, the largest number (3.00±0.46), $p<0.05$ – in boys from the Dnistrovsky district, the smallest (1.30±0.30) – in girls from the same region. The number of fillings was the highest among residents of Vyzhnytsia district (1.72±0.32), particularly among boys from this region; the lowest (0.54±0.16) among boys of the Dnistrovsky district.

A demonstrative indicator of the quality of dental care for children is component "M" in the DMF formula. As you know, according to the WHO recommendations, children and adolescents under the age of 18 should not have their permanent teeth removed. In our study, the average number of extracted teeth in examined 12-year-old children was 0.03±0.03. The most of them are in the residents of Vyzhnytsky district (0.06±0.02), $p<0.05$, the smallest (0.01±0.01), $p<0.05$ – in Dniestr. In the share of the DMF index, extracted teeth in Vyzhnytsia district accounted for 1.76%, in Dnister – 0.34%, and in Chernivtsi – 1.03%.

In Chernivtsi and Dnister districts, the level of caries intensity is average, and in Vyzhnytsia it is high. The structure of caries incidence indicates

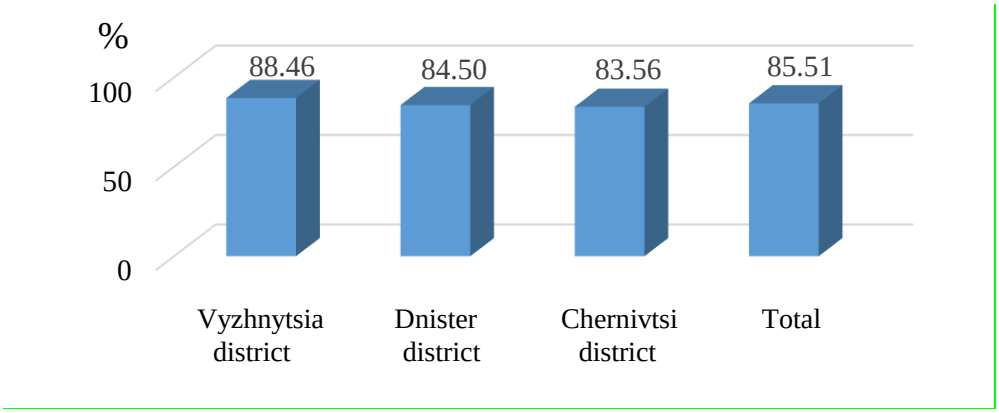

Fig. Prevalence of caries of permanent teeth in children aged 12, depending on the area of residence

Table 1. The structure of caries intensity of permanent teeth in 12-year-old children

District / indicator		DMF	D	M	F
Vyzhnytsia	boys (n=29)	3.75±0.41	1.93±0.30	1.72±0.32	0.10±0.05
	girls (n=49)	2.93±0.23	1.77±0.24	1.36±0.20	0.04±0.02
	total (n=78)	3.39±0.21	1.83±0.19	1.50±0.17	0.06±0.02
Dnister	boys (n=38)	3.57±0.48	3.00±0.46***	0.54±0.16	0.02±0.02***
	girls (n=36)	2.22±0.28**	1.30±0.30	0.91±0.17	–
	total (n=74)	2.88±0.28*	2.14±0.29	0.73±0.12	0.01±0.01*
Chernivtsi	boys (n=60)	2.50±0.28***	1.56±0.25	0.88±0.17	0.05±0.03
	girls (n=86)	3.18±0.23	2.18±0.20	0.97±0.14	0.02±0.01
	total (n=146)	2.90±0.18	1.93±0.15	0.93±0.11	0.03±0.01

Notes. *** – the difference between the boys' indicators is significant ($p<0.05$); ** – the difference between the indicators of girls, probable ($p<0.05$); * – the difference between the total indicators of girls and boys is significant ($p<0.05$).

that the share of children with a low level of intensity is the lowest and ranges from 10.25% in Vyzhnytsia district to 19.86% in Chernivtsi. The average level was characterized by a slight difference between the indicators in the regions from 39.04% to 40.54%. The largest number of children with a high level of intensity was observed in Vyzhnytsia district (38.46%), in other regions it is less: 24.32% in Dnister and 26.02% in Chernivtsi. 72.73% of all cavities are located on the first molars. Then on second molars (7.72% of cases), second premolars (5.62%), central incisors (5.51%), first premolars (4.21%) and lateral incisors (3.86%). The rarest carious lesions were diagnosed on canines (0.35%).

Caries on the lower jaw was diagnosed more often (in 55.38% of cases) (*Table 2*). The structure of the affected teeth was dominated by the first molars: lower – in 43.32% of children and upper – in 29.15%. Caries of hard tissues was detected in upper first premolars and lower second molars with the same frequency (16.39% each).

Regarding the rest of the teeth: lateral incisors, lower premolars, upper and lower second molars, even canines were cariously affected and their share was low, less than 5%. In the presence of chronic foci of carious infection of teeth, newly erupted premolars, second molars are subject to faster damage due to weakly mineralized and immature enamel.

For children of this age, as well as for 6-year-olds, a combined lesion of several groups of teeth is characteristic. The general trends in the structure of damaged teeth were preserved depending on the region of residence.

Half of all carious cavities (52.88%) were diagnosed on the chewing surface of molars and premolars, a quarter – on the contact surfaces of all groups of teeth: 16.08% – on the medial and 9.51% – on the distal. Further, lesions were detected in 14.49% of cases on the vestibular surface, mostly incisors, and in 7.02% – on the oral surface of lateral incisors (blind pits were affected). It is worth noting that in children of this age we observed damage to two or three surfaces within one tooth. Such cases were less than 10% and were observed mainly in the inhabitants of the mountainous region.

In general, trends in the location of cavities were maintained, and differences were still found in different regions of the region. In particular, in the Vyzhnytsia district, 65.39% of cavities were located on chewing surfaces, a fifth – on contact surfaces, the rest less than 10% each: vestibular (8.35%) and oral (4.94%). In the Dniester region, a third (34.07%) is fissural caries, almost the same

Table 2. Structure of the location of carious cavities on different surfaces of permanent teeth in 12-year-old children

Surfaces	Vyzhnytsia district (n=78)		Dnister district (n=74)		Chernivtsi district (n=146)		Total	
	abs.	%	abs.	%	abs.	%	abs.	%
medial	27	10.26	34	18.99	81	18.36	142	16.08
distal	29	11.02	26	14.52	29	6.57	84	9.51
vestibular	22	8.36	44	24.58	62	14.05	128	14.49
oral	13	4.94	14	7.82	35	7.93	62	7.02
occlusal	172	65.39	61	34.07	234	53.06	467	52.88

share is caries of contact surfaces (33.51%), a quarter (24.58%) is the vestibular surface, and less than 10% is the oral surface. In children of the Chernivtsi region, the location of the cavities corresponded to the average values of this age period.

We obtained slight differences in the localization of cavities between regions, but we associate such results with the rapid damage of immature enamel in newly erupted teeth and the lack of timely treatment and prevention measures.

In 12-year-old children, 53.56% of carious cavities in permanent teeth were located on the enamel surface (code 1–2), 26.95% – in the thickness of the enamel (code 3), 19.47% – within the mantle layer (code 4–5) and pulpal dentin (code 6) (*Table 3*).

Table 3. Analysis of carious lesions of temporary teeth in 12-year-old children according to the ICDAS II 1–6 index

Code	Vyzhnytsia district (n=78)		Dnister district (n=74)		Chernivtsi district (n=146)		Total	
	abs.	%	abs.	%	abs.	%	abs.	%
1–2	119	45.24	116	64.80	238	53.96	473	53.56
3	69	26.23	32	17.87	137	31.06	238	26.95
4–5	37	14.06	17	9.49	24	5.44	78	8.83
6	38	14.44	14	7.82	42	9.52	94	10.64

45.24% of children living in the Vyzhnytsia district were diagnosed with initial caries (code 1–2), 26.23% with superficial caries (code 3), and 14.06% with medium caries (4–5). In 14.44%, a deep dentin lesion was detected (code 6).

As for the Dnister district, two thirds of children have enamel damage (codes 1–3): in 64.80% – the stage of the stain and in 17.87% – a defect in the thickness of the enamel. And only in 14.96% of the examined, the medium-deep layers of dentin were affected (codes 4–6).

For children of Chernivtsi district, the results are the same as in the previous region and correspond to the average values.

Conclusions

Therefore, the analysis of the results of the examination of children made it possible to reveal a high level of prevalence and intensity of dental caries according to the WHO criteria and an insufficient level of providing dental care to children under 12 years of age. The obtained data indicate that children of this age need timely and high-quality treatment and preventive measures, and actually measures with a predominance of prevention should be carried out for children of the previous age period, since the incidence increased by 52.56% in Vyzhnytsia, 77.51% in Dnister and 71.31% in Chernivtsi districts.

DECLARATIONS:

Disclosure Statement

The author has 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 author has no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the author.

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CORRELATIONS BETWEEN CLINICAL, LABORATORY AND INSTRUMENTAL CHARACTERISTICS OF PATIENTS WITH COVID-19 INFECTION

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ABSTRACT

Background. COVID-19 is a leading disease in terms of prevalence (more than 100 million cases) and mortality (more than 10.0%). Most often, COVID-19 is accompanied by hemostatic disorders (manifestations of COVID-19-associated coagulopathy) and blood coagulation.

Aim. To determine the levels of correlation between clinical and laboratory characteristics of hemostatic and coagulation disorders (according to the characteristics of ThromboElastoGraphy, TEG) in patients with COVID-19 infection.

Materials and Methods. The study was performed at the Department of Infectious and Pediatric Infectious Diseases, Parasitology, Phthisiology and Pulmonology of Kharkiv National Medical University in accordance with the existing recommendations of bioethical norms and rules. All patients signed an informed consent. 179 patients with COVID-19 were examined. The levels of correlation between laboratory and instrumental characteristics were determined using Spearman's rank correlation coefficient. The probability of differences was determined using the Mann-Whitney U-test.

Results & Conclusions. According to the results of the study, significant direct and inverse correlations were found. The identified correlations determined the possible interaction between TEG parameters and the characteristics of the systemic inflammatory response. The obtained results play a significant role for patients with COVID-19, because they can predict shifts in inflammatory systemic response parameters, which characterize the severity of the disease, based on the characteristics of TEG. The interrelationships of hemostatic and coagulation system disorders have been reliably determined by the presence of significant correlations between the characteristics of the inflammatory systemic response of patients with COVID-19 and TEG values. The obtained significant correlations were mostly weak, but there were also interdependencies of medium strength. In particular, Interleukin-6 and some other indicators on days 5–6 after hospitalization.

Keywords: *thromboelastography, TEG, coagulation system disorders.*

Introduction

Since the end of 2019, COVID-19 has become a major threat in a relatively short period of time, taking a leading position in terms of prevalence and mortality [1–10]. Scientists estimate the mortality rate from COVID-19 to be more than 10.0% [4]. Severe acute respiratory syndrome caused by coronavirus type 2 has infected more than 100 million people and caused the death of more than 2.5 million infected patients.

Among the significant variety of clinical symptoms, an extremely high level of hemocoagulation disorders and thromboembolic complications is particularly noteworthy. Based on the clinical and laboratory characteristics of hemostatic disorders (increased fibrinogen levels, mild or moderate thrombocytopenia, and significant increase in D-Dimer levels), they were identified as a separate type – COVID-19 associated coagulopathy [11].

Hypercoagulability in patients with COVID-19 has been widely confirmed, which is detected in at least 20% of infected patients [12], according to other reports, the rate reaches 55% [13]. Activation of the body's inflammatory reactions signi-

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ficantly increases the production of proinflammatory cytokines that stimulate coagulopathic changes [1; 13]. A significant proportion of patients with COVID-19 have coagulation disorders that can develop into disseminated intravascular coagulation or thrombotic microangiopathies [2]. Ahmed S. et al. [7] emphasize the high incidence of thrombosis, both arterial (myocardial infarction, stroke, etc.) and venous (pulmonary embolism, deep vein thrombosis, etc.). In moderate-to-severe COVID-19, coagulopathies are detected in almost all patients, which is a significant factor in in mortality [12]. At the same time, a sharp impact on the body's coagulation homeostasis is a trigger for the development of coagulopathy of exhaustion [1].

In addition, the development of sepsis-induced coagulopathy and disseminated intravascular coagulation has been identified in patients with COVID-19 [1]. These pathological conditions are the result of a complex interaction of cytokine storm and coagulopathy [7]. Changes in the coagulation system in patients with COVID-19 are described as COVID-19-associated coagulopathy [11], which has significant mortality rates [2], although the SARS-CoV-2 virus does not have a procoagulant effect on its own [1]. It is believed that changes in the coagulation system are due to an intense inflammatory response in these patients [1].

In recent years, ThromboElastoGraphy (TEG) has been used quite successfully to determine the existing disorders of the blood coagulation system, which determines the viscoelastic properties of the thrombus and identifies the degree and severity of such disorders [14].

Thus, given the high prevalence of coagulation disorders in patients with COVID-19 with the development of severe COVID-19-associated coagulopathies, determining the correlation levels of interdependencies between clinical and laboratory characteristics of hemostatic disorders and TEG parameters is of clinical relevance.

The aim of the study was to determine the levels of correlation between clinical and laboratory characteristics of hemostatic disorders and thromboelastographic parameters in patients with coronavirus infection.

Materials and Methods

The study was conducted at the Department of Infectious and Pediatric Infectious Diseases, Parasitology, Phthisiology and Pulmonology of Kharkiv National Medical University and at the Municipal Non-Profit Enterprise "Kharkiv Regional Infectious Diseases Hospital" of Kharkiv Regional Council in 2020–2024.

179 patients (96 men (53.63%) and 83 women (46.37%)) with COVID-19 aged 20–88 years (average age [58.75±13.82] years) were examined. The study was conducted in accordance with current international and national recommendations on bioethical norms and rules for research involving human subjects. All patients signed an informed consent.

COVID-19 was diagnosed using Enzyme-Linked ImmunoSorbent Assay (ELISA) and Polymerase Chain Reaction (PCR) in accordance with existing international and national recommendations. In addition to ELISA and PCR, all patients were examined using:

- biochemical blood tests (determination of interleukin-6 (IL-6), D-dimers, ProCalciTonin (PCT) and C-Reactive Protein (CRP) by conventional methods);

- TEG results (determination of the levels of Maximum Rate of Thrombus Formation (MRTG), Time to reach the Maximum Rate of Thrombus Generation (TMRTG), total Thrombus Generation (TG), Maximum Rate of Lysis (MRL), Time to Maximal Lysis Rate (TMRL), total Lysis (L36), Reaction time (R), clot formation time (K), a-Angle, Maximum Amplitude (MA), maximum amplitude time (PMA), maximum clot elasticity (G), clot density immediately (A) and After 30 (A30) min and After 60 (A60) min, Coagulation Index (CI), degree of amplitude reduction after 30 min (LY30) and 60 min (LY60), estimated value of LY30 (EPL), degree of area reduction after 30 (CL30) min and 60 (CL60) min time of A decrease by 2 mm (CLT), clot formation rate (TPI), maximum A (TMA), maximum Elasticity (E), time of formation of the first fibrin filaments (SP) and calculated CLT after 30 seconds (LTE)).

Statistical calculations of the results were performed using IBM SPSS 25.0 for Windows (USA). The levels of correlation were determined using Spearman's rank correlation coefficient (ρ). If it was in the range from 0 to -1.0, the correlation was considered inverse; if it was from 0 to 1.0, it was considered direct. Value ρ from 0 to 0.3 (from 0 to -0.3) was considered as a weak connection between the studied features; from 0.4 to 0.7 (from -0.4 to -0.7) – as moderate; and from 0.7 to 1.0 (from -0.7 to -1.0) – as high strength. The result was presented in the form of a ρ coefficient and the corresponding level of confidence p.

The probability of differences in the obtained features was determined using the Mann-Whitney

U-test. The threshold value of the statistical significance of the calculated traits was taken as 0.05 (p=0.05).

Results and Discussion

According to the correlation analysis of TEG indicators and characteristics of the inflammatory systemic response of the examined patients with COVID-19 infection (IL-6, quantitative values of D-Dimer, PCT, CRP), we identified significant correlations (both direct and inverse), which indicated the possibility of interdependencies between them (*Table*).

Table. Correlation matrix of IL-6, D-Dimer, CRP, PCT and TEG parameters of patients with acute respiratory failure obtained at hospitalization and on day 5–7 (5–6)

Indices		IL-6 (hospitalization), pg/ml	IL-6 (5–7 days) pg/ml	D-Dimer (hospitalization), FEU, ng/ml	D-Dimer (5–6 days), FEU, ng/ml	CRP (hospitalization), mg/l	CRP (5–6 days), mg/l	PCT (hospitalization), ng/ml	PCT (5–7 days), ng/ml
1		2	3	4	5	6	7	8	9
MRTG, mm/min	ρ	0.042	0.120	0.062	0.025	0.118	0.119	-0.054	-0.033
	p	0.573	0.110	0.413	0.744	0.117	0.112	0.469	0.665
TMRTG, min	ρ	-0.162*	-0.175**	-0.181**	-0.232**	-0.343***	-0.312**	-0.012	-0.039
	p	0.030	0.019	0.016	0.002	0.000	0.000	0.872	0.605
TG, mm/min	ρ	0.100	0.173*	-0.116	-0.185**	-0.130	-0.015	-0.092	-0.036
	p	0.184	0.021	0.123	0.013	0.084	0.843	0.220	0.634
MRL, mm/min	ρ	-0.085	-0.129	-0.012	0.011	0.096	0.030	0.058	0.126
	p	0.259	0.084	0.868	0.880	0.201	0.692	0.439	0.093
TMRL, min	ρ	-0.044	-0.034	-0.242***	-0.291***	-0.307***	-0.231**	-0.115	-0.180**
	p	0.562	0.651	0.001	0.000	0.000	0.002	0.125	0.016
L36, mm/min	ρ	-0.020	-0.132	0.045	0.100	0.134	0.031	0.055	0.068
	p	0.788	0.079	0.547	0.183	0.074	0.677	0.465	0.363
R, min	ρ	-0.030	-0.074	-0.190**	-0.312***	-0.258***	-0.177**	-0.029	-0.102
	p	0.689	0.327	0.011	0.000	0.000	0.017	0.696	0.175
K, min	ρ	-0.049	-0.106	-0.023	0.062	-0.157*	-0.190**	-0.024	-0.059
	p	0.517	0.160	0.765	0.409	0.036	0.011	0.751	0.433
A-Angle, °	ρ	0.117	0.156*	-0.001	-0.067	0.155*	0.191**	-0.044	0.071
	p	0.120	0.038	0.985	0.369	0.038	0.011	0.556	0.347
MA, min	ρ	-0.001	0.125	-0.191**	-0.184**	-0.065	-0.053	-0.083	-0.088
	p	0.985	0.095	0.010	0.014	0.385	0.483	0.267	0.241
PMA	ρ	-0.192**	-0.159*	0.161*	0.152*	-0.043	0.015	0.054	0.109
	p	0.010	0.033	0.031	0.042	0.565	0.844	0.473	0.146
G, d/sc	ρ	0.057	0.139	-0.226**	-0.239***	-0.083	0.030	-0.052	-0.080
	p	0.447	0.063	0.002	0.001	0.268	0.687	0.493	0.286
EPL, %	ρ	-0.190**	-0.269***	0.207**	0.268***	0.177**	0.116	0.067	0.130
	p	0.011	0.000	0.005	0.000	0.018	0.122	0.374	0.083
A, mm	ρ	0.157*	0.308***	-0.147*	-0.164*	-0.164*	0.007	-0.105	-0.122
	p	0.035	0.000	0.049	0.028	0.028	0.931	0.164	0.103
CI	ρ	0.013	0.128	-0.108	-0.099	-0.056	0.042	-0.019	0.017
	p	0.867	0.089	0.152	0.187	0.456	0.581	0.799	0.823
LY30, %	ρ	-0.134	-0.239***	0.106	0.150*	0.145	-0.011	0.053	0.038
	p	0.075	0.001	0.159	0.045	0.053	0.880	0.485	0.614
A30, mm	ρ	0.031	0.176**	-0.218**	-0.197**	-0.200**	-0.121	-0.112	-0.101
	p	0.678	0.018	0.003	0.008	0.007	0.107	0.136	0.179

Continuation of Table

1		2	3	4	5	6	7	8	9
CL30, %	ρ	0.118	0.189**	-0.193**	-0.191**	-0.167*	-0.054	-0.133	-0.069
	p	0.115	0.011	0.009	0.010	0.025	0.476	0.077	0.356
A60, mm	ρ	0.050	0.099	-0.111	-0.110	0.008	-0.089	0.018	0.026
	p	0.504	0.187	0.140	0.143	0.914	0.235	0.812	0.727
CL60, %	ρ	0.058	0.105	-0.219**	-0.211**	-0.153*	-0.155*	-0.070	-0.067
	p	0.444	0.160	0.003	0.005	0.041	0.038	0.355	0.376
LY60, %	ρ	-0.128	-0.152*	-0.040	-0.029	0.057	-0.008	-0.037	-0.149*
	p	0.087	0.042	0.600	0.703	0.449	0.914	0.626	0.046
CLT, min	ρ	0.014	-0.064	-0.284***	-0.197**	-0.148*	-0.118	-0.165*	-0.171*
	p	0.850	0.395	0.000	0.008	0.048	0.116	0.027	0.022
TPI, sec	ρ	0.093	0.205**	-0.007	-0.047	-0.002	0.187**	-0.023	0.079
	p	0.215	0.006	0.928	0.530	0.977	0.012	0.757	0.291
TMA, min	ρ	0.071	0.094	-0.198**	-0.125	-0.182**	-0.114	-0.069	-0.120
	p	0.345	0.211	0.008	0.097	0.015	0.128	0.361	0.108
E, d/sc	ρ	0.026	0.167*	0.062	0.030	0.098	0.136	0.017	0.030
	p	0.727	0.025	0.413	0.687	0.191	0.069	0.820	0.687
SP, min	ρ	-0.067	-0.048	-0.126	-0.215**	-0.230**	-0.126	-0.099	-0.104
	p	0.374	0.522	0.092	0.004	0.002	0.094	0.189	0.165
LTE, min	ρ	0.125	0.087	-0.065	0.000	-0.101	-0.021	-0.102	-0.232**
	p	0.095	0.248	0.387	0.996	0.177	0.779	0.175	0.002

Notes: probability of differences * – p≤0.05; ** – p≤0.01; *** – p≤0.001; L36 – total Lysis; R – Reaction time; K – clot formation time; PMA – maximum amplitude time; G – maximum clot elasticity; A – clot density immediately; A30 – clot density After 30 min; A60 – clot density After 60 min; LY30 – degree of amplitude reduction after 30 min; LY60 – degree of amplitude reduction after 60 min; EPL – estimated value of LY30; CL30 – degree of area reduction after 30 min; CL60 – degree of area reduction after 60 min; CLT – time of A decrease by 2 mm; TPI – clot formation rate; TMA – maximum A; E – maximum Elasticity; SP – time of formation of the first fibrin filaments; LTE – calculated CLT after 30 seconds.

In the analysis of correlation relationships, direct and inverse significant correlations were identified, which determined the possible interaction between TEG parameters and characteristics of the inflammatory systemic response. The identified interdependencies play a significant role for patients with COVID-19, as they can predict shifts in inflammatory systemic response parameters (IL-6, D-dimers, CRP), which characterize the severity of the disease, based on the characteristics of TEG. So, there were significant direct correlations between IL-6 levels (obtained during hospitalization) and TEG values, which indicated a possible increase in IL-6 with an increase in A values (ρ=0.157; p=0.035) and the opposite (a decrease in IL-6 levels was noted) with an increase in TMRTG (ρ=-0.162; p=0.030), PMA (ρ=-0.192; p=0.010) and EPL (ρ=-0.190; p=0.011). It should be noted that the correlations obtained in all cases were of a weak nature.

When determining the correlation relationships between the IL-6 values of patients with COVID-19 infection obtained on days 5–7 after hospitalization, a greater number of existing significant relationships were noted. Thus, there were direct interdependencies of weak strength, indicating the possibility of increasing the quantitative levels of IL-6 with an increase in TG (ρ=0,173, p=0.021), A-Angle (ρ=0.156, p=0.038), A (ρ==0.308, p=0.000), A30 (ρ=0.176, p=0.018), CL30 (ρ=0.189, p=0.011), TPI (ρ=0.205, p=0.006) and E (ρ=0.167, p=0.025). In turn, inverse weak correlations were also identified, which stated a possible increase in IL-6 in patients with COVID-19 infection with an increase in the following TEG values: TMRTG (ρ=-0.175, p=0.019), PMA (ρ==-0.159, p=0.033), EPL (ρ=-0.269, p=0.000) and LY30 (ρ=-0.239, p=0.001) and LY60 (ρ=-0.152, p=0.042).

Correlations were determined for D-Dimer of patients with COVID-19 obtained during hospitalization and on day 5–6. Thus, we found probable weak correlation effects that determined possible increases in the levels of D-Dimers obtained during hospitalization: direct, with an increase in the values of PMA (ρ=0.161, p=0.031) and EPL (ρ=

=0.207, p=0.005), and inverse - with a decrease in the values of A (ρ=-0.147, p=0.049), A30 (ρ=-0.218, p=0.003), CL30 (ρ=-0,193, p=0.009), CL60 (ρ=-0.219, p=0.003), CLT (ρ=-0.284, p==0.000), TMA (ρ=-0.198, p=0.008), TMRTG (ρ==-0.181, p=0.016), TMRL (ρ=-0.242, p=0.001), R (ρ=-0.190, p=0.011) and MA (ρ=-0.191, p==0.010) and G (ρ=-0.226, p=0.002).

In addition, we found significant correlations for the quantitative levels of D-dimers in patients with COVID-19 obtained on days 5–6 after hospitalization. We identified the available direct probable weak correlations, which indicated a reliable possibility of increasing the levels of D-Dimers with an increase in PMA (ρ=0.152, p=0.042), EPL (ρ=0.268, p=0.000) and LY30 (ρ=0.150, p=0.045) and vice versa, that determined the increase of D-dimers with a decrease in the values of TMRTG (ρ=-0.232, p=0.002), TG (ρ=-0.185, p=0.013), TMRL (ρ=-0.291, p=0.000), R (medium strength, ρ=-0.312, p=0,000), MA (ρ=-0.184, p=0.014), G (ρ=-0.239, p=0.001), A (ρ=-0.164, p=0.028), A30 (ρ=-0.197, p=0.008), CL30 (ρ=-0.191, p=0.010), CL60 (ρ=-0.211, p=0.005) and CLT (ρ=-0.197, p=0.008) and SP (ρ=-0.215, p=0.004).

It should be noted that the correlation relationships for CRP and TEG in patients with COVID-19 showed a similar trend. Thus, CRP values obtained during hospitalization showed significant direct weak correlations, which indicated a possible increase in its levels with an increase in A-Angle (ρ=0.155, p=0.038) and EPL (ρ=0.177, p=0.018). At the same time, inverse (mostly weak) interdependencies were also identified, which determined the possibility of increasing CRP levels with a decrease in TMRTG (medium strength, ρ==-0.343, p=0.000), TMRL (medium strength, ρ==-0.307, p=0.000), R (ρ=-0.258, p=0.000), K (ρ==-0.157, p=0.036), A (ρ=-0.164, p=0.028), A30 levels (ρ=-0.200, p=0.007), CL30 (ρ=-0.167, p=0.025), CL60 (ρ=-0.153, p=0.041), CLT (ρ==-0.148, p=0.048) and TMA (ρ=-0.182, p=0.015) and SP (ρ=-0.230, p=0.002).

For the CRP values of patients with COVID-19 infection obtained on day 5-6 after hospitalization, we determined mainly unreliable correlations of low strength. Thus, there were significant direct, mostly weak interdependencies that determined the possibility of increasing CRP levels with an increase in A-Angle (ρ=0.191, p=0.011) and TPI (ρ=0.187, p=0.012) and inverse, indicating a possible increase in CRP in patients with COVID-19 with a decrease in TMRTG values (medium strength, ρ=-0.312, p=0.000), TMRL (ρ=-0.231, p=0.002), R (ρ=-0.177, p=0.017) and K (ρ=-0.190, p=0.011) and CL60 (ρ=-0.155, p==0.038).

A similar trend was identified in relation to the correlations between PCT parameters of patients with COVID-19 obtained on days 5–7 after hospitalization and TEG characteristics. Thus, the presence of probable weak inverse correlations was noted only for TMRL (ρ=-0.180, p=0.016), LY60 (ρ=-0.149, p=0.046), CLT (ρ=-0.171, p=0.022) and LTE (ρ=-0.232, p=0.002), which determined possible increases in quantitative PCT levels with a decrease in these TEG values.

Our conclusions regarding the relationship between clinical and laboratory characteristics of hemostatic disorders (manifestations of COVID-19-associated coagulopathy) and coagulation disorders (determined by TEG) are fully consistent with other global studies. Thus, the meta-analysis conducted by Coomes E.A. et al [15] identified significant positive correlations between IL-6 levels and bilateral lung damage and maximum body temperature: ρ=0.45 (p=0.001) and ρ=0.52 (p==0.001), respectively. They determined that increased dysregulation of the immune response to an antigen is a leading element in the development of target organ damage and subsequent mortality [15]. An increase in the cytokine response in patients with COVID-19 and acute respiratory distress syndrome, accompanied by a significant predominance of IL-6, is an integral part of the pathogenesis and dysregulation of the immune response [15].

Other studies have shown that along with diffuse alveolar lesions, patients with COVID-19 are diagnosed with fibrin thrombi [3]. Studies have shown a 9-fold higher incidence of alveolar-capillary microthrombosis in patients with COVID-19 compared to patients with influenza [6]. At the same time, fibrin-rich microthrombosis of the small pulmonary vasculature is detected in almost 80–100% of cases [6]. In addition to elevated levels of D-dimers, they may have skin manifestations on the extremities as a clinical sign of microvascular thrombosis [3]. Thus, plasma levels of D-Dimers are considered as a direct prognostic marker of COVID-19: the levels of this fibrin degradation product are significantly increased in patients with severe COVID-19 [6; 13].

Conclusions

Based on the study, the interrelationships of hemostatic and coagulation disorders were reliably determined by the presence of significant correlations (mostly of low strength) between the

characteristics of the inflammatory systemic response of patients with COVID-19 and thromboelastographic values.

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

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THE PREVENTIVE DIRECTION OF MODERN THEORIES OF HEALTH AND HEALTH-SAVING IN PUBLIC HEALTH AND EDUCATION

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ABSTRACT

Background. The modern understanding of health is related to the need to prevent diseases caused by infections, lifestyle, environmental and genetic factors. Ukrainian legislation guarantees health care, but the practice of implementing laws is imperfect. The teaching of valeological disciplines in educational institutions is of great importance for the prevention of diseases. But the content of these disciplines requires constant revision from the point of view of evidence-based medicine, and the creation of new preventive programs requires theoretical justification.

Aim. To determine the content and practical significance of the modern understanding of health care in public health care and education.

Materials and Methods. Methods of bibliosemantic and system analysis were used.

Results. The theory of health and health-saving is considered using cross-cultural, discursive, norm-centric, phenomenological, holistic, axiological and integral approaches, from the perspective of evidence-based and "4P" medicine. Health-saving is shown as derived from a healthy lifestyle and valeological competence formed in the population. The best environment for the formation of a healthy lifestyle is shown to be an educational environment, the tools of formation are valeological disciplines and education of medical and social non-government organizations. The need for joint efforts of the population and medical workers to achieve better results in the prevention of socially significant diseases is determined.

Conclusions. Improvement of the preventive direction of valeological education is closely related to the competence approach, in particular, with the formation of valeological competence. The public health system should use the potential of educational valeological programs to form a healthy lifestyle in new generations during their studies at higher education institutions. For the formation of high-quality valeological programs, a permanent partnership of educators and medical professionals is necessary.

Keywords: *valeological competence, evidence-based medicine, 4P medicine, Health Pedagogy.*

Introduction

The need for health-saving is generally recognized by Ukrainian society and the state. Health care is guaranteed by the Constitution, regulated by the law of Ukraine "Fundamentals of the Legislation of Ukraine on Health Care" [1], provided by targeted national and regional programs in health care and social protection fields. The state guarantees regarding health care relate primarily to sanitary and epidemiological well-being, organization of conditions for diagnosis, treatment and prevention of diseases based on modern scientific methods [2, Art. 3, 27, 49, 50], however, the preventive direction of health-saving in Ukraine is implemented to a large extent due to the teaching of valeological disciplines in educational institutions and medical (sanitary) training.

Health is a personal and social value [3]. Its preservation and restoration depend on 50% of a person's lifestyle, 20% on the influence of environmental factors, 20% on heredity, and another 10% on the state of the health care system [4]. Thus, prevention of diseases has a greater impact on health care than their treatment.

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An important component of health is well-being, which the WHO appeals to in its definition of health [5]. To some extent, this well-being is characterized by satisfaction with one's own life, social adaptability and resistance to psychosocial stress, which is the basis for a wide professional discussion about mental adaptation and maladaptation. Psychological and sociocultural ideas about health are actually reduced to three models: ancient (which is based on internal consistency), adaptation (in which the individual is adapted to the natural and social environment), and anthropocentric (in which all-round self-realization and the disclosure of the creative potential of the individual are important) [6]. All of them describe numerous mechanisms of health preservation (for example, options for social and psychological adaptation to excessive stress), but do not take into account modern medical approaches (for example, evidence-based medicine [7]). But the preventive direction of medicine needs further theoretical investigation and scientific substantiation in order to improve its practical implementation.

The aim of the study is to determine the content and practical significance of the modern understanding of health-saving in public health and education.

Materials and Methods

The bibliosemantic method (using PubMed and Google Scholar materials) and the system analysis method (using the methodology of Golubkov E.P. [8]) were used for the investigation. The system analysis method involves a sequence in the research: setting the problem, conducting the research, analyzing the results, preliminary judgment, confirmation or refutation, final judgment, implementation of the decision. The feedback to determine success in achieving the aim, with opportunities to adjust conclusions and additional research also used.

Results and Discussion

In academic psychology, cross-cultural, discursive, norm-centric, phenomenological, holistic, axiological, and integral approaches are used to study health [9–11]. A cross-cultural approach allows us to identify national influences on perceptions of normal health. The discursive approach illuminates the logic of constructing ideas about health, considers different health systems and individual health practices. Within the holistic approach, natural and scientific principles of analysis are complemented by humanitarian ones. The axiological approach consists in treating health as a universal human value. In the practice of valeological education, a competency-based approach is used, the driving force of which is the transformation of knowledge into skills, and skills into active, motivated actions. The latter are the key to health. Among such actions, key positions are occupied by giving up bad habits, rational nutrition, sufficient physical activity, rational regime of work and rest, avoidance of injuries, environmental, radiological and toxicological risks, cooperation with the medical system (vaccination of infectious diseases, timely treatment of detected diseases, participation in screening examinations, for example, annual fluorography, etc.), psychohygiene (maintaining emotional balance), safe sex [12–16]. The population's understanding of these issues depends on the quality of valeological education, which takes into account the current trends in the development of health theory and focuses on its paradigms.

The transformation paradigm of modern medicine consists in the transition from a reactive model of health care work to a preventive one. This is the so-called "4P medicine" model (Predictive, Personalized, Preventive and Participatory medicine). "Participatory" means "involved in achieving a common result." Its practical implementation requires the participation of the patient himself [17]. The participation of the patient implies responsibility for maintaining one's own physical and mental health, and medicine performs only a service function [18]. Within the framework of the "4P medicine" model, effective prevention of diseases requires partnership between doctors and the population, commitment of citizens to a healthy lifestyle, readiness for valeological education and self-education. The formation of readiness for a healthy lifestyle should begin in childhood, but the conviction to practice only safe behavior patterns and to minimize all possible disease risk factors is finally formed at the age of 16–20 years [19–21], that is, at the age of the majority of higher education graduates in Ukraine.

Disease prevention in Ukraine is carried out at the international, national, regional, population, group and individual levels [22]. At the international level, events are held within the framework of world days of support for patients with various diseases, days of remembrance of those who died from various diseases, etc. At the national and regional levels, programs are being implemented to overcome various diseases (respectively), their consequences, promotion and organization of mass physical culture and sports, rational nutri-

tion, giving up chemical addictions, eliminating the consequences of environmental disasters, man-made disasters, etc. Mass media, medical workers, politicians, public figures, professional medical and social public organizations and doctors systematically engaged in sanitary education (for example, Dr. Komarovsky E.O. [23]) participate in prevention. We specify some mechanisms of preventive work.

According to a number of researchers [24–26], medical and social non-government organizations, unfortunately, cannot cover all students with preventive work, but with systematic work with individual student groups, they are able to form valeological competence at a high level. Educators are trying to transfer the content of their educational work to the educational programs of valeological disciplines ("Valeology", "Fundamentals of Life Safety", "Health Pedagogy", "Fundamentals of Medical Knowledge and Health-Saving", etc.) [27]. It is advisable to train students of higher non-medical education in these disciplines after studying the supporting disciplines "Human Biology", "Anatomy", "Physiology" and "Hygiene", as indicated by the authors of the training programs of the relevant disciplines [28; 29].

Personal communication between the doctor and patient is effective for individual disease prevention. But doctors usually communicate with citizens who have diseases, so they act within the scope of secondary and tertiary prevention of diseases, aimed at preventing their complications and relapses, at the transition of diseases into chronic stages. At the same time, the optimal environment for the systemic primary prevention of diseases and the formation of commitment to a healthy lifestyle is educational [30], which in turn should be safe for those seeking education. In order to create a healthy educational environment, special attention should be paid to the issues of physical safety of learning and stress reduction [31].

The State Service of Education Quality of Ukraine recommends that the organizers of the educational process in martial law conditions give preference to distance learning, and in classrooms to arrange the educational space more safely (remove open shelves, stands that may fall during shelling; remove things that will interfere with quick evacuation from premises), study evacuation routes, location of storage facilities, conduct evacuation drills, periodically repeat safety briefings and evacuation drills. It is necessary to monitor more carefully the signs of distress and professional burnout of participants in the educational process. Psychological trainings, support groups and individual consultations of psychologists, emotion management techniques (self-training) are forms of psychological assistance that allow students to overcome the stress of wartime. Teachers are recommended to pay more attention to conflict resolution; prevention of bullying; development of empathy and communication skills of participants in the educational process; setting up the collective of education seekers and teachers to provide greater support to forcibly displaced persons, persons with disabilities, persons who have survived the stress of war; to teach methods of rescuing victims and providing emergency first aid [32].

Given the greater risk of injury in wartime conditions, prompt and effective emergency care is both health-saving and life-saving. For training in emergency care in non-medical higher education institutions, it is advisable to involve practicing doctors and students of higher medical education in senior years. Especially those who study and work in practical health care at the same time [33]. It is worth noting that before graduation, a graduate of higher education medical institution is already sufficiently motivated to engage in prevention, understanding the advantages of prevention over the treatment of a disease that has already developed [34]. But the interaction of non-medical higher education institutions of Ukraine with the health care system for the construction of health care education is not systematic, it is based on volunteer models. The higher education system does not order educational services from representatives of the health care system. The main achievement of the episodic interaction is actions dedicated to a healthy lifestyle and prevention of certain diseases, which medical non-governments organizations conduct in higher education institutions, as well as individual attempts to create valeological disciplines with the participation of medical professionals.

Valeological disciplines for students of higher non-medical education also consider the health-saving educational process from the point of view of ensuring the physical safety of learning and reducing the level of stress of participants in the educational process [35]. Physical safety includes issues of ergonomics, microclimate and room lighting, safety of physical culture and sports as part of the educational process, safety of work in educational and production workshops, with electrical equipment, chemicals, etc. Stress is often seen as a manageable risk factor for the development of

hypertension, peptic ulcer disease, obesity, myocardial infarctions, cerebral strokes, and other diseases that can affect students. Diseases with controlled and conditionally controlled risk factors are the main objects of preventive interventions and sanitary education [36; 37]. Stress is caused by overload during education, high competitiveness in the educational environment, and conflicts between students [38].

Educational programs of higher education students of Ukraine and other countries of the world, according to a number of researchers [39; 40], were compiled without proper calculation of a rational academic load, which causes chronic stress, against the background of which the risk factors of diseases are more easily realized negatively, existing diseases are aggravated or go to the chronic stage.

Excessive requirements regarding the number of program competencies in the higher education standards contribute to the information overload of the students. The discussion about the need to reduce the number of such competencies has been going on for two decades. But, in our opinion, the list of competencies in the standards of higher non-medical education cannot be shortened at the expense of valeological competence [41]. However, the content of this competence should be separated from issues of spiritual development, which can be discussed within other disciplines. When studying valeological disciplines ("Health Pedagogy", "Fundamentals of Medical Knowledge and Health-Saving", etc.), it is important to discuss only certain issues of psychology, ecology, moral and ethical norms (when discussing abortions, contraception, euthanasia, rights and responsibilities of patients, relationships with doctors, other higher education students, family members, disabled people, respect for family, religious and cultural food traditions, etc.). But the transfer of emphasis from medical issues to moral, ethical and spiritual issues while simultaneously ignoring the issues of physiology, pathology, and the possibilities of prevention harms the formation of valeological competence and optimal understanding of the principles of a healthy lifestyle. The inclusion of pseudo-scientific data about the "undeniable benefit" of folk medicine methods into the program causes even more damage; naturopathy; homeopathy; the advantages of Eastern medicine over European medicine; refusing vaccinations not because of medical reasons, but because of personal convictions; home births; practices of "hungry", vegan diets; hardening methods, etc. [42–44].

The inclusion of some issues in the programs of valeological disciplines and the refusal to discuss others is the right of the authors of such disciplines, but it is advisable to check the formed programs for compliance with the recommendations of leading international organizations. For example, "Characteristics of an Effective Health Education Curriculum" of the USA Center for Disease Control and Prevention (CDC) [44]. According to the developers of these recommendations, an effective educational program should be aimed at achieving behavioral results, without overloading with scientific facts. In addition, according to the CDC's experts, it is necessary to practice health care skills in order to teach a healthy lifestyle; the formation of personal values and beliefs that support healthy behavior, which corresponds to our ideas about the components of valeological competence [12]. The best health-saving curricula go beyond the cognitive level and consider determinants of health, risk factors for diseases, social opinions, values, norms of behavior, customs that affect health, build educational strategies on theoretical approaches (for example, on the theory of social cognition by Berger P. & Lukman T. [45]), are aimed at a long-term result. Meanwhile, health care values should promote protective behavior and negative perception of risky behavior, reinforce positive beliefs of a healthy lifestyle based on the principle of feedback using critical thinking, and help confidently overcome social pressure. An effective curriculum should take into account the needs and interests of learners, levels of development and emotional maturity, experience, knowledge and skill levels, provide tools for everyday life, cover topics in a logical sequence; should not contain culturally biased information, but provide examples of various cultures, customs, traditions, ways of life, take into account cultural diversity, teach intercultural interaction; if possible, rely on the cultural resources of families and communities. An effective curriculum devotes sufficient time to both key health concepts and practical skills. Changing behavior requires systematic and long-term training, is based on previously learned concepts and skills, and takes into account age determinants. An effective curriculum connects learners with influencers promoting health and successful learning strategies.

This understanding of health-saving programs demonstrates a close connection with competencies, the list of which contains both scientific publications and some national education standards [46–48], according to which a healthy lifestyle is

associated with the absence of harmful habits, protective behavior, prevention of known health risks.

Conclusions

Our findings suggest that the improvement of the preventive direction of valeological education is closely connected with the competence approach, in particular, with the formation of valeological competence. The public health system should use the potential of educational valeological programs to form a healthy lifestyle in new generations during their studies at higher education institutions. For the formation of high-quality valeological programs, a permanent partnership of educators and medical professionals is necessary.

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

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RETROSPECTIVE ANALYSIS OF THE CONSTRUCTION OF THE NATIONAL SYSTEM OF HOSPICE AND PALLIATIVE CARE IN GREAT BRITAIN

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ABSTRACT

Today, Great Britain has one of the best hospice care systems for palliative patients in the world, which leads to interest in the path of building a Hospice and Palliative Care (HPC) system in this country. The hospice care system is mainly financed by the volunteer sector, which indicates a significant development of the state-society partnership in the organization of HPC. The national HPC system consists of inpatient care, day palliative care, care in the community and emergency hospitals. 2004–2008 is considered the key moment in the formation of the country's HPC system, which will be the focus of this study. For specialist palliative care, the National Health Service of Great Britain allocated almost £50 million a year in those days until 2004. At the same time, volunteer support was about 4 times greater. More than 220 volunteer support groups for palliative patients operated in the country. The success of building a national HPC system is described in the Palliative Care White Paper. A number of interrelated national programs may be used as a standard of palliative care in 20 years by many other countries. The development of the HPC system has influenced the British homes for the elderly, the system of primary care, the attitude to the HPC problem of doctors, local communities and society as a whole, increased the quality and availability of palliative care. Palliative care since those years has been provided 24/7, managed by coordination centers located outside medical facilities and hospices. High national HPC standards and mechanisms for monitoring their compliance have been created. Narcotic analgesia for palliative patients with chronic pain, the necessary medical, psychological, social and spiritual care is mostly available. The public debates the question of a dignified death without restrictions. The value for money of HPC is recognized by British society as acceptable. Therefore, studying the British experience of HPC organization as one of the "best practices" is useful for other countries with less developed HPC systems.

Keywords: *"best practices", place of death, palliative care quality standards*.

INTRODUCTION

Great Britain is one of the countries in which Hospice and Palliative Care (HPC) is organized at a high level, which allows us to consider the organization of this type of medical and social care in this country as one of the "best practices" and makes it a subject of study in the health care organization [1]. The main needs of palliative patients in Great Britain are the same as in other countries [2], but the approaches to their satisfaction have an original meaning and history.

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The country's hospice care system is mainly financed by the volunteer sector, which indicates a significant development of the state-society partnership in the organization of HPC. The national HPC system consists of inpatient care, day palliative care, community care and acute care hospitals. The period of 2004–2008 is considered the key moment in the formation of the country's HPC system, which will be the focus of this study. During this period of development of the HPC system, national programs were launched in the country, which changed approaches to the organization of this type of care, increased the coverage of palliative patients of various age groups, expanded the list of palliative diagnoses, influenced the attitude to palliative care of the government, communities and the whole society.

For specialist palliative care, the National Health Service (NHS) of Great Britain allocated

almost £50 million a year in those days until 2004. At the same time, volunteer support was about 4 times greater. More than 220 volunteer support groups for palliative patients operated in the country [3]. The success of the development of the national HPC system is described in the Documents of the Council of Europe and the "White Book of Palliative Care" (2003–2010) [4–6].

The purpose of the study was to determine the problems of building a national system of palliative and hospice care in Great Britain for 40 years (1964–2004) and ways to overcome them.

Materials and Methods

The bibliographic, historical and systematic analysis methods were used in the research.

Results and Discussion

Of the half a million people who died each year, nearly two-thirds were over 75. 99.0% of the dead were adults aged 18 and over. 58.0% of deaths occurred in NHS hospitals; 18.0% of these patients died at home; 17.0% – in homes for the elderly; 4.0% – in hospices; and 3.0% – elsewhere. The distribution of deaths by place of death depended on region, age, and primary palliative diagnosis. For example, hospital mortality ranged from 52.7% in the South West to 64.7% in London, and hospice mortality ranged from 2.5% in the North West to 5.9% in the South East. The highest home mortality occurred among young (15–44 years) and middle-aged (45–64 years), the highest mortality in hospitals – among children (under 14 years) and the elderly (75–84 years), the highest mortality in hospices – for middle-aged people (45–64 years old). Patients with palliative oncological and respiratory diagnoses mostly died in hospitals (up to 50.0% and 67.0% of the total number of deaths, respectively). At the same time, the main causes of death were chronic diseases of the heart and respiratory tract, cancer, stroke, neurological diseases and dementia. If we compare this picture with the situation in 1900, then the majority (85.0%) of people died at home, and the main causes of death were infections. In addition, many more deaths occurred in childhood.

In 1950, only about 50.0% of people died at home. At the beginning of the twenty-first century, hospitals became the most common place of death. Subsequently, the problem of death and dying began to be discussed more often and openly in public, which contributed to the development of the system of care for dying patients. The improvement of her work was aimed at creating conditions for dying with dignity, without pain, surrounded by loved ones, with the choice to be at home, in a hospital or in a nursing home. Care for the dying among other vulnerable categories has become an indicator of the development of the health care and social assistance system. Gradually, the difference in attitude towards those who were dying (their age, gender, ethnic origin, religious beliefs, disability, sexual orientation, diagnosis, socio-economic deprivation, etc.) decreased. "Voluntary hospices" emerged (e.g. St Christopher's Hospice, founded in 1967 by Cecil Saunders).

The UK NHS Palliative Care Program (2004–2007) was the impetus for the development of other programs, including the Gold Standards Framework (GSF) [7], the Liverpool Care Pathway for the Dying Patient (LCP) [8] and Preferred Priorities for Care (PPC) [9; 10], Delivering Choice programs [11], etc. The NHS Palliative Care Program (2004–2007) included identification of people nearing the end of life, assessment of their needs, patient care and support for carers in the last years/days of life and after death. According to the results of its assessment, partnerships between communities and local authorities (interaction with schools, religious groups, funeral homes, homes for the elderly, hospices, medical and social non-government organizations, employers), local Departments of Health with the National Council were improved on issues of palliative care. It was possible to draw society's attention to the problems of treatment at the end of life, to change the attitude towards death and dying in society.

The programs took into account the difference in the needs of palliative patients depending on the region of residence and diagnosis. A lot of attention was paid to the conclusion of contracts and monitoring of the provision of medical and social services, training of personnel (on the issue of identifying palliative patients, determining the scope of optimal care, communication skills with patients and their relatives, care, emergency assistance (temporary life saving)), coordination of resources, creation regional registers of people approaching the end of life. At that time, the Marie Curie Cancer Care Delivering Choice Program was considered a good example of a centralized coordination mechanism of efforts [12]. The program demonstrated options for end-of-life choice, rapid access to 24/7 care, including hospices, nursing homes, assisted living facilities.

The development of the GSF, PPC and LCP programs had a synergistic effect: the experience of working with patients of one profile often spread to other categories. For example, an impor-

tant result of the LCP program was the transfer of models developed initially for palliative cancer patients to palliative patients with other diseases. The principle of choosing the place of end of life, introduced by the programs, is an established practice of the UK health care system [13].

The development of educational programs for relatives of palliative patients took into account the fact that for many children, close friends and informal caregivers, preparing a relative for death was the first and quite traumatic experience in life. At the same time, the relatives of the palliative patient had not only to adapt to the situation themselves, but also to provide effective practical and emotional support to the dying person.

The education and continuous professional development of medical and social workers working with palliative patients included the provision of the necessary knowledge and skills in caring for seriously ill patients. Depending on the frequency of providing palliative care services to patients (on a permanent basis, often or occasionally), the "Skills for Care" and "Skills for Health" training programs of the Academy of Medical Royal Colleges [14] contained various competencies.

Numerical measurable indicators, necessary for ongoing monitoring of their implementation, were laid down in the programs. Some of these indicators were determined by self-assessment. Measurability has been useful to health and social workers, program managers, politicians, the media, and society. It was used to create standards for the quality of treatment and care, calculate the need for personnel and finance services. To evaluate the results of the programs, data from national statistics on the dead, data from surveys of relatives of the deceased, and their complaints were also used.

Calculating funding has always been a difficult task, given the uncertainty of when palliative care will begin for many critically ill patients. Funding was calculated for hospitalizations, maintenance of hospices and specialized palliative care services, community nursing services, nursing homes. Spending was measured in billions of pounds, but there was an understanding that the efficiency of using these funds could be increased. Part of the costs of palliative care remained unaccounted for: costs of other government departments (for example, for disability), costs of unpaid carers, etc. Since the beginning of financing the programs, expenditures have gradually increased. For example, £88 million was spent on palliative care from the state budget in 2009–2010, and £198 million in 2010–2011. But the quality and coverage of patients with help did not always increase proportionally. Optimizing the "costs/(quality+coverage)" ratio was associated with a reduction in the number of hospitalizations and the length of hospital stay while simultaneously increasing the standards of care. Naturally, as a result of such a policy, the number of deaths at home increased with stable total costs. Costs included 24/7 home care, administrative services of focal points, ambulance transport costs for home care. Attention to the problem of palliative care has increased the contributions of communities and philanthropists to nursing homes and community hospitals, and improved educational programs for staff, patients and their relatives.

The end-of-life care strategy for patients and their carers included the possibility of professional consultations. Each professional service knew its priorities and took into account the preferences of patients and their relatives where possible. Coordinated care and support followed the principles of the Gold Standards Framework (www.goldstandardsframework.nhs.uk). Coordination centers were established outside medical institutions and professional organizations that provided palliative care services to patients and their relatives. Patient registries increased the chances of responsiveness to patient preferences by service providers. 24-hour helplines have made access to home care services faster. The creation of specialized palliative care services allowed to raise the standards of care. Relatives and carers of palliative patients were given the opportunity to stay in hospitals together with patients.

Services were provided in accordance with quality standards, compliance with which was constantly monitored. The opinions and evaluations of the quality of services of relatives and caregivers of palliative patients based on the successful program "Views of Informal Carers – Evaluation of Services (VOICES) program" were also taken into account [15; 16]. Best practices were analyzed by a national team of experts and disseminated.

Great Britain considered the lack of open discussion of death and dying to be a problem in its society. Older people did not often discuss their own dying care preferences with close relatives or friends, so it was difficult to determine the extent to which their wishes were met. Health and social care staff often found it difficult to start a discussion with people about the fact that they were approaching the end of life. And by clinicians, death

was often viewed as a professional failure. In order to change this situation, it was important to realize that only frank and timely discussion will allow identifying needs and planning care, improving coordination of services, allowing conscious choice of place of death (home, hospital, nursing home, hospice, etc.), providing care and support 24/7, not to carry out unnecessary hospitalizations, train medical and social workers to provide professional care, and, in fact, ensure maximum comfort, the necessary support of caregivers, reduce suffering and prepare a dignified death. It became clear that such training has a significant impact on the condition of carers.

The extent of the problems of inadequate organization of medical care for palliative patients throughout their improvement helped to assess the survey and analysis of complaints. Thus, in 2004–2006, the NHS analyzed more than 16,000 complaints. 54% of them were related to end-of-life care. Most of these complaints were related to poor communication, lack of basic comfort, violations of privacy, insufficient psychological care, late referral or lack of referral to specialized palliative care, inadequate invasive procedures before death. Relatives often said that they, and not the doctors, were the first to notice that the patient was dying. Inappropriate invasive procedures were often used even in the dying phase. The commission examined in detail and published 50 typical cases that demonstrated the main aspects of the problem.

The shortcomings of the existing system were eliminated step by step thanks to the performance of a number of tasks:

- increasing public awareness of HPC problems, broad discussion of death and dying, preferences of palliative patients regarding the place of death, analgesia and other types of symptomatic treatment, care and support;
- a dignified and respectful attitude towards the dying;
- provision of medical and psychological assistance, social and spiritual support;
- coordination of palliative care for its quick start and continuity;
- assistance to relatives providing care (their training and psychological rehabilitation after the death of the patient);
- special education for medical and social workers;
- implementation of palliative care quality standards and monitoring of their compliance;
- equal treatment of all patients, regardless of their religious and ethnic affiliation, social status;
- state and community support of hospices and homes for the elderly;
- objective control of cost and quality indicators of the HPC system;
- inclusion of HPC issues in medical reform programs;
- decentralization of financing and decision-making regarding the work of local institutions of the HPC system;
- preferential taxation;
- bringing services closer to patients by increasing the network of institutions that provide HPC.

Conclusions

The UK has had a long and difficult 60-year journey to a successful HPC system. Since the 2000s, palliative care has been provided on a 24/7 basis, managed by coordination centers located outside of hospitals and hospices. High national HPC standards and mechanisms for monitoring their compliance have been created. Narcotic analgesia for palliative patients with chronic pain, the necessary medical, psychological, social and spiritual care is mostly available. The public debates the question of a dignified death without restrictions. The value for money in HPC is recognized by British society as acceptable. Therefore, studying the British experience of HPC organization as one of the "best practices" is useful for other countries with less developed HPC systems, in particular, Ukraine. Taking into account the experience of Great Britain in the development of the national HPC can significantly improve the quality of management decisions in this area.

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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PRACTICAL ASPECTS OF PAIN RELIEF IN PALLIATIVE MEDICINE

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ABSTRACT

Background. Treatment of chronic pain in adults and children is regulated by the national standard of Ukraine, which recommends adherence to the choice of painkillers in accordance with the WHO three-step protocol. But the treatment standard does not detail the use of painkillers according to nosological units.

Aim. To determine the need for different types of analgesia in palliative patients depending on the main palliative diagnosis.

Materials and Methods. System analysis, aggregation and bibliosemantic methods were used. The list of palliative diagnoses was determined when studying the need and forecasting the need for palliative and hospice care according to the methodology of the Ukrainian Center for Social Data (2019), improved by us in 2021–2024.

Results and Conclusions. The conducted research made it possible to determine the predominant types of pain, their possible intensity and corresponding groups of pharmaceutical drugs with an analgesic effect in the units from the list of palliative diseases proposed by us. Neuropathic pain is mainly present in diabetes (diabetic polyneuropathy) and phenylketonuria. Predominantly nociceptive pain is present in cardiovascular diseases of palliative stages, tuberculosis, rheumatoid arthritis, cystic fibrosis and chronic hepatitis in children. Predominantly mixed (nociceptive and neuropathic types of pain at the same time) characteristic of HIV/AIDS, epilepsy, dementia, multiple sclerosis, fibrosis and cirrhosis of the liver, chronic obstructive pulmonary disease, palliative stage kidney disease in adults, cerebral palsy, inflammatory diseases of the central nervous system and mucopolysaccharidoses in children. We proposed to clarify the national standard for treatment of chronic pain in adults and children, and to define the necessary non-steroidal anti-inflammatory drugs, non-narcotic analgesics, weak and strong opioids, anticonvulsants, antidepressants, and other adjuvants with an analgesic effect. The perspective of further studies is to detail the dosage of drugs with an analgesic effect and to calculate the need at the national level for reimbursement under the "Affordable Medicines" program.

Keywords: *neuropathic pain, nociceptive pain, analgesics, opioids, reimbursement.*

INTRODUCTION

The Ministry of Health of Ukraine includes malignant stage 3–4 neoplasms, HIV/AIDS, congenital malformations, cardiovascular, respiratory, neurological, atrophic-degenerative diseases, and post-traumatic conditions that cannot be cured by modern available drugs in the list of palliative diseases [1]. The need for Palliative and Hospice Care (PHC) is growing: 1.5 million Ukrainians need it immediately before the end of life, and about 600,000 in the last year of life. Unfortunately, the list of palliative diseases according to such a number of patients is not detailed by the Ministry of Health of Ukraine. In 2023, only 130,000 people received palliative care in Ukraine (11.5–46.2% of the need). In the world, the need for PHC is 20 million at the end of life. Some 6% of these are children. 80% of such patients live in low- and middle-income countries. Coverage of palliative care in the world also does not exceed 50% of the need [2–4].

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The medical component of palliative care is elimination of life-threatening symptoms (carrying the risk of premature death even with an incurable disease) by carrying out pathogenetic therapy, palliative surgical interventions, as well as symptomatic therapy, to relieve pain, first of all. Timely and sufficient analgesia significantly improves the quality of life of patients and is one of the main needs of palliative patients [2; 5].

Among the 289 disabling diseases that were responsible for the global burden of disease in the world during 1990–2010, a significant part belonged to palliative diseases and were accompanied by chronic pain [6]. Among these diseases, the first place was occupied by psychoneurological disabling disorders: dementia, demyelinating diseases, strokes in adults; severe and profound mental retardation and other diseases of children (congenital malformations, inflammatory diseases of the central nervous system, severe perinatal conditions, cerebral palsy). Chronic pain is also accompanied by damage to the musculoskeletal system and joints [7], frequent periodic pain of significant force – tension headache and migraine. About 3% of the world's population has a disability due to injuries that are accompanied by chronic pain. At the same time, the number of such patients is even greater in terms of the number of Years Lived with Disability (YLD): according to [7], the number of victims of injuries was more than 6%, that is, it was twice as large. The results of studying the number of Years of Life Lost (YLL) [8] are also important for our research. Correlations between YLD and YLL indicators are usually not established: some diseases predict long-term disability and a palliative state, others require palliative treatment and care during the last year of life [9]. For example, neurological disorders were responsible for almost 43 million cases of YLD during the period, but they accounted for only about 9 million YLL. Another example of the absence of correlative relationships is the following: in the older age group in studies [7; 8] most cases of YLD were associated with Alzheimer's and Parkinson's diseases, while YLL was associated with cancer.

Considerable attention of the medical community and the society during the period of research of YLD and YLL indicators (1990–2010) was focused on HIV/AIDS, which was called the "plague of the 20th century". In the last stages of development, the disease is palliative and associated with intense pain in the case of neuroAIDS. Today, there are 39 million people living with HIV/AIDS in the world, with an annual increase in the number of infected people by 1–1.5 million people and annual AIDS deaths in the range of 600–700 thousand [10; 11]. Without the use of AntiRetroviral Therapy (ART), it takes 7–12 years from HIV infection to the development of AIDS. Drug use shortens the period before the development of AIDS to 3–4 years [12]. There are more than 190,000 HIV-infected people in Ukraine, and only 150,000 of them receive ART. Therefore, more than 21% of HIV-infected people are at risk of rapid AIDS development in the forecast period. They will need constant pain relief for at least the last two months of life. In the last stages, AIDS progresses quite quickly, therefore, in order to assess the impact of the correct organization of medical care on the quality of life and the adequacy of palliative analgesia in patients diagnosed with HIV/AIDS, it is YLL that should be taken into account.

According to the same principle, among vascular crises, which are responsible for the highest mortality in the world, the YLL indicator is more relevant for the assessment of strokes, and the YLD indicator of heart attacks. After all, by the end of the year, 20% of victims of myocardial infarction in Ukraine survive. After strokes, 30–40% of patients die in the first 30 days, another 50% die within a year. Of those who survive, up to 40% become dependent on assistance (often living with chronic pain), and only 10% return to a full life [13]. In general, disability from cerebrovascular diseases in the world increased from 2.3 million cases in 1990 to 4.3 million in 2010 [7].

Trends in onset and duration of disability, calculated by YLD, have multidirectional vectors, which must be taken into account when planning the volumes of necessary analgesia. Thus, YLD due to neonatal conditions in the world during 1990–2010 decreased by 13.5% (from 159 per 100 thousand population to 137 per 100 thousand population). On the contrary, YLD due to oncopathology, which has a significant burden of pain and is treated palliatively in stages 2 and 4, increased from 2.5 million first registered cases in 1990 to 4.5 million cases in 2010.

A global study of YLL and YLD in the world during 1990–2010 also showed that national health systems are not sufficiently responding to the challenges of palliative diseases. The strategies of the PHC organization are insufficiently effective, first of all, in matters of determining the list of palliative diseases, creating centers for coordinating the routes of palliative patients in the

system of medical institutions, and organizing adequate analgesia. The majority of palliative care patients do not receive the necessary analgesia due to strict drug restrictions, lack of political will of governments, insufficient qualification of medical professionals and lack of scientific research. This is also evidenced by the data of Ukrainian researchers [14–17]. Therefore, the issue of pain relief is insufficiently studied, both at the world and national levels.

The aim of the study was to determine the need for different types of analgesia in palliative patients depending on the main palliative diagnosis.

Materials and Methods

To carry out this study, we used the method of systematic analysis and bibliosemantic (searching for sources by keywords on PubMed and Google Scholar). The aggregation method [18] summarizes information on types of pain in various palliative diagnoses and painkillers recommended in Ukraine. The need for various painkillers for adults and children with palliative diagnoses was assessed.

In our calculation and forecast of the need for PHC in Ukraine, made according to the improved methodology (2021–2024) [19] of the Ukrainian Center for Social Data (2019) [20], the indicator hovered around the figure of 200 thousand and included malignant neoplasms, cardiovascular diseases, tuberculosis, diabetes, HIV/AIDS in adults and children; dementia, rheumatoid arthritis, fibrosis and cirrhosis of the liver, kidney disease in adults; congenital malformations, severe perinatal conditions, cerebral palsy, severe and profound mental retardation, inflammatory diseases of the central nervous system, chronic hepatitis, phenylketonuria, cystic fibrosis, mucopolysaccharidoses in children. Obtaining statistical data on congenital malformations [21], severe and profound mental retardation in children; chronic obstructive pulmonary disease [22], dementia in adults was complicated. Complications were related to the collection of disease statistics. We also consider it necessary to expand the list of palliative diseases to include epilepsy in adults and children, as well as multiple sclerosis in adults [23].

Results and Discussion

Painless dying is considered from the perspective of human dignity [24]. Even under adequate anesthesia, it is difficult for palliative patients to overcome the emotional problems associated with the awareness of imminent death. In the presence of chronic pain, the psychological state of patients deteriorates to the point of clinical depression with suicide attempts, therefore, the treatment of many palliative diseases relies on the use of sedatives, tranquilizers, neuroleptics, anticonvulsants, which simultaneously have analgesic properties [25].

According to the results of a systematic review of ten prospective studies of palliative sedation, found by Arantzamendi M. et al. (2021) in the PubMed, CINAHL, Cochrane, MEDLINE and EMBASE databases for the period 2014–2019 [26], 25–65% of palliative patients required chronic pain treatment. Most of them were cancer patients. (Our own observations in the Kharkiv hospice [27] are similar). Evaluation of the effectiveness of sedation according to the conclusions of Arantzamendi M. et al. performed according to the Glasgow Coma Scale, Ramsay Sedation Scale, Richmond Agitation Sedation Scale, and Bispectral Index monitoring. The most used drugs were midazolam, phenobarbital, promethazine and the anesthetic propofol.

But according to the WHO three-stage pain treatment strategy [28], adopted as a basis in Ukraine [29], the main drugs for pain relief are narcotic and non-narcotic analgesics. The three levels of pain relief are based on the intensity of the pain. For mild pain, non-narcotic painkillers are used (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), acetaminophen (paracetamol), adjuvant drugs); with moderate – weak opioids (hydrocodone, codeine, tramadol); in severe cases, strong opioids (morphine, methadone, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone) with the addition of adjuvants if necessary.

Opioid pharmacotherapy is the basis of cancer pain treatment [30]. It can be supplemented by treatment with adjuvant analgesics, psychotherapy and physiotherapy. In order to choose methods that will be effective in the complex for the vast majority of patients, it is necessary that clinicians are well aware of methods of pain assessment and therapeutic strategies that must consider the balance between the effectiveness of analgesia and the side effects of analgesics. The choice of drugs is based on understanding the pathophysiology of pain. But if it is not about hospice in a medical institution, but about a home for the elderly, in which a palliative patient ends his life, or about "hospice at home", the choice of drugs for pain relief is usually insufficient [31]. The situation is often complicated by comorbidity, which increases the need in drug treatment, its duration, number of drugs, necessary doses, risk of polypharmacy [32].

Specialized hospice facilities and palliative care units often have more options than home hospices and nursing homes in terms of drug delivery routes, which affects their effectiveness. Thus, for example, morphine is 2–3 times more effective when administered intravenously and subcutaneously than when administered orally [33]. The need for long-term analgesia in palliative medicine prompts to pay considerable attention to the possible side effects of painkillers, to change these drugs to those that do not have side effects, to combine them to reduce the dosage. From doctors who do not specialize in patients with a palliative profile, such actions require special knowledge and a lot of time to study the features of pain relief depending on the age of the patient and the main palliative diagnosis. Therefore, it is advisable to improve the protocols for the treatment of chronic pain: to include in them recommendations on the lists of painkillers for each diagnosis with the appropriate dosage depending on the severity of the disease, assessment of pain intensity, age, comorbidity. It is also necessary to indicate the possibility of replacing drugs in cases of pronounced side effects and the sequence of such replacement. The legalization of medical cannabis in Ukraine significantly expands the possibilities of pain relief [34]. A list of these drugs must be offered to the National Health Service for reimbursement under the "Affordable Medicines" medical guarantee program [35]. Currently, only valproic acid, haloperidol, carbamazepine, acetylsalicylic acid, clozapine, lamotrigine, morphine, phenytoin, and fluoxetine are included in the list of reimbursement drugs that can be used in palliative medicine in the presence of chronic pain (with reimbursement of 43–100% of the cost) [36].

We have compiled a *Table* of the correspondence of palliative diseases of adults and children to the types and possible intensity of pain, indicating the groups of drugs with an analgesic effect. Types of pain are listed in accordance with national standards of care and evidence-based clinical guidelines for chronic pain syndrome in adults and children [37]. Nerve irritation causes nociceptive pain, damage – neuropathic. We will describe the pathogenetic mechanisms of pain in palliative diseases selected by us for inclusion in the list that can be recommended by the Ministry of Health of Ukraine from the WHO list.

The nature of pain in ***malignant neoplasms*** can change with the progression of the disease. Nociceptive pain predominates in the early stages, and neuropathic pain in the later (palliative) stages. Nociceptive pain can be caused by the pressure of a growing tumor on the adjacent tissues (nerves, bones), irritation of nerves by products of inflammation accompanying the neoplastic process, tumor growth into nerves. Long-term compression of nerves disrupts their functionality; thus, the pain can be considered neuropathic. Nerve damage can be caused by surgery, radiation therapy, or the effects of certain anticancer drugs (cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, vincristine, vinblastine, and others). Pain increases the development of osteoporosis [38–40].

Pain in ***cardiovascular diseases*** is mainly nociceptive. It occurs due to ischemia of the myocardium, stretching of the aneurysm walls, inflammation of the pericardium and endocardium, blockage of blood vessels by blood clots. Severe pain is characteristic of angina pectoris, myocardial infarctions and strokes. The intensity of pain in heart failure is usually moderate. Pathogenetic therapy with nitroglycerin in angina pectoris reduces the level of pain [41].

Pain in ***pulmonary tuberculosis*** is mainly nociceptive, caused by inflammation of lung tissue, formation and disintegration of cavities with pleural irritation. When bones and kidneys are affected by tuberculosis, neuropathic pain is added. Pain reduction occurs as a result of pathogenetic treatment with antibiotics and analgesia using paracetamol, NSAIDs, and weak opioids [42].

Most often, pain in ***diabetes*** has a neuropathic character, which is reflected in the name of a common complication of diabetes "diabetic neuropathy" (E10.4, E11.4 according to the ICD-10), which is more characteristic of adult patients. Pain, paresthesias, and numbness are initially localized in the feet and lower legs, with possible spread higher up the lower limb. The intensity of pain in diabetic neuropathy ranges from mild to severe. The presence of arthritis and osteoporosis increases pain [43; 44], while the normalization of the blood sugar level lowers it. Treatment of pain in diabetes is pathogenetic (non-narcotic analgesics of central action (pregabalin, gabapentin) (first therapeutic line); carbamazepine (effective in some types of neuropathic pain); tricyclic antidepressants (amitriptyline); sugar-lowering drugs, insulin, diet) and symptomatic (weak and strong opioids (tramadol, codeine, morphine, oxycodone), alpha-lipoic acid, capsaicin). Physiotherapy, reflexology, acupuncture, and cognitive-behavioral therapy are effective [45–49].

In ***HIV/AIDS***, pain is most often mixed: it includes nociceptive pain (from inflammatory pro-

Table. Palliative diagnoses of adults and children, corresponding types of pain and analgesia

The main palliative diagnosis	Codes according to ICD-10	Age*	Predominant types of pain			Groups of pharmaceutical drugs depending on the intensity of chronic pain		
			NP	NC	Md	mild	moderate	severe
Malignant grade 3–4 neoplasms	C00–C97, D00–D48	Adults	+	+	+		WO	SO
	C00–C97	Children						
Cardiovascular diseases	I00–I99	Adults		+			PT, WO, NSAIDS, NA	PT, SO
		Children						
Tuberculosis	A15–A19	Adults		+	+	PT, NSAIDS, NA	PT, WO, NSAIDS	
		Children						
Diabetes	E10–E14	Adults	+			PT	NA, PT, AC, AD, WO	NA, PT, AC, AD, SO
		Children					WO	
HIV/AIDS	B20–B24	Adults			+	NSAIDS	WO, AC, AD	SO, AC, AD
		Children						
Epilepsy	G40–G41	Adults			+	AC, NSAIDs, NA	AC, AD, NSAIDs, NA	AC, AD, NA
		Children						
Dementia	F00–F09	Adults			+	NSAIDs	NSAIDs, AC, AD	AC, AD, SO
Multiple sclerosis	G35				+	NSAIDs, PT	WO, PT, AC, AD	SO, PT, AC, AD
Rheumatoid arthritis	M05–M06			+		NSAIDs, PT	NSAIDs, PT	NSAIDs, PT, AD, NA
Fibrosis and liver cirrhosis	K74				+	PT, NA, NSAIDs	PT, NA, NSAIDs	PT, NA, NSAIDs
COPD	J43–J47				+	NSAIDs, NA,	NSAIDs, NA, AC, AD	
Kidney disease	N00–N15, N20–N23				+	NSAIDs, NA,	NSAIDs, NA, WO, PT	NSAIDs, NA, SO, PT
Congenital malformations	Q00–Q99	Children	+	+	+	NSAIDs, NA	NSAIDs, NA, WO, PT	SO, PT
Perinatal conditions	P05–P96		+	+	+	NSAIDs, NA	NSAIDs, NA, WO, PT	SO, PT
Children's cerebral palsy	G80				+	NSAIDs, NA	NSAIDs, NA, WO, PT, AC, AD	NSAIDs, NA, SO, PT, AC, AD
Mental retardation (heavy and deep)	F72–F79		+	+	+	NSAIDs, NA	NSAIDs, NA, WO, PT, AC	NSAIDs, NA, SO, PT, AC
Inflammatory diseases of the CNS	G00, G03, G04, G06, G08, G09				+	PT, NSAIDs, NA	PT, NSAIDs, NA, WO	PT, NA, SO
Phenylketonuria	E70.0		+			PT, NSAIDs, NA	PT, NSAIDs, NA, WO	

Continuation of the Table

The main palliative diagnosis	Codes according to ICD-10	Age*	Predominant types of pain			Groups of pharmaceutical drugs depending on the intensity of chronic pain		
			NP	NC	Md	mild	moderate	severe
Cystic fibrosis	E84	Children		+		NSAIDs, NA	NSAIDs, NA, WO, PT	NSAIDs, NA, SO, PT
Mucopolysaccharidoses	E76				+	PT, NSAIDs, NA	NSAIDs, NA, CO, PT	NSAIDs, NA, SO, PT
Chronic hepatitis	K73, K75.2, K75.3			+		PT, NSAIDs, NA	PT, NSAIDs, NA	

Notes:
COPD - chronic obstructive pulmonary disease;
CNS - central nervous system;
ICD-10 – International Statistical Classification of Diseases and Related Health Problems 10th revision;
*Children: age 0–17 years (according to WHO);
NP - neuropathic;
NC - nociceptive;
Md - mixed (neuropathic-nociceptive)

NSAIDs – non-steroidal anti-inflammatory drugs;
NA – non-narcotic analgesics;
WO – weak opioids (hydrocodone, codeine, tramadol);
SO – strong opioids (morphine, methadone, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone);
PT – pathogenetic therapy;
AC – anticonvulsant drugs;
AD – antidepressants

cesses, tumors, and treatment complications) and neuropathic pain (from the direct effect of the virus or opportunistic infections (cytomegalovirus, cryptococcosis) on the nervous system in neuroAIDS). The intensity of pain in HIV/AIDS ranges from mild to severe. The presence of tuberculosis, cryptococcosis, or Kaposi's sarcoma can increase pain. NSAIDs (ibuprofen, naproxen – for nociceptive pain), weak (codeine) and strong (morphine) opioids, anticonvulsants (pregabalin, gabapentin – for neuropathic pain), antidepressants (amitriptyline, duloxetine) are used to treat pain.

Kluger B.M. et al. [50] write about the treatment of patients with epilepsy as palliative patients with this disease. The disease is accompanied by convulsions of varying degrees of manageability [51; 52]. Treatment should cover both the attacks themselves and their anticipation (anxiety, fatigue, depression) [53; 54]. Adequate treatment of sleep disorders, cognitive disorders, psychotic manifestations, anxiety symptoms, rage attacks also contribute to reducing the level of pain in epilepsy. Drug therapy of epilepsy can be supplemented with psychotherapy. The cognitive clarity it achieves can get rid of attacks, make them less frequent and last longer. Reducing the frequency and strength of attacks reduces the risk of sudden death by 2–4 times, the intensity of chronic pain by 30–60% [55–61]. Family members of epilepsy patients (caregivers) have high rates of anxiety, depression, and premature mortality due to chronic stress and fatigue [62–65]. Their condition negatively affects the quality of care and support for patients.

A combination of nociceptive and neuropathic pain is often observed in epilepsy. Nociceptive pain can be associated with injuries sustained during seizures (for example, when falling), or with muscle pain after intense seizures. Neuropathic pain is caused by epilepsy itself or by side effects of antiepileptic drugs. The intensity of the pain ranges from mild to severe. Having a migraine or fibromyalgia increases the pain. Drug therapy is used to treat pain, and neurostimulation and blockades are used for severe pain. For the treatment of neuropathic pain, anticonvulsants are used (pregabalin, gabapentin – drugs of the first therapeutic line; carbamazepine – for treatment of trigeminal neuralgia; lamotrigine), antidepressants (including tricyclic antidepressants (amitriptyline, nortriptyline) – for night pains and related sleep disorders; selective serotonin and norepinephrine reuptake inhibitors (duloxetine and venlafaxine)). NSAIDs (ibuprofen, naproxen, ketoprofen) and

paracetamol are used to treat nociceptive pain. Physiotherapy, thermal procedures, massage, physical therapy, psychotherapy are also effective.

Starting from 2019, Ukraine no longer collects statistical data on the number of dementia patients (in adults) and severe and profound mental retardation (in children) [66; 67]. This fact significantly complicates the calculation of the need for PHC for these nosological units, but still requires clarification regarding the necessary analgesia.

In ***dementia***, the predominant type of pain is mixed, which consists of nociceptive pain from infections, injuries, bedsores, as well as neuropathic pain due to degeneration of the nervous system. In Alzheimer's disease, beta-amyloid plaques have a toxic effect on nerve cells. NSAIDs are used to treat nociceptive pain, and anticonvulsants and antidepressants are used to treat neuropathic pain. Non-medicinal methods are also effective: physiotherapy, massage, thermal procedures. Bedridden patients need special anti-bedsore care. In some patients with dementia, the pain sensitivity threshold may change, ranging from overestimation to underestimation. The intensity of the pain ranges from mild to severe. Pain is increased by comorbid arthritis, osteoporosis, some pharmaceutical drugs for the treatment of dementia (haloperidol, biperiden, prednisone, dexamethasone, lamotrigine, gabapentin, pregabalin). Severe headache is often present with vascular dementia. For the treatment of severe pain in dementia, strong opioids (morphine, oxycodone) are used with caution (given the difficulty of determining the level of pain in patients with cognitive disorders) [68–71].

In ***multiple sclerosis***, pain has a mixed nature, the neuropathic component of which is associated with disturbances in the conduction of nerve impulses due to demyelination and inflammatory processes that damage nerve fibers. The nociceptive component is also associated with inflammatory processes or with injuries due to muscle spasms, contractures or other concomitant diseases. It is more pronounced in the early stages of the disease. In the later stages, neuropathic pain is more pronounced. The nature and strength of the pain depends on the stage of the disease and the localization of the damage to the nervous system. The disease mainly affects women (up to 80%) aged 20–35. The onset of the disease in most men occurs at the age of 35–45. After 10 years from the onset of the disease about a third of patients, and after 15 years half of patients are unable to move without assistance. The loss of the ability to move often correlates with an increase in pain from mild in the initial stages of the disease to very severe in the last stages [72; 73]. Many complications of the disease are accompanied by pain: spastic conditions, contractures, bedsores, delayed urination and defecation, swallowing disorders, aspiration pneumonia. Some medical and diagnostic procedures (catheterization, epicystostomy, and others) are also painful [74; 75].

Early initiation of treatment using pathogenetic therapy using glucocorticosteroids, plasmapheresis, interferons, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethylfumarate, ocrelizumab improves the prognosis: delays the development of disability [76–78]. The presence of deficient chronic viral diseases, stress, obesity, depression and vitamin D deficiency increase the level of pain; adequate physical therapy, thermal procedures, massage, transcutaneous electronic neurostimulation, yoga, meditation, acupuncture, other methods of complementary medicine – reduce [79–81].

For the treatment of neuropathic pain in multiple sclerosis, anticonvulsants (gabapentin, pregabalin), tricyclic antidepressants, selective serotonin reuptake inhibitors, and opioids are used. NSAIDs can reduce nociceptive pain. With the right treatment, the life expectancy of patients can be the same as that of other people without multiple sclerosis. But in Ukraine, unfortunately, correct and timely treatment of multiple sclerosis is rarely carried out. Correct treatment is also hampered by the high cost of therapy [26; 27; 82].

In ***rheumatoid arthritis***, the pain is mainly nociceptive, caused by inflammation of the synovial membrane of the joints and the destruction of their tissues, which irritates pain receptors. Only with a long course due to complications, neuropathic pain can be added. The intensity of pain usually increases with the progression of the disease from mild to severe, and correlates with the strength of the inflammatory process. it starts from one joint and later spreads to others, more in the case of damage to large joints, the presence of osteoarthritis and fibromyalgia. As with all other diseases, the intensity of pain depends on the threshold of individual sensitivity. But with predominant nociceptive pain, the objective assessment in points on standard scales depends more on individual perception than with neuropathic pain. For the treatment of pain in rheumatoid arthritis at all levels of its intensity, NSAIDs (ibuprofen, naproxen) are used, in moderate and severe cases – glucocorticosteroids. The key drugs of pathogenetic treat-

ment are basic antirheumatic drugs (methotrexate, sulfasalazine, which inhibit the inflammatory reaction), biological drugs (cytokines, tumor necrosis factor inhibitors, which slow down the destruction of joints). Non-medicinal methods (physical therapy, massage, thermal procedures), ergotherapeutic devices to facilitate movement, yoga, meditation are effective. A healthy diet, sufficient sleep, and moderate physical activity also have a positive effect on the course of the disease, reduce pain and delay the onset of disability. Tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors are used to treat severe pain in rheumatoid arthritis. The use of opioids is limited and not long-term [83–85].

In ***fibrosis and cirrhosis of the liver***, pain is of a mixed type. Its nociceptive component is associated with stretching of the liver capsule (visceral pain) and appears already in the early stages of the disease. The neuropathic component occurs when the nerves of the liver are damaged, against a background of hepatic encephalopathy or vitamin deficiency. The intensity of pain ranges from mild in the early stages to severe in the later stages. Pain can be aggravated by hepatic encephalopathy, ascites, portal hypertension, varicose veins of the esophagus. Pathogenetic pharmacotherapy (entecavir, tenofovir, interferons, sofosbuvir, ledipasvir, simeprevir, essentials, karsil, vitamin E, obelirosan, cencrelide, TGF-β inhibitors, aldosterone inhibitors, etc.) or donor liver transplantation is used for treatment. For pain relief, non-narcotic analgesics and NSAIDs (paracetamol, ibuprofen), antispasmodics (buscopan, no-spa, drotaverin) are used; with ascites – diuretics (verospiron, furosemide). For the treatment of fibrosis and cirrhosis of the liver and their complications, thermal procedures and physiotherapy are used. Patients are recommended a diet and restrictions on physical activity [86–88].

In ***Chronic Obstructive Pulmonary Disease*** (COPD), pain is mostly of a mixed nature. Its nociceptive component is associated with inflammation of the respiratory tract, chronic cough, suffocation with accelerated breathing, which causes overstrain of the respiratory muscles, and chronic hypoxemia. Neuropathic pain occurs as a result of nerve damage caused by chronic inflammation, compression of nerves by enlarged lymph nodes or tumors. Osteoarthritis, a frequent concomitant disease, contributes to the development of pain in COPD. The pain can be mild to moderate, with localization in the chest (due to coughing and muscle tension), in the back (also due to coughing and incorrect posture), in the joints (due to lack of oxygen). Headache may be caused by chronic hypoxemia and/or neck muscle tension. For the treatment of neuropathic pain, anticonvulsants (gabapentin, pregabalin, carbamazepine), muscle relaxants (baclofen, tizanidine) and antidepressants are effective, and for nociceptive pain in muscles and joints – NSAIDs (ibuprofen, naproxen), paracetamol. Physiotherapy, massage, heat treatments (mustards, warming compresses), acupuncture, cognitive-behavioral therapy, removal of lung tumors, oxygen therapy are also effective for reducing pain [22; 89–91].

In palliative ***kidney diseases***, the pain is mainly of a mixed nature. Its nociceptive component can be associated with renal colic, inflammatory processes (pyelonephritis), tumors. The neuropathic component of pain in kidney diseases can be associated with ureterohydronephrosis, diabetic nephropathy, nerve damage during surgery. The intensity of the pain ranges from mild to severe. Pharmacotherapy of pain involves the use of NSAIDs, paracetamol, antispasmodics, diuretics (to remove stones and reduce pressure in the kidneys), weak and strong opioids (codeine, morphine). Physiotherapy (electrophoresis, ultrasound), massage, heat procedures or, on the contrary, cold (in case of acute inflammation), acupuncture, psychotherapy, epidural anesthesia, neurostimulation, changing the position of the body during treatment to reduce the load on the kidneys, physical therapy, diet, relaxation techniques (yoga, meditation) are also effective [92–94].

In ***congenital malformations***, the pain can be equally neuropathic, nociceptive or mixed, from mild to severe (for hydrocephalus, spina bifida (split spine) in intensity, depending on the nature and localization of the defect. Pain can be constant and periodic, disappear in periods of remission. Determining the level of pain is difficult in young children who cannot describe their feelings. The pain is aggravated by the presence of spasms, contractures, and infection. Narcotic and non-narcotic pain killers, blockades, anticonvulsants, antidepressants, physiotherapy (massage, thermal procedures, physical exercises, electrical stimulation), surgical interventions, orthopedic devices (ortheses) [21; 95; 96].

Pain in ***severe perinatal conditions*** that cause palliative illnesses can range from mild to severe in intensity, nociceptive, neuropathic and mixed in origin. Narcotic and non-narcotic pain relievers (paracetamol, ibuprofen, opioids), anticonvulsants (gabapentin, pregabalin), antidepressants,

epidural anesthesia, physiotherapy (massage, heat procedures, physical exercises, electrical stimulation), compression therapy (bandages, stockings), positional therapy (change in body position), surgical interventions [97–101].

In children with ***cerebral palsy***, the pain is mostly mixed. Its nociceptive component is associated with muscle contracture, spasticity, bedsores. The intensity of the pain ranges from mild to severe. In all forms of the disease, the headache is associated with increased intracranial pressure or spasms of blood vessels. Increased muscle tone often causes muscle and joint pain. Contractures limit the mobility of the joints, which, moreover, are often deformed and require surgical treatment. The treatment uses analgesic anti-inflammatory NSAIDs (ibuprofen, naproxen, ketorolac), weak and strong opioid analgesics (tramadol, morphine), muscle relaxants of central (baclofen, tizanidine) and peripheral (dantrolene) action, anticonvulsant drugs (gabapentin, pregabalin – for neuropathic pain), antidepressants (amitriptyline, venlafaxine – for chronic pain), botulinum toxin (reduces spasticity), physical therapy, massage, kinesiotherapy, psychotherapy [102–105].

Pain in ***mental retardation (severe and deep)*** is associated with complications of diseases that occur or progress faster in such children: cardiovascular (heart failure, strokes), respiratory system (pneumonia, bronchitis, food aspiration), epilepsy, infectious diseases in in combination with weakened immunity (with sepsis), with complications after surgical interventions, bedsores. Therefore, nociceptive, neuropathic and mixed types of pain of all degrees of intensity are inherent in this disease. NSAIDs, opioid analgesics, muscle relaxants, anticonvulsants, physiotherapy, acupuncture, positional therapy, art therapy, psychotherapy are used to treat pain [106–109].

In ***inflammatory diseases of the central nervous system*** in children, the pain is mainly of a mixed nature. The nociceptive component of pain is associated with increased intracranial pressure and brain swelling, the neuropathic component is associated with demyelination. Nociceptive pain is usually present from the beginning of the disease, neuropathic pain joins in the last stages. In meningitis, there is an intense headache, which is often accompanied by stiffness of the occipital muscles and photophobia. In encephalitis, there is also frequent headache, chronic neuropathic spinal pain, convulsions, and loss of consciousness. The pain gradually increases from mild to severe. For the treatment of pain, etiotropic therapy (antibiotics and antiviral drugs), pathogenetic therapy (glucocorticoids), the entire range of painkillers [110–113] are recommended.

In ***phenylketonuria*** the pain is usually neuropathic, resulting from nerve damage during convulsions. The intensity of such pain does not exceed a moderate level. A mild headache and muscle pain may also be present after the seizure [114].

In ***cystic fibrosis***, the pain is mainly nociceptive, associated with irritation of the nerves of the chest and throat during coughing and the abdominal cavity during pancreatitis or intestinal obstruction. In pancreatitis and pneumonia, the pain can be severe. Dehydration and muscle tension can lead to headaches. Pain reduction occurs in response to adequate analgesia (using NSAIDs, weak and strong opioids) and pathogenetic therapy (to improve lung function using postural drainage, breathing exercises, inhalations, mucolytics, antibiotics; treatment of pancreatitis and intestinal obstruction). Physiotherapy, massage, kinesiotherapy, relaxation techniques (yoga, meditation, breathing exercises), thermal procedures (mustards, warming compresses), psychotherapy are also effective [115–119].

In ***mucopolysaccharidoses***, the pain is mostly mixed. Its nociceptive component is associated with joint inflammation, bone deformation, and compression of nerve roots. Neuropathic pain is associated with neurodegenerative processes. The intensity of the pain ranges from mild to severe. Mild persistent pain is often localized in the joints and worsens with physical exertion. Moderate chronic pain in the back is associated with deformation of the spine, in the abdomen – with an increase in internal organs. Severe acute pain often occurs when nerve roots are compressed or joints are inflamed. The reduction in pain level corresponds to the effectiveness of pathogenetic therapy (enzyme replacement therapy and correction of metabolic disorders) and analgesia (with frequent use of NSAIDs and infrequent opioids). Kinesiotherapy, massage, acupuncture, thermal procedures, psychotherapy are also effective [120–123].

In children with ***chronic hepatitis***, the pain is mainly nociceptive, associated with stretching of the liver capsule, compression of neighboring organs and nerve endings by an enlarged liver. The presence of gallstones increases the pain. With the development of cirrhosis of the liver, neuropathic pain is added, due to the degeneration of the nerves

of the liver. Etiotropic and pathogenetic therapy (treatment of the main disease, for example, virostatic therapy, immunomodulators-suppressors) together with painkillers (NSAIDs, paracetamol), antispasmodics, physiotherapy (ultrasound, electrophoresis with pharmaceuticals, magnetic therapy) and diet (restriction of fatty, fried, smoked, spicy) help to reduce the level of pain [124–126].

Conclusions

The treatment of chronic pain in Ukraine is regulated by the treatment standard, which recommends following the WHO three-step protocol the use of non-steroidal anti-inflammatory drugs and non-narcotic analgesics for the treatment of mild pain, mild opioids for moderate pain, and strong opioids for severe pain. A significant number of diseases that are accompanied by chronic pain should be treated as palliative. But the treatment standard does not detail the use of painkillers according to nosological units.

The conducted research made it possible to determine the predominant types of pain, their possible intensity and corresponding groups of pharmaceutical drugs with an analgesic effect in nosological units from the list of palliative diseases proposed by us. We also proposed to introduce clarifications to the national standard for the treatment of chronic pain in adults and children. The perspective of further studies is to detail the dosage of drugs with an analgesic effect and to calculate the need at the national level for reimbursement under the "Affordable Medicines" program.

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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