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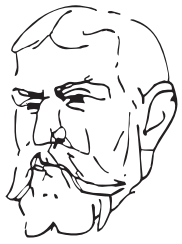

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ORIGINAL ARTICLE

POSSIBILITIES OF COMPLEX CORRECTION OF MORPHOLOGICAL GASTRODUODENAL CHANGES WITH COMORBIDITY OF CHRONIC PANCREATITIS AND CHRONIC *H. PYLORI* – GASTRITIS

DOI: 10.36740/WLek202110201

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ABSTRACT

The aim: To investigate the efficacy of Doctovit, a combination of dexpanthenol (provitamin B5) and methylmethionine (vitamin U), in the treatment of patients with chronic pancreatitis in combination with chronic erosive gastritis associated with *H. pylori* by studying the dynamics of stomach lining morphological changes.

Materials and methods: Forty-five outpatients with CP and *H.pylori* CG were examined. The degree of excretory insufficiency of the pancreas was determined by the level of fecal α-elastase-1. At the beginning of the study and two months after the treatment has started, esophagogastroduodenoscopy + urease test for *H. pylori* + biopsy from 5 sites with histological examination has been performed.

Results: It was found that a significant decrease in lymphohistiocytic infiltration of stomach lining, restoration of the structure of glands which have not undergone atrophy, increased focal hyperplasia (proliferation) of the glandular epithelium as signs of morphological restoration of the epithelium, reduction of epithelial dysplasia signs against the complete absence of positive dynamics of epithelial dysplasia in the group of patients receiving standard treatment of CP and CG, are clear and reliable signs of the effectiveness of vitamin Doctovit in complex therapy of CG associated with *H.pylori*, which indicate the feasibility of using the medicine to restore SL, which is the basis for effective carcinoprevention.

Conclusions: The effectiveness of both treatment complexes in the correction of exocrine insufficiency of the pancreas by the dynamics of fecal α-elastase-1 was proved and which was statistically significantly higher when using the program with the inclusion of Doctovit: respectively 28.12% vs. 20.74% ($p< 0.05$). The total dynamics of morphological state improvement of stomach lining in the 1st group of patients was 0.9 points against 1.6 points in the 2nd group of patients, which was 17% and 32%, respectively ($p <0.05$), which activates clinical data on the effectiveness and feasibility of using a combination of dexpanthenol and methylmethionine according to the suggested scheme in the treatment of patients with chronic pancreatitis in comorbidity with *H. pylori* erosive CG.

KEY WORDS: chronic pancreatitis, chronic erosive gastritis associated with *H. pylori*, stomach lining, morphological features, combination of dexpanthenol (provitamin B5) and methylmethionine (vitamin U)

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INTRODUCTION

Chronic pancreatitis (CP) and chronic gastritis (CG) are frequent variants of comorbidity of pathologies of the digestive system. The gastroduodenogenic scenario of formation of pathology of a pancreas (P) is not uncommon, and on the contrary against CP there can be pathological gastroduodenal changes. This combination of nosologies enhances the clinic polymorbidity, significantly worsens physical dysfunction and causes higher mortality in patients [1, 2].

One of the most important issues for the effective management of such patients with CP and *H.pylori*-associated diseases (chronic gastritis (CG), including atrophic, associated with H.pylori, autoimmune atrophic chronic gastritis, functional dyspepsia, nonsteroidal anti-inflammatory medicine gastropathy and others) is carcinoprevention of gastric cancer and pancreatic cancer. Significantly complicates the management of such patients, the presence of excretory insufficiency of the pancreas (EIP), which also worsens the clinic of diseases, reduces the quality of life of patients [3-5]. The comorbid course of these pathologies requires the formation of an effective treatment complex that would take into account all pathogenetic and etiological factors [2, 6, 7]. For the treatment of *H. pylori*- CG, Maastricht IV offers rational and effective regimens [8, 5, 9]. Complex therapy of CP according to the "Unified clinical protocol of primary, secondary (specialized) medical care and medical rehabilitation of patients with chronic pancreatitis", approved by the order of the Ministry of Health of Ukraine No.638 (2016) includes the enzyme medicine of pure pancreatin in adequate dose, antispasmodic and / or prokinetic during meals if necessary [3, 10, 11]. According to Maastricht IV, it is well defined that eradication of *H.pylori* is the most promising strategy to reduce the incidence of gastric cancer, as it is known that the risk of noncardiac gastric cancer with *H.pylori* infection increases 20 times or more (level of evidence 1a degree; recommendation level A) [8, 5]. An important motive for the complex therapy of comorbidity of CP and CG is also carcinoprevention of pancreatic cancer, because the risk of this terrible disease during 10 years of CP existing is 15% [12]. A serious problem in the treatment of *H. pylori*-associated processes

of the digestive system, as well as carcinoprevention is the solution of the final overcoming of post-radiation therapy consequences – long-term chronic inflammation of stomach lining (SL). After *H. pylori* eradication, an inflammatory infiltrate remains, which produces reactive oxygen species, which in turn, according to researchers, causes DNA damage, as well as changes in the expression of oncogenes and oncosuppressants [9]. Lymphocytic infiltration, leukocyte neutrophil infiltration, which produces reactive oxygen species and causes oxidative stress, hyperproduction of pepsin, which breaks down epidermal growth factor, which restores damaged stomach lining, are all residual effects of post-radiation therapy. These residual effects require additional effects, which, in our opinion, can provide a synergistic combination of dexpanthenol (provitamin B5) and methylmethionine (vitamin U), which is the active basis of the Ukrainian medicine Doctovit [13, 14].

THE AIM

The aim of the study was to investigate the efficacy of Doctovit, a combination of dexpanthenol (provitamin B5) and methylmethionine (vitamin U), in complex therapy of patients with chronic pancreatitis in combination with chronic erosive gastritis associated with *H. pylori* by studying the dynamics of stomach lining morphological changes.

MATERIALS AND METHODS

45 outpatients with CP and *H. pylori* CG were examined. The comparison group consisted of 20 almost healthy people who did not have any clinical and anamnestic and instrumental signs of digestive system diseases. Verification of the diagnosis was performed in accordance with standardized protocols for the diagnosis and treatment of diseases of the digestive system [3, 11, 15]. The degree of EIP was determined by the level of fecal α-elastase-1, which was determined by enzyme-linked immunosorbent assay using standard kits from Bioserv Elastase-1-Elisa [14, 15]. All patients with CG underwent a standardized clinical and laboratory examination. At the beginning of the study and two months after the treatment has started, esophagogastroduodenoscopy + urease test for *H. pylori* + biopsy from 5 sites with histological examination has been performed. Assessment of the morphological state of was performed according to the following most significant signs of H.pylori CG, which were found in the biopsies of SL of studied patients, evaluated qualitatively and quantitatively by the authors: lymphohistiocytic infiltration of the mucous membrane stroma (0 – no signs; 1 – fine focal; 2 – diffuse; 3 – diffuse with the formation of follicle-like structures); atrophy of the glands of the mucous membrane (0 – no morphological signs of atrophy; 1 – almost no glands, the entire field of view is covered with infiltrate; 2 – no glands, total infiltration); acute leukocyte infiltration (a sign of aggressive acute gastritis); the presence of epithelial dysplasia (0 – no signs; 1 – a small number of altered glands; 2 – small focal; 3 – significant); focal hyperplasia of the glands; the presence of erosions of SL epithelium.

Statistical processing of the results was performed on a personal computer Intel Pentium Core Duo using one-way analysis of variance (licensed software packages Microsoft Office 2007, Microsoft Excel Stadia 6.1 / prof and Statistica).

Criteria for inclusion of patients in the study were: persons of both sexes; the presence of a diagnosis of CP, *H. pylori* HG. All subjects signed an informed consent to participate in the study in accordance with the protocol approved by the Ethics Committee of I. Horbachevsky Ternopil National Medical University Ministry of Health of Ukraine.

Criteria for patients exclusion from the study were: decompensation of cardiopulmonary disease, acute myocardial infarction, arrhythmia, acute surgery during the last month, type I and type II diabetes, chronic hepatitis, use of systemic glucocorticosteroids, chronic renal failure thyroid pathology, pregnancy, severe exhaustion, bleeding tendency, malignant neoplasms (and suspicion of them), diseases of blood and blood-forming organs, infectious and parasitic diseases, mental and behavioral disorders, congenital anomalies and chromosomal disorders, unstable coronary heart disease; hypertension II-III centuries and refusal to participate in the study.

Patients comparable by clinical, gender criteria, severity of CP and CG and treatment received were divided into two groups:

Group 1 (20 patients) received treatment according to the scheme for 10 days: pantoprazole 40 mg × 2; amoxacillin 1000 mg (or metronidazole 500) × 2; clarithromycin 500 × 2 without Doctovit.

Group 2 (25 patients) received a similar scheme with the additional inclusion of a combination of dexpanthenol (provitamin B5) and methylmethionine (vitamin U) – Doctovit 2 tablets per day after meals for 2 months.

Mandatory components of medical complexes were outpatient regimen and normotrophic nutrition with mechanical and chemical sparing of the digestive organs in order to prevent abdominal pain, reduce the activity of the pancreas. Caloric content and chemical composition: 2500-2800 kcal, proteins – 130-140 g (low-fat cheeses, hard cheese, meat, fish), fats – 70 g, carbohydrates – 350 g. Diet – small portions 5-6 times per day [10, 15].

RESULTS

Analysis of the obtained indicators of the level of fecal α-elastase-1 in the study groups showed the presence of EIP in both study groups – respectively (148.72 ± 5.29) μg \ g and (154.81 ± 4.93) μg \ g – in comparison with the control group (240.15 ± 6.19) μg \ g). After the treatment there was a statistically significant increase in the level of fecal α-elastase-1 in the 1st group to the level (179.56 ± 5.10) μg \ g, and in the 2nd – to the level (198.34 ± 3.86) μg \ g, which in the dynamics was respectively 20.74% and 28.12% ($p<0.05$).

The data of the morphological study of EGD biopsies of SL before and after treatment in the comparison groups are represented in a table I.

Table I. Dynamics of morphological parameters of SL state under the influence of different treatment programs

Morphology indicator SL	Group 1 (n=20)		Group 2 (n=25)	
	Before treatment	After treatment	Before treatment	After treatment
Lymphohistiocytic infiltration of SL, points	2,40± 0,07	2,10± 0,08*	2,33± 0,09**	1,07± 0,06*** p_{2-4}<0,05
Atrophy of the glands, points	1,60± 0,06	1,22± 0,03*	1,81± 0,08**	0,66± 0,02*** p_{2-4}<0,05
Acute leukocyte infiltration, points	1,02± 0,05	0,20± 0,03*	0,87± 0,15**	0,13± 0,05*** p_{2-4}<0,05
Epithelial dysplasia of SL, points	1,30± 0,08	1,30± 0,06*	1,47± 0,02**	0,40± 0,06*** p_{2-4}<0,05
Erosions of SL epithelium, points	0,90± 0,04	0,37± 0,03*	0,73± 0,04**	0,11± 0,02*** p_{2-4}<0,05
Focal hyperplasia of the glands, points	0,80± 0,04	0,30± 0,04*	0,71± 0,05**	0,04± 0,05*** p_{2-4}<0,05
The total number of available pathological signs of SL	5,40± 0,07	4,50± 0,07*	5,07± 0,09**	3,47± 0,09*** p_{2-4}<0,05

Notes: 1) * - (<0,05); 2) ** - (<0,05); 3) *** - (<0,05).

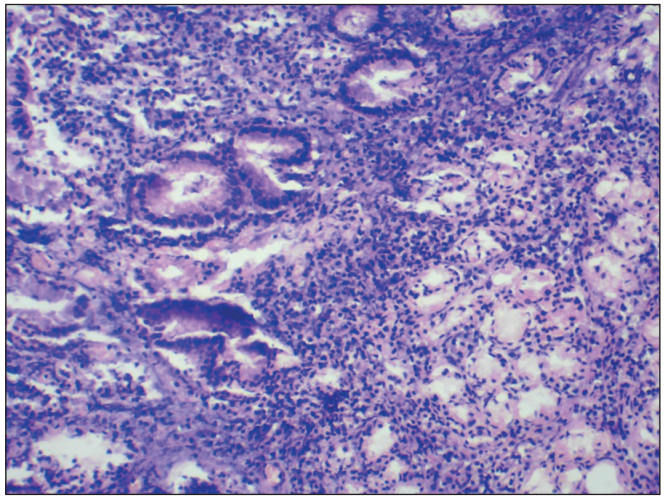

Fig. 1. The structure of the stomach lining surface of patient M. before treatment (control group).

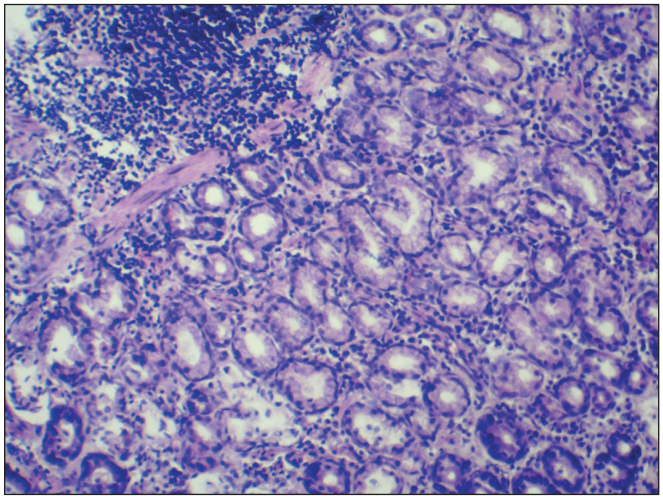

Fig. 2. The structure of the stomach lining surface of patient M. after conventional treatment (control group).

Here is an example of the dynamics of morphological changes min. J. under the influence of standard conventional treatment without the inclusion of Doctovit (Fig 1 (before treatment) and 2 (after treatment)).

Diffuse lympho-histiocytic infiltration of a mucous membrane stroma, dystrophic-necrotic changes, superficial erosions, moderate atrophy of the glands, partial expansion of their lumens, accumulation of lymphocytes with the formation of small lymphoid structures. Hematoxylin and eosin colouring. × 100.

Significant lympho-histiocytic infiltration of a mucous membrane stroma of the lumens of the glands remained dilated, secretory activity – increased, moderate focal dystrophic changes of epitheliocytes, small focal clusters of lymphocytes. Hematoxylin and eosin colouring. × 100.

To confirm the conclusions based on the results of morphological examination, we present pictures with signs of positive dynamics of the gastric biopsy of the stomach lining before and after treatment with the complex including Doctovit for patient H. (Fig 3 and 4) and min. K (Fig 5 and 6).

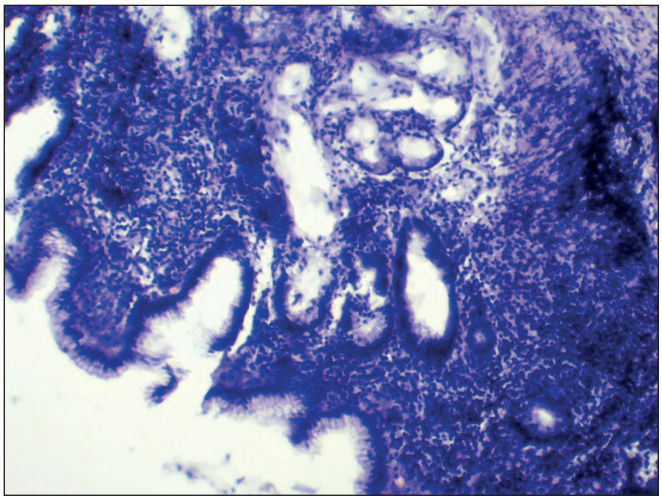

Fig. 3. The structure of the stomach lining surface of patient H. before treatment with the inclusion of Doctovit.

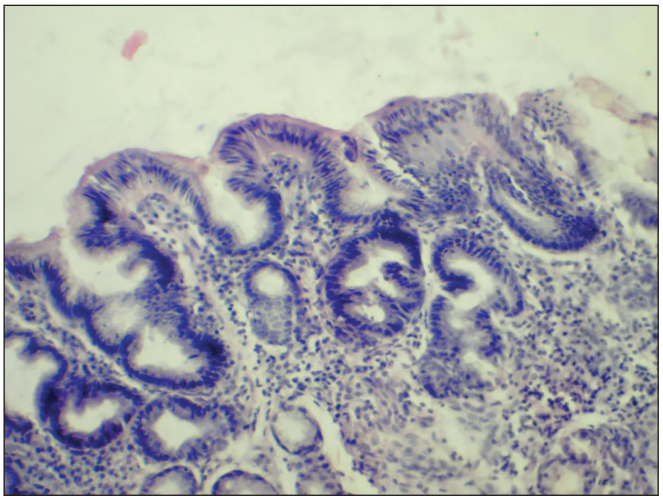

Fig. 4. The structure of the stomach lining of patient H. after treatment with the inclusion of Doctovit.

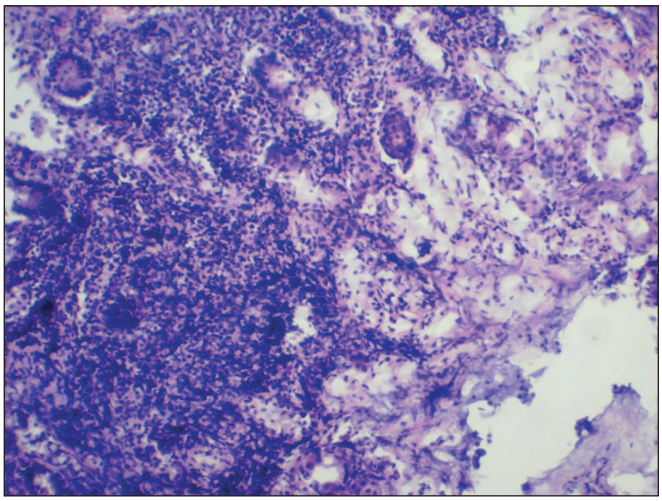

Fig. 5. The structure of stomach lining of patient K. before treatment with the inclusion of Doctovit.

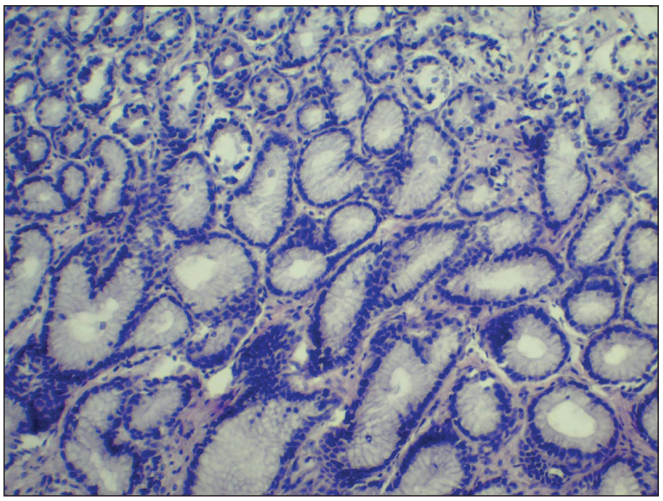

Fig. 6. The structure of stomach lining of patient K. after treatment with the inclusion of Doctovit.

The expressed atrophy of glands, diffuse lympho-histiocytic infiltration of a mucous membrane stroma, significant, gleams of glands are expanded, the increased secretory activity of epitheliocytes, small focal accumulation of lymphocytes with formation of follicle-like structures. Hematoxylin and eosin colouring. × 100

A sharp decrease in inflammatory infiltration, including lympho-histiocytic infiltration, restoration and enhancement of the proliferative activity of mainly superficial epithelium. Hematoxylin and eosin colouring. × 100.

Severe atrophy of glands, diffuse lympho-histiocytic infiltration of the stroma of the mucous membrane, focal dystrophic-necrotic changes of the epithelium, hematoxylin and eosin colouring. × 100.

A sharp decrease in lympho-histiocytic infiltration of the stroma, restoration and enhancement of the proliferative activity of mainly glandular epithelium, focal hyperplasia of the glands and virtually unchanged superficial epithelium. Hematoxylin and eosin colouring. × 100.

DISCUSSION

Morphological examination of stomach lining biopsies (data of table I) showed an accurately significant effectiveness of the proposed treatment complex with the inclusion of Doctovit on the influence on the established pathological signs of Hp-associated CG: lymphohistiocytic infiltration of the mucosa stroma from small focal to diffuse; atrophy of the glands of the mucous membrane from minimal morphological signs of atrophy to the level of virtually no glands on the background of the field of view covered with infiltrate, sometimes to total infiltration; in some aggressive cases – acute leukocyte infiltration (a sign of aggressive acute gastritis); the presence of epithelial dysplasia from a small number of altered glands to small focal and significant dysplasia; focal hyperplasia of the glands; the presence of superficial and deep erosions of the epithelium of the stomach lining.

The study revealed the following signs of histological improvement after a course of treatment with doctovit[5]: 1) a significant decrease in lymphohistiocytic infiltration of the stomach lining (by 1.26 points in group 2 against 0.3 points in group 1);

2) restoration of the structure of glands that have not undergone atrophy (1.15 points against 0.38 points); 3) increased focal hyperplasia (proliferation) of the glandular epithelium as signs of morphological restoration of the epithelium (0.67 points in the group 2 against 0.50 – in group 1); 4) reduction of signs of epithelial dysplasia in the group 2 of patients was 1.07 points against the complete absence of positive dynamics of epithelial dysplasia in the group 1.

The total dynamics of improvement of the morphological condition of the stomach lining in the 1st group of patients was 0.9 points against 1.6 points in the group of patients where the course of Doctovit was used in treatment ($p < 0.05$), considering one available pathological morphological sign, detected during the study. Thus, morphological improvement in the 1st group occurred by 17%, and in the group with doctovit – by 32% ($p < 0.05$), which objectifies the clinically obtained data on the effectiveness and feasibility of using Doctovit in complex treatment and rehabilitation of patients with CP in combination with CG.

Thus, a significant reduction in lymphohistiocytic infiltration of stomach lining, restoration of the glands structure which have not undergone atrophy, increased focal hyperplasia (proliferation) of the glandular epithelium as signs of morphological restoration of the epithelium, reduction of signs of epithelial dysplasia in the complete absence of treatment of CP and CG, are clear and reliable signs of the effectiveness of the vitamin medicine Doctovit in the complex therapy of CG associated with *H. pylori*, which indicate the feasibility of using the medicine to restore the stomach lining, which is the basis for effective carcinoprevention[3].

CONCLUSIONS

1. The effectiveness of both treatment complexes in the correction of exocrine insufficiency of the pancreas by the dynamics of fecal α-elastase-1 was proved, which was statistically significantly higher when using the program with the inclusion of Doctovit: respectively 28.12% vs. 20.74% ($p < 0.05$).
2. The total dynamics of improvement of the morphological state of the gastric mucosa in the 1st group of patients was 0.9 points against 1.6 points in the 2nd group of patients, which was 17% and 32%, respectively ($p < 0.05$), which activates clinical data on the efficacy and feasibility of using Doctovit (a combination of dexpanthenol (provitamin B5) and methylmethionine (vitamin U)) according to the suggested scheme in the complex treatment and rehabilitation of patients with chronic pancreatitis in comorbidity with *H. pylori*.

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ORIGINAL ARTICLE

PERFORATIVE PERITONITIS IN NEWBORNS: INSTRUMENTAL AND MORPHOLOGICAL EXAMINATION FINDINGS

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ABSTRACT

The aim: To study and analyze the results of instrumental diagnostic measures and morphological verification of perforations of abdominal viscera in peritonitis in newborns, their importance in timely diagnosis, as well as to present authors' experience of examining newborns with PP, taking into account the complexity of diagnosis and treatment of these patients.

Materials and methods: The study is based on the results of examining 59 newborns with PP of various etiologies. Instrumental methods that were used in the diagnosis of PP and differential diagnosis of other emergencies involved the following: radiological examination (plain abdominal radiography), abdominal and retroperitoneal ultrasound, neurosonography, echocardiography, diagnostic abdominal paracentesis.

Morphological verification of hollow viscus perforations was performed by methods of histologic examination in 54 newborns who underwent surgery.

Results: It is emphasized that perforations in NEC and spontaneous gastrointestinal perforations have clinical and morphological differences. The analysis of morphological data showed absence of intestinal musculature or muscular wall defect in spontaneous gastrointestinal perforations. Perforations in NEC had massive gastric or bowel wall necrosis. Morphogenesis of gastrointestinal perforations in newborns is crucial for developing correct treatment strategy and choosing surgical approach.

Conclusions: Diagnosis of PP in newborns should be comprehensive and include modern instrumental studies that enable to reliably establish the cause of peritonitis and indications for surgical treatment. Differential diagnosis of PP in newborns with other diseases aims to differentiate PP from a number of similar clinical symptoms of urgent conditions in order to conduct adequate preoperative preparation and appropriate surgery. Diagnostic markers of PP involve the following: pneumoperitoneum, free fluid in the abdomen, sentinel loop (intestinal distention), fixed bowel loop, cloudy brown or greenish intra-abdominal fluid with a large number of leukocytes and bacteria.

KEY WORDS: newborns, hollow viscus perforation, instrumental examination, histologic study

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INTRODUCTION

Peritonitis due to perforation of hollow viscus or perforative peritonitis (PP) in newborns is a problem of great concern in neonatal surgery, which requires immediate identification of the cause of the disease, as timely etiopathogenetic surgery is crucial for prognosis [1,2]. PP in newborns is a dangerous complication of various diseases and congenital malformations of the abdominal organs. According to various authors, mortality in PP in newborns reaches 50-80% and even 100% in premature infants with severe comorbidities [3-6]. The causes of PP in newborns might involve:

- congenital abnormalities of the gastrointestinal tract (GIT)
- necrotizing enterocolitis (NEC)
- spontaneous gastrointestinal perforation (also referred to as isolated perforation)
- acute perforated appendicitis
- iatrogenic perforations of hollow viscus, etc.

Without underestimating the importance of clinical laboratory examination of newborns with peritonitis and features of clinical progression of the disease which are familiar to neonatologists and pediatric surgeons, instrumental diagnostics can identify the cause of the disease, assess the degree of intestinal lesion and the state of other abdominal organs, perform differential diagnosis of other emergencies in newborns. In view of this, the findings of instrumental examination in PP in newborns should be correctly interpreted and considered when choosing treatment strategy.

At present, numerous mechanisms of pathological process in perforations of hollow viscus in newborns remain to be investigated, which leads to the lack of a generally accepted concept of pathogenesis of these conditions [4,5]. Therefore, studying the nature of the morphogenesis of this pathology remains a priority in solving the problem. This will allow the introduction of pathogenetic surgical techniques for PP in newborns into clinical practice, and thus lead to a favorable treatment outcome.

Having in consideration clinical differences, etiopathogenetic mechanisms and pathomorphological features of the development of perforations of abdominal viscera, isolated (also referred to as spontaneous or localized) perforations of the gastrointestinal tract in newborns are considered by most clinicians as an independent nosological unit today.

According to the literature, perforations caused by NEC account for about 53% of the total number of cases, and spontaneous perforations – 27% [3,4].

THE AIM

The aim of the work is to study and analyze the results of instrumental diagnostic measures and morphological verification of perforations of abdominal viscera in peritonitis in newborns, their importance in timely diagnosis, as well as to present authors' experience of examining newborns with PP, taking into account the complexity of diagnosis and treatment of these patients.

MATERIALS AND METHODS

The study is based on the results of examining 59 newborns with PP of various etiologies. The number of boys enrolled in the study is almost twice as large as the number of girls: 36 (61.02%) and 23 (38.98%), respectively. The proportion of premature babies was 83.05% (49 newborns). There were 14 (23.73%) newborns with extremely low body weight in the group of premature infants.

A comprehensive diagnosis was carried out, which involved clinical laboratory and instrumental methods of pathology detection.

Instrumental methods that were used in the diagnosis of PP and differential diagnosis of other emergencies involved the following:

1. Radiological examination (plain abdominal radiography)
2. Abdominal and retroperitoneal ultrasound, neurosonography, echocardiography
3. Diagnostic abdominal paracentesis
4. Morphological examination of gastrointestinal resection specimens.

Morphological verification of hollow viscus perforations was performed by methods of histologic examination in 53 newborns who underwent surgery. They were divided into 2 groups: 40 (75.47%) patients with perforated NEC, and 13 (24.53%) patients with spontaneous perforations.

To perform histologic examination, the material was fixed in a 10% neutral solution of formalin and then after standard preparation it was filled with paraffin. After that 5-7 μm paraffin sections were stained with hematoxylin-eosin and picro-fuchsin. Histologic specimens were examined under the optical microscope Carl Zeiss Axio Imager 2.

RESULTS

In our observation the causes of PP in newborns were as follows:

- Congenital intestinal obstruction – 2 (3.39%)
- Perforated NEC – 40 (67.80%)
- Isolated intestinal perforations – 13 (22.03%)
- Perforated appendicitis – 1 (1.69%)
- Perforated Meckel's diverticulum – 1 (1.69%)
- Iatrogenic rectal perforation – 1(1.69%)
- Iatrogenic gastrointestinal perforation – 1 (1.69%).

In 5 newborns (8.47%) perforations were detected in stomach, in 34 (57.63%) –at different levels of small bowel, in 12 (20.34%) – in large bowel and 8 newborns (13.56%) had multiple perforations of small and large bowel.

RADIOLOGICAL EXAMINATION

One of the main, most important and objective methods of diagnosing PP in newborns is radiological examination of patients. Radiological signs specifically attributed to PP can be seen on roentgenologic flat plates:

1. *Sentinel loop* is one of the most common symptoms, which according to the literature is found in at least 55% of patients in the early stages of the disease. A significant sentinel loop and the presence of horizontal lines indicate the severity of the disease and its progressive course. In the studied group, sentinel loop was registered in 66.10% of newborns with peritonitis (39 patients).

2. The presence of *fixed bowel loop* indicates intestinal ischemia. Such loops might be single or multiple and can be located in any part of the abdominal cavity. We are supporters of those researchers who consider this symptom pathognomonic for intestinal necrosis, and therefore an indication for surgery. Among 59 newborns who underwent surgery for PP, fixed bowel loops were found in the vast majority of patients – in 49 newborns, which amounted to 83.05%.

3. The presence of *free fluid in the abdominal cavity* which was observed in 16 newborns with PP (27.12%) is an adverse symptom indicating a reaction of the peritoneum to bacterial peritonitis, and a probability of covered intestinal perforation.

4. Gastric dilatation is a symptom caused by gastric atony due to the action of bacterial toxins, or pseudo-obstruction of the pyloric region due to swelling of the mucous membrane. Gastric dilatation in newborns with peritonitis is a fairly common symptom. It was found in the vast majority of newborns with PP (53 newborns, 89.83%).

5. Pneumoperitoneum – gas in the peritoneal cavity, under the cupula of the diaphragm, which indicates perforation of hollow viscus. However, this symptom was found in 49 (83.05%) patients who were diagnosed with perforation during the surgery. The absence of gas in the peritoneal cavity in the presence of perforation on X-ray plate is explained by the fact that perforation can be covered or open into peritoneal omental sac, which is isolated from free abdominal cavity. Pneumoperitoneum can be observed without hollow viscus perforation, for example in children with pulmonary pathology who underwent ALV. In this situation, barotrauma leads to alveolar rupture and air penetration through the mediastinum into the abdominal cavity.

ABDOMINAL ULTRASOUND

All newborns with PP underwent abdominal and retroperitoneal ultrasound, which made it possible to detect

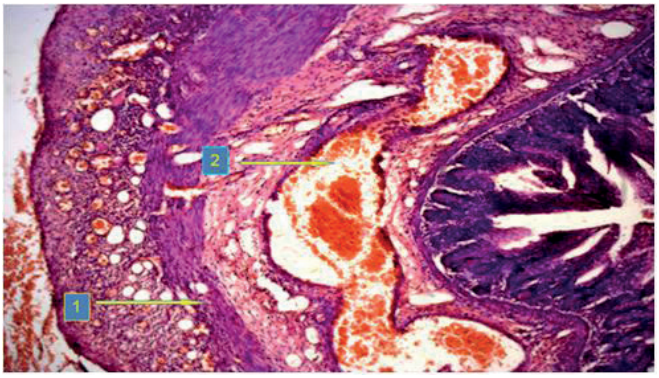

Fig.1. Fibromuscular dysplasia of the small intestinal wall in spontaneous perforation. Hematoxylin-eosin staining. Magnification 10 oc., 40 ob.
1 – a sharp thinning of the muscular membrane of the intestinal wall;
2 – aneurysm of the vessel in the submucosal layer.

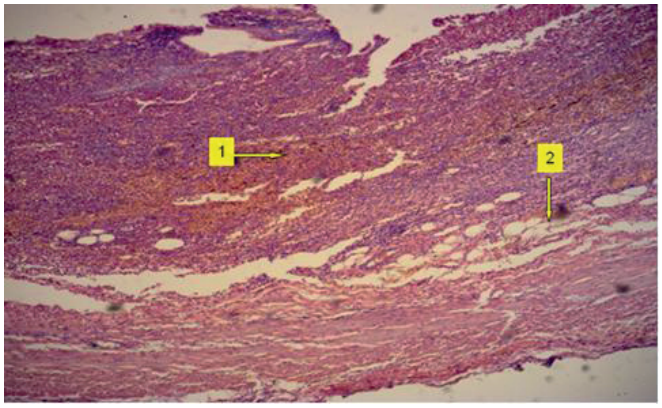

Fig.2. Necrosis of the ileal wall in perforated necrotic enterocolitis with severe leukocyte infiltration (1) and pneumatosis (2). Hematoxylin-eosin staining. Magnification 10 oc., 40 ob.

infiltrates, abscesses, fluid in the abdomen. Although ultrasound is considered to be a screening method and usually requires diagnosis specification by other methods, our records indicate that in some cases (eg, abscesses or free fluid accumulation) ultrasound is diagnostically reliable and should therefore be widely used in the diagnosis of peritonitis. Ultrasound can also detect the localization of free fluid in the abdominal cavity for paracentesis. Abdominal ultrasound revealed free fluid between the intestinal loops, decreased intestinal pneumatization, disorders of blood supply in the intestinal wall in almost all newborns with PP. In 15 (25.43%) newborns abdominal ultrasound revealed infiltrates, which included fixed intestinal loops, in 6 newborns it showed abscesses.

ABDOMINAL PARACENTESIS

The treatment of peritonitis is accompanied by diagnostic difficulties in premature infants who are in critical condition due to neurological disorders or deterioration of the function of vital organs, when the clinical picture of intra-abdominal complications is associated with more pronounced symptoms of background pathology. In such cases, abdominal paracentesis should be used for diagnostic and therapeutic purposes. Abdominal paracentesis is performed under local anesthesia with Sol.Novocaini 0.25%-5.0 with an insertion point 0.5-1.0 cm below the navel or in the right iliac region. More than 1 ml of yellow-brown or green turbid contents from the abdominal cavity during aspiration indicates intestinal necrosis. Aspirated fluid with no impurities of intestinal contents is taken for bacterioscopy. Bacterial contamination of the contents of the abdominal cavity confirms the diagnosis of intestinal necrosis.

The use of abdominal paracentesis, lavage and drainage in premature infants with low and extremely low body weight and children in critical condition has a number of advantages as it enables the following:

1. to release free air, infected contents and endotoxins from the abdominal cavity,
2. to improve cardiac activity and ventilation of the lungs due to the decrease in intra-abdominal pressure,
3. to stabilize the condition of newborns with sepsis, uncompensated metabolic disorders, coagulopathy and shock,
4. to avoid the next laparotomy in extremely premature infants with a body weight less than 1000 g.

Abdominal paracentesis and drainage were performed in 11 extremely premature infants with low and extremely low body weight and in 4 premature infants in critical condition.

MORPHOLOGICAL EXAMINATION OF BIOPSY SAMPLES OF THE INTESTINAL WALL

Gastrointestinal perforatrions can be intranatal and postnatal. In the study group 11 (18.64%) newborns had intranatal perforations, and 46 (77.97%) newborns had postnatal perforations. Postnatal gastrointestinal perforations were always accompanied by diffuse fibrinopurulent and fecal peritonitis.

Pathomorphological features of spontaneous perforation of hollow viscus in newborns involved their localization mainly in the upper gastrointestinal tract associated with congenital hypoplasia of the muscular membrane of the intestinal wall and limited pathological process (Figure 1).

The main links in the pathogenesis of perforations in NEC are ischemic and reperfusion lesions of the mucous membrane of the cavity associated with prolonged fetal hypoxia (Figure 2).

Surgical approach to PP in newborns depended on the type of perforation, its localization, pathological process progression in the wall of the hollow viscus and the general condition of the child.

DISCUSSION

The results of examining newborns with PP focuses on the main causes and diagnostic measures of peritonitis in newborns. Results of our study showed that the main causes of PP in newborns were perforated necrotizing enterocolitis

(in 67,80% patients) and spontaneous gastrointestinal perforations (in 22,03% newborns). Our studies showed that gastrointestinal perforations in newborns have clinical, instrumental and morphological differences.

Radiological examination, abdominal ultrasound and abdominal paracentesis are the most important and objective methods of diagnosing PP in newborns[4].

In the studied group sentinel loop was registered in 66,10% patients, fixed bowel loop – in 83,05% patients, gastric dilatation – in 89,83% newborns, pneumoperitoneun was found in 83,05% infants.

Ultrasound can detect the localization of free fluid in the abdominal cavity for paracentesis. Also in 15 (25.43%) newborns abdominal ultrasound revealed infiltrates, which included fixed intestinal loops, in 6 newborns it showed abscesses.

Abdominal paracentesis and drainage were performed in extremely premature infants with low and extremely low body weight and in premature infants in critical condition.

Morphological features of spontaneous perforation of hollow viscus in newborns involved their localization mainly in the upper gastrointestinal tract associated with congenital hypoplasia of the muscular membrane of the intestinal wall and limited pathological process. The microstructure analysis of hematoxylin-eosin also can show the absence of muscular portion of intestinal wall in spontaneous perforation.

Massive necrosis of the bowels wall is in perforated necrotic enterocolitis with severe leukocyte infiltration and pneumatosis[3].

Surgical treatment of newborns with PP and its effectiveness depends on not only general condition of patient but largely on type and localization of gastrointestinal perforations and their quantity.

CONCLUSIONS

1. Diagnosis of PP in newborns should be comprehensive and include modern instrumental studies that enable to reliably establish the cause of peritonitis and indications for surgical treatment.
2. Differential diagnosis of PP in newborns with other diseases aims to differentiate PP from a number of similar clinical symptoms of urgent conditions in order to conduct adequate preoperative preparation and appropriate surgery.
3. Diagnostic markers of PP involve the following: pneumoperitoneum, free fluid in the abdomen, sentinel loop (intestinal distention), fixed bowel loop, cloudy brown or greenish intra-abdominal fluid with a large number of leukocytes and bacteria.
4. Surgical approach to PP in newborns depends on the type of perforation, its localization, pathological process progression in the in the wall of the hollow viscus and the general condition of the child.
5. Hollow viscus perforations in newborns have morphological differences whereby most clinicians consider them as independent nosological units. These differences make it possible to diagnose a probable type of perforation and choose surgical approach in the preoperative period.

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ORIGINAL ARTICLE

PAIN SYNDROM IN CASES OF PATIENTS WITH A COMBINATION OF CHRONIC PANCREATITIS AND HYPERTENSION: RELATIONSHIPS, INTERACTIONS, CORRECTION

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ABSTRACT

The aim: To identify the relationships and interactions of the pain development in cases of patients with a combination of Chronic Pancreatits and Arterial Hypertension, with the next correction

Materials and methods: We have conducted a comprehensive examination of 102 patients with a diagnosis of Chronic Pancreatitis in combination with stage II Arterial Hypertension during 2018-2020. The investigative contingent was divided by two study groups which depended from the treatment regimen. The first (I) group (n = 53) received basic therapy (BT) in accordance with the requirements of the relevant clinical protocols; the treatment of the second (II) group (n = 49) included the basic therapy with optimization (OT) by mineralocorrection (Zinc, Selenium, which have antioxidant properties), ω-3 polyunsaturated fatty acids and Folic Acid. The therapy duration was 8 weeks.

Results: The performed regression analysis was mathematically substantiated the influence of the studied laboratory parameters of the inflammatory response and antioxidant system on the formation, dynamics of abdominal pain (the main clinical sign of CP) and the value of PAP (hypertensive vascular remodeling marker and risk predictor of cardiovascular events). The severity of abdominal pain is significantly influenced by leukocytes, ESR, α1-AT, cortisol, CRP, Bilirubin and Urea, and the value of PAP – CRP and selenium, from laboratory parameters of the inflammatory response and AOS,

Conclusions: The effectiveness of the assigned optimized treatment scheme has been proven, which is indicated by the appearance of a reliable regression coefficient on the parameter of glutathione peroxidase after completion of treatment in comparison with patients used basic therapy

KEY WORDS: patients, pain syndrom, Chronic Pancreatitis with Arterial Hypertension, correction

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INTRODUCTION

Chronic Pancreatitis (CP) is a chronic inflammatory disease of the pancreas, which is characterized by the gradual destruction of the exocrine parenchyma of the parenchymal organ with its subsequent atrophy and progressive fibrosis. The prevalence of CP confirms the relevance of the studied problem. Thus, the prevalence of CP ranges from 42 to 73 per 100,000 adults in the United States [1], and in European countries there are 25 cases per 100,000 population [2]. The epidemiological rates of CP In Ukraine are 3-4 times more than in Europe, while the morbidity have tendency to the steady growth (Stepanov Yu. M., 2018; Filippov Yu. O., 2016) [3].

The main signs of CP are pain, exocrine and endocrine pancreatic insufficiency. In current situation, we are able to partially correct the Pancreas function inadequacies with using of replacement therapy. However, abdominal pain, which has a chronic duration, is not always fully treatable by pharmacological standart scheme. These, of course, are significantly impairs for the improving the quality of CP patients life. The pain pathogenesis include the following components: inflammatory mechanisms, disorders of the prooxsidant-antioxidant system [4], structural problems (obstruction of the ducts by strictures and micro-macroliths, leading to ductal and parenchymal hypertension), visceral hypersensitivity (neuropathic pain) and centralization of pain. All of the above leads to chronic pain syndrome [5].

Our attention was drawn to the insufficiency of the antioxidant system (AOS) and the persistence of the inflammatory response in patients with CP., we obtained quite contradictory data on the effectiveness of antioxidant therapy in cases of patients with CP, according to the literature data. Thus, Singh N. et al. conducted a double-blind, randomized, placebo-controlled study of 107 patients and did not find significant reduction in pain in CP patients who used antioxidant therapy in comparison with the placebo group [6]. Instead, P. Bhardwaj et al., Who prescribed combination antioxidant therapy, which included selenium, β-carotene, vitamin C, vitamin E and methionine in 86 patients with CP (35 – with alcohol and 92 – with idiopathic) indicate a significant effectiveness of the proposed scheme therapy. The study of prooxidant status with usage of combination antioxidant therapy showed a regression of lipid peroxidation markers and an increase in the non-enzymatic AOC concentration. The antioxidant therapy is effective in relieving pain and reducing oxidative stress levels in patients with CP, according to the authors [7].

Most scientific studies convincingly prove that the vast majority of people who were diagnosed with non-infectious chronic disease have more than one disease [8]. This fact requires taking into account all the risks, factors of interaction and modification of a comprehensive treatment regimen. Our attention was drawn to the presence of Arterial Hypertension (AH) in patients with CP. More than 1 billion people have high blood pressure (BP), up to 45% of all adults have this disease, according to the worldwide data. In 2016, the "Lancet» published a report on a global health study of patients from 67 countries. The conclusion of this study establishes AH as the leading death cause of disability worldwide since 1990 [9].

The Oxidative stress and chronic inflammatory reactions certainly play an important role in the hypertension formation and worsen of the disease course. AH accompanied of an increasing in the reactive oxygen species production. There is a decreasing in antioxidant protection of enzymatic and non-enzymatic origin, at the same time, which caused endothelial dysfunction, vascular remodeling and tissue damage [10-13].

We considered to study the modification therapy possibility in patients with a combination of CP and AH, given the abovementioned information.

THE AIM

The aim was to identify the relationships and interactions of the pain development in patients with a combination of CP and AH, with the next correction

MATERIALS AND METHODS

We conducted a comprehensive examination of 102 patients who were hospitalized in the therapeutic department of Khust Central District Hospital with a diagnosis of CP in combination with stage II AH during 2018-2020.

Diagnosis and treatment tactics of CP and AH were carried out in accordance with the requirements of the "Unified clinical protocol of primary, secondary (specialized) medical care and medical rehabilitation approved by the order of the Ministry of Health of Ukraine.

The investigative contingent was divided into two study groups which depended from the treatment regimen. The first (I) group (n = 53) received basic therapy (BT) in accordance with the requirements of the relevant clinical protocols; the treatment of the second (II) group (n = 49) included the basic therapy with optimization (OT) by mineralocorrection (Zinc, Selenium, which have antioxidant properties), ω-3 polyunsaturated fatty acids and Folic Acid. The therapy duration was 8 weeks.

There was not significant difference between the studied groups by age: the average age of patients in group I – 49.7 ± 9.6 years, group II – 52.1 ± 9.5 years. The analysis of the gender distribution indicated a slight predominance of females in both groups (54.7% and 57.1%, respectively). The duration of CP was 7.00 ± 3.00 years, and AH – was 5.00 ± 2.00 years.

All patients underwent a clinical laboratory-instrumental study. Pain intensity was determined with using a 10-point visual analog scale (J. J. Bonica, 1990). Measurements were made in the serum of the following indicators: glutathione peroxidase (GPO), selenium (Se), zinc (Zn), albumin, transferrin, bilirubin, urea. For the antioxidant status evaluation. We determined the level of interleukins in the serum: proinflammatory IL-6 and anti-inflammatory IL-4, leukocytes, C-reactive protein (CRP), fibrinogen, α1-antitrypsin (α1-AT)), cortisol and erythrocyte sedimentation rate (ESR). These analyses presented the body's response on the activation of chronic inflammation in studied groups patients. Informative agreement was btained from all patients for the participate in the necessary research, in accordance with the requirements of the Declaration of Helsinki (1975) and its revision (1983). Statistical analysis of the results was performed using the computer program "Statistica for Windows" version 10.0.

RESULTS

Since the initial examination of patients was carried out in the stage of CP exacerbation, all patients were diagnosed with pain (n = 102; 100%). The epigastric region was the center of localization of pain (in 31 (30.4%) persons in the left hypochondrium) in the majority of patients (n = 71; 69.6%). The intensity of abdominal pain is shown on Figure 1.

The measurement of blood pressure indicated its increase within 1-2 degrees of hypertension. The obtained results of blood pressure and heart rate (HR) are given in table I.

We performed regression analysis of dynamic patients data of the formation and development of pain, modeling the level of PUP to determine the effect and interdependence of inflammatory markers and indicators of the antioxidant system The patients had the different treatment scheme, according the groups.

The main significant laboratory components of pain development were leukocytes, ESR, α1-AT, cortisol and CRP ($p < 0.05$), from the inflammatory response indicators,

Table I. Blood pressure level and heart rate in groups of patients with comorbid pathology

Parameters	SAP (mm.Hg.)	DAP (mm.Hg	PAP (mm.Hg	Heart Rate (beats/min)
I grope (n=53)	154,15 ± 9,24	94,53 ± 9,05	59,62 ± 11,52	80,26 ± 10,73
II grope(n=49)	153,27 ± 9,71	93,98 ± 8,84	59,29 ± 11,77	83,53 ± 8,46
Statistical significance of differences (p)	0,64	0,76	0,88	0,09

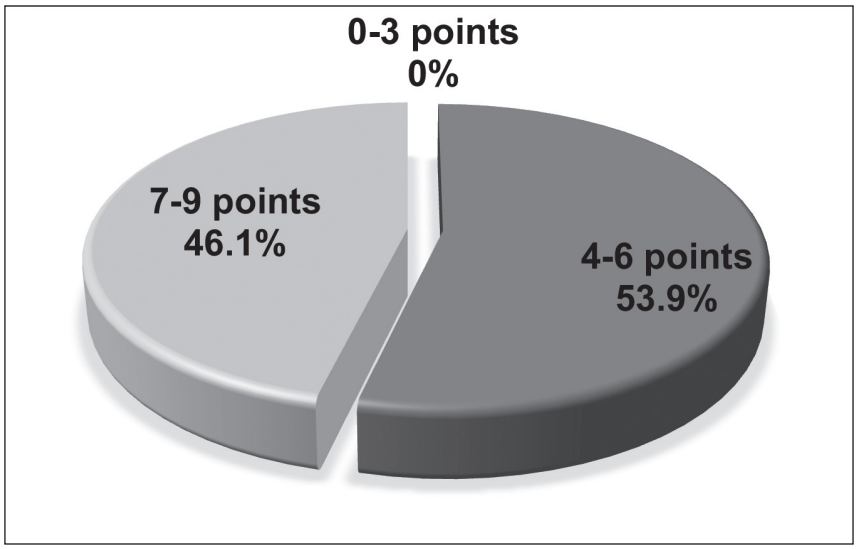

Fig. 1. The intensity of abdominal pain

Table II. The Influence of inflammatory indicators on pain syndrome

	Parameters	Before treatment	After treatment	
			BT	OT
Pain	Leukocytes	B=0,09 p=0,000005	B=-0,01 p=0,89	B=0,01 p=0,40
	ESR	B=0,06 p=0,000002	B=0,005 p=0,81	B=-0,01 p=0,59
	α1 – AT	B=0,78 p=0,0003	B=0,18 p=0,66	B=-0,02 p=0,91
	IL-4	B=0,004 p=0,99	B=0,14 p=0,53	B=0,19 p=0,1
	IL-6	B=0,02 p=0,53	B=0,01 p=0,84	B=0,002 p=0,93
	Cortisol	B=0,0005 p=0,03	B=0,00003 p=0,95	B=0,0003 p=0,06
	Fibrinogen	B=0,16 p=0,08	B=0,12 p=0,46	B=0,08 p=0,35
	CRP	B=0,11 p=0,04	B=-0,04 p=0,85	B=0,13 p=0,48

Table III. The influence of antioxidants on pain syndrome

	parameters	Before treatment	After treatment	
			BT	OT
Pain	Bilirubin	B=0,02 p=0,00004	B=0,01 p=0,72	B=0,0006 p=0,95
	Urea	B=0,11 p=0,0002	B=0,04 p=0,55	B=-0,01 p=0,78
	Folic acid	B=-0,02 p=0,36	B=-0,02 p=0,42	B=-0,01 p=0,43
	Zn	B=-0,0007 p=0,08	B=-0,0003 p=0,53	B=0,0001 p=0,61
	Se	B=0,002 p=0,69	B=0,01 p=0,25	B=-0,002 p=0,48
	Glutathione peroxidase	B=-0,008 p=0,31	B=-0,02 p=0,05	B=0,01 p=0,18
	Transferrin	B=-0,2 p=0,43	B=-0,18 p=0,54	B=0,04 p=0,67

Table IV. The Influence of inflammatory markers on the level of pulse arterial pressure

	Parameters	Before treatment	After treatment	
			BT	OT
PAP	Leukocytes	B=-0,52 p=0,23	B=0,61 p=0,49	B=0,03 p=0,97
	ESR	B=-0.15 p=0,49	B=-0,13 p=0,72	B=-0,39 p=0,35
	α1 - AT	B=-5,41 p=0,28	B=-1,37 p=0,84	B=2,55 p=0,74
	IL-4	B=1,37 p=0,79	B=2,39 p=0,53	B=5,84 p=0,19
	IL-6	B=-1,02 p=0,16	B=-1,31 p=0,17	B=0,03 p=0,97
	Cortizol	B=-0,001 p=0,82	B=0,01 p=0,36	B=0,0002 p=0,97
	Fibrinogen	B=1,82 p=0,39	B=0,7 p=0,8	B=0,06 p=0,98
	CRP	B=3,53 p=0,008	B=-1,04 p=0,74	B=6,41 p=0,38

Table V. The role of antioxidants in the formation of pulse arterial pressure

	Paramenrs	Before treatment	After treatment	
			BT	OT
PAP	Bilirubin	B=-0,06 p=0,59	B=-0,63 p=0,27	B=-0,3 p=0,44
	Urea	B=0,78 p=0,13	B=-0,17 p=0,87	B=0,44 p=0,62
	Folic acid	B=-0,26 p=0,51	B=-0,07 p=0,88	B=-0,1 p=0,7
	Zn	B=0,009 p=0,22	B=0,004 p=0,6	B=0,002 p=0,79
	Se	B=-0,29 p=0,007	B=0,02 p=0,89	B=-0,014 p=0,14
	Glutathione peroxidase	B=0,14 p=0,37	B=-0,02 p=0,89	B=0,1 p=0,5
	Transferrin	B=0,74 p=0,88	B=6,94 p=0,19	B=-1,55 p=0,68

according to our data (Table II). The regression analysis (before treatment) was performed for the whole patients contingent without distribution into groups, because the primary data did not have significant difference between the study groups

The influence of the studied inflammation markers on the pain severity is undeniable, because in the inflammatory reaction cascade, cytokines synthesized by macrophages in the inflammatory focus are the first to react (table II).

The values of regression coefficients (B) varied in both groups after treatment, but no reliable indicators were recorded in either of them. However, it was important, that more significant value reduce of the coefficient B in the group of patients who received OT, when studying the effect of the following parameters at the end of drug correction:

- ESR – reduction of the regression coefficient in patients of group II on 0.07 units (from 0.06 to -0.01). In cases of patients of the group I – on 0,05 units (from 0,06 to 0,005);
- α1-AT – dynamic index decreased on 0.8 units (from 0.78 to -0.02), and in patients receiving BT – on 0.6 units (from 0.78 to 0.18).

An important pathogenetic link in the combined pathology of CP and AH is the level of antioxidant activity of the organism and its dynamic indicators of the influence on the abdominal pain severity (Table III).

The data obtained indicate that the formation of abdominal pain was significantly influenced by the following parameters of AOS: bilirubin and urea (low molecular weight non-enzymatic antioxidants).

The pathogenetic effect of bilirubin on the intensity of abdominal pain includes the following points. The main pancreatic duct is anatomically connected to the common bile duct, which opens at the level of the large duodenal papilla, controlled by the sphincter of Oddi. Oddi's sphincter dysfunction is a fairly common combination, since 35 (34.3%) patients showed the signs of chronic cholecystitis. It is known that the dysfunction of the sphincter of Oddi disrupts the outflow of both pancreatic and bile secretion, which is accompanied by an increase in intraductal pressure, both in the Virsung duct and in the biliary tract. The pressure in the biliary ducts is higher, which causes bile reflux in the duct of the pancreas. The consequence is the activation of proenzymes with subsequent autolysis of pancreatic tissue, and clinical manifestations of pancreatic abdominal pain. This whole pathogenetic chain is accompanied by the appearance of laboratory markers that indicate the appearance or exacerbation of CP, and the obligatory, at least a slight increase in bilirubin, which is consistent with the of pancreatology scientists opinion [14].

Since the results of our analysis indicate that urea also affects the formation of pain in CP, we need to determine its pathogenetic potential. The assumption about the effect of urea on the development of pain is that, in some patients, in addition to the visceral component of pain caused by inflammation of the pancreatic tissue. There is a component of parietal pain due to a pathological process in the urinary system. vessels with high blood pressure, with increasing urea levels as a marker of elimination of low molecular weight uremic toxins. Another explanation may be the presence of oxidative stress, which also forms a pain syndrome that requires immediate activation of the AOS protection, which includes urea. The antioxidant properties of the latter have been shown to be associated with chelation of free iron and inhibition of L-arginine resynthesis to L-citrulline [15].

However, the consideration of the mechanisms of influence of urea and bilirubin on the development of abdomenalgia, there is a tendency to reduce the impact of the following indicators, with a more pronounced group of patients with OT. Thus, the coefficient B (bilirubin effect) in patients of group II decreased 33 times (from 0.02 to 0.0006) against 2 times in patients of group I (from 0.02 to 0.01). The subjects of group II decreased by 0.12 units (from 0.11 to -0.01), and patients of group I by 0.07 units (from 0.11 to 0.04), according to the parameters of urea exposure. Although, credible results have not been achieved, the dynamic indicators are significant and have tendency to decrease.

The next step was to study the effect of the investigated laboratory parameters on blood pressure. Because PAP abnormalities are an early marker of hypertensive vascular remodeling and an increased risk of cardiovascular events, consideration and analysis of levels of this parameter is appropriate and scientifically sound. Markers of the inflammatory reaction affected the PAP dynamics as follows (Table IV).

Therefore, the obtained results indicate the dominant role of CRP in the formation of the level of PAP ($B = 3.53$; $p = 0.008$). Since the value of PAP is statistically significantly correlated with SAP ($r = 0.66$; $p < 0.01$) and DAP ($r = -0.60$; $p < 0.01$), then, accordingly, CRP will have a significant effect on SAP and DAP. In addition to actively participating in the dynamics of the inflammatory response, CRP actively increases the production of endothelin-1, which is a powerful vasoconstrictor. Thus, vascular spasm and elevated blood pressure are as results of endothelial dysfunction. Therefore, the role of CRP, both for the development and progression of systemic inflammatory response, and GC is quite significant.

Regarding the influence of other studied parameters of inflammation on the development of AH, no reliable values were recorded.

We conducted a regression analysis of AOS, in order to study the participation of antioxidants in the formation of the level of PAP. The results present in table V.

After treatment (table V*)*, no significant regression coefficients were found in any of the study groups. However, it should be noted that in the group of patients with OT there is a more significant tendency to reduce the effect of the studied trace element on the level of PAP ($B = 0.02$ and $B = -0.014$, respectively, by groups).

DISCUSSION

Cytokines synthesized by macrophages in the inflammatory focus are the first to react in the inflammatory reaction cascade and have the influence of the studied inflammation markers on the pain severity. The latter increase the production of Glucocorticoids, promote the appearance of leukocytosis, ESR growth. The next step is the intensification of CRP production, the synthesis of which is activated by the influence of Cytokines, Glucocorticoids. So, these given laboratory parameters (CRP, leukocytes, ESR, cortisol) are basic mechanism in the inflammation and pain pathogenesis. The Interleukin levels had a less important role in the pathogenesis of pain, according to regression analysis. This phenomenon is a specific feature, due to the fact that life cycle of Cytokines is short.

Another inflammation indicator (α1-AT) had significant affects on the pain formation. Its involvement in the inflammatory response which initiated pain caused by the specific neutralization of Lysosomal proteases, which appear as a result of inflammatory-activated macrophages and leukocytes actions[4].

Although there are no reliable indicators of the Cortisol exposure on the pain formation after treatment, but the results show a tendency to regression coefficient decrease in both groups. Therefore, we can assume, that both treatment regimens are close to the regulatory value of the studied hormone, but the determining effect of therapeutic measures to reduce the Cortisol level of ("stress hormone") to the reference values was not observed in either group.

The dynamics of fibrinogen levels in the group of patients with OT is indicative, despite the absence of regression

coefficient probable values, which confirms a more inflammatory response intense attenuation of the compared with the group of patients receiving BT.

The prescribing OT expediency is confirmed by the appearance of a reliable regression coefficient on the parameter of GPO after treatment in the group of patients who received BT. GPO is a selenium-containing metalloprotein, and in the conditions of Se deficiency, which was found in both groups. The further synthesis of GPO will not be regulated, without the additional introduction of this factor. In patients of group II by additional introduction of Se, as a structural component of the synthesis of GPO, was possible to eliminate the negative effects of the detected deficiency and achieve a positive trend of the intensity abdominal pain reducing[2]. This is primarily due to the ability of this metal to accumulate in the focus of ischemia, which occurs under conditions of oxidative stress and to carry out a direct membrane-stabilizing effect. Although the regression coefficient, which reproduces the effect of Se on the severity of abdominal pain, in none of the groups did not reach a probable value, but in the examined group I its level increased compared to the initial value (from 0.002 to 0.01), and in patients group II – on the contrary, decreased from 0.002 to -0.002. In group I, metalloenzyme deficiency maintained the persistence of abdominal pain after treatment, indicating an insufficient level of AOS protection and continued pathological effects of free radicals on tissues and cells.

The obtained results show the dominant role of Se in the formation of the PAP indicator. Since the value of blood pressure directly depends on the balance between vasodilation and vasoconstriction factors, under conditions of oxidative stress there is an imbalance of endothelium-producing factors. These cause the appearance and progression of vasospasm. Due to the presence of Se deficiency (as an element of antioxidant protection) at the beginning of treatment in the entire contingent of patients, it is natural to have endothelial dysfunction due to damage of the vascular wall by free radicals.

CONCLUSIONS

1. The performed regression analysis was mathematically substantiated the influence of the studied laboratory parameters of the inflammatory response and antioxidant system on the formation, dynamics of abdominal pain (the main clinical sign of CP) and the value of PAP (hypertensive vascular remodeling marker and risk predictor of cardiovascular events).
2. The severity of abdominal pain is significantly influenced by leukocytes, ESR, α1-AT, cortisol, CRP, Bilirubin and Urea, and the value of PAP – CRP and selenium, from laboratory parameters of the inflammatory response and AOS.
3. The effectiveness of the assigned optimized treatment scheme is proved, which is indicated by the appearance of a reliable regression coefficient on the parameter of glutathione peroxidase after completion of treatment in comparison with patients used basic therapy.

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ORIGINAL ARTICLE

EVALUATION OF PARAMETERS OF ACTUAL TYPICAL PATHOGENETIC SYNDROMES IN COMORBIDITY OF TYPE 2 DIABETES MELLITUS AND CHRONIC PANCREATITIS

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ABSTRACT

The aim: To assess the state of typical pathogenetic syndromes (inflammation, endotoxicosis, liperoxidation, enzymatic and non-enzymatic antioxidant deficiency) in the comorbidity of type 2 diabetes mellitus (DM2) and chronic pancreatitis (CP).

Materials and methods: We examined 137 patients (112 patients with comorbidity of CP and DM2 and 25 patients with isolated CP. Typical pathogenetic syndromes (inflammation, endotoxicosis, liperoxidation, enzymatic and non-enzymatic antioxidant deficiency) were determined.

Results: It was proved that patients with CP even in the remission phase of the active course of EI and LPO, which was significantly more significant in comorbidity with DM2. Statistically significant more significant changes in the parameters of antioxidant protection in the comorbidity of CP and DM2 in relation to those in isolated CP.

Conclusions: Treatment of CP and DM2 is a difficult task and should take into account the impact on the studied common typical pathogenetic syndromes – inflammation, endotoxicosis, lipid peroxidation, and enzyme and non-enzymatic antioxidant protection – to address short-term and prevent long-term complications.

KEY WORDS: chronic pancreatitis, type 2 diabetes mellitus

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INTRODUCTION

Most diseases of the pancreas are considered as conditions affecting both the excretory and incretory parts of the body, leading to the development of chronic pancreatitis (CP) and diabetes mellitus (DM), which are often combined [1]. The problem of comorbidity and polymorbidity of such patients remains extremely relevant, as it creates additional difficulties in diagnosing and conducting adequate therapy, given the close etiopathogenetic links of these conditions, which lead to poor quality of life, increase the cost of diagnosis and treatment, increase the frequency and duration of stay in the hospital [2, 3].

THE AIM

The aim of the study was to assess the state of typical pathogenetic syndromes (inflammation, endotoxicosis, liperoxidation, enzymatic and non-enzymatic antioxidant deficiency) in the comorbidity of type 2 diabetes mellitus (DM2) and chronic pancreatitis (CP).

MATERIALS AND METHODS

We examined 137 patients (112 patients with comorbidity of CP and DM2 and 25 patients with isolated CP who were on outpatient treatment at the Ternopil Center for Primary Health Care during 2019-2020. The average age of patients was (59.43±7, 41) years (from 29 to 81 years) (CP and DM2 – (57.76±5.81) years, CP – (58.23±5.44) years); there were 70 women (51.09%) and 67 men (48.91%) (CP and DM2: women – 57 (50.89%), men – 55 (49.11%), CP: women – 13 (52.00%), men – 12 (48.00%)). The control group consisted of 30 healthy people. Exclusion criteria were cancer, acute and exacerbation of chronic pathologies of vital organs, type 1 diabetes, active gastric and duodenal ulcers, viral hepatitis and liver cirrhosis, Crohn's disease, nonspecific ulcerative colitis, cystic fibrosis. The duration of comorbidity of CP and DM2 ranged from 1 to 27 years, the average duration was (9.89±2.68) years.

The materials of the clinical study were considered at the meeting of the commission of bioethics of Ternopil National Medical University Protocol № 60 from 01.09.2020. The work was carried out in accordance with the Code of Ethics of the Declaration of Helsinki. All patients signed an information agreement to participate in the study.

The diagnosis of DM2 was verified by the Order of the Ministry of Health of Ukraine from № 1118 from 21.12.2012 "On approval and implementation of medical and technological documents for the standardization of medical care for type 2 diabetes mellitus." The diagnosis of CP was established according to the clinical and statistical classification proposed by the State Institution "Research Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine" in 2003, as well as the Order of the Ministry of Health of Ukraine dated 10.09.2014 № 638 "On approval and implementation of medical documents».

Table I. Comparative analysis of the parameters of endotoxicosis, pro- and antioxidant protection in CP depending on the presence of concomitant DM2

Parameter EI, LPO-AOP	Control group (n=30)	Patients with CP (n=25)	Patients with CP and DM2 (n=112)	p_1	p_2	p_3
IEI,%	27,25±1,22	49,76±2,13	58,57±1,14	<0,05	<0,05	<0,05
MWP1	334,11±2,64	438,87±21,14	568,77±18,23	<0,05	<0,05	<0,05
MWP2	147,53±1,23	206,38±10,23	279,75±7,77	<0,05	<0,05	<0,05
MA, μmol/l	2,81±0,095	5,36±0,15	5,67±0,15	<0,05	<0,05	<0,05
CIC, con. un.	64,19±1,65	104,26±1,23	129,76±1,46	<0,05	<0,05	<0,05
GF, μmol/l	60,51±2,13	58,19±2,12	52,23±0,77	>0,05	<0,05	<0,05
SOD, con. un.	62,15±2,85	44,77±1,17	40,94±0,54	<0,05	<0,05	<0,05
Catalase, %	17,48±0,87	16,11±0,39	13,55±0,11	>0,05	<0,05	<0,05
Ceruloplasmin, mg/l	245,60±2,61	305,11±8,77	341,72±9,47	<0,05	<0,05	<0,05
Ascorbic acid, mg/l	10,26±0,25	5,28±0,29	4,25±0,17	<0,05	<0,05	<0,05
Tocopherol, μmol/l	113,04±0,24	71,11±5,67	68,18±2,57	<0,05	<0,05	<0,05
Retinol, μmol/l	1,61±0,02	1,58±0,09	0,95±0,15	>0,05	<0,05	<0,05
Complement, hem. un.	289,30±4,91	165,23±2,21	145,84±2,77	<0,05	<0,05	<0,05

Note: p_1 – the significance of the difference in the parameters of patients with CP in relation to such control groups;
p_2 – the significance of the difference in the parameters of patients with CP and diabetes mellitus in relation to such control groups;
p_3 – the significance of the difference in the parameters of patients with CP and DM2 in relation to such groups of isolated CP.

A number of parameters of endogenous intoxication (IEI) were studied. IEI was determined by the method of universal adsorption capacity of erythrocytes. Also, evaluate the levels of medium molecular weight peptides (MWPs) MWP1 and MWP2: studied the optical serum density at wavelengths of 254 and 280 nm, thus determining the content of those MWP, which contain aromatic amino acids, and those that do not contain them. The level of circulating immunocomplexes (CIC) was determined by selective precipitation in 3.75% ethylene glycol followed by photometry. Lipid peroxidation (LPO) was evaluated by the content of malonic aldehyde (MA), which was determined by reaction with 2-thiobarbituric acid. A number of parameters of antioxidant protection (AOP) were investigated. Glutathione free (GF) was determined by reaction with sodium n-mercurbenzoate. SOD activity was determined in the reaction with nitrotetrazolium. Catalase activity was determined in the H2O2 substrate cleavage reaction. Determination of ceruloplasmincontent was performed taking into account its exceptional ability to oxidize n-phenylenediaminedihydrochloride. The content of vitamin C in blood plasma was determined by the Farmer method. Tocopherol and retinol levels were determined spectrophotometrically.

The conformity of the distribution of clinical study data to the law of normal distribution was checked by the Kolmogorov-Smirnov test. The arithmetic mean and standard error (M±m) were used to describe the data in the normal distribution. Since the data obtained as a result of the clinical study had deviations from the normal distribution of the variation series, we used nonparametric statistical methods to compare groups – the Mann-Whitney U-test (for independent groups). We used the software and mathematical complex for the personal computer "Microsoft Exel 2016" (Microsoft) and computer programs for statistical analysis and data processing "STATISTICA® 8.0".

RESULTS

A comparative analysis of certain parameters of EI, lipid peroxidation (LPO), as well as the state of AOP systems was performed (data in Table I).

It was proved that even in the remission phase of CP the active course of EI and LPO, which was statistically significantly more significant when the comorbidity of CP with DM2 ($p<0.05$).

The study revealed statistically significant changes in the parameters of AOP in the comorbidity of CP and DM2 relative to those in isolated CP: weakening of the enzyme unit of AOP by SOD and catalase levels, as well as non-enzymatic unit by GF level, which summarize the state of glutathione AOP.

There was also a significant decrease in blood levels of vitamin non-enzymatic antioxidants in patients with CP relative to the control group and the deepening of this decrease in patients with comorbidity of CP and DM relative to those with isolated CP ($p<0.05$). This proved not only the decrease in the capacity of AOP for non-enzymatic antioxidant vitamins, but also the deepening of trophological vitamin deficiency in the combined course of CP and DM2 in comparison with the isolated course of CP. Depletion of the complement system was found in groups of patients with CP and CP with DM2, which proved the complicating role of diabetes mellitus on the protective potential of the complement system, and confirmed the assumption of more significant depletion of visceral protein pool in CP in comorbidity with DM2. On the basis of the received data it is possible to assert about a predictor role of chronic nonspecific inflammatory process in the course of CP and deepening of displays of trophological insufficiency at the examined patients.

However, CP activation was also found ($p<0.05$), which can be explained by the presence of certain AOP reserves even in such comorbid patients. The statistically significant increase

in CP in CP relative to the control group and especially in concomitant DM2 relative to the group of isolated CP can also be explained by the activity of torpid inflammation and endotoxicosis even in the remission phase of CP.

DISCUSSION

An important result of the study is to establish that the comorbidity of CP and DM2 significantly worsens the patient's condition and contributes to the progression of both comorbid pathologies in terms of endotoxicosis, pro- and antioxidant status. Patients with this comorbidity are at risk for the possible development of unpredictable complications. In most clinical trials, patients with comorbidity of CP and DM are usually excluded, although in practice this is not possible [4]. Treatment of comorbidity of CP and diabetes is a difficult task, and it requires a multidisciplinary approach because it is necessary to take into account the specifics of treatment of exocrine pancreatic insufficiency and chronic hyperglycemia, taking into account the pathogenetic manifestations of inflammation, endotoxicosis, oxidative stress, and oxidative stress.

An analysis of the literature convincingly proves that the relationship between CP and DM2 is quite complex. All pathological processes in DM2 make a significant contribution to the development and progression of CP and vice versa [5,6]. Polymorbidity of CP and DM is causal, given the development of diabetes in the first functional disorders of the pancreas, and later organic disorders of the pancreas, which are based on established in the study of inflammatory phenomena, signs of EI, LPO, and attenuation of AOP [7]. Based on the analyzed data from the scientific literature and our own research, it can be stated that the problem of functional and organic lesions of the pancreas in patients with DM2 is insufficiently studied [8]. Prospects for further research are to expand the understanding of changes in the CP on the background of DM2 and the development of schemes for diagnosis and drug therapy of the combined course of DM2 and CP. Treatment of CP and DM2 is a difficult task and should take into account the impact on the studied common typical pathogenetic syndromes – inflammation, endotoxicosis, lipid peroxidation, and enzyme and non-enzymatic AOP – to address short-term and prevent long-term complications.

CONCLUSIONS

1. It was proved that patients with CP even in the remission phase of the active course of EI and LPO, which was significantly more significant in comorbidity with DM2.
2. Statistically significant more significant changes in the parameters of AOP in the comorbidity of CP and DM2 in relation to those in isolated CP. There was a significant decrease in blood levels of vitamin non-enzymatic antioxidants in patients with CP relative to the control group and the deepening of this decrease in patients with comorbidity of CP and DM2 relative to those with isolated CP. This proved not only the decrease in the capacity of AOP for non-enzymatic antioxidant vitamins, but also the deepening of trophological vitamin deficiency in the combined course of CP and DM2 in comparison with the isolated course of CP.
3. Depletion of the complement system in groups of patients with CP and CP with DM2 was found, which proved the complicating role of DM2 on the protective potential of the complement system, and confirmed the assumption of more significant depletion of visceral protein pool in CP in comorbidity with DM2.

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ORIGINAL ARTICLE

INTESTINAL LESIONS OCCURRING IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AFTER SUFFERING THE COVID-19 INFECTION

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ABSTRACT

The aim: To investigate the effectiveness of determining the activity of faecal calprotectin for detecting colonic lesions in patients with nonalcoholic fatty liver disease who have had a COVID-19 acute respiratory infection.

Materials and methods: The study included 46 patients with non-alcoholic fatty liver disease NAFLD at the stage of outpatient observation after suffering a COVID-19 acute respiratory infection.

Results: One of the main clinical signs indicating intestinal lesions among the COVID-19-infected patients with NAFLD at the time of admission to hospital was diarrhea (identified in 43.5% of cases during the patients' examination), as well as bloating and pain in the colon (identified in 26.1% and 32.6% of cases during the patients' examination, respectively). The analysis of the data obtained indicates a slight increase in the level of faecal calprotectin among NAFLD patients infected with COVID-19 during hospital treatment, and in this regard the indicators did not exceed the reference values. A more pronounced deviation from the norm was observed 2 months after hospital treatment, namely, its increase to 101.6 ± 2.5 μg / L.

Conclusions: A frequent clinical manifestation of intestinal lesions among NAFLD patients infected with COVID-19 is defaecation disorder, which at the beginning of the disease is more often manifested through alternating diarrhea (up to 43.5%) and constipation (32.6% of the examined patients). NAFLD patients infected with the COVID-19 virus are diagnosed with an intensified activity of faecal calprotectin and α1-antitrypsin in the blood serum and faeces, as well as the clearance, and this indicates the presence of inflammatory changes in the colon, which requires conducting further research of these patients' cases.

KEY WORDS: non-alcoholic fatty liver disease, intestine, COVID-19, faecal calprotectin, α1-antitrypsin

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INTRODUCTION

Novel Coronavirus disease (COVID-19) is a newly discovered contagious disease caused by severe acute respiratory syndrome (SARS)–coronavirus (CoV)-2 virus, primarily manifesting as an acute respiratory illness with interstitial and alveolar pneumonia, but it can affect multiple organs such as the kidney, heart, digestive tract, blood, and nervous system [1].

Recent years have seen an increase in the spread of non-alcoholic fatty liver disease (NAFLD) along with an increase in the incidence of obesity and type 2 diabetes. Non-alcoholic fatty liver disease takes on a leading role among other etiological forms of chronic liver damage in Western countries, and is currently considered as one of the main causes of the development of cryptogenic liver cirrhosis. In Western countries, 17-46% of the adult population is diagnosed with NAFLD and the figure reaches 90% in cases with obese patients [2, 3].

The liver and the intestine are closely connected and the interaction between them is bidirectional since products of intestinal origin enter the intestine, passing through the portal vein to the liver, while the bile and antibodies secreted by the liver travel from the liver through the intestinal tract. Consequently, patients with NAFLD experience that the liver dysfunction also negatively affects the functional state of the intestines. A growing body of evidence indicates a close relationship between dietary and environmental factors (food contaminants, bacteria, viruses are among them), intestine, blood flow and metabolism in the liver with pathways including intestinal permeability, composition of intestinal microbiota, bacterial products, immunity, local and systemic inflammation [4].

Of particular importance is the studying of the course and formation of metabolically associated diseases and their complications in the face of the COVID-19 (or SARS-CoV-2) pandemic when it has been proved that persons with metabolic disorders such as obesity, diabetes, non-alcoholic fatty liver disease, cardiovascular diseases are prone to a more severe COVID-19 course, they are more likely to require treatment in intensive care units as well as treatment with the help of artificial lung ventilation apparatus; yet among these people the mortality rate due to being infected with the COVID-19 virus is higher. It should be noted that intestinal disorders in the presence of chronic

diffuse hepatic lesions, including NAFLD, may adversely affect the functioning of the immune system, which again is of importance under the COVID-19 pandemic when it comes to patients with a high risk of metabolic diseases.

THE AIM

The aim of the research is to investigate the effectiveness of determining the activity of faecal calprotectin for detecting colonic lesions in patients with nonalcoholic fatty liver disease who have had a COVID-19 acute respiratory infection.

This scientific research is part of the thematic areas studied by the Department of Propaedeutics of Internal Diseases «Polymorbid Pathology in Cases with the Digestive System Diseases, Pathogenesis, the Correction Possibilities (state registration number 0118U004365) and «Clinical and Pathogenetic Peculiarities of Emerging Polymorbid Diseases in the Presence of the Digestive System Lesions and the Development of Differentiated Schemes of Their Therapy in the Context of the COVID-19 Pandemic.

MATERIALS AND METHODS

A comprehensive examination and treatment of patients was conducted on the clinical basis of the Department of Propaedeutics of Internal Diseases at the Medical Faculty of state higher educational establishment «Uzhhorod National University». The study included 46 patients with NAFLD at the stage of outpatient observation after suffering a COVID-19 acute respiratory infection. All examined patients were previously hospitalized in the department for treating COVID-19 infected patients based on communal non-profit enterprise «The Transcarpathian Regional Clinical Hospital Named after A. Novak» of Transcarpathian Regional Council during the period between October 2020 and March 2021 and had a confirmed diagnosis of COVID-19 pneumonia (the positive polymerase chain reaction (PCR test) to SARS-CoV-2 RNA (the RdRP SARS-CoV-2 gene, the E SARS-CoV-2 gene), as well as lung lesions manifested through «ground glass» opacities in computed tomography scans with the maximum percentage of lung tissue damage up to 50%) and did not require patients be connected to the artificial ventilator. The hospitalized patients were treated according to the standards of medical care provided to patients with the COVID-19 infection, which included the prescription of antiviral therapy, glucocorticoids, anticoagulants, vitamin D3, zinc and antibiotic therapy.

Among the examined patients there were 27 men (58.7%) and 19 women (41.3%). The average age was 53.7 ± 3.1 years. The control group included 20 healthy individuals (there were 12 men (60.0%) and 8 (40.0%) women). The average age was 51.4 ± 4.6 years).

Criteria for exclusion from the study were severe and extremely severe condition of patients infected with COVID-19, a positive test for Clostridium defficile antigens in feces, the presence of alcohol, autoimmune, viral (hepatitis B, C, D viruses) liver lesions, nonspecific ulcerative colitis, with past medical history of Crohn's disease.

All research was conducted with the patients' consent (all patients received a written consent for appropriate diagnostic and treatment measures), and the research methodology corresponded to the Declaration of Helsinki of 1975 and its revision in 1983, the Convention on Human Rights and Biomedicine developed by the Council of Europe and legislation of Ukraine.

All examined patients were subjects to research carried out in accordance with the general clinical, anthropometric, instrumental and laboratory methods. In order to verify the diagnosis attention was paid to the nature of complaints, medical history. In anthropometric research, height, weight, waist circumference were measured, and the body mass index (BMI) was calculated. According to WHO recommendations, the patients were distributed depending on the BMI where the BMI sore of 16.0 or less corresponded to a pronounced deficit of body weight; 16.0–18.5 corresponded to insufficient body weight; 18.0–24.9 – normal weight; a BMI of 25.0–29.9 corresponds to being overweight; 30.0–34.9 – class I obesity; 35.0–39.9 – class II obesity; 40.0 and more – class III obesity [5].

The ultrasound examination of all the patients' abdominal organs was carried out according to the generally accepted procedure. There were done standard general and biochemical tests based on the blood serum to determine the functional state of the liver (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT)), indicators of lipid metabolism (total cholesterol), triglycerides (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL), very-low-density lipoproteins (VLDL), the atherogenic index was calculated), carbohydrate metabolism (glucose, insulin, glycated hemoglobin (HbA1c,%)).

NAFLD was diagnosed in accordance with the criteria of the unified clinical protocol (Order of the Ministry of Health of Ukraine dated 06.11.2014 № 826) and the EASL-EASD-EASO clinical recommendations on the diagnosis and treatment of NAFLD [6]. The degree of liver damage was calculated using surrogate markers of fibrosis by means of online calculators NAFLD fibrosis score (NFS), the Fibrosis 4 calculator (FIB-4) as well as FibroTest and the liver elastograpthy results.

The level of α1-antitrypsin in the blood serum and faeces was measured using the method of enzyme-linked immunosorbent assay (ELISA), followed by calculating its clearance with the help of the test system from Immundiagnostik AG (Germany). The activity level of faecal calprotectin was determined using the ELISA method too. The study of these indicators was carried out when the patients were being treated in the hospital (upon admission as well as immediately before discharge from the inpatient department) and 2 months after discharge from the hospital.

The analysis and processing of the results of examining the patients was performed using the computer program STATISTICA 10.0 (StatSoft Inc, USA) using parametric and non-parametric methods of evaluating the received results.

RESULTS

The inpatient treatment of an acute respiratory infection associated with COVID-19 lasted on average 21.7 ± 3.4 days. Upon admission to the hospital all examined patients were diagnosed with steatohepatitis of minimal activity level (Table I). Notably, the level of ALT was 68.9 ± 2.0 U/L – p-value <0.01, and AST was 47.9 ± 1.4 U/L – p-value <0.05. Before discharge from the hospital another test revealed a significant increase of transaminases in blood serum (2.3 times ALT and 3.0 times AST – p-value <0.01), which is probably due to toxic liver damage caused under the received treatment, yet an increase in GGT (up to 86.5 ± 2.8 U/L with 43.2 ± 2.6 U/L on admission to the hospital) also indicates to it. If the level of TBIL and ALP in the blood serum at the beginning of treatment was within normal limits, then at the end of the therapy in the hospital it was found out that their level increased by 20.8 ± 1.9 mmol/L and 40.2 ± 0.2 mmol/L respectively (p-value <0.05). The control test of these parameters in the blood serum (2 months after being discharged from the hospital) points to the normalization of TBIL, ALP and GGT levels, while the activity of AST and ALT decreased only by 1.6-1. 5 times respectively (– p-value <0.05).

The study of lipid profile indicators also points to the fact that at the time of admission for hospital treatment all examined patients with NAFLD had dyslipidemia. The complex therapy aimed at maintaining the body's impaired vital functions and preventing their disorders. It is quite probable that the very COVID-19 virus contributes to lipid metabolism disorders in patients with NAFLD, which is manifested through a slight increase in total cholesterol (TC), TG, LDL and VLDL levels (Table II).

The study of carbohydrate metabolism in cases with the COVID-19-infected patients with NAFLD, at the time of being admitted to the hospital indicates to the presence of insulin resistance with normal serum glucose and HbA1c levels (Table III). It should be noted that at the end of the inpatient treatment phase there was identified a slight sugar level increase in the blood serum and hyperinsulinemia and this was accompanied by an even higher HOMA-IR index (it reached 6.87±0.71 – p-value <0.01). The liver function tests

Table I. The change of the indicators of the functional state of liver in the examined patients' blood serum

Indicator	Control group (n=20)	The examined patients (n=46)		
		Inpatient treatment phase		2 months after inpatient treatment
		Upon admission	Upon discharge	
ALT, U/L	23.4±1.1	68.9±2.0**	156.4±3.2++	103.2±2.2^
AST, U/L	22.7±1.4	47.9±1.4*	144.7±3.5++	88.3±4.2^
TBIL, mmol/L	13.3±0.7	20.8±0.9	32.7±2.8+	20.6±1.8
ALP, mmol/L	68.8±2.9	84.1±3.3	124.3±3.1+	74.7±3.0^
GGT, U/L	34.1±1.7	43.2±2.6	86.5±2.8++	40.1±2.9^^

NB: the statistically-valid difference between the indicators of the control group and the examined patients upon admission to the hospital was: * – p-value <0.05; ** – p-value <0.01; the statistically-valid difference between the indicators upon admission to the hospital and upon discharge from the hospital was: + – p-value <0.05; ++ – p-value <0.01; the statistically-valid difference between the indicators at discharging the patients from the hospital and 2 months afterwards was: ^ – p-value <0.05; ^^ – p-value <0.01.

Table II. The change of lipid metabolism indicators in the examined patients' blood serum

Indicator	Control group (n=20)	The examined patients (n=46)		
		Inpatient treatment phase		2 months after inpatient treatment
		Upon admission	Upon discharge	
TG, mmol/L	1.12±0.05	2.44±0.17**	3.24±0.22+	2.38±0.27^
TC, mmol/L	4.38±0.56	7.22±0.48**	7.68±0.25	7.20±0.31
LDL, mmol/L	1.66±0.29	3.32±0.16**	3.89±0.20	3.28±0.19
VLDL, mmol/L	0.56±0.04	1.77±0.23**	1.88±0.16	1.84±0.35
HDL, mmol/L	1.90±0.09	0.94±0.11*	0.97±0.11	1.22±0.14
Atherogenic index	1.58±0.18	5.78±0.61**	5.95±0.44	5.83±0.41

NB: the statistically-valid difference between the indicators of the control group and the examined patients upon hospital admission was: * – p-value <0.05; ** – p-value <0.01; the statistically-valid difference between the indicators upon hospital admission and discharge from the hospital was: + – p-value <0.05; the statistically-valid difference between the indicators at discharging the patients from the hospital and two months after it was: ^ – p-value <0.05.

Table III. The change of indicators of carbohydrate metabolism in the examined patients' blood serum

Indicator	Control group (n=20)	The examined patients (n=46)		
		Inpatient treatment phase		2 months after inpatient treatment
		Upon admission	Upon discharge	
Glucose in blood on an empty stomach, mmol/L	4.46±0.18	5.21±0.23	7.88±0.25+	8.26±0.28
HbA1c, %	4.22±0.25	5.28±0.28	5.66±0.48	7.02±0.29^
Insulin, U/L	9.27±0,44	15.11±1.43	19.95±0.77	21.15±0.98
C-peptide, ng/ml	4.36±0.28	7.89±0.56*	10.12±0.51	12.44±1.07
HOMA-IR	1.18±0.33	3.65±0.27**	6.87±0.71++	7.67±0.45^

NB: the statistically-valid difference between the indicators of the control group and the examined patients at being admitted to the hospital was: * – p-value<0.05; ** – p-value<0.01; the statistically-valid difference between the indicators upon hospital admission and when being discharged from the hospital was: + – p-value<0.05; ++ – p-value<0.01; the statistically-valid difference between the indicators at the end of the patients' hospital stay and 2 months afterwards was: ^ – p-value<0.05.

Table IV. Clinical manifestations of intestinal lesions among the examined COVID-19-infected patients with NAFLD

Indicator	The examined patients (n=46)		
	Inpatient treatment phase		2 months after inpatient treatment
	Upon admission	Upon discharge	
Diarrhea	43.5 %	56.5 %	30.4 % ^
Constipation	4.3 %	17.4 % ++	32.6 % ^^
Diarrhea alternating with constipation	-	26.1 %	37.0 %
Flatulence	26.1 %	52.2 % ++	73.9 % ^
Colon pain	32.6 %	63.0 % ++	26.1 % ^^

NB: the statistically-valid difference between the indicators on admission to hospital and upon discharge from the hospital was: + – p-value <0.05; ++ – p-value <0.01; the statistically-valid difference between the indicators upon discharging the patients from the hospital and 2 months afterwards was: ^ – p-value<0.05; ^^ – p-value<0.01.

Table V. The change of faecal calprotectin and α1- antitrypsin indicators among the examined patients

Indicator	Control group (n=20)	The examined patients (n=46)		
		Inpatient treatment phase		2 months after inpatient treatment
		Upon admission	Upon discharge	
Faecal calprotectin, μg /L	26.3±1.15	36.1±1.6	45.9±2.3	101.6±2.5^^
		α_1-antitrypsin level		
in blood plasma, mg/dL	121.71±2.21	188.07±3.15*	221.12±3.66+	446.12±4.70^^
in stool, mg/dL	14.25±0.23	17.11±0.67	31.10±0.51+	22.88±0.44
α_1-antitrypsin clearance, mL/24hrs	17.33±0.45	19.56±0.45	89.87±0.36++	106.07±1.12^

NB: the statistically-valid difference between the indicators of the control group and the examined patients upon hospital admission was: * – p-value <0.05; the statistically-valid difference between the indicators upon hospital admission and upon discharge from hospital was: + – p-value <0.05; ++ – p-value <0.01; the statistically-valid difference between the indicators at the end of the patients' hospital stay and two months afterwards was: ^ – p-value <0.05; ^^ – p-value <0.01.

and lipid metabolism indicators that the COVID-19-infected patients with NAFLD had, tended to be normal and on the contrary, 2 months after undergoing inpatient treatment, more pronounced negative changes in the level of carbohydrate metabolism indicators were identified, and together with hyperinsulinemia and insulin resistance an increase in both the serum glucose (up to 8.26 ± 0.28 mmol / L) and HbA1c (up to 7.02±0.29 – p-value <0.05) levels was diagnosed.

Hence, the COVID-19 virus itself is likely to contribute to the occurrence or progression of disorders of lipid and carbohydrate metabolism in cases with patients having NAFLD, and the very treatment, aimed at eliminating the virus and maintaining vital functions of the body, leads to the impaired functional activity of the already compromised liver.

One of the main clinical signs indicating intestinal lesions among the COVID-19-infected patients with NAFLD at the

time of admission to hospital was diarrhea (identified in 43.5% of cases during the patients' examination), as well as bloating and pain in the colon (identified in 26.1% and 32.6% of cases during the patients' examination, respectively) – Table IV. The progression of COVID-19 infection, as well as the received comprehensive antiviral, antibacterial therapy contributed to an increase in the number of patients with diarrhea (up to 56.5% of cases), and the increased frequency of defaecation acts (up to 8-12 times a day) was identified too. An increase of the frequency of abdominal pain and discomfort, and bloating were also diagnosed.

It is noteworthy that at the time of admission to the hospital, only 4.3% of patients complained of constipation, while 2 months after inpatient therapy, the number of patients with constipation increased to 32.6% (p-value <0.01). Constipation was accompanied by severe bloating. There were identified some cases when a feeling of evacuation was incomplete, especially among patients who experienced alternating periods of constipation and diarrhea.

We have determined the level of faecal calprotectin and α1-antitrypsin in the blood serum and faeces, and also calculated its clearance among the examined patients with NAFLD in order to study the severity of inflammation and identify these patients' intestinal barrier permeability (Table V).

The analysis of the data obtained indicates a slight increase in the level of faecal calprotectin among NAFLD patients infected with COVID-19 during hospital treatment, and in this regard the indicators did not exceed the reference values. A more pronounced deviation from the norm was observed 2 months after hospital treatment, namely, its increase to 101.6 ± 2.5 μg / L. The level of α1-antitrypsin in the blood serum of NAFLD patients increased by 1.5 times already during the first days of the COVID-19 infection. The maximum deviation from the norm was also identified 2 months after confirming the COVID-19 infection among NAFLD patients. An increase in the clearance of α1-antitrypsin among the examined patients indicate the intestinal barrier dysfunction and increased permeability of the intestinal wall. In this connection, the maximum deviation from the norm was also diagnosed 2 months after the repeated PCR test for COVID-19 which turned out to be negative.

DISCUSSION

As is known, SARS-CoV-2 mainly infects cells by binding to the ACE 2 receptor (*Angiotensin I converting enzyme 2)* which is involved in maintaining homeostasis-angiotensin-aldosterone system that plays a crucial role in physiological and pathological mechanisms in all organs. The significant expression level of ACE 2 is observed in the tissue of the lungs and this determines their vulnerability to infection, but this receptor is also expressed in the heart, liver and intestines. The probable mechanisms of infecting the gastrointestinal tract by SARS-CoV-2 include the following: 1) dysregulation of ACE 2 whose deficiency increases the susceptibility to the intestinal inflammation. It is possible that SARS-CoV-2, which reduces the expression of ACE 2 in the lungs, similarly reduces it in the intestines; 2) «the change in the composition and functions of the microflora as a result of hypoxia caused by COVID-19; 3) the intestinal barrier dysfunction due to local inflammation or virus replication; 4) the involvement of «the intestine-brain» axis. The intestinal nervous system can be damaged either directly by a viral infection or by components of the immune response, resulting in intensified diarrhea and possibly stimulating the vagus nerve, which causes vomiting [7].

According to the findings of our research, it was revealed that the NAFLD patients infected with the COVID-19 virus, against the background of liver lesion progression, experience an increased preassure on the intestines, which is clinically manifested through daefecating disorders, pains and bloating of the intestines. The increased activity of faecal calprotectin and α1-antitrypsin among NAFLD patients indicates the intestinal barrier dysfunction and development of inflammatory lesions of the colon. The obtained data point to the need for the long-term monitoring of NAFLD patients infected with COVID-19, and also confirm the rationale for prescribing imaging methods in order to study the state of these patients' mucous membrane.

Thus, the study of various possible mechanisms of intestinal damage caused by SARS-CoV-2 infection is of particular interest among patients with chronic diffuse liver diseases, including NAFLD. The search for informative markers enabling the identification of inflammatory changes and disorders of the intestinal barrier function is a crucial task today. The study of the levels of faecal calprotectin and α1-antitrypsin in the blood serum and faeces has shown that they turn out to be these specifically highly effective markers; this has made it possible to recommend them for a wide range of applications for the early diagnosis of intestinal disorders among NAFLD patients who have had COVID-19.

Hence, the determination of the functional state of the intestine among patients with NAFLD who have had the COVID-19 acute respiratory infection is an urgent issue of modern medicine in view of the fact that research in this area can reveal new links in the pathogenetic mechanisms of the course of this infection in case of metabolically caused diseases with an emphasis on finding new effective methods of their detection for the timely prescription of an adequate pathogenetically determined therapy.

CONCLUSIONS

1. NAFLD patients infected with the COVID-19 virus were diagnosed with disorders of lipid and carbohydrate metabolism and their progression in accordance with the severity of functional lesions of the liver.
2. A frequent clinical manifestation of intestinal lesions among NAFLD patients infected with COVID-19 is defaecation disorder, which at the beginning of the disease is more often manifested through alternating diarrhea (up to 43.5%) and constipation (32.6% of the examined patients).
3. NAFLD patients infected with the COVID-19 virus are diagnosed with an intensified activity of faecal calprotectin and α1-antitrypsin in the blood serum and faeces, as

well as the clearance, and this indicates the presence of inflammatory changes in the colon, which requires conducting further research of these patients' cases.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

PECULIARITY OF ADAPTATION OF BABIES ARE BORN PREMATURELY FROM MOTHERS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA

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ABSTRACT

The aim: To evaluate the peculiarity of clinical manifestations of neonatal respiratory distress syndrome (NRDS) in deeply premature infants from mothers with phenotypic markers of undifferentiated connective tissue dysplasia (UCTD).

Materials and methods: The study represent the results of a retrospective clinical and statistical analysis of 268 premature birth report card and newborn report sheet. .The main (1 group) included 50 pregnants with obvious phenotypic markers of UCTD, the comparison group (group 2) consisted of 50 pregnant women without phenotypic markers of UDCTD.

Results: According to the study, in 12 (24%) pregnant women of the main group at the time of admission to the clinic had contractions,which required specific therapy. Cervical cerclage was performed in 38 (76%) patients of the main group due to the presence of cervical insufficiency (CI). In these cases, the severity of the CI on the Steinber scale was 7.2 ± 0.4 points in the main group against 4.4 ± 0.2 points in the comparison group ($p < 0.05$). Group I patients were more likely to have complications of labor such as:premature rupture of membranes, uterine contraction abnormalities and fetal distress, which required in most cases cesarean delivery (7% and 2%), respectively ($p < 0.05$). The incidence of neonatal complications requiring respiratory support was 67% in group I and 48% in group II. According to our observations, the clinical manifestations of bronchopulmonary dysplasia were twice as high in infants of the main group (66%) against (44%) of the comparison group ($p < 0.05$).

Conclusions:1.Neonatal respiratory distress syndrome in premature infants is more often associated from mothers with UDCTD. 2. The high importance of steroid prophylaxis of NRDS and antioxidant therapy in reducing the frequency of mechanical ventilation and the development of bronchopulmonary pathology, especially in infants from mothers with UDCTD syndrome, has been proven. 3. The possibility of diagnosing disorders of functional maturation of the lungs in the fetal period using a non-invasive method of ultrasonography has been confirmed.

KEY WORDS: Fetal distress, neonatal respiratory distress syndrome, cervical insufficiency, undifferentiated connective tissue dysplasia

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INTRODUCTION

Premature labour is one of the urgent problems of modern obstetrics and neonatology, an important task of which is to optimize care for premature infants in order to avoid serious complications and chronic diseases [1-3]. Premature births range from 8% to 30% of their total number and 70-75% are the leading cause of perinatal morbidity and mortality [4-7]. Prematurity is a complex medical and social problem for both society and the family. The incidence among premature infants is 33 times higher than among full-term infants and is 70% of all perinatal mortality, where the main cause is neonatal respiratory distress syndrome (NRDS) [8].

It should be noted that pregnant women with undifferentiated connective tissue dysplasia (UDCTD) are a group at high risk of premature labour on the background of cervical insufficiency(CI) [9]. Therefore, the presence of UDCTD in the mother, the frequency of which according to various authors reaches from 20% to 30% of pregnancies [10] affect the development and formation of lungs in the fetus during organogenesis and postnatal development.

One of the manifestations may be neonatal respiratory distress syndrome and bronchopulmonary pathology that require respiratory support in the neonatal period. Therefore, more and more attention has recently been paid to the study of the effectiveness of various methods of respiratory support for NRDS in premature infants[11].

Contradictory data on the management of premature infants from mothers with UDCTD syndrome, justify the need for additional research aimed at optimizing medical care for these babies.

THE AIM

To evaluate the peculiarity of clinical manifestations of neonatal *respiratory distress syndrome* (N*RDS*) in deeply premature infants from mothers with phenotypic markers of **undifferentiated connective tissue disease** (UCTD).

MATERIALS AND METHODS

The study represent the results of a retrospective clinical and statistical analysis of 268 premature birth report card

Table I. Features of gestation and childbirth in patients of the main and comparison groups, (%)

Indicators	I group (n=50)	II group (n=50)
Cervical cerclage	39(78%)	19(38%)
Premature labour	17(34%)	6(12%)
Full-term labour	33(66%)	44(88%)
Complications in labour:		
- premature rupture of membranes	18(36%)	7(14%)
- uterine contraction abnormalities	11(22%)	5(10%)
- fetal distress	21(14%)	9(18%)
Cesarean section	7(14%)	2(4%)

and newborn report sheet. The main (1 group) included 50 pregnants with obvious phenotypic markers of UCTD, the comparison group (group 2) consisted of 50 pregnant women without phenotypic markers of UDCTD.

Two representative groups were formed: the main (group I) included 50 patients with phenotypic markers of undifferentiated connective tissue dysplasia (myopia, varicose veins, mitral valve prolapse, joint pathology), the comparison (group II) was 50 pregnant women without phenotypic markers of UDCTD.Statistical processing of research results was performed by using Excel.

RESULTS

According to the study, in 12 (24%) pregnant women of the main group at the time of admission to the clinic had contractions,which required specific therapy. Cervical cerclage was performed in 38 (76%) patients of the main group due to the presence of cervical insufficiency (CI). In these cases, the severity of the CI on the Steinber scale was 7.2 ± 0.4 points in the main group against 4.4 ± 0.2 points in the comparison group ($p < 0.05$).

According to the obtained data in the I group of observation there is a high risk of ante- and intranatal damage to the fetus.

As is seen from table I, the most frequent correction of cervical insufficiency with cervical cerclage was performed for patients with UDCTD . Group I patients were more likely to have complications of labor such as:premature rupture of membranes, uterine contraction abnormalities and fetal distress, which required in most cases cesarean delivery (7% and 2%), respectively ($p < 0.05$).

Newborns had a low score of 1 min. at birth on the Apgar scale, so for 5 minutes of life, 4 points in the main against 7 points in the comparison group.

The incidence of neonatal complications requiring respiratory support was 67% in group I and 48% in group II. Among them, respiratory distress syndrome had a more severe course, which required artificial lung ventilation (ALV), especially in babies from mothers with UDCTD, whose gestational age was <28 weeks.

At the same time, the concentration of oxygen more than 60% during mechanical ventilation required 8 (16%) newborns in the main group and 5 (10%) in the comparison group ($p < 0,05$).

It is known that mechanical ventilation increases the survival of particularly premature infants, however, quite often during mechanical ventilation there are ventilator-associated lung damage and bronchopulmonary dysplasia.

According to our observations, the clinical manifestations of bronchopulmonary dysplasia were twice as high in infants of the main group (66%) against (44%) of the comparison group ($p < 0.05$).

It should be noted that carrying out in the intranatal periods of steroid prophylaxis and antioxidant therapy significantly reduced the chances of mechanical ventilation in newborns.

DISCUSSION

Our research allowed us to identify contributing risk factors for lung tissue damage ante- and intranatally, as well as to assess the long-term consequences in children born from mothers with UDCTD.

Studies have shown that one of the leading factors of ante- and intra-pulmonary complications in the fetus can be both distress and meconium aspiration. In patients with premature rupture of membranes in whom the assessment of biophysical profile in the fetus indicated the presence of a fetal distress [5]. It is in these cases that abnormal pattern of breathing of the fetus of the "gasps" type (predominance of inspiration over exhalation) with a pronounced amplitude of diaphragm movements were noted. In these cases, the cardiotocogram (CTG) of the fetus was characterized by low variability, the presence of late decelerations of the heart rate. Dopplerography showed reverse or zero blood flow in the diastole phase. Amniotic fluid had a moderately viscous or thick consistency. In these cases, 7 (14%) had meconium aspiration in the fetus, which required rehabilitation of the tracheobronchial tree and respiratory support.

The above data show that preterm infants from mothers with UDCTD in the neonatal period are more likely to have respiratory disorders with the need for ventilation than in the comparison group, which affects the incidence of bronchopulmonary pathology 56% vs. 14%, respectively.

The studies revealed the risk factors for the formation of bronchopulmonary pathology, which requires further study of individual mechanisms of damage to immature components of lung tissue and their protection during respiratory support.

CONCLUSIONS

1.Neonatal respiratory distress syndrome in premature infants is more often associated from mothers with UDCTD.
2. The high importance of steroid prophylaxis of NRDS and antioxidant therapy in reducing the frequency of mechanical ventilation and the development of bronchopulmonary pathology, especially in infants from mothers with UDCTD syndrome, has been proven.
3. The possibility of diagnosing disorders of functional maturation of the lungs in the fetal period using a non-invasive method of ultrasonography has been confirmed.

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ORIGINAL ARTICLE

CORRECTION OF AUTONOMIC DYSFUNCTION IN YOUNG WOMEN BY OPTIMIZATION OF COMPONENT BODY COMPOSITION

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ABSTRACT

The aim: The article aims toevaluate the possibility of optimizing the state of the autonomic nervous system in almost healthy young females with different component body composition through physicalactivity and sensible nutrition.

Materials and methods: The study involved 30 young females. Body weight of women was measured both before and after the proposed weight correction program. Such parameters as body mass index (BMI, kg / m^2),fat mass percentage(FMP,%),visceral fat content (VF,unit) and fat free mass content (FFM, %) using a bioimpedance analyser"TANITA BC-601"were measured. Also, the study of the state of the autonomic nervous system (ANS) based on the registration of the rhythmogram using the computer hardware complex "CARDIOLAB" (HAI – Medica) was carried out.

Results: Analysis of the results of the study revealed that the regulation of functions in women with suboptimal ratio of adipose and muscle tissues in the body was carried out mainly through suprasegmental levels of regulation (VLF%) and was accompanied by a decrease in the activity of segmental autonomic influences.At the same time, the theoretical assumption about the possibility of correction of autonomic disorders by normalizing adipose and muscle tissueswas experimentally confirmed.Under the influence of a two-month program of body weight correction an increase in the functional activity of the autonomic control loop and improvement of the internal structure of the spectrum of neuroautonomicregulation (reduction of VLF-oscillations and increase of LF-effects and HF-effects) in the examined women were observed.

Conclusions: Thus, physical activity and sensible nutrition have a positive effect on the rheology of adipose tissue and the mechanisms of regulation of body functions, so they can be used to correct their disorders.

KEY WORDS: autonomic nervous system, heart rate variability, physical activity, sensible nutrition, dysautonomy

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INTRODUCTION

Currently, a large number of pathophysiological integrations and causal relationships between excess weight and autonomic dysfunction have been established.However, the scientific view on the root cause of their formation is ambiguous [1].According to some scientists, obesity is the cause of destabilization of the autonomic nervous system (ANS), since chronic subclinical inflammation plays a significant role in its pathogenesis. This is a source of proinflammatory cytokines (tumour necrosis factor (TNF), interleukin-6 (IL-6), C-reactive protein (CRP)), which are marked by a variety of biological effects on many tissues and organs at different structural levels [2-4].Other scientists believe that changes that occur in regulatory systems, namely ANS, cause metabolic and energy disorders, change the nature of eating behaviour [1,5], and therefore they can be used as an early prognostic sign of weight gain.

However, the reason for concern of scientists and doctors is the assertion that obesity and dysautonomy, due to the initiation of metabolic and hormonal changes in the body, act as trigger mechanisms for the formation of many diseases with severe and prognostic course, such as type 2 diabetes mellitus, metabolic syndrome, ischemic heart disease, arterial hypertension, reproductive dysfunction, oncological diseases, destructive changes of the musculoskeletal system, etc. [3,6,7].Moreover, a meta-analysis of epidemiological and clinical observations indicates a rapid and catastrophic increase in the population with excess weight of various degrees and autonomic disorders, as well as their rejuvenation [6,8].

Since both obesity and autonomic dysfunction are reversible, timely prevention and treatment make them clinically significant. Understanding this fact necessitates the development of measures that would effectively correct these conditions and be possible for long-term use, as only this guarantees a reduction in the transformation of reversible processes into irreversible ones.

THE AIM

The article aims to evaluate the possibility of optimizing the state of the autonomic nervous system in almost healthy young females with different component body composition through physical activity and sensible nutrition.

MATERIALS AND METHODS

The study involved 30 females of different stature aged 18 to 25.The average age of the subjects was 22.01 ± 2.36 years. The study was conducted on the basis of the Department of Fundamental Medical Disciplines of the Medical Faculty № 2 at the State Higher Educational Institution "Uzhhorod National University" in compliance with the basic bioethical norms of the Helsinki Declaration of the World Medical Association on ethical principles of scientific and medical research.Written informed consents were obtained from each study participant.At the time of the experiment the selected individuals did not complain about their health, had not been previously engaged in health-improving physical culture and sports.Their program for weight and body composition correction lasting 2 months, included comprehensive exercise (cardio and strength training) 3 times a week and sensible nutrition.

The components of body weight and the state of ANS of all selected participants were measured and studied before and after the body weight correction program.

To objectively characterize the functional state of the ANS, heart rate variability (HRV) values obtained by a 5-minute rhythm recording were used. Rhythmogram registration was performed using the computer hardware complex "CARDIOLAB" (XAI-Medica).

HRV assessment was performed according to standard protocols with calculation of time, autocorrelation and spectral parameters in accordance with the International Standards of Measurement, Physiological Interpretation and Clinical Use, developed by a working group of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[2,9-12].

The initial autonomic type was determined on the basis of the values of the TP index [11,13].Thus, the normotonic (eutonic) type of autonomic regulation corresponded to the values of TP – from 1100 to 3100 ms^2, sympathicotonic type – TP <1100 ms^2, parasympathicotonic type – TP> 3100 ms^2.

A relatively new, simple, inexpensive and non-invasive method of bioimpedance analysis was used to study the component body composition [14,15].It is based on measuring the impedance (Z) of tissues when passing through the body of a safe, low-sensitivity electric current with a force of 50 kHz.Of the developed devices, a vertical type of bioimpedance meters was used, namely the hardware and software complex TANITA BC-601 (Japan).Using this device, the following values were measured: body mass index (BMI, kg / m^2), fat mass percentage(FMP,%),visceral fat content (VF, unit), fat free mass content (FFM, %).The normalfat free mass content (FFM, %)for women aged 16-39 is from 65% to 79.9%, FFM> 80% is typical for women engaged in physical training.Fat mass percentage(FMP,%)for women aged 16-39 is normally 21-32%, FMP within 33-35% is regarded as excessive fat mass percentage, FMP> 35% is considered as obesity.Values of visceral fat are normally in the range of 1-4 units, an interval of 5-8 units is considered an acceptable level, 9 or more units indicate obesity [11].The BMI is measured in the following way: the range from 18.5 to 25 kg / m^2 is regarded as the norm, the value below 18.5 kg / m^2 is considered as a deficit of body weight, the value from 25 to 30 kg / m^2 is regarded as overweight, more than 30 kg / m^2 – as obesity.

Statistical processing of the obtained data was performed using the software Jamovi 0.8-1.0 (Affero General Public License 3).Quantitative variables were represented as arithmetic mean (M) and arithmetic mean error (m). AStudent's t-test was used to assess the significance of changes in the mean values. The difference at $p < 0.05$ was considered statistically significant.

RESULTS

According to the BMI values, before the weight correction program there were 12 individuals (40%) with obesity of I degree, 10 individuals (33.3%) with excess weight and 8 individuals (26.7%) with normal weight.Analysing the results of their autonomic status, according to the results of TR, eutonia was observed in 20 women(66.7%), parasympathicotonia – in 8 women (26.7%), sympathicotonia – in 2 women (6.7%).After re-examination of the selected contingent at the end of a two-month course of weight correction and analysis of their parameters, the redistribution of women in relation to the BMIvalue was observed: there were 6 individuals (20%) with obesity of I degree, 12 individuals (40%) with excess weight and 12 individuals (40%) with normal weight.The type of their autonomic orientation was also different: 14 individuals (46.7%) had eutonia, 12 individuals (40%) had parasympathicotonia, and 4 individuals (13.3%) had sympathicotonia.

When comparing the values of body composition components before and after the body weight correction program the following changes were detected: a statistically significant weight loss of 3.640 ± 3.696 kg ($p = 0.002$), BMI of 1.393 ± 1.237 kg / m^2 ($p < 0.001$), FMP of 2.840 ± 2.538% ($p < 0.001$), VFat 1,000 ± 1,000 units ($p = 0.002$) and statistically significant increase in FFM by 2,800 ± 2,376% ($p < 0,001$). The obtained data are presented in the Table I and illustrated in the Fig. 1.

In order to assess the peculiarities of autonomic regulation in almost healthy women before and after the body weight correction program, we assessed the initial autonomic tone and autonomic support, as well as compared the obtained values of temporal, spectral and autocorrelation analysis of HRV, which are listed in the Table II.

A comparative analysis between HRV values before and after the body weight correction program showed a tendency to change, although it was not significant between most values.The analysis of HRV frequency values revealed that most of them tended to increase and were significantly different (mRR increased by 80.9 ± 104.1 cm ($p = 0.009$), RMSSD – by 13.93 ± 13.57 cm ($p = 0.001$), pNN50 – by 12.07 ± 13.16 ($p = 0.003$)), except for CV, which remained virtually unchanged at 0.000 ± 1.773% ($p = 1,000$) and SDNN, which increased by 6.33 ± 14.74 ms ($p = 0.118$).

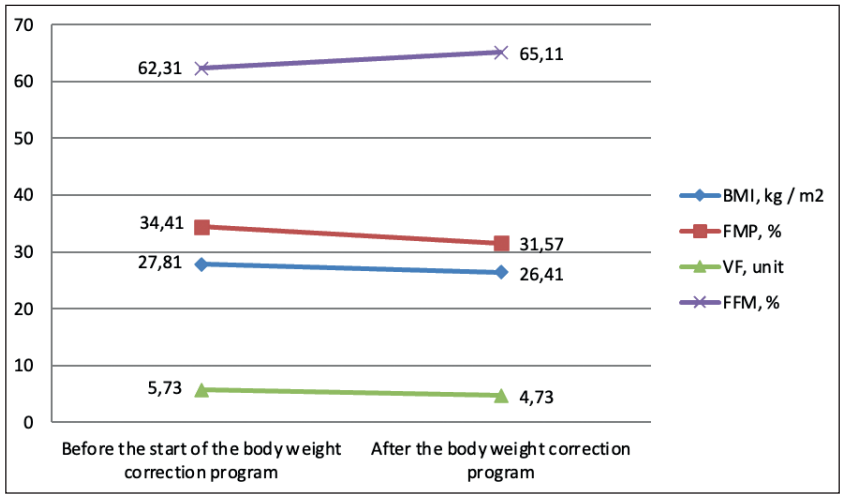

Fig. 1. Dynamics of the Values of Body Component Composition Under the Influence of the Body Weight Correction Program

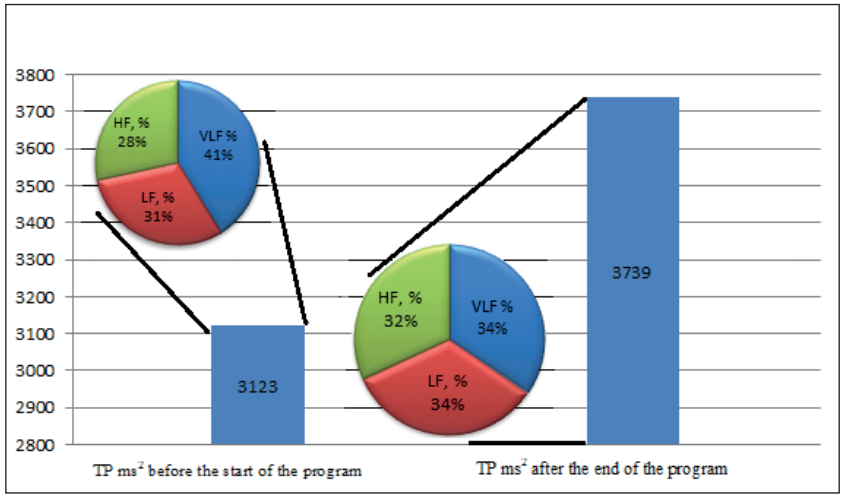

Fig. 2. Dynamics of TP and Changes in the Ratio of ANS Channels of Influence on Heart Rate Under the Influence of the Body Weight Correction Program

Table I. Comparison of the Values of Body Weight Components of Young Women Before and After the Body Weight Correction Program (M±m)

Component body composition values under study	Before the start of the program (n=30)	After the end of the program (n=30)	Difference	Statistical significance of the difference
BMI, kg / m²	27,81±5,51	26,41±4,92	1,393±1,237	0,001**
FMP, %	34,41±9,81	31,57±8,91	2,840±2,538	0,001**
VF, unit	5,733±3,634	4,733±3,173	1,000±1,000	0,002**
FFM, %	62,31±9,31	65,11±8,53	-2,800±2,376	0,001**
Weight, kg	75,44±16,22	71,80±14,15	3,640±3,696	0,002**

Note: differences are statistically significant at the level * - p≤0,05; ** p≤0,01

Estimation of changes in HRV spectral parameters did not reveal any significant differences. The TP value, which reflects the total level of activity of regulatory systems, increased by 615 ± 2304 ms², however, this increase was not statistically significant (p = 0.319). The activity of the contribution of the value of humoral and metabolic effects of VLF to the total power of the spectrum had only a tendency to increase (VLF increased from 1303 ± 1804 ms² to 1391 ± 1468 ms² (p = 0.864)). As for the contribution of the sympathetic link of the ANS on the basis of some values, there was its activation, and on the basis of others – a decrease in its impact, but these data were not statistically significant: (LF increased from 793 ± 817 ms² to 938 ± 567 ms² (p = 0.477)), (LFnorm decreased from 54.13 ± 16.69 to 52.73 ± 21.04 (p = 0.761)). As for the activity of the parasympathetic channel of regulation, no significant differences were found: HF increased from 953 ± 1158 ms² to 1353 ± 1611 ms² (p = 0.188), HFnorm – from 45.87 ± 16.69 to 47.27 ± 21,04 (p = 0.761)). Along with the dynamics of absolute values, the dynamics of relative valueswas noted, which led to a change in the ratio of the channels of influence of ANS on heart rate, namely: VLF decreased by 6.67 ± 15.15% (p = 0.110), and LF and HF increased (by 3.13 ± 15.97% (p = 0.460), and 3.40 ± 14.30% (p = 0.373)) (Fig. 2).

Table II. Dynamics of HRV Values of Young Women Before and After the Course of the Body Weight Correction Program (M±m)

HRV values under study	Before the start of the program (n=30)	After the end of the program (n=30)	Difference	Statistical significance of the difference
General level of HRV regulation				
SDNN, ms	52,67±23,94	59,00±23,17	-6,33±14,74	0,118
CV, %	6,000±2,507	6,000±2,138	0,000±1,773	1,000
TP, ms^2	3123±3544	3739±2848	-615±2304	0,319
BAP, ms	239,1± 62,0	247,5±74,3	-8,3±38,7	0,419
mRR, ms	872,1±114,5	953,1±132,8	-80,9±104,1	0,009**
HR, beats / min	70,00± 9,58	64,13±8,90	5,87±7,39	0,008**
HRV Ti	11,40 ±3,66	13,73±4,82	-2,333±2,769	0,006**
Mo, ms	836,7±117,2	923,3±145,0	-86,7±115,7	0,012*
The activity of the sympathetic ANS				
LF, ms^2	793±817	938±567	-146±771	0,477
AMo, %	39,80±9,89	37,07±12,40	2,73±8,14	0,214
LF norm	54,13±16,69	52,73±21,04	1,40±17,51	0,761
The activity of the parasympathetic ANS				
RMSSD, ms	43,93±30,14	57,87±34,76	-13,93±13,57	0,001**
pNN50, %	19,53±22,19	31,60±24,64	-12,07±13,16	0,003**
HF, ms^2	953±1158	1353±1611	-400±1117	0,188
HFnorm	45,87±16,69	47,27±21,04	-1,40±17,51	0,761
The activity of higher regulatory system				
VLF, ms^2	1303±1804	1391±1468	-88±1943	0,864
Sympathetic and parasympathetic balance				
LF/HF	1,664±1,559	1,794±1,941	-0,130±1,896	0,794
IC	4,34±3,61	4,33±4,17	0,01±3,93	0,993
IH (SI)	112,5 ±50,1	101,7±69,1	10,80±37,74	0,286
Percentage contribution of frequency components of the spectrum in TP				
VLF %	41,20±17,96	34,53±16,83	6,67±15,15	0,110
LF, %	30,47±9,46	33,60±15,21	-3,13±15,97	0,460
HF, %	28,47±15,29	31,87±18,71	-3,40±14,30	0,373

Note: differences are statistically significant at the level * - p≤0,05; ** p≤0,01

Valuesof IC and LF / HF practicallydidnotchange (IC decreasedby 0.01 ± 3.93 (p = 0.993), and LF / HF increasedby 0.130 ± 1.896 (p = 0.794).

The dynamics of autocorrelation indicators of HRV was also analysed. A statistically significant dynamic difference was observed between the values of Mo (up to 836.7 ± 117.2 ms, after 923.3 ± 145.0 ms (p = 0.012)).The VAR value also had the tendency to increase; it increased by 8.3 ± 38.7 ms (p = 0.419)). Other values, on the contrary, had a tendency to decrease, namely: AMo decreased by 2.73 ± 8.14% (p = 0.214), IN – by 10.80 ± 37.74 (p = 0.286).

DISCUSSION

The analysis of the results confirmed the presence of autonomic imbalance in women with non-compact content of adipose tissue in the body (34.41 ± 9.81%) before the start of the body weight correction program.The values of VLF% in them were 41.20 ± 17.96% (at a rate of 15-30% of the total spectrum power) [9], LF – 30.47 ± 9.46% and HF – 28.47 ± 15, 29%. An increase in the value of VLF indicates hyperactivation of higher regulatory mechanisms, including the central, hypothalamic-pituitary-adrenal system and the sympathetic division of the ANS [16].This isalso indicated by the low value of SDNN (52.67 ± 23.94 ms) in these subjects. It should be noted that a decrease in SDNN to 50 ms or less is an unfavourable sign of the functioning of the cardiovascular system and is associated with a risk of cardiovascular diseases [2,13]. According to modern notions, obese people are characterized by a steady decrease in the parasympathetic division of the ANS and the overall variability of heart rate [2,17]. As for the power indicators of the low frequency spectrum, which reflect the sympathetic domain of the ANS, the results are ambiguous, however with increasing degree

of obesity a decrease in their values takes place [10]. This is indicated by the results of our research.

Correction of excess body weight and ANS have some common principles.The use of dosatedphysical activity has a positive effect on both subcutaneous and visceral rheology of adipose tissue, reducing the production of proinflammatory cytokines and reducing inflammatory cell infiltration [14], as well as on the autonomic regulation of heart rate due to the predominance of the parasympathetic ANS [18].

Subsequent HRV monitoring after a two-month body weight correction program showed a redistribution of the constituent domains in the total power of the spectrum. An inverse relationship was found between the growth of HF, RMSSD, pNN50, which reflect the influence of the parasympathetic link of the ANS and the strainof the sympathetic regulatory mechanisms with the centralization of heart rate regulation.Due to the growing influence of the parasympathetic division of the ANS, there is an increase in HRV, which reflects the total activity of the autonomic circuit on the cardiac arrhythmia: TP ms^2, mRR, HRV Ti, Mo and SDNN ms.The use of the proposed program contributed to the change of HRV indicators and optimization of the ANS, which is consistent with the data of A. L. Maksimov and A. A. Artemenkov[13,19].

CONCLUSIONS

Non-compact content of adipose and muscle tissues in the body is accompanied by autonomic dysfunction, which in turn complicates metabolic changes in the body.

Traditional measures to normalize weight and correct body shape can be used as non-drug therapy to improve regulatory mechanisms, optimize the condition and increase the effects of autonomic nervous regulation, which leads to reduced functional stress and increased functional capacity of the body due to redistribution of body adipose and muscle mass in favour of the growth of the latter.

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ORIGINAL ARTICLE

THE EFFECTIVENESS OF COMPLEX THERAPY WITH THE INCLUSION OF THE URSODEOXYCHOLIC ACID IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN COMBINATION WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The aim: Was increase the effectiveness of treatment in patients with non-alcoholic fatty liver disease (NAFLD) comorbid with chronic obstructive pulmonary disease (COPD) by using ursodeoxycholic acid (UDCA) in combination with ademethionine.

Materials and methods: Under observation was 98 patients with a diagnosis of NAFLD and COPD group II or their combination. Patients were divided into 3 groups: 1 (n = 36) – COPD + NASH – in addition to standard COPD therapy received UDCA 15 mg / kg / day – 6 months and ademethionine 1000 mg IV once a day for 10 days, followed by oral administration of 500 mg 2 times per day – 20 days, and group 2 (n = 32) – COPD + hepatic steatosis – in addition to standard therapy – UDCA 15 mg / kg / day – 6 months. Group 3 (n = 30) – COPD received standard therapy for COPD.

Results: UDCA with ademethionine on the background of standard COPD therapy reduces the clinical manifestations of NAFLD and normalizes liver function. The combination of UDCA with ademethionine not only has a positive effect on the course of NAFLD, but also reduces the intensity of dyspnea, systemic inflammation, improves the external respiration function and reduces anxiety and depression. Patients receiving UDCA + ademethionine for 6 months of follow-up had no exacerbations of COPD.

Conclusions: UDCA in combination with ademethionine in COPD courses have a positive effect on the course of NAFLD, and also reduces the intensity of dyspnea, improves the external respiratory function and reduces the frequency of COPD hospitalization.

KEY WORDS: NAFLD, COPD, UDCA, ademethionine, systemic inflammation

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world, and continues to grow every year [1,2]. According to the European Respiratory Society (ERS), there is a steady increase in mortality and disability from chronic obstructive pulmonary disease (COPD) [3]. Pulmonary and extrapulmonary manifestations are observed in patients with COPD, in the pathogenesis of which there is immunological inflammation, which leads to chronic tissue hypoxia and to disruption of all organs and systems [4-6]. The World Health Organization classifies COPD as a major social burden [7]. The high prevalence of NAFLD and COPD causes a frequent combination of these pathological conditions. And the selection of a therapeutic approach should be carried out taking into account all the pathophysiological mechanisms of formation of these conditions.

Recently, for the treatment of various liver diseases, ursodeoxycholic acid (UDCA) drugs are used. Many randomized trials have proven the multifactorial effects of UDCA. Belgian researchers have concluded that UDCA reduces eosinophilic inflammation in the bronchopulmonary system [8]. Scientists from Turkey have demonstrated the effectiveness of UDCA in respiratory diseases by effectively modulating Th-2 cytokine derivatives [9], and experiments by Chinese scientists have shown that UDCA helps prevent edema and pulmonary fibrosis, which are common complications of COVID-19 [10]. Also of great interest is the drug ademethionine, which plays a central role in the biochemical reactions of transmethylation, transsulfation, aminopropylation and has antifibrotic activity. However, studies to study the concomitant use of UDCA and ademethionine in patients with comorbid liver disease have not been sufficiently studied.

THE AIM

The aim was to increase the effectiveness of treatment in patients with NAFLD comorbid with COPD by studying the possibility of using UDCA in combination with ademethionine.

MATERIALS AND METHODS

The observation revealed 98 patients who were treated at the Zakarpattia Regional Clinical Hospital named after

Andriy Novak during 2018-2020 with a diagnosis of NAFLD and COPD group II or their combination. Among the surveyed were 61.2% (60) men and 38.8% (38) women. The average age was 57.8 ± 1.5 years.

The studies were conducted with the informed consent of patients, and their methodology complies with the Helsinki Declaration of 1975 and its 1983 revision approved by the Local Bioethics Commission (Protocol №1 from 10.01.2020). The inclusion criteria in research study confirmed the diagnosis of chronic obstructive pulmonary disease COPD (GOLD II) and age over 40 years and less than 70 years and / or NAFLD. Exclusion criteria in the study were the presence of markers of viral hepatitis B and C, markers of autoimmune hepatitis, alcohol consumption, toxic liver damage.

The diagnosis of NAFLD was established according to the unified clinical protocol "Non-alcoholic steatohepatitis" (2014) and to the recommendations of the European Association for the Study of the Liver (EASL). The diagnosis of COPD was confirmed according to the order of the Ministry of Health of Ukraine №555 from 27.06.2013 "On approval of clinical protocols for medical care in the specialty" Pulmonology "and the provisions set out in the document GOLD [2017]. A modified Medical Research Council (mMRC) dyspnea scale and a COPD assessment test (CAT) were used to assess the clinical course of COPD and the intensity of the main symptoms.

The external respiration function was determined using a microprocessor device «Pulmovent-2» (Ukraine) with a bronchodilation test. Spirometry parameters such as: forced vital capacity (FVC), forced expiration volume in one second (FEV1) and their ratio, mean forced expiratory flow (FEF) between 25%, 50% and 75% of the expired vital capacity. The evaluation of these indicators was performed as a percentage of the corresponding values. FEV1 / FVC <0.7 after bronchodilation test became the basis for the diagnosis of COPD.

All patients with exacerbation of COPD received a basic treatment regimen, which included inhaled M-cholinolytic long-acting tiotropium bromide (drug in capsules with powder for inhalation 18 mcg with delivery device) and standard therapy for exacerbation of COPD: bronchodila-

Table I. Number of patients with persistent clinical syndromes after treatment depending on the treatment regimen

Syndromes 1 (n=36)		Groups, abs/%	
		2 (n=32)	
Asthenovegetative syndrome	a	33 / 91,7	29 / 90,6
	b	5 / 13,9*	7 / 21,9*
Dyspeptic syndrome	a	27 / 75,0	25 / 78,1
	b	6 / 16,7*	9 / 28,1*
Pain	a	21/ 58,3	19 / 59,4
	b	1 / 2,8*	5 / 15,6 *
Hepatomegaly	a	33 / 91,7	30 / 93,7
	b	2 / 5,5*	11 / 34,4*

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

Table II. Dynamics of biochemical parameters before and after treatment

Indexes		Groups		
		(n=30) Control group	1 (n=36) UDCA	2 (n=32) Ademethionine + UDCA
Bilirubin, mg/dL	a	15,3±1,4	29,2±3,7	30,9±1,2
	b		19,4±1,3*	12,4±0,8*,**
ALT, IU/L	a	22,1±3,7	147,8±42,7	122,1±3,4
	b		48,2±2,3*	32,6±1,3*,**
AST, IU/L	a	14,2±2,1	78,5±7,8	74,7±2,6
	b		57,4±1,6*	32,6±1,3*,**
ALP, IU/L	a	52,3±5,7	137,2±22,5	112,4±5,2
	b		69,2±1,5*	37,5±1,9*,**
GGT, IU/L	a	24,4±3,0	77,2±9,4	79,7±6,2
	b		46,1±3,1	21,7±5,1*,**

Notes: Significance of the difference: * - group I; **- group II (p values are calculated by Fisher's exact test, p <0,05-0,01). a - before treatment; b - after treatment

Table III. Assessment of the clinical symptoms according to mMRS and CAT scores before and after treatment

Groups		mMRC, point	CAT, point
Group 1	a	1,7± 0,4	16,8± 0,5
	b	1,1±0,5*	12,1±0,3*
Group 2	a	1,8±0,3	17,3±0,4
	b	1,3±0,1*	12,8±0,2*
Group 3	a	1,8±0,4	17,1±0,4
	b	1,6±0,2*	13,6±0,3*

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

Table IV. Dynamics of spirometry parameters during treatment

Groups		FVC, %	FEV1,%	FEV1 / FVC,%
Group 1	a	42,3± 3,2	48,4± 2,8	61,7±1,5
	b	62,4±2,5*	63,4±2,3*	69,2±1,7*
Group 2	a	42,4±4,3	49,2±3,3	63,5±1,3
	b	60,9,3±2,1*	60,2±3,6*	68,4±1,4*
Group 3	a	43,5±3,4	49,5±3,4	62,4±1,6
	b	60,2,6±2,3*	58,4±2,9*	66,5±1,5*

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

tor – methylxanthine – eufilin 2.4% solution – 10 ml IV in 10 – 20 ml of isotonic sodium chloride solution or teotard 200 mcg 2 times / day) and mucolytic (bromhexine 8 – 16 mg 3 times / day or ambroxol hydrochloride 30 mg 3 times) / day), as well as dexamethasone IV for 7 days.

In the sample in patients with COPD, depending on the stages of concomitant NAFLD, three groups of application of the following treatment complexes were identified:

Group 1 (n = 36) patients with COPD + NASH – in addition to standard therapy from the 7th day of treatment of COPD exacerbation (after elimination of the most acute phenomena of bronchoobstruction and systemic inflammation) on the background of lifestyle modification (weight loss, low-calorie diet, dosed physical activity) ademethionine 1000 mg IV once a day for 10 days, followed by oral administration of the drug (500 mg in the morning and at lunch) for 20 days and UDCA 15 mg / kg / day for two hours before bedtime.

Group 2 (n = 32) patients with COPD + hepatic steatosis – in addition to standard therapy from the 7th day of treatment of COPD exacerbation on the background of lifestyle modifications received UDCA 15 mg / kg / day two hours before bedtime. It should be noted that all patients

Table V. Dynamics of systemic immune inflammation activity under the influence of therapy

Inflammatory indexes		Group 1 (n=36)	Group 2 (n=32)	Group 3 (n=30)	Control group (n=30)
CRP, mg/L	a	16,4±0,5	18,2±0,7	17,4±0,6	2,7±0,9
	b	5,5±0,3*	8,6±0,4*	10,3±0,5	
IL-6, (normal 0-10 pg/mL)	a	45,4 ±1,3	49,5 ±0,8	47,8±1,7	3,9±1,2
	b	10,6±0,7*	16,3±0,6*	22,4±1,04	
TNF-a, (normal 0-6 pg/mL)	a	407,5 ±10,3	465,3 ±12,5	207,5 ±10,3	9,5±0,7
	b	53,8±0,61*	93,76±0,64*	77,71±0,83*	
Neopterin (normal up to 10 nmol / l)	a	447,3±0,3	378,6±1,5	109,5±1,8	7,2±1,2
	b	58,26±1,24*	104,88±0,5*	90,27±1,37	
IgG neutrophil elastase antibodies, IU / ml	a	49,2±5,2	47,4±3,8	48,5±4,6	3,2±0,8
	b	22,4±2,4*	24,5±2,5*	28,4±2,6	

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

Table VI. Dynamics of quality of life as a result of treatment

Indexes	Group 1		Group 2		Group 3	
	a	b	a	b	a	b
PF	77±2,5	86±1,4	72±1,2	79±1,8	77±2,1	81±1,7
RP	39±2,2	45±1,5	41±3,6	49±2,5	51±3,3	58±1,2
BP	35±41	42±1,7*	42±4,2	45±3,1	53±1,1	62±2,2
GH	36±3,5	45±4,4*	43±3,1	49±2,1	52±2,0	59±2,4
VT	37±4,2	46±5,4*	46±2,0	51±2,5	54±2,3	61±3,2
SF	45±1,2	50±2,5	52±2,5	58±2,7	59±2,0	69±4,4
RE	27±1,7	33±2,1*	33±2,5	39±2,1	41±2,1	45±2,6
MH	41±3,5	48±1,1*	44±3,3	48±2,0	51±1,9	60±1,7
PH	44±1,8	52±3,5	50±1,2	56±1,4	55±2,2	60±1,7
MH1	40±1,7	51±1,2	44±1,1	51±5,2	48±3,3	55±1,5

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

completed treatment on an outpatient basis. Taking UDCA 500 mg at night in group 1 and 2 continued for 6 months.

Group 3 (n = 30) – patients with COPD received the above standard exacerbation therapy.

Evaluation of the effectiveness of treatment was performed on the indicators of clinical course, liver tests, systemic inflammation (CRP, TNF-a, IL-6, neopterin, IgG antibodies to neutrophil elastase), respiratory function, quality of life. Quality of life (QOL) was assessed using a non-specific questionnaire «SF-36». Observation of included persons of the study lasted 12 months.

Enzyme-Immuno-Sorbent-Assay (ELISA) was used to determine levels of C-reactive protein (CPR), concentrations of TNF-a, IL-6, neopterin and IgG antibodies to neutrophil serum elastase. The results of the studies were taken into account on an automatic enzyme-linked immunosorbent assay "STATFAX" according to the instructions included with the reagent kits Diagnostics Biochem Canada and DRG (USA). To determine the degree of steatosis and liver fibrosis used a non-invasive method of diagnosis – FibroMax. The analysis and processing of the results was performed using Microsoft Windows 10 and STATISTICA application packages.

RESULTS

In groups 1 and 2 of patients, the treatment reduced the manifestations of dyspeptic syndrome, pain and hepatomegaly, with a predominance in patients receiving UDCA + ademethionine (table I).

Positive changes are registered not only in the well-being of patients, but also in the biochemical parameters of the blood. At the end of the treatment there is a decrease in the levels of total bilirubin, alkaline phosphatase, gamma-glutamyltranspeptidase in groups 1 and 2, compared with the levels of these parameters before treatment (table II).

In the course of treatment, positive dynamics of clinical features (reduction of dyspnea according to mMRC and intensity of the main symptoms according to CAT was revealed in all clinical groups (Table III). The changes were more pronounced in patients taking UDCA + ademethionine (group 1) at the same time, compared with group 2 and 3.

During the assessment of parameters of external respiration function under the influence of complex treatment, a significant increase in FVC, FEV1 and FEV1 / FVC in all clinical groups, with more pronounced dynamics in group 1 (Table IV).

After treatment, patients in all three groups tended to normalize the cytokine levels of the immune system. Decreased activity of pro-inflammatory cytokines, in particular TNF-α, IL-6 and neopterin, and decreased levels of IgG antibodies to neutrophil elastase. (Table V).

As a result of use the complex therapy with UDCA and ademethionine, the levels of TNF-α and neopterin were most significantly reduced by 7.5 and 7.7 times ($p < 0.01$) and IL-6 by more than 4 times ($p < 0.05$). The level of CRP decreased by almost 3 times ($p < 0.05$). Also, the level of IgG antibodies to neutrophil elastase decreased by 2 times ($p < 0.05$).

After a course of treatment in patients with COPD without NAFLD showed a tendency to improve all quality of life indicators (QOL). Analyzing the integrated index of physical and mental components of health on the whole SF-36 scale in patients with NAFLD combined with COPD by groups, we found the following dynamics: the average values of the integrated physical component of health (PH) in patients of group 1 showed maximum improvement – by 8 ± 1.7 points compared with pre-treatment index, and in patients of groups 2 and 3 increased by 5 ± 1.5 and 6 ± 0.2 points ($p < 0.05$). When assessing the integrated mental component of health (MH1), namely: in patients of group 1 the indicator increased by 11 ± 0.5 points, and in patients of groups 2 and 3 – by 7 ± 1.8 points and 7 ± 4.1 points (Table VI).

DISCUSSION

Two-thirds of the patients improved their general well-being and reduced pain in the right hypochondrium, apparently due to a normalization of the cytokine of the immune system. Hepatomegaly disappeared in almost all patients receiving concomitant ademethionine and UDCA. As a result of treatment in patients with NAFLD with comorbidity with COPD, a significant decrease in systemic inflammation was found, which is one of the common triggers for the progression of liver pathology and COPD, which is closely associated with the development of steatohepatitis and cardiovascular risk. [11,12]

It must be noted that the level of IgG antibodies to neutrophil elastase and the absence of exacerbation of COPD for 6 months in patients receiving ademethionine + UDCA, which proves the anti-inflammatory efficacy of the therapy.

The positive effect of the combined use of ademethionine and UDCA on the manifestations of asthenovegetative syndrome, characteristic of almost all patients at the beginning of the observation, was established.[13] During treatment in clinical groups of patients with NAFLD in combination with COPD, a positive dynamics of clinical and functional status was observed, which indicated a decrease in shortness of breath and intensity of COPD symptoms, as well as improvement of quality of life under the influence of treatment.

At the same time, the positive dynamics was more pronounced in the group of patients receiving additional UDCA + ademethionine in comparison with other groups. The most objective assessment of the effectiveness of treatment is the assessment of spirometry parameters of patients with NAFLD combined with COPD. Significant positive dynamics of both physical and mental components of QOL in groups of patients with COPD and NAFLD, which additionally used UDCA with ademethionine.

Significant reduction in dyspnea by mMRC and the intensity of the main symptoms in patients receiving complex therapy was accompanied by a decrease in the severity of depression and anxiety due to the antidepressant effect of ademethionine. [14]

CONCLUSIONS

The results showed that taking UDCA with ademethionine according to the proposed scheme helps to reduce the intensity, duration and frequency of the main manifestations of NAFLD. UDCA in combination with ademethionine has a positive effect not only on the course of NAFLD, but also improves the clinical and functional state in COPD. The positive effect on the clinical course of COPD is characterized by a decrease the intensity of dyspnea, improved respiratory function, reduces the intensity of the inflammatory process and leads to improved quality of life, reducing levels of anxiety and depression. The absence of side effects of therapy allows its widespread and long-term use in clinical practice.

The absence of side effects of therapy allows its widespread and long-term use in clinical practice. The proposed therapy may be an alternative for the treatment in patients with NAFLD comorbid with COPD not only at the stage of activation of the inflammatory process in the liver tissue, but also at the stage of maintenance therapy to prevent disease progression.

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ORIGINAL ARTICLE

ASSESSMENT OF THE IMPACT OF ANTIREFLUX THERAPY ON THE COURSE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The aim: To examine the effect of antireflux therapy on the course of COPD.

Materials and methods: Under observation were 60 patients who were hospitalized in the «Transcarpathian Regional Clinical Hospital named after Andrei Novak» with a diagnosis of COPD II gr B in combination with GERD and 36 patients diagnosed with GERD who were treated on an outpatient basis.

To study the effectiveness of antireflux therapy and its impact on the course of COPD, patients are divided into 2 groups: 1 group (main) (n = 60) – patients with COPD in combination with GERD, group 2 (control) (n = 36) – patients with isolated GERD. Patients with positive Helicobacter pylori status received antihelicobacter therapy.

Patients in group 1 were divided into subgroups: 1a (n = 34) – COPD in combination with esophageal manifestations of GERD and 1b (n = 26) – COPD in combination with extraesophageal manifestations of GERD. Group 1a received complex therapy, which consisted of basic therapy of COPD in combination with antireflux and with rebapimide, group 1b – only basic therapy of COPD in combination with antireflux.

Results: After treatment, the clinical signs of GERD significantly decreased in all patients receiving complex therapy, improved the course of respiratory symptoms of COPD. After treatment, patients showed a clinically significant reduction in systemic inflammation, which is best seen in the group with the use of rabipimide.

Conclusions: Comprehensive treatment of combined pathology with the use of antireflux therapy has a positive effect not only on the clinical symptoms of the disease, but also on the indicators of external respiratory function in patients with combined COPD and GERD.

KEY WORDS: rabipimide, function of external respiration, influence

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an extremely common medical and economic problem not only in Ukraine but also worldwide, due to its high prevalence, severity, high risk of death and huge costs for the management of patients [1-3]. Modern scientific research is paying increasing attention to the prevalence of development and progression of combined pathology of the digestive and respiratory systems [4,5]. The problem of managing patients with a combination of gastroesophageal reflux disease (GERD) and chronic obstructive pulmonary disease is especially relevant [6,7]. GERD is an independent risk factor for exacerbations of COPD and is associated with deteriorating health of patients [8].

In the modern literature the question of treatment of patients with GERD [9] is sufficiently studied, but there are no data concerning treatment of GERD connected with COPD. Proton pump inhibitors (PPIs), which are also used to treat GERD in patients with COPD, are undoubtedly the drugs of choice in the treatment of GERD. However, the question of the importance of PPIs in reducing the frequency of COPD exacerbations and the possibility of preventing these events remains not fully studied and somewhat controversial [10]. Therefore, the study of the impact of antireflux therapy on the course of COPD is promising.

THE AIM

The aim of the research was to examine the effect of antireflux therapy on the course of chronic obstructive pulmonary disease in the period of exacerbation.

MATERIALS AND METHODS

Under observation were 60 patients who were treated in the pulmonology department of the Municipal Non-Profit Enterprise «Transcarpathian Regional Clinical Hospital named after Andrei Novak» with a diagnosis of COPD II gr B in combination with GERD and 36 patients diagnosed with GERD were treated by a gastroenterologist. The mean age of the subjects was 55 ± 1.64 years. Among the examined patients, men predominated by sex – 78.1% (75 out of 96).

All subjects signed an informed consent, the methodology of which was in line with the Helsinki Declaration of 1975 and its revision in 1983 and was approved by Uzhhorod National University's Commission on Bioethics (Protocol №1 of 10.01.2020). The inclusion criteria confirmed the diagnosis of chronic obstructive pulmonary disease (GOLD II) and age over 40 years and less than 70 years. Exclusion criteria: age under 18 and over 70 years, taking corticosteroids per os, the presence of concomitant diseases of the respiratory, digestive,

cardiovascular system, malignant neoplasms, the patient's refusal to study.

The diagnosis of COPD was confirmed in accordance with the order of the Ministry of Health of Ukraine №555 dated 27.06.2013 «On approval of clinical protocols for medical care in the specialty «Pulmonology « and the provisions set out in the document GOLD [2017] [5].

The diagnosis of gastroesophageal reflux disease (GERD) was made in the presence of relevant complaints and the results of instrumental studies – a positive test with rabeprazole, fibrogastroduodenoscopy (FGDS) and intragastric pH-metry, taking into account the Montreal Consensus (2006), 10H as well as in accordance with domestic protocols for medical care (order of the Ministry of Health of Ukraine № 943 of 31.10.2013).

Positive Helicobacter pylori status (Hp +) was registered in 69.8% (67 out of 96), with a distribution by groups of 47.9% (46 out of 96) in group 1 and 21.9% (21 out of 96) in group 2 respectively.

To study the effectiveness of antireflux therapy and its impact on the course of COPD, patients are divided into 2 groups: 1 group (main) (n = 60) – patients with COPD in combination with GERD, group 2 – (control) (n = 36) – patients with isolated GERD. Groups of patients were homogeneous in age and sex. The study evaluated the effectiveness of complex therapy of patients with COPD in combination with GERD. All patients received basic treatment for COPD according to existing national and international guidelines, which included long-acting beta-2 agonists, long-acting anticholinergics, inhaled glucocorticosteroids, and short-acting beta 2-agonists as needed.

Patients in group 1 were divided into subgroups: 1a (n = 34) – COPD in combination with esophageal manifestations of GERD and 1b (n = 26) – COPD in combination with extraesophageal manifestations of GERD. All patients with positive *Helicobacter* status (Hp +) received antihelicobacter therapy, which included amoxicillin 1000 mg, clarithromycin 500 mg, rabeprazole 20 mg – 1t x 2 times a day with each drug – 14 days and probiotic Saccharomyces boulardii 2 times 1 capsule per day – 10 days. After successful eradication of Helicobacter pylory (Hp), all patients were prescribed antireflux therapy, which included: measures to change lifestyle; appointment of rabeprazole at a dose of 20 mg in the morning 30 minutes before meals for 8 weeks with the transition to therapy «on demand» and itopride hydrochloride 50 mg 3 times a day for 1 month. Therapy «on demand» included – in the case of recovery of heartburn in a patient after a course of PPIs, taking rabeprazole at a dose of 20 mg for 7 days, with the transition to 10 mg for another 14 days.

Patients of subgroup 1a on the background of basic COPD therapy received antireflux therapy with additional inclusion of rebapimide 100 mg 3 times a day for 1 month, and patients of subgroup 1b received basic therapy of COPD in combination with antireflux without the use of rebapimide. The effectiveness of the therapy was evaluated by the dynamics of the following indicators: assessment of clinical manifestations of GERD, assessment of dyspnea by mMCD, indicators of inflammation (CRP, leukocytes, neutrophils, ESR, procalcitonin), cytokine activity (IL-4, IL-6, IFNγ, IFN 4), the parameters of the function of external respiration (FEV 1%, FVC, FEV1 / FVC). Statistical analysis of the data was performed using Jamovi, version 2.0.0 using the paired Student's t test, Pearson's χ^2 test and Fisher's exact test, depending on the type of source data. The average values of the numerical data were represented as M ± SD. The normality of the distribution was evaluated by the Shapiro-Wilk test. The critical level of reliability was considered to be $\alpha = 0.05$.

RESULTS

Analysis of the results showed that the leading clinical symptom in patients of group 1a and group 2 was heartburn and acid regurgitation, in 50% (30 of 60) and 55% (33 of 60), respectively,

Table I. Dynamics of clinical symptoms in the examined patients before and after treatment

Indication	Groups					
	Group 1 COPD + GERD (n=60)				Control group GERD (n=36)	
	1a (n=34)		1b (n=26)			
	before	after	before	after	before	after
Heartburn (abs /%)	30/50,0*	6/10,0	0/0	0/0	29/80,5	5/13,9
Sourbelching (abs /%)	33/55,0*	7/11,7	0/0	0/0	33/91,6	10/27,8
Dysphagia (abs /%)	28/46,7	11/18,3	0/0	0/0	17/47,2	7/19,4
A lump in the throat (abs /%)	31/51,7	9/15,0	0/0	0/0	12/33,3	3/8,3
Itching in the throat (abs /%)	0/0	0/0	7/11,7**	1/1,6	2/5,5	1 / 2,7
Hoarseness of voice (abs /%)	0/0	0/0	4/6,6	2/3,3	0/0	0/0
Dry, barking cough that worsens at night (abs /%)	0/0	0/0	14/23,3**	4/6,6	3/8,3	0/0
Chest pain along the esophagus (abs /%)	0/0	0/0	2/3,3	0/0	3/8,3	0/0
Irregular heart rhythm (abs. / %)	0/0	0/0	2/3,3	1/1,6	1/2,8	1 /2,8

Note. Significance of the difference: * - incomparison with patients of group 1b and 2 at p <0,05, ** - incomparison with patient of group

Table II. Assessment of the degree of dyspnea and the need for SAB in patients of both groups before and after treatment

Indication	Group 1a (n=34)		Group 1b(n=26)	
	before	after	before	after
The degree of shortness of breath in points	3±0,88*	2±0,4	3±0,91**	2±0,6
The need to use short-acting bronchodilators per day	4±0,7*	2±0,4	4±0,9**	2±0,5

Note. Significance of the difference: * - in comparison with patients of group 1b at p <0,05, ** - in comparison with patients of group 1a at p <0,05

Table III. Dynamics of spirometry before and after treatment

Indication	Group 1a (n=34)		Group 1b (n=26)		Group 2 (n=36)	
	before	after	before	after	before	after
FEV 1 %	63,2 ± 1,8*	68,4 ± 1,7	66,1 ± 1,4	67,3 ± 1,5	81,4±0,4	84,8 ± 1,1
FVC %	73,3 ± 1,9*	79,2 ± 3,1	75,4 ± 1,7	78,1 ± 3,1	85,3±1,2	88,8 ± 2,3
FEV 1/ FVC %	63,2 ± 0,9*	71,7 ± 2,14	65,2 ± 0,7	69,8 ± 2,1	88,3±1,2	87,8 ± 0,9

Significance of the difference: * - in comparison with patients of groups 1b and 2 at p <0,05.

Table IV. Dynamics of laboratory parameters as a result of treatment

Indication	Before/ After (1/2)	Group 1a (n=34)	Group 1b (n=26)	Group 2 (n=36)
Leukocytes 10 * 12 / l	1	12,1±0,6	13,2±1,1	6,5±1,3
	2	7,3±0,7	9,2±0,8	6,3±1,2
Neutrophils %	1	73,2±2,4	74,1±2,6	67,2±3,1
	2	67,2±1,7	68,1±1,6	69,1±2,8
Neutrophils in sputum in p / s	1	30,6±1,3	34±1,4	-
	2	22±1,4*	24±2,8**	-
ESR mm / year	1	16 ±3,2	15 ±3,7	6±4,1
	2	11 ±1,2	10 ±2,5	5±3,5
CRP mg / l	1	14,3±2,8*	16,2±2,5**	3,3 ±1,5
	2	3,3±0,6	3,4±0,8	2,1 ±1,9
Procalcitonin ng / ml	1	0,1±0,04	0,1±0,05	0,03 ±0,01
	2	0,04±0,03	0,04±0,04	0,04±0,01
IL-4, pg / ml	1	10,4±2,1*	13,5±0,5**	4,1±0,6
	2	7,4±1,1	8,5±0,7	3,2±0,4
Interferon gamma (IFNγ) pg / ml	1	318,2±11,8*	359,1±11,9**	126,9±12,4
	2	201,1 ±6,8	213,1±5,5	124,5±12,4
IFNγ/ ІЛ-4	1	23,7±11,2*	29,3±9,2**	7,1±1,4
	2	6,6±3,2	9,2±2,2	6,7±1,3
IL-6, pg / ml	1	17,4 ±1,3*	18,5 ±0,8**	6,8±1,7
	2	7,1±0,9	8,2±1,3	5,3±1,4

Notes: * - the difference is significant (p <0,05) in comparison with group 1b and 2; the difference is significant (p <0,05) in comparison with group 1a and 2; a - before treatment; b - after treatment.

and 81% (29 of 36) and 92% . (33 of 36) at p <0.05, compared with group 1b, where dry cough and sore throat prevailed – in 23% (14 of 60) and 12% (7 of 60), respectively, at p <0.05 . After the treatment, a significant decrease in the intensity of clinical signs of combined pathology was registered in both groups, with a predominance in group 1a (table I).

When assessing the severity of shortness of breath on the scale of mMKD and the use of short-acting bronchodilator (SAB) «on demand» before and after treatment, the following data were obtained (table II) .

When assessing the degree of shortness of breath in both groups of patients before and after treatment, there was a significant decrease in 1.5 ± 0.3 or the severity of the symptom of shortness of breath, and antireflux therapy reduced the frequency of short-acting bronchodilators «on demand» 2 times at p <0.05.

When measuring the function of external respiration before and after treatment, the following results were obtained (table III).

Spirometric monitoring revealed improvements in key indicators of external respiratory function, such as FVC, FEV1 / FVC % – and FEV1 in patients of all groups. However, patients who received complex treatment with rabipimide had a more pronounced positive dynamics of the mean: FEV1 increased from 63.2 ± 1.8% to 68.4 ± 1.7% ($p < 0.05$), FVC – from 73 , 3 ± 1.9% to 79.2 ± 3.1% ($p < 0.05$) and FEV1 / FVC % – from 63.2 ± 0.9% to 71.7 ± 2.14% compared with patients of group 1b, where these indicators were: from 65.2 ± 1.8% to 67.3 ± 1.5% ($p < 0.05$), FVC – from 74.3 ± 1.7% to 78.1 ± 3.1% ($p < 0.05$) and FEV1 / FVC % – from 64.1 ± 0.9% to 69.8 ± 2.1%. In group 2 with isolated GERD significant changes in ERF were not detected at $p < 0,05$.

Patients also underwent laboratory evaluation of inflammation according to the general analysis of blood, the level of ESR, C-reactive protein (CRP), procalcitonin and cytokine profile (table IV).

As can be seen from table IV, patients in groups 1a and 1b after treatment showed a significant decrease in acute phase parameters in the serum (CRP), the level of neutrophils in the sputum, levels of IFNγ, IFNγ / IL-4 and IL-6 at $p < 0.05$. Procalcitonin levels in patients of all groups are not prognostically significant at $p < 0.05$.

DISCUSSION

Therefore, in patients with combined pathology there is leukocytosis and an increase in acute phase parameters in the serum (ESR and CRP), indicating active systemic inflammation [11].

The presence of increased levels of neutrophils in the sputum of patients indicates the presence of an inflammatory process in the bronchi [12]. Also in patients of the above groups there is an increase of almost 2 times the level of IFNγ, which involves the activation of the cellular immune system in combined pathology. Increased, almost 3 times compared with the control group, the ratio between IFNγ / IL-4 indicates the presence of an imbalance in the immune system in patients with concomitant GERD [13]. Elevated pro-inflammatory cytokine IL-6 in these patients in the pro-inflammatory cytokine IL-6 stimulates an excessive and unregulated immune response, which in turn maintains chronic inflammation even in remission [14].

After treatment, all patients showed a clinically significant reduction in systemic inflammation, in clinical symptoms of GERD and respiratory symptoms, improved respiratory function which is more pronounced in patients taking rabipimide. Thus, antireflux therapy in patients with COPD in combination with GERD eliminates the main pathogenetic factor (acid reflux), which is an activator of the inflammatory process in the esophagus and airways.

CONCLUSIONS

1. Complex treatment of combined pathology with the use of antireflux therapy has a positive effect not only on the clinical symptoms of reflux, but also on the indicators of the function of external respiration in patients with combined COPD and GERD.
2. Addition of rabipimide to antireflux therapy in patients with combined pathology normalizes the indicators of systemic inflammation, which indicates a pronounced anti-inflammatory effect of the applied therapeutic complex.

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ORIGINAL ARTICLE

PERINATAL ASPECTS OF PREGNANCY AND CHILDBIRTH ON THE BACKGROUND OF VITAMIN D LACK IN PREGNANT WOMEN

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ABSTRACT

The aim: To study the features of the course of gestation and perinatal outcomes of delivery in women with vitamin D lack.

Materials and methods: The article presents the results of studies of the characteristics of the course of pregnancy and delivery outcomes in 50 patients with vitamin D lack compared with a group of 50 somatically healthy pregnant women with normal level of 25 (OH) D.

In order to establish a lack of vitamin D in pregnant women in the 10-12, 20-22, 30-32 weeks of gestation electrochemiluminiscence method by using a test system EURIMMUN (Germany) in the blood serum level of 25-hydroxycalciferol (25 (OH) D) in pregnant women.

Results: When analyzing the structure of complications in women with vitamin D lack during pregnancy and childbirth we found out that risk of premature birth and premature births dominated among all the complications, respectively (58.0% and 36.0%) against (12.0% and 16.0%), p <0.05. Vitamin D lack in pregnant women is often associated with a wide range of obstetric and perinatal complications, namely: preeclampsia, gestational diabetes, bacterial vaginosis , premature rupture of membranes, placental abruption, abnormal labor activity, fetal distress that required delivery by Caesarean section.

Conclusions: An analysis of the course of pregnancy and childbirth in women of thematic groups proved the expediency of an individual approach to the therapy of obstetric pathology among women with vitamin D lack. Despite the level of 25 (OH) D in the blood serum of a pregnant woman of 30 ng / ml and below, it is advisable to prescribe vitamin D for prophylaxes and treatment of Vitamin D deficiency in mother and fetus.

KEY WORDS: vitamin D , pregnancy, childbirth, complications

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INTRODUCTION

One of the urgent problems of modern health care for mothers and children is the problem of public health in many countries of the world [1-3]. Such problems, as it turned out, include the problem of vitamin D deficiency in pregnant women during gestation [4,5].

Many scientific works have been devoted to the study of various aspects of vitamin D deficiency in pregnant women [6,7].

However, the risk factors that contribute to vitamin D deficiency during pregnancy and its effect on the mother-fetus biosystem remain unspecified. There is no unified approach to diagnostics, prevention and treatment of vitamin D deficiency and prognosis for newborns.

The above facts substantiate the relevance of this scientific direction.

THE AIM

To study the features of the course of gestation and perinatal outcomes of delivery in women with vitamin D deficiency.

MATERIALS AND METHODS

In the comparative aspect of pregnancy, childbirth and the assessment of the perinatal consequences of delivery in 100 somatically healthy women with miscarriage was carried out. They were divided into two representative groups: the main group consisted of 50 patients with miscarriage, where the level of 25 (OH) D <30 ng / ml indicated lack of vitamin D in the body of a pregnant woman, the second included 50 pregnant women with a normal level of 25 (OH) D in the serum of a pregnant woman (30-50 ng /ml) [5].

Definition 25-hydroxycalciferol (25 (OH) D) was carried out electrochemiluminiscence method by using a test system EURIMMUN (Germany).

According to the nomogram, the level of vitamin D deficiency in the body of the pregnant woman was assessed.

Statistical processing of research materials was carried out using the Statistica V .6.1 ® software package. The critical value of the significance level (P) was taken as <0.05.

RESULTS

Pregnant women were examined between the age of 21 to 30 years, on average 25.1 ± 2.6 years in the main group and 24.9 ± 1.9 years in the comparison group, p > 0.05.

Table I. Characteristics of labor complications in women of thematic groups (abs ., %)

Pathology	Group	
	The main n = 50	Comparison n = 50
Untimely discharge of amniotic fluid	15 (30.0%)[x]	7 (14.0%)
Abnormalities of labor activity	8 (16.0%) [x]	3 (6.0%)
Delay of part of the litter	17 (34.0%) [x]	1 (2.0%)
Perineal rupture grade I	6 (12.0%)	5 (10.0%)
Fetal distress	7 (14.0%) [x]	3 (6.0%)
Premature detachment of a normally located placenta	3 (6.0%) [x]	1 (2.0%)

Note: [x] $p < 0.05$ relative to the comparison group.

In the study of obstetric history in the study group was observed high frequency of spontaneous abortion during early pregnancy, stillbirth and premature labor.

As a result of our study, the most common complications of vitamin D deficiency were risk of miscarriage, which was observed in 29 (58,0 %) women in the main group and in 6 (12%) women in the comparison group, $p < 0.05$. Preeclampsia of mild severity was diagnosed in 18 (36,0 %) women in the main group and in 4 (8,0%) women in the comparison group, $p < 0.05$.

The threat of premature birth in the main group was observed in 18 (36,0 %) women in the main group and 8 (16,0%) women in the comparison group, $p < 0.05$.

Preeclampsia of moderate severity was diagnosed in 9 (18,0 %) women in the main group and in none of the control women, severe preeclampsia in 2 (4,0 %) women of the main group, which was not characteristic for the comparison group.

Based on the glucose tolerance test in women in the main group, the diagnosis of gestational diabetes (GD) was established in 17 (34.0%) pregnant women in the second trimester, and in 7 (14.0%) – in the third trimester. In this study, it was found that GD was accompanied by obesity of I stage in 7 (14,0 %) women of the main group.

Bacterial vaginosis (BV) at 10-12 weeks was diagnosed in 19 pregnant women – in 15 (30.0%) women in the main group and in 4 (8.0%) women in the comparison group, $p < 0.05$.

An asymmetric form of intrauterine growth retardation (IUGR) of fetus of I degree was found in 7 (14%), II – degree – in 3 (6.0%) pregnant women in the main group and no cases in women in the comparison group. The most frequent complications of childbirth are shown in table I.

The reason for an urgent cesarean section at 30-33 weeks of gestation was placental abruption in 3 (6.0%) of the study group and in 1 (2.0%) in the comparison group, $p < 0.05$. Also, in 7 (14.0%) and 3 (6.0%) women in the main and comparison group, an urgent cesarean section was performed as a result of fetal distress during pregnancy and childbirth at 32-33 weeks of gestation, in 3 (6.0%) women in the main group, the indication for cesarean section was severe preeclampsia at 34-36 weeks. Other complications in the main group occurred from 6% to 17% and from 1% to 7% in the comparison group.

DISCUSSION

The results of the study revealed a high incidence of preclampsia among women. These data confirm the feasibility of taking vitamin D in pre-pregnancy training for the prevention of miscarriage and the development of pre-eclampsia [8,9].

These data confirm the advisability of taking vitamin D in pregravid preparation for the prevention of miscarriage and development of preeclampsia [10], confirming our data.

Taking into account the data obtained, it can be assumed that the lack of vitamin D may be an additional risk factor for the development of dysbiosis of the mucous membranes of the genital tract. Therefore, according to [11], the appointment of vitamin D can effectively contribute to dysbiosis prophylaxes.

CONCLUSIONS

1. Analysis of the course of pregnancy and childbirth in women of formed groups proved the advisability of an individual approach to the treatment of obstetric pathology with a lack of vitamin D.
2. When the level of 25 (OH) D in the serum of a pregnant woman is 30 ng / ml and below, it is advisable to prescribe vitamin D for the preventive and therapeutic purpose of Vitamin D deficiency in the mother and fetus.

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ORIGINAL ARTICLE

DIAGNOSTIC VALUE OF GLOBAL LONGITUDINAL STRAIN IN PATIENTS WITH CORONARY ARTERY DISEASE

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ABSTRACT

The aim: To investigate the global longitudinal strain (GLS) in patients with preserved left ventricle systolic function and the presence of varying degrees of coronary artery disease.

Materials and methods: The study is based on data obtained during a prospective analysis of 131 patients aged 51 to 82 years in the period from January to December 2019,whose complaints indicate coronary heart disease. The main instrumental method of examination was coronary angiography, patients were divided into 3 groups according to the results. The control group (group I) consisted of 30 patients in whom no coronary artery disease was detected; patients with single vessel lesions or non-stenotic coronary atherosclerosis were included into group II (n = 35) and patients with multivessels lesions (n = 66) were included in group III. For each patient, the extent of the lesion was assessed using the SYNTAX Score. The groups were comparable in age, sex and comorbidities.

Results : GLS was -19.71 ± 2.22 (SI -18.88 to -20.54%) in the group without coronary lesions, the group with multivessel lesions was the lowest -14.34 ± 3.47 (SI -13.49 to -15.2%). There was a significant correlation between GLS average and LV EF (r = 0.681; p <0.0001), LV ESV (r = -0.576; p <0.0001), EPSS (r = -0.528; p <0.0001). A moderate correlation was observed GLS, linear and volumetric parameters.

Conclusions: Global longitudinal strain is recommended for echocardiographic assessment of patients with coronary artery disease, as one of the main areas of application of this technique because its use provides additional information and maybe used in the same patient to assess the treatment.

KEY WORDS: Global longitudinal strain, speckle tracking, coronary artery disease

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INTRODUCTION

The main method to study the pathology of the cardiovascular system is echocardiography (Echo). Its value is undeniable since this method has a lot of benefits such as lower cost compared to other imaging, no ionizing effect, rapid study results and the ability to perform not only in patients with stable haemodynamics, but also in intensive care, where the results can affect the choice of further treatment for a patient.

The parameter assessed by echo includes the ejection fraction (EF) of the left ventricle (LV), which is mandatory as an indicator of the pumping function of the heart. This surrogate marker of LV systolic function was proposed in 1965 by psychiatrist Stuart Bartle and co-authors [1] and is a mathematical expression of the stroke volume to LV volume at the end of diastole.

However, over the past 15 years, the value of EF as an assessment of LV function has been placed in question because it does not allow assessing the presence of remodeling, relaxation disorders or local changes in contractility when this parameter remains within normal limits in LV pathology [2].

Speckle tracking has become widely used in the search for an objective assessment of regional myocardial function. This technique is based on the Doppler effect and tracks the motion and speed of greyscale speckles. With the help of processing algorithms for two-dimensional echocardiographic images, small stable points of the myocardium, formed by the interaction of ultrasound tissue with the myocardium, in a certain area of interest are identified. The frame by frame is tracked during the cardiac cycle, the distance between the points or their spatio-temporal displacement (regional velocity vectors), which provide information about the global and segmental myocardial deformation.

The speckle tracking technique was first introduced by a group of co-authors from Norway in 1998 [3]. Since then, a lot of data has been accumulated on the use of strain analysis, namely global longitudinal strain (GLS), in patients with various pathologies, such as hypertrophic cardiomyopathy, amyloidosis, Fabry disease, Takotsubo cardiomyopathy, coronary heart disease and others.

One of the meta-analyses comparing EF LV and GLS in predicting adverse cardiovascular outcomes in patients found a prognostic value GLS exceeded the importance of EF LV for predicting all-cause mortality, cardiac death, malignant arrhythmia, hospitalization for heart failure, and emergency surgery one of the heart valves or heart transplantation, as well as an acute ischemic coronary event [4].

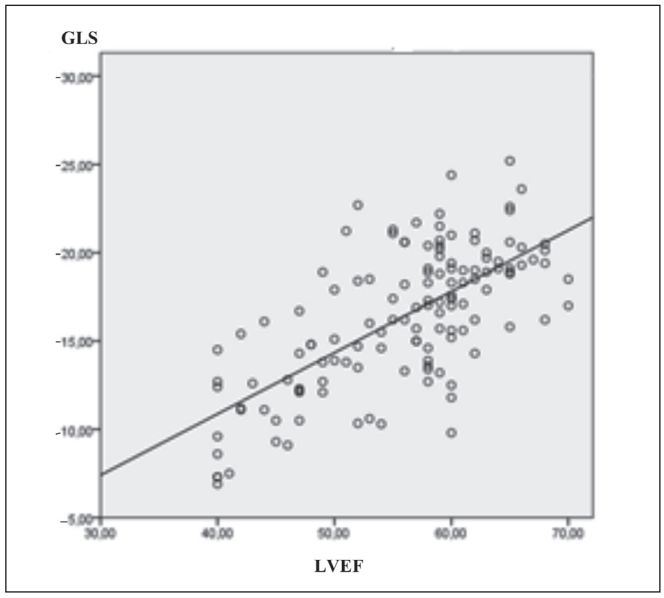

Fig. 1. Significant correlation plots between left ventricular ejection fraction (LVEF) and left ventricular global longitudinal strain (GLS) : r=0.353 (p<0.0001)

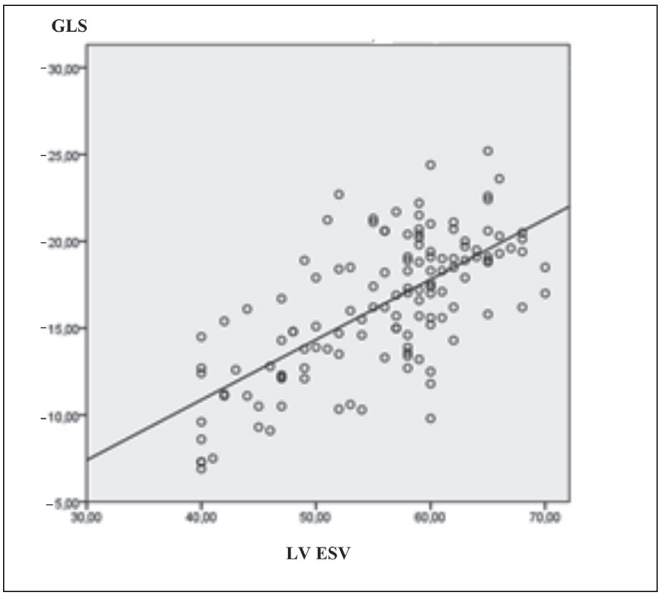

Fig. 2. Significant correlation plots between left ventricular global longitudinal strain (GLS) and left ventricular end-systolic volume (LV ESV) : r=-0.528 (p<0.0001)

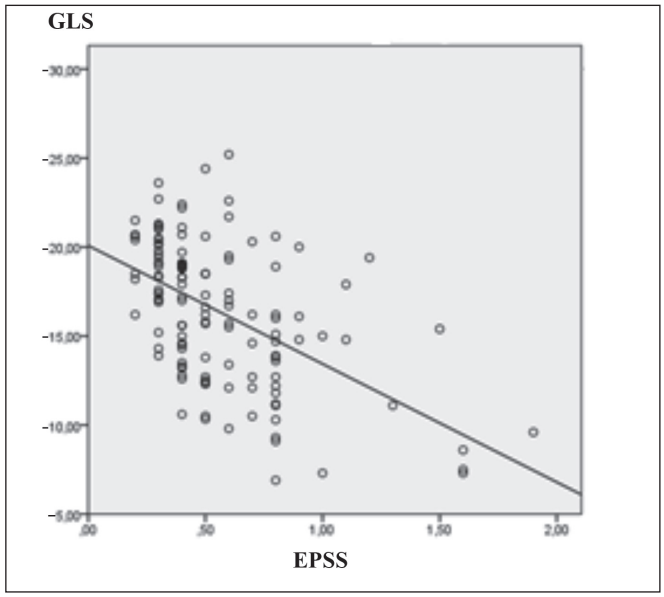

Fig. 3. Significant correlation plots between left ventricular global longitudinal strain (GLS) and E-point septal separation (EPSS) : r=-0.528 (p<0.0001)

THE AIM

The aim of this study was to investigate the GLS in patients with preserved LV systolic function with different degrees of coronary artery lesions.

MATERIALS AND METHODS

The work was performed in the Ukrainian Children`s Cardiac Center (Ukraine, Kyiv) in 2019. 131 patients were examined,whose complaints indicated the possible presence of coronary artery disease (CAD). Depending on the results of coronary angiography, patients were divided into 3 groups. The control group (group I) consisted of 30 patients without CAD. Study group II consisted of 35 patients with single-vessel lesion or non-stenotic coronary atherosclerosis. Study group III included 66 patients with multivessel lesions. The groups were comparable on age, body mass index (BMI) and most comorbidities.

The mean age of patients in group II was the highest and was 64.31 ± 1.62 years, in group III – 63.0 ± 1.14 years and the lowest values were in group I – 60.53 ± 1.77 years, but the difference was not significant in the age structure of patients (p = 0.39).

In the control group, the majority of patients were female (70%) compared with groups II and III, where the number of women was 31.2% and 21.2%, respectively (p = 0.0001).

The highest BMI values corresponding to obesity of the first degree was in group I – 31.74 ± 1.09 kg / m2. In the third group – 30.71 ± 0.62 kg / m2, this also corresponds to the first degree of obesity. Group II had the lowest BMI – 29.76 ± 0.77 kg / m2, but the difference between the groups was not significant (p = 0.432). There were no patients who abused alcohol in group I; in group II – 1 patient (2.9%) and in group III – 5 patients (7.6%). The percentage of smokers in the groups was almost the same: in group I 7 patients smoked (23.3%), in group II – 11 patients (31.4%), in group III – 23 patients (34.8%). The data indicate the homogeneity of the studied groups (p = 0.529).

According to the Syntax score I, groups with atherosclerotic lesions differed. In group II, the median was 5 (0; 10) points, which corresponded to the low risk, in group III – 27.75 (18; 38) points, which corresponded to the intermediate risk.

Echocardiography (Echo) was performed on an ultrasound diagnostic apparatus Vivid iq (manufactured by GE Healthcare, USA) with electrocardiographic synchronization and use of a phased transducer (a frequency of

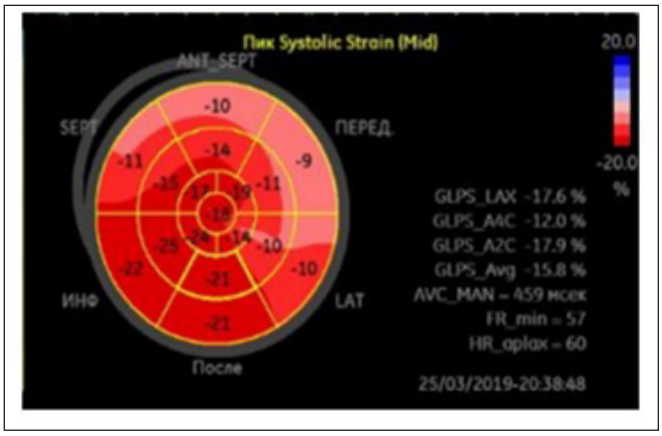

Fig. 4. Left ventricular global longitudinal strain

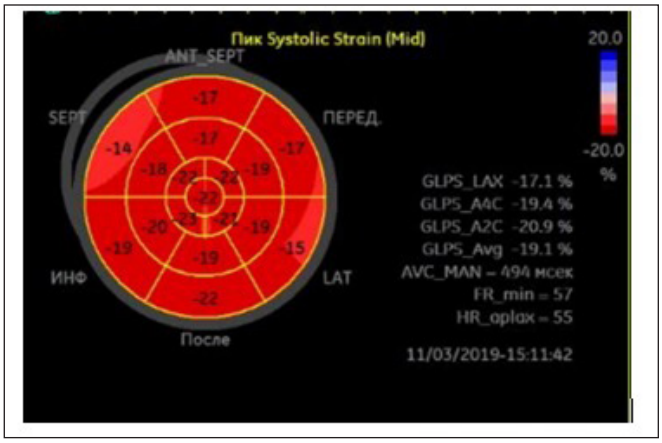

Fig. 6. Left ventricular global longitudinal strain

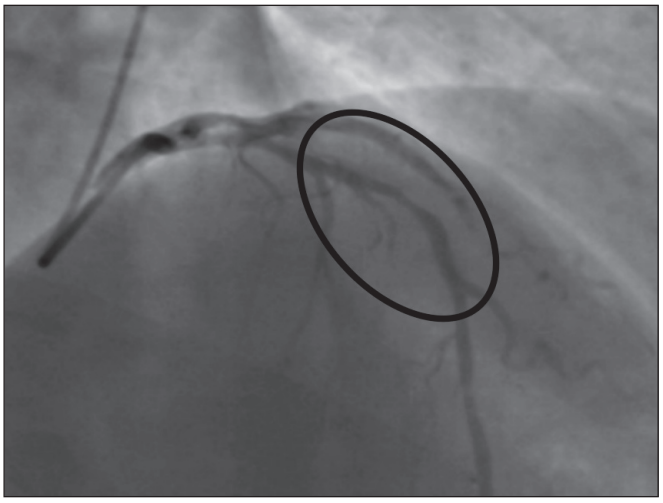

Fig. 5. Coronary angiography of patient G with left coronary artery stenosis

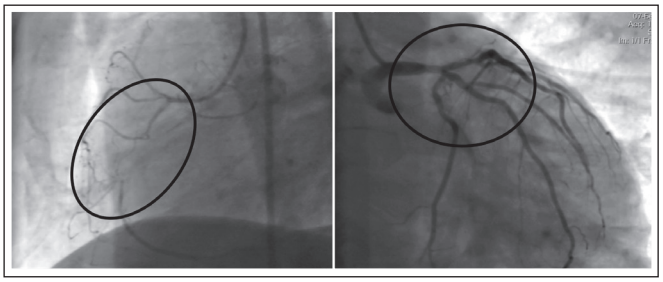

Fig. 7. Coronary angiography of patient A with multivessel coronary artery disease

2-4 MHz and a frame rate of 40 to 80 Hz) according to the standard protocol.

The following indicators were obtained: end-diastolic size (EDS), end-systolic size (ESS), interventricular septal thickness (IVS), posterior wall thickness (PW), end-diastolic volume (EDV), end-systolic volume (ESV), left ventricular myocardial mass (LVMM), ejection fraction (EF), fractional contraction (FS), cardiac output (CO), stroke volume (SV), cardiac index (CI), stroke volume index (SVI), distance from the edge of the anterior mitral valve leaflet to IVS in diastole (EPSS), indexed left atrial volume (iLA), global longitudinal strain (GLS).

To determine the global longitudinal strain of the LV, the image was analysed in 2-chamber, 3-chamber and 4-chamber positions from the apical access and evaluated in 17 segments of the LV model (bull's-eye diagram). Landmarks were set at the base of the anterior and posterior leaflets MV, and at the top of the LV; the contours of the segments were corrected to optimize tracking.

Coronary angiography was performed on an angiography machine Artis Zee biplane (manufacturer SIEMENS, Germany).

The obtained data were processed by statistical programs «Excel», SPSS Statistics 20.0. and were both parametric and non-parametric (by Shapiro-Wilk criterion), so the data was performed as a mean value with standard error (M ± m) and 95% confidence interval,

Table I. Longitudinal strain in groups

	I group		II group		III group		p-value*
	Mean±SD	95% CI	Mean±SD	95% CI	Mean±SD	95% CI	
Apical three chamber,%	-19.89 ± 3.15	-18.72 to -21.07	-16.88 ± 4.76	-15.24 to -18.52	-14.51± 4.52	-13.39 to -15.62	0.0001
Apical 4 chamber,%	-19.8±3.09	-18.64 to -20.96	-17.96 ±4.57	-16.39 to -19.5	-14.64± 4.06	-13.65 to -15.65	0.0001
Apical 2 chamber,%	-19.15±2.88	-18.08 to -20.22	-17.03±3.58	-15.8 to - 18.26	-13.89± 3.81	-12.95 to -14.82	0.0001
GLS average,%	-19.71±2.22	-18.88 to -20.54	-17.27±3.78	-15.97 to -18.57	-14.34± 3.47	-13.49 to -15.2	0.0001

CI – confidence interval; GLS – global longitudinal strain, SD – standard deviation.
* p-value differences between groups.

Table II. Correlation of GLS average with the left ventricle indices

Index	GLS average
LV EDD	r=-0.476; p<0.0001
LV ESD	r=-0.331; p<0.0001
LV EDV	r=-0.482; p<0.0001
iLV EDV	r=-0.354; p<0.0001
iLV ESV	r=-0.486; p<0.0001
LV mass	r=-0.404; p<0.0001
iLVmas	r=-0.342; p<0.0001
CI	r=0.419; p<0.0001
SVi	r=0.386; p<0.0001
SS	r=-0.427; p<0.0001

LV EDD- left ventricular end-diastolic dimension, LV ESD- left ventricular end-systolic dimension, LV EDV- left ventricular end-diastolic volume, iLV EDV- indexed left ventricular end-diastolic volume, iLV ESV- indexed left ventricular end-systolic volume, LV mass – left ventricular mass, iLVmas – indexed left ventricular mass, CI – cardiac index, SVi – stroke volume index, SS – syntax score.

and a median with 25 and 75 quartiles (Me (25; 75%)). Quantitative group comparisons were performed using the Mann-Whitney U test for independent samples. The χ^2 Pearson and Kruskal-Wallis test was used to assess the significance between the two independent samples. p-values of less than 0.05 were regarded as statistically significant.

RESULTS

According to echocardiographic parameters, it was found that EF in all three groups was within normal limits. The lowest EF was in group III and amounted to 54.0 (47.0; 59.0)%; groups I and II did not differ in this indicator and were 60.0 (59.0; 65.0)% and 58.0 (51.5; 62.0)%, respectively.

FS in all groups was also within the norm range and was 34.0 (32.0; 36.0)% in group I, 32.0 (30.0; 34.5)% in group II and 29.0 (24.0; 32.0)% in group III.

Analysing the value of GLS separately in each of the three positions (in 2- chamber, 3-chamber and 4-chamber) and GLS average revealed a significant difference in all indicators. The data are presented in Table I.

The strain was the highest significantly for group I in all the positions. In 3-chamber view the indicator was -19.89 ± 3.15%, in 4-chamber – -19.8 ± 3.09%, in 2-chamber – -19.15 ± 2.88%. The value of the GLS average was -19.71 ± 2.22%.

The group with multi vessel lesions had the smallest values, namely, in the 3, 4 and 2-chamber positions the indicators were -14.51 ± 4.52%, -14.64 ± 4.06% and -13.89 ± 3.81%, respectively. Average GLS was below normal – -14.34 ± 3.47%.

There was a significant correlation between GLS average and the following indicators: LV EF (r = 0.681; p <0.0001), LV ESV (r = -0.576; p <0.0001), EPSS (r = -0.528; p <0.0001). Figure 1,2,3.

In addition, there were moderate correlations between the GLS average and LV EDD,LV ESD, LV EDV, iLV EDV, iLV, ESV, LV mass, iLVmas, CI, SVI, SS. The degree of correlation and the significance are shown in table II.

These results indicate the relationship of GLS average with linear, volumetric parameters, as well as the degree of damage to the coronary vessels.

The explanation of the mechanisms of GLS reduction in coronary heart disease also has a pathophysiological basis, namely the reduction of the movement of longitudinal LV fibers, which are the first to be affected by ischemic atherosclerosis of the coronary vessels. For example, consider the example of patient G, 52 years old with typical angina. We performed echocardiography, where we found reduced GLS to -15.8% due to the segments of the anterior and lateral walls (Figure 4).

The coronary angiography revealed a proximal lesion of the left descending artery (Figure 5).

However, exceptions to any rule are possible. Patient A, a man of 66 years old, according to the indices of GLS had -19.1%, which is a variant of the norm, but coronary angiography revealed multi vessel lesions (both right and left coronary arteries) The data are presented in Figure 6 and Figure 7.

These data maybe an example of an exception in the GLS. Patient A was only one of the group with multi vessel lesions of the coronary arteries and accounted for 0.15% of the total group, which did not affect the overall result.

DISCUSSION

Global longitudinal strain is recommended to be use for the echocardiographic assessment of patients with CAD, as one of the main areas of storing this technique [5]. Despite the variability of the data due to differences in terminology describing myocardial mechanics, the types of stored data used for quantitative analysis, the modality of measuring the main parameters or the different definiteness of the tracking area for the same parameter, the derivation results [6] , its use provides additional information and can be used in the same patient to evaluate treatment.

In our study, the group without coronary GLS lesions was -19.71 ± 2.22% (SI -18.88 to -20.54%), which was significantly different (p = 0.0001) from patients with multivascular coronary lesions -14.34 ± 3.47 (SI -13.49 to -15.2%). On the contrary to GLS, ejection fraction in groups was within the norms.

The data shown that GLS maybe more sensitive echocardiographic indicator in patients with lesions of coronary arteries and sparing systolic function of LV. Thus, low GLP levels increase the likelihood of suggesting that a patient has coronary heart disease and allow early diagnosis of more significant myocardium due to coronary insufficiency due to multiple vascular lesions.

The correlation between the longitudinal strain and scores on the Syntax Score scale, as an indicator of the

severity of vascular lesions, is described in the works of various authors [7, 8] that describe its significance. But the «gold standard» for the estimation of the coronary artery lesions is coronary angiography.

The obtained data significantly correlate ($p < 0.0001$) with linear and volumetric indicators and confirm the data of Dahle GO which indicates the value of preload and afterload by the GLS value [9]. The interconnection between GLS and EDV is shown in Vaidya GN and the co- authors work [10], which indicates the correlation between these parameters.

The correlation between EPSS and GLS ($r = -0.528$; $p < 0.0001$) was significant in our study. Sarahazti M. and the co-authors had similar results, which they identified as a useful parameter [11].

The excellent diagnostic value of GLS in patients with CAD was demonstrated by Kevin Liou and the co-authors, who evaluated the results of 10 studies from the data number of 1,669 patients [12]. It was revealed that the average value of GLS in the patients with CAD was significantly lower compared with the patients without coronary artery lesions.

CONCLUSIONS

Global longitudinal strain is recommended for the echocardiographic assessment of patients with coronary artery diseases as one of the main areas of application of this technique. Despite the variability of the data due to differences in terminology describing the mechanics of the myocardium, the types of stored data used for quantitative analysis, the modality of measurement of basic parameters, its application provides additional information and can be used in the same patient to evaluate the quality of treatment. Currently, the assessment of GLS for this group of patients, as one of the echocardiography examinations, is recommended by the European Association of Cardiovascular Imaging and the American Society of Echocardiography.

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The Author declare no conflict of interest.

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ORIGINAL ARTICLE

INSULIN RESISTANCE AS AN INDICATOR OF DIFFERENTIATION FOR THE FORMATION OF RISK GROUPS FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITHOUT TYPE 2 DIABETES MELLITUS, AS A PART OF ONTOLOGICAL MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT

The aim: Using cluster analysis, to identify a high-risk group for NAFLD and develop a differential approach to examination, treatment and prevention of the disease based on IR indices, among NAFLD and non-NAFLD patients without type 2 diabetes mellitus (T2DM).

Materials and methods: Clinical, anthropometric, laboratory methods, ultrasound, computational and statistical techniques were applied.

Results: Cluster analysis was performed on the laboratory tests results: glucose, insulin, HOMA-IR index, HOMA2 Calculator (%B – beta-cell function, %S – insulin sensitivity, IR – insulin resistance). 5 groups of patients were formed, according to increasing HOMA-IR index and IR. Group II was found to be transient in IR formation, it included the majority of non-NAFLD patients (87%), and we consider it to be the risk group for NAFLD. Group V – with the highest IR scores, where 92% of patients had NAFLD and 73% had a high Fatty Liver Index – is considered to be a very high-risk group for developing T2DM.

Conclusions: 1. According to the results of cluster analysis, 5 groups of patients with different IR levels were identified. 2. In the second group, where non-NAFLD patients predominate, insulin resistance begins to form. 3. Groups III and IV – patients with high HOMA-IR index – had significant ultrasound findings indicating hepatic steatosis. 4. Group V included patients with NAFLD, with high HOMA-IR index and the highest risk of developing T2DM.

KEY WORDS: NAFLD, insulin resistance, HOMA-IR index, HOMA2 Calculator, ontology

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic disease characterized by excessive accumulation of fat in the liver [1-6]. In most patients, NAFLD is associated with metabolic comorbidities such as obesity, type 2 diabetes mellitus (T2DM) and dyslipidemia [1-6]. According to a meta-analysis of epidemiological studies on NAFLD in 2016, the overall regional incidence of NAFLD in Asia is 52.34 per 1,000 person-years, while the incidence in the West is estimated at 28 per 1,000 person-years [7]. The global prevalence of NAFLD confirmed by computed tomography is about 25.24% [5, 7]. According to the American Association for the Study of Liver Diseases (AASLD), the prevalence of NAFLD in the general population ranges from 1.5% to 6.45% [5, 7, 8].

We analyzed and systematized the data from a 2016 article by Buzzetti E et al. [9], which set out a new perspective on NAFLD pathogenesis and revisited the previous "two-hit theory". Currently, a "multiple-hit theory" of NAFLD pathogenesis is predominant, the "hits" being lipotoxicity [10, 11]and insulin resistance (IR), microbiota impact ("gut-liver axis") [12, 13], dietary [14, 15], epigenetic [16, 17], genetic factors [17], adipose tissue dysfunction [18, 19], IL-6 and TNF-α, endoplasmic reticular stress [20, 21] and mitochondrial dysfunction[9, 22-25].

Insulin resistance is one of the key factors in steatosis and non-alcoholic steatohepatitis (NASH) development and leads to increased hepatic de novo lipogenesis (DNL) and impaired inhibition of lipolysis resulting in increased fatty acid uptake by the liver [9, 26-28]. Insulin resistance contributes to adipose tissue dysfunction which leads to altered production and secretion of adipokines and inflammatory cytokines [9, 29]. The "Consensus document. Management of non-alcoholic fatty liver disease (NAFLD) Clinical practice guideline" published in 2018 states that insulin resistance is a trigger factor in liver damage, which causes fat deposition in its tissue [5]. IR is an abnormal biological response of insulin effector tissues (liver, muscle and adipose tissue) and is reflected by plasma insulin levels above 20 μU/ml, associated with adverse cardiovascular events and NAFLD progression [5]. The consensus also states that IR is associated with reticular and oxidative stress which induces serine and threonine phosphorylation at insulin receptors, resulting in reduced efficiency of the insulin signaling cascade [5].

Table I. Patients distributed into groups according to cluster analysis

N 151	Group I	Group II	Group III	Group IV	Group V
n (%)	34 (23%)	45(30%)	27(1%)	19(13%)	26(17%)
male (%) female (%)	13(38) 21(62)	23(51) 22(49)	12(44) 15(56)	9(47) 10(53)	19(73) 7(27)
NAFLD(%)	3 (9%)	10 (22%)	17(22%)	17(89%)	24(92%)
Without NAFLD (%)	31 (91%)	35(78%)	35(78%)	2(11%)	2(8%)

We focused on studying insulin resistance in NAFLD patients and non-NAFLD patients who do not have T2DM, by utilizing the indirect IR measures recommended in 2014 "Surrogate measures of insulin sensitivity vs the hyperinsulinaemic-euglycaemic clamp: a meta-analysis" and others [30, 31].

THE AIM

Using cluster analysis, to identify patients that form a risk group for NAFLD and further develop a differential approach to examination, treatment and prevention of the disease based on IR indices, among patients with confirmed NAFLD and without NAFLD who do not have type 2 diabetes mellitus (T2DM).

MATERIALS AND METHODS

We analyzed results from 151 patients' examinations in the "INTO-SANA" clinic (according to the agreement on scientific cooperation between Shupyk National Healthcare University of Ukraine and Medisvit Medical Centers MMC) throughout 2018 – 2020. Prior consent for data processing had been obtained. We analyzed data from patients with NAFLD without T2DM (n 71), including 44 males (61%) and 54 females (39%), as well as patients without NAFLD who do not have T2DM (n 80), including 32 males (40%) and 48 females (60%). The diagnosis of NAFLD was established according to the National Ukrainian Unified Clinical Protocol for Primary and Secondary (Specialized) Medical Care "Non-Alcoholic Steatohepatitis".

Clinical, anthropometric, laboratory methods, as well as ultrasound, computational and statistical techniques were applied.

The workup algorithm included examination of patients with the assessment of anthropometric parameters (body weight, height, body mass index (BMI), waist circumference (WC)), laboratory tests (complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), fasting glucose, fasting insulin, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), atherogenic index of plasma (AIP), HBsAg, total anti-HCV antibodies.

HOMA-IR is a laboratory alternative for the "gold standard" of IR diagnosis – hyperinsulinaemic-euglycaemic clamp test. The HOMA-IR index is calculated using the following formula [30, 31]:

fasting glycaemia (mmol/l) x fasting insulin (μOD/ml))/22.5.

Values: no IR – <1.82; prediabetic (IR) – ≥1.82 – <3.63; diabetic (high IR) ≥ 3.63. The values are valid for adult middle-aged Europeans [32].

To calculate the HOMA2 index (%B – beta-cell function, %S – insulin sensitivity, IR – insulin resistance), an on-line calculator was utilized [33]. This model has been calibrated to obtain %B and %S values of 100% for healthy young people using currently available insulin assays.

Fatty Liver Index was calculated using the following formula [34]:

$(FLI) = e^y / (1 + e^y) \times 100$

$y = 0.953 \times \ln(TG, mg/dL) + 0.139 \times BMI, kg/m2 + 0.718 \times \ln(GGT, U/L) + 0.053 \times WC, cm - 15.745$

FLI <30 – low risk, hepatic steatosis ruled out; FLI = 30 – <60 – the risk is uncertain, steatosis possible; FLI ≥ 60 – high risk, hepatic steatosis ruled in.

Laboratory tests were performed and results identified according to the unified methods approved by the Ministry of Health of Ukraine.

All patients were examined with an abdominal ultrasound (US). Ultrasound criteria for hepatic steatosis are: parenchymal hyperechogenicity due to diffuse fatty infiltration, fine- or medium-grain echoes, deep beam attenuation, portal vessels hypoechogenicity, hepatomegaly; sometimes within the fatty infiltration pattern areas of reduced echogenicity may be seen – reflecting patches of normal parenchyma.

An online calculator "The alcoholic liver disease/Non-alcoholic fatty liver disease index (ANI)" was used to differentiate between NAFLD and alcoholic liver disease (ALD). This is a statistical model that takes into account alanine aminotransferase (ALT), aspartate aminotransferase (AST), mean erythrocyte volume (MCV), patient's body weight, height and sex. An index value greater than zero was assessed as alcoholic liver disease (ALD) and less than zero as NAFLD.

Patients taking statins were excluded from the study.

Cluster analysis was performed using the results of laboratory tests: glucose, insulin, HOMA-IR index, HOMA2 values (%B, %S, IR).

The calculations were performed with the SPSS Statistics 26 program, using cluster analysis. When evaluating indicators with normal distribution M ± SD [95% CI] was applied, and for indicators with a non-normal distribution – Me [Q1 25%; Q3 75%].

RESULTS

By conducting cluster analysis (Fig. 1), the following groups were formed with characteristic differences in certain indicators:

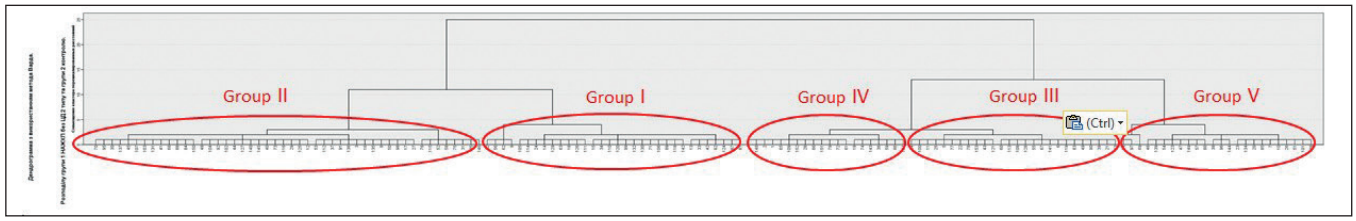

Fig. 1. Cluster analysis-grouping results.

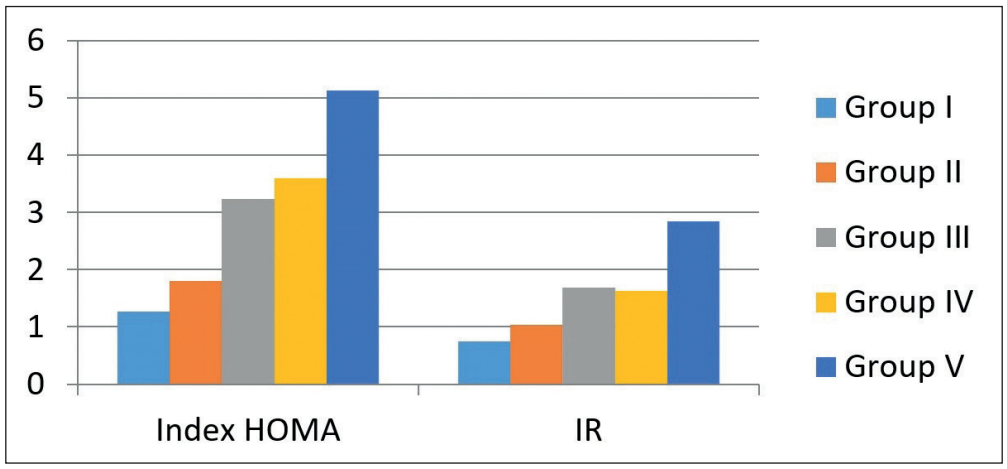

Fig. 2. HOMA and IR values in each group.

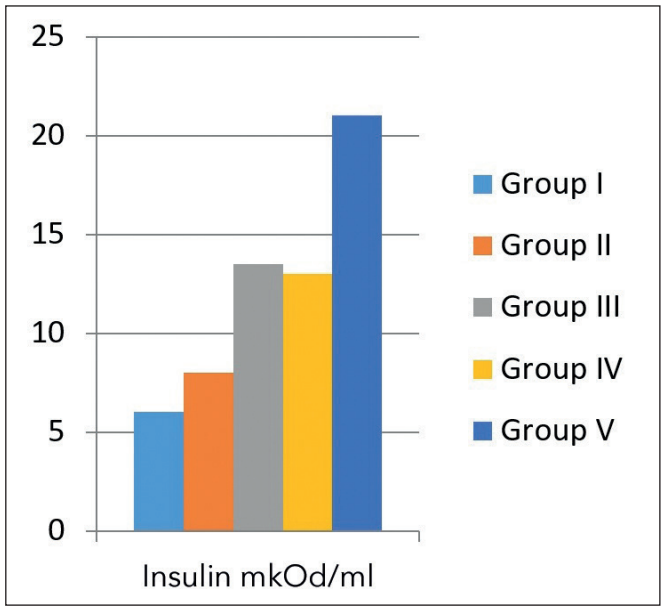

Fig. 3. Insulin levels in each group.

• *Group I*: n 34 (23%), 13 males (38%) and 21 females (62%). Among them 31 (91%) from the non-NAFLD group, 3 (9%) from the NAFLD group with mean HOMA-IR – 1.3, %B – 78%, %S – 135%, IR – 0.8, glucose – 5, insulin – 6,2; 26 patients (77%) with low FLI, 8 (23%) with indeterminate FLI, 0 with high FLI.

• *Group II*: n 45 (30%), 23 males (51%) and 22 females (49%). Among them, 35 (78%) non-NAFLD patients, 10 (22%) NAFLD patients with mean HOMA-IR – 1.8, %B – 105%, %S – 95%, IR – 1.1, glucose – 5.9, insulin – 8; 29 patients (64%) with low FLI, 12 (27%) with indeterminate FLI and 4 (8%) with high FLI.

• *Group III*: n 27 (18%), 12 males (44%) and 15 females (56%). Among them 10 (37%) non-NAFLD patients, 17 (63%) NAFLD patients with mean HOMA-IR – 3.8, %B – 122%, %S – 58%, IR – 1.7, glucose – 5.3, insulin – 13,5; 7 patients (26%) with low FLI, 7 (26%) with indeterminate FLI, 13 (48%) with high FLI.

• *Group IV*: n 19 (13%), 9 males (47%) and 10 females (53%). Among them 2 (11%) non-NAFLD patients, 17 (89%) NAFLD patients with mean HOMA-IR – 3.6, %B – 99%, %S – 56%, IR – 1.8, glucose – 6, insulin – 13.7; 3 patients (16%) with low FLI, 3 (16%) with indeterminate FLI, 13 (68%) with high FLI.

Group V: n 26 (17%), 19 males (73%) and 7 females (27%). Among them 2 non-NAFLD patients, 24 (92%) NAFLD patients with mean HOMA-IR – 5, %B – 174%, %S – 41%, IR – 6.5, glucose – 5.3, insulin – 21; 0 patients (0%) with low FLI, 7 (27%) with intermediate FLI, 19 (73%) with high FLI. (Tabl.I)

Applying cluster analysis (Fig. 1), all patients were divided into groups based on HOMA-IR values (Fig. 2).

Between groups II and III there is a cut-off transition from patients with normal HOMA-IR index (0.8 ± 0.3) in group II to the values indicating IR (3.23 ± 0.83) in group III. In group III, the HOMA-IR index is already (3.23 ± 0.83), in group IV it is (3.6 ± 1.5), which indicates high IR, in group V it is (5.13 ± 2, 15). The IR index calculated with HOMA2 Calculator also increases with each group: 0.75 [0.69; 0.8] in group I, 1.04 [0.95; 1.18] in group II, 1.68 [1.56; 2.1] in group III, 1.63 [1.45; 1.81] in group IV, 2.84 [2.18; 4.2] in group V (Fig. 2). Between groups II and III there is a cut-off transition from the normal IR index of 1.04 [0.95; 1.18] to an increased value – 1.68 [1.56; 2.1]. Insulin levels progressively increase from group I (6 ± 2.71) to group V (21 ± 7.46) (Fig. 3).

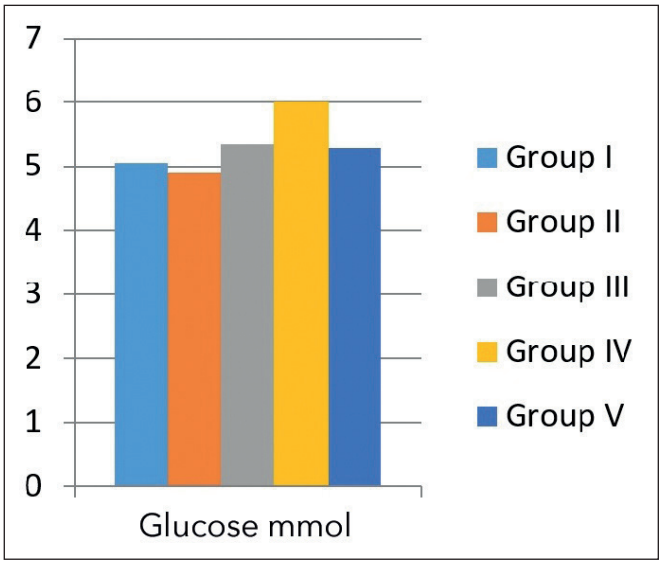

Fig. 4. Glucose levels in each group.

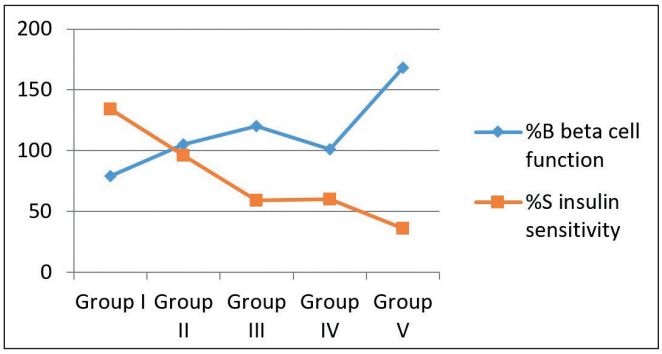

Fig. 5. %B and %S in each group.

Patients' blood glucose levels in all these groups were normal. Only group V had borderline values – 6 mmol/l (Fig.4).

Similarly, other HOMA2 Calculator indicators (%B – B-cell function, %S – insulin sensitivity) in the groups change expectedly (Fig. 5). %B increases from 78% in group I to 174% in group V, %S – insulin sensitivity – decreases from 135% in group I to 41% in group V. Transition from normal to abnormal high IR occurs between groups II and III, as shown in Figure 5.

It is important to note that in our study the criteria for the metabolic syndrome associated with NAFLD [1], such as TG (> 1.7 mmol/l) and HDL-C (<1 in males/1.3 mmol/l in females) were identified only starting from group IV for TG, and from group V in females for HDL-C.

DISCUSSION

In our study, having applied cluster analysis, we performed an original distribution between patients not by a known NAFLD differentiation cluster, such as hepatic steatosis on ultrasound, but by IR measures. The key was that patients with T2DM and those taking statins were excluded from the study. We found the transition between groups II and III to be the most valuable, since it indicated the transition from normal insulin sensitivity to low sensitivity. It was significant that these groups included patients with both existing NAFLD and without it. Given that the correction of IR, with existing NAFLD or without it (taking into account that the ultrasound method might not detect steatosis in the liver with a fat content <20% [1-6], includes a lifestyle modification, regular exercise and nutrition correction, we consider it important to actively identify patients with insulin resistance who do not yet have NAFLD, to prevent its development [1-6]. It can be concluded that testing for fasting blood glucose without checking insulin level makes it impossible to detect patients who are already developing insulin resistance, but have no ultrasound findings characteristic for hepatic steatosis. Based on the obtained data, the future works will be focusing on anthropometric indicators for all five groups of patients with the development of an algorithm for clinical decision-making depending on measured anthropometric, clinical and laboratory indicators, which may be of practical importance.

HOMA-IR provides a surrogate estimate of IR in persons without diabetes and can therefore be recommended provided proper reference values have been established (A1 recommendation), according to EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease [1]. Its use was limited due to the absence of established age-adjusted reference values for Ukraine. According to Horáková D et al. 2019 study, we may use their defined HOMA-IR cut-offs for middle-aged Europeans to improve T2DM prevention. [32] There are also published HOMA-IR reference values for Turkey, Brazil and other regions [35, 36].

In July 2020 Eslam M. et al. published an article [37] suggesting to redefine non-alcoholic fatty liver disease (NAFLD) as a metabolic dysfunction-associated fatty liver disease (MAFLD). HOMA-IR ≥ 2,5 is one of the diagnostic criteria for MAFLD in patients with confirmed hepatic steatosis and body mass index < 25 kg/m2 in Caucasians and < 23 kg/m2 in Asians. Aligning these values, we determine that individuals with HOMA- IR ≥1,82 and <2,5 already have insulin resistance, but they do not yet fit into NAFLD criteria – therefore, they are a risk group.

According to the American Diabetes Association (ADA) "Standards of Medical Care in Diabetes 2020", fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), or A1C criteria are recommended for diabetes and prediabetes screening. HOMA-IR is not mentioned in the guideline. "Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal. Prediabetes is not viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. [38].

As we see, early insulin resistance detection and prevention are highlighted in all guidelines for in insulin resistance-associated diseases, emphasizing the fundamental diet and lifestyle modification.

CONCLUSIONS

1. According to the obtained results of cluster analysis, 5 groups of patients with different levels of insulin resistance were identified.
2. It was found that from group II, where non-NAFLD patients predominate, 35 (78%) begin to from insulin resistance.
3. Groups III and IV – patients with high HOMA-IR index – had significant ultrasound findings indicating hepatic steatosis. In group III the characteristic findings were seen in 1/2 of patients, while in group IV – in 2/3 of patients.
4. Group V included patients with NAFLD (24 92%), with high HOMA-IR index (5.13 ± 2.15), IR 2.84 [2.18; 4.2] and %B – beta-cell function of 174%. Insulin sensitivity %S was only 41%. This group of patients is at a very high risk of developing T2DM.
6. Systematization of knowledge, as the basis for the ontological model of NAFLD, regarding the importance of testing for blood insulin level to identify insulin resistance in patients without T2DM allows to identify a risk group for NAFLD, prevent the disease and improve care for patients.

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The study was performed within the research work "Prevention, diagnosis and treatment of liver and intestinal diseases associated with the pathology of other organs and systems" (National registration number: 0117U000908) carried out by the Gastroenterology, Dietology and Endoscopy department of Shupyk National Healthcare University of Ukraine and is a fragment of research "Substantiation for the ontological model of care for patients with nonalcoholic fatty liver disease" (National registration number: 0118U100267).

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Conflict of interest:
The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

PROSPECTIVE ANALYSIS OF THE EPIDEMIOLOGY OF CEREBROVASCULAR DISEASE AND STROKE AMONG THE ADULT POPULATION OF KYIV CITY, UKRAINE

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ABSTRACT

The aim: We aimed to conduct a prospective analysis of the epidemiology of cerebrovascular disease and stroke among the adult population of Kyiv City, Ukraine the last 12 years.

Materials and methods: We analyzed sectoral statistical reports of cerebrovascular disease and stroke in Kyiv City for 2009-2020. The statistical method and the method of system approach were used in this study.

Results: We established that during the last 12 years there was a decrease in the incidence of cerebrovascular disease and stroke among the adult population of Kyiv (reduction of 1.83 times ($p < 0.05$) with t reliability criteria 26.89). However, the incidence remains high (476.62 per 100,000 population). At the same time, the prevalence of cerebrovascular disease remains stable, and among the working-age population tends to increase. The incidence of stroke indicates a positive trend (251.3 per 100,000 adult population of Kyiv in 2009 and 95.0 – in 2020, respectively). In particular, the number of primary registered strokes decreased 2.64 times ($p \leq 0.05$) with a reliability criterion of 5.7 which is 1.94 ($p \leq 0.05$) times lower than in Ukraine generally. During the study period, 27,928 people died in Kyiv from a stroke. The mortality rate of stroke among the adult population in the city decreased from 96.14 per 100,000 in 2009 to 57.17 in 2020. This significant decline occurred over the past two years.

Conclusions: A significant reduction in the incidence of cerebrovascular disease and stroke in the adult population of Kyiv during the last 12 years has been established. This might be caused by increased stroke prevention work, provided to the city population, and by a higher level of availability and quality of medical care in recent years.

KEY WORDS: cerebrovascular disease, CVD, stroke, epidemiology, morbidity, prevalence

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INTRODUCTION

Cerebrovascular disease (CVD) is the second leading cause of death and the main cause of adult long-term disability in developed countries [1-6]. However, there is a gap of knowledge about trends in CVD incidence and prevalence in adults from middle-income countries.

Little is known about trends in the overall combined burden of CVD in one of the largest middle-income European countries, located in the geographical center of Europe, Ukraine [7-19]. Nevertheless, a detailed analysis of the epidemiology of CVD is an essential tool in creating health programs, aiming to reduce CVD [20-30].

THE AIM

We aimed to conduct a prospective analysis of the epidemiology of cerebrovascular disease and stroke among the adult population of Kyiv City, Ukraine for the last 12 years.

MATERIALS AND METHODS

STUDY SETTING

Data from 2009 to 2020 were prospectively collected from the sectoral statistical reports of CVD and the stroke registry of Kyiv City. The methods of the study, inclusion and exclusion criteria have been reported in detail previously. [31-33] In brief, using multiple overlapping sources, all inpatient and outpatient adults with CVD and stroke were identified. We have prospectively analyzed sectoral statistical reports of CVD and stroke in Kyiv City for 2009-2020. The informational base of the study was data from the information-analytical center of medical statistics, reporting statistical forms: form No. 12 "The report on diseases registered in patients living in the area of service of the hospital and out-hospital facilities", form No. 20 "The report of the disease treating and preventing institutions", form No. 14 "The report on the causes of disability and indications for medical, professional, and social rehabili-

tation", form C-8 "Distribution of deaths by sex, age, and causes", and analysis of 1575 cases of acute cerebrovascular accident.

In Ukraine, there is no methodology for epidemiological studies on the type of population registers, as recommended by WHO. The analysis of indicators is carried out according to statistics [34-36]. The statistical method and the method of systematic approach were used in this study.

DIAGNOSTIC CRITERIA

We defined stroke as the presence of signs of sudden focal or global cerebral dysfunction lasting >24 hours without any apparent nonvascular cause. TIA was defined according to the World Health Organization and American Heart Association criteria [37, 38] as an acute onset of a focal cerebral or ocular functional deficit lasting <24 h. CVD was defined according to WHO and [39] and includes all disorders in which an area of the brain is temporarily or permanently affected by ischemia or bleeding and one or more of the cerebral blood vessels are involved in the pathological process. This includes stroke, TIA, carotid stenosis, vertebral and intracranial stenosis, aneurysms, and vascular malformations. [40] Etiologies of TIA and stroke were classified according to the modified TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria [41]. These criteria were the same throughout the period of analysis.

RESULTS

According to the official statistics of the Ministry of Health of Ukraine, in 2015, 25,51654 patients with various forms of cerebrovascular pathology were registered, which is 7,200.3 cases per 100,000 population [42]. The highest prevalence of CVD was found in Donetsk (12230.2 per 100,000 population), Odessa (10935.8 per 100,000 population), and Zaporizhzhia (11282.8 per 100,000 population) regions. The lowest occurs — in Rivne (2426.0 per 100,000 population), Zakarpattia (2839.3 per 100,000 population), and Lviv (3846.2 per 100,000 population) regions.

At that time, the corresponding prevalence of CVD in Kyiv was 6413.4 per 100,000 population and was lower than the national average. The prevalence of CVD in Kyiv remains stable during the last 12 years with slight tends to increase among the working-age population.

At the same time, the incidence of CVD among the adult population of Kyiv decreased during the last 12 years (reduction of 1.83 times ($p < 0.05$) with t reliability criteria 26.89). However, it still remains high (476.62 per 100,000 population).

The incidence of stroke in Kyiv indicates a positive trend (251.3 per 100,000 adult population of Kyiv in 2009 and 95.0 – in 2020, respectively). In particular, the number of primary registered strokes decreased 2.64 times ($p \leq 0.05$) with a reliability criterion of 5.7 which is 1.94 ($p \leq 0.05$) times lower than in Ukraine generally.

During the study period, 27,928 people died in Kyiv from a stroke. The mortality rate of stroke among the adult population in the city decreased from 96.14 per 100,000 in 2009 to 57.17 in 2020. This significant decline occurred over the past two years.

DISCUSSION

It should be noted that the dynamics of the prevalence of CVD in Ukraine from 2007 to 2013 had a clear upward trend. Thus, in 2014 – 2015, the prevalence of CVD decreased from 8220 to 7260 cases per 100,000 population, which was due to the territorial changes in the country [43].

In the capital of Ukraine, Kyiv, from 2009 to 2020, the prevalence of CVD among the adult population was almost stable. There were small fluctuations over the years of observation in the range of 6277.8 – 6583.8 per 100,000 adult population and was lower than the average in Ukraine (7967, 2 in 2018). In all years of follow-up in the city, up to 38 (40)% of patients with CVD were patients of working age. The prevalence among this cohort of patients in recent years has had an insignificant tendency to increase and amounted to 2395.9 per 100,000 population in 2018. Analysis of the dynamics of the incidence of CVD among the adult population of Kyiv is presented in Fig.1.

As can be seen from the figure, over the past 12 years the reduction in the incidence rate occurred 1.83 times ($p < 0.05$) with t reliability criteria of 26.89. This reached the level of 476.62 per 100,000 in 2020.

If we compare the last two years, in 2020 the primary incidence decreased by 24,905 cases compared to the previous year. In the structure of morbidity traditionally in all years, women prevailed in a ratio of 1,4-1,5 : 1,0 to men.

Thus, in the course of the analysis of data dynamics, a significant decrease in the incidence of CVD among the adult population of Kyiv City occurred. At the same time, the prevalence of CVD not only remained stable but also tended to increase among the working-age population. This probably characterized the process of the prevalence of "chronic" forms of CVD in the city. The reason for this is the untimely treatment of the population for medical care. To some extent, these results can also be determined by the completeness of the accounting of patients with CVD and, accordingly, the reliability of statistical reporting.

In 2009, 2,109 people with various types of primary stroke were registered in Kyiv, which accounted for 1.46% of the total population. Subsequently (until 2015) the number of stroke incidence increased in the city, but the population increased also. Thus, in the following years, there was a sharp decline in the number of registered strokes and by the end of 2020, there were 2246 people with primary stroke, which amounted to 0.76% of the total population. Traditionally, more than a third of patients were of working age. The rest were people of retirement age.

The dynamics of the detected primary cases of all types of stroke in the city over the years of dynamic observation are presented in Fig. 2.

As can be seen from this figure, the number of stroke patients in the city has decreased 2.3 times over the last 5 years and has almost returned to the rate of incidence of ten years ago (2109 cases detected in 2009). The distribution

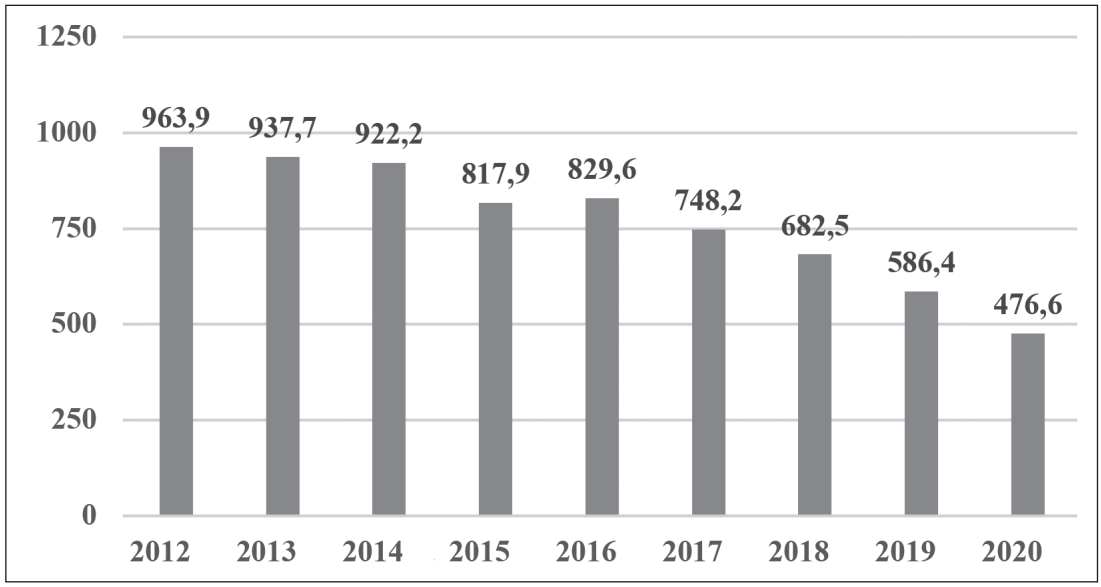

Fig.1. Dynamics of the incidence rate of CVD of the adult population in Kyiv for 2009-2020

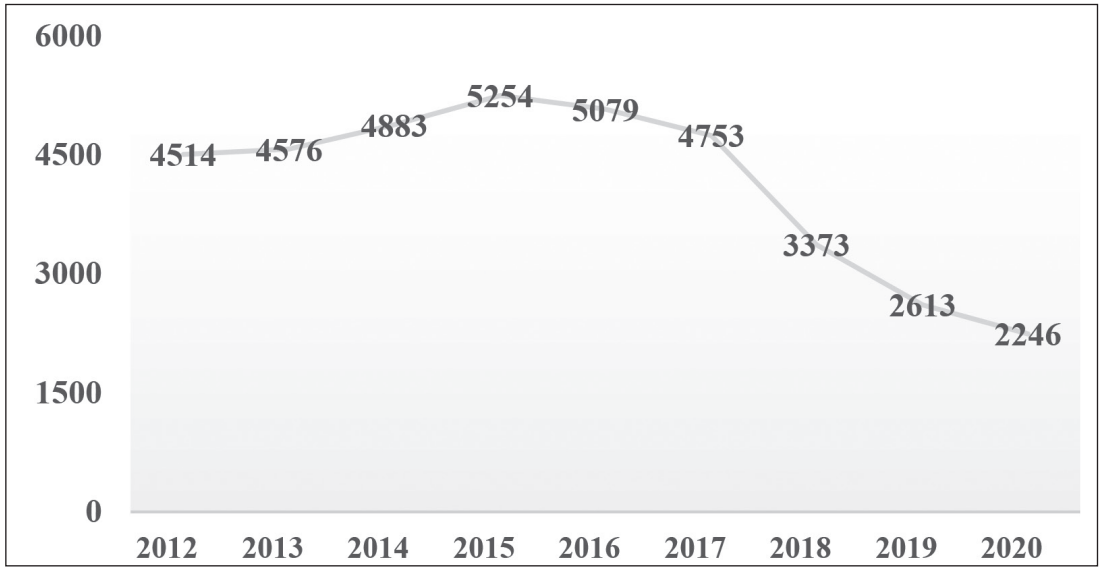

Fig.2. Dynamics of cases of primary stroke incidence in the Kyiv City during 2012-2020.

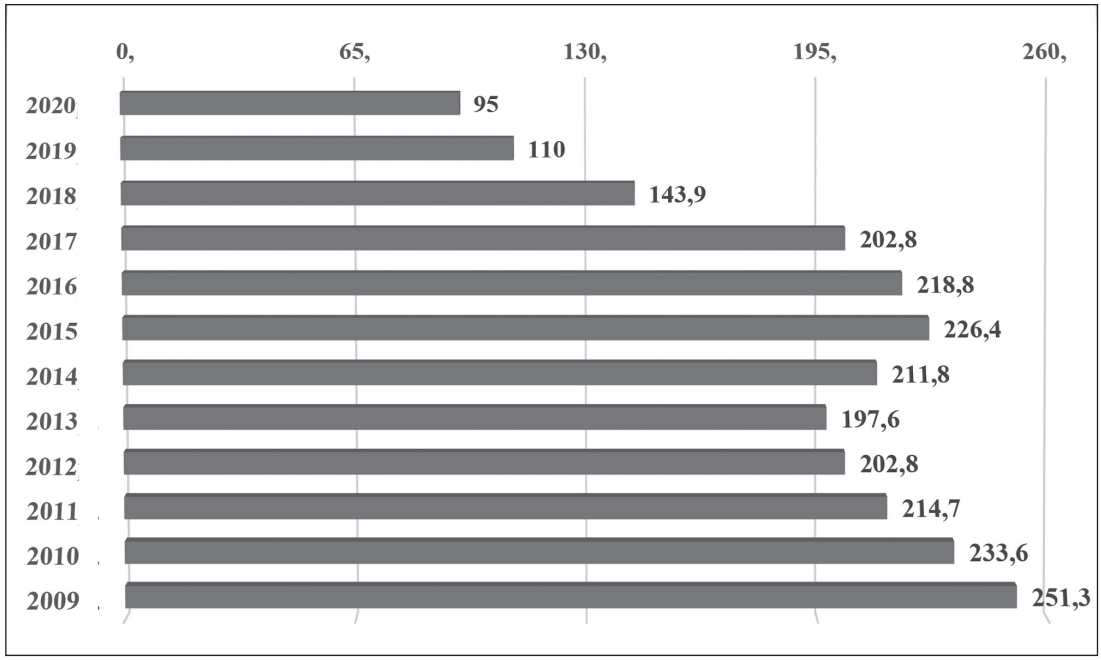

Fig.3. Dynamics of the incidence of stroke in the adult population of Kyiv, 2009-2020 (per 100,000 of the population).

Table I. Mortality of the adult population of Kyiv after stroke, 2009-2020

Year	Number of Death	Mortality Rate (per 100 000 population)
2009	2619	96,14
2010	2487	90,17
2011	2278	82,37
2012	2371	85,02
2013	2381	84,53
2014	2497	86,62
2015	2510	87,85
2016	2476	86,13
2017	2415	83,61
2018	2493	85,93
2019	1743	60,10
2020	1658	57,17

of the incidence of stroke per 100,000 adult population of Kyiv for the last 12 years is presented in Fig. 3

The data represented in Fig. 3 shows a positive trend over the years of observation of the incidence of cerebral stroke in the adult population of Kyiv, in particular, their number decreased by 2.64 times ($p \leq 0.05$) with a T criterion of 5.7.

A significant reduction in the incidence of cerebral stroke in the adult population of Kyiv can be explained by a substantial increase in preventive work among the population. This provided 1.94 ($p \leq 0.05$) times lower than in the capital compared to data for Ukraine as a whole. It should be noted that the highest annual level of reduction in the incidence of stroke was registered in the city in 2017-2020 retrospective observation when in these years the most active preventive work was carried out.

The structure of stroke incidence among the adult population of Kyiv depending on sex was studied separately. Long-term retrospective observation shows that during 2009-2020 the gender structure of stroke patients did not change significantly statistically. In patients with all forms of cerebral stroke. Men predominated (up to 53.2%), while in the structure of CVD by sex women prevailed (up to 61.2%). The findings support the hypothesis that men are less responsible for their health than women and mostly seek help for complications, including stroke.

Given that the available statistics on the type of stroke in the city indicate only its ischemic, hemorrhagic, and unspecified nature, we used the results of our pragmatic observation in 2016 to clarify the information, analyzing 1575 registration cards of acute stroke [44]. The study revealed ischemic stroke in 1328 (86.1%) patients, hemorrhagic – in 121 (7.8%), mixed stroke (presence of ischemic and hemorrhagic stroke at the same time). In 17 (1.1%), hemorrhagic transformation of the site of cerebral stroke infarction – in 19 (1.2%), unspecified nature of stroke – in 57 (3.7%) patients. The share of patients with hemorrhagic stroke was maximum among men of 60-75 yo – 31 (9.8%) patients, decreased in the senile men of 75-90 yo, while in middle-aged, elderly, senile, and long-lived women, with age ranged from 44 yo to over 100 yo, the share of hemorrhagic stroke remained at the same level – 7.6-8.4%. Cases of mixed stroke or hemorrhagic transformation of the ischemic stroke were reported mainly in elderly and senile patients of both sexes.

In Kyiv, as in Ukraine generally, in contrast to the leading countries of the world, including the former Soviet Union, there is no statistical accounting, and accordingly, there is no statistical reporting of CVD in children under 18 years of age. At the same time, children with such pathology are hospitalized in pediatric hospitals. In this regard, we were unable to analyze the incidence of CVD and stroke in the children in Kyiv. According to the statistical reports of the Ministry of Health of Ukraine for 2018, eighteen children under the age of majority with intracranial hemorrhages were treated in hospitals in Kyiv. There is no more information about CVD and stroke in children patients in Kyiv.

The high incidence of stroke in Ukraine is due to several factors. Since stroke is an age-related pathology, the demographic situation that currently exists in the country with registered 12 million pensioners that are counted of 27.9% of the population, has a great influence. [45]. However, the main reason is the growing prevalence of stroke risk factors among the population. Thus, hypertension in Ukraine affects more than 12 million people (28.3% of the population), diabetes – 1.5 million people (3% of the population), and coronary artery disease (CAD) – 18.1% of the population.

A long-term study of the dynamics of the incidence and prevalence of hypertension (HBP) and CAD among the adult population of Kyiv are cited as the main factors in the development of CVD for over 10 years (2009-2018). Thus, the incidence of HBP among the adult population of Kyiv decreased during this period by 1.24 ($p \leq 0.05$) times. In 2018, amounted to 2006.1 per 100,000 adults (compared to 1997.6 per 100,000 adult population in Ukraine). The prev-

alence of CAD in the city is almost stable and was 27241.8 in 2018. The share of women in all years reached 62-64%.

For a more detailed statistical analysis of epidemiology, we considered it appropriate to assess the mortality of the adult population of Kyiv due to a stroke. During the 12-year study period, 27,928 adults died due to a cerebral stroke in the city. Data on this stroke mortality among the adult population of Kyiv for the period 2009-2020 is given in table I.

The statistics shown in Table I represent a steady downward trend in the adult mortality rate of stroke in the city for the period 2009-2020. In particular, during the study period, the adult mortality rate decreased by 38.97 per 100,000 adults (1.7 times, $p = 0.05$), with a particularly significant decrease during the last two years. This situation is primarily due to the higher level of availability and quality of medical care for stroke patients.

CONCLUSIONS

To summarize, we would like to highlight that a significant reduction in the incidence of CVD and stroke in the adult population of Kyiv may be due to increased preventive work among the city population and a higher level of availability and quality of medical care.

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ORIGINAL ARTICLE

RISK PREDICTION FOR ARRHYTHMIA IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The aim: To evaluate P-wave dispersion (PwD), as an independent predictor of atrial fibrillation, corrected QT interval dispersion (cQTD), the noninvasive marker of ventricular arrhythmia and sudden cardiac death, investigate the atrial electromechanical delay in patients with COPD and assess their relation with the severity of the disease.

Materials and methods: We prospectively enrolled consecutive patients with newly diagnosed COPD (n = 53, age 41.2 ± 6.8 years), compared with an age-matched healthy control group (n = 51, age 40.9 ± 6.5 years). A standard 12-lead electrocardiogram of each patient was analyzed for PwD and cQTD. Atrial electromechanical delay was analyzed by echocardiographic tissue Doppler imaging. The difference between PAs-PAI, PAs-PAt, and PAI-PAt were defined as left intra-atrial, right intra-atrial, and interatrial electromechanical delays (EMD), respectively.

Results: PwD was higher in COPD patients than in control subjects (39.47 ± 3.12 ms vs. 30.29 ± 3.17 ms, $p < 0.05$). In comparison between control group and COPD subgroups (mild, moderate and severe), there was a statistically significant difference among these free groups in terms of PwD. Subgroup analyses showed that this difference was mainly due to patients with severe COPD. Regarding cQTD, there was a statistically significant increase in COPD patients 57.92 ± 3.43 ms vs 41.03 ± 5.21 ms, $p < 0.05$ respectively. PAs, PAI and PAt durations, right intra-atrial and interatrial EMD were also significantly longer in COPD patients ($p < 0.05$). Furthermore, there were significant negative correlations between FEV_1 and PwD ($r = -0.46$, $p < 0.05$), right intra-atrial ($r = -0.39$ ms, $p < 0.05$), interatrial EMD ($r = -0.35$ ms, $p < 0.05$) and cQTD ($r = -0.32$, $p < 0.05$).

Conclusions: Atrial conduction time, such as inter- and intra-atrial EMD intervals, PwD and cQTD were longer than in healthy controls and correlated with the severity of COPD. These parameters offer a non-invasive and cost-effective assessment method for detecting patients at high risk of arrhythmia. Nevertheless, further prospective investigations on this issue are required.

KEY WORDS: P-wave dispersion, corrected QT interval dispersion, atrial conduction time, chronic obstructive pulmonary disease

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INTRODUCTION

Cardiovascular comorbidities are highly prevalent in patients with chronic obstructive pulmonary disease (COPD) and associated with considerable morbidity and mortality [1].

A meta-analysis of observational studies supports a two-fold increase in the odds of having any cardiovascular diseases in people with COPD relative to COPD-free patients [odds ratio (OR) = 2.46; 96% CI; 2.02–3.00], and ORs in the range 2–5 for ischaemic heart disease, arrhythmias, heart failure and diseases of the arterial circulation [2].

Overall, the prevalence of cardiac arrhythmias in COPD patients are typically between 10% and 15% and is associated with the degree of lung function impairment [3].

Pulmonary hypertension, elevated right ventricular filling pressure and raised intrathoracic pressure are also responsible for the higher incidence of atrial arrhythmias in COPD patients, probably due to a dual effect of direct raised RV pressure, hypoxemia, hypercapnia, pro-inflammatory environment and also side effects of drugs in COPD patients. The greater the degree of RV dysfunction at baseline, the greater the hemodynamic significance of any added vascular load [4].

Supraventricular arrhythmia, particularly atrial fibrillation (AF) is the most common arrhythmia in patients with COPD exacerbation and may complicate differential diagnosis, which is strongly associated with ischemic stroke [5].

However, according to 24-h Holter recordings patients with acute COPD exacerbation, had a higher prevalence of sustained or nonsustained ventricular tachycardia [6]. In addition, it has been reported that severity of COPD is an independent risk factor for developing a ventricular tachycardia [7].

The overall elevated risk for sudden cardiac death increases after five years from initial diagnosis as well as in patients with frequent exacerbations. Most often, ventricular arrhythmias are made responsible [8].

Patients with COPD are more likely to die at night, due to more ventricular ectopic episodes, as a result of hypoventilation [9].

Abnormal corrected QT interval dispersion is associated with decreased functional capacity, and is predictive for arrhythmias and mortality [10].

The significance of a prolonged QT interval, which indicates unstable ventricular repolarization, is a surrogate marker for the risk of malignant ventricular arrhythmias

(eg, Torsade de Pointes) and sudden cardiac death, is under investigation in a number of cardiopulmonary diseases. For instance, it was recently shown to be an independent predictor of worse clinical outcomes in pulmonary hypertension [11].

QTc interval reflects the atrial effective refractory period, suggesting that QTc interval may be used as a marker of atrial refractoriness relevant to assessing AF risk and mechanism-specific therapeutic strategies [12].

P-wave dispersion (Pwd), measured by 12-lead electrocardiogram (ECG) is commonly used as noninvasive tool to assess the risk of AF [13]. An increased PwD shows the prolongation of intraatrial and interatrial conduction times of sinus node impulses [14].

An atrial electromechanical delay (EMD) — temporal delay between the detected onset of electrical activity and the realization of force in the myocardium, can be measured not only by invasive electrophysiologic study but also by echocardiographic tissue Doppler imaging (TDI) [15]. Recent studies found that TDI-derived atrial EMD had an advantage to predict AF recurrence over LA diameter and P-wave duration [16].

Since COPD is related with an increased risk of cardiovascular events, especially in the more advanced phase of the disease and in patients with exacerbations, screening for predictors of arrhythmia in at-risk groups plays a key role in preventing the complications.

THE AIM

The aim of the study was to evaluate P-wave dispersion (PwD), as an independent predictor of AF, corrected QT interval dispersion (cQTD), the noninvasive marker of ventricular arrhythmia and sudden cardiac death, investigate the atrial EMD in patients with COPD and assess their relation with the severity of the disease.

MATERIALS AND METHODS

We prospectively enrolled consecutive patients with newly diagnosed COPD (n = 53, age 41.2 ± 6.8 years), compared with an age-matched healthy control group (n = 51, age 40.9 ± 6.5 years).

There were no statistically significant differences between the two groups regarding age, gender, systolic or diastolic blood pressure, heart rate, body mass index or smoking.

Chronic obstructive pulmonary disease was defined as a post-bronchodilator airflow limitation of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of < 70%. According to the Global initiative for chronic obstructive lung disease (GOLD), the severity of chronic obstructive pulmonary disease was divided into 4 grades based on FEV_1% predicted: grade I: $FEV_1 \geq 80\%$, grade II: $79\% < FEV_1 \geq 50\%$, grade III: $49\% < FEV_1 \geq 30\%$ and grade IV: $FEV_1 < 30\%$.

Exclusion criteria were patients with known cardiovascular diseases, any documented previous arrhythmias or developing an arrhythmia during the examination.

All subjects underwent pulmonary function test, ECG and standard transthoracic echocardiography including tissue Doppler examination.

P-wave dispersion, a noninvasive ECG marker for atrial remodeling and predictor for AF, is defined as the difference between the widest and the narrowest P-wave duration recorded from the 12 ECG leads.

Correction of the QT interval for heart rate (QTc) was performed using Bazett's formula. Corrected QT interval dispersion (cQTD) was calculated as the difference between maximum and minimum precordial values.

Atrial EMD findings (defined as the time interval from P wave onset on the ECG to the beginning of the late diastolic wave (Am wave), is calculated from the lateral (PA lateral) and septal (PA septum) mitral annuli, as well as the lateral tricuspid annulus (PA tricuspid)) were measured by Tissue Doppler Echocardiography. Values for atrial EMD were averaged over three consecutive beats. The difference between PA lateral and PA tricuspid (PA lateral-PA tricuspid) is called the interatrial EMD. The difference between PA septum and PA tricuspid (PA septum-PA tricuspid) is defined as the right atrial EMD. Lastly, the difference between PA lateral and PA septum (PA lateral-PA septum) is the left atrial EMD).

Statistical analyses were carried out in SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois).

Continuous variables were presented as the mean ± standard deviation (SD) and were compared using an independent samples t test. The differences between groups were checked by Chi-square test for categorical variables and by independent t-test for continuous variables.

Pearson's test was performed to assess the correlation between atrial EMD, PwD, cQTD and the severity of COPD. The results were analyzed with a 95% confidence interval at a significance level of $p < 0.05$ or with a 99% confidence interval at a high significance level of $p < 0.01$.

RESULTS

The PwD was higher in COPD patients than in control subjects (39.47 ± 3.12 ms vs. 30.29 ± 3.17 ms, $p < 0.05$) (Table I). The normal value of PwD is 29 ± 9 ms and refer a maximum PwD value of 36 ms. PwD ≥40 ms indicates the presence of heterogeneous electrical activity in different regions of the atrium that might cause atrial tachyarrhythmias (ATAs). Thus, PwD is a strong predictor of ATAs and especially AF.

In comparison between control group and COPD subgroups (mild, moderate, severe and very severe airflow limitation), there was a statistically significant difference among these 4 subgroups in terms of PwD.

Subgroup analyses showed that this difference in PwD was mainly due to patients with GOLD grade 3 and 4 (40.23 ± 1.26 ms and 41.16 ± 1.43 respectively). This might partially explain the increased risk of atrial tachyarrhythmias in patients with severe and very severe airflow limitation.

Table I. Mean values of PwD and cQTD in COPD patients and control subjects

	Control group (n=51) Mean±SD	COPD, Grade1 (n=14) Mean±SD	COPD, Grade 2 (n=13) Mean±SD	COPD, Grade 3 (n=13) Mean±SD	COPD, Grade 4 (n=13) Mean±SD
PwD, ms	30.29 ± 3.17 *	37.42 ± 1.07 *	39.08 ± 1.19*	40.23 ± 1.26 *	41.16 ± 1.43*
cQTD, ms	41.03 ± 5.21 *	55.27 ± 0.78 *	57.21 ± 1.46 *	59.03 ± 1.23 *	60.17 ± 1.18 *

*: $p < 0.05$ compared to the control group

Table II. Intra-and interatrial electromechanical delays in patients with COPD and control subjects

	COPD patients (n=53) Mean±SD	Control group (n=51) Mean±SD
PA lateral, ms	69.72 ± 12.43 *	52.48 ± 10.27 *
PA septal, ms	45.38 ± 11.90 *	31.62 ± 10.54 *
PA tricuspid, ms	32.51 ± 8.46 *	24.97 ± 9.28 *
Left intra-atrial electromechanical delay, ms	24.34 ± 10.69	20.86 ± 11.30
Right intra-atrial electromechanical delay, ms	12.87 ± 2.51 *	6.65 ± 2.72 *
Interatrial electromechanical delay, ms	37.21 ± 4.84 *	27.51 ± 5.36 *

*: $p < 0.05$ compared to the control group

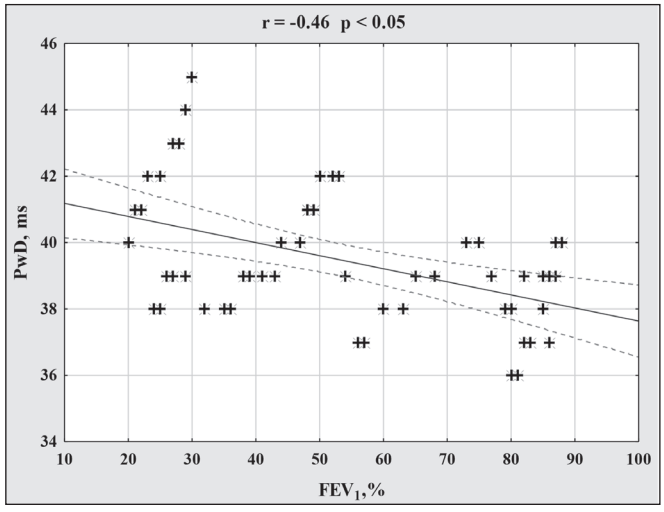

Fig.1. Correlation between PwD and FEV1 in patients with COPD

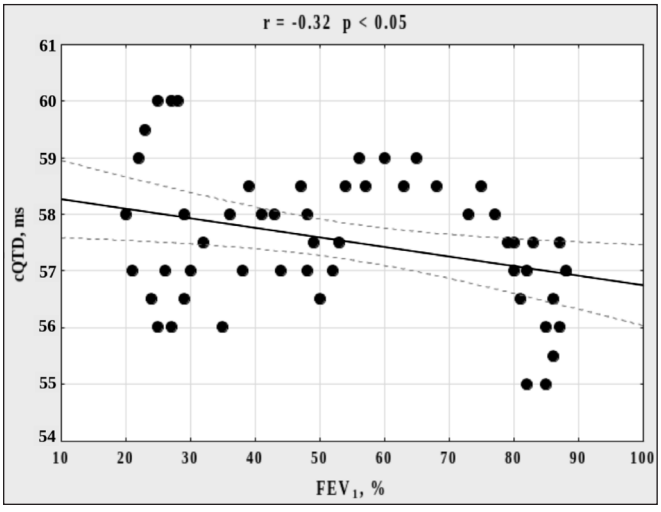

Fig.2. Correlation between cQTD and FEV1 in patients with COPD

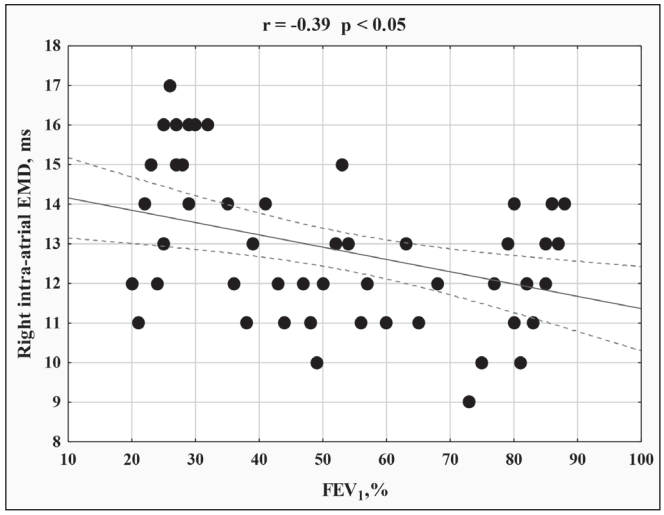

Fig.3. Correlation between right intra-atrial EMD and FEV1 in patients with COPD

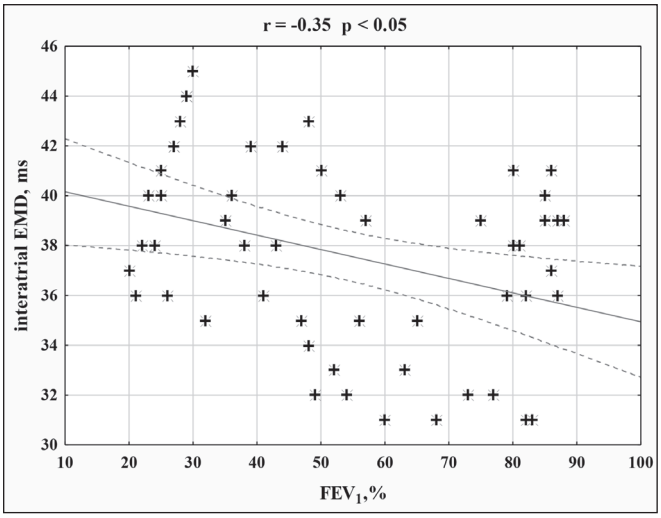

Fig.4. Correlation between interatrial EMD and FEV1 in patients with COPD

The Malmo Preventive Project, the largest to date population-based cohort study reported that after adjustment for age, height, weight, current smoking status, systolic blood pressure, erythrocyte sedimentation rate, and fasting blood glucose, FEV_1 was inversely related to incidence of AF [HR: 1.39 [95% confidence interval (CI): 1.16–1.68; p = 0.001] for women, and HR: 1.20 (95% CI: 1.13–1.29; p < 0.0001) for men].

Corrected QT interval dispersion, an electrocardiographic index of ventricular repolarization heterogeneity, showed a significant increased in COPD patients compared to matched controls (57.92 ± 3.43 ms vs 41.03 ± 5.21 ms, p < 0.05 respectively) (Table I).

The value of cQTD above 59 ms is associated with the development of malignant ventricular arrhythmias and sudden cardiac death. However, the value of cQTD in risk stratification is still the subject of debate.

The mean±SD of corrected QT interval dispersion in COPD grade 3 and 4 patients were 59.03 ± 1.23 ms and 60.17 ± 1.18 ms respectively, which is significantly higher than expected. This difference was statistically significant (p < 0.05).

Thus, hypoxia may be a risk factor for a prolonged cQTD interval. However, the mechanisms contributing to altered cardiac repolarization in patients with COPD are currently unknown.

Pearson correlation analyses were performed to investigate the correlation of PwD with $FEV_{1.}$ Correlation analysis showed that PwD was moderately and negatively correlated with FEV_1, especially in higher-risk patients with COPD (r = – 0.46 p < 0.05) (Fig.1).

The corrected QT interval dispersion values were also inversely correlated with FEV_1 in all patients with COPD but mildly (r = – 0.32, p < 0.05) (Fig.2).

All atrial EMD values are given in Table II.

PA lateral (69.72 ±12.43 ms vs 52.48 ±10.27 ms, p < 0.05), PA septum (45.38 ± 11.90 ms vs 31.62 ± 10.54 ms, p < 0.05) and PA tricuspid (32.51 ± 8.46 ms vs 24.97 ± 9.28 ms, p < 0.05) were significantly higher in patients with COPD as compared to controls (Table II).

However, left intra-atrial EMD (24.34 ± 10.69 ms vs 20.86 ± 11.30 ms, p > 0.05) was slightly prolonged in patients with COPD compared to matched controls. But this difference was not statistically significant (p > 0.05).

Prolonged right intra-atrial EMD (12.87 ± 2.51 ms vs 6.65 ± 2.72 ms, p < 0.05) and interatrial EMD (37.21 ms ± 4.84 ms vs 27.51 ± 5.36 ms, p < 0.05) were observed in all patients with COPD patients as compared to controls.

Prolonged intra-and interatrial electromechanical conduction times are the major predisposing risk factors for tachyarrhythmias, especially AF.

Furthermore, it was found that right intra-atrial and interatrial EMD were significantly negative correlated with FEV_1 in patients with COPD, especially in higher-risk subjects (r = – 0.39 p < 0.05; r = – 0.35 p < 0.05 respectively) (Fig. 3,4).

DISCUSSION

A study reported that arrhythmia risk may increase with a decline in respiratory function in patients with COPD, even if left ventricular function is intact [17]. A recent study revealed prolonged atrial depolarization time and increased PwD in patients with COPD due to increased right atrial (RA) pressure and RA diameter.

In addition, a significant correlation between PwD and size of the right atria was found in COPD patients, regardless of age and body mass index [18].

One of the limitation is the absence of computer-assisted calculation system for the measurement of Pmax and Pmin times in echocardiographic assessment.

In patients with COPD, an increase in the severity of disease is associated with a prolonged QT interval [19]. In addition, the QT interval was noted to be associated with mortality, and it is significantly prolonged in the acute stage of COPD [20]. Excess prolongation of QT intervals increases the risk of VAs such as torsades de pointes [21].

Analyzing the 22 clinical studies, it has been concluded that cQTd was significantly associated with arrhythmic events and all–cause mortality but not with sudden cardiac death in coronary heart disease and/or heart failure patients.

An explanation about the association between QTd and arrhythmogenesis is the increased disparity of regional ventricular repolarization times which predisposes to sustained ventricular arrhythmias. Identification of the exact role of cQTd in arrhythmogenesis remains a challenge [22].

Multivariate logistic regression analysis revealed that only interatrial EMD may predict AF. But determining the cut-off value of interatrial EMD predicting AF in COPD patients is a significant advantage in early diagnosis and treatment [23].

In a recent study, the high Systolic Pulmonary artery pressure values strongly negatively correlated with COPD stage determinant FEV_1 and FEV_1/FVC values. In severe COPD, negative FEV_1/FVC ratio had prolonged the tricuspid PA. Right atria remodeling slows down the electrical conduction paths [24].

Prediction of arrhythmia can facilitate better treatment decision-making and prognostic assessment among COPD patients. But unfortunately, nowadays there is no robust strategy for risk-stratification of arrhythmias in patients with COPD.

CONCLUSIONS

Atrial conduction time, such as inter- and intra-atrial EMD intervals, P wave dispersion and corrected QT interval dispersion were longer than in healthy controls and correlated with the severity of COPD. These parameters offer a non-invasive and cost-effective assessment method for detecting patients at high risk of arrhythmia. Nevertheless, further prospective investigations on this issue are required.

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ORIGINAL ARTICLE

EFFECTS OF BIOLOGICAL THERAPY ON QUALITY OF LIFE AND PSYCHOEMOTIONAL STATUS OF PATIENTS WITH ULCERATIVE COLITIS

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ABSTRACT

The aim: To compare the effects of tofacitinib, adalimumab and budesonide on the quality of life and psychoemotional status of patients with moderate UC.

Materials and methods: The study included 104 patients with moderately severe UC aged between 18 and 75 years old. Patients were divided into 3 groups. Group I consisted of patients with UC treated with budesonide 9 mg 1 g / d (BUD; n = 34). Group II – of patients receiving adalimumab at an initial dose of 160 mg and 80 mg at week 2, followed by maintenance dose of 40 mg weekly (ADA; n = 38) and group III, who received tofacitinib 10 mg 2p / d (TOF; n = 32). Evaluation of quality of life and psycho-emotional status of patients was performed using IBDQ, SF-36 and MMRI questionnaires .

Results: According to the IBDQ-questionnaire, all groups after treatment had a statistically significant increase in their results: BUD (from 146,44 ± 2,23 to 151,36 ± 2,40), ADA (from 144,28 ± 3,10 to 172,36 ± 3,12), TOF (from 149,22 ± 2, 86 to 184.36 ± 2.88), respectively, $p < 0.05$.

Also, after treatment statistically significant changes were seen in patients of all groups in regards to the psychological and physical components of the SF-36 scale.

Analysis of the personality profile using MMRI of all groups of patients showed a change in scales 2 (depression), 3 (hysteria), 5 (tenderness-femininity), 6 (paranoia) and 0 (social introversion), which significantly improved in the ADA and TOF groups.

Conclusions: Tofacitinib and adalimumab in patients with nonspecific ulcerative colitis of moderate severity had a better effect on quality of life and psychoemotional status compared with budesonide treatment.

KEY WORDS: ulcerative colitis, articular syndrome, tofacitinib, adalimumab

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INTRODUCTION

Ulcerative colitis is a chronic inflammatory disease, affecting the colon, with highest disease instances occurring between the ages of 30 and 40 years. The disease is characterized by recurrent course, most common manifestations are frequent bloody stools and diarrhea, tenesmus and fatigue, and causes significant disability, especially among people of working age [1,2] . In recent years, there has been a significant increase and prevalence of this disease [3,4] . Diagnosis of UC is based on clinical, endoscopic data, histology and exclusion of intestinal infections [5] .

Many studies have shown that the gastrointestinal symptoms and fecal incontinence associated with ulcerative colitis have a significant impact on the quality of life of patients. This covers the psychological, physical, sexual and social spheres of life [6-8]. Depression and anxiety among patients with ulcerative colitis are the most common mental disorders. Also, most patients report the presence of fatigue and sleep disorders [9] . These factors should be considered when treating such patients, as they may affect the course of the underlying disease. Questionnaires on inflammatory bowel disease (IBDQ) and questionnaire SF-36 [10] are among the tools, used for assessing the quality of life of patients.

The main goal of treatment is to achieve clinical and endoscopic remission in order to minimize disability and prevent colectomy or the development of colorectal cancer, as well as improving the quality of life of patients [11,12]. It has been observed that treatment that leads to and maintains remission restores both physical and mental health [13] . Modern drug treatment mainly includes aminosalicylates, corticosteroids, thiopurines and calcineurin inhibitors . But they do not always allow to adequately control disease activity.Therefore, in recent years in gastroenterology, biological therapy has become one of the alternative ways to treat UC. Several studies have shown that induction treatment with biologic medicines such as adalimumab, vedolizumab, tofacitinib has a high potential for improving the quality of life in patients with UC [14, 15]. Treatment with these substances allows to optimize the overall treatment of moderate and severe UC with a lower frequency of surgery and achieve better clinical results [16].

THE AIM

The aim to compare the effects of tofacitinib, adalimumab and budesonide on the quality of life and psychoemotional status of patients with moderate UC.

MATERIALS AND METHODS

The study included 104 patients diagnosed with moderate UC aged 18 to 75 years, with a disease duration of at least 6 months. Patients were divided into 3 groups. Group I consisted of patients with UC treated with budesonide 9 mg 1 g / d (BUD; n = 34). Group II – of patients receiving adalimumab at an initial dose of 160 mg and 80 mg at week 2, followed by maintenance dose of 40 mg weekly (ADA; n = 38) and group III, who received tofacitinib 10 mg 2p / d (TOF; n = 32). Evaluation of quality of life and psycho-emotional status of patients was performed using IBDQ, SF-36 and MMRI questionnaires .

RESULTS

According to the IBDQ-questionnaire, all groups after treatment had a statistically significant increase in their results: BUD (from 146,44 ± 2,23 to 151,36 ± 2,40), ADA (from 144,28 ± 3,10 to 172,36 ± 3,12), TOF (from 149,22 ± 2, 86 to 184.36 ± 2.88), respectively, p <0.05.

Also, after treatment statistically significant changes were seen in patients of all groups in regards to the psychological and physical components of the SF-36 scale. In the group where patients received budesonide, changes in the score of SF-36 psychological scale were 39.42 ± 1.08 against 37.12 ± 1.76, p <0.05. Similar changes took place in other groups: ADA (46.56 ± 1.46 vs. 37.08 ± 1.12, p <0.05), TOF (47.66 ± 0.86 vs. 38.02 ± 1.08, p <0.05). In regards to the physical component of the SF-36 scale, after the treatment only in the budesonide group there was no significant difference between the indicators. In other groups, these indicators improved: ADA (52.88 ± 1.06 vs. 48.6 ± 1.68, p <0.05), TOF (53.09 ± 1.56 vs. 49.23 ± 1.68, p <0.05).

The results indicate that the treatment improved the quality of life and psycho-emotional status of patients with moderate UC, which is associated with achieving remission. (Table I).

Also, all patients were examined for psychological status using MMRI. During analysis of testing results, it was found that the patients attitude toward the test was adequate and reflected the attitude for cooperation at the time of the examination.

Table I. Indicators of the IBDQ scale, physical (f) and mental (m) components of SF-36 (M ± m)

		BUD (n=34)	ADA (n=38)	TOF (n=32)
IBDQ	Before treatment	146,44±2,23	144,28±3,10	149,22±2,86
	8 week	148,23±2,45	152,24±2,88	156,28±2,66
	52 week	151,36±2,40	172,36±3,12	184,36±2,88
SF-36 f	Before treatment	45,12±1,88	48,6±1,68	49,23±1,68
	8 week	45,02±1,26	49,78±1,22	51,12±1,08
	52 week	44,88±1,36	52,88±1,06	53,09±1,56
SF-36 m	Before treatment	37,12±1,76	37,08±1,12	38,02±1,08
	8 week	38,24±1,88	38,88±1,07	39,68±1,56
	52 week	39,42±1,08	46,56±1,46	47,66±0,86

p <0.05 for all groups

Table II. Significance of MMRI profile scales in the study groups treated with budesonide, adalimumab, tofacitinib (M ± m)

Scales profiles	healthy	BUD (n=34)		ADA (n=38)		TOF (n=32)	
		Before treat	After treat	Before treat	After treat	Before treat	After treat
K	48,46±0,87	43,08±1,16	43,69±0,68	43,53±1,12	45,22±0,80	44,28±0,46	48,03±0,58
L	47,18±0,78	50,24±0,72	46,89±0,76	48 ,56±0,64	47,56±0,89	49,52±1,45	47,40±0,56
F	63,44±1,86	66,87±1,88	63,44±0,88	66,78±1,45	54,68±0,86	63,97±10,12	55,27±0,49
1	52,25±1,38	56,88±1,09	54,67±0,78	56,87±0,91	54,22±0,67	55,68±2,04	51,77±2,04
2	51,28±0,88	57,46±0,87	56,71±0,33	57,09±0,56	52,27±0,96	57,36±0,96	51,97±1,06
3	55,44±0,87	58,32±0,98	56,92±0,48	57,98±1,14	55,68±1,06	59,08±0,47	54,25±1,08
4	44,36±0,69	54,66±1,96	55,28±0,46	54,22±1,28	50,26±1,16	54,22±0,46	50,68±1,40
5	43,78±7,18	46,89±7,18	47,88±0,27	48,92±0,96	48,82±0,96	47,89±0,99	48,97±0,96
6	50,28±1,08	56,38±1,08	54,36±1,06	56,15±1,28	50,33±1,16	54,67±0,88	50,46±1,08
7	44,26±0,89	55,87±1,68	52,78±1,12	55,68±0,67	49,95±0,85	56,24±1,15	48,98±1,56
8	45,68±1,36	64,46±2,68	62,86±1,56	66,02±2,84	55,34±1,12	63,87±2,09	53,02±2,05
9	56,12±0,98	62,46±1,48	57,46±1,44	62,06±1,05	62,38±0,90	60,13±2,18	57,86±0.98
0	46,88±1,20	54,27±0,89	54,12±1,02	56,04±1,02	54,57±0,99	56,39±0,94	54,39±0,57

p <0.05 for all groups

According to the obtained data, in general, all personal profiles of patients with UC were in the range of 20-70 standard units, which indicated a sufficient psychological balance of patients. Among the patients of the examined groups there was a general stereotype, expressed mainly in the negative slope of the profile, ie dominated by indicators on the "neurotic" triad scales. These data indicate that patients in these groups have a tendency to low mood and the use of neurotic mechanisms of psychological defense.

It was noticed that scales 1 (hypochondria), 2 (depression), 4 (psychopathy) and 7 (psychasthenia) were most prominent. This shows that patients can be characterized as anxious and distrustful, with severe anxiety and indecisiveness. They also have a tendency to transform unidentified anxiety caused by unknowable causes into concern about their health.

At the beginning of treatment, all groups had a high incidence of depression, which affects the severity and prognosis of the disease. After treatment with budesonide MMRI analysis showed that the structure of the personal profile is dominated by the following scales: 1 (hypochondria), 6 (paranoia), 2 (depression), 7 (psychasthenia), 9 (hypomania), and 0 (social introversion), which indicates high emotional lability, tendency to aggression and mood instability in patients of this group. However, these changes are evidence of only minor personality disorders that are not characterized by psychopathological reactions.

In the ADA and TOF groups, the scales 8 (schizophrenia), 9 (hypomania), and 0 (social introversion) came to the fore. After treatment with adalimumab and tofacitinib, it was observed that this therapy had the least effect on scale 0 (social introversion), in contrast to scales 8 (schizophrenia), 9 (hypomania), where the indicators improved.

During analysis using MMRI of personal profiles of patients in all groups, some general features were common. This refers to scales 2 (depression), 3 (hysteria), 5 (tenderness-femininity), 6 (paranoia) and 0 (social introversion). This indicates that patients with UC are characterized by a predominance of a neurotic profile (Table II).

DISCUSSION

The results are similarto the results of a recent study that analyzed the clinical outcomes and quality of life of 463 patients with moderate and severe ulcerative colitis who received adalimumab [17] . At 26 weeks of treatment, in addition to improvement of clinical outcomes, there was a significant improvement in quality of life.

At the same time, according to the OCTAVE study, a significant improvement in quality of life was reported among patients receiving tofacitinib [18].

A closer look and comparison of all studies found that induction treatment with these drugs improved the quality of life of patients with UC and their psychoemotional status compared with placebo.

CONCLUSIONS

From this we can conclude that ulcerative colitis is a clear example of a psychosomatic illness, in which deviations in the psychological sphere are registered in most cases. According to the results obtained after treatment, significantly better quality of life and psychoemotional status were among patients treated with adalimumab and tofacitinib. But these data still need further study and analysis.

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ORIGINAL ARTICLE

IMMEDIATE IMPLANTATION AND AESTHETIC COMPONENT AS A RESULT OF SUCCESSFUL FORECAST TREATMENT

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ABSTRACT

The aim: Improving the method of immediate implantation in the aesthetic zone in case of bone deficiency to obtain the highest aesthetic and predictable treatment result.

Materials and methods: Under clinical observation were 32 patients with different clinical diagnoses in the anterior part of the upper jaw aged 30 to 55 years. In the course of recent advances, the following methods have been used: clinical protocol of immediate implantation with passive exceptional loads by temporary orthopedic constructions, X-ray method using cone-beam computed tomography, statistical analysis.

Results: After surgical treatment of patients 1 year after surgery, the distribution of biotypes was as follows: in group 1 – thick biotype 12.87%, medium – 87.13%; in group 2 – thick biotype 27.04%, medium – 72.96%, with $p < 0.05$. According to the results of CT, the distance between the implant and the vestibular in the first group was after 6 months – 1.67 ± 0.04 mm ($p < 0.05$); in the second group of the study we obtained the following results after 6 months – 1.59 ± 0.06 mm ($p < 0.05$).

Conclusions: The advanced method of immediate implantation in the anterior part of the upper jaw allows to change the biotype of soft tissues, improve the color spectrum of the gums, increase the thickness of soft tissues with connective tissue autograft, and increase gum density and fixation of osteoplastic material in the presence of defect), as well as reduce the risk of recession.

KEY WORDS: Immediate implantation, immediate passive loading, mucosal biotype, smile zone aesthetics, connective tissue graft (CTG)

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INTRODUCTION

The focus of promising research in the field of oral implantology has shifted towards addressing the issues of achieving long-term and stable results of implant treatment, especially in the anterior aesthetic segments of the jaws [1]. Bone remodeling, which actively takes place in the first 3-6 months after tooth extraction, is characterized by the loss of almost 50% of bone mass, as well as significant negative dynamics of the condition and volume of soft tissues: with the development of «tension syndrome», which further complicates the clinical situation, especially in the aesthetic department of the jaws [2,3]. Such changes require multi-stage preparation for implant placement (bone and soft tissue augmentation), which increases the duration of rehabilitation, and often does not provide a successful outcome [4,5]. At the present stage of development of implantology, the focus is on immediate implantation [6]. Thus, implantation in the cavity of a removed tooth is considered an acceptable and quite predictable procedure. Moreover, in many cases, single-stage implantation gives better results compared to the classical two-stage technique [7-9]. Widespread introduction of the method of immediate implantation minimizes the loss of bone and soft tissue and the likelihood of aesthetic and functional defects [10-12]. Therefore, often all possible multi-stage surgical interventions lead to unsatisfactory aesthetic results and the development of gingival recessions [9]. This problem is always difficult to solve and may occur some time after implant placement and prosthetics (weeks, months, years), which does not provide a high and predictable aesthetic result [7]. All of the above determined the relevance of this study.

THE AIM

Improving the method of immediate implantation in an aesthetic area with a different biotype of the gums with a deficiency of bone tissue to obtain the most predictable high aesthetic outcome of treatment.

MATERIALS AND METHODS

The clinical study was conducted on the basis of the Department of Postgraduate Dentistry of Uzhhorod National University and the Dental Clinic «Art Dentistry» (Zaporozhye, Ukraine). Under clinical observation were 32 patients with different clinical diagnoses in the anterior part of the upper jaw – from the second premolar on one side to the second premolar on the other side. At diagnosis used the generally accepted classification of ICD-10. The study group included: 13 patients (40.63%) with a diagnosis of «fracture of the anterior tooth root» of which 8 people

(61.54%) who had previously undergone orthopedic or endodontic treatment have destruction of the vestibular wall of the alveoli, treatment or recovery which is impossible, and 19 people (59.37%) have «chronic periodontitis». The study was carried out taking into account the main provisions of GCP ICH and the Helsinki Declaration on Biomedical Research, the Council of Europe Convention on Human Rights and Biomedicine (2007) and the recommendations of the Bioethics Committee of the Presidium of NAMS of Ukraine (2002) and the positive conclusion of the Uzbek . The age of patients ranged from 30 to 55 years, including men – 12 people (37.5%), women – 20 people (62.5%). Characteristics of patients by age are presented in table I.

All patients before the operation were examined according to the developed «Aesthetic cards», which are based on a modified scale of «pink aesthetics» R. Fürhauser et al. [13] (Figure 1).

X-RAY EXAMINATION

Using a cone-beam CT scan (ORTHOPHOS XG 5, Sirona, Germany), all patients measured the thickness and height of the bone mass of the alveolar ridge, as well as the thickness of the vestibular wall of the alveoli in millimeters at points A1, A2, A3 (Figure 2). At the same time determined the indicators of soft tissues in the area of intervention – radiodensity of the gums on the Hounsfield scale (HU). All these parameters were measured 6 months and 1 year after surgery. The indicators received in the remote postoperative period – in 1 year became especially significant as emergence of recessions in the field of implants with development of aesthetic complications is registered at this time.

PROTOCOL OPERATIONS

Patients underwent immediate implantation with passive occlusal loading with temporary orthopedic structures [14] according to the traditional protocol (Figure 3) in the area of the anterior maxillary tooth (Schwartz-Arad D. et al., 2007) under local anesthesia Sol. Articaini 4% with vasoconstrictor 1: 100000 and with a single change of gum biotype to prevent the formation of a recession in the implant and reduce aesthetics in the future orthopedic structure using a free connective tissue graft (CTG). At the end of the study, patients were divided into two groups of 16 patients each: 1 – immediate implantation and plastic surgery using a connective tissue graft (CTG) according to the standard protocol and 2 – using a connective tissue graft with an epithelial edge (invention patent [15]). The distribution of patients into groups was carried out randomly and was not fundamental. All grafts were removed from the hard palate in the projection from the first premolar to the second molar, where the glandular zone of the hard palate was located [16]. Collection of connective tissue graft was performed under local anesthesia in the area of missing teeth on the upper jaw or receding 2-3 mm from the teeth with a scalpel 15C. Collection of connective tissue autograft was performed y the method of two or three incisions according to standard methods [16].

STATISTICAL ANALYSIS

The results of laboratory and clinical studies were processed by the methods of variational statistics with determination of the average value, its errors, the Student's t test for multiple comparisons, using Excel (MS Office 2010, Microsoft, USA) and STATISTICA 6.0 (StatSoft, USA). Differences of indicators at significance level $p < 0.05$ were considered statistically significant.

RESULTS

When examining patients, the main parameters were entered in the «Aesthetic Card» six months and a year after immediate implantation. In patients of both groups, in addition to the main indicators, the thickness, width and length of the soft tissue autograft were measured. The average thickness of the autograft in group 2 (CTG + EM) – 1.29 ± 0.18 mm in the epithelial edge was 1.72 ± 0.09 mm, while in group 1 (CTG) it did not exceed 1, 24 ± 0.06 mm. After surgical treatment of patients after 6 months in both groups there was a significant increase in the thickness of the mucous membrane on the vestibular side (group 1 by 46.84% with thin biotypes and 66.88% with medium biotypes, and in group 2 by 87.07% with thin biotypes, by 57.94% with the average biotype ($p < 0.05$), which indicates a change in biotypes in the operation (Figure 4).

One year after surgery, the distribution of biotypes was as follows: in group 1 – thick biotype 12.87%, medium – 87.13%; in group 2 – thick biotype 27.04%, medium – 72.96%, with $p < 0.05$. Patients with a thin biotype were absent due to transformation of mucosal thickness (Figure 5).

Compared with group 1, where immediate implantation was performed using a connective tissue graft, in the group using a connective tissue graft with an epithelial margin, there was a positive dynamics of change of «pink aesthetics», namely improvement of the color spectrum of gums in the implantation area (table II).

During the study, the width of the area of keratinized attachment of the gums in group 1 at the end of 6 months after surgery was 4.75 ± 0.28, $p < 0.05$, and after 1 year – 4.61 ± 0.37, $p < 0.05$,

Table I. Distribution of Patients by Age and Gender Categories.

Age category, years	30-36	37-43	44-50	51-55	TOTAL
Number of women (%)	4(20)	3(15)	6(30)	7(35)	20(62,5)
Number of men(%)	2(16,6)	4(33,4)	3(25)	3(25)	12(37,5)

Table II. Comparative dynamics of changes in aesthetic parameters after 6 months and 1 year after dental implantation of the shell in group 1 (CTG) and group 2 (CTG+EM) (M ± m)

Indicator	Group 1 (CTG)			Group 2 (CTG+EM)		
	Before the operation	After 6 months	After 1 year	Before the operation	After 6 months	After 1 year
The width of the area of keratinized attachment of the gums (WAKAG)	4,78±0,33, p <0,05	4,75±0,28, p <0,05	4,61±0,37, p <0,05	7,02±1,12, p <0,05	6,96±1,02, p <0,05	6,82±1,17, p <0,05
The difference between the zeniths of the gingival contour	0,08±0,06, p <0,05	0,08±0,06, p <0,05	0,07±0,05, p <0,05	0,12±0,06, p <0,05	0,12±0,06, p <0,05	0,11±0,05, p <0,05
The thickness of the alveolar process, taking into account the mucous membrane	9,21±0,64, p <0,05	9,22±0,78, p <0,05	9,24±0,81, p <0,05	9,24±0,98, p <0,05	9,28±1,12, p <0,05	9,31±1,09, p <0,05
Height of the mesial interdental papilla	2,14±0,56, p <0,05	2,12±0,74, p <0,05	2,09±0,68, p <0,05	2,34±0,72, p <0,05	2,32±0,54, p <0,05	2,29±0,42, p <0,05
Height of the distal interdental papilla	2,21±0,46, p <0,05	2,18±0,76, p <0,05	2,16±0,74, p <0,05	2,34±0,68, p <0,05	2,33±0,48, p <0,05	2,3±0,28, p <0,05

Table III. Indicators of changes in vestibular wall thickness in patients of group 1 (CTG) and group 2 (CTG + EM) (p <0,05), mm.

	Group 1 (CTG)		Group 2 (CTG+EM)	
	Before the operation	After 6 months	Before the operation	After 6 months
Point A1	0,38 ±0,46	0,26 ± 0,06	0,42 ±0,34	0,21 ± 0,04
Point A2	0,63 ±0,62	0,24 ± 0,04	0,49 ±0,61	0,23 ± 0,05
Point A3	0,87 ±0,74	0,43 ± 0,05	0,79 ±0,74	0,33 ± 0,04

Table IV. Dynamics of changes in the range of radiodensivity of the gums in patients of the first and second groups (HU).

	A1(HU)		A2(HU)		A3(HU)	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Before the operation	From +59 to -447	From +62 to -450	From +288 to -229	From 287 to -237	From +599 to -238	From +611 to -242
After the operation	From +516 to -149	From +520 to -154	From +588 to -398	From +593 to -403	From +661 to -270	From +650 to -275

which is 0.17 ± 0.35 less than before surgery. In group 2, the width of the area of keratinized attachment of the gums at the end of 6 months after surgery was 6.96 ± 1.02, p <0.05, and after 1 year – 6.82 ± 1.17, p <0.05, which is 0.2 ± 1.15 less than before surgery. The difference between the zeniths of the gingival contour remained stable relative to preoperative parameters at the end of 6 months in group 1 was 0.08 ± 0.06, p <0.05, after 1 year – 0.07 ± 0.05, p <0.05, and in group 2 – after 6 months 0.12 ± 0.06, p <0.05, and after 1 year – 0.11 ± 0.05, p <0.05. In both groups there was a slight positive dynamics of the thickness of the alveolar ridge, taking into account the mucous membrane (Figure 6). In group 1 (CTG) there was a slight decrease in the height of the mesial interdental papilla both after 6 months 2.12 ± 0.74, p <0.05, and after 1 year 2.09 ± 0.68, p <0.05 after surgery. After 1 year, the difference relative to preoperative parameters averaged -0.05 ± 0.62, p <0,05. In the second group (CTG + EM) there was also a slight negative dynamics of the height of the mesial interdental papilla as after 6 months 2.32 ± 0.54, p <0.05 and after 1 year 2.29 ± 0.42, p <0.05 after surgery. After 1 year, the difference relative to preoperative parameters averaged -0.05 ± 0.57, p <0.05. In both study groups there was a decrease in the distal height of the interdental papilla, after 1 year the difference relative to the values before surgery for group 1 was (-0.05 ± 0.6, p <0.05), and for group 2 – -0, 04 ± 0.48, p <0.05).

According to the results of conical – computed tomography (CT) (table III) in patients of the first group of the study, the thickness of the vestibular wall at point A1 at 6 months after surgery was 0.26 ± 0.06 mm (p <0,05), in at point A2 after 6 months there was a significant decrease in the index to 0.24 ± 0.04 mm (p <0.05), and at point A3 the thickness of the vestibular wall after 6 months did not exceed 0.43 ± 0.05 mm (p <0 , 05). In patients of the second group, the thickness of the vestibular wall, measured at point A1 6 months after surgery was 0.21 ± 0.04 mm (p <0.05). At point A2 after 6 months there was a significant decrease in the index to 0.23 ± 0.05 mm (p <0.05). At point A3, the thickness of the vestibular wall after 6 months did not exceed 0.33 ± 0.04 mm (p <0.05). The dynamics of the change in the indicator in groups 1 and 2 is shown in Figure 7.

Ranges of radiodensivity of gum tissues after 6 months in the studied groups are distributed in table IV. Measurements in Hounsfield units of soft tissue density on the basis of CPCT data are not objective enough, however,

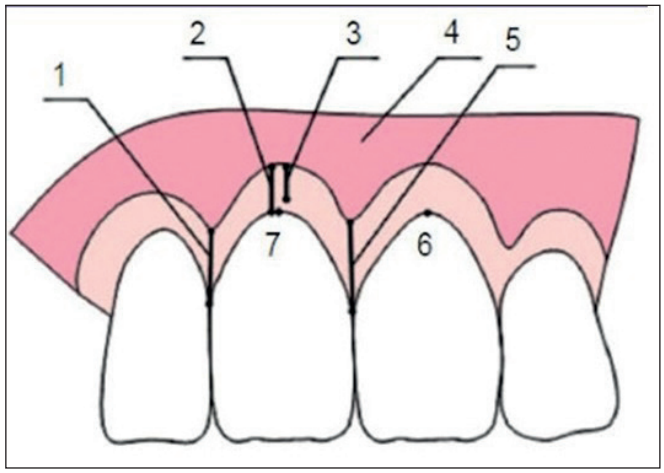

Fig. 1. The main aesthetic parameters of soft tissues: 1- the height to the distal interdental papilla, mm; 2 – the depth of the vestibule of the oral cavity, mm; 3 – zone of keratinized (attached) gums, mm; 4 – zone of non-keratinized (unattached) gums, mm; 5-the height to themesial interdental papilla albo the mesial, mm; 6- zenith of the gingival contour of the tooth of the same name on the opposite side; 7- zenith of the gingival contour of the examined tooth.

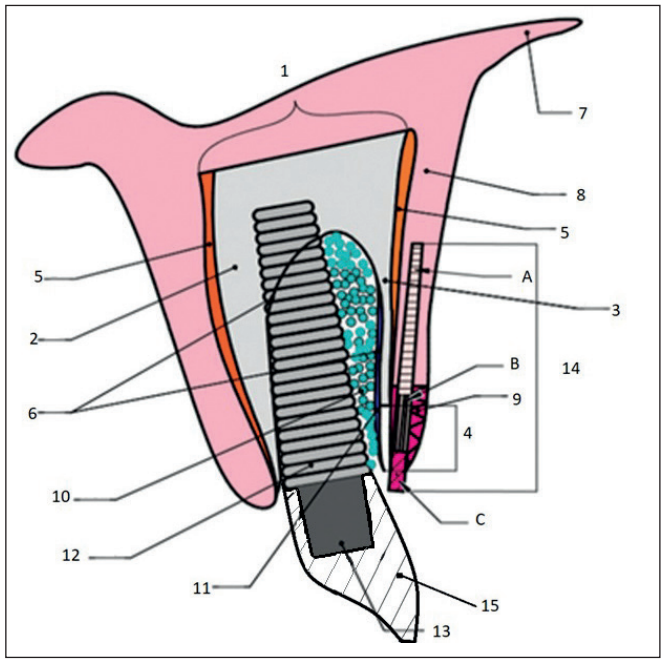

Fig. 3. Scheme of dental implant in stallation. 1-alveolar process; 2- palatal wall of the alveolar process; 3-vestibular wall of the alveolar process; 4- bone defect of the vestibular wall; 5 – periosteum; 6 – the boun daries of the hole of the removed tooth; 7-ransitional fold; 8-non-keratinized gums; 9-keratinized gums, 10- osteoplastic material; 11 – collagen membrane; 12-dental implant; 13 – shaper clear; 14-combined soft tissue autograft: A–connective tissue area; B- deep ithelialized zone; C – epithelial edge (1.5 mm), 15 – temporary orthopedic structure.

based on changes in radiodensity ranges at 6 months after surgery that the use of connective tissue graft (CTG) and connective tissue autograft with epithelial edge (CTG + EM) during implantation can increase the density of soft tissues in the field of surgery.

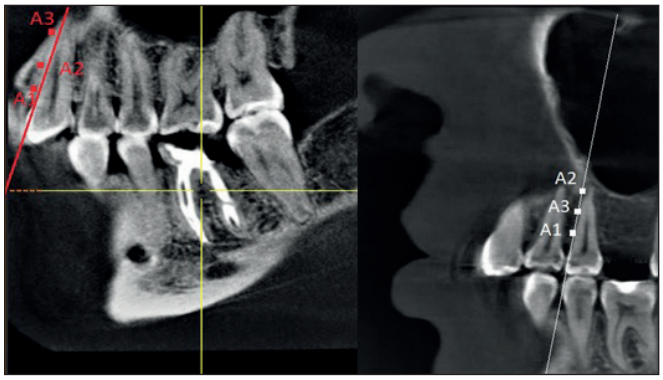

Fig. 2. Diagnostic points for determining the thickness of the vestibular wall (A1, A2, A3). A1-point in the projection of the top of the alveolarridge; A2- point in the projection of the apex of the tooth root on the vestibular wall; A3 is a point in the middle of the line drawn between A1 and A2.

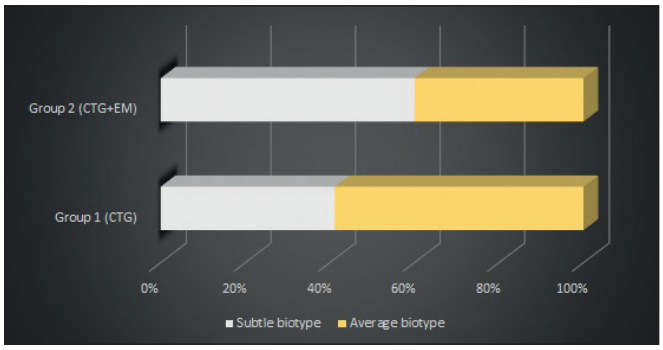

Fig. 4. Comparative dynamics of changes in the thickness of the mucous membrane in group 1 (CTG) and group 2 (CTG+EM) 6 months after surgery.

The distance between the implant and the vestibular wall immediately after surgery according to the CT in the first group was 1.76 ± 0.05 mm, and after 6 months – 1.67 ± 0.04 mm ($p < 0.05$); in the second group of the study, we obtained the following results: before surgery – 1.71 ± 0.04 mm, and after 6 months – 1.59 ± 0.06 mm ($p < 0.05$) (Figure 8).

DISCUSSION

In a short time after tooth extraction there is a significant deficit of bone, which leads to a lack of soft tissue. A number of anatomical and physiological processes occurring in the alveolar ridge after extraction are determined by the close phylogenetic relationship of tooth structures and surrounding bone and gums (Rodriguez A. M. et al., 2012; Araujo M. G. et al., 2015). One of the most important prognostic criteria for long-term implant life is the width of the area of keratinized attached gum. It is this area that becomes a powerful barrier that protects the adjacent bone from bacterial invasion and subsequent resorption [17]. In our study in both the 1st and 2nd groups, the indicator remained stable: almost unchanged or not significantly compared with the value before surgery ($p > 0.05$). This once again confirms that immediate implantation allows to preserve the architecture of soft tissues, and the use of soft tissue graft helps to preserve interdental papillae, preventing the formation of «black triangles» and providing a high aesthetic

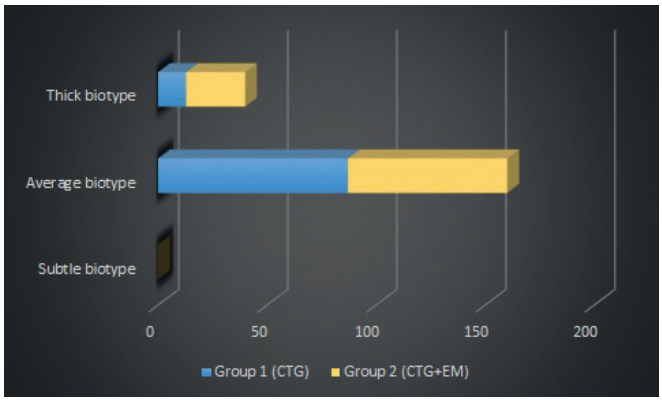

Fig. 5. Comparative dynamics of changes in the thickness of the mucous membrane in group 1 (CTG) and group 2 (CTG+EM) 1 year after surgery.

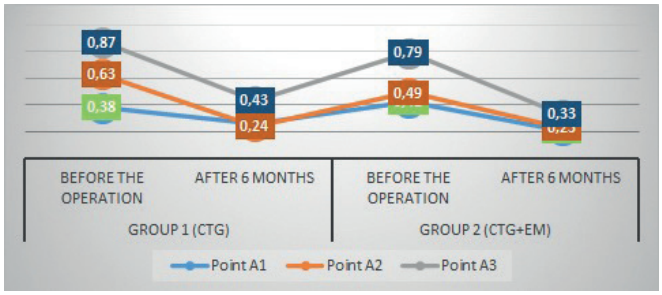

Fig. 7. Comparative dynamics of changesin vestibular wall thickness in patients of group 1 (CTG) and group 2 (CTG + EM) (p <0,05), mm.

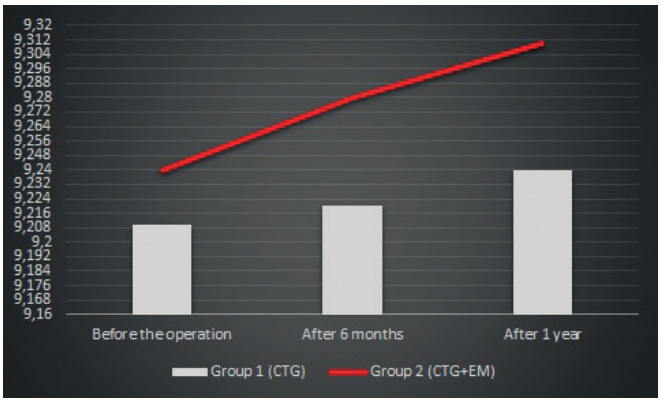

Fig. 6. Comparative dynamics of changes in the thickness of the alveolarridge, taking in to account the mucous membrane in group 1 (CTG) and group 2 (CTG + EM) relative to the values of the preoperative period (p <0,05).

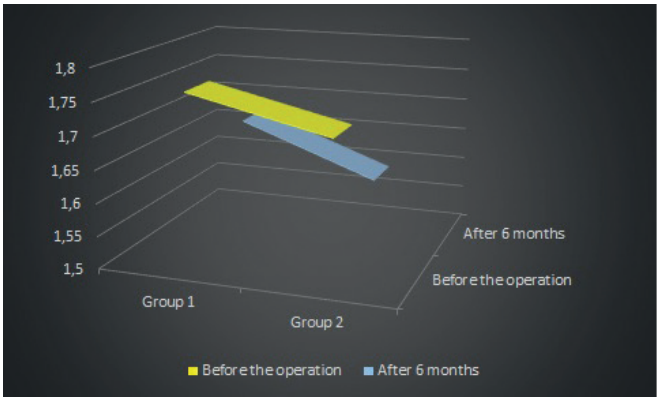

Fig. 8. Comparative dynamics of changes in the distance between the implant and the vestibular wall in patients of the study groups, mm.

result [17,18,19]. The decrease in vestibular wall thickness in the 1st and 2nd groups in comparison with the values before surgery was more than 50%, which confirms the data of works [2,3,20]. The use of soft tissue grafts for immediate implantation allowed to change the biotype of soft tissues, increase the thickness of the gums by 68% ($p \leq 0.05$), preserve and correct the zenith of the marginal margin. In the anterior part of the jaws, the vestibular wall is most prone to destructive processes, due to the large number of Sharpeev fibers contained in it and its small thickness (Lin G.- H. et al., 2014). According to a number of studies [21] in the anterior jaw, the thickness of the anterior wall of the alveoli rarely reaches 1 mm and in almost 100% of cases is resorbable (Braut V. et al., 2011; Januario et al., 2011; Vera C. et al., 2012; Wang HM et al., 2014). Various pathological processes of inflammatory and traumatic nature enhance the natural mechanism of resorption and lead to irreversible destructive changes, especially in the teeth of the aesthetic zone (Alvarez-Camino J. C. et al., 2013). In connection with the above, research in modern dentistry is aimed at finding methods of rehabilitation of patients that will reduce the level of bone resorption, preserve the primary volume of soft tissues, reduce treatment time, while maintaining the most natural appearance of the smile zone. One such method is immediate implantation (Schwartz-Arad D. et al., 2012; Malchiodi L. et al., 2013). However, in a detailed study of this issue, some researchers began to limit the indications for this method due to the development of aesthetic complications: recession in the field of implants installed immediately after removal of the teeth of the anterior maxilla, soft tissue discoloration, which is especially relevant in fine biotypes of the gums and with a high smile line, the appearance of «black triangles» between the restoration and the teeth (Lindeboom JA et al., 2006; Palatella P. et al., 2008; Block MS et al., 2009; Chen ST et al. , 2009 Roe P. et al., 2012; Vera C. et al., 2012). The problem is not fully resolved, there are many controversial issues, so this paper conducted research, the main purpose of which was to improve the method of immediate implantation with passive loading of temporary orthopedic structures in the aesthetic zone with bone deficiency with different mucosal biotype to obtain the highest aesthetics the predicted outcome of treatment.

CONCLUSIONS

Thus, immediate implantation in the anterior part of the jaws is an alternative and promising method, as it allows to preserve the anatomy of the alveolar ridge, to provide an acceptable aesthetic result, to reduce the time of rehabilitation of patients. The use of immediate implantation according to the classical protocol is limited in conditions of destructive changes or insufficient thickness of the vestibular wall due to the high risk of recession in the implant in the long term and gum discoloration in the structure due to lysis of the cortical plate and metal translucency through soft tissues. The advanced method of immediate implantation in the anterior part of the upper jaw allows you to install the implant directly into the hole of the removed tooth; change the biotype of

soft tissues, improve the color spectrum of the gums, increase the thickness of soft tissues with a connective tissue autograft, and the presence of a dense epithelial edge and deepithelialized zone with a large number of collagen fibers can increase gum density and fixation of osteoplasty walls (not more than 5 mm), and reduce the risk of recession. The use of CTG + EM allows you to save the volume of the interdental papillae, thereby preventing the formation of «black triangles»; to preserve the area of keratinized gums, excluding the development of «tension syndrome» and the volume of the alveolar ridge, thereby ensuring a high aesthetic result and increase the life of the implant.

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ORIGINAL ARTICLE

TRANSFASCIAL THROMBOSIS SURGERY IN THE GREAT SAPHENOUS VEIN BASIN

DOI: 10.36740/WLek202110217

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ABSTRACT

The aim: To evaluate the effectiveness of surgical treatment of varicothrombophlebitis complicated by transfascial thrombosis.

Materials and methods: The results of examination and treatment of 45 patients with varicothrombophlebitis of the great saphenous vein complicated by transfascial thrombosis.

Results: The indications for surgical prophylaxis of pulmonary embolism in transfascial thrombosis in the basin of the great saphenous vein have been substantiated. In the postoperative period, all patients with transfascial thrombosis, regardless of the radical nature of the surgical intervention, were offered to prescribe treatment as in deep vein thrombosis. The introduction of active surgical tactics in transfascial thrombosis allows for effective prevention of pulmonary embolism.

Conclusions: In varicothrombophlebitis complicated by transfascial thrombosis, thrombectomy with further prevention of recurrence of the disease and pulmonary embolism should be considered the main standard of treatment. For perforating vein thrombosis, subfascial thrombectomy followed by perforating ligation should be performed. All patients with transfascial thrombosis, regardless of the volume of surgery, should be treated as for deep vein thrombosis.

KEY WORDS: varicothrombophlebitis, transfascial thrombosis, pulmonary embolism, pulmonary embolism, thrombectomy

Wiad Lek. 2021;74(10 p.II):2620-2623

INTRODUCTION

One of the most common complications of varicose veins is acute superficial thrombophlebitis. In 39.2 – 95.9% of cases, superficial thrombophlebitis develops in the system of the great saphenous vein (GSV) and only in 1.6 – 20% – in the basin of the small saphenous vein (SSV), simultaneous damage to the GSV and SSV – in 1.0 – 1.8% of patients [1–6] In 4.1 – 29.3% of patients, the thrombotic process in varicothrombophlebitis reaches the mouth of the GSV, in 13.2 – 66.7% – the mouth of the SSV [5, 7]. Quite often, the spread of the thrombotic process is observed, in patients with varicothrombophlebitis (VTHPH), through the sapheno-femoral (in 3.6 – 13.5%) or sapheno-popliteal anastomosis (2.2 – 28%), incompetent perforating veins (in 4 , 3 – 55%), muscular venous sinuses of the leg (in 2.1 – 18%) to the deep venous system [1, 3, 7, 8]. It is with him that the threat of deep vein thrombosis (DVT) and pulmonary embolism (PE) is associated. According to some authors, a thrombus can grow up to 20 – 35 cm per day, where the upper limit of thrombotic lesion is 10 – 20 cm higher than clinical manifestations, and the moment of transition of the thrombotic process to deep veins is hidden and clinically not manifested [9]. Thus, the incidence of DVT in VTHPH is at the level of 6.7 – 40% [[2, 3, 6, 10]], while in 4.2 – 31.6% of cases, occlusive varicothrombophlebitis has embologic properties [6, 9], and in 0.5–49% of patients with VTHPH, symptoms of PE are diagnosed [2, 6], although according to scintigraphy, the asymptomatic course of PE of small branches with varicothrombophlebitis is diagnosed in 33.3% of patients [3, 11]. Mortality from pulmonary embolism in GSV reaches 0.4 – 5% [6, 9].

In such cases, according to interdisciplinary clinical guidelines (2013), the concept of transfascial thrombosis is distinguished, that is, the spread of a thrombotic process from the great or small saphenous vein to deep veins [12]. Most often this occurs at the confluence of the trunks of the saphenous veins into the femoral or popliteal vein, less often – blood clots spread through the insolvent perforating veins.

At the same time, mortality in the acute period from PE, despite the widespread use of anticoagulant therapy, remains extremely high, and while maintaining life, the risk of chronic postembolic pulmonary hypertension increases sharply, which sharply worsens the quality of life and often leads to patient disability.

THE AIM

To evaluate the effectiveness of surgical treatment of varicothrombophlebitis complicated by transfascial thrombosis.

MATERIALS AND METHODS

The paper analyzes the results of examination and urgent surgical treatment of 45 patients with transfascial thrombosis in the basin of the great saphenous vein aimed at eliminating the threat of PE. Of these, 17 (37.8%) patients were men and 28 (62.2%) women. The patients' age ranged from 19 to 78 years, the average age was 51 ± 2.4 years.

Table I. Surgical interventions were performed in patients with transfascial thrombosis

№№	Operational interventions	Quantity
1.	Open thrombectomy from the mouth of the great saphenous vein, crossectomy, phlebectomy	28
2.	Semi-open thrombectomy from the common femoral vein, crossectomy, phlebectomy	7
3.	Open thrombectomy from the common femoral vein (with venotomy of the common femoral vein), crossectomy, phlebectomy	4
4.	Open thrombectomy from the external iliac vein (with venotomy of the common femoral vein), crossectomy, phlebectomy	3
4.	Open thrombectomy from perforating veins with their extermination, crossectomy, phlebectomy	3
Total:		45

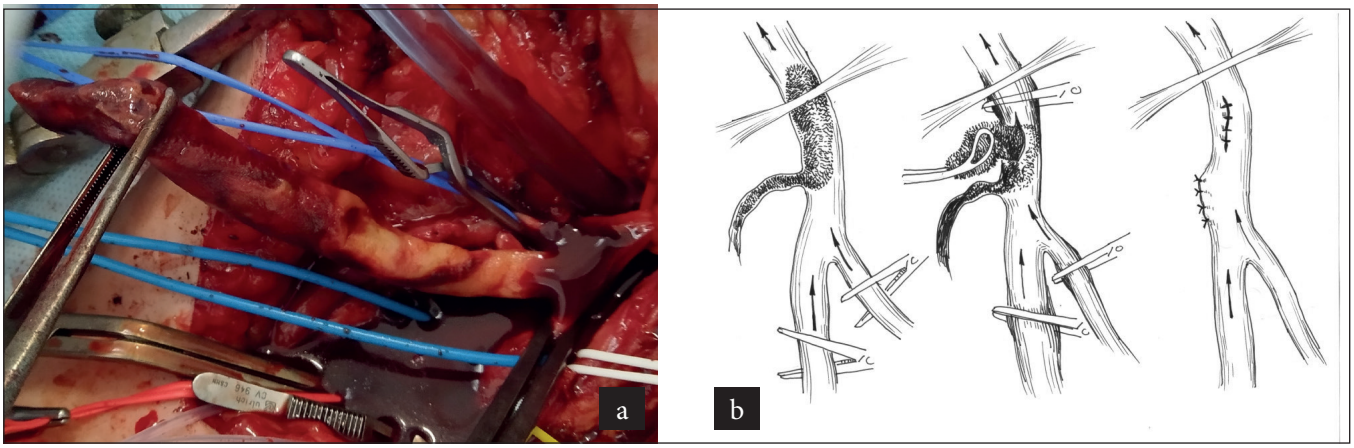

Fig. 1. Thrombectomy from the external iliac vein – intraoperative photo (a) and schematic vibration (b), followed by suturing of the venotomic section of the common femoral vein (c).

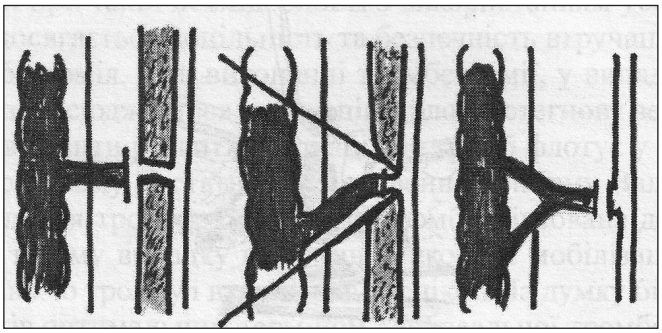

Fig. 2. Types of operations for thrombosis of perforators: perforation resection (a), perforation excision (thigh thigh and upper third of shin) (c), perforation extermination (lower third of shin) (c).

To examine the patients, we used general clinical, laboratory research methods, ultrasound Doppler and ultrasound duplex scanning (ULTIMA PRO-30, z.one Ultra, ZONARE Medical Systems Inc., USA), which were performed in the dynamics of the patient's stay in the hospital.

RESULTS

Doppler and duplex scanning were performed on each patient immediately after admission to the hospital. The localization of the apex of thrombotic masses in transfascial thrombosis was as follows:

- the level of the saphenofemoral anastomosis – in 28 (62.2%) patients, while the length of thrombotic lesion from the lower leg was diagnosed in 5 patients, from the lower third of the thigh – in 21 and total (on the lower leg and thigh) – in 2 patients;
- the level of the common femoral vein – in 11 (24.4%) patients, while the length of thrombotic lesion from the lower leg was diagnosed in 3 patients, from the lower third of the thigh – in 4 and total (on the lower leg and thigh) – in 4 patients;
- the level of the external iliac vein – in 3 (6.7%) patients, while the length of thrombotic lesion from the lower leg was diagnosed in 1 patient, from the lower third of the thigh – in 2 patients;
- incompetent perforating veins of the leg – in 3 (6.7%) patients.

All surgical interventions for transfascial thrombosis were performed urgently on the day of the patient's admission. Surgical interventions in patients with VTHPH of the great saphenous vein complicated by transfascial thrombosis are presented in Table I.

DISCUSSION

The main method for diagnosing VTHPH is ultrasound examination methods, in particular Doppler and duplex scanning, which were performed on each patient immediately after admission to the hospital [13, 14]. Ultrasound examination was performed in a horizontal position of the patient on his back using compression tests, in a sitting and standing position, as well as using a Valsalva test. The state of the superficial, deep and perforating venous systems was consistently assessed. In the presence of VTHPH, the

deep venous system was carefully examined: the femoral, popliteal and tibial veins, and the gastrocnemius veins. To examine the small saphenous and popliteal veins, the patient was placed on his stomach. Studies of the contralateral lower extremity were mandatory.

When VTHPH was detected, the localization, length, boundaries of thrombotic occlusion, the level of proximal and distal boundaries of thrombotic occlusion, the nature of thrombotic masses, the presence of flotation of the apex of thrombotic masses, and the presence of vertical and horizontal refluxes were assessed.

When thrombotic occlusion of the anastomosis was detected, a more detailed examination of the popliteal, femoral and iliac veins was carried out in order to determine the proximal border of thrombosis. In the presence of flotation of the thrombus apex, its length was assessed, the echogenicity of the thrombus, the effect of venous reflux on it, the nature of the external contour, the degree of mobility of thrombotic masses, and the ratio of the thrombus cross-sectional diameter to the vein diameter in the standing position were determined.

All surgical interventions for transfascial thrombosis were performed urgently on the day of the patient's admission. The main task of the surgical intervention in the case of VTHPH of the great saphenous vein complicated by transfascial thrombosis was the elimination of the threat of deep vein thrombosis and the prevention of pulmonary embolism. Considering the need for a half-open thrombectomy on the Valsalva test from the saphenofemoral junction, the volume of the surgical intervention consisted of thrombectomy, crossectomy, longitudinal suturing of the saphenous vein orifice, and short stripping on the thigh (Fig. 1). With a thrombus more than 3 cm long or partial fixation of the floating apex to the anterior wall of the common femoral vein, as well as during flotation in the external iliac vein, thrombectomy through a venous incision of the great saphenous vein is dangerous for intraoperative pulmonary embolism during traction of thrombotic masses through saphenofemoral anastomosis and migration of the latter into the pulmonary vascular bed. In such cases, thrombectomy should be performed through a venotomy incision of the common femoral vein. A necessary condition for performing venotomy of the common femoral vein is wide mobilization and isolation of the femoral veins and their tributaries on the supports. After performing thrombectomy and visual assessment of the absence of parietal overlays on the walls of the common femoral vein, the mouth of the great saphenous vein should be cut off, and the venotomic incision should be closed with a continuous suture with 5/0 "Prolen" suture. Before performing venectomy, 5 thousand units of heparin must be injected intravenously.The standard of surgical treatment included crossectomy and short stripping of the great saphenous vein in the thigh.

In case of thrombotic occlusion of an incompetent perforated vein on the lower leg, open thrombectomy was performed until satisfactory retrograde blood flow was obtained, followed by subfascial ligation of the latter (Fig. 2). Which, in the presence of total vertical reflux, was supplemented with crossectomy and short stripping.

It is fundamentally important that in case of failure of the perforating and communicating veins, their dissection is performed, and in case of thrombosis, resection and / or extermination with preliminary thrombectomy is performed.

All patients with VTHPH of the great saphenous vein complicated by transfascial thrombosis in the pre- and postoperative period were prescribed conservative treatment according to the protocols for the treatment of deep vein thrombosis.

Against the background of the treatment, not a single patient in the early postoperative period showed signs of pulmonary embolism.

In the long-term postoperative period, no relapse of varicose veins was observed in patients during the year.

Thus, the surgical treatment of varicothrombophlebitis in the basin of the great saphenous vein complicated by transfascial thrombosis can prevent deep vein thrombosis and prevent pulmonary thromboembolism, and liquidate ascending forms of varicothrombophlebitis.

Prospects for further research. The following issues remain unresolved:

1. What to do with the varicose dilated trunk of the great saphenous vein on the lower leg, which remains after crossectomy and short stripping on the thigh?
2. What to do to end the operation with crossectomy + phlebocentesis in case of total varicothrombophlebitis, in order to avoid pushing thrombotic masses into deep veins during venextraction with a probe or perform a total stripping?
3. Is it enough to limit yourself to crossectomy and short stripping for varicothrombophlebitis on the lower leg?
4. If varicothrombophlebitis occurs on the thigh, is crossectomy and short stripping on the thigh sufficient?

CONCLUSIONS

1. In varicothrombophlebitis complicated by transfascial thrombosis, thrombectomy with further prevention of recurrence of the disease and pulmonary embolism should be considered the main standard of treatment.
2. For perforating vein thrombosis, subfascial thrombectomy followed by perforating resection or exterpation should be performed.

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ORIGINAL ARTICLE

SPECIFICS OF THE ECZEMA PATIENTS` IMMUNE SYSTEM DEPENDING ON THE CLINICAL COURSE OF DERMATOSIS

DOI: 10.36740/WLek202110218

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ABSTRACT

The aim: Definition of the systemic immunity cellular components and autoimmune factor in eczema patients depending on the clinical manifestations of dermatosis.

Materials and methods: The study involved 95 eczema patients. 29 of them were diagnosed the true dermatosis form, while 39 and 27 subjects had infectious (microbial) and infectious (mycotic) form of the disease, accordingly. The control group consisted of 30 healthy individuals. CD3+, CD4+, CD8+, CD16 +, CD22 + and CD 95+ cells and autoantibodies to TPO and TG were counted.

Results: The eczema patients present uniform, but somewhat labile changes in the state of the immune system. For example, cellular disorders, except for CD8+ count, do not statistically significantly depend on the clinical form of dermatosis, the severity of inflammatory process, and the duration of the disease. At the same time, the decrease of CD8+ count in infectious (mycotic) form of the disease and in acute and subacute course reflects a certain variability of changes in cellular immunity with intact values in true and infectious (microbial) genesis and chronic manifestations of eczema.

Conclusions: Eczema patients should be subjected to valuation of cellular components of the systemic immunity and autoimmune profile. The CD8 + count of eczema patients can serve as one of the "conditional markers" of a degree of involvement of systemic immunity in the progression of eczema. Therapy of eczema patients should include medicines that possess a wide range of immunomodulatory effect.

KEY WORDS: eczema, disease form, disease course, immunity

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INTRODUCTION

Currently, eczema is considered a medical and social problem, the fact of which is substantiated by its high prevalence ranging from 8 to 30% among all dermatoses, unclear etiology and pathogenetic factors, torpid recurrence and often refractivity to traditional therapy [1 -3]. Such patients were found having a statistically significant association with HLA B22, B27 and CW1 antigens, which suggests a genetic predisposition and a significant diversity of disorders related to this dermatosis. Among the eczema triggering factors, somatic pathology (disorders of the central and peripheral nervous system, vascularization, changes in the immunological status, pathology of the gastrointestinal tract, endocrine imbalance) and the effects of infectious agents, domestic, industrial and environmental factors are considered the most significant ones [4-6].

However, immune changes are considered the priority element of eczema pathogenesis [7,8]. The course of the immunological reaction cascade has proven to occur in several ways: disorders of immune mechanisms of antigen recognition, the immune response to contact of macroorganism with allergen(s), antigen-antibody interaction imbalance, and defects of suppressor cells regulating IgE production. The skin, as an immune organ, is the first one interacting with harmful environmental substances and exerting its barrier effect. Haptens are transformed into native antigens only after interaction with individualized skin proteins. In the sensitization phase, the antigens/haptens enter the epidermis, bind to cells or extracellular proteins, and are captured by antigen-presenting cells (APCs)/Langerhans cells (LCs), or other dendrocytes, which transform them for subsequent exposure to lymphocytes. Following the antigen encounter, LCs switch to the activated state. APCs activate under the influence of mere antigen on interleukin (IL-1, TNFα). These bioactive compounds are produced by keratinocytes, APCs and dermal cells. The activated LCs then leave the skin and travel to regional lymph nodes, where they expose the antigen to lymphocytes. However, it remains unclear which subpopulation of these bioelements is responsible for further development of eczematous reactions. In the effector phase, sensitized T-lymphocytes migrating from the lymph nodes re-recognize the antigen. The widely accepted concept that T-lymphocytes are constantly circulating, entering the skin, lingering over and accumulating in it only after repeated exposure to antigen, is currently doubted. Not only dendrocytes and LCs, but also keratinocytes, endothelial cells and mast cells can act as APCs in the effector phase. Other factors are CD 28+, CD 40+, etc. [9-11].

THE AIM

Definition of the systemic immunity cellular components and autoimmune factor in eczema patients depending on the clinical manifestation of dermatosis.

MATERIALS AND METHODS

We observed 95 eczema patients (58 male and 37 female patients) aged 18 to 65 years. 29 of them were diagnosed the true dermatosis form, while 39 and 27 subjects had infectious (microbial) and infectious (mycotic) form of the disease, accordingly. The duration of the disease ranged from 5 weeks to 23 years, including 15 patients with the history below 5 years, 36 patients – 5 to 10 years, 28 patients – 11 to 15 years, and 16 subjects – over 15 years. Acute dermatosis was identified in 42, subacute – in 28, and chronic one in 25 patients. The control group consisted of 30 healthy individuals, comparable by sex and age.

CD3+, CD4+, CD 8+, CD 16+, CD 22+ and CD 95+ cell in the peripheral blood were counted using a set of Leu monoclonal antibodies (Becton Dickinson, USA) and a FACScan cytometer (Becton Dickinson, USA) by a method of two and three-color fluorescence flow cytometric analysis. Autoantibodies to thyroperoxidase (TPO) and thyroglobulin (TG) were detected using a "sandwich" method of solid-phase enzyme-linked immunosorbent assay (ELISA) involving reagent kits aTPO EIA and aTG EIA, accordingly.

The methods used were recommended for use by the Ethics Commission of Uzhhorod National University.

RESULTS

It was found that patients with true eczema presented a statistically significant decrease of CD 3+ count down to 52.02 ± 1.73% (in the control group – 65.18 ± 2.08%; $p < 0.05$),CD4 + – down to 34.50 ± 0.95 (in the control group – 19.11 ± 0.28%; $p < 0.05$), CD22+ – down to 15.71 ± 0.35% (in the control group – 19.11 ± 0.28%, $p < 0.05$), combined with an increase of SD16 + count up to 18.95 ± 0.42% (in the control group – 15.96 ± 0.31%: $p < 0.05$) and SD95 + – up to 21.18 ± 0.49% (in the control group – 15.96 ± 0.31%; $p < 0.05$). The CD8 + count remained within the range of control values – 23.18 ± 1.75% (in the control group – 22.54 ± 0.58%; $p > 0.05$). Similar data were obtained in patients suffering from the infectious (microbial) dermatosis form. In contrast to the true and infectious (microbial) forms of the disease, the infectious (mycotic) eczema presented also a suppression of CD8± down to 17.37 ± 0.63% ($p < 0.05$) with underlying decrease of CD3+, CD4+, CD22+, and elevation of SD16+ and SD95+ count.

The concentration of autoantibodies to TPO and TG in the observed patients statistically significantly increased, reaching in true eczema subjects 17.65 ± 0.48 IU/ml (in the control group – 14.08 ± 0.54 IU/ml; $p < 0.05$) and 117.62 ± 3.45 IU/ml (in the control group – 83.15 ± 1.79 IU/ml; $p < 0.05$), in infectious (microbial) subjects – 19.73 ± 1.13 IU/ml ($p < 0.05$) and 132.47 ± 4.26 IU/ml ($p < 0.05$), and in infectious (mycotic) patients – 24.89 ± 1.55 IU/ml ($p < 0.05$) and 147.63 ± 5.12 IU/ml ($p < 0.05$), accordingly.

Assessment of the dependence of the immune system on the severity of inflammatory phenomena demonstrated that in the acute dermatosis course, the CD3 + cell count decreased down to 45.14 ± 2.17% ($p < 0.05$), CD4 + – to 30.72 ± 1.25% <0.05), CD8 + – to 16.18 ± 0.75% ($p < 0.05$), and CD22 + – down to 13.90 ± 0.25% ($p < 0.05$), while CD16+ and CD95+ counts increased, on the contrary, up to 23.03 ± 0.48% ($p < 0.05$) and 24.08 ± 0.51% ($p < 0.05$), respectively. Similar changes were registered in subacute eczema patients. In contrast to subacute and acute disease form, the chronic course of dermatosis associated with CD8+ count remained within physiological fluctuations – 24.25 ± 1.95% ($p > 0.05$).

The concentration of autoantibodies to TPO and TG statistically significantly increased regardless of the severity of inflammatory process, reaching in case of acute eczema course 25.46 ± 0.98 IU/ml ($p < 0.05$) and 149.56 ± 4.98 IU/ml ($p < 0.05$), in the subacute form – 18.32 ± 1.32 IU/ml ($p < 0.05$) and 130.17 ± 3.74 IU/ml ($p < 0.05$), and in the chronic form – 16.95 ± 0.78 IU/ml ($p < 0.05$) and 119.68 ± 3.17 IU/ml ($p < 0.05$), respectively.

The study of cellular immunity in respect to the disease duration showed that the observed patients presented statistically significant suppression of CD3+, CD4+ and CD22+ count combined with an elevation of CD16+ and CD95+ count regardless of the disease duration. CD8+ count remained within the control values.

The content of autoantibodies to TPO and TG remained statistically significantly elevated regardless of the disease duration.

DISCUSSION

Thus, the eczema patients presented uniform, but somewhat labile changes in the state of the immune system. For example, cellular disorders, except for CD8+ count, did not statistically significantly depend on the clinical form of dermatosis, the severity of inflammatory process, and the duration of the disease. At the same time, the decrease of CD8+ count in infectious (mycotic) form of the disease and in acute and subacute course reflected a certain variability of changes in cellular immunity with intact values in true and infectious (microbial) genesis and chronic manifestations of eczema. This allows us to consider these values as a "conditional marker" of the pathological process.

Considering established branching of changes in the immune system, it is well-founded by the development of a unified approach to therapy patients with eczema using methods of a wide range of action. The intradermal administration of autoplasma enriched with platelets looks quite promising in this direction. PRP is obtained by reallocating hemoelements by centrifugation, which leads to a sedimentation in the lower part of the test tube of the heavier blood compounds (platelets). It differs from the usual blood plasma by presence in a composition a lot of accumulated platelets (not less than 1 million in 1 ml) [12].

It is established that PRP therapy has an immunotropic, metabolic and bacteriostatic activity, anti-inflammatory effect and significantly improves local microcirculation [13]. The additional attractiveness of the method provides the possibility of using its four variants, depending on presence or absence in PRP of leukocytes and fibrin. The

first variant (P-PRP) – pure (without leukocytes and fibrin) platelet-rich plasma; second variant (L-PRP) – platelet-rich plasma with leukocytes; third variant (P-PRF) – pure, platelet-rich fibrin; fourth variant (L-PRF) – platelet-rich fibrin with leukocytes [14].

Obtained results of PRP therapy will be published in the following article after the appropriate analysis.

CONCLUSIONS

1. In order to assess the depth and trends of the emerging immunological changes, eczema patients should be subjected to valuation of cellular components of the systemic immunity and autoimmune profile.
2. The CD8 + count of eczema patients can serve as one of the "conditional markers" of a degree of involvement of systemic immunity in the progression of eczema.
3. Therapy of eczema patients should include medicines that possess a wide range of immunomodulatory effect.

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ORIGINAL ARTICLE

EXPERIENCE USING LASER IN THE TREATMENT OF POLYPES OF THE EXTERNAL URETHRAL ORIFICE

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ABSTRACT

The aim: To improve the results of treatment of patients with polyps of the external urethral orifice by using minimally invasive surgery.

Materials and methods: The materials of the work are based on clinical examination and treatment of 22 patients with polyps of the external urethral orifice in the treatment of which, along with classical treatment were used minimally invasive methods of removal of polyps of the external urethral orifice using high-intensity laser.

Results: We managed to reduce the duration of surgery and treatment twice less, to avoid typical complications, which accelerated the regeneration process and the rehabilitation period.

Conclusions: The use of minimally invasive surgical methods to remove urethral polyps can reduce the duration of treatment by reduction of the thermal and mechanical load on the surrounding tissues and reducing the time of surgery.

KEY WORDS: polyp, urethra, external urethral orifice, laser

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INTRODUCTION

Benign tumors are a pressing problem today. Due to the fact that their preliminary detection and timely use are announced as direct preventive measures against the occurrence of criminal tumors. Urethral polyp is a neoplasm of benign nature, which occurs mainly in elderly and middle-aged women, and shows its hypertrophied fibrous tissue of dark red color. In addition, its head is also easily damaged due to mechanical and chemical exposure. It is located both proximally and distally on restoration of external urethral orifice. Sometimes the polyp comes from the external urethra, which even turn to the lower, closing its lumen causing these or other disorders of urination [1-3].

The urethra is lined with a cylindrical epithelium from the middle and its tumors form a separate group by morphological structure. They are divided into pre-benign and malignant, and benign occur more often, especially in women. In men, urethral tumors are relatively rare. The disease usually affects middle-aged people. Men are affected mainly at the age of 20-50 years, women – 40 years and older [4].

It is considered that the etiological factors in the formation of urethral polyps are chronic infectious and inflammatory diseases of the urethra (urethritis), chlamydia, trichomoniasis, gonorrhea, mycoplasmosis, ureaplasmosis, herpes genius. In addition, the disease may be associated with human papilloma virus [4,5].

Urethral polyps in women are more likely to occur from the posterior labia of the external urethral orifice, are more often observed in the postmenopausal period and are associated with hormonal imbalance – estrogen deficiency, mechanical trauma and chronic inflammatory diseases of the urinary tract of infectious origin. The development of an urethral polyp is initially asymptomatic, and later manifestations of the polyp may be difficulty urinating, discomfort in the urethra, splashing urine during urination, manifestations of chronic cystitis, micro- and macrohematuria. Infravesical obstruction resulting from urethral polyps is accompanied by persistent cystitis, often leading to complications: secondary diverticulum of the bladder, ureterohydronephrosis, chronic pyelonephritis [4,5].

Several different methods of treatment of benign urethral tumors are used: conventional surgical excision, transurethral and electroresection, cryodestruction [5,6], and in recent years – laser vaporization [7].

THE AIM

To improve the results of treatment of patients with polyps of the external urethral orifice by using minimally invasive surgery.

MATERIALS AND METHODS

During 2018 – 2021 on the basis of the clinic of the Department of General Surgery of Uzhhorod National University 22 patients with polyps of the urethra were treated, including 20 (90.9%) women and 2 men (10%). The age of patients ranged from 40 to 69 years.

The main complaints during hospitalization were disorders, difficulty urinating, itching, contact bleeding,

physiological and aesthetic discomfort. The duration of the disease ranged from 6 months to 4 years.

Benign urethral tumors in women have long been asymptomatic. Such tumors were detected, as a rule, during preventive gynecological and urological examinations. Sometimes women were bothered by dysuric phenomena, contact bleeding, pain during intercourse, movements, exercise, urinary incontinence. In men, there were characteristic changes in the flow of urine (weakening, difficulty, spraying, feeling of obstruction), dysuric phenomena, initial hematuria.

The diagnosis was based on the data of general examination, palpation, urethrography, urethroscopy, cytological examination, biopsy. It was also important to distinguish the polyp from the outwardly similar prolapse of the female urethra, in which its wall was easily fixed.

The pathology is often associated with inflammation and prolapse of the pelvic organs. Differential diagnosis of urethral polyps is performed with urethral papillomas, which are also located in the area of the external urethral orifice, have a broad base, round shape, pink color and resemble warts with a large number of granular and villous processes. Prolapse and pinching of the mucous membrane of the urethra is an indication for urgent surgery – circular excision of the fallen mucosa and circular suturing of a healthy urethral mucosa with the vaginal mucosa using catgut sutures [8-10].

Classical electrocoagulation of polyps was performed in 12 patients (54.5%). In 10 patients (45.5%) during the last three years in order to remove polyps of the external urethral orifice, we used a high-intensity diode laser "Lika-surgeon" manufactured by Cherkasy MP "Photonics-plus" with a capacity of up to 8 W in the mode of continuous emission, wavelength 980 nm.

Laser emission was applied to the polyp using a monovolo-equine fiber with a diameter of 0.4 – 0.8 mm. For anesthesia, mainly local anesthesia with 2% lidocaine solution was used, in 4 cases (18%) intravenous anesthesia was used. The polyp was completely removed by removing the leg with additional treatment of the bed, in order to stop the bleeding and to prevent recurrence. After removal of the polyp, a two-channel Foley silicone boat was installed in the bladder cavity to prevent chemical irritation of the postoperative area with urine. Miramistin-based gels and solutions were used to rehabilitate the postoperative area, and gauze pads impregnated with sea buckthorn oil were used to accelerate regeneration.

Evaluated the duration of surgery, the dynamics of the wound process, the presence of complications and recurrences, the duration of treatment.

RESULTS

In all patients treated with laser vaporization of the polyp of the external urethral orifice, the first signs of improved urination were observed during the first day, with electrocoagulation – for 3-4 days. The duration of surgery was 5-7 minutes, with electrocoagulation – 13-18 minutes. The vaporization of the polyp in the vast majority was not accompanied by bleeding, in electrocoagulation – in most of cases, more or less pronounced bleeding was observed, which sometimes required suturing. The peculiarity of laser polypectomy is also the absence of excessive thermal load of the surrounding and deeper tissues due to the point, dosed and controlled effect of high-intensity semiconductor laser on soft tissues, which warns as early (during and in the first days after surgery) and late (after scab rejection) bleeding. There were no complications in the form of cicatricial deformation (urethral stricture), with electrocoagulation – in 4 patients (18%). Foley's urinary catheter was removed on the second day, with electrocoagulation – on day 4-6, in 3 patients catheterization of the bladder after laser vaporization was not performed. The number of bed-days in patients was 3.4 days, with electrocoagulation – 8.4 days, in the presence of complications – up to 16 days. Complete wound healing occurred within 6-7 days, with electrocoagulation – 14-16 days.

DISCUSSION

There are three groups of benign tumors of the urethra:

a) from the mucous membrane of the urethra and its glands (papilloma, polyp, caruncle, condyloma);
b) from the connective tissue and muscular membrane of the urethra (fibroma, fibroid, fibromyoma);
c) from nervous and vascular tissue (neurofibroma, angioma) [1-3].

Benign tumors of this anatomical area are also divided into urethral (papillomas, polyps, condyloma) and paraurethral (fibroids, fibroids, fibromyomas, angiomas, neurofibromas) in men more often occur acute condyloma, polyps and papillomas, papillomas, – polyps, less often – papillomas [1-4].

According to the microscopic structure, a polyp of the urethra is a benign tumor (papilloma, adenoma), but can turn into malignant (malignancy). In the context of modern oncology, early diagnosis and radical, minimally invasive removal of urethral polyps are an example of timely prevention of malignant tumors of the urinary system.

Urethral polyp can be suspected and subsequently diagnosed on the basis of anamnestic data, complaints and physical examination. The vast majority can be absorbed: difficult and painful urination, the appearance of a soft formation in the urethra, which the patient can detect on their own, the appearance of blood in the urine, burning in the urethra provoked by urination or without a cause, splashing urine, foreign body sensation in the urethral lumen , feeling of incomplete emptying of the bladder, pain during intercourse, urinary retention [5,6,10].

The advantage of high-intensity semiconductor laser is the absence or minimal bleeding during surgery and minimal thermal load of the surrounding tissues, which allows for manipulations with minimal tissue damage, to avoid most of the complications characteristic of traditional methods of treatment of this pathology. prevent recurrence [7].

CONCLUSIONS

The use of a high-intensity semiconductor laser with a wavelength of 980 nm and a continuous emission power of

up to 8 W allows to reduce the time of surgery and reduce the psycho-emotional load of patients.

After using a high-intensity laser, rapid regeneration of the structural elements of the urethra is observed, without loss of elasticity, which allows to significantly reduce the duration of treatment (up to 3.4 days), increase the "comfort" of treatment.

Supply of high-intensity laser emission to the pathological formation with the help of a monofiber fiber allows to limit the area of intervention, is technically accessible and easy to use.

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ORIGINAL ARTICLE

A COMPARATIVE STUDY OF LIPID PROFILE AND LEPTIN RESISTANCE IN CHILDREN WITH METABOLIC SYNDROME DEPENDING ON HYPERTENSION IN KYIV

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ABSTRACT

The aim: To compare lipid metabolism and leptin levels among the children with and without hypertension to identify associated risk factors for the course of metabolic syndrome in children.

Materials and methods: This observational, cross-sectional study recruited children from the Rheumocardiology Department of Children's Clinical Hospital No 6 in Kyiv, with metabolic syndrome, identification of waist-to-height ratio, leptin level, homeostasis model assessment of insulin resistance and lipid profile. The main group included 41 children with metabolic syndrome and hypertension and the control group included 40 children with metabolic syndrome without hypertension. Statistical data analysis was performed using the MedStat 2.6.2. package.

Results: A total of 81 children aged 10 to 17 with metabolic syndrome were examined. The group of children with hypertension had significantly lower high-density lipoprotein cholesterol (0.85±0.04) than children without hypertension (0.94±0.03), with $p < 0.05$. Leptin resistance was detected in 65.2% of children with hypertension and 35.3% of children with normal blood pressure ($p < 0.01$).

Conclusions: Children with metabolic syndrome and hypertension had a significantly higher body mass index and waist circumference as opposed to children with normal blood pressure. In the lipid profile high-density lipoprotein cholesterol was significantly lower in hypertensive children. There was no reliable difference in other lipid profile indicators between the two groups, but there was an upward trend of them in group with hypertension. Leptin resistance is also significantly higher in hypertensive children.

KEY WORDS: hypertension, metabolic syndrome, lipid profile, leptin resistance, insulin resistance

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INTRODUCTION

According to a WHO report, about 124 million children between the ages of 5 and 19 all over the world are obese. Overweight children may have cardiovascular pathologies, including hypertension, dyslipidemia and endocrine pathology associated with metabolic syndrome [1].

The pathogenesis of the metabolic syndrome is based on insulin resistance, an evolutionarily fixed mechanism of survival in starvation [2]. Normally, the satiety hormone leptin increases in response to an increase in insulin levels in plasma [3,4]. Constant activation of leptin receptors from adipose tissue leads to leptin resistance [5]. Recently, the hypothesis of the role of hypertriglyceridemia, which is the main dyslipidemia in metabolic syndrome, in violation of the transport of leptin through the blood–brain barrier, became increasingly widespread. It was firstly confirmed by the experimental studies of W.A. Banks et al. that have shown that mice with impaired triglyceride synthesis are protected from developing both diet-induced obesity and obesity-induced resistance of leptin [6]. Later studies have shown that triglycerides are able to change the function of receptors in the brain not only to leptin, but also to insulin, and to cause insulin resistance [7].

Although the role in the regulation of hunger is the main function of leptin, it also plays a role in other physiological processes in the body. A number of studies have shown that leptin correlates with the activity of angiotensin II and noradrenaline in plasma, which may indicate a pathogenetic connection in the development of hypertension due to activation of the sympathetic nervous system [8-11].

Unhealthy lifestyle in childhood with subsequent development of the obesity is associated with a high chance of premature death and disability in adulthood. Hypertension as one of the criteria complicates the course of the metabolic syndrome.

THE AIM

The aim of the study is to compare lipid metabolism and leptin levels among the children with and without hypertension to identify associated risk factors for the course of metabolic syndrome in children.

MATERIALS AND METHODS

A comprehensive examination of 81 children aged from 10 to 17 with metabolic syndrome was conducted at the Rheu-

Table I. Comparative characteristics of average values and median of biochemical parameters

Parameters	Value of the parameter in groups (M ± m)	
	MetS without HTN (n=40)	MetS with HTN (n=41)
Sex: Male Female	 28 12	 35 6
BMI, kg/m²	27.7±0.6	30.6±0.8*
WC, cm	88.9±0.3	94.4±1.2*
Fasting glucose, mmol / l	4.92±0.11	4.75±0.13
Leptin, ng/ml	15.16±4.8	24.6±5.2
TC, mmol/l	3.6±0.3	3.8±0.2
TG, mmol/l	0.9±0.3	1.2±0.2
HDL-C, mmol/l	0.94±0.03*	0.85±0.04*
LDL-C, mmol/l	2.3±0.2	2.5±0.1
VLDL-C, mmol/l	0.36±0.05	0.43±0.1
AC, IU	1.85±0.36	2.6±0.24

Note. * - the difference of parameters in the group of MetS with HTN is reliable compared to those in the group of MetS without HTN ($p < 0,05$)

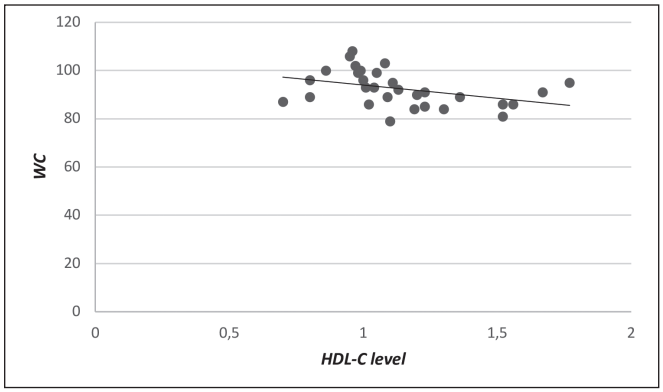

Fig. 1. Correlation field in coordinates: HDL-C level (X axis) and WC (Y axis). Correlation relation, Ro <0 (Ro = -0,529), at significance level p <0,01 is revealed.

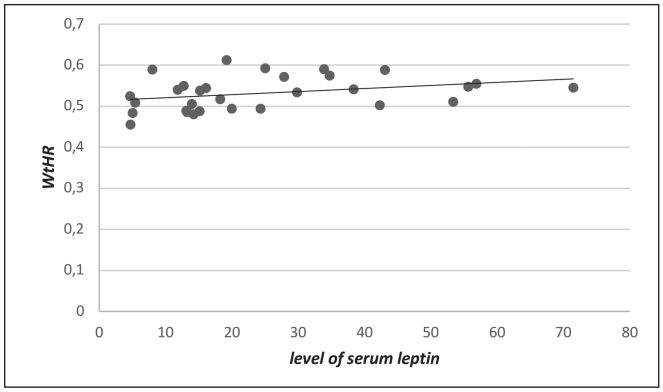

Fig. 2. Correlation field in coordinates: level of serum leptin (X axis) and WtHR index (Y axis). The correlation relation, Ro> 0 (Ro = 0.436), at the significance level p = 0.02 is revealed

mocardiology Department of Children's Clinical Hospital No.6 in Kyiv. The diagnosis "metabolic syndrome" (MetS) was established according to IDF 2007 criteria, which includes abdominal obesity and 2 or more of the following indicators; triglyceride level ≥ 1.7 mmol / l, high-density lipoprotein cholesterol <1.03 mmol / l, blood pressure ≥ 130 / 85 mmHg, fasting plasma glucose ≥ 5.6 mmol / l [12]. Exclusion criteria are as follows patients with other conditions and nosologies, associated with genetic syndromes and obesity associated with treatment.

According to the ambulatory blood pressure monitoring diagnosis of hypertension (HTN), children were divided into two groups: the main group included 41 children with HTN, the control group included 40 children without HTN. 24-h ambulatory blood pressure monitoring was performed using ABM-04 («Meditech», Hungary). Blood pressure was measured every 15 minutes over the day (6:00-22:00) and every 30 minutes at night (22:00-6:00) [13,14]. All children were checked a body mass index (BMI), waist circumference (WC), and the WtHR (Waist-to-height ratio) of ≥0.5 recommended by meta-analysis 2018 [15]. BMI was calculated as the ration of weight (kg) to height (m²) and was assessed according to WHO growth charts. Abdominal obesity was established by measuring the WC ≥90 percentile for age and sex-specific WC based on WHO reference in adolescents [16]. The fasting plasma glucose was measured. Serum leptin was measured using the LDN immunoassay (Germany). Leptin Resistance was calculated using the formula leptin/BMI > 0.7 [17]. Lipid profile included the determination of total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL-C), low-density lipoproteins (LDL-C), very low density lipoproteins (VLDL-C), atherogenic coefficient (AC) by enzymatic colorimetric method of analyzer and test system Cobas 6000, Roche Diagnostics (Switzerland). Statistical data analysis were performed using the MedStat 2.6.2. package.

RESULTS

There was a predominance of boys – 77,8% (n=63) over girls – 22,2 % (n=18) among children with metabolic syndrome. Median age of boys was 14±0.46, girls 14±0.74 (p=0.724). It was found that 50.6% of children (n = 41) with metabolic syndrome had hypertension. The BMI (30.6 ± 0.8) and WC (94.4 ± 1.2) were significantly higher in the group of children with MetS with HTN, as opposed to the group of children without HTN (27.7 ± 0.6 and 88.9 ± 0.3 respectively). (Table I).

The lipid profile was characterized by an increase in LDL-C in 80.2% of children (n = 65) and a decrease in HDL-C in 38.3% (n = 31), hypertriglyceridemia in 23.5% (n = 19), increased TC in 8.6% (n = 7) and VLDL-C only in 4.9% of all children (n = 4).

The group of children with HTN has significantly lower HDL-C <1.03 mmol/l (0.85±0.04) than children without

HTN (0.94±0.03), with p<0.05. There was no reliable difference in other lipid profile indicators between the two groups (p >0.05). Characteristics of the groups are presented in the table I.

The correlation was also found between WC and HDL-C level with r = -0,529 (p <0,01) (Fig.1)

At the same time, with changes in the lipid profile, an increase in the adipose tissue hormone leptin was found in 86.4% of children (n = 70). Although there is no significant difference between the medians of both groups, there is a tendency to an increase in leptin in the group with hypertension.

Statistically, we found that the higher the BMI, the greater the WC (r = 0.375) and WtHR (r = 0.584). In the group with hypertension, WtHR was in 63% and in the other group – 57.5%. WtHR ≥ 0.5 is defined in 67% of children with hyperleptinemia from both groups . It was confirmed in our study, that WtHR is closely correlated with serum leptin levels (r = 0.436). (Fig.2)

Leptin resistance was significantly more common in the group of children with HTN – 65.2% (n = 27), as opposed to children without HTN – 35.3% (n = 15) (p < 0.01).

DISCUSSION

Analysing the Mets IDF criteria [12] in the children participating in the study, it should be noted that all children were obese, just over half of the children had HTN, 38.3% had low levels of "protective" HDL-C and 23.5% had high levels of TG. Although LDL-C is not included in the Mets criteria, high levels of this parameter were found in 80.2% of children in both groups. WtHR≥ 0.5 was found in 61% of children, which according to the 2018 meta-analysis indicates a high cardiometabolic risk [15]. We also recommended this anthropometric tool for mass screening of obese children. The results obtained indicate a high prevalence of abdominal obesity and the possible inclusion of the WtHR parameter in one of the additional criteria for Mets in the next IDF review.

Analysis of patient groups with and without hypertension showed that 'bad' LDL-C levels in hypertensive children were significantly higher.

It was found that 80.4% of children had high levels of leptin, and 51.8% of children had leptin resistance, which may be due to the acquired non-sensitivity of tissues to the "satiety hormone", including at the level of blood-brain barrier, and/or genetic mutations of the defect in the leptin receptor. The correlation between the level of leptin and WtHR was also found, which proves the role of this laboratory indicator in the development of abdominal obesity. Such relationship has been found in children and adults in recent studies [18, 19]. According to our results, leptin resistance has been reliably identified more frequently in hypertensive patients (65.2%), which proves the aforementioned pathogenetic mechanism of the action of leptin in the activation of the sympathetic nervous system[8-11].

These results indicate a burden of HTN in the development of obesity and Mets.

This study did not examine how the development of Mets will be affected, but identified key parameters for future studies.

CONCLUSIONS

1. In the lipid profile of the two groups, the changes were mainly due to an increase in LDL-C and a decrease in "protective" HDL-C. It was found that HDL-C was significantly lower in hypertensive children. There was no reliable difference in other lipid profile indicators between the two groups, but there was an upward trend of them in group Mets and HTN.
2. Elevated WHtR was found in more than half of children with Mets, which indicates a high cardiometabolic risk. Children with hypertension had a significantly higher BMI and WC as opposed to children with normal blood pressure. In the analysis of correlated links, it was found that WHtR is associated with serum leptin levels and WC with HDL-C level.
3. Hyperleptinemia was found in the majority of children and more than half of the children with Mets lost tissue sensitivity to leptin. Leptin resistance is significantly higher in the group of children with hypertension, in contrast to children without hypertension.
4. Although patients were selected according to defined criteria of Mets, we have shown that children with and without HTN have significantly different indicators of cardiometabolic risk factors such as increased WC, WHtR, dislipidemia, hyperleptinemia with consequent development of leptin resistance. Children at high cardiometabolic risk require regular check-ups and lipid monitoring to prevent complications of the metabolic syndrome such strokes and heart attacks.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

THE CLINICAL PRESENTATION OF SUBCLINICAL HYPOTHYROIDISM IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ASSOCIATED WITH OBESITY, ITS IMPACT ON CARDIOVASCULAR RISK, AND WAYS OF ITS CORRECTION

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ABSTRACT

The aim: Calculate CVR in patients with T2DM, obesity and SH and analyze it.

Materials and methods: The selection of patients was carried out based on the Uzhhorod District Clinical Hospital, in the period from November 2016 to July 2021. All examined patients were divided into 3 groups: 1 (n=108) with T2DM and concomitant obesity and SH, 2 (n=91) with T2DM and SH, 3 (n=46) with obesity and SH. The observation and treatment period lasted 1 year. Using American College of Cardiology (ACC) / American Heart Association Guideline on the Assessment of Cardiovascular Risk (AHAGACR) (2013) (ASCVD Risk) and Framingham Risk Score (FRS), CVR was determined in all patients before and at the end of the study.

Results: According to the data obtained, patients in each group had a 10-year risk of CVE, however, worse CVR was observed in patients in group 1. In a more detailed analysis and comparison of the obtained data of patients with 10-year risk of CVE, worse CVR values were observed in patients with concomitant SH than without it ($p<0.05$).

Conclusions: The presence of SH in consumers may be an additional risk factor for unwanted CVE over a 10-year period.

KEY WORDS: type 2 diabetes mellitus, obesity, subclinical hypothyroidism, diagnostics, treatment, dapagliflozin, cardiovascular risk

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INTRODUCTION

T2DM, obesity, and SH belong to the group of endocrine diseases that contribute to the complex disruption of metabolic processes, the emergence of pathological conditions, and complications in the body.

Obesity, and especially active abdominal adipose tissue, produces pro-inflammatory adipocytokines, which are involved in the stimulation of inflammatory processes, while excessive amounts of leptin, adiponectin, and resistin are closely associated with decreased insulin sensitivity, forming disorders insulin resistance (IR), associated with impaired glucose uptake into peripheral tissues [1]. Thus, in patients with T2DM, a relationship has been established between thyroid-stimulating hormone (TSH) levels, insulin sensitivity, and plasma lipid levels [2].

Several clinical studies have shown that anthropometric parameters (AP) are indicators of the risk of cardiovascular disease (CVD): body mass index (BMI), waist circumference (WC), hip circumference (HC), and subsequent waist-to-hip ratio (WHR) [3].

Hyperinsulinemia leads to an increase in adipose tissue in the liver and contributes to the development of non-alcoholic fat disease (NAFLD) [4]. Hypothyroidism contributes to the development of NAFLD and can provoke functional disorders of the heart: left ventricular diastolic dysfunction and others [5, 6].

Iodine deficiency plays an important role in the development of thyroid disease, which is almost always combined with selenium deficiency, especially this trend is observed in endemic areas, although there are data on the genetic condition of these diseases [7, 8].

Instead, studies show that thyroid hormone replacement therapy, primarily levothyroxine, normalizes lipid metabolism and consequently reduces the manifestations of fatty liver disease and reduces the risk of cardiovascular events (CVE) [9]. The obtained data meta-analysis from several prospective studies showed that individuals with SH and serum TSH levels were greater than 10 mU/L and had age-independent increases in CVE levels [10].

T2DM is considered an absolute risk factor (RF) for atherosclerosis [11]. Disorders of lipid metabolism cause a predisposition to atherosclerosis and contribute to endothelial dysfunction [12]. Lipid-protein glycan complexes contribute to the development of diabetes micro- or macro angiopathy [13, 14].

Data from studies demonstrate that SH is associated with hypercholesterolemia and increased levels of low-density lipoprotein (LDL) [15]. People with elevated levels of TSH and IP have an increased chance of developing dyslipidemia and cardiovascular disease [16].

According to the recommendations of the European Thyroid Association (ETA) in people under 65 years with

TSH levels of 4.0 – 10.0 mU/L and in the presence of symptoms of hypothyroidism, it is advisable to consider levothyroxine replacement therapy [17]. According to the results of randomized placebo-controlled studies, the efficacy and appropriateness of levothyroxine in different of patients with SH were substantiated [18].

In case of suspicion in a patient CVR in the 10-year perspective for evaluation purposes risk of occurrence cardiovascular events (CVE) in the next 10 years, it is calculated on the following scales: Q risk 2 score calculator and Modified Q risk 2, absolute CVD risk calculator, PROCAM score, Heart Disease Risk Calculator, The Framingham risk score (FRS) for hard chronic heart diseases (CHD), SCORE, ACC/AHAGACR (2013) (ASCVD Risk) [19, 20, 21, 22, 23]. ASCVD Risk is categorized as low-risk (LR) (<5%), borderline risk (BR) (5% to 7.4%), intermediate-risk (IMR) (7.5% to 19.9%), high risk (HR) (≥20%) of 10-year risk of myocardial infarction (MI) and/or stroke [22, 24]. FRS which evaluates the 10-year risk of CVD (CHD, stroke, death) is determined in percentages and classified accordingly LR (<10%), MR (10–20%), and HR (>20%) [21].

THE AIM

Examine patients with T2DM, obesity, and concomitant SH and identify in patients of experimental groups indicator CVR at 10-year CVE risk.

MATERIALS AND METHODS

The selection of patients took place based on the therapeutic department of the Municipal Non-Profit Enterprise "Uzhhorod District Clinical Hospital of Uzhhorod District Council of Transcarpathian region", and at outpatient treatment department of the therapy and the family medicine of the Faculty of Postgraduate and Pre-University Education of the State Higher Educational Establishment «Uzhhorod National University» in the period from November 2016 to July 2021. In the course of the study, 108 people with T2DM and concomitant obesity, who were included in the 1st group (n=108), were examined and 139 medical cards of an inpatient with a diagnosis of T2DM and ambulatory card data included in the 2nd group were retrospectively analyzed. group (n=91), while group 3 included patients diagnosed with obesity (n=46). Before dividing patients into groups, TSH and FT4 levels were determined, and depending on TSH (>4.0 mU/L) and FT4 (normal level), they were further divided into subgroups: 1a, 2a, 3a – patients with SH, and 1b, 2b, 3b – patients without SH. Instead, patients with hyperthyroidism, hypothyroid, subclinical hyperthyroid were excluded from this study. The period of treatment and observation of patients of all groups lasted 1 year and included dietary and exercise recommendations. All patients with T2DM received metformin 850 mg two times a day in combination with dapagliflozin 10 mg one time daily. Patients with SH were given levothyroxine individually at a dose of 25 or 50 μg daily, and if necessary, increasing the dose by 25 μg daily every 14-21 days until a replacement dose was reached, according to ETA recommendations.

All subjects were examined: general clinical examination, AP, measurement WC, HC, calculation of BMI and WHR, data of lipid profile, glycosylated hemoglobin (HbA1c), TSH, Free Thyroxine (FT4) levels, gathering of medical and social anamnesis, and bad habits. Using the American Diabetes Association (ADA) and ACC / AHAGACR and ETA, patients were provided with dietary advice.

CVR was determined at the time of inclusion in the study and after 1 year of treatment. The following calculators were used to calculate the CVR: 1) ACC/AHAGACR (2013) ASCVD Risk is categorized as LR (<5%), BR (5% to 7.4%), IMR (7.5% to 19.9%), high risk (HR) (≥20%) of 10-year risk of MI and/or stroke [22-24], and 2) FRS for hard CHD which evaluates the 10-year risk of CVD (CHD, stroke, chronic heart failure, death) in percentage was calculated by total points was classified as LR (<10%), IMR (10–20%), and HR (>20%) [21, 25]. В обрахунку ACC/AHAGACR (2013) ASCVD Risk used an online calculator (OC) – https://tools.acc.org/ASCVD-Risk-Estimator-Plus/?_ga=2.9302513.517413228.1631233238-717547926.1631233238#!/calculate/estimate/, instead, an OC was used to calculate FRS – https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease.

Additionally, to find the potential risk for patients with T2DM, obesity, subclinical hypothyroidism, a bibliographic search was performed on the keywords "treatment of type 2 diabetes mellitus", "type 2 diabetes mellitus", "subclinical hypothyroidism", "treatment of subclinical hypothyroidism", "obesity", "dapagliflozin", "metformin", "levothyroxine", "risk factors", "cardiovascular risk" in the following databases PubMed, MEDLINE, Web of Science, Cochrane Library, Google Scholar.

The diagnosis criteria for T2DM were established based on the ADA. The diagnosis of obesity was established by measuring BMI≥30 kg/m^2, and the value of BMI was assessed by the degree of obesity. It was evaluated depending on laboratory indicators and recommendations ETA thyroid function as euthyroid, hyperthyroid (known diagnosis of hyperthyroidism or TSH<0.3 mU/L and FT4>24 pmol/L), hypothyroid (known diagnosis of hypothyroidism or TSH>4.0 mU/L and FT4<10 pmol/L), SH (TSH>4.0 mU/L and normal FT4), and subclinical hyperthyroid (TSH<0.3 mU/L and normal FT4) [17].

The statistical processing of the research results was performed using the program software International Business Machines Corporation Statistical Package for the Social Sciences Statistics. The statistical analysis of the materials, the summary, and also the summary of the conclusions were made by the method of the variation statistics, taking into account the average values (mod, median, arithmetic mean) and the average error (M±m), with the estimation of the reliability of the values by the Student's t-criterion, as well as with the determination of the correlation coefficient using the Pearson's paired method to identify the relationships between the obtained indicators. For the minimum threshold of probability, the values $p<0.05$ were taken.

Table I. Anthropometrical parameters in group 1, 2 and 3.

Parameter	Group								
	Group 1 (n=108)	Subgroup 1a (n=28)	Subgroup 1b (n=80)	Group 2 (n=91)	Subgroup 2a (n=17)	Subgroup 2b (n=74)	Group 3 (n=46)	Subgroup 3a (n=11)	Subgroup 3b (n=35)
BMI ^{B} (kg/m^2)	32,9 ± 1,8	33,76± 2,51	32,55± 0,9	28,55± 0,12	28,83 ±2,19	28,26± 0,71	32,08± 0,19	32,69± 2,57	31,48± 0,14
BMI ^{AT} (kg/m^2)	31,43± 0,22	31,73± 2,07	31,58± 0,14	26,92± 0,15*	27,96± 2,34 $^{\mu}$	25,87± 0,63	30,57± 0,29#	31,03± 2,15$^{¥}$	30,1± 0,25
WC ^{B} (cm)	112,9± 1,4	114,6± 2,1	111,2± 1,5	88,6± 1,9	92,1± 2,4	88,3± 1,1	109,3± 1,6	111,0± 3,2	107,5± 1,6
WC ^{AT} (cm)	106,9± 1,3	107,5± 2,7	106,3± 1,1	86,35± 1,18*	87,4± 2,41$^{\mu}$	85,3± 1,4	102,7± 1,9#	103,5± 2,9$^{¥}$	101,9± 1,3
HC ^{B} (cm)	104,9± 1,1	105,7± 2,3	104,1± 1,9	91,9± 1,4	92,7± 2,1	91,1± 1,2	106,1± 0,7	106,8± 1,5	105,3± 1,2
HC ^{AT} (cm)	101,8± 1,04	102,5± 2,1	101,1± 1,6	91,0± 1,6*	91,3± 2,7$^{\mu}$	90,7± 1,8	102,7± 0,9$^{\#}$	103,9± 1,3$^{¥}$	101,5± 1,2
WHR ^{B}	1,08± 0,1	1,08± 1,1	1,07± 0,4	0,96± 0,2	0,99± 0,8	0,97± 0,1	1,03± 0,1	1,04± 0,2	1,02± 0,1
WHR ^{AT}	1,05± 0,2	1,05± 1,3	1,05± 0,1	0,95± 0,2*	0,96± 1,1$^{\mu}$	0,94± 0,2	1,00± 0,2 #	1,00± 0,4$^{¥}$	1,00± 0,1

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; BMI - Body Mass Index; WC - Waist circumference; HC - the hip circumference; WHR - waist-to-hip ratio; * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 ($p<0.05$); μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); # - a statistically significant difference when comparing the indicators between the respective groups 1 and 3 ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

Table II. TSH and FT4 levels in patients of 1a, 2a, 3a subgroups

Subgroup	Parameter			
	TSH (mU/L) ^{B}	TSH mU/L) ^{AT}	FT4 (ng/dL) ^{B}	FT4 (ng/dL) ^{AT}
Subgroup 1a (n=28)	5,6±1,9	4,9±1,3	0,8±1,2	1,4±1,7
Subgroup 2a (n=17)	5,2±1,1	4,6±1,5$^{\mu}$	1,1±1,9	1,3±1,2
Subgroup 3a (n=11)	4,7±0,1	4,4±1,2$^{¥}$	1,6±0,2	0,9±1,1

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; normal values of TSH – 0.5–4.0 mU/L; normal values of FT4 – 0.7 to 1.9 ng/dL; μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

The whole set of the surveys were by the Articles 3,44 of the Fundamentals of the Legislation of Ukraine on Healthcare, the Articles 7, 8 of the Law of Ukraine "On Medicines", the Law of Ukraine "On Protection of Personal Data", taking into account the requirements of the European Parliament and Council Directives 2001/20/ EU of April 4, 2001, 2001/83/ EU of November 6, 2001, the Decisions of the European Parliament and of the Council 1901/2006 of December 12, 2006, and 1902/2006 of December 20, 2006, ICH GCP, International Ethical Principles for Biomedical human-related research and physician code of conduct, and order in the Ministry of Health of Ukraine No. 690 of September 23, 2009.

RESULTS

All patients included in this study were ≥40 years old. The mean age of the patients in the 1st group was 53.5±1.1 years, compared with 54.2±1.3 years of the patients in the 2nd group, whereas in group 3 the age of patients was 55.3±1.1 years. The ratio of men and women in group 1 was 44 men and 64 women against 33 men and 58 women in group 2 and 21 men and 25 women in group 3. The mean duration of T2DM in group 1 was 13.4±2.8 years, as opposed to 13.1±1.4 years in group 2 (Table I).

Currently, the status of a smoker was in group 1 – 34 patients, group 2 – 21 patients, and group 3 – 25 patients. Instead, in the past, there were additionally smokers in group 1 – 14 patients,

Table III. FPG and HbA1C levels

Parameter	Group								
	Group 1 (n=108)	Subgroup 1a (n=28)	Subgroup 1b (n=80)	Group 2 (n=91)	Subgroup 2a (n=17)	Subgroup 2b (n=74)	Group 3 (n=46)	Subgroup 3a (n=11)	Subgroup 3b (n=35)
FPG ^{B}	9,45±0,1	9,7±0,3	9,2±0,4	8,9±0,2	9,1±0,1	8,7±0,3	5,9±0,1	6,1±0,4	5,7±0,2
HbA1C (%) ^{B}	8,5±0,2	8,7±0,3	8,3±0,1	8,1±0,2	8,3±0,1	7,9±0,2	6,1±0,2	6,2±0,4	6,0±0,1
FPG ^{AT}	7,25±0,1	7,4±0,4	7,1±0,2	6,65±0,2*	6,8±0,5$^{\mu}$	6,5±0,3	5,6±0,1$^{\#}$	5,8±0,3$^{¥}$	5,4±0,1
HbA1C (%) ^{AT}	7,55±0,2	7,69±0,3	7,41±0,1	6,35±0,04*	6,4±0,02$^{\mu}$	6,3±0,02	5,4±0,1$^{\#}$	5,1±0,6$^{¥}$	5,7±0,2

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; FPG – Fasting plasma glucose; HbA1C – glycated hemoglobin; normal values of FPG – 3.3-5.5 mmol/l; normal values of HbA1C – 4-6.4%; * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 ($p<0.05$); μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); # - a statistically significant difference when comparing the indicators between the respective groups 1 and 3 ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

Table IV. Assessment of CVR on the ACC/AHAG on the Assessment of CVR (2013) (ASCVD Risk)

Group	Parameter	
	ASCVD Risk (%) ^{B}	ASCVD Risk (%) ^{AT}
Group 1 (n=108)	12,9±0,2	9,7±0,3
Subgroup 1a (n=28)	13,6±1,5	10,4±1,2
Subgroup 1b (n=80)	12,2±0,3	9,7±0,8
Group 2 (n=91)	11,8±0,1	9,2±0,2*
Subgroup 2a (n=17)	12,1±1,6	9,6±1,6$^{\mu}$
Subgroup 2b (n=74)	11,4±0,2	8,8±0,4
Group 3 (n=46)	6,8±0,2	6,4±0,1#
Subgroup 3a (n=11)	7,1±1,8	6,5±1,3$^{¥}$
Subgroup 3b (n=35)	6,5±0,3	6,2±0,2

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 ($p<0.05$); μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); # - a statistically significant difference when comparing the indicators between the respective groups 1 and 3 ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

Table V. Assessment of CVR on the Framingham Risk Score (FRS)

Group	Parameter	
	FRS (%) B	FRS (%) AT
Group 1 (n=108)	25,2±0,4	23,1±0,6
Subgroup 1a (n=28)	26,6±1,9	24,7±1,5
Subgroup 1b (n=80)	23,8±0,5	21,5±0,8
Group 2 (n=91)	18,7±0,2	16,7±0,4*
Subgroup 2a (n=17)	19,8±1,6	17,4±0,9μ
Subgroup 2b (n=74)	17,6±0,1	15,9±0,7
Group 3 (n=46)	15,0±0,8	12,2±0,2#
Subgroup 3a (n=11)	15,3±1,7	12,9±1,1¥
Subgroup 3b (n=35)	14,8±0,2	11,4±0,3

Note: B - patient data at the beginning of the study; AT - patient data after 12 months of treatment and follow-up; FRS - Framingham Risk Score; * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 ($p<0.05$); μ - statistically significant difference when comparing the indicators between the respective groups 1a and 2a ($p<0.05$); # - a statistically significant difference when comparing the indicators between the respective groups 1 and 3 ($p<0.05$); ¥ - statistically significant difference when comparing the indicators between the respective groups 2a and 3a ($p<0.05$).

in group 2 – 9 patients, and group 3 – 7 patients. Arterial hypertension diagnosis and received treatment for it: in group 1 – 49 patients, in group 2 – 37 patients, and group 3 – 24 patients. MI was suffered in the past: in group 1 – 13 patients, in group 2 – 9 patients, and group 3 – 5 patients. Instead, during 1 year of observation, MI was additionally transferred: in group 1 – 5 patients, in group 2 – 2 patients, and group 3 – 4 patients. Stroke was suffered in the past: in group 1 – 11 patients, in group 2 – 4 patients, and group 3 – 3 patients. Instead, during 1 year of follow-up, an additional stroke: in group 1 – 3 patients, in group 2 – 4 patients, and in group 3 – 2 patients. Aspirin therapy was taken: in group 1 – 45 patients, in group 2 – 17 patients, and group 3 – 14 patients. Statins were taken: in group 1 – 27 patients, in group 2 – 14 patients, and in group 3 – 9 patients.

At the beginning of the study (BS), according to the obtained data on BMI: in group 1 – 63 patients were with grade I obesity, 31 patients had grade II obesity, 14 patients had grade III obesity; in group II – 56 patients were overweight, while 35 patients were normal weight; in group 3 – 28 patients were with I degree of obesity, 13 patients had II degree of obesity and 5 patients with obesity of III degree (Table I).

According to the data obtained as a result of the measuring AP of the patients of the 1-st and the 2-nd group and 1st and the 3rd group at the BS, no statistically significant difference was found between them ($p>0.05$). The BMI at the BS in group 1 was 32,9±1,8 kg/m^2, respectively 28,55±0,12 kg/m^2 in group 2 and 32,08±0,19 kg/m^2 in group 3. The WC index in group 1 at the BS was 112,9±1,4 cm, respectively 88,6±1,9 cm in group 2, and 109,3±1,6 cm in group 3. WHR after treatment (AT) in the group 1 was 1,05±0,2 and 0,95±0,2, respectively in the group 2 and 1,00±0,2 cm in the group 3 (Table I).

It is noteworthy that 12 months after the course of comprehensive treatment and observation, between AP of patients of the 1st and 2nd group there was a statistically significant difference, the same dynamics were also observed when comparing the 1st and 3rd groups (p<0.05) (Table I).

At the beginning of treatment, TSH in patients of subgroup 1a was 5,6±1,9 mU/L, subgroup 2a – 5,2±1,1 mU/L, and subgroup 3a 4,7±0,1 mU/L, respectively. At the end of treatment (EOT) TSH level in patients of the 1a subgroup 4,9±1,3 mU/L, the 2a subgroup – 4,6±1,5 mU/L, and the 3a subgroup 4,4±1,2 mU/L, respectively. There was a statistically significant difference between TSH levels at EOT in patients of subgroups 1a and 2a and subgroups 2a and 3a (p<0.05). FT4 – was been in normal ranges in all subgroups before and AT (Table II).

If at the BS in group 1 HbA1C was 8,5±0,2%, then after 12 months of complex treatment and observation 7,55±0,2%, against the response of 8,1±0,2% and 6,35±0,04%, respectively, in the 2-nd group. In contrast, in patients of group 3 before and after 12 months of complex treatment and observation, indicators within the norm of HbA1C were observed – 6,1±0,2% and 5,4±0,1%, respectively. According to the obtained laboratory data of FPG and HbA1C, in patients of the 1st and 2nd groups and the 1st and 3rd groups at the BS, no statistically significant difference was found between them (p>0.05). Analyzing the biochemical (BP) of the blood, namely the metabolism of hydrocarbons, there is a tendency to reduce the level of fasting plasma glucose (FPG) and HbA1C in groups 1 and 2. There was a statistically significant difference between FPG and HbA1C in patients of groups 1 and 2 and groups 1 and 3 after 12 months of study (p<0.05) (Table III).

In all study groups, at the BS, there was an increased level of triglycerides, a decrease in high-density lipoprotein, and an increase in low-density lipoprotein. The level of triglycerides slightly decreased AT, compared with a baseline before treatment, but was still extremely high, a statistically significant difference between patients 1 and 2 groups and between patients 1 and 3 groups was not observed (p>0.05). In groups 1 and 2 at the BS, there was an increase in the concentration of apolipoprotein B over 120 mg/dl, while in groups 3 this figure was within normal limits. Targets of the lipid profile in the experimental groups after the course of treatment were not achieved.

The other BP obtained at different stages of the study did not reveal the statistically significant changes in the indicators of the groups 1 and 2 and 1 and 3 (p>0.05).

At the beginning of treatment, ASCVD Risk in patients of group 1 was 12,9±0,2%, group 2 – 11,8±0,1%, and group 3 – 6,8±0,2%, respectively. At the EOT, ASCVD Risk in patients of group 1 was 9,7±0,3%, group 2 – 9,2±0,2%, and group 3, respectively 6,4±0,1%. There was a statistically significant difference between ASCVD Risk, between patients in groups 1 and 2 and groups 1 and 3 after 12 months of study (p<0.05). Patients with concomitant SH subgroups 1a, 2a, 3a before treatment (BT) and AT were statistically significantly worse than in subgroups without concomitant SH (p <0.05) (Table IV).

At the beginning of treatment, FRS in patients of group 1 was 25,2±0,4%, group 2 – 18,7±0,2%, and group 3 15,0±0,8%, respectively. At the end of FRS treatment in patients of the 1st group 23,1±0,6%, the 2nd group – 16,7±0,4%, and the 3rd group 12,2±0,2%, respectively. Patients with concomitant SH subgroups BT and AT were statistically significantly worse than in subgroups without concomitant SH (p<0.05) (Table V).

DISCUSSION

Even though many medical instruments help to individually assess the CVR in a 10-year period, covering several clinical and laboratory data of the patient, they remain quite rough instruments. More individual scales for CVR assessment are currently being developed. Future CVR scales on the way to personalized medicine may take into account individual genetic characteristics, which will significantly increase their sensitivity. However, there is no unequivocal position among scientists that the presence of SH in patients may increase CVR [5-8], so further research data may establish more accurate effects on CVR. Rarely in routine practice without targeted laboratory search, patients are diagnosed with SH and prediabetes, or a combination of these, which may be a prerequisite for T2DM, obesity, and therefore may increase CVR and CVE in the future. Meanwhile, prediabetes may not always progress to T2DM or provoke obesity. So far no definitive point has been made in their pathogenesis.

CONCLUSIONS

As a result of our study on the search and identification of RF to calculate the 10-year risk of CVR, after a course of treatment, there was a tendency to reduce this indicator in all groups. It should be noted that in subgroups 1a, 2a, 3a, ie in patients with SH there was a significantly worse CVR than in patients without SH. Despite 12 months of treatment and follow-up, new episodes of CVE were recorded in patients, which unfortunately could not be prevented. As a result, patients were provided with additional and further treatment recommendations and advice on continuing lifestyle modifications and monitoring BP with their follow-up. Given the data obtained, it can be argued that the presence of obesity in patients with SH, especially in patients with T2DM, significantly increases the risk of CVR and CVE, respectively. It is also important that in the long run CVR can be corrected due to complex and individual treatment.

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ORIGINAL ARTICLE

FEASIBILITY OF CYSTATIN C DETERMINATION FOR EARLY DIAGNOSIS OF KIDNEY DAMAGE IN PATIENTS WITH TYPE 2 DIABETES COMBINED WITH NONALCOHOLIC FATTY LIVER DISEASE AND OBESITY EXPOSED TO COVID-19 INFECTION IN THE PAST

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ABSTRACT

The aim: To examine the diagnostic possibilities of determining the level of cystatin C in the blood serum in order to ascertain the functional status of the kidneys in patients with type 2 diabetes (those who recovered from COVID-19 infection) depending on the presence or absence of non-alcoholic fatty liver disease (further – NAFLD) and malnutrition.

Materials and methods: We investigated 18 patients with type 2 DM, who were included in the first group of the patients examined; group 2 consisted of 20 patients with type 2 DM and non-alcoholic fatty liver disease (NAFLD), namely with non-alcoholic steatohepatitis; and group 3 of the patients examined consisted of 30 patients with type 2 DM and obesity**.**

Results: Renal damage in patients with metabolically associated diseases in the background of respiratory disease due to COVID-19 infection was also indicated by changes in urine test indicators, and namely – proteinuria and erythrocyturia, leukocyturia in urine sediment. The examination of cystatin C (Cys C) level indicates its statistically significant increase in patients of all examined groups, with the highest levels established in group 3 patients (with its increase up to 2.58 ± 0.11 mg/L, compared with the norm of 0.75 ± 0.04 mg/L in the control group – $p < 0.01$). The examination of GFR by calculation, where the Cys C index in serum was used, revealed a significant decrease in this parameter in all the examined groups of patients. At the same time, the maximum values were found in group 1 patients (65.7 ± 1.4 ml/min per 1.73 m^2 of the body surface), and the minimum values – in group 3 patients (48.3 ± 2.7 ml/min per 1.73 m^2 of the body surface).

Conclusions: An increase in serum cystatin C levels was determined in type 2 diabetes patients, with the lowest level in group 1 patients (1.24 ± 0.07 mg/L – $p < 0.05$), and the highest level in patients suffering from type 2 diabetes combined with NAFLD and obesity (2.58 ± 0.11 mg/L – $p < 0.01$). A moderate to severe course of COVID-19 infection in patients with type 2 diabetes as well as with its combination with NAFLD and obesity contributes to the development of renal functional disorders in these patients. Moreover, an increase in serum Cys C levels is a more sensitive and earlier marker of renal damage development in comorbid pathology.

KEY WORDS: type 2 diabetes mellitus, non-alcoholic fatty liver disease, obesity, kidney damage, cystatin C

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INTRODUCTION

Considering its rapid spread, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease in 2019 (COVID-19) pandemic, will probably emerge as one of the most relevant infectious diseases of this century [1]. The global COVID-19 pandemic, which has lasted for more than a year, has led to significant advances in the diagnosis, prevention and treatment of infected patients, promoting the increase in survival rates and the decrease in disabling complications. At the same time, patients having suffered from the coronavirus infection demonstrate the exacerbation and chronic progression of diseases, the emergence of new cases of cardiovascular and metabolic pathology [2, 3].

Individuals with diabetes mellitus (DM) are not known to have an increased risk of developing COVID-19 infection but they are vulnerable to the infection and a particularly severe course of COVID-19. The analysis of 72 thousand cases of COVID-19 indicates an increased risk of death by 3 times (2.3% in the general population and 7.3% among patients with diabetes). Concomitant conditions, such as cardiac pathology, chronic kidney disease, old age, increase the risk of developing COVID-19 [4].

Thus, the early detection of concomitant conditions in patients with metabolically induced diseases, as well as the search for informative markers indicating the possible risk of progression or formation of these conditions is a particularly important task of modern medicine in the conditions of COVID-19 pandemic.

THE AIM

The aim of the research is to examine the diagnostic possibilities of determining the level of cystatin C in the blood serum in order to ascertain the functional status of the kidneys in patients with type 2 diabetes (those who

recovered from COVID-19 infection) depending on the presence or absence of non-alcoholic fatty liver disease (NAFLD) and malnutrition.

The academic study is a fragment of a research project at the Department of Propaedeutics of Internal Deceases "Polymorbid Pathology in Diseases of the Digestive System, Features of Pathogenesis, the Possibility of Correction" (state registration number is 0118U004365) and "Clinical and Pathogenetic Features of Polymorbid Diseases in the Digestive System and the Development of Differentiated Schemes of their Therapy in COVID-19 Pandemic Setting".

MATERIALS AND METHODS

Comprehensive examination and treatment of patients was conducted in the setting of the Department of Propaedeutics of Internal Diseases of the Medical Faculty of Uzhhorod National University. The study is based on the sample of 68 patients with type 2 diabetes who were treated in the COVID-center of CDC "Transcarpathian Regional Clinical Hospital named after A. Novak" within the period from October 2020 to March 2021 and were diagnosed with COVID-19 pneumonia (positive polymerase chain reaction (PCR test) to SARS-CoV-2 RNA (RdRP gene SARS-CoV-2 , gene E SARS-CoV-2), as well as lung lesions in the form of "frosted glass" on a computed tomography with a maximum percentage of lung tissue damage (up to 50.0 %) and did not require to be connected to the artificial lung ventilation machine. The decision was made to provide inpatient treatment for these patients due to the high risk of possible complications and more severe viral infection on the background of comorbid pathology. Patients were treated according to the standards of medical care for patients with COVID-19 infection, which included the appointment of antiviral therapy, glucocorticoids, anticoagulants, vitamin D3, zinc, and antibiotic therapy. It should be noted that the examined patients with type 2 diabetes before admission to the hospital for COVID-19 infection were not previously diagnosed with kidney damage.

The criteria for exclusion from the study include severe and extremely severe condition of patients infected with COVID-19, the presence of congenital malformations of the urinary system, acute and chronic glomerulonephritis and pyelonephritis, type 1 diabetes, alcohol, autoimmune, viral (hepatitis B, C, D viruses) liver damage.

The patients have been divided into three groups depending on the presence of NAFLD and the body mass index disorder, namely:

- group 1 included 18 patients with type 2 diabetes mellitus (among them there were 10 men (55.6%), 8 women (44.4%); the average age was 49.7 ± 5.4 years)
- group 2 consisted of 20 patients with type 2 diabetes mellitus in the combination with NAFLD, namely with non-alcoholic steatohepatitis (there were 12 men (60.0%) among them, 8 women (40,%; the average age was 48.8 ± 6.9 years);
- group 3 included 30 patients with type 2 diabetes mellitus in combination with NAFLD and obesity (there were 17 men (56.7%) among them, 13 women (43.3%; the average age was 51.6 ± 4.4 years).

The control group included 20 healthy individuals (there were 12 men (60.0%), 8 women (40.0%) with the average age 49.6 ± 7.1 years).

All studies were performed with the patients' consent (written consent for appropriate diagnostic and treatment measures was obtained), and the employed research methodology was consistent with the 1975 Helsinki Declaration of Human Rights and its revision (1983), the Council of Europe Convention on Human Rights and Biomedicine and the legislation of Ukraine.

All patients were subjected to examination using general clinical, anthropometric, instrumental, and laboratory methods. To verify the diagnosis, attention was paid to the present complaints, medical history. In anthropometric research, height, weight, and waistline were measured, as well as body mass index (BMI) was calculated. According to the recommendation of World Health Organization, patients were distributed depending on the rate of BMI, where 16.0 or less corresponded to a pronounced deficit of body weight; 16.0–18.5 – insufficient body weight; 18.0–24.9 – normal weight; 25.0–29.9 – overweight; 30.0–34.9 – obesity of the first degree; 35.0–39.9 – obesity of the second degree; 40.0 and more – obesity of the third degree [5].

All patients underwent ultrasound examination of the abdominal cavity and kidneys according to conventional methods. At the beginning of the inpatient phase of treatment, as well as on the eve of discharge from the hospital, standard general and biochemical studies were performed in the blood serum to determine the functional status of the liver (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB) and its fractions), kidneys (creatinine, urea), lipid metabolism, carbohydrate metabolism (glucose, insulin, glycosylated hemoglobin (HbA1c,%). Moreover, the examined patients were tested to determine the level of cystatin C (Cys C) by enzyme-linked immunosorbent assay, using a test system of the company "BioVendor" (the Czech Republic).

The diagnosis of type 2 diabetes was established in accordance with the recommendations of the IDF (2005), as well as taking into account the criteria of a unified clinical protocol (order of the Ministry of Health of Ukraine from 21.12.2012 № 1118) [6]. The severity of type 2 diabetes was assessed by the level of HbA1c (normal – up to 6.0%).

The diagnosis of NAFLD was made in accordance with the criteria of the unified clinical protocol (order of the Ministry of Health of Ukraine dated of 06.11.2014 № 826) and clinical recommendations EASL-EASD-EASO for the diagnosis and treatment of NAFLD [7]. The degree of liver damage was assessed using surrogate markers of fibrosis with the help of online calculators NAFLD fibrosis score (NFS), Fibrosis 4 calculator (FIB-4), as well as fibrotest, and the results of liver elastometry.

For the studies of renal function in the examined patients, the glomerular filtration rate (GFR) was calculated using the creatinine index, MDRD formula (Modification of Diet in Renal Disease) and Cockroft-Gault formula (CG) [8], as well as the formula using the level of Cis C [9], namely:

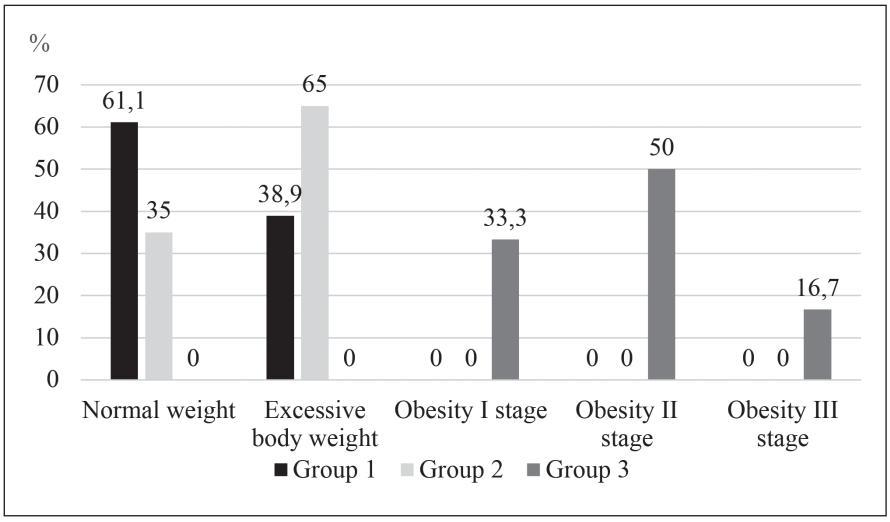

Fig. 1. Distribution of the examined patients according to their BMI index
Note: the difference between the parameters in the examined patients of groups 1 and 2 is statistically reliable: * – p<0.05.

Table I. Indicators of anthropometric research of the examined patients

Indication	Control group (n=20)	Examined patients		
		Group 1 (n=18)	Group 2 (n=20)	Group 3 (n=30)
BMI, kg/m^2	20.7±1.6	26.3±1.1	28.9±1.5	36.6±1.9*,+

Note: the difference between the indicators in patients and the control group is reliable: * – p <0.05; the difference between the indicators in patients of groups I and III is statistically reliable: + – p <0.05.

Table II. Change in indicators of the functional state of the liver in the examined patients and the control group

Indication	Examined patient			
	Control group (n=20)	Group 1 (n=18)	Group 2 (n=20)	Group 3 (n=30)
ALT, IU/L	24.7±1.7	38.3±2.3*	126.7±4.4 **,++	158.5±6.7**,++
AST, IU/L	22.3±1.4	36.5±2.0*	103.6±2.9 **,++	124.1±4.8**,++
TB, mmol/l	14.6±0.5	26.9±1.8*	29.0±1.4*	31.3±1.9*
ALP, mmol/l	72.6±3.4	131.1±5.2*	139.9±2.9*	144.7±6.1**

Note: the difference between the indicators of the control group and the examined patients is statistically reliable: * – p<0.05; ** – p<0.01; the difference between the indicators in the examined patients of groups 1 and 2 and 3 is reliable: + – p<0.05; ++ – p<0.01.

1) MDRD formula:

$$GFR_{MDRD} = 186 \times (Cr : 88.4)^{-1.154} + C + A^{-0.203}$$

where: Cr – serum creatinine, μmol / l;
C = 0.742 (for women) and 1.0 (for men);
A – age, years.

2) CG formula:

$$GFR_{CG} = [(140 - A) \times W] / a \times Cr$$

where: Cr – serum creatinine, μmol / l;
a = 0.8 (for men) and 0.95 (for women);
W – weight, kg;
A – age, years.

3) formula for calculating the GFR taking into account the level of Cys C:

$$GFR_{CysC} = 94.652 \times Cys\ C^{-1.2478}$$

The analysis and processing of the results of the examined patients were performed with the help of the computer program STATISTICA 10.0 (StatSoft Inc, USA) using parametric and non-parametric methods of evaluation of the results.

RESULTS

All examined patients had type 2 diabetes mellitus of moderate severity (subcompensated carbohydrate metabolism).

The anthropometric study allowed to establish obesity of varying severity in patients of group III, as well as BMI disorders in patients of groups I and II. At the same time, the BMI in patients of group 3 was 1.3 times higher than in patients of group 1 (p < 0.05). The results are presented in Table. I.

Following the distribution of patients according to their BMI, it was established that the overwhelming majority of Group 1 and 2 patients were overweight at the time of their admission to hospital – Fig. 1.

According to Fig. 1, the overwhelming majority of the examined patients had a nutritional disorder at the time of their admission to hospital. Moreover, in the group of patients with type 2 diabetes, patients with normal body weight (61.1% of cases – p < 0.05) were diagnosed more frequently, whereas in the combination of type 2 diabetes and NAFLD, patients with excessive body weight were diagnosed more

Table III. Markers of pathological changes of the urinary system in the examined patients

Indication	Examined patient			
	Control group (n=20)	Group 1 (n=18)	Group 2 (n=20)	Group 3 (n=30)
Creatinine, mmol/L	81.3±2.5	92.5±3.4	103.5±2.1*	146.7±2.3*,+,^
Urea , mmol/L	5.3±0.8	7.3±0.6	7.8±0.7	8.2±0.6*,+
Cys C, mg/L	0.75±0.04	1.24±0.07*	1.67±0.07*,+	2.58±0.11**,++,^
Proteinuria , mg/d	53.3±4.1	287.7±7.7**	332.0±6.1**	340.7±3.7**,+
Changes in urine sediment:				
Erythrocyturia, in sight	0.73±0.08	6.35±0.78	7.12±0.77	11.40±1.15
Leykocyturia, in sight	1.22±0.07	8.56±0.45	10.11±0.58	14.78±2.12

Note: the difference between the indicators of the control group and the examined patients is statistically reliable: * – p<0.05; ** – p<0,01; the difference between the indicators in the examined patients of groups 1, 2 and 3 is reliable: + – p<0.05; ++ – p<0,01; the difference between the indicators in the examined patients of groups 2 and 3 is statistically reliable: ^ – p<0,05.

Table IV. Indicators of GFR in the examined patients and the control group

Indication	Examined patient			
	Control group (n=20)	Group 1 (n=18)	Group 2 (n=20)	Group 3 (n=30)
GFR MDRD, mL/min/1.73m^2	105.1±2.8	83.1±2.4	78.7±2.8	61.3±3.9^
GFR CG, mL/min/1.73m^2	110.1±3.2	96.9±3.6*	92.4±2.5+	84.9±3.0^
GFR Cys C, mL/min/1.73m^2	106.7±2.2	65.7±1.4	59.5±2.2	48.3±2.7

Note: The difference between the indicators of GFR according to the CG formula and Cys C in the examined patients of the 1st group is statistically reliable: * – p<0.05; between the indicators of GFR according to the CG formula and Cys C in the examined patients of the 2nd group is statistically reliable: + – p<0.05; between the indicators of GFR according to the CG formula, MDRD and Cys C in the examined patients of the 3rd group is statistically reliable: ^ – p<0.05.

frequently (65.0 % of examined patients – $p < 0.05$). Group 3 consisted of patients with multimorbid pathology, namely the combination of type 2 diabetes, NAFLD and I-III classes of obesity. The results of our studies indicate that the II class obesity was more frequently diagnosed in patients (in 50.0 % of the examined cases), and morbid obesity of the III class was diagnosed only in 16.7 % of patients.

The laboratory blood tests at the time of the patients' admission for inpatient treatment revealed the presence of non-alcoholic steatohepatitis in the examined patients of groups 2 and 3, which was manifested by the increased levels of AST and ALT in the blood serum (Table II). It is noteworthy that an increase in total bilirubin and alkaline phosphatase in blood serum was revealed in type 2 diabetes patients (group 1), while AST and ALT levels were within the reference values. Consequently, patients with type 2 diabetes irrespective of the presence of NAFLD and obesity suffer from an impaired functional state of the hepatobiliary system.

Upon hospital admission, serum creatinine and urea values did not exceed the reference values in the examined patients of groups 1 and 2 with a metabolically associated disease, and only in patients with the combination of type 2 diabetes, NAFLD, and obesity, an increase in these indicators was diagnosed (by 1.8 and 1 5 times, respectively – $p < 0.05$) – Table III.

Renal damage in patients with metabolically associated diseases in the background of respiratory disease due to COVID-19 infection was also indicated by changes in urine test indicators, and namely – proteinuria and erythrocyturia, leukocyturia in urine sediment. Herewith, the daily proteinuria in group 3 patients was 340.7 ± 3.7 mg/day and was statistically significantly different from that of group 1 ($p < 0.05$). It is worth noting that erythrocyturia and leukocyturia in the background of COVID-19 infection were established in all the groups of the examined patients.

The examination of Cys C level indicates its statistically significant increase in patients of all examined groups, with the highest levels established in group 3 patients (with its increase up to 2.58 ± 0.11 mg/L, compared with the norm of 0.75 ± 0.04 mg/L in the control group – $p < 0.01$). A detailed analysis has revealed a correlation between creatinine level and Cys C, and it was maintained both at increased values of creatinine (group 3 – $r = 0.92$; $p < 0.01$) and in individuals with normal levels (group 1 – $r = 0.70$; $p < 0.05$; group 2 – $r = 0.78$; $p < 0.01$).

The determination of GFR revealed a decrease in kidney filtration capacity in group 3 patients, regardless of the method of estimation (Table IV).

The evaluation of GFR according to creatinine level (MDRD formula) indicates its moderate decrease in all groups of the examined patients with its maximum deviation from the norm in patients of the 3rd group with polymorbid pathology (decrease up to 61.3 ± 3.9 ml/min per 1.73 m^2), while the estimation of GFR according to

Cockroft-Gault formula, which also uses creatinine index, shows its level above 80,0 ml/min per 1.73 m^2 of the body surface in all groups of the examined patients (Table III). The examination of GFR by calculation, where the Cys C index in serum was used, revealed a significant decrease in this parameter in all the examined groups of patients. At the same time, the maximum values were found in group 1 patients (65.7 ± 1.4 ml/min per 1.73 m^2 of the body surface), and the minimum values – in group 3 patients (48.3 ± 2.7 ml/min per 1.73 m^2 of the body surface).

Consequently, the estimation of serum Cys C level, as well as the further GFR calculation, is a more objective criterion for assessing the functional state of kidneys in patients with metabolically associated diseases (type 2 diabetes, NAFLD, obesity) than by the creatinine indicator in the blood serum. It is especially crucial for predicting renal damage during inpatient treatment of this group of patients with a moderate to severe course of COVID-19 respiratory disease.

DISCUSSION

Previous studies indicate that SARS and MERS-CoV infections have resulted in acute renal failure (ARF) in 5.0 % to 15.0 % of cases and a high mortality rate (60% to 90%). Early reports suggest a lower incidence rate (3.0 % – 9.0 %) of ARF in COVID-19 patients. However, recent epidemiological data have shown a higher incidence of kidney damage with COVID-19 infection. A study of 59 patients with COVID-19 revealed that 34.0 % of patients developed massive albuminuria on the first day of inpatient treatment as a result of acute COVID-19 respiratory infection, and in 63.0 % of patients, proteinuria occurred during their hospital treatment [2].

The research of Chinese scientists (Cheng Y, Luo R, Wang K, et al., 2020) indicates a high prevalence of renal failure (changes in urine tests, renal dysfunction) in hospitalized patients with COVID-19 infection. At the same time, renal dysfunction was associated with a high risk of in-hospital mortality [10]. Evidence reported that COVID-19 represents a real threat for patients with comorbidities such as diabetes, hypertension, and cardiovascular, renal, or hepatic impairment [1].

The results of our research also indicate the development of kidney damage in patients with metabolically associated diseases, such as type 2 diabetes, obesity, NAFLD during COVID-19 infection. Moreover, with high comorbidity, the probability of lesions in other organs and systems, including the kidneys, increases during the inpatient treatment phase of acute respiratory infection caused by COVID-19. Furthermore, according to the results, even acute renal dysfunction can be accompanied by normal or slightly elevated serum creatinine levels, which, in turn, leads to erroneous indicators in the GFR estimation. A more sensitive and informative method of kidney function testing is the determination of serum cystatin C value, which is especially relevant during the pandemic in patients with a high risk of a more severe course of acute respiratory infection caused by COVID-19.

Consequently, practitioners should raise their awareness of impaired renal function in hospitalized patients with COVID-19. The early detection and effective intervention regarding impaired renal function may contribute to reducing mortality in COVID-19 patients in clinical practice, especially among patients with type 2 diabetes combined with a nutritional disorder and NAFLD.

CONCLUSIONS

1. An increase in serum cystatin C levels was determined in type 2 diabetes patients, with the lowest level in group 1 patients (1.24 ± 0.07 mg/L – $p < 0.05$), and the highest level in patients suffering from type 2 diabetes combined with NAFLD and obesity (2.58 ± 0.11 mg/L – $p < 0.01$).
2. A moderate to severe course of COVID-19 infection in patients with type 2 diabetes as well as with its combination with NAFLD and obesity contributes to the development of renal functional disorders in these patients. Moreover, an increase in serum Cys C levels is a more sensitive and earlier marker of renal damage development in comorbid pathology.

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ORIGINAL ARTICLE

ALGORITHM OF COMPLEX REHABILITATION OF PATIENTS WITH IATROGENIC OCCLUSAL DISORDERS COMBINED WITH VERTICAL MALOCCLUSION

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ABSTRACT

The aim: To propose the algorithm of complex rehabilitation of patients with iatrogenic occlusal disorders combined with vertical malocclusion and prove its efficiency.

Materials and methods: 55 patients with iatrogenic occlusal disorders combined with vertical malocclusion aged from 23 to 47 years old (mean age 36.1±5.2 years) including 32 females and 23 males were examined at Dental Medical Center of Bogomolets National Medical University during 2019-2021 years. All patients before and 6 months after treatment underwent clinical and laboratory examination, X-ray, electromyography, T-Scan Digital Occlusal Analysis.

Results: In all 3 groups of patients we observed complete disappearance or significant reduction of complaints and symptomatic manifestations after 6 months of complex rehabilitation.

Conclusions: Our study showed that the proposed algorithm of complex rehabilitation of patients with iatrogenic occlusal disorders combined with vertical malocclusion, which provides a multidisciplinary and individualized approach, improves the efficiency of orthodontic treatment of such patients and significantly reduces the duration of treatment in all 3 groups. This sequence of diagnostic and treatment measures gives the best opportunities for the patient to achieve maximum functional and aesthetic result.

KEY WORDS: dental occlusion, dysfunction, temporomandibular joint, malocclusion, complex rehabilitation

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INTRODUCTION

The treatment process in patients with occlusal problems and functional disorders of masticatory muscles or temporomandibular joint (TMJ) is very complex and requires individualization in each case. This is especially evident in cases where this pathology occurs against the background of mistreated malocclusion and as a result of incorrect restorative or prosthetic intervention. J. Ghafari (2013) emphasizes that malocclusions with predominantly vertical problems (open bite and deep bite) are challenging to treat because the skeletal and dentoalveolar components defining the vertical discrepancy are subject to a myriad of arrangements [1].

Many studies have shown that the lack of effective and in time carried out orthodontic and restorative dental treatment unfavorably affects the course of pathology of the TMJ and masticatory muscles and is accompanied by an increase in prevalence and severity of this disorders [2]. Elimination of occlusal disorders at a young age can eliminate or reduce the clinical manifestations of TMJ dysfunction as well as reduce the clinical manifestations of masticatory muscle parafunctions and normalize the muscle's activity [3, 4]. But contrary to the old concept that malocclusion and occlusal interferences are the main factors in TMJ disorder (TMD) development, occlusal changes, especially those observed as sudden, may be secondary and reflect TMJ or muscle disorders. Based on the fact that occlusal changes may reflect the presence of TMJ, W. Caldas (2016) suggests that all plans for irreversible therapy, such as orthodontics or prosthetic rehabilitation, should be preceded by a detailed analysis of TMD signs and muscle problem symptoms. When present, TMD symptoms and muscle disorders must always be controlled to reestablish a normal occlusion and allow proper treatment strategy [5].

Orthodontic treatment of adult patients has its peculiarities associated with the presence of concomitant pathology (tooth loss, periodontal problems, TMD, consequences of incorrect previous treatment etc.) as well as possible inability to correct some pathologies only with orthodontic treatment, unlike children. In case of severe malocclusion, complicated by tooth loss, the combination of surgical, orthodontic and prosthetic methods allows to reach the best results [6]. The key to successful treatment of such patients is detailed diagnostics and a well-designed rehabilitation plan.

THE AIM

The aim of the study was to propose the algorithm of complex rehabilitation of patients with iatrogenic occlusal disorders combined with vertical malocclusion and prove its efficiency.

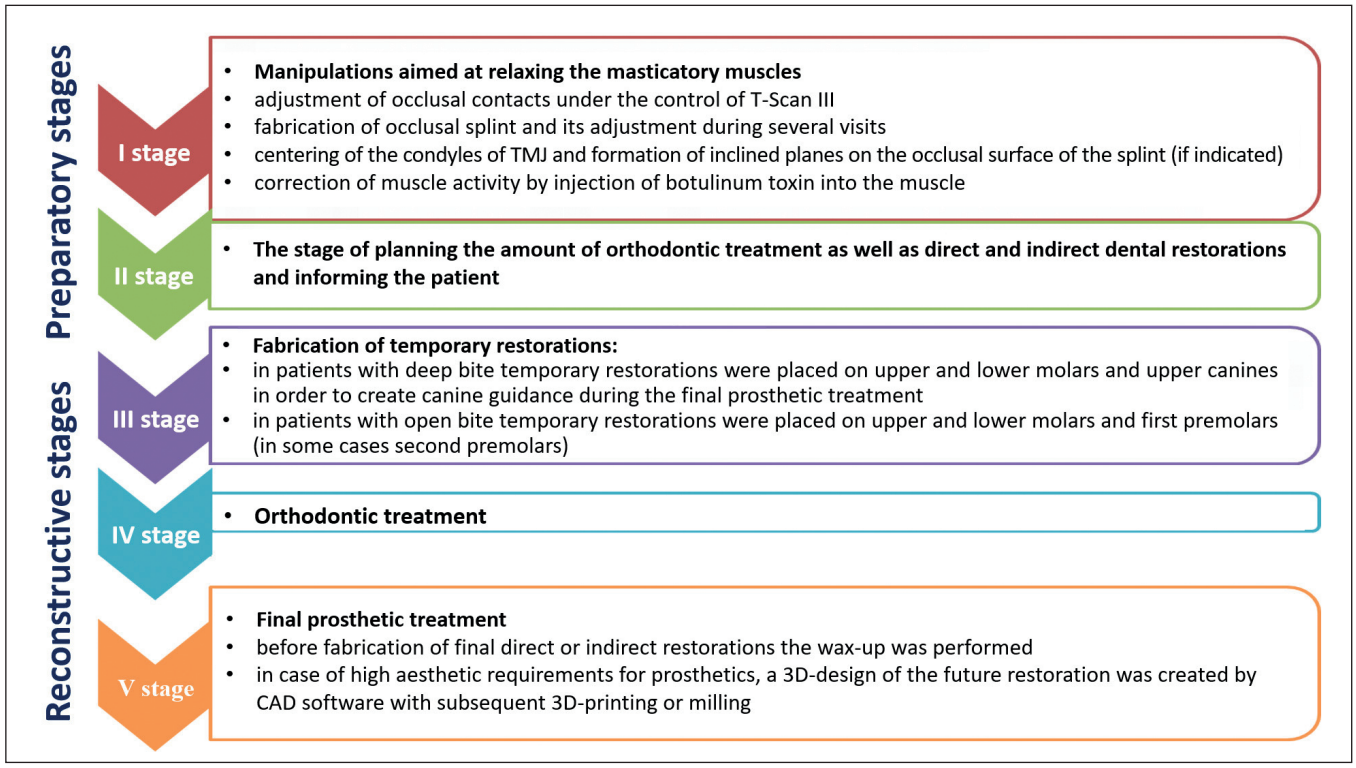

Fig. 1. Algorithm of complex rehabilitation of patients from the I group

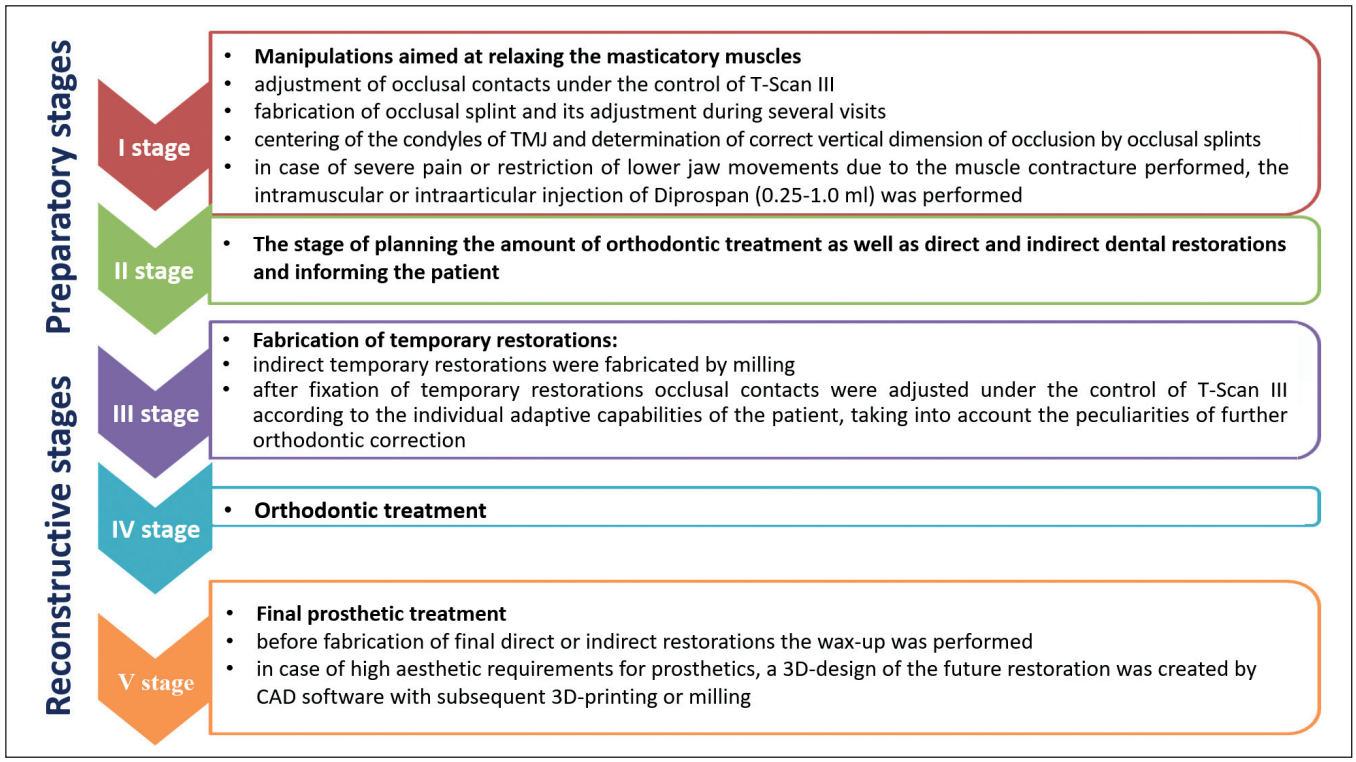

Fig. 2. Algorithm of complex rehabilitation of patients from the II group

MATERIALS AND METHODS

55 patients with iatrogenic occlusal disorders combined with vertical malocclusion aged from 23 to 47 years old (mean age 36.1±5.2 years) including 32 females and 23 males were examined at Dental Medical Center of Bogomolets National Medical University during 2019-2021 years.

The patients were divided into three groups depending on their complaints and clinical manifestations. The first group (n=16) included patients with iatrogenic occlusal disorders complicated by vertical malocclusion who suffered from musculoskeletal dysfunction without pain or TMJ involvement (trismus, lateral pterygoid muscle contracture,

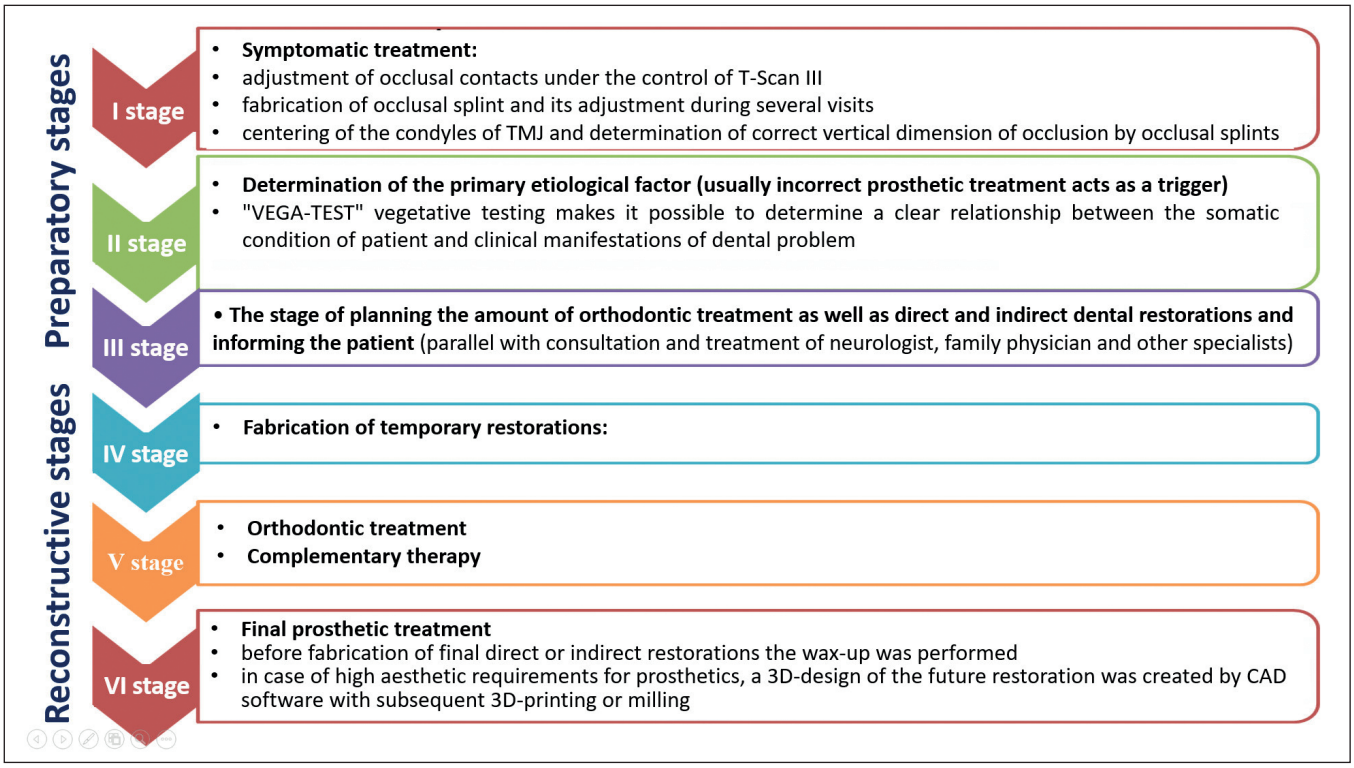

Fig. 3. Algorithm of complex rehabilitation of patients from the III group

bruxism etc.). The second group (n=18) included patients with iatrogenic occlusal disorders complicated by vertical malocclusion who suffered from myofascial disorders and TMJ dysfunction without pain symptoms. The third group (n=21) included patients with iatrogenic occlusal disorders complicated by vertical malocclusion who suffered from myofascial and TMJ dysfunction with orofacial pain symptoms.

All patients before and 6 months after the treatment underwent the following examination: conventional clinical evaluation; usage of additional and laboratory methods such as X-ray (panoramic, lateral cephalometry, CBCT), analysis of dental rows interrelations of dental casts mounted in Artex CP semi-adjustable articulator (Amann Girrbach AG, Austria), electromyography of masticatory muscles with BioEMG III electromyograph (BioRESEARCH Associates, Inc., USA); T-Scan III Digital Occlusal Analysis (Tekscan, Inc., USA).

Considering the variety of symptoms and manifestations, we used an interdisciplinary approach in the treatment of patients of all III clinical groups, which allowed to systematize and optimize the sequence of diagnostic and treatment stages. In particular, while planning orthodontic treatment, we followed the stages of all interventions, both dental and those aimed at correcting the general somatic condition of each individual patient.

Our algorithm of complex rehabilitation included:

A. Measures aimed at eliminating of local dental factors consisted of:

I. Preparatory stages:

1) the use of occlusal splints with the aim to find a correct position of the mandible, which enables elimination of symptoms and relaxation of masticatory muscles;

2) application of physical therapy such as laser therapy, electrophoresis;

3) in case of presence of neurogenic symptoms, the consultation by neurostomatologist is mandatory with further proper treatment if needed;

4) carrying out of professional hygiene and therapeutic rehabilitation of the oral cavity;

5) carrying out of surgical treatment, in particular the removal of wisdom teeth or vestibuloplasty, frenuloplasty, frenectomy or frenotomy of maxillary labial frenulum, mandibular labial frenulum or lingual frenulum according to the indications; sometimes it is possible during the stages of orthodontic treatment.

II. Restorative stages:

1) carrying out of diagnostic wax-up in order to plan the amount of dental interventions;

2) transfer of designed occlusal interrelations into temporary restorations fabricated according to the indications;

3) orthodontic treatment;

4) fabrication of permanent restorations according to the indications.

B. Measures aimed at eliminating factors from other organs and systems which include the involvement of specialists from other fields of medicine such as endocrinologist, gynecologist, immunologist, neurologist, psychotherapist, vertebrologist.

According to clinical peculiarities, we have developed different algorithms of complex rehabilitation for each clinical group (Fig 1-3).

RESULTS

In all 3 groups of patients we observed complete disappearance or significant reduction of complaints and symptomatic manifestations after 6 months of complex rehabilitation.

Occlusal equilibration and normalization of balance of occlusal contacts under the control of T-Scan III Digital Occlusal Analysis was achieved in all patients during the initial preparatory stage and was controlled and maintained during all further stages of complex rehabilitation.

Positive dynamics in change of position of TMJ condyles (verified by CBCT) after using of occlusal splints was observed in all patients and served as a marker for deciding on the transition to next stage of dental treatment, including orthodontic correction.

Also, implementation of our algorithm of complex rehabilitation resulted in normalization of bioelectrical activity of masticatory muscles according to electromyographic examination and, which is one of the most important criteria for the transition to the next stage of the treatment and changing temporary restorations with permanent ones.

DISCUSSION

It was found that one of the most debatable issues in complex rehabilitation of patients with iatrogenic occlusal disorders in combination with malocclusion is determining the sequence of diagnostic and treatment manipulations [7]. It is often unclear, how and in what sequence to perform diagnostic and treatment manipulations, specialists in which branches of medicine should be additionally involved in treatment and what dental equipment should be used at different stages of diagnostics and treatment.

The rehabilitation of patients with occlusal disorders combined with vertical malocclusion should not be limited to orthodontic treatment, but must be based on the interdisciplinary approach. It is necessary to combine elimination of the cause of dysfunction and dental deformity development, usage of orthodontic appliances, surgical correction of structural disorders of the stomatognathic system and restorative or prosthetic rehabilitation when needed [2, 7, 8].

The treatment of muscular dysfunctions traditionally includes the use of analgesics, blockades of the motor branches of trigeminal nerve, the use of occlusal splints and other appliances. However, a unified approach in many cases does not lead to success. Often the short-term effect is followed by exacerbation with increased pain and limited mouth opening [2, 3, 7].

Considering great variety of symptomatic manifestations and different dental status of patients, we paid great attention to the individualization and personification of complex treatment in each case. It was also important to achieve a close cooperation of specialists in various fields of dentistry and medicine in general. In order to avoid overdiagnosis and delay of treatment stage, the consultation with a specialist in a particular field was appointed after careful study of the anamnesis and analysis of results of additional methods of examination.

Considering the long duration and high cost of orthodontic interventions, we tried to find ways to solve the problem of achieving maximum functional and aesthetic result without harming the patient's health and prevent recurrence after orthodontic correction. To do this, we have developed an algorithm of complex treatment for each clinical group of patients. It considers the examination and treatment of the patient by a dentist not just as an object for local interventions, but as a whole organism.

Any orthodontic and prosthetic interventions should be performed as an accompaniment against the background of treatment of general somatic pathology, which can be dominant in the development of symptomatic manifestations as well as just support it. All dental manipulations that are invasive can be performed only after achieving of relative remission [7]. This will help to increase the quality of orthodontic care, reduce treatment time and avoid mistakes.

CONCLUSIONS

Our study showed that the proposed algorithm of complex rehabilitation of patients with iatrogenic occlusal disorders combined with vertical malocclusion, which provides a multidisciplinary and individualized approach, improves the efficiency of orthodontic treatment of such patients and significantly reduces the duration of treatment in all 3 groups. This sequence of diagnostic and treatment measures gives the best opportunities for the patient to achieve maximum functional and aesthetic result.

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REVIEW ARTICLE

LEGAL REGULATION OF HUMAN ORGANS AND TISSUE TRANSPLANTATION: INTERNATIONAL AND FOREIGN EXPERIENCE

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ABSTRACT

The aim: To highlight and analyze the international aspect of the legal regulation of human organs and tissues transplantation, as well as foreign experience of regulation in this area within the relevant national legal systems (for example, US, Germany, Israel, Switzerland, Spain, Argentina, China and India).

Materials and methods: Methodologically, this work is based on the system of methods, scientific approaches, techniques and principles with the help of which the realization of the research aim is carried out. There have been applied universal, general scientific and special legal methods.

Conclusions: Thus, the efforts of the international community and the countries under study in the field of transplantation are focused on a wide range of important issues that need to be regulated. The international legal regulation of transplantation covers the results of the activities of such international organizations as the World Health Organization, the Council of Europe, and the World Medical Assembly. The acts adopted by them are mainly of a recommendatory nature (with the exception of some Council of Europe acts on trafficking in human organs) and are addressed primarily to States, offering guidelines and standards for the legal regulation of transplantation within national legal orders. Therefore, the issues of donation and transplantation of human organs and tissues in the respective states are determined by special legislative acts, which comprehensively regulate the procedure for their transplantation.

KEY WORDS: transplantation, donor, donation, recipient

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INTRODUCTION

Decades of experience in transplantation have demonstrated the importance of this institution in medicine, as well as the need for its proper regulation at the level of international and national legislation. The increasing attention of the international community and modern states to the legal regulation of transplantation of human organs and tissues is caused by several main factors: first, the acute shortage of donor organs and human tissues, in which the needs of all patients are not de facto met; secondly, the motivation to protect the rights of participants in the transplant process, compliance with ethical requirements; thirdly, a significant intensification of illegal activities in this area, the development of human organs trafficking, which indicates the need for effective measures to combat such acts.

THE AIM

The aim of the work is, therefore, to study and analyze the international aspect of the legal regulation of human organs and tissues transplantation, as well as foreign experience of regulation in this area within the relevant national legal systems (for example, US, Germany, Israel, Switzerland, Spain, Argentina, China and India).

MATERIALS AND METHODS

The study required the author to use a number of methods – both general and special. Among general scientific methods the following ones were applied: methods of analysis, synthesis, generalization, formal-logical, structural-systemic and some others, special methods were: logical-semantic, formal-legal, historical-legal and the method of comparative analysis. In particular, logical-semantic and formal-legal methods were used in the disclosure of the concept of "transplantation" in the legislation of some foreign countries; historical-legal method was used to determine the dynamics of the historical aspect in the development of legal relations regulation in the field of transplantation; the method of comparative analysis directed the author towards a comparative analysis of legislation on the donorship and transplantation of human organs and tissues within different national legal systems.

REVIEW AND DISCUSSION

First of all, we will provide some explanations of the concept "transplantation". For example, the Oxford Dictionary considers transplantation as the process of transplanting to the recipient organs or tissues taken from a donor [1]. The World Health Organization (WHO) defines transplantation as the transfer of human cells, tissues and organs from donor to recipient to restore body functions [2]. The Law of Ukraine "On the use of transplantation of body materials to humans" contains an interpretation of transplantation as a special method of treatment, which consists in transplant-

ing human body material from a donor to a recipient, and aims to restore human health [3]. Researchers attribute the eligibility to use transplantation (from both a living and a deceased donor) and its further consequences for health to an individual who needs a donor or to an individual who is a donor, as donation can lead to adverse consequences for both participants in these relations [4]. It is generally accepted to divide transplantation into several types: 1) autotransplantation – transplantation of organs and tissues within one organism; 2) allo- (homo) transplantation – transplantation of organs and tissues from one person to another; 3) xeno- (hetero) transplantation – transplantation of organs and tissues from one species to another (for example, from animal to human) [5].

INTERNATIONAL ASPECT OF THE LEGAL REGULATION IN HUMAN ORGANS AND TISSUES TRANSPLANTATION

The need and importance of the transplant procedure, including its purpose, as well as the progressive development of modern medical technologies and the factor of dynamic activity in the field of illegal organs and tissues transplantation, cause feedback from international governmental and non-governmental organizations, after which documents are given a new legacy which determines principles and framework of transplantation activities and counteract their illegal conduct. Therefore, the international legal support for transplantation covers the functioning of the Council of Europe, WHO, the World Medical Assembly and other international organizations.

Therefore, at the level of the Council of Europe, first of all, it is worth paying attention to the Convention on Human Rights and Biomedicine of 1997, which, among other things, establishes fundamentally important conditions for transplantation, including the consent of the recipient (Articles 19-20),and also prohibits the use of the human body and its parts for financial gain (Article 21), as well as determines the rules forb the use of the removed part of the human body (Article 22) [6]. In 2002, the Additional Protocol to the Convention on Transplantation of Human Organs and Tissues was adopted. This act establishes the basic rules and standards of transplantation, informing issues, participants protection in this procedure, confidentiality issues, the prohibition of financial benefits from organ and tissue transplantation and other aspects [7].

In addition to the above-mentioned Convention, it is necessary to mention such important documents of the Committee of Ministers of the Council of Europe as: The 1978 Resolution on the Harmonization of the Legislation among Member States on the removal, transferring and transplantation of body materials is an impulse to the Coucil of Europe member states to bring their national legislation in accordance with rules of this Resolution(the rules on the removal, transferring and transplantation of body materials extracted or collected for therapeutic or diagnostic purposes [8]; The Xenotransplantation Recommendation of 2003, which presents the principles and issues aimed at protecting patients and medical staff during the xenotransplantation procedure, as well as the animals used in it [9]; Recommendation "On Donor Registers" of 2003 – defines the main issues of the donors national register, which should provide ample opportunities to the person to formulate their will (decision) regarding transplantation [10]; The Recommendation «On Organ Trafficking» (2004) contains a list of measures to be taken to combat trafficking of human organs [11]; Recommendation "On Quality Improvement Programs regarding organs donorship" (2006) contains the measures to be taken to improve the quality of organ and tissue donorship at hospitals conducting transplant procedures [12]; The 2006 Recommendation "On the Preconditions, Functions and Responsibilities of the National Transplant Organization" provides issues of the legal status of the national transplant organization, which must be established at the each state level [13].

Among the important documents of the Council of Europe protecting the principles of transplantation and responsibility for trafficking of human organs and tissues, the following ones should be mentioned – the Convention against Human Trafficking (2005) [14] and the Convention against Human Organs Trafficking (2015) [15]. They contain regulations on measures preventing and combating trafficking of human beings (body organs), criminalization and penalization of human trafficking (human organs), protection of the victim rights, ensuring effective investigation, and international cooperation in this area.

In addition, the leading role in the international legal regulation of transplantation, of course, belongs to the WHO. Its most important document is the Guidelines for the Transplantation of Human Cells, Tissues and Organs, adopted at its 63rd session in May 2010. This document contains a Preamble and 11 guidelines, the role of which is to define an orderly, appropriate basis for procedures for the obtaining and transplantation of human cells, tissues and organs for therapeutic purposes in compliance with ethical principles. These regulations do not apply to the transplantation of germ cells, ovarian tissues or embryos for reproductive purposes, as well as to blood and its components transfusion [16]. Among the WHO resolutions on human organs and tissue transplantation are the following ones: Resolution WHA57.18 (2003), which appeals to countries to: effectively supervise the procurement, processing and direct transplantation of human organs and tissues; take measures to harmonize the world transplantation practices; take measures to protect the poorest and most vulnerable strata of the population against the so-called "transplant tourism" and the sale of human organs and tissues; to support international cooperation and coordination in xenotransplantation performance [17]; Resolution WHA63.22 (2010), which provides recommendations to states on: promoting the development of altruistic voluntary and unpaid organ and tissue donation, raising public awareness of these issues; promoting a system of transparent and equitable organs and tissues distribution, as well as equal access to transplantation services; maximizing donations

from deceased donors, protecting the health and well-being of living donors, etc. [18].

Therefore, a number of documents regulating the transplant procedure have been adopted at the level of the World Medical Assembly as an international non-governmental organization. In particular, they include: Declaration on Human Organ Transplantation(1987) which contains recommendations for physicians involved in transplantation, their behavior and interaction with all its participants [19]; Regulations on fetal tissue transplantation (1989) defines the list of conditions under which the use of fetal tissues (aborted fetal tissues) for transplantation is possible [20]; The 1985 Regulation on Trafficking of Live Organs is directed against the sale of human organs for transplantation, as well as the adoption of the necessary measures to prevent the commercial use of human organs [21]; The 1994 resolution on the attitude of doctors to the problem of human organ transplantation adheres to national medical associations to follow the principles set out in the 1987 Declaration on Human Organ Transplantation and to bring to justice doctors who have committed violations.

In our opinion, it is relevant to focus on another international document, namely: the Istanbul Declaration on Transplant Tourism and Organ Trade, adopted by experts from the Association of Transplantologists and the International Association of Nephrologists in 2008. It contains a Preamble, some terminology new to international law, key positions on transplantation, as well as suggestions to increase the effectiveness of post-mortem donation, the fight against transplant tourism, human organ trafficking, and the protection and safety of living donors. The significance of this document lies in professional attitude of the international expert community towards combating transplant tourism and organ trade, which can be used by governments around the world as a guide for the development of national legislation [23].

We now turn to the analysis of the legal regulation experience concerning transplantation of human organs and tissues in such foreign countries as the United States, Germany, Israel, Switzerland, Spain, Argentina, China and India.

USA

In October 1984, the United States adopted the National Transplant Act, the result of which was a creation of a task force for organ transplantation, aimed to study the main directions of organ donorship development. In the same year, the United Network for Organ Sharing was formed to oversee the national registration of donors and the procedure for receiving organs from recipients. In 2006, the United States approved the Unified Act on Anatomical Gift. An anatomical gift is a gift of all human body or its part after the donor's death for transplantation or scientific purposes. The testamentary form of this gift implementation was provided. However, in 2007 the testamentary form of gift was replaced by a simple mark in the driver's license. The reason for this simplification was a significant shortage of donor organs and tissues in the country [24]. Lifetime donors in the United States are divided into three types: genetically related; independent (friend, husband (wife), other person emotionally connected to the recipient); altruistic (persons who donate their organs and tissues to an anonymous candidate on a waiting list) [25]. The Transplant Act prohibits trafficking of human organs by imposing a fine of up to $ 50,000 or imprisonment for up to five years for the crime.

GERMANY

In Germany, the Law on Organ Donation, Collection and Transplantation of 1997 is in force at the federal level. This act broadly regulates the procedure of organ and tissue collection from dead and living donors, the status and activities of donor tissue banks, research laboratories, transplant centers, coordination centers and other institutions involved in transplantation. There is a strict ban on the threat of criminal liability for trafficking in human organs or tissues [27]. In general, transplantation is possible under German law only with the consent of the donor. In this case, in the absence of such consent or with a written objection, the doctor may apply to the immediate family of the deceased, following two stages. In the first stage, the doctor finds out if the donor has applied for a donation in his lifetime. In the second one, the doctor asks the relatives of the deceased if they agree to transplant his organs. When making a decision, it is assumed that the relatives of the deceased must respect and be able to predict his will. In practice, a potential donor is maintained in a stable state after the establishment of brain death with the help of appropriate drugs. During this time, the doctor conducts a conversation with the relatives of the deceased, involving the presence of the transplant coordinator. It is believed that due to the professionalism of the transplant coordinator, the chances of obtaining consent for transplantation are significantly increased [28].

ISRAEL

The Law on Anatomy and Pathology has been in force in Israel since 1953. Among other things, it regulates the body use of the deceased for research for medical purposes, as well as patient treatment and his life rescue. The Law also determines the cases of consent or refusal for organs removal, the procedure for notifying the relatives of the deceased donor, the procedure for the doctors conduct in these circumstances. Interestingly, this piece of legislation presupposes three levels of priority in the organs and tissues distribution: first of all, the advantage is given to people whose relatives have already donated their donor organs after death; then come people registered as donors for at least three years; and at last people whose relatives are registered as donors for at least three years [29].

In its turn, in 2008 the Law on Organ Transplantation was adopted, which broadly regulates the legal, organizational and ethical aspects of organ donation, transplantation and

distribution in the country. Organ trafficking is a criminal offense leading to three years of imprisonment and a large fine. As an incentive for altruistic organ donation, the Law on Transplantation provides for various types of compensation, namely: compensation for losses during forty days based on the average income of the donor for the last three months (for the unemployed ones the minimum wage is taken into account); transport costs (all trips of the donor and his relatives to and from the hospital); for medical care, in case of disability and life insurance (if insurance policies and relevant receipts are provided); the cost of five psychological consultations and treatment (with receipts) [30].

SWITZERLAND

The peculiarity of the legal relations regulation in the field of transplantation in Switzerland first of all lies in the fact that the fundamental regulations of such relations are appointed to the Federal Constitution of the Swiss Confederation. It contains Article 119 "Medical Transplantation", which highlights the need to protect human dignity, privacy and health in transplantation procedures, establishing a fair organs distribution; free donation of human organs, tissues and cells and prohibition of human organs trafficking [31]. Therefore, at a special normative level, in 2001 the Union Law on Organs, Tissues and Cells Transplantation was adopted, the norms of which provide for: the powers division between federal and cantonal bodies in the field of transplantation; licensing procedure; various legal regimes of human organs, animal organs and stem cells transplantation; mechanism of legal protection in this area; special legal regimes for Swiss citizens (both donors and recipients); issues of criminal and administrative liability [32].

SPAIN

First of all, it should be noted that the Spanish model for organ donation is nowadays recognized by the WHO as the best in the world. Its main principles are systemic and organizational approaches to the donation process at both the institutional and regulatory levels.

The key legal acts on transplantation in Spain today are: the 1979 Law "On Organ Collection and Transplantation" and the 2012 Decree of the Ministry of Health and Social Services "On the activities of obtaining, clinical use and territorial coordination of human organs intended for transplantation and setting quality and safety requirements". Thus, the first of these acts (small in size) is aimed at determining the basic principles of activities in the field of transplantation, in particular: its altruism, ie the absence of a commercial element; carrying out this procedure exclusively for therapeutic or scientific purposes; identification of requirements for a living donor (reaching the age of majority, free and conscious consent, warning of the consequences of transplantation); the possibility of removing organs from a deceased donor only after the statement of his death, etc. [33]. The decree of the Ministry of Health and Social Services, first of all, contains the understanding of transplantation as a process aimed at restoring certain functions of the human body by replacing a diseased organ or its function with another from a living or dead donor. It regulates the protection of donor and recipient rights; the procedure for obtaining, transporting and exchanging organs; activity of transplantation centers; issues of quality and safety of organs; coordination of activities in this area by authorized authorities, etc. [34].

In 1989, the National Transplant Organization was established in Spain to coordinate all donation and transplantation issues. There is a network of organizations that deal with this procedure at the national, regional (seventeen focal points) and hospital (hospitals where transplantation is possible) levels. The main link in the Spanish system is the transplant coordinator, an intensive care physician who is appointed by each hospital (its management and reports to it) and is designed to facilitate the early detection and referral of potential donors [35]. Spain is characterized by the number of organ and tissue transplant operations – more than one hundred and four per one million population. There is also a government Quality Assurance Program, aimed at conducting ongoing audit of mortality, donor audit and donor capacity of hospitals [36].

It also should be added that since 1991, more than fifteen thousand specialists have been trained in organ donation. These are not only doctors who are directly involved in transplant procedures, but also specialists whose activity is related to organ donation: resuscitation, emergency care, stroke department, etc. [37].

ARGENTINA

At the federal level, the legal regulation of transplantation activities in Argentina has long been ensured by the 1993 Law on Transplantation of Human Organs and Tissues. It provided for the possibility of transplantation only if other methods and possible means have already been used or are insufficient or inappropriate, or if it is a therapeutic alternative for the patient's health. It was necessary to adhere to the following principles: respect for human dignity; autonomy of the will of the person; justice in the organs distribution of and donors tissues; equal access to transplantation; adherence to ethical principles in research activities; voluntariness and altruism. Donors and recipients or their legal representatives had to give voluntary informed consent for the transplant. In addition, it was assumed that the donor – an able-bodied adult – could confirm or deny his will for transplantation, limit it to the provision of only certain organs or tissues, and express the purpose of donation – for specific people, for educational or research purposes [38].

It should be noted that a few years ago there was a situation in Argentina that led to significant legislative changes in the field of transplantation, as a result of which the 1993 Law expired. This is the case of Khustina Lo Cane, who needed a transplant at the age of twelve due to heart disease. When she was included in the waiting list in 2017, she decided to fight not only for her own life, but also for the development of the donation system in the country. At her request, her

parents organized a campaign "Multiply yourself by 7" on the social network, the main content of which was that each person can save seven more after their death. In the end, the girl did not wait for a transplant, because her heart stopped. However, her example inspired not only society but also legislators. If previously the consent of the donor or the consent of his relatives was required to obtain an organ for transplantation, then under the new law called by the girl's name ("Law of Khustina" of July 26, 2018), anyone who did not record refusal in life (i.e. all adult citizens of Argentina). In addition to novelties at the legislative level aimed at radically simplifying transplant procedures, the number of people wishing to become donors has increased significantly since the death of Khustina Lo Cane [39].

CHINA

Starting from the 1970s, China developed the practice of removing organs from prisoners who had been sentenced to death without their consent or the consent of their families. Under the 1984 Provisional Regulations on the Use of Dead Bodies or Organs from Convicted Criminals, organs were confiscated from executed prisoners provided that their bodies were not required, or the prisoner voluntarily agreed to the donation or his family agreed. In this case, the removal of organs had to be strictly confidential. Under these circumstances, in many cases, families of prisoners received only the results of cremation without reporting what had happened to their relatives. Later, after several decades of human rights violations and after the adoption in 2007 of the Regulation on Human Organ Transplantation, China's national transplant system has been reformed. It is currently assumed that human organ transplantation requires the donor's written consent. In 2013, within the framework of the National Congress on Transplantation, a unanimous decision was made by experts on the inadmissibility of trafficking in the organs of prisoners sentenced to death. Prior to that (in 2010), the Chinese government recognized organ trafficking as a crime, while launching a voluntary donation program.

With regard to the established order of donor organs distribution, the following principles apply in China: 1) compliance with medical needs; 2) the hospital has the right on the basis of a medical opinion to refuse to accept organs unsuitable for transplantation; 3) avoiding "waste" of organs in order to maximize the chances of patients for transplantation and increase the efficiency of distribution; 4) optimization of compliance with the quality of organs, as well as improving the postoperative health and recipients life standards; 5) fair distribution of organs and reduction of the impact on this process of physical, pathological and geographical differences; 6) regular review of organ allocation policy [42].

INDIA

The law on transplantation in India was adopted in 1994. It regulates the following main aspects of the relevant legal relationship: the procedure for removing organs from deceased people, from living donors, the status of hospitals and health workers, as well as the issue of liability for illegal transplantation. According to this Law, transplantation is defined as the transplantation of any human organ from a living or dead person to another living person for medical purposes. It has been established that any person may consent to the removal of his or her body after death in the presence of two or more witnesses. Such a permit can be specified in the driver's license. If the person did not provide it during his lifetime, another person who legally disposes of the deceased body may consent to the removal of organs, provided that none of the close relatives of the deceased objects to this. An important aspect of organ donation after death is the certification of brain death by a board of medical experts [43].

The Indian Transplant Act separately regulates the procedures when the donor is a relative of the recipient and when the donor is a third party. Thus, in the first case, the patient's relative submits an application for donation to the competent authority (the director of the hospital or a special commission of the hospital). If the decision is made by the commission, a conversation is held with the donor, recipient and their relatives, on the basis of which a decision is made on permission for transplantation. Interestingly, all actions are subjected to video recording. In the second case – when the donor is a third party – a two-level inspection of the recipient, donor and their relatives is performed. Initially, it is carried out by a special commission of the hospital, and then – by the State committee that also interviews the recipient, the donor, and their relatives to ensure that there is no commercial element of the relationship between the donor and the recipient.

CONCLUSIONS

Thus, the efforts of the international community and the countries under study in the field of transplantation are focused on a wide range of important issues that need to be regulated. The international legal regulation of transplantation covers the results of the activities of such international organizations as the World Health Organization, the Council of Europe, and the World Medical Assembly. The acts adopted by them are mainly of a recommendatory nature (with the exception of some Council of Europe acts on trafficking in human organs) and are addressed primarily to States, offering guidelines and standards for the legal regulation of transplantation within national legal orders. Therefore, the issues of donation and transplantation of human organs and tissues in the respective states are determined by special legislative acts, which comprehensively regulate the procedure for their transplantation. The exception here is Switzerland, whose Constitution formulates the key principles of its implementation. The main attention in the special normative act is focused on more detailed aspects: determination of the procedure for giving consent to organ and tissue donation; the legal status of hospitals that perform

transplant activities, as well as transplant coordinators; ensuring fair distribution of donor organs; protection of the rights of donors and recipients; fixing the ban on transplantation on a commercial basis and establishing criminal liability for trafficking in human organs. The Israeli experience, among other things, demonstrates how the state can encourage altruistic donations from donor elements (to cover the costs of medical care, loss of earnings, insurance, etc.). The practice of human organ and tissue transplantation procedures in China demonstrates the importance of donor consent for organ and tissue transplantation, as well as the need to ensure fair and efficient distribution. The Indian Transplant Act sets out the specifics of pre-transplant preparations (depending on whether the recipient is a relative of the recipient or an outsider), which aim to eliminate the commercial factor in the appropriate form of medical intervention. To this we will add that among the countries analyzed by us, the experience of Spain, whose model of organ donation is recognized by the WHO as the best in the world, deserves special attention. Its main principles are systemic and organizational approaches to the donation process at both the institutional and regulatory levels. In particular, in Spain, a network of focal points has been set up to provide transplant procedures, doctors have been systematically trained, and a government program has been adopted to carry out ongoing audits in the field of transplantation.

And at the very end we state the urgent need for further scientific research on the peculiarities of the legal regulation of human organs and tissues transplantation (in in the context of international and foreign experience), which is obvious based on the Ukrainian state and legal realities. Thus, Ukraine, which has just embarked on the "transplant path", has shown itself quite successfully in this direction over the past few years. First, it should be noted the basic legal act – the Law "On the application of anatomical materials to humans" from 17.05.2018, which was amended accordingly. Secondly, the adoption of the Resolution of the Cabinet of Ministers of Ukraine of 23.12.2020 [45] was an indicator that in Ukraine from January 1, 2021 the Unified State Information System of Organ and Tissue Transplantation de facto started its activity, which stores and accumulates in electronic form information on donors and recipients, as well as on donor organs and tissues. Thirdly, every year, starting from 2019, there is a positive trend in the number of organ and tissue transplant operations performed in our country.

At the same time, in Ukraine in the context of transplantation procedures there are still problematic aspects of legal and organizational nature, among which, for example, experts note: the presence of a "presumption of disagreement" (which should be replaced by a "presumption of consent" as it's applied in a number of foreign countries); lack of transplant coordinators and specialists in the field of transplantation; the complexity of the procedure for posthumous donation, including the lack of donation consent in driver's license; lack of information campaign aimed at encouraging the population to donate.

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REVIEW ARTICLE

COVID-19 AND PRIMARY CARE: POSSIBILITIES FOR INCREASING POSITIVE OUTCOMES

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ABSTRACT

The aim: Determine the most common non-communicable diseases which are associated with an increased rate of moderate and severe COVID-19 infection. Identify the best tools for diagnosing COVID-19 and predicting the deterioration of the disease.

Materials and methods: Publications were processed and analyzed according to the keywords of the topic of work "COVID-19", "non-communicable disease", "obesity", "hypertension", "Comorbidities", "frailty", "diabetes", "chronic obstructive pulmonary disease", "cardio-vascular diseases", "liver diseases", "diagnostic tools", "outcomes" in the databases of PubMed, MEDLINE, Web of Science.

Conclusions: As a result of the analysis, we found that patients with concomitant obesity, diabetes mellitus, COPD, CVD and liver diseases have an increased the risk of severe forms and death from COVID-19.

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

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INTRODUCTION

In 2020, the world was hit by a global pandemic of the SARS-CoV-2 virus, which causes COVID-19. Currently, there is no reliable data on any specific treatment of this disease, and the only method of prevention is vaccination. Despite the fact that the campaign began at the end of 2020, several types and brands of vaccines are available and vaccination is promoted widely, the number of people in the world who have undergone a full vaccination course as of August 2021 is about 1 billion, which is insufficient to create collective immunity [1–3]. Combined with the rise of vaccine hesitancy, the emergence of new strains and the threat of a new spike in the number of infected people, this may mean that the pandemic will continue further and will not be gone soon [4]the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2.

In most countries of the world and in Ukraine in particular, patients seek medical help from family doctors. Therefore, to minimize the spread of the virus and to prevent and timely detect a severe case of the disease, it is important that physicians of first contact have data on vulnerable populations and diagnostic algorithms. Special attention should be paid to the criteria for timely early detection of risk groups requiring hospitalization in order to prevent severe form of the disease.

THE AIM

Determine the most common non-communicable diseases which are associated with an increased rate of moderate and severe COVID-19 infection. Identify the best tools for diagnosing COVID-19 and predicting the deterioration of the disease.

MATERIALS AND METHODS

Publications were processed and analyzed according to the keywords of the topic of work "COVID-19", "non-communicable disease", "obesity", "hypertension", "comorbidities", "frailty", "diabetes", "chronic obstructive pulmonary disease", "cardio-vascular diseases", "liver diseases", "diagnostic tools", "outcomes" in the databases of PubMed, MEDLINE, Web of Science.

REVIEW AND DISCUSSION

Non-communicable diseases and COVID-19 infection have similar risk factors and although infectious and non-communicable diseases differ in the way they spread and how they effect the body, it should not be assumed that they cannot complement and worsen each other's course [5]. As the number of COVID-19 cases increases, a link has been established between comorbid conditions and the severity of COVID-19 infection [6]. One review article published in July 2020 showed that, the most common concomitant diseases observed in patients with COVID-19 ending in death were: obesity (observed in 48% of patients and in 68% of cases ended in death), liver disease (43 and 29%, respectively), chronic obstructive pulmonary disease (COPD, 52 and 20%, respectively), cardiovascular diseases (CVD, 17 and 15%, respectively), diabetes mellitus (58% and

8%, respectively), hypertension (23 and 6%, respectively) [6] mild, or severe pneumonia-like symptoms. COVID-19 patients with diabetes, chronic obstructive pulmonary disease (COPD. In addition, it is noted that patients over 50 years of age are significantly more likely to get infected [7].

Obesity was often observed in patients with COVID-19, which may be due to the fact that the obesity pandemic is currently ongoing. A review study that analyzed and compiled data regarding any links between COVID-19 and an increased BMI and obesity found that obese patients were 46% more likely to have a positive COVID-19 test result, were hospitalized and ended up in the intensive care unit (ICU) 2.13 and 1.74 times more often, and mortality increased by 48% compared to persons without obesity [8].

An analysis of data from 7,606 patients of the American Heart Association's COVID-19 Cardiovascular Disease Registry showed that with an increase in body mass index (BMI), the risk of hospitalization also increased, with patients with third stage obesity having a 26% higher risk of in-hospital death [9]. Obese patients of I, II and III stages were more likely to die in hospital or receive mechanical ventilation of the lungs (by 28, 57 and 80%, respectively) [9]. Currently, it is known that adipocytes produce hormones – adipokines, which have regulatory function and affect energy metabolism. At the same time, their effect on systemic inflammatory diseases is also worth noting, the manifestations of which are enhanced with excessive amounts of adipose tissue in the body. Studies suggest that leptin and adiponectin play a role in inflammatory lung diseases [10]. By intensifying the overall inflammatory reaction of the body, obesity can lead to a more severe course of acute COVID-19. Given that the obesity pandemic is currently underway and the implementation of conditions that adversely affect the physical activity and mental state of the population, which in turn leads to chronic stress, we can assume that the number of obese people will increase. This in turn will increase the frequency of other comorbid conditions, such as hypertension and CVD, creating a vicious circle of deteriorated health [11].

Another frequent condition is diabetes mellitus (DM). A cohort study of the population of Scotland in the first wave of the COVID-19 pandemic showed that out of 2,724 patients with acute COVID-19 and concomitant DM, 1,082 people were hospitalized in ICU, of which 963 died [12]. Compared to the population without concomitant DM, the risk of being transferred to ICU for patients with DM was higher by 39.5% [12].

In addition, in a case-control study of patients with DM and COVID-19, it was found that old age (>60 years), higher levels of alkaline phosphatase (>270 U/L) and urine nitrogen (>=20 mg/dL) were predictors of impaired course and death in these patients [13].

DM is a serious risk factor for many diseases and often leads to a deterioration in the quality of life and a more severe course of disease. DM, especially in the stage of decompensation, causes a chronic inflammatory reaction, increases the risk of infectious diseases and blood thickness [14,15]. Patients with DM had a severe course of COVID-19, and inflammation mediators in combination with viral load caused damage to the pulmonary tissue [16].

It is well known that patients with COPD have an increased risk of respiratory tract infections, which is especially relevant for community acquired pneumonia and influenza. When assessing the impact of COPD on the course of COVID-19, it was found that it also worsens the course of infection. For example, a meta-analisis of data regarding the impact of COPD on COVID-19 up until July 2020 showed that in patients with pre-diagnosed COPD, the risk of death from COVID-19 was 3 times higher compared to patients without COPD [17]. A similar paper, in which the impact of COPD on the frequency of hospitalization, transfer to ICU and death as a result of COVID-19 was analyzed, showed that the presence of COPD in patients significantly increased the risk of their hospitalization, transfer to ICU and mortality from COVID-19 (by 39, 34 and 28%, respectively) [18].

A certain link was also found between liver diseases, liver lesions and COVID-19. Thus, according to a meta-analysis that assessed the link between manifestations of the gastrointestinal tract , liver disease and COVID-19 infection, the most significant symptoms are diarrhea and anorexia, especially in ICU patients. In such patients alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was elevated (higher than 40 and 64 U/L) [19]. Another study assessed the effect of nonalcoholic fatty liver disease (NAFLD) on the course of coronavirus infection and found that the presence of NAFLD in patients history was associated with a worsened course of COVID-19 [20]. In regards to the link between abnormal liver function tests and the course of infection, it was found that in addition to the significant elevation of AST and ALT levels in patients with acute COVID-19, other liver indicators were also increased, namely, total bilirubin (> 22 μmol/L), gamma-glutamyl transferase (>30 IU/L), alkaline phosphatase (>116 U/L) [21]. Higher levels of AST were observed in patients with severe COVID-19, compared to patients with a mild or medium course [21].

Currently, the main factors that cause liver damage in severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) are direct damage to cholangiocytes, cytokine storm and drug-induced liver damage. It is assumed that drug-induced liver damage plays the most important role. During hospitalization, most patients with acute COVID-19 had a deterioration in liver performance. This was especially true for elderly patients [22]there have been more than one hundred million confirmed cases of coronavirus disease 2019 (COVID-19.

CVD rank first among causes of death worldwide. Obviously, this group of diseases will affect the course of infectious diseases, including acute COVID-19. In the course of a meta-analysis that examined CVD burden among COVID-19 patients showed that among this group of diseases, acute myocardial infarction, heart failure and coronary artery disease were associated with a greater risk of death with COVID-19 (in 13.29, 6.72 and 3.78 times higher respectively) [23]. In addition, patients with concomitant CVD, namely arrhythmia, acute myocardial infarction, coronary artery disease and hypertension, had a higher risk of getting requiring treatment in ICU compared to patients without concomitant pathologies (in 7.03, 15.58, 2.61 and 1.95 times, respectively) [23].

Special attention should be paid to older people and with frailty. COVID-OLD study in the Netherlands showed that mortality of COVID-19 patients over 70 years of age was 38%.

At the same time, frailty was an independent predictor of a severe course of COVID-19, despite the fact that such patients had previously experienced less pronounced symptoms [24]. In addition, a meta-analysis of the relationship between the clinical frailty score (CFS) and COVID-19 assessment showed that an increase of 1 point on the CFS scale increased the risk of death by 12% [25].

It is known that persons of the older age group (>50 years) are more likely to suffer from chronic diseases of various origins [26]. This is due to the peculiarity of low intensity systemic inflammation at this age, without clinical symptoms of inflammation [27]. In addition, the gradual depletion of T-cell immunity and a general decrease in immune function, as well as frailty, put this group at a disadvantage not only in relation to COVID-19, but also other infectious and non-communicable diseases. The combination of these factors may play a role in the worsened course of COVID-19 in this age category, the risk of death and the development of residual symptoms after the acute phase of the disease [28]. Taking into account the increasing number of elderly people in the world, accompanied by the simultaneous growth of people with frailty, the presence of a convenient clinical method for assessing the severity of this condition, which is CFS, enables physicians to manage such patients more carefully and recommend more intense healthcare options in order to prevent the deterioration of their condition [29].

Among the prognostic indicators of the adverse course of COVID-19, d-dimer is worth noting. At the beginning of the pandemic, a cohort study found that d-dimer levels above normal ranges during hospitalization were associated with a higher risk of in-hospital mortality [30]2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19. A meta-analysis of the link between d-dimer levels on admission and the severity of the disease and risk of death in COVID-19 showed that d-dimer levels in non-survivors were significantly higher compared to survivors (weighted mean difference was 5.32 mg/L) [31]. In addition, levels of d-dimer above normal limits were strongly correlated with a higher risk of severe course of the disease and death (1.58 and 1.82 risk ratios respectively) [31].

An important component of COVID-19 management at the primary level is its reliable diagnosis and prognosis of a deteriorating course of the disease. One review comparing the sensitivity and specificity of polymerase chain reaction (PCR) testing and computer tomography (CT) scans showed that CT had sufficient specificity (up to 98%), but low sensitivity (up to 25%). The main diagnostic criterion for COVID-19 infection was the consolidation of the opaque area with smoothing the edges of the bronchus and blood vessels (the so-called "ground-glass opacification"). PCR showed sensitivity at 60-71%, but this test gives many false negative results [32]the most appropriate approach to control this infection is to quarantine people and isolate symptomatic people and suspected or infected cases. Although real-time reverse transcription-polymerase chain reaction (RT-PCR. A meta-analysis of data on the sensitivity and specificity of radiological diagnostic methods of COVID-19 showed that the total sensitivity and specificity of chest CT is 87.9% and 80%, respectively. For chest X-ray, these figures were 80.6 and 71.5%, respectively, and for lung ultrasound – 86.4 and 54.6%, respectively [33].

One retrospective study which analyzed most common findings in COVID-19 patients in relationship to duration of infection found that chest CT changes were more frequently seen in patients 3-5 and 6-12 days after symptoms onset, and 44% of the patients had abnormal CT-scan findings at 0-2 days after onset [34]chest CTs of 121 symptomatic patients infected with coronavirus disease-19 (COVID-19.

CONCLUSIONS

As a result of the analysis, we found that patients with concomitant obesity, diabetes mellitus, COPD, CVD and liver diseases have an increased the risk of severe forms and death from COVID-19. Therefore, primary care physicians and doctors of first contact, when treating patients with these conditions in the presence of a positive PCR test for COVID-19, regardless of the presence of clinical symptoms at the time of referral, recommended to preform the following set of examinations: chest X-ray or chest CT, d-dimer (normal range (NR) – <0.5 g/L), ALT (NR <40 U/L), AST (NR <40 U/L), total bilirubin (NR – < 22 μmol/L), alkaline phosphatase (NR – <116 U/L), urine nitrogen(NR – <=20 mg/dL). If a patient has any abnormalities detected during radiologic studies and/or any of the aforementioned laboratory signs higher than their respected upper limit, we recommend transferring these patients to inpatient treatment for further evaluation and prevention of severe and lethal outcomes.

Special attention should be paid to persons older than 60, because of higher risks of severe infection and death, especially in the presence of signs of frailty. In such patients, in addition to the above examinations, we recommend evaluating them on the CFS scale. If a patient scores 4 (vulnerable) or higher, you should be consider referring them to inpatient treatment to prevent rapid deterioration of their health status due to COVID-19.

Objectively, in Ukraine X-ray is much more affordable and available, especially in rural and mountainous regions, in addition, compared to CT, which is several times more expensive. Given this, as well as a slight difference in the sensitivity and specificity of these methods, we recommend using chest x-ray as a routine method in COVID-19 patients.

We believe that such measures lead to a reduced risk of developing severe forms, as well as mortality from COVID-19 in patients from appropriate risk groups.

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REVIEW ARTICLE

ESSENCE OF SOMATIC HUMAN RIGHTS IN THE PROCESS OF BIOMEDICAL RESEARCH

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ABSTRACT

The aim: To study the constitutional and legal principles and the influence of various factors on the mechanism of realization of somatic rights in the process of biomedical research.

Materials and methods: Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of somatic human rights among other human and civil rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main stages of the formation of biomedical research with human participation were identified.

Conclusions: The historiography of somatic human rights in biomedical research in a broad sense is a field of scientific knowledge. Studies the development of constitutional and legal science and its patterns; in the narrow sense, it is a set of works on various problems of the history of modern constitutionalism, human rights, the influence of religion on human rights and the mechanism of their implementation and protection in a certain historical period.

KEY WORDS: human rights and freedoms, fourth generation human rights, somatic human rights, historiography, legal doctrine, medicine

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INTRODUCTION

In order to create a reliable modern scientific foundation for understanding the essence of somatic human rights in the process of biomedical research, it is advisable to digress into the specifics of the study of a legal issue of constitutional and legal principles of consolidation of individual somatic rights. previous and current legislation. This will highlight certain trends in the development of both legal doctrine and rule-making activities, the result of which is a radical improvement of current legislation of Ukraine, including codified content, to outline certain issues while clarifying ways to solve them in different historical periods. to avoid negative in the future and borrow positive experiences.

THE AIM

The aim is to study the constitutional and legal principles and the influence of various factors on the mechanism of realization of somatic rights in the process of biomedical research.

MATERIALS AND METHODS

Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of somatic human rights among other human and civil rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main stages of the formation of biomedical research with human participation were identified.

REVIEW AND DISCUSSION

Historiographical analysis as a scientific method of historical research, L. Berezivska rightly points out, has become widespread in historical and legal research. Today, historiography in historical science has become a separate scientific field and is included in the list of disciplines studied by future historians. At the same time, the application of the historiographical method in historical and legal works is accompanied by a number of problems: unpreparedness of researchers to apply the historiographical method, as the vast majority of them have no historical education; misunderstanding of the importance and necessity of historiographical analysis; the absence of a historiographical section in some dissertations, which reduces the probability of novelty of the study, etc. It should be noted, the scientist writes, that historiographical analysis allows to identify unexplored or little-studied scientific problems, to concentrate research efforts around them, provides relevance and theoretical significance of research, in addition, the application of this method is a manifestation of researcher culture. Historiographical analysis, which involves the study of historians in the field of law, differs from source analysis, which focuses on primary sources[1,p. 5].

Creating a historiography of any field of knowledge, say V. Chernysh and V. Stepanenko, is an indicator of the maturity of a science, a necessary element of its self-awareness: following the historical development of the institute, scientists have the opportunity to better understand its current state, problems and contradictions. Therefore, it is natural that as the science of human rights develops, interest in its history grows, and the emergence of historiographical works is evidence of this[2,p. 5].

History and methodology of legal science, according to E. Yarkova– a new discipline for the system of domestic legal education. Its appearance is due to a number of reasons. One of the main reasons can be considered a radical, in comparison with the scientific revolution, a change in the paradigmatic foundations of domestic jurisprudence. The essence of this change can be defined as a transition from the monistic model of legal science, in which historical and dialectical materialism qualified as the only truly scientific theory and methodology, and the history of science emerged as the history of the Marxist-Leninist scientific paradigm; to a pluralistic model based on the idea of theoretical and methodological diversity and the idea that the way to create a true theory and methodology of legal science lies through the study of the history of this science [3,p. 7].

Historical and legal knowledge is the basis of modern and future legal culture, provides coordinates and tools for orientation in the problems of jurisprudence. Accordingly, the modern historian in the field of legal knowledge must be clearly aware of the commonalities and differences between historiography and the source base of research. Therefore, a necessary component of the professional training and skills of a historian of law is the scientific organization and high culture of elaboration and use of historiographical works and sources. Helplessness in their practical use has a negative impact not only on the quality of research, but also on the effectiveness of scientific activity in general. A historian in the field of law must be able to find the necessary historiographical works and sources, thoroughly research and correctly interpret them, objectively assess the level of reliability and information capabilities of relevant documents, is have the skills of scientific criticism [4,p. 11].

Source studies, notes O. Petrenko, has its own specific subject and uses a special method of cognition of objective reality. The main task of source studies is to study cultural objects as sources of information about people and society [4,p. 11]. At the same time, the basis of source studies in the field of human rights is the understanding of the source of law as a product of purposeful human activity, as a phenomenon of legal culture. In turn, writes O. Petrenko, it focuses on the systematic study of sources, to appeal to works of culture created in the process of human activity, which reflected the social, psychological, managerial, pedagogical and other aspects of society and personality, power and law, morality, motives and stereotypes of human behavior in certain conditions. Sources contain the full amount of social, political, cultural, historical and pedagogical, etc. information, which serves as a basis for obtaining new factual knowledge [4,p. 11]. Thus, in the study of somatic human rights and the mechanism of their implementation in biomedical research, it is important not so much the interpretation of the content of the text, as the interpretation of the source as a phenomenon of legal culture.

Comparative analysis of the disciplinary historiography of the Institute of Somatic Human Rights (here we fully share the opinion of T. Demetradze) contribute to a better vision of the whole block of legal disciplines, their hierarchy in the legal science system, in the humanities in general, overcoming "disciplinary barriers". In the scientific activity of lawyers, the ability to predict transformation processes, search for different options for interdisciplinary and multidisciplinary synthesis in the specialization of legal research on the institute of somatic human rights and the mechanism of their implementation in biomedical research [5, p. 34].

The history of legal science, writes T. Popova, in this case has a special place, because it acts not only as a "means of analysis" of the disciplinary history of the whole "family" of legal disciplines, but also plays on the very system of legal professional knowledge. "Integrative role". The disciplinary jurisprudence of the history of legal science, taking into account its national and regional specifics helps to identify the typological diversity of its disciplinary images in the system of European and world legal practices, to provide a clearer understanding of the structure of reflective disciplines, development of optimal principles including at the stage of its disciplinary development. That is why, the scientist notes, the creation of "cartography" of historiographical disciplinary legal traditions in order to find their place in legal science will contribute to identification stability, improving the paradigmatic foundations of the "historiographical basis", strengthening the epistemological status of the legal institution[6,p. 233].

According to O. Mikhno, the study requires systematization of sources not on a chronological or typical basis, but on the nature of the reflection of legal reality in them. Carrying out such historical and legal research, it is necessary to clearly distinguish the main processes. Thus, official documents, recommendations, instructions, dissertations, monographs, etc. reflect mainly theoretical and legal and partly educational and methodological aspects. But the result of this study – the actual research – draws up a scientist in the form of an official document. Therefore, invisible in the flow of officialdom, but the most interesting side – the internal – is presented in the texts themselves, which are the result of study and are of particular research interest. [7,p. 17].

Polysemantism of the concept of "historiography of somatic human rights" involves the concretization of the institution of somatic rights within the mechanism of protection of human and civil rights and freedoms in general, which reveals one of its possible meanings – the history of legal knowledge. In this coordinate system it is necessary to position the historiography of the Institute of Somatic Rights in the process of biomedical research as an intellectual history, which, according to T. Sidorova

studies the process of understanding the historical past in space-time systems and subjective-personal perceptions: personalities, their subject of study, epistems, technologies, scientific tools in the study of the institute of notary as a body for the protection of human and civil rights and freedoms. In this case, the history of science, the scientist notes, is characterized by the function of retransmission in a concentrated form of clumps of collective memory of its past, if we mean the combined experience of understanding the "historical", reproducing images of the past, reflected in theories and concepts the seal of the individuality of their creators and the "signs" of their time. Modern qualitative research on the history of science is complex, systematic, based on an interdisciplinary approach that synthesizes the possibilities of related legal sciences[8,p. 236].

That is, as we see, the history of the formation and development of the mechanism of realization and protection of somatic human rights is an integral part of the historical and legal process. The study of positive experiences in this field, which has deep historical roots and is closely linked to socio-economic and political processes, is important for both theory and practice. An integral element of scientific intelligence of any level and direction is a thorough source base, critical analysis and systematization of which is the primary task of a true scientist. This is what makes it possible to carry out objective and impartial research in the field of jurisprudence, as modern scholars emphasize [9, p. 23].

If we talk about the analysis of the main sources on the subject of our study, we should first highlight the works of D. Belov, Y. Voloshin and A. Krusyan on the general theory of modern constitutionalism.

D. Bielov in his dissertation research "Paradigm of Ukrainian constitutionalism" (Bielov, 2012)highlights the features of the category paradigm of modern Ukrainian constitutionalism, taking into account the constitutional and legal realities of domestic practice. The problems of formation and development of the paradigm of modern Ukrainian constitutionalism are studied. Using a historical approach, the concept and genesis of the scientific and practical paradigm of constitutionalism are revealed. Based on the analysis of the constitutional legislation of Ukraine, judicial and administrative practice, scientific and theoretical research, the author reveals the content of constitutionalism and provides a description of its structure. The components of modern Ukrainian constitutionalism are identified and studied, in particular, it is established that the concept of "constitutional order" as the main and integrating category of the science of constitutional law, which has a more normative content. The legal properties of the norms enshrining the principles of the constitutional order are revealed. Scholars, in particular, have proved that the Constitution defines the entire paradigm of constitutional and legal relations. The legal nature of the transformation of the constitution is studied, three main ways of transforming the content of constitutional norms without changing the text of the constitutions themselves are identified. D.Bielov reveals the peculiarities of the evolution of constitutional models of power in Ukraine, defines the conceptual foundations of constitutional transit, as well as the peculiarities of constitutional reform in Ukraine as a consequence of the formation of a new paradigm of Ukrainian constitutionalism [10, p. 34].

In our opinion, Yu.Voloshyn's work "Constitutional and Legal Support of European Interstate Integration: Problems of Theory and Practice" is interesting [11], where scientists consider the process of formation of the constitutional and legal mechanism of integration in the context of globalization. The author pays special attention to the constitutionalization of international law, as well as its internationalization. The scholar rightly concluded that the constitutional and legal provision of integration absorbs a complex and dynamic system that encompasses norms, means and doctrine, thus enabling this process, and globalization affects even constitutionalism. The concept of "supranational constitutionalism" is characterized as the constitutional and legal support of state participation in integration processes, and the law should set the vectors in this progressive development. The dissertation also considers the issue of transformation of sovereignty in modern conditions, which is related to political, economic and social elements.

A. Krusian in his dissertation "Modern Ukrainian constitutionalism: theory and practice" [12]for the first time proposed the periodization of the genesis of the scientific and practical paradigm of constitutionalism, its development and formation. Analyzed the constitutional and legal freedom of man, his protection, turning to protection from the state and protection by the state itself (this is important when analyzing the admissibility of state interference in the life of the individual), and proposed a functional mechanism of modern Ukrainian constitutionalism.

An important part of our research has been work in the field of somatic rights. At the same time, it is necessary to single out such scientists as V. Kruss and M. Lavryk, Y. Turyanski and V. Pishta. In particular, the general approaches of somatic rights were gradually introduced into scientific circulation by the scientist V. Kruss, namely as an opportunity of the person to dispose of the body independently. His work "Theory of Constitutional Law Enforcement" is especially noteworthy [13]. At the same time, we should agree with Yu. Turyanski, that the topic of somatic human rights has been the subject of research by many scientists in the post-Soviet space, but in Ukraine at present we can not state the intensification of its development [14, p. 34].

Extremely important for our study are the works of M. Lavrik, among them, in particular, we can highlight "Guarantees of constitutional human rights (somatic aspect)" [15], where somatic human rights are analyzed through the prism of constitutional guarantees, which seems acceptable given their component composition. The author also reveals the concept of constitutional human rights, seeing under the guarantees and legal, and political, economic and spiritual components that ensure the implementation and protection of constitutional human rights, which are the basis of human ability to dispose of their bodies. It is quite thoroughly noted that the legal guarantees of somatic

(constitutional) human rights are contained in the constitution of a state and in other legislation, which can be demonstrated by the domestic example.[14, p.34].

In our opinion, the dissertation work of Yu. Turyanskyi "Somatic human rights in the modern doctrine of constitutionalism: theoretical and legal research" is also important (Turianskyi, 2020,p. 34). In the dissertation, among other things, on the basis of the analysis of international regulations, monitoring reports, practice of foreign countries, national legislation and law enforcement practice, statistical data, author's public opinion poll, analysis of scientific doctrine the complex theoretical and legal research of somatic human rights in modern doctrine of constitutionalism is carried out. Scientists have identified the prerequisites for the emergence and further development of the group of somatic human rights: scientific and technological progress, the complementarity of scientific research, changes in social psychology and the correction of moral and ethical norms. It is proved that in the modern doctrine of constitutionalism the formation of a group of somatic rights can be traced, which does not yet have a clear scientifically formed structure. This is due, in particular, to the progress of technical capabilities in the field of human corporeality. Then the author's position on the structure of the group of somatic rights is presented and the following are singled out: the right to one's own genome; reproductive human rights; sexual human rights; the right to transplant organs, tissues, cells; the right to gender identity; the human right to modify one's body; the right to a painless death; the right to dispose of one's body and its parts after death; the right to use drugs and psychotropic substances to alleviate suffering.

Interesting, from the point of view of the subject of our research, is the work of V. Pishta "Administrative and legal regulation of transplantation in Ukraine". In his dissertation, the scientist conducted a study of administrative and legal regulation of transplantation in Ukraine. Theoretical and practical problems are determined and the directions of their improvement are worked out. The development of administrative and legal norms in the field of transplantation in Ukraine is studied. Scientists focus on the period of existence of the Ukrainian Soviet Socialist Republic, because at this time the field of transplantation first became the object of administrative regulation, and later formed a full administrative and legal framework governing the transplantation of kidneys, lungs, intestines, gastrointestinal tract. costal cartilage, bones, as well as issues of international legal cooperation in this area. It is also important that the paper examines the case law of the European Court of Human Rights in the field of transplantation on the example of the cases "Petrova v. Latvia" and "Elberte v. Latvia". In both cases, the European Court of Human Rights found a violation of Article 8 of the Convention for the Protection of Human Rights and Fundamental Freedoms, and in Elberte v. Latvia, a violation of Article 3 of the Convention. In a separate opinion in the case of Petrova v. Latvia, K. Voitishek emphasizes that the European Court of Human Rights did not answer the question of the further role of the deceased's relatives in deciding whether or not to remove anatomical materials from the corpse donor: whether whether the relatives are autonomous subjects, or they are only expressions of the will of the deceased. This is where we see the further development of the case law of the European Court of Human Rights in the field of transplantation.

In our opinion, the work "Protection of constitutional human rights and freedoms in the process of conducting biomedical research", which we co-authored with S. Kozodaev, D. Belov and Y. Bisaga, deserves special attention [16,17]. Thus, in particular, the paper examines the features of the essence and content of the constitutional principles of human rights as a basis for legal regulation of biomedical research. The authors reveal the essence and content of international and national legal standards for human biomedical research. Scientists have found that there are currently no standards for legal regulation of human rights in biomedical research at the national level and at the level of international instruments in this field. The monograph logically reveals the features of the content of biomedical research as an object of constitutional and legal regulation, as well as identifies the features of the constitutional and legal status of participants in biomedical research. It is established that the terms "medical experiment", "clinical study", "clinical trial", "human experiments" are used in domestic legislation and scientific sources as single-order categories, meaning the same phenomenon, but more accurate. is the use of the term "biomedical research". Scientists have studied the limits of permissible interference in conducting biomedical research with human participation, as well as identified the ethical examination of biomedical research as a way to protect human rights. We would like to note that a significant part of the scientific material related to the actual biomedical research was used just from our joint work with the above scientists.

CONCLUSIONS

Based on the analysis of the works of theorists of state and law, constitutionalists, scientists directly involved in the study of somatic human rights, religious scholars, we can conclude that the historiography of somatic human rights in biomedical research in a broad sense is a field of scientific knowledge. Studies the development of constitutional and legal science and its patterns; in the narrow sense, it is a set of works on various problems of the history of modern constitutionalism, human rights, the influence of religion on human rights and the mechanism of their implementation and protection in a certain historical period.

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REVIEW ARTICLE

PERINATAL ASPECTS OF INTRAUTERINE INFECTIONS

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ABSTRACT

The aim: To analyze Ukrainian and foreign literature data on the consequences of perinatal infection and the peculiarities of their manifestation.

Materials and methods: Literature sources on the peculiarities of the course of infection that occur in the perinatal period and are a threat of congenital malformations or diseases in the newborn are collected.

Conclusions: The analyzed data of the clinical picture and management of the early neonatal period fully reflect the coherence and timeliness of medical care for infants born with signs of perinatal infection. It should be noted that the tactics of such a newborn depend on the clinical manifestations, the general condition of the baby, and the duration of infection of the mother with a particular infection.

KEY WORDS: fetus, newborn, congenital infections

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INTRODUCTION

To date, one of the biggest problems is an intrauterine infection of the fetus due to its involvement in maternal morbidity and mortality, as well as the fetus. Infections cause the termination of every fifth pregnancy. The causes of infection are different. These include sexually transmitted infections, vaginal dysbiosis, and infections that are part of *TORCH infections*. The list of pathogens that cause perinatal lesions of the fetus is being updated. [1]

Perinatal infection is an infection that is transmitted from mother to child during its fetal development (intrauterine infections), during childbirth (intranatal), or immediately after birth (postnatal). [1] In other words, infection with the pathogen can occur at any time: during pregnancy, during childbirth, or immediately after birth. Intrauterine infections are transmitted to the fetus from the mother transplacentally, intranatal infections – through the infected anogenital area, postnatal – through direct contact of the mother during breastfeeding.

Fetal damage occurs mainly during the early fetal period (9-22nd week of gestation) with the formation of congenital malformations or specific symptom complex (ZVUR, hydrocephalus, brain calcifications, hepatosplenomegaly, severe jaundice).

Possible adverse effects of perinatal infections during pregnancy:
– delay of fetal development;
– premature birth;
– congenital malformations;
– perinatal losses;
– acute infections in the newborn;
– persistent infections in the newborn;
– asymptomatic infections with late clinical manifestations;
– disability from childhood. [2-5]

Among the causes of infant mortality in recent years, fetal VUI occupies one of the first places, causing from 11% to 45% of perinatal losses. VUI is the cause of the whole spectrum of antenatal pathology: infectious diseases of the fetus, malformations, stillbirths, prematurity, development of fetoplacental insufficiency, and fetal growth retardation. [6]

The period of pregnancy at which the pregnant woman becomes infected is the most important pathogenetic factor in the development of VUI. There is an inverse relationship between the stage of pregnancy and the risk of infection: in the first trimester, the risk of infection is 15%, in the second – 45%, and in the third – 70%. [7]

Urogenital infection, which occurred in the mother's body in the first (embryonic) period of pregnancy, is a serious threat because during this period the formation of the placental barrier is not yet complete and can be realized by ascending or hematogenous infection of the ovum. In the second (fetal) three months of pregnancy, the main manifestations of intrauterine infection of the fetus include signs of inflammatory pathology in the amniotic membranes and tissues of the placenta from the placenta, and from the fetus, there is a generalization of the infectious process, various fetopathies, fetal growth retardation. Increased permeability of the fetoplacental barrier causes a high risk of transplacental infection during the trimester. There are four stages of fetal infection. At the first stage, there is excessive growth of opportunistic pathogens or

the presence of pathogenic microorganisms in the mother's body. After the pathogenic flora enters the uterine cavity, the decidual membrane becomes infected (second stage). The resulting local inflammatory process passes to the chorionic membrane – chorionitis. Subsequently, fetal vessels – choriovasculitis and/or amniotic membrane – amnionitis are involved in the infectious process, with subsequent infection of amniotic fluid (third stage). Rupture of the membranes is not a necessary prerequisite for water infection, as the ability of microorganisms to penetrate intact membranes has been established. After bacterial contamination of amniotic fluid, infection of the fetus (fourth stage) can occur in several different ways.

The most common infections that cause perinatal infection are the following:

- *Herpes simplex virus (HSV) type 1 or type 2.*
- *Cytomegalovirus (CMV)*
- *Chlamydial infection*
- *Toxoplasmosis*
- *Rubella*
- *Syphilis*

THE AIM

To analyze Ukrainian and foreign literature data on the consequences of perinatal infection and the peculiarities of their manifestation.

MATERIALS AND METHODS

Literature sources on the peculiarities of the course of infection that occur in the perinatal period and are a threat of congenital malformations or diseases in the newborn are collected.

REVIEW AND DISCUSSION

HERPES SIMPLEX VIRUS TYPES 1 OR *TYPE 2*

Herpes infection is a common cause of minor symptoms in the mother and a rare cause of extremely severe neonatal infection. Congenital intrauterine infection is very rare. However, neonatal infection is associated with high mortality and occurs in approximately 1 case per 3000-5000 births. [8]

Neonatal herpes is a very rare but serious viral infection with a high incidence and mortality. It is classified into three subgroups depending on the locus of infection of the baby:

- skin, eyes, and/or oral mucosa;
- the localized disease of the central nervous system (CNS) (encephalitis);
- disseminated infection with damage to several organs.

Herpetic lesions of the skin, eyes, and/or oral mucosa: Children with symptoms of lesions of the skin, eyes, or oral mucosa have a better prognosis, accounting for about 30% of all cases of neonatal herpes infection. With appropriate antiviral therapy, the rate of neurological and/or ophthalmic morbidity does not exceed 2%. Localized CNS disease and disseminated infection 70% of infants with neonatal herpes have disseminated and/or CNS infection, and in approximately 60% of cases, the disease is characterized by no infection of the skin, eyes, and/or mouth. Localized CNS damage in newborns is usually detected quite late – usually at the age of 10 days to 4 weeks. Against the background of antiviral treatment, mortality from this form of infection is about 6%, and neurological morbidity (the disease can last a lifetime) – 70%. At the disseminated infection, the worst forecast is defined. With the use of appropriate antiviral drugs, the mortality rate reaches 30%, 17% of patients have long-term neurological complications. The bad consequences of disseminated infection and localized CNS damage are explained by the delay between the onset of symptoms and the appointment of treatment. Neonatal infection occurs as a result of infection of the newborn during childbirth, in contrast to congenital herpes, which is extremely rare and is associated with the transmission of infection to the fetus in uterus. [9]

The incidence of neonatal herpes in the UK is about 50% of the number of reports from other European countries. In the United States, the average incidence reaches 1 in 15 thousand live births per year, but there are significant differences between populations, in particular in some disadvantaged groups of the urban population (1: 7500).

The tactics of managing newborns born to mothers with HSV infection, which arose in the third trimester, is to monitor the baby during the first 24 hours after birth, informing parents about the hygiene of child care. It is established that the risk of transmission of the infection from the mother in the case of infection with the herpes simplex virus in the third trimester is very low and does not pose a threat to the baby.

Intranatal herpes virus infection has a high risk of infecting the baby, so swabs from the mouth and nasopharynx, skin, rectum, and conjunctiva are needed to test for the presence of the herpes simplex virus by PCR. Also, prescribe therapy with acyclovir at a dose of 20 / kg every 8 hours until the exclusion of the presence of active infection in the infant. However, cohabitation with the mother and breastfeeding is not prohibited if the woman does not have herpetic rashes around the nipples. If the condition of the newborn is unsatisfactory, in addition to the above smears for PCR testing and active therapy with acyclovir, a spinal tap is taken for examination, even in the absence of CNS damage.

If a woman has a recurrent herpes infection, the risk of infecting the baby is very low. In this case, swab collection and treatment of newborns are not performed.

CYTOMEGALOVIRUS (CMV)

In the world, cytomegalovirus infects up to 2% of newborns and 45-60: in the first year of life. In addition, according to the WHO, the detection of antibodies to *CMV* in different segments of the population is tweed 40 to 100%.

The virus belongs to the family of parvoviruses and is transmitted only from person to person. The most danger-

ous moment of infection of the child is the passage of her birth canal. The virus also enters breast milk. [10]

Intrauterine infection can occur at any time. In newborns, the most common manifestations of infection were respiratory distress syndrome (RDS), anemia. Intrauterine *CMVI* can occur in the form of generalized and local forms, there are acute, subacute, and chronic stages.

In the early stages of ontogenesis, the fetus is most sensitive to the action of *CMV*, because the virus has tropism to cells with a high level of metabolic processes. The fetus may die, or a malformation of the internal organs and brain. For such newborns, acute and subacute stages of infection occur in utero, they are born with manifestations of chronic *CMVI*. They are dominated by the following defects: holoprosencephaly, microcephaly, spinal hernia, hydrocephalus, coloboma, cataracts, underdevelopment of the eyeball, syndactyly, cyst fibrosis of the pancreas, heiloschis, palatoschis, and others. After birth, signs of generalization of the infection develop in the form of interstitial pneumonia, hepatitis, and other diseases. Among the neurological signs prevails and long-lasting syndrome of CNS depression, develops, if not formed in utero, hydrocephalus.

When infected in the late fetal period or during childbirth, children are born with signs of acute *CMVI*, which is most characterized by a generalized form of infection.

The generalized form often simulates the course of hemolytic disease of newborns, especially its prenatal form. The main symptom is jaundice. Hepatosplenomegaly, which is characteristic of 95% of newborns with intrauterine *CMVI*, appears early.[11]

In the blood serum, there are high levels of indirect and direct bilirubin, increased activity of transaminases, and alkaline phosphatase. The general signs of intoxication are expressed. *Cytomegalovirus* hepatitis is characterized by damage to the bile capillaries. Clinically, this is manifested by cholestasis and subsequent development of liver failure and portal hypertension.

Changes in the liver are often accompanied by CNS damage in the form of meningoencephalitis, dominated by CNS depression. The process is associated with the direct action of the virus on neurons, as well as with toxic effects on small vessels of the brain with disruption of their nutrition and oxygen transport and the development of autoimmune mechanisms of CNS damage.

Characteristic and such local manifestations of *CMVI* as respiratory distress syndrome, anemia. Polychromic anemia is accompanied by reticulocytosis, normoblastosis, thrombocytopenia. Hemorrhagic syndrome develops in the form of petechiae, ecchymoses, nasal, umbilical hemorrhages, melena.

Jaundice on the background of hepatosplenomegaly, anemia, hemorrhagic syndrome, and meningoencephalitis – the most typical manifestations of generalized intrauterine *CMVI*.

Localized forms, in addition to those listed above, are also characterized by interstitial chronic pneumonia, obstructive bronchitis. At involvement in process of small bronchial tubes and bronchioles, peribronchitis develops, at the transition to a chronic stage – fibrosis, and pneumosclerosis.

The prognosis in such newborns is unfavorable, mortality reaches 60-80%. More than 90% of surviving children have psychoneurological disorders, delayed psychomotor reactions, intellectual and speech development, deafness, chorioretinitis with optic nerve atrophy, dental development disorders, diabetes mellitus. [12]

Chlamydial infection (XI). In the structure of STIs, chlamydial infection (XI) occupies a leading position. The results of studies by European scientists have shown that 80% of acute PID develop due to STIs, with 60% due to XI and only 20% due to other infections [8]. XI leads to a variety of reproductive health disorders in women, including the development of chronic salpigophoritis, tubal-peritoneal infertility, and ectopic pregnancy. 70% of patients with chlamydial cervicitis often have an erased clinic, in some cases – asymptomatic course of the disease.

The share of chlamydia infection in pregnant women is 5-40%, and with a burdensome obstetric and gynecological history (salpingo-oophoritis, infertility, miscarriage) – up to 63%, while in 4-11% urogenital XI occurs without clinical manifestations in pregnant women XI can lead to asymptomatic bacteriuria, inflammatory diseases of the urinary and genital tract, the development of cervicitis, obstetric complications with possible antenatal infection of the fetus. The main pathogenetic factor contributing to the development of intrauterine infection is an infection of amniotic fluid, at the same time with chlamydial cervicitis infection of the fetus can occur during childbirth. When involved in the process of the fallopian tubes, endometrium *Ch. trachomatis* penetrates the decidual membrane, the chorion, which contributes to the pathogen entering the amniotic fluid, in the future the infection can affect the conjunctiva, urethra, vagina, causing various clinical forms of perinatal infections. During the passage of infected birth canals in newborns may develop a chlamydial infection in the form of neonatal conjunctivitis (22-44% of cases). Also, 2-12 weeks after birth, the respiratory system may be damaged up to pneumonia, which can give complications in older age (11-20%). When infecting women *Ch. trachomatis* in the early stages, when the embryo develops, there are infectious embryopathies, which are manifested by congenital malformations of the fetus. In the early stages of pregnancy, primary placental insufficiency begins to form, which can lead to miscarriage or miscarriage.

At the infection of the woman in later terms of gestation threatening miscarriage, formation of secondary placental insufficiency, polyhydramnios, premature childbirth are more often observed. XI also causes complications during childbirth, most often premature rupture of the amniotic sac. Ingestion of infected amniotic fluid often leads to the defeat of *Ch. trachomatis* of the lungs and digestive tract of the fetus, as evidenced by infection of the entire amniotic sac in the case of removal of the fetus by cesarean section.

Intrauterine infection of the fetus is verified by morphological examination of dead newborns, reveals the defeat of

Ch. trachomatis meninges, vascular plexuses of the brain, and lungs. With the hematogenous route of infection in the fetus, there are various pathological changes in the form of the edema-hemorrhagic syndrome, hemorrhage into the ventricles of the brain, pneumopathy, hepato-renal and adrenal insufficiency, which is the direct cause of antenatal fetal death or early neonatal death. [13]

TOXOPLASMOSIS

Toxoplasmosis is a parasitic disease caused by protozoa, which is characterized by damage to the nervous and lymphatic systems, eyes, skeletal muscles, myocardium, and other organs. The causative agent of this disease is an intracellular parasite – *Toxoplasma gondii* (belongs to the type of protozoa and has a crescent shape, size 4-7x1.5 μm). The final host is cats and other animals of the same family,intermediate – man and several other mammals and birds. Human infection occurs through food when eating insufficiently cooked meat.

The pathogenesis of toxoplasmosis remains poorly understood. getting into the human body in different ways, toxoplasmas are captured by macrophages, transported to the lymph nodes, where they multiply and enter the bloodstream. On lymphatic and blood vessels parasites can extend on bodies and fabrics, be fixed there, and cause inflammatory changes of alternative-productive character. Exudative, especially purulent inflammation is uncharacteristic of toxoplasmosis. [14-16]

Within 3 weeks in an organism, antibodies are made and accumulate, serological reactions become positive. Further toxoplasmas form real cysts in the tissues, the inflammatory reaction disappears, the foci of necrosis are organized or calcareous.

There are acquired and congenital toxoplasmosis. Acquired toxoplasmosis affects adults and older children, congenital occurs in fetuses and newborns in the first months of life. The gate of infection in acquired toxoplasmosis, as a rule, is the ileum. This is evidenced by a pronounced reaction of the mesenteric lymph nodes. In the latter, there is hyperplasia with the presence of giant multinucleated cells. Quite characteristic liver damage: there is hepatitis with cholestasis, small foci of necrosis, and billion granulomas. Typical lesions of the muscles of the lower leg and lower back, myocardium, rarely in the muscle tissue of other organs. They are areas of intermediate productive myositis, rarely focal muscle necrosis. Encephalitis sometimes develops against the background of immunodeficiency. [17]

The occurrence of congenital toxoplasmosis is due to the ability of toxoplasmosis to penetrate the placental barrier. The risk of transplacental transmission of the infection increases with increasing gestational age. Intrauterine infection of the fetus is possible only in cases of infection of women during pregnancy. The most dangerous for the fetus is the infection of women between the 10th and 24th weeks of pregnancy, as at this time the relatively high risk of transplacental infection of the fetus is combined with severe damage to the brain and other internal organs. [18]

There are three scenarios of toxoplasmosis infection for the baby: 1. Primary infection in a pre-seronegative mother. 2. Reactivation of the pathogen during pregnancy in a mother who had the fact of infection before pregnancy. 3. After re-infection of a previously immune pregnant mother with a new, more virulent strain (for example, after international travel or after eating undercooked meat from areas where more virulent atypical strains predominate). [19]

Clinical manifestations of congenital *toxoplasmosis* are characterized by significant polymorphism from subclinical variants to severe lethal forms of the disease. Clinically manifest forms of congenital toxoplasmosis (VT) develop in 12-25.5% of cases [9] and are prognostically unfavorable. Without adequate treatment, infected children develop hydrocephalus and microcephaly, movement disorders, mental retardation, episyndrome, and loss of vision and hearing after months or years. Subclinical forms of VT also do not go unnoticed, in 50-60% of cases the development of late manifestations of VT during puberty is possible. Exacerbations of chorioretinitis are common, with serious consequences in the form of decreased vision and intellectual deficits.

To date, the most effective treatment for toxoplasmosis infection is the administration of a combination of sulfadoxine/pyrimethamine, which acts synergistically and blocks the metabolism of folic acid in replicating tachyzoites. Additional administration of folinic acid prevents the toxic effects of pyrimethamine on the red bone marrow. Cells in the human body can use folinic acid to synthesize nucleic acids, but toxoplasma cannot. Sulfadoxine / pyrimethamine is prescribed to children in the first 2 days in a saturation dose – pyrimethamine 2 mg / kg per day (maximum 50 mg / day), and then – in a maintenance dose – 1 mg / kg per day (maximum – 25 mg / day) . The dose of drug saturation is 75 mg/kg per day, maintenance – 50 mg/kg every 12 hours. Of the antibiotics used to treat toxoplasmosis, including in pregnant women and infants, spiramycin is used; in case of intolerance, clindamycin and azithromycin are prescribed. [20]

RUBELLA

Congenital rubella occurs in the primary infection of the mother during pregnancy. It is known that the rubella virus can penetrate the placenta, causing hypoplasia, and the formation of conglomerates of fibrin-fused villi in the first half of pregnancy. There is also evidence that maternal and fetal macrophages are actively involved in the transmission of infection across the blood-brain barrier. Depending on the duration of infection, different types of fetal damage are caused. The most pronounced lesions are observed when infected in the first trimester. During this period, infant mortality is 10-25%. At later infection, congenital malformations of fruit are observed. [21]

In pregnant women, rubella may be asymptomatic or with catarrhal phenomena of the upper respiratory tract, a slight fever, swollen lymph nodes (especially occipital and auricular), and maculopapular rash. The disease may be accompanied by joint damage.

Congenital rubella syndrome (CRS) is a situation where the fetus develops death in the womb or multiple abnormalities, or there may be no consequences. The most common anomalies include:
- Delayed fetal development
- Microcephaly
- Meningoencephalitis
- Cataracts
- Retinopathy
- hearing loss
- heart defects (non-overgrowth of the ductus arteriosus and pulmonary artery stenosis);
- hepatosplenomegaly
- bone thinning

Less common manifestations include thrombocytopenia with purpura, cutaneous erythropoiesis, which causes bluish-red skin lesions, lymphadenopathy, hemolytic anemia, and interstitial pneumonia. Continuous monitoring is required to detect subsequent hearing loss, mental retardation, behavioral disorders, endocrinopathy (eg, diabetes mellitus), or, in some cases, progressive encephalitis. Infants with congenital rubella may develop immunodeficiencies such as hypogammaglobulinemia. [22]

Treatment of rubella, like other viral infections, is symptomatic. Since vaccination is the best way to prevent this disease, it is the only sure way to avoid infecting the fetus and causing it to be infected with the virus.

SYPHILIS

The causative agent of syphilis belongs to the order *Spirochaetales*, family *Spirochaetaeceae*, genus *Treponema*, species *Treponema pallidum*, subspecies pallidum (syn. *Spirochaeta pallidum*). Pale treponema is easily destroyed under the influence of external agents: drying, heating at 55 ° C for 15 minutes, exposure to 50-56% solution of ethyl alcohol. At the same time, low temperatures contribute to the survival of pale treponema. Pale treponema is a spiral-shaped microorganism; the number of revolutions of the spiral from 8 to 12, its curls are uniform, have an identical structure. Performs characteristic types of movement: rotational, translational, wavy, and bending. Propagated mainly by transverse division into two or more segments, each of which then grows into an adult. The microorganism can also exist in the form of cysts and L-forms. The cyst is a form of survival of pale treponema in adverse environmental conditions, is considered a dormant stage of T. pallidum, and has antigenic activity. L-form is a way of survival of pale treponema, which has weak antigenic activity.

According to official state statistical reports, the epidemiological situation regarding the incidence of syphilis in Ukraine is generally characterized by a gradual decline (in 2014 – 3674 cases (8.6 per 100,000 population) in 2015 – 3228 cases) (7.6 per 100 000 population).

There is early and late congenital syphilis. Early syphilis is any syphilitic condition that occurs before the age of 2 years. The main manifestations and types of syphilis include:
- skin lesions
- lesions of the mucous membranes
- visceral
- laryngitis
- oculopathy
- osteochondropathy
- pharyngitis
- pneumonia
- rhinitis.

Late congenital syphilis is attributed
- Late congenital syphilitic investment keratitis
- Late congenital oculopathy
- Neurosyphilis.

For the treatment of syphilis use the following treatment regimen:
- benzylpenicillin sodium crystalline salt (B): children under 1 month – 100 thousand IU per kg of body weight per day, divided into 4 injections (every 6:00). Given the anatomical and physiological features of the urinary system in newborns and children in the first month of life, it is permissible to reduce the frequency of administration of penicillin to 4 times a day.
- intramuscularly; children aged 1 to 6 months – 100 thousand IU per kg of body weight per day, divided into 6 injections (every 4 hours), intramuscularly; children older than 6 months – 75 thousand IU per kg of body weight per day intramuscularly; children older than 1 year – 50 thousand IU per kg of body weight per day intramuscularly for 20 days with monosymptomatic and latent forms of early congenital syphilis and for 28 days – with manifest syphilis and central nervous system damage (confirmed by positive serological reactions of cerebrospinal fluid)) [1,2,3]. If the mother refuses to perform a lumbar puncture on the child, the course of treatment should also be 28 days). These terms of treatment should also apply to alternative therapies (ampicillin, ceftriaxone) [23]

CONCLUSIONS

The analyzed data of the clinical picture and management of the early neonatal period fully reflect the coherence and timeliness of medical care for infants born with signs of perinatal infection. It should be noted that the tactics of such a newborn depend on the clinical manifestations, the general condition of the baby, and the duration of infection of the mother with a particular infection.

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REVIEW ARTICLE

THE HUMAN RIGHT TO STERILIZATION: MEDICAL AND LEGAL ASPECT

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ABSTRACT

The aim: To consider the general principles of the human right to sterilization in terms of medicine and law.

Materials and methods: Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of right to sterilization among other human rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main stages of the formation of category "right to sterilization" with human participation were identified.

Conclusions: The issue of surgical sterilization should not be considered during contractions, as happened in this particular case, but before or after childbirth, because a woman in childbirth can not adequately perceive information and make such important decisions. If this decision is made after delivery, the doctor must make sure that the patient is psychologically healthy. In addition, the consent for surgical sterilization of the spouses must be signed together. Although this procedure follows from the human right to dispose of one's own body, however, in the presence of marriage, referring to Part 2 of Art. 54 of the IC of Ukraine, which states that all important issues of the family should be resolved by the spouses together, on the basis of equality. If such a decision is made by the wife alone, she must be considered to have committed the wrongful conduct.

KEY WORDS: right to sterilization, bioethics, medical procedures, termination of human life, transgender people

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INTRODUCTION

The relevance of the subject of this structural element of the dissertation is due to the fact that in accordance with the rapid development of medical technology there is a problem in determining the role of reproductive rights, which are part of somatic rights. In international legal documents, which enshrine the basic principles of biomedicine, much attention is paid to the legal regulation of somatic human rights. Somatic rights are increasingly being studied in legal science, because the separation of these rights into a separate category is a logical process that arises as a result of the development of subjective rights of the individual.

THE AIM

The aim is of our study is to consider the general principles of the human right to sterilization in terms of medicine and law.

MATERIALS AND METHODS

Formal-logical methods of analysis and synthesis allowed to reveal the content of the concepts that make up the subject of research, to classify them, as well as to formulate intermediate and general conclusions. The systematic method allowed to study the role and significance of right to sterilization among other human rights and freedoms. Using the historical method, the doctrinal basis of the study was analyzed, and the main stages of the formation of category "right to sterilization" with human participation were identified.

REVIEW AND DISCUSSION

One of the reproductive human rights should be the right to voluntary sterilization. Despite the fact that Article 281 of the Civil Code of Ukraine enshrines the possibility of sterilization of a person as one of the elements of the right to life, in our opinion, such a right applies to reproductive. After all, surgical sterilization involves the irreversible loss of the human body's ability to reproduce, is to reproduce its own kind [1].

Analyzing these documents, it can be argued that this refers to the voluntary consent of only the person in respect of whom sterilization is carried out. However, given the fact that in most countries infertility is a ground for divorce, the legislator must take into account the position not only of the woman or man undergoing sterilization, but also the interests of the other spouse.

In the analysis of medical sterilization, one should agree with the thesis that the refusal of reproduction affects not only the rights of the person who consented to the medical intervention, but also the rights of his wife (husband). Impossibility to conceive is recognized by many countries as

one of the reasons for divorce. Ukraine is no exception. In particular, in Part 2 of Art. 49 and Part 2 of Art. 50 of the IC of Ukraine states that the unwillingness of a husband (wife) to have a child or his (her) inability to conceive a child may be the cause of divorce. At the same time, Art. 49 of the Fundamentals requires consent to sterilization only from a person who wishes to perform such surgery. Disclosure of the intentions of such a person by a doctor should be qualified as disclosure of medical secrets (Article 40 of the Fundamentals) and will have corresponding negative legal consequences [1].

The European Court of Human Rights notes that the "adequacy of medical care" remains one of the most difficult indicators, and therefore the European Court retains sufficient flexibility in setting the necessary standard of medical care, determining it in each case [2]. Yes, one of the high-profile cases is the case In the case of V.C. v. Slovakia a romanian woman was sterilized while in a public hospital. The medical records contain the consent to the surgical sterilization procedure certified by its signature. However, the applicant alleged that she had not understood the meaning of the term "sterilization" at the time of signing this agreement. International standards generally stipulate that "sterilization" can only be carried out with prior informed consent, except in exceptional emergencies. In the applicant's case, there was no need for such urgent medical intervention, without which there would have been an inevitable risk of irreparable harm to her life.

It follows that the requests of the medical staff to consent to sterilization during childbirth did not allow her to make a decision of her own free will. The paternalistic manner of the hospital staff left the applicant no choice but to agree. This conduct led to a violation of Article 3 of the Convention on Human Rights complained of by the applicant. After all, according to this article, "no one shall be subjected to torture or to inhuman or degrading treatment or punishment".

That is why we believe, first, that the issue of surgical sterilization should not be considered during contractions, as happened in this case, but before or after childbirth, because a woman in childbirth can not adequately perceive information and make such important decisions. If this decision is made after delivery, the doctor must make sure that the patient is psychologically healthy. Second, the consent to perform surgical sterilization of the spouses must be signed together. Although this procedure follows from the human right to dispose of one's own body, however, in the presence of marriage, referring to Part 2 of Art. 54 of the FC of Ukraine, which states that all important issues of the family should be resolved by the spouses together, on the basis of equality. If such a decision is made by the wife alone, she must be considered to have committed the wrongful conduct.

We cannot ignore the issue of sterilization of transgender people. Thus, in the last few decades, biologists, anthropologists, psychologists and sociologists have begun to study intensively both the issue of sexual orientation and the issue of gender identity. Persons with so-called "non-traditional" sexual orientation and those who identify with a gender other than that obtained at birth demand protection of their rights. If for the former this human rights issue mainly lies in the plane of non-discrimination and the creation of structures of same-sex partnership, then the latter face a number of obstacles related to the physical existence of the person and his fundamental rights and freedoms [3].

It should be noted that today 14 countries in Europe require sterilization as a prerequisite for gender recognition. At the same time, forced sterilization is a violation of Article 3 of the UN Convention on Human Rights, which protects the principles of dignity, personal autonomy and non-discrimination. The UN Special Rapporteur on Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment called on all States to "legally prohibit forced or involuntary sterilization under any circumstances and to provide special protection for persons belonging to marginalized groups", explicitly mentioning transgender people [4].

At the same time, we support the assertion that at the European Union level, little attention is paid to issues related to the ability of transgender people to start a family, act as parents of children, etc. One of the remarks in this regard is contained in the European Parliament's Resolution "On the situation of fundamental rights in the European Union" – in which MEPs deplore the fact that the legislation on the legal recognition of transgender people in 14 Member States still includes a mandatory requirement. on sterilization and call on Member States to review these provisions so that they fully respect the right of transgender people to dignity, physical integrity and the family [5].

In particular, the case law of the ECtHR, on the other hand, is rich in cases where applicants have insisted that their right to start a family has been violated. In 1998, the ECtHR ruled that a person who changed sex could marry a person with a gender opposite to that of a transgender person. However, in 2002 the Court rejected previous case-law and stated that transsexuals who underwent surgery were not deprived of the right to marry because, by law, they remained capable of marrying a person of their former opposite sex [6].

In Ukraine, a person who changed sex had to undergo a mandatory sterilization procedure. The current Gender Correction Procedure contains changes made to the implementation of the Action Plan for the implementation of the National Strategy in the field of human rights for the period up to 2020. According to this Procedure, indications for gender correction are divided into two groups: medical and biological (there is a mental and behavioral disorder "transsexualism" according to the International Classification of Diseases of the Tenth Revision); socio-psychological (discomfort or distress due to the discrepancy between the gender identity of the individual and the sex established at birth) [7].

Currently, the gender reassignment procedure takes place in three stages. In the first of them, the person turns to a family doctor, who refers him to a specialist (psychiatrist). In the second stage, the latter establishes the diagnosis and

determines how much the person needs psychological, endocrinological and surgical care. The third stage is optional and involves a potential revision of the diagnosis. Unlike the previous procedures, the current one sets the term of observation of the patient at least two years. According to the current procedure, surgical delivery is not mandatory. However, only its conduct is the basis for a person to obtain a medical certificate of change (correction) of gender (the basis for legal recognition). After receiving such a certificate, the person must apply to the registry office to amend the birth certificate. Therefore, on the basis of a new act record and medical certificate, a person has the opportunity to obtain a passport that would correspond to his new sex. After that, all other documents are changed – individual tax number, education documents, driver's license, etc. At present, the procedure of mandatory sterilization is not provided by law [4].

Another issue related to our research is forced sterilization as a criminal punishment. In July 2019, the relevant Committee of the Verkhovna Rada of Ukraine on Legislative Support of Law Enforcement Recommendations to the Parliament to Adopt Bills № 6607 "On Amendments to Certain Laws of Ukraine for crimes committed against sexual freedom and sexual integrity of a minor or a minor)" [8]. This bill provided for the use of chemical castration as a medical measure on the basis of a voluntary appeal of a convicted person for crimes. Chemical castration was to be ordered by a court decision and in the presence of a relevant conclusion of forensic psychiatric and forensic medical examinations, as a substitute for unserved punishment in the form of imprisonment [9].

Despite some remarks on this bill, it is the work of experts and is based on thorough research, says L. Tokar [9]. Bill 49 6449 "On Amendments to Certain Legislative Acts of Ukraine Concerning Strengthening Liability for Crimes Committed Against a Minor or Underage Mature" was also put to the vote, which provided for the use of forced chemical castration as a type of criminal punishment" [10]. Despite the lack of a comprehensive approach to improving legislation to combat child sexual abuse [11] and unfounded position, this bill was taken as a basis and adopted by the Verkhovna Rada of Ukraine, and later promised by the President [9].

Consider the basic rules of law in this regard:

- The Constitution of Ukraine explicitly prohibits any actions that may be degrading and interpreted as medical experiments (Article 28): Everyone has the right to respect for his dignity. No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. No person may be subjected to medical, scientific or other experiments without his or her free consent";

- The Convention for the Protection of Human Rights, which is also part of our legislation, also states in Article 3 that no one shall be subjected to torture or to inhuman or degrading treatment or punishment;

- Part 3 of Art. 58 of our Criminal Code: "Punishment is not intended to cause physical suffering or degrade human dignity";

- Explanatory note to the Rome Statute, which Ukraine signed but did not ratify: "They (crimes against humanity, including forced sterilization) are not isolated or isolated cases, but are part of one government policy (although the perpetrators should not identify themselves). with this policy), or widespread atrocities that are silenced or justified by the government or the de facto authorities".

That is, the law states unequivocally that a person cannot be subjected to forced sterilization under any circumstances, even if such sterilization is introduced by the government as an official punishment [12].

Given the above, we fully share the opinion of O. Drozdova that the parliament passed a law that obliges to forcibly castrate all those convicted under Part 4 of Article 152 of the Criminal Code, including healthy people. The procedure of forced castration of healthy people is not provided by the legislation of any country of the world. After all, in this format, chemical castration becomes a punishment, not a cure, which is contrary to all norms and practices of international law.

CONCLUSIONS

One of the reproductive human rights should be considered the right to sterilization, which, in our opinion, consists of at least 3 main types of sterilization: voluntary sterilization; sterilization as a prerequisite for gender recognition; chemical castration as a criminal punishment. We consider:

- The issue of surgical sterilization should not be considered during contractions, as happened in this particular case, but before or after childbirth, because a woman in childbirth can not adequately perceive information and make such important decisions. If this decision is made after delivery, the doctor must make sure that the patient is psychologically healthy. In addition, the consent for surgical sterilization of the spouses must be signed together. Although this procedure follows from the human right to dispose of one's own body, however, in the presence of marriage, referring to Part 2 of Art. 54 of the IC of Ukraine, which states that all important issues of the family should be resolved by the spouses together, on the basis of equality. If such a decision is made by the wife alone, she must be considered to have committed the wrongful conduct.

- although today, as more than 10 European countries require sterilization as a precondition for gender recognition, such a procedure is contrary to Article 3 of the UN Convention on Human Rights, which protects the principles of dignity, personal autonomy and non-discrimination. Therefore, in our opinion, it should be legally prohibited in relation to transgender people;

- The procedure of forced castration in relation to healthy people is not provided for in the legislation of any country in the world (except Poland and the state of Florida in the USA), because in this case it becomes a punishment, not treatment of a person contrary to international law. In view of the above, we fully support the decision of the President of Ukraine in the context of vetoing the bill adopted by the Verkhovna Rada № 6449 "On Amendments to Certain

Legislative Acts of Ukraine to Strengthen Liability for Crimes Committed Against a Minor, Juvenile, Underage", which provided for the use of forced chemical castration as a form of criminal punishment.

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CASE STUDY

EXTENSIVE PERITUMORAL BRAIN EDEMA IN A SMALL CLINOIDAL MENINGIOMA: CLINICAL CASE

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ABSTRACT

Peritumoral brain edema (PTBE) is seen in 40-78% of all cases of intracranial meningiomas. It may vary in shape and size, occasionally being two to three times larger than the tumor. We present a case of a 62-year-old female patient, suffering from seizure and progressive headache. She was diagnosed with left medial sphenoid wing meningioma and referred for treatment to Uzhhorod Regional Center of Neurosurgery and Neurology. The patient had no major focal neurological deficit and Karnofsky Performance Scale (KPS) of 70 on admission. The preoperative magnetic resonance imaging (MRI) with and without contrast showed a 2.1×2.2×2.5 cm solid mass at the inner third of the left sphenoid wing, with homogenous enhancement and encasement of middle cerebral artery (MCA). In addition, there was a disproportionately extensive PTBE in the left cerebral hemisphere that caused midline shift and mass effect. The patient underwent left pterional craniotomy and gross total resection of the mass. The postoperative course was without complications or new neurological deficit, MRI within 48 hours revealed gross total tumour resection with residual brain edema and the patient was discharged with a KPS of 80 on day 7. Based on several studies, significant correlation between PTBE and tumor volume was observed: larger tumors cause larger PTBE. This particular case had a very large hemispheric PTBE, which was disproportionate to the small size of the meningioma. Most likely, the PTBE in this patient was caused by venous congestion, but this had no influence on surgical outcome. Therefore, the presence of a large PTBE does not necessarily indicate a poor prognosis and isn't always the reason of surgical complications.

KEY WORDS: MedialSphenoid Wing Meningioma; Brain Edema: Surgical Outcomes

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INTRODUCTION

Peritumoral brain edema is seen in 40-78% of intracranial meningiomas. PTBE may vary in shape and size, and sometimes can be two to three times larger than the tumor [1], and in the majority of cases correlates with tumor volume [2]. Several studies have reported that PTBE may raise morbidity and mortality of patients by progressive brain shift and increased intracranial pressure [3-5]. Moreover, PTBE has been associated with a higher riskof postoperative intracranial hematoma [6]. To our knowledge, most studies have shown that PTBE is dependently associated with large tumor size, and the occurrence of PTBE may raise the difficulty of complete resection and increase risk of complication. Herein, we present a patient with a small medial sphenoid wing meningioma (MSWM) associated with sever and extensive brain edema. The patient had a good outcome after surgical resection and within one year of follow-up the tumor was completely cured. The aim was to demonstrate surgical outcome with a rare case of extensive edema in a small clinoidal meningioma.

CASE REPORT

A 62-year-old female patient, suffering from progressive headaches for 6 months, seizures and blurred vision on the left side for one month prior to admission, was referred to Uzhhorod Regional Center of Neurosurgery and Neurology for treatment. Clinical examination revealed that the patient had no focal neurological deficit and her KPS was 70. Furthermore, the patient had early bilateral papillary edema, which was found on fundoscopy. All laboratory data upon admission were normal. Brain MRI with gadolinium enhancement, demonstrated a 5.8 cm^3 solid extra-axial mass with homogenous enhancement at the inner third of the left sphenoid wing with encasement of MCA (Figure 1b) and extensive PTBE.

In our study, the tumor and edema volume were measured using pre-operative contrast-enhanced MRI scans. The sagittal and coronal diameters were determined from the axial images. The coronal images were used to measure the axial diameter. These measurements were employed to estimate the volume of the lesion by applying the formula abc/2, where (a) is the sagittal, (b) is the coronal and (c) is the axial diameter [7,8]. Calculated tumor volume on pre-operative MRI was 5.8 cm^3 (Figure 1a). Same formula was used to measure PTBE by identifying high signal intensity changes on T2-weighted images. In this case PTBE volume was 104.8 cm^3 (Figure 1b). Edema index (EI) represents the degree of peritumoural edema compared with tumor volume and is calculated by dividing the PTBE volume on the tumor volume. EI of more than 1.0 means that edema is present, and in this particular case it was 18 indicating a severe PTBE.

The patient underwent surgery under general anesthesia with endotracheal tube in supine position.With her head turned contralaterally at a 30-degree angle and fixed with three pin head clamp, a standard pterional craniotomy was performed.

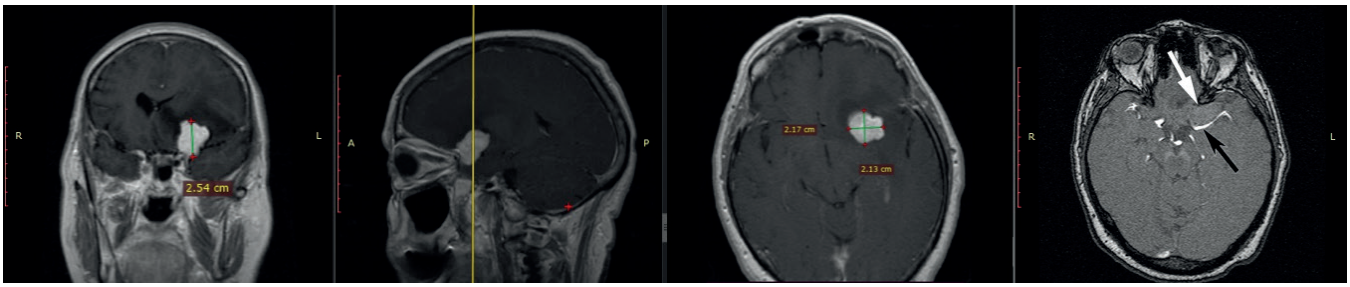

Fig. 1a. Preoperative brain magnetic resonance images (MRI) with Gadolinum demonstrated a 2.1×2.2×2.5 cm3, extra-axial enhanced mass in the inner third of sphenoid wing with irregular shape. The mass (white arrow) encases middle cerebral artery (black arrow)

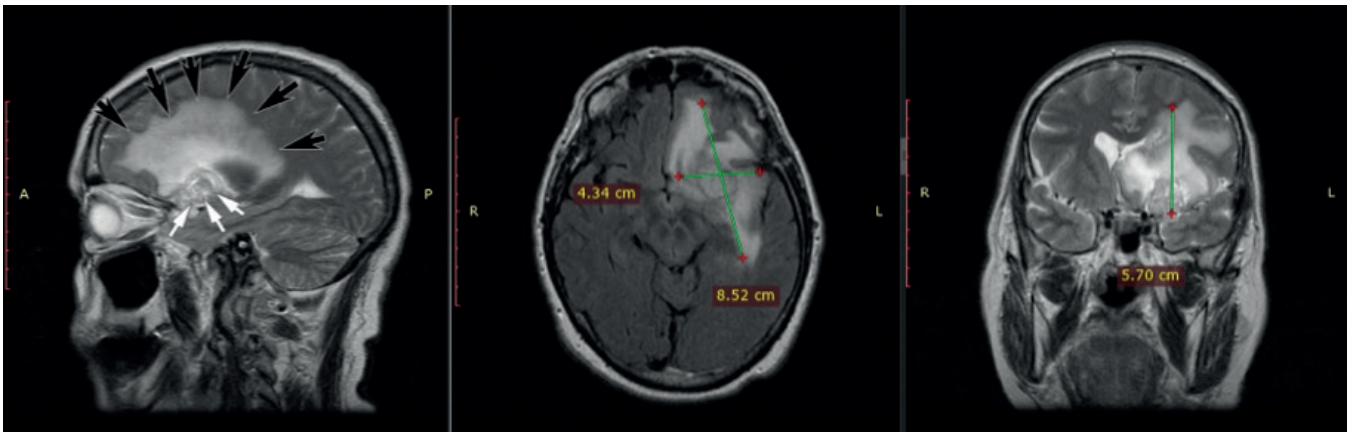

Fig. 1b. Preoperative brain T2-weighted MRI showed extensive PTBE, 4.3×8.5×5.7 cm3, causing midline shift and mass effect. The mass (white arrow) is surrounded by massive edema (black arrow).

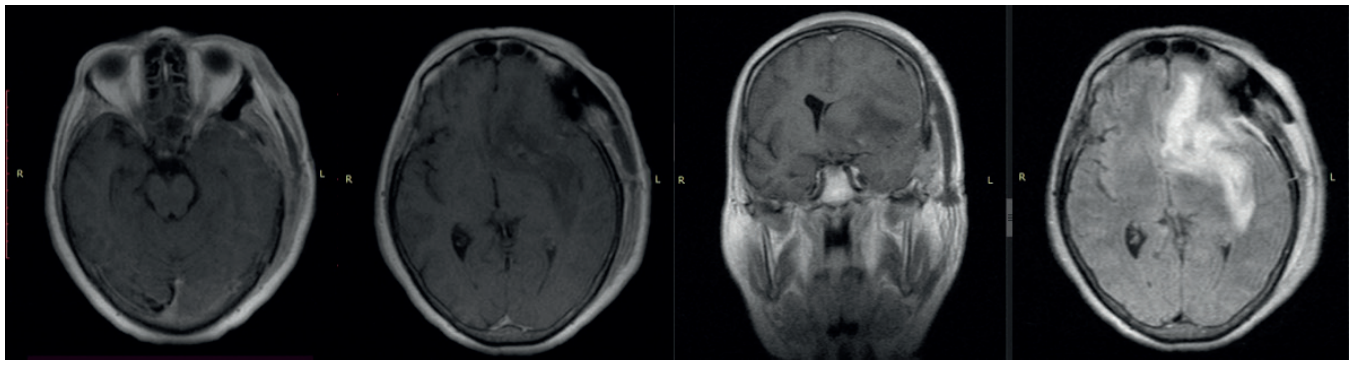

Fig. 2. Two days postoperative follow-up MRI revealed brain edema without residual mass.

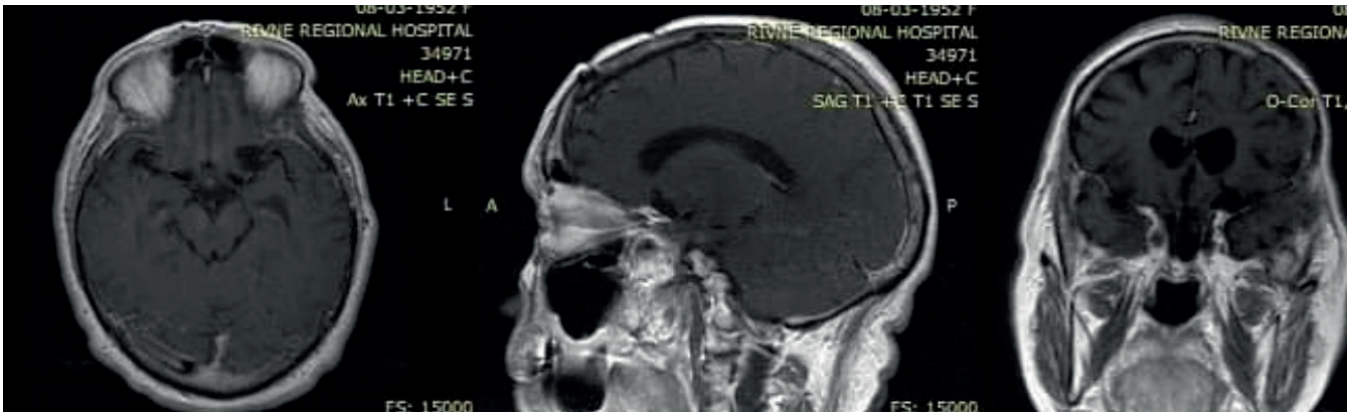

Fig. 3. Last follow-up MRI three years after surgery without any sign of recurrence.

After curvilinear durotomy, Sylvian fissure was dissected proximally under microscopic magnification until tumor was visualised. Gentle debulking of the tumor following cautery of tumor's dural attachment was done. Peripheral dissection of the tumor from the brain parenchyma was performed, following bipolar cautery of the feeding vessels. Finally, delicate tumor

dissection from middle cerebral artery was done following the arachnoidal plane. After hemostasis and dural closure, bone and wound were closed in multiple layers.

After the surgery, the patient was transferred to intensive care unit for close observation.In the first postoperative day after neurological exam which was normal, the patient was transferred to the regular patients' ward. In the second postoperative day the patient's MRI revealed brain edema without residual tumor (Figure 2). The patient was discharged 7 days after surgical treatment with normal clinical findings and improvement of vision and headache, with a KPS of 80. The histopathological report of the mass indicated WHO Grade I (meningiothelial subtype) meningioma.

At three year follow-up, no signs of tumor on MRI were noted (Figure 3), patient is not on antiepileptic drugs and is currently symptom-free with a KPS of 100.Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

DISCUSSION

Despite primarily extra-axial locations, slow progression rates, and usually benign histological characteristics, meningiomas are frequently associated with PTBE [9]. Brain edema is defined as an expansion of brain volume due to increased water and sodium content.[10] However, different theories of PTBE pathogenesis were described and suggested, one of which is the venous compression theory, reported by Bitzer M et al. [11]. Extensive PTBE usually occurs in cases of malignant brain tumors or benign masses with invasion into adjacent normal brain tissue. It has been proposed that brain edema in meningiomas is associated with many factors, including size, location, histological features of the tumor, the secretory activity of meningioma cells, positive sex hormone receptors, venous channel compression and occlusion by the tumor [2,5,6]. Moreover, the size and extent of the PTBE correlates with the prognosis of meningioma. The extent of edema is associated with larger size of tumor, higher grade and a more invasive meningioma with a higher recurrence rate [12-14].

This patient had a very extensive PTBE (EI – 18), which was disproportionate to the small size of the meningioma. Despite the absence of direct invasion to adjacent brain tissue, the tumor had irregular margins and was hyperintense on T2-weighted images. Histopathological report revealed WHO Grade I meningioma (meningiothelial subtype). Nakano et al. reported that the hyperintense signal on T2WI is considered a multifactorial process and is correlated with tumor consistency and vascularity, indicating higher water content. Furthermore, the more water content tumors have, the easier edema fluid can diffuse to the surrounding brain tissue according to the water pressure gradient [15]. Simis et al. noted that the extent of PTBE in meningiomas had a positive correlation with the presence of irregular margins of the tumor [12]. Based on histopathological findings, the transitional, meningothelial, angioblastic and malignant meningiomas lead to edema more frequently than other histological subtypes [13].

However, several studies showed no significant correlation between histological subtypes of meningiomas and PTBE [2, 16]. Despite the small volume of the tumor, our patient had progression of symptoms and signs one month prior to admission, most likely due to extensive PTBE. Several studies indicated higher risk of intraoperative complications in the presence PTBE, like loss of dissection plane at brain-tumour interface and surgical difficulty during resection; pre and post-operative seizures; post-operative neurological deficit; postoperative intracranial haematoma and subsequent intracranial hypertension [3, 15, 17].

CONCLUSIONS

In this particular case, our patient had good surgical outcome immediately and after one year of follow-up. Despite the extensive PTBE, gross total resection was achieved without intraoperative complications. We suggest that the extent of PTBE in our patient was caused by venous compression and advise preoperative CT or MR venography in such cases. Our experience demonstrates that extensive PTBE in patients with meningioma does not necessarily predict poor prognosis and isn't always the reason of complications. However, it does not mean that PTBE shouldn't be taken into account.

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