UDC 616.33/342-092
DOI https://doi.org/10.32782/2226-2008-2026-1-13

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LIVER DAMAGE IN PATIENTS WITH GASTRIC AND DUODENAL ULCERS IN CHRONIC HELICOBACTER PYLORI INFECTION

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The purpose. To identify and determine the state of the liver according to the activity of hepatic enzymes and ultrasound diagnostic data in patients with gastric and duodenal ulcers in chronic helicobacteriosis.

Materials and methods. 54 gastroenterological patients (21 men and 34 women) with gastric and duodenal ulcer caused by chronic *Helicobacter pylori* infection and a control group of patients (n = 20) have been examined. Control group patients additionally underwent biochemical blood tests.

Results. During a comprehensive examination of the main group patients concomitant pathology was detected: chronic pancreatitis, chronic acalculous cholecystitis, post-cholecystectomy syndrome, arterial hypertension, ischemic heart disease, chronic kidney disease was diagnosed in patients.

The average degree of contamination of the gastric mucosa with inactive forms of *Helicobacter pylori* infection by topographic zones was analyzed. In the majority of gastric and duodenal ulcer patients in chronic *Helicobacter pylori* infection, concomitant changes in the gallbladder, pancreas, and liver were observed.

Conclusions. The results of our own studies indicate a high frequency of pathological changes in the ultrasound picture of the liver parenchyma, the structure of the gallbladder and pancreas in patients with gastric and duodenal ulcer disease in chronic *Helicobacter pylori* infection.

The results of clinical and laboratory studies showed that in the main group patients signs of cytolysis are determined in the form of a significant increase in transaminases, namely alanine transaminase and aspartate transaminase, indirect bilirubin, thymol test. The signs of cholestasis – an increase in gamma-glutamyltransferase and bilirubin, both direct and indirect, were present as well.

Keywords: Gastric ulcer, duodenal ulcer, chronic *Helicobacter pylori* infection, liver, *Helicobacter Pylori.*

УДК 616.33/342-092

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УРАЖЕННЯ ПЕЧІНКИ У ХВОРИХ НА ВИРАЗКОВУ ХВОРОБУ ШЛУНКА ТА ДВАНАДЦЯТИПАЛОЇ КИШКИ ПРИ ХРОНІЧНОМУ ГЕЛІКОБАКТЕРІОЗІ
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Метою дослідження стало виявлення та визначення стану печінки за показниками активності печінкових ферментів та даних ультразвукової діагностики у хворих на виразкову хворобу шлунка та дванадцятипалої кишки при хронічному гелікобактеріозі.

Результати власних дослідження свідчать про високу частоту патологічних змін ультразвукової картини паренхіми печінки, структури жовчного міхура та підшлункової залози, а також визначаються признаки цитолізу в вигляді підвищення показників трансаміназ, а саме аланінтрансамінази та аспартаттрансамінази, непрямого білірубіну, тимолової проби, та признаки холестазу – підвищення показників гамма-глутамілтрансферази та білірубіну як прямого так і непрямого у хворих на виразкову хворобу шлунка та виразкову хворобу дванадцятипалої кишки при хронічному гелікобактеріозі.

Ключові слова: виразкова хвороба шлунка, виразкова хвороба дванадцятипалої кишки, хронічний гелікобактеріоз, печінка, Helicobacter Pylori.

Introduction

According to various literary data, the atypical course of gastric and duodenal ulcer in chronic *Helicobacter pylori (HP)* infection is determined in 8 – 25 % of patients [3; 4; 9; 12; 14], mainly in women. Half of them complain of a "cholecyst-like" variant of ulcer disease course. At the same time, signs of chronic non-calculous cholecystitis are detected in 53 % of cases [1; 6–8], and the combination of inflammatory and ulcerative lesions of the stomach and duodenum with cholelithiasis occurs in 21–25 % of cases [10, 13, 18].

Therefore, on the example of patients' specified contingent we are dealing with the comorbid pathology formation which manifestation characterizes by a changed

nature of the inflammatory damage of anatomically closed stomach and duodenum and its spread to gastrohepatopancreatoduodenal region parenchymal organs [2]. In such cases, the diagnostic search in patients is quite complicated, since at the specific moment of the doctor's visit, any organ can give an inflammatory reaction exacerbation with all the pathophysiological mechanisms inherent in this and the "vicious circle" of enteral activity dysregulation [16].

Such a situation, unfortunately, is frequent, in modern practice of family medicine and, in particular, gastroenterology as evidenced by statistical indexes [7]. We are experienced in certain part of patients with gastric and duodenal ulcers with concomitant liver involvement in the pathological process examination and treatment. Some similar clinical cases were already analyzed, however, there were isolated publications [11]. That's why we consider it fundamentally justified and clinically important to analyze the pathogenetic contribution of inflammatory liver parenchymal lesions to gastroduodenal ulceration clinical manifestation.

The purpose. To identify and determine the state of the liver according to the activity of hepatic enzymes and ultrasound diagnostic data in patients with gastric and duodenal ulcers in chronic helicobacteriosis.

Materials and Methods

54 patients (21 men and 34 women) aged 62 to 54 years (the average age was equal to 38.6 ± 4.4 years) with gastric and duodenal ulcer in chronic HP infection were under observation during the 2022–2025 years in therapeutical department the Municipal Non-Profit Enterprise "Odessa Regional Clinical Medical Center".

As a control group we examined clinically 20 practically healthy individuals without pathological changes in abdominal organs and hepatobiliary system.

Patients were examined and anamnesis was taken in accordance with the Declaration of Helsinki. All patients and healthy volunteers were informed about their objective examination results use with scientific purposes. Written agreement was signed by each of them.

The following criteria were used to include patients in the study: established clinical diagnosis of chronic non-atrophic gastritis, gastric ulcer, duodenal ulcer (confirmed by endoscopic and histological examination with the HP presence in active or inactive forms on the gastric mucosa); disease duration from 6 months to 12 years; the patients comprehensive examination including biochemical blood test, esophagogastroduodenoscopy (EGD) and the abdominal organs ultrasound diagnostics).

The criteria for patients excluding from the study were the following: the above-mentioned diagnosis without HP active or inactive forms confirmation on the gastric mucosa; short disease duration (up to 3 months); incomplete patients' comprehensive examination; presence of oncological disease of the gastrohepatoduodenal organs.

HP infection was verified as etiological factor with further confirmed endoscopially biopsy material. Urease and microbiological tests for HP were positive in all patients. For this aim double testing for HP was used (the urease test and stained smears microscopy).

All patients of the control and clinical groups were undergone to blood biochemical investigation upon admission to the clinic and before the start of treatment. Patients who were referred for biochemical blood tests had not been on anti-Helicobacter therapy over the past 6 months.

The patients' comprehensive examination included pH-metry, EGD (using the end-face fibrogastroduodenoscope FG-29V, "PENTAX", Japan) and ultrasound examination of the abdominal organs (using portable ultrasound device "LOGIC eR8", GE Healthcare, USA).

An ultrasound examination (USE) was performed using generally accepted method, on an empty stomach, with patients' position on back, on the left side and after changing position. The condition of the liver, gallbladder walls, its shape and size (volume), motor activity, nature of the contents (presence of sediment, polyps and concrements), pancreas, spleen, abdominal vessels were studied and analyzed.

The sequence of the examination was as follows: pH-metry was performed firstly, then EGD with biopsy material for PH testing and gastric mucosa histological studies. The examinations were done in the morning, on an empty stomach, 12-14 hrs after the last food intake.

Anti – helicobacter therapy is the treatment standard for chronic non-atrophic gastritis, gastric and duodenal ulcer associated with HP. It includes proton pump inhibitors (PPIs) in a standard dose twice a day + clarithromycin 500 mg twice a day + amoxicillin 1000 mg or metronidazole 500 mg twice a day. The duration of the course of threatment is 7 days. The functional state of the hepatobiliary system was examined at the stage of anti-helicobacter therapy in the main group patients.

The obtained results were statistically analysed using the one0way ANOVA parametric criterion. The minimum statistical significance threshold was set at $p < 0.05$.

Research results and their discussion

Gastric and duodenal ulcer patients in chronic HP infection complain of heartburn in 71.9 % of cases, acid regurgitation in 66.6 %, pain, feeling of heaviness in the epigastric region had 81 % of patients, nausea was present in 83.7 % of patients, vomiting in 2.6 %, flatulence in 10.8 %, stomach upset (constipation, diarrhea) in 77.9 %, manifestations of intoxication were observed in 98.5 % of cases.

A comprehensive examination of gastric and duodenal ulcer patients in chronic HP infection revealed concomitant pathology. 23 patients had chronic pancreatitis, 29 had chronic acalculous cholecystitis, post-cholecystectomy syndrome was present in 2 persons, arterial hypertension had 14 patients, ischemic heart disease – 6, chronic kidney disease – 9 patients.

Based on the data obtained, we considered it necessary to draw attention to the state of the hepatobiliary system in chronic HP infection. In connection with the above, functional and biochemical studies of the state of the hepatobiliary system were conducted.

The results of the mucous membrane of various topographic zones of the stomach with active and inactive forms of HP infection with microscopy of stained smears – prints in patients with chronic HP infection and the degree their contamination are presented in Fig. 1.

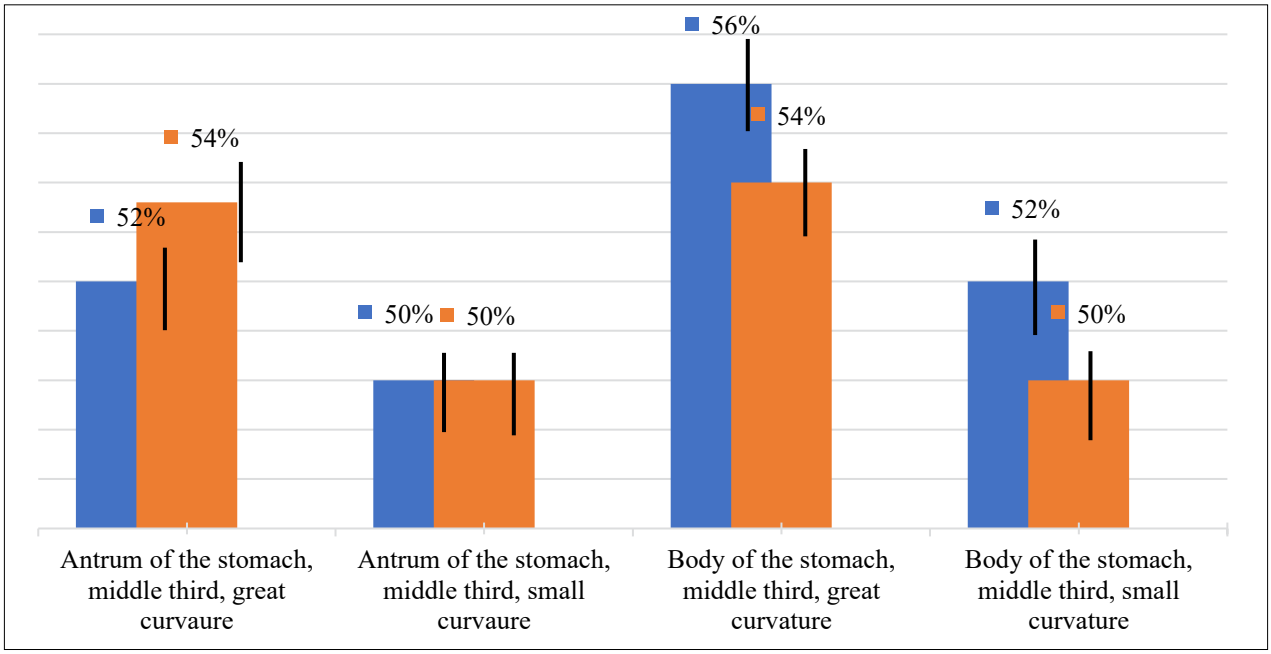

Fig. 1. Frequency of detection and degree of contamination of the gastric mucosa with active and inactive forms of HP infection by topographic zones in patients with chronic Helicobacter pylori (n = 54)

In total, 58 % of cases of intracellular "depot" of HP infection were detected in the gastric mucosa.

When compare the average degree of gastric mucosa contamination with active and inactive forms of HP infection by topographic zones, a significantly ($p < 0.05$) higher degree of contamination was detected in the body of the stomach along the greater curvature in relation to the topographic zones of the antrum, while there were no significant differences between the zones of the antrum or between the zones of the stomach body ($p > 0.05$).

Analysis of the results obtained showed that in chronic HP infection patients, precancerous changes in the gastric mucosa (atrophy, dysplasia, colonic metaplasia) in the antrum took place in 55.8 % of cases; in the middle – upper third of the stomach body along the greater curvature they were met in 30.7 % of cases and along the lesser curvature in 27.8 % of cases.

Ultrasound examination showed minor signs of the hepatobiliary system damage in chronic HP patients at the stage before the prescrition of anti-helicobacter therapy, mainly these were diffuse changes in the liver parenchyma – 35.4 % and fatty infiltration of the liver – 37.9 %.

At the initial stage of examination (before treatment), biochemical blood test was performed on 54 chronic HP patients (21 men, 34 women) and on 20 control group patients.

Patients who were referred for biochemical blood tests had not taken drugs included in the anti-HP therapy (AHPT) regimen, which is the standard of care for chronic non-atrophic gastritis, gastric and duodenal ulcer associated with HP, for the past 6 months (Table 1).

An increase in alanine transaminase, aspartate transaminase, alkaline phosphatase by 1.5–2 times was noted in patients after the specified treatment (Table 2).

Table 1

Biochemical test results in patients with chronic non-atrophic gastritis, gastric ulcer and duodenal ulcer in chronic *Helicobacter pylori* infection before the prescription of anti-Helicobacter therapy

Indicators	Control (n=20)	Before prescription of anti-HP therapy (n=54)
Total bilirubin, μmol/l	14,05±2,35	16,61±3,58*
Direct bilirubin, μmol/l	4,04±0,79	3,16±1,67
Inderect bilirubin, μmol/l	10,82±2,41	11,31 ±3,51
ALT, U/l	21,49±1,87	17,51±2,63 *
AST, U/l	19,51±3,19	22,84±2,34*
Alkaline phosphatase, U/l	167,68±11,39	188,53±12,89
Thymol test, U	1,66±0,77	1,67±0,81
Urea, mmol/l	5,41±0,41	5,46±0,63
Glucose, mmol/l	5,21±0,83	5,26±1,81
Total protein, g/l	74,62±1,71	77,13±5,25
Cholesterol, mmol/l	4,87±0,92	5,18±1,87

Note: n – number of studies;

*statistically significant changes vs the control group, $p < 0.05$

Table 2

Biochemical state of the liver in patients of the study group with chronic *Helicobacter pylori* infection during anti-Helicobacter therapy on the 7th and 15th day (M ± m)

Indicators	Control (n=20)	During anti-HB therapy, 7 days (n=54)	After anti-HB therapy, 15 days (n=54)
Total bilirubin, μmol/l	14,05±2,35	30,31±3,52*	34,21±2,64*
Direct bilirubin, μmol/l	4,04±0,79	9,11±1,06*	9,52±0,46*
Indirect bilirubin, μmol/l	10,82±2,41	23,34±1,07 *	25,19±2,13*
ALT, units/l	21,49±1,87	106,09±4,93*	186,21±5,44*
AST, units/l	19,51±3,19	64,04±3,26*	72,07±4,76*
Alkaline phosphatase, units/l	167,68±11,39	289,19±16,54*	317,81±15,14*
Thymol test, units	1,66±0,77	3,16±1,93	3,21±0,73
Urea, mmol/l	5,41±0,41	5,33±1,07	5,43±1,24
Glucose, mmol/l	5,21±0,83	5,26±0,71	5,24±0,59
Total protein, g/l	74,62±1,71	78,31±3,56	78,43±5,28
Cholesterol, mmol/l	4,87±0,92	5,41 ±1,19	5,59±1,46

Note: n – number of studies;

*statistically significant changes vs the control group, $p < 0.05$

This indicates a violation of the functional state of the hepatobiliary system mainly by the mechanism of cytolysis – the activity of transaminases increased, especially alanine transaminase, by 5 times.

It is known that the imbalance of intestinal microflora most often develops when macrolides (clarithromycin, azithromycin) and tetracycline are prescribed. They have the most detrimental effect on the intestinal flora, including *E. coli.* This can lead to a disruption of the bacterial balance and dysbacteriosis symptoms development

Indeed, the results obtained showed that during and especially after anti-helicobacter therapy, 42 % of patients complained of flatulence and bloating, 46.8 % – of pain along the intestinal loops, 42 % had complaints of rumbling in the stomach after eating, constipation had 34.7 % of patients, diarrhea 13.9 %. This indicated a disruption of the intestinal microbiocenosis balance. Also, according to the results of US-examination in 21 days after the start of anti-helicobacter therapy, hepatic parenchyma diffuse changes were observed in 72.3 % of patients and fatty infiltration of the liver in 64.9 %.

Additional confirmation of cholestasis presence was an increase of gamma-glutamyltransferase level by 10 times during anti-helicobacter therapy on the 7th day and its increase by 20 times on the 15th day from the start of eradication therapy in patients with chronic non-atrophic gastritis, gastric and duodenal ulcer in chronic helicobacteriosis (Fig. 2).

Thus, the main idea of the obtained data analysis is that the anti-helicobacter therapy use in patients with chronic non-atrophic gastritis, gastric and duodenal ulcer in chronic helicobacteriosis was accompanied by even more expressed symptoms of hepatobiliary system damage. This may be a consequence of both the direct hepatotropic effect of drugs included in the anti-helicobacter therapy regimen and the development of intestinal microflora disorders, which was detected in the patients under observation.

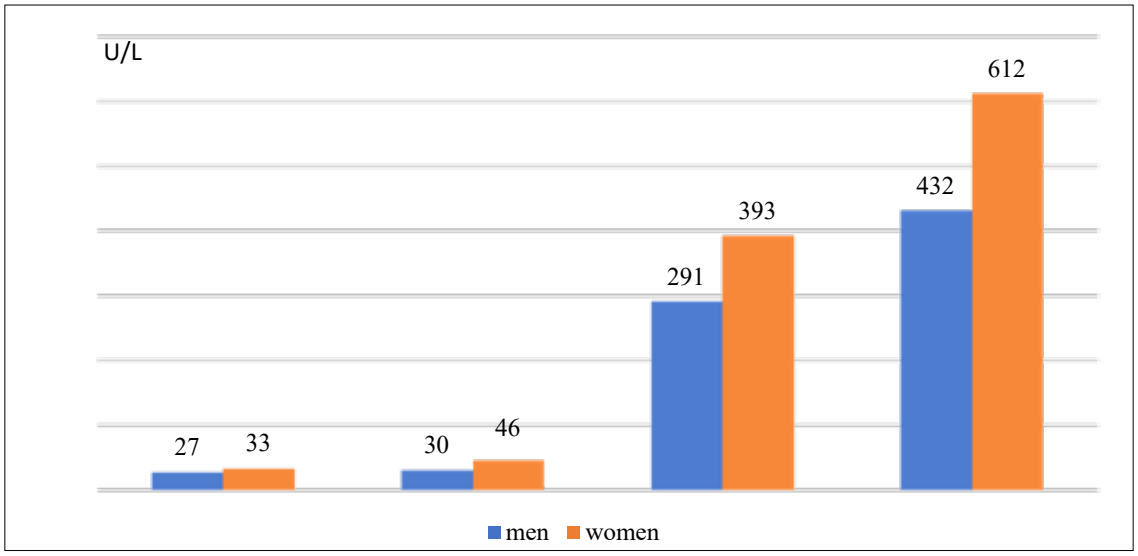

Fig. 2. Dynamics of gamma-glutamyltransferase in patients of the groups under observation, on the 7th and 15th day from the start of AGBT

*statistically significant changes relative to the control group, $p < 0.05$

To discuss the data obtained we would like to accent attention on the following three items. Firstly, we outline the liver involvement into the pathophysiological cascade of chain reactions in patients with stomach and duodenum ulceration is due to its critical functional role in organisms' both metabolism and detoxification [10]. Moreover, its extremely close anatomical location with the stomach and intestines predisposes it to shared pathophysiological mechanisms of responses to alternating inflammatory stimuli. Situations of concomitant liver parenchymal damage resulting from the inappropriate or erroneous prescription or administration of pharmacological agents with hepatotoxic effects are extremely dangerous [17].

The second, one could register the enteral dysbacteriosis in the selected patients development with progressive hepatic parenchyma failure. HP is well known to be the initial link of a long pathogenetic chain that leads to the development of the gastrointestinal tract dysbacteriosis [5, 15].

Long-term persistence of HP infection in the gastrointestinal tract accompanied by the development of chronic helicobacteriosis, massive eradicative antibiotic therapy causes possible secondary immunodeficiency due to the suppression of primarily bifidoflora with subsequent colonization of the mucous membrane by opportunistic and pathogenic microflora. This leads to a decrease of the microorganism resistance to infection due to the suppression of immune reactivity. Under the influence of HP, local immunodeficiency of the gastrointestinal tract mucous membrane may develop. This can close the pathogenic vicious circle of the inflammatory process on the mucous membrane of the digestive organs.

It is known that the microbiocenosis through various mechanisms participates in almost all human's body processes. This applies to both the metabolism of food components and the maintenance of the activity of the central nervous system. Further study of the gastrointestinal tract microflora allows us to discover new mechanisms of its influence on the body functions.

Thirdly, the severity of the clinical condition of our patients and the general pathological dysregulation with the disruption or absence of compensatory mechanisms contributed to the development of cholelithiasis that was as indicated by a 3-fold increase in the amount of direct bilirubin with a simultaneous increase in the activity of alkaline phosphatase, indirect bilirubin and thymol test. Cholestasis and cytolysis phenomena led to a decrease in the functional capabilities of the liver.

The detected phenomena of cytolysis indicate the hepatotoxic effect of drugs included in the treatment regimen for chronic helicobacteriosis. Thus, we noted an increase in the level of transaminases, with a predominant increase in alanine aminotransferase by 5 times on the 7th day and 9 times on the 15th day of anti-helicobacter therapy compared to the control group indicators. We believe that cytolysis is the cause of the decrease in the functional activity of hepatocytes, as indicated by an increase in the content of indirect bilirubin and the thymol test indicator twice during anti-helicobacter therapy. Hepatocyte damage probably leads to impaired bile passage due to increased pressure in the bile ducts, the criteria for which are increased direct bilirubin and alkaline phosphatase activity.

The changes in the functional and biochemical state of the liver are most likely associated with the hepatotropic effect of drugs used in anti-helicobacter therapy, which can be combined with the etiotropic effect of HP, after effective therapy on day 15, judging by clinical data and complete eradication – HP was not detected in patients by any of the methods.

At the same time, data indicating that the phenomena of cytolysis and cholestasis remain almost the same were obtained. An increase in gamma – glutamyltransferase indicators is an additional confirmation of the development of cholestasis

Resuming, we summarize the need for diagnostic measures strengthening in patients with gastrointestinal tract prolonged ulcerative lesions with the obvious abdominal ultrasound investigation focusing on the hepatobiliary system. Such a methodological approach will optimize the management of this patients' contingent and refine the comprehensive, pathogenetically based treatment schemes for concomitant liver dysfunction associated with gastrointestinal tract ulcerative lesions.

Conclusions

Our ultra-sound-examinations detected hepatic parenchyma changes in patients with chronic non-atrophic gastritis, gastric ulcer and duodenal ulcer with chronic helicobacteriosis. This coincides with the literature data.

Hepatic laboratory tests in patients with chronic non-atrophic gastritis, gastric and duodenal ulcer with chronic helicobacteriosis reveal signs of cytolysis, namely a significant increase in alanine and aspartate transaminase, indirect bilirubin and a positive thymol test.

At the same time, increases in the indicators of gamma-glutamyl transferase and bilirubin, both direct and indirect, indicates the presence of cholestasis. During anti-helicobacterial therapy these indicators are increasing even more.

Based on the results of our research, it is recommended to include in the complex treatment of patients with chronic non-atrophic gastritis, gastric and duodenal ulcer in chronic *Helicobacter pylori* ultrasound examination of the hepatobiliary system, as diffuse changes in liver tissue and its fatty infiltration were detected.

Thus, based on changes in laboratory and biochemical indicators that characterize the hepatic condition and are combined with the structural features of the organ, having been revealed by ultrasound, we can confirm the presence of pathological changes developing in the liver.

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Надійшла до редакції 19.06.2025.
Прийнята до друку 26.02.2026.
Електронна адреса для листування iryna.shukhtina@onmedu.edu.ua