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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

MALABSORPTION SYNDROME AND ITS REGULATION IN SURGICAL DISEASES OF THE HEPATOBILIARY ZONE

Speciality: 3213.01– Surgery

Field of science: Medicine

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Baku – 2024

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Dissertation Council ED 2.06 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University.

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GENERAL DESCRIPTION OF WORK

Relevance and degree of development of the research topic. The hepatobiliary system is one of the complex, multifunctional systems responsible for vital processes such as the elimination (excretion) of waste and metabolites from the body. Functional impairments of the hepatobiliary system, comprised of the excretory (liver) and bile excretory (gallbladder, intrahepatic and extrahepatic bile ducts) systems, occupy a prominent place among gastrointestinal diseases [1]. amage to the hepatobiliary system results in disruptions of metabolic exchange and detoxification processes, as well as weakening of the immune system and antimicrobial defense. Pathologies associated with impairment of bile production and secretion (cholelithiasis, cholecystitis, biliary dyskinesia, etc.) are prevalent, along with diseases such as echinococcosis and non-parasitic cysts of the liver (e.g., hemangiomas). In healthy individuals, during the processes of digestion, absorption, and transportation of nutrients, metabolic by-products (bilirubin) and excess cholesterol are naturally excreted from the body. Hepatobiliary diseases manifest with clinical symptoms such as pain in the right hypochondrium, epigastric discomfort, bitter taste in the mouth, nausea, diarrhea, constipation, flatulence, and pruritus, resulting from alterations in the physical-chemical properties of bile[2]. Impairment of the liver's excretory function predisposes to stone formation and also affects the digestion and absorption of nutrients. The aforementioned changes are associated with disturbances in the emulsification of fats, the formation of micelles, and decreased activity of digestive enzymes. Consequently, the intake of unsaturated fatty acids necessary for the

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[2] Кукош, М.В., Федоров, В.Э., Логвина, О.А. Эпидемиологические особенности течения неопухолевой механической желтухи (сравнительный клиникостатистический обзор) // Медицинский альманах, – 2019, (3-4 (60)), – с102-109.

formation of phospholipid components of cell membranes decreases, absorption of lipophilic vitamins is impaired, intestinal tone decreases, and peristalsis weakens[3].

Conservative therapy and surgical interventions are employed in the treatment of hepatobiliary diseases. Minimally invasive surgical interventions, laparoscopic surgeries, and hepatoprotectors that quickly restore the function of hepatobiliary system organs are used during systematic comprehensive treatment of these diseases[4].

The functional status of the hepatobiliary system has not been sufficiently elucidated following the treatment of diseases such as cholelithiasis, cholecystitis, hepatic echinococcosis, and non-parasitic lesions such as hemangiomas.

According to information from the International Society of Surgeons, surgical interventions in the hepatobiliary system result in recovery for the majority of patients. However, some patients experience deteriorations in their quality of life following surgery. Signs observed before the operation persist in some of these patients, and new symptoms emerge in the postoperative period. Among the causes of postoperative deterioration are functional impairments related to concomitant diseases of the hepatobiliary system, inflammatory conditions, surgical and technical errors made during the operation, as well as the importance of correcting metabolic disturbances and evaluating newly formed anatomical-physiological conditions in the postoperative period[5].

Early and differential diagnosis of surgical patients with hepatobiliary zone malabsorption syndrome can facilitate the adequate treatment of pathologies contributing to the development of this condition and ensure clinical improvement in patients. The therapeutic measures undertaken at this time, namely the provision of treatment

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[4] Джуманиязов, С.С. Желчнокаменная болезнь: современное состояние проблемы / С.С. Джуманиязов. — Текст: непосредственный // Молодой ученый. — 2020. — № 27 (317). — С. 337-339.

[5] Tsilimigras D.I, Pawlik, T.M, Moris, D. Textbook outcomes in hepatobiliary and pancreatic surgery. World J Gastroenterol. – 2021. 27(15), – 1524-1530.

for diseases resulting from malabsorption syndrome and correction of impaired digestive processes in the intestines, can lead to successful outcomes.

The diversity of nosological causes of malabsorption syndrome during surgical diseases of the hepatobiliary zone presents the clarification of all mechanisms involved in the development of this syndrome as an important issue. In recent years, there has been particular attention to the study of antimicrobial peptides (AMPs) and cytokines in the pathogenesis of malabsorption syndrome. In addition to their bactericidal effects, AMPs activate immunomodulatory, cytotoxic, and antiviral effects, inducing apoptosis.

The object of the research. In the course of research, laboratory and diagnostic results of patients with various surgical diseases of the hepatobiliary zone (HBZ) have been utilized. Differences between pre- and post-treatment indicators have been investigated.

The research aims to elucidate the pathogenetic mechanisms of malabsorption syndrome developing into surgical diseases of the hepatobiliary zone and to establish early diagnosis and provide adequate treatment.

Objectives of the study:

1. Clinical-statistical categorization of complications observed in surgical diseases of the hepatobiliary zone (HBZ).
2. Investigation of the dynamics of indicators reflecting the functional-metabolic status of the liver, biliary tract, and pancreatic gland in the blood of healthy individuals and patients with complications of the hepatobiliary zone (HBZ), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (γ-GT), total bilirubin, albumin, α-amylase, lipase, and elastase.
3. Assessment of the diagnostic informativeness of certain cytokines (IL-6 and TNF-α) before and after surgery.
4. Evaluation of certain antimicrobial peptides (lactoferrin, zonulin, and calprotectin) before and after surgery.
5. Comparative analysis of the effectiveness of complex surgical and medical treatment methods and investigation of their prognostic significance in dynamics.

The research methods. In the research, diagnostic, biochemical, and immunoassay analysis methods have been used.

The main provisions of the dissertation submitted for defense:

1. Surgical diseases of the HBZ are accompanied by MS both during the perioperative period and in the postoperative phases.

2. In the early diagnosis of MS developed in association with surgical diseases of the HBZ, there is particular importance in determining both the biochemical indicators of blood and the involvement of antimicrobial peptides and the activity of elastase-1 enzyme in feces.

3. The treatment carried out from the preoperative period to the postoperative period of MS developed in association with surgical diseases of the HBZ normalizes the participation of the liver and pancreatic gland in metabolic processes.

4. The use of hepatoprotectors in the postoperative period of surgical diseases of the HBZ prevents the development of MS and improves the quality of life of patients.

Scientific novelty of the research. The conducted research has elucidated that MS occurring during the perioperative period and after surgery is attributable to different pathogenetic mechanisms, allowing for the development of early and differential diagnostic measures. The study of AMPs and cytokines involved in the pathogenesis of MS associated with surgical diseases of the HBZ has provided an opportunity to evaluate additional diagnostic measures, enhancing the traditional treatment regimen. The inclusion of therapeutic agents that normalize metabolic disturbances observed in the liver, biliary tract, pancreatic gland, and intestines in the main disease's conventional treatment scheme ensures more favorable treatment outcomes.

Practical significance of research. The initiation of the pathogenetic treatment of MS before surgery and its continuation after surgery contributes to the reduction of the syndrome's accidental occurrence, acceleration of patient rehabilitation, and improvement in the quality of life of patients.

Approbation and application. The materials of the dissertation work were discussed at the conferences "International Black Sea

Coastline Countries Scientific Research Symposium-VI," "International Siirt Conference on Scientific Research," and "4th International Marmara Scientific Research and Innovation Congress." The dissertation materials were also discussed at the seminar session of the ED 2.06 Dissertation Council at Azerbaijan Medical University (Baku, 2023).

Application of the obtained results. The results of the dissertation work are being implemented in the teaching process of the Department of Surgical Diseases and Biochemistry at Azerbaijan Medical University.

The organization where the dissertation work was performed. Department of III Surgical Diseases of the Azerbaijan Medical University and the teaching clinical biochemistry laboratory.

The scope and structure of the dissertation. The dissertation was written in Azerbaijani, consisting of 172 pages (total 238.943 characters) and printed on a computer. It includes the following sections: introduction, literature review, materials and methods of research, results of personal research, discussion of obtained results, conclusions, practical recommendations (531 characters), list of references used, and lists of abstracts and personal references. The dissertation is illustrated with 26 tables and 25 figures. The list of references comprises 178 sources, including 13 Azerbaijani, 1 Turkish, 92 Russian, and 72 works by scholars from other foreign countries.

MATERIALS AND METHODS OF RESEARCH

The research study was conducted on a total of 120 individuals, comprising 17 patients with liver hemangiomas, 29 patients with liver hydatid cysts (echinococcosis), and 74 patients aged 30-60 years with a history of recurrent and long-standing episodes of biliary colic due to Cholelithiasis (Gallstone Disease). Among the patients with Gallstone Disease, 29 (34.3%) were male, and 45 (65.7%) were female. The control group consisted of 18 healthy individuals of corresponding age (males - 7 (37.0%), females - 11 (63.0%)) (Figure 1).

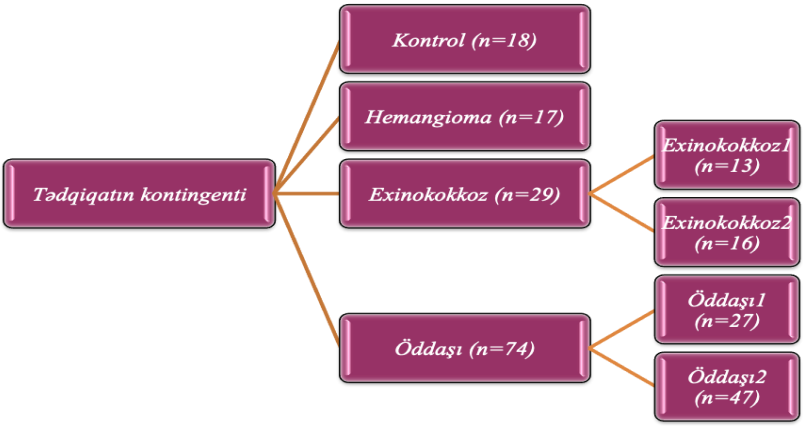

Figure 1. The general characteristics of research groups

The patients enrolled in the research were selected from among individuals who underwent examination and surgery for hepatobiliary organs at the Department of Surgical Teaching Clinic of Azerbaijan Medical University.

Clinical-anamnestic inquiries were conducted with the recruited patients, their complaints were listened to, and the degree of manifestation of observed clinical signs was noted.

The complex diagnosis of MS developed during the clinical course of hepatobiliary surgical diseases and after surgery was conducted using ultrasound imaging techniques (radiological, computed tomography, and magnetic resonance imaging).

The general characteristics of the treatment applied. 44 patients with malabsorption syndrome (MS) underwent appropriate treatment aimed at correcting the hepatopancreatobiliary system. Following cholecystectomy surgery in individuals with Gallstone Disease (GSD), a treatment regimen was prescribed involving the use of appropriate hepatoprotectors and combined enzyme preparations.

Patients with GSD and hydatid cysts were divided into two subgroups according to different treatment directions. In Group I, the treatment of MS involved the use of "Essentiale Forte N," "Hepabest," "Heptral," and "Kreon" preparations, which normalize the functions of the liver, biliary tract, and pancreatic gland. All patients received

"Essentiale Forte N" - 2 capsules three times a day during meals for a duration of 6 months. Additionally, in one group of patients, "Hepabest" was prescribed at a dose of 1 capsule three times a day or "Hepabest forte" at a dose of 1 capsule three times a day after meals for a duration of 3 months, while in the other group, "Heptral" was prescribed at a dose of 1 capsule twice a day during meals for a duration of 3 months. The therapeutic dose of Kreon was determined based on the severity of malabsorption syndrome (MS).

In patients with hydatid cysts, desensitizing agents, hepatoprotectors, combined enzyme preparations, pre- and probiotics were included in the conservative treatment regimen following laparoscopic hydatid cystectomy.

Biochemical and immunoassay research methods. Blood samples taken from the cubital vein were centrifuged to obtain serum, and the levels of total bilirubin, albumin, and fractions, as well as ALT, AST, ALP, γ-GT, amylase, and lipase enzymes were determined using colorimetric and kinetic methods with reagent kits from "Human" (Germany) and another firm.

Before surgery, the presence of IgG antibodies against Echinococcus in the blood serum of the patients included in the study was determined using the enzyme-linked immunosorbent assay (ELISA) method with the "Echinococ-IGG-IFA-BEST" reagent kit. The concentration of TNF-α and IL-6 cytokines in the blood serum was measured using the "sandwich" method with reagent kits from "Vector-Best" (Russian Federation).

Considering the significant role of gastrogenic etiology factors and the conflict of the external secretory activity of the pancreatic gland in the development of malabsorption syndrome (MS) accompanying surgical diseases of the hepatobiliary organs, the level of elastase-1 enzyme in fecal samples was determined. The analysis method for elastase-1 enzyme in fecal samples is based on the principle of a sandwich immunoassay ("Immuno Diagnostic", Germany).

The levels of zonulin, calprotectin, and lactoferrin in fecal samples were determined using the enzyme-linked immunosorbent assay (ELISA) method with reagent kits from "Immuno Diagnostic"

(Germany) and analyzed on the Stat Fax 303 Plus (USA) immunoassay analyzer (λ = 450 nm, differential filter 650 nm).

The obtained results were subjected to mathematical-statistical analysis using methods such as variation, discriminant, correlation, and ROC analysis.

RESULTS AND DISCUSSION OF RESEARCH

Classification of clinical signs during surgical diseases of hepatobiliary organs

Upon admission to the clinic, patients presented with epigastric pain and postprandial gastric heaviness, decreased appetite (anorexia in some cases), dysphagia, satiety after meat ingestion, vomiting, weight loss, generalized weakness, irregular bowel movements, subfebrile temperature, among other symptoms.

Clinical examinations revealed that among patients with hemangiomas, 8 (47.1%) experienced stomach heaviness after eating, 9 (52.9%) had epigastric pain, 7 (41.2%) reported decreased appetite, 5 (29.4%) felt reflux after eating meat, 9 (52.9%) experienced general weakness, 7 (41.2%) had weight loss, 5 (29.4%) had dysphagia, 6 (35.3%) experienced belching, 4 (23.5%) had hiccups, 8 (47.1%) felt heartburn, 4 (23.5%) experienced vomiting, 6 (35.3%) had subfebrile temperature, 8 (61.5%) had irregular bowel movements, 7 (41.2%) had diarrhea and mucous stools, and 6 (35.3%) had steatorrhea.

Before surgery, among patients with echinococcosis in Group I, 8 (61.5%) experienced stomach heaviness after eating, 7 (53.8%) had epigastric pain, 8 (61.5%) reported decreased appetite, 7 (53.8%) felt reflux after eating meat, 8 (61.5%) experienced general weakness, 6 (46.2%) had weight loss, 6 (46.2%) had dysphagia, 10 (76.9%) experienced belching, 5 (38.5%) had hiccups, 8 (61.5%) felt heartburn, 6 (46.2%) experienced vomiting, 6 (46.2%) had subfebrile temperature, 8 (61.5%) had irregular bowel movements, 7 (53.8%) had diarrhea and mucous stools, and 7 (53.8%) had steatorrhea.

In Group II of patients with echinococcosis, before surgery, 11 (68.8%) experienced stomach heaviness after eating, 11 (68.8%) had epigastric pain, 11 (68.8%) reported decreased appetite, 10 (62.5%)

felt reflux after eating meat, 11 (68.8%) experienced general weakness, 8 (50.0%) had weight loss, 8 (50.0%) had dysphagia, 6 (37.5%) experienced belching, 5 (31.3%) had hiccups, 9 (36.3%) felt heartburn, 5 (31.3%) experienced vomiting, 8 (50.0%) had subfebrile temperature, 9 (56.3%) had irregular bowel movements, 8 (50.0%) had diarrhea and mucous stools, and 7 (43.8%) had steatorrhea.

Results of conducted clinical examinations have revealed that in Group I of patients with Cholelithiasis Disease (CD) identified before surgery, 21 individuals (77.8%) experienced postprandial epigastric heaviness, 20 individuals (74.1%) reported epigastric pain, 16 individuals (59.3%) exhibited decreased appetite, 12 individuals (44.4%) manifested aversion to fatty foods, 18 individuals (66.7%) complained of general weakness, 14 individuals (51.9%) displayed weight loss, 14 individuals (51.9%) reported dysphagia, 11 individuals (40.7%) experienced belching, 7 individuals (25.9%) had hiccupping, 16 individuals (59.3%) complained of palpitations, 11 individuals (40.7%) suffered from vomiting, 14 individuals (51.9%) had subfebrile temperature, 17 individuals (63.0%) had irregular bowel movements, 15 individuals (55.6%) experienced diarrhea and steatorrhea-like feces, and 14 individuals (51.9%) were observed to have steatorrhea.

In Group II of patients with CD, identified before surgery, 30 individuals (63.8%) experienced postprandial epigastric heaviness, 28 individuals (59.6%) reported epigastric pain, 23 individuals (48.9%) exhibited decreased appetite, 14 individuals (29.8%) had aversion to fatty foods, 22 individuals (46.8%) complained of general weakness, 16 individuals (34.0%) manifested weight loss, 21 individuals (44.7%) reported dysphagia, 19 individuals (40.4%) experienced belching, 15 individuals (31.9%) had hiccupping, 31 individuals (66.0%) complained of palpitations, 21 individuals (44.7%) suffered from vomiting, 17 individuals (36.2%) had subfebrile temperature, 28 individuals (59.6%) had irregular bowel movements, 22 individuals (46.8%) experienced diarrhea and steatorrhea-like feces, and 24 individuals (51.1%) were noted to have steatorrhea.

In all patients with exacerbation of MS, sharp weight loss was observed.

Assessment of the functional status of the liver, bile ducts, and gallbladder before surgery for surgical diseases of the hepatobiliary organs

During the assessment of hepatic enzymatic activity in patients with hemangioma, it was determined that the activity of ALT, AST, γ-GT, and ALP in the blood is increased by 24.7% ($p=0.004$), 37.6% ($p=0.001$), 42.4% ($p=0.005$), and 15.6% ($p=0.099$) respectively compared to healthy individuals. In patients with echinococcosis, the activity of ALT, AST, γ-GT, and ALP enzymes in Group I and II is increased by 2.1 times ($p<0.001$) and 2.0 times ($p<0.001$); 2.0 times ($p<0.001$) and 2.1 times ($p<0.001$); 76.3% ($p<0.001$) and 58.6% ($p=0.001$); 44.7% ($p=0.001$) and 34.7% ($p=0.013$) respectively compared to the control group.

Among the patients included in our clinical investigation, in Groups I and II of patients with CD, the activity of ALT, AST, γ-GT, and ALP enzymes in the blood is observed to increase by 2.9 times ($p<0.001$) and 2.8 times ($p<0.001$); 2.3 times ($p<0.001$) and 2.4 times ($p<0.001$); 2.2 times ($p<0.001$) and 2.4 times ($p<0.001$); 55.1% ($p<0.001$) and 62.6% ($p<0.001$) respectively compared to the control group.

In Groups I and II of patients with echinococcosis, the total protein and albumin content in the blood are decreased by 6.7% ($p=0.003$) and 7.3% ($p=0.003$); 13.1% ($p=0.001$) and 13.6% ($p<0.001$) respectively compared to the control group. During the perioperative period in patients with CD, the total protein and albumin content in the blood in Groups I and II are decreased by 9.1% ($p<0.001$) and 8.4% ($p<0.001$); 16.8% ($p<0.001$) and 18.5% ($p<0.001$) respectively compared to the control group.

In Groups I and II of patients with echinococcosis, the total bilirubin content in the blood is increased by 41.3% ($p<0.001$) and 42.9% ($p<0.001$), conjugated bilirubin by 31.5% ($p=0.013$) and 41.0% ($p<0.001$), and unconjugated bilirubin by 45.2% ($p<0.001$) and 48.7% ($p<0.001$) respectively compared to the control group. In patients with CD in Groups I and II, the total, conjugated, and unconjugated bilirubin content in the blood is increased by 60.8% ($p<0.001$) and 58.5% ($p<0.001$), 2.1 times ($p<0.001$) and 2.2 times ($p<0.001$), 42.7%

(p<0.001) and 39.3% (p<0.001) respectively compared to the control group.

The determination of lipase and α-amylase enzyme activity carries diagnostic significance in assessing pancreatic exocrine function. Additionally, the determination of elastase-1 enzyme activity is considered the gold standard in evaluating the external secretory functions of the pancreas. The research conducted revealed that in patients with hemangioma, the activity of α-amylase and lipase is increased by 27.7% (p=0.013) and 11.5% (p=0.373) respectively compared to the control group. In Groups I and II of patients with echinococcosis, the activity of α-amylase and lipase is increased by 63.7% (p<0.001) and 52.7% (p<0.001); 33.8% (p=0.020) and 37.4% (p=0.008) respectively compared to the control group. In patients with CD in Groups I and II, the activity of α-amylase and lipase is increased by 94.5% (p<0.001) and 2.0 times (p<0.001); 70.0% (p<0.001) and 63.1% (p<0.001) respectively compared to the control group.

The results of the research indicate that the activity of elastase-1 enzyme tends to decrease by 9.9% (p=0.109) compared to the control group in patients with hemangioma, while in Groups I and II of patients with echinococcosis, it decreases by 33.7% (p<0.001) and 30.3% (p<0.001) respectively, and in patients with CD in Groups I and II, it decreases by 2.7 times (p<0.001) and 2.8 times (p<0.001) respectively.

The activity of ALT, AST, ALP, α-amylase, and lipase enzymes in the blood of patients increases significantly, while the activity of elastase-1 enzyme in stool decreases significantly, indicating structural-functional damage to the liver, biliary tract, and pancreatic secretory cells.

The levels of cytokines and antimicrobial peptides during surgical diseases of the hepatobiliary organs.

The study of cytokine and AMP levels during the evaluation of immunological changes in the pathogenesis of MS syndrome plays a significant role in understanding the mechanisms involved in the treatment of this disease and the resolution of postoperative purulent-inflammatory processes.

Analyses conducted before surgery revealed that in patients with hemangioma, the levels of IL-6 and TNF-α are increased by 84.8% ($p=0.009$) and 45.9% ($p=0.084$) respectively compared to the control group; in patients with echinococcosis in Group I, the levels are increased by 5.3 times ($p<0.001$) and 2.3 times ($p=0.003$), and in Group II, by 6.1 times ($p<0.001$) and 2.5 times ($p<0.001$); in patients with CD in Groups I and II, the levels are increased by 5.0 times ($p<0.001$) and 4.8 times ($p<0.001$), 3.5 times ($p<0.001$) and 3.1 times ($p<0.001$) respectively. Our research also studied LF, calprotectin, and zonulin AMP levels in the feces of patients with hemangioma, echinococcosis, and CD. In the feces of patients with hemangioma, there is a tendency for an increase in zonulin and LF levels by 23.9% ($p=0.642$) and 50.6% ($p=0.525$) respectively compared to the control group, while calprotectin levels increase by 2.0 times ($p=0.007$). In patients with echinococcosis, the intensification of the inflammatory process results in a significant increase in zonulin, calprotectin, and LF levels in Groups I and II by 2.0 times ($p=0.035$) and 74.8% ($p=0.005$), 4.5 times ($p<0.001$) and 4.2 times ($p<0.001$), 38.6 times ($p<0.001$) and 40.1 times ($p<0.001$) respectively compared to the control group. In patients with CD, zonulin, calprotectin, and LF levels increase significantly in Group I by 2.2 times ($p=0.012$), 5.8 times ($p<0.001$), and 60.0 times ($p<0.001$), and in Group II by 91.7% ($p=0.011$), 5.8 times ($p<0.001$), and 52.8 times ($p<0.001$) respectively compared to the control group.

According to the results of correlation analysis, during surgical diseases, there is a positive correlation between ALT enzyme activity and AST ($\rho=0.288$; $p<0.001$), ALP ($\rho=0.206$; $p=0.003$), γ-GT ($\rho=0.415$; $p<0.001$), α-amylase ($\rho=0.431$; $p<0.001$), and lipase ($\rho=0.355$; $p<0.001$) activities, while there is a negative correlation with elastase-1 activity ($\rho=-0.596$; $p<0.001$). Correlation analysis also revealed dependencies between cytokines and some biochemical parameters in the studied patients. For instance, there is a positive correlation between IL-6 levels and ALT ($\rho=0.261$; $p=0.033$), total ($\rho=0.260$; $p=0.034$) and unconjugated bilirubin ($\rho=0.268$; $p=0.028$), and a negative correlation with elastase-1 ($\rho=-0.248$; $p=0.050$). An increase in γ-GT activity in the blood during surgical diseases

correlates with an increase in zonulin levels, and high zonulin levels correlate with diarrhea (ρ=0.370; p=0.013) and steatorrhea (ρ=0.314; p=0.038). An increase in LF levels in the feces of these patients may be one of the indicators of steatorrhea (ρ=0.414; p=0.005). Correlation analysis also revealed correlations between AMPs and proinflammatory cytokines; for example, there is a positive correlation between IL-6 and TNF-α (ρ=0.530; p<0.001), and between IL-6 and calprotectin (ρ=0.366; p=0.015).

Evaluation of the functional status of the liver, bile ducts, and gallbladder during surgical diseases of the hepatobiliary organs after surgery.

In the course of the study, patients with hemangiomas were observed clinically for 1 year. The functional state of the liver, bile ducts, and pancreas, as well as the involvement of cytokines and AMP, was assessed dynamically at 3 months, 6 months, and 1 year.

The examinations revealed that in patients with hemangiomas, the activity of ALT, AST, γ-GT, and ALP enzymes remained significantly higher compared to control group indicators by 17.0% (p=0.039), 35.0% (p=0.004), 33.1% (p=0.006), and 11.6% (p=0.187), respectively, during the first 3 months of observation, with minimal changes compared to the initial results. After 6 months, the activity of AST and γ-GT enzymes decreased significantly by 17.4% (p=0.019) and 22.5% (p=0.023), respectively, compared to previous indicators.

After 1 year, the activity of ALT, AST, and γ-GT enzymes decreased significantly by 17.4% (p=0.039), 22.3% (p=0.009), and 25.3% (p=0.006), respectively, compared to initial indicators, showing much less difference from the control group indicators. In this group, albumin involvement was lower at 3 months, 6 months, and 1 year, by 5.1% (p=0.015), 6.1% (p=0.005), and 5.7% (p=0.003), respectively, compared to controls.

Monitoring of pancreatic activity in patients with hemangiomas over 1 year showed a tendency for a decrease in the activity of α-amylase and lipase enzymes towards normal levels compared to initial results. The activity of elastase-1 enzyme increased by 11.9% (p=0.015) compared to initial results after 1 year, without significant difference from the control group (p=0.895).

One of the main correction methods for MS is enzyme replacement therapy. A course of enzyme therapy was conducted for 35 patients after exinoectomy and cholecystectomy surgeries. The daily dose of drug preparations used was determined based on the degree of activity of the studied enzymes. The results of enzyme replacement therapy were evaluated over 3 months, 6 months, and 1 year based on both clinical signs and biochemical analyses.

In the treatment group of patients with echinococcosis, primarily the activity of ALT and ALP enzymes showed a tendency to decrease compared to pre-treatment results: by 27.4% ($p=0.011$) and 34.5% ($p=0.064$) at 3 months into the treatment course; by 22.9% ($p=0.033$) and 21.9% ($p=0.116$) at 6 months. However, after 1 year of treatment, the activity of ALT, AST, and γ-GT enzymes remained significantly higher compared to the control group by 67.9% ($p<0.001$), 93.1% ($p<0.001$), and 70.1% ($p<0.001$), respectively.

In the treatment group of patients with echinococcosis, the decrease in the activity of α-amylase after treatment was determined to be 20.0% ($p=0.021$), 13.7% ($p=0.101$), and 16.9% ($p=0.033$) at 3 months, 6 months, and 1 year, respectively, compared to pre-treatment results. The activity of lipase and pancreatic elastase-1 enzymes did not significantly differ during the treatment period compared to pre-treatment results in this investigated group.

In the treatment group of patients with echinococcosis, the overall level of impairment increased significantly at 3 months, 6 months, and 1 year after surgery, reaching 71.8±1.4 q/l ($p=0.001$), 72.3±1.4 q/l ($p=0.001$), and 72.1±1.9 q/l ($p=0.001$), respectively. However, after the enzyme replacement therapy course, albumin involvement increased by 10.3% ($p=0.011$), 9.4% ($p=0.010$), and 10.5% ($p=0.019$) at 3 months, 6 months, and 1 year, respectively, showing no significant difference compared to the control group.

In patients with echinococcosis in Group I, the involvement of bilirubin fractions decreased compared to pre-treatment results over the course of 1 year. Specifically, after 3 months of treatment, the involvement of total and direct bilirubin decreased by 24.3% ($p=0.001$) and 31.0% ($p=0.005$) respectively; after 6 months, by 24.9% ($p=0.001$) and 30.3% ($p=0.004$); and after 1 year, by 28.5%

(p=0.001) and 32.0% (p=0.001), respectively, approaching normal levels.

In patients with echinococcosis in Group II, the application of specific hepatoprotective therapy alongside standard treatment played a significant role in restoring liver function. In this group, after 3 months of treatment, ALT activity decreased by 25.0% (p=0.015); ALT, AST, and γ-GT enzyme activities decreased by 41.2% (p=0.001), 27.8% (p=0.006), and 21.1% (p=0.034) respectively after 6 months; and after 1 year, they decreased by 45.8% (p=0.001), 47.2% (p=0.001), and 27.0% (p=0.010) respectively, compared to pre-treatment levels, reaching levels comparable to the control group. The activity of α-amylase and lipase decreased after 3 months, 6 months, and 1 year of treatment, approaching normal levels by 15.5% (p=0.015) and 20.9% (p=0.038); 18.9% (p=0.007) and 19.7% (p=0.121); and 21.0% (p=0.002) and 21.9% (p=0.030) respectively, compared to pre-treatment levels. Notably, the decrease in α-amylase and lipase activity was more pronounced after 1 year, indicating the superior effectiveness of the applied treatment compared to standard therapy. The activity of pancreatic elastase-1 increased significantly after 3 months (p=0.044), and after 6 months and 1 year, by 26.9% (p=0.003) and 35.8% (p=0.002) respectively, approaching levels similar to the control group.

In Group II patients with echinococcosis, the involvement of total protein and albumin decreased significantly after 3 months, by 4.8% (p=0.039) and 8.4% (p=0.002) respectively; after 6 months, by 6.1% (p=0.007) and 9.9% (p<0.001) respectively; and after 1 year, by 6.5% (p=0.009) and 12.4% (p<0.001) respectively, compared to pre-treatment levels, showing a significant difference from the control group. The involvement of total, conjugated, and unconjugated bilirubin decreased significantly after 3 months by 24.9% (p<0.001), 15.6% (p=0.001), and 28.5% (p=0.001) respectively; after 6 months by 27.0% (p<0.001), 25.7% (p=0.001), and 27.6% (p=0.002) respectively; and after 1 year by 30.0% (p<0.001), 29.0% (p<0.001), and 30.3% (p=0.001) respectively, compared to pre-treatment levels. After 6 months of treatment, the involvement of conjugated bilirubin increased compared to Group I (p=0.016).

In patients with GS undergoing cholecystectomy in Group I, it was observed during the study of liver excretory function after 3 months of enzyme therapy that ALT activity decreased significantly by 30.7% ($p<0.001$) compared to pre-treatment levels. After 6 months and 1 year, ALT enzyme activity increased by 28.4% ($p<0.001$) and 24.5% ($p=0.001$) respectively, compared to pre-treatment levels, while AST enzyme activity did not change significantly ($p=0.923$ after 6 months; $p=0.801$ after 1 year). The activity of ALT and AST enzymes remained significantly higher than the control group after 1 year of treatment, by 2.2 times ($p<0.001$) and 2.3 times ($p<0.001$) respectively.

In patients with GS undergoing cholecystectomy, the activity of ALP enzyme in blood serum decreased significantly after 3 months, 6 months, and 1 year of treatment, by 24.7% ($p<0.001$), 22.3% ($p=0.001$), and 24.7% ($p<0.001$) respectively, compared to pre-treatment levels, approaching levels similar to the control group. The activity of γ-GT enzyme remained significantly higher than the control group, by 2.1 times ($p<0.001$).

The results obtained indicate that standard treatment in Group I patients with cholelithiasis (GSD) cannot ensure full restoration of liver and bile duct enzymes. In this group, the activity of α-amylase and lipase decreased by 26.4% ($p<0.001$) and 25.4% ($p<0.001$) respectively after 3 months of treatment, 28.3% ($p<0.001$) and 21.3% ($p<0.001$) after 6 months, and 25.4% ($p=0.001$) and 20.8% ($p<0.001$) after 1 year, compared to pre-treatment levels. The activity of pancreatic elastase-1 increased significantly after 3 months ($p<0.001$), 6 months, and 1 year, by 75.1% ($p<0.001$), 63.8% ($p<0.001$), and 61.2% ($p<0.001$) respectively, compared to pre-treatment levels.

In this group, the involvement of total protein and albumin increased compared to pre-treatment levels over the course of 1 year, with increases of 6.3% ($p=0.001$) and 9.3% ($p=0.002$) after 3 months, 4.8% ($p=0.015$) and 14.3% ($p<0.001$) after 6 months, and 5.9% ($p=0.001$) and 12.0% ($p<0.001$) after 1 year.

In Group I patients with GSD, the involvement of total, conjugated, and unconjugated bilirubin decreased significantly after 3 months by 22.6% ($p<0.001$), 34.9% ($p<0.001$), and 15.7% ($p=0.003$)

respectively; after 6 months by 21.8% ($p<0.001$), 41.6% ($p<0.001$), and 10.6% ($p=0.007$); and after 1 year by 21.2% ($p<0.001$), 41.5% ($p<0.001$), and 9.6% ($p=0.038$) respectively, compared to pre-treatment levels. The decrease in the involvement of total and conjugated bilirubin remained significant after 1 year compared to the control group ($p<0.001$), while the involvement of unconjugated bilirubin differed significantly ($p=0.094$).

In Group II patients with GSD, the activity of ALT and AST enzymes decreased significantly after 3 months of treatment, by 29.3% ($p<0.001$) and 16.7% ($p=0.001$) respectively; after 6 months, by 38.2% ($p<0.001$) and 35.5% ($p<0.001$); and after 1 year, by 2.2 times ($p<0.001$) and 2.1 times ($p<0.001$) respectively, compared to pre-treatment levels. The decrease in ALT and AST enzyme activity was significantly more pronounced after 1 year compared to Group I ($p<0.001$).

In Group II patients with GSD, the involvement of γ-GT and ALP enzymes decreased significantly after 3 months of treatment, by 15.1% ($p<0.001$) and 27.4% ($p<0.001$) respectively; after 6 months, by 24.5% ($p<0.001$) and 31.7% ($p<0.001$); and after 1 year, by 41.8% ($p<0.001$) and 37.1% ($p<0.001$) respectively, compared to pre-treatment levels. While the involvement of γ-GT remained significantly higher than the control group after 1 year ($p<0.001$), the involvement of ALP approached normal levels ($p=0.803$).

The activity of α-amylase and lipase enzymes decreased significantly compared to pre-treatment levels after 3 months of treatment by 31.5% ($p<0.001$) and 19.6% ($p<0.001$) respectively; after 6 months by 38.0% ($p<0.001$) and 35.8% ($p<0.001$); and after 1 year by 44.6% ($p<0.001$) and 42.1% ($p<0.001$) respectively, approaching normal levels. Compared to Group I, the decrease in the activity of α-amylase and lipase enzymes during the treatment period was observed to be 23.0% ($p<0.001$) and 29.9% ($p<0.001$) respectively after 1 year. The activity of elastase-1 increased significantly compared to pre-treatment levels after 3 months ($p<0.001$), 6 months, and 1 year, by 75.5% ($p<0.001$), 2.3 times ($p<0.001$), and 2.4 times ($p<0.001$) respectively, matching the results of the control group.

After 3 months of treatment, there was a significant reduction in the involvement of total protein and albumin, by 6.1% ($p<0.001$) and 14.2% ($p<0.001$) respectively. After 6 months, the reduction was 6.7% ($p<0.001$) and 16.0% ($p<0.001$), and after 1 year, it was 7.3% ($p<0.001$) and 17.7% ($p<0.001$) compared to baseline levels, approaching those of the control group. In this cohort, the levels of total, conjugated, and unconjugated bilirubin decreased significantly after 3 months of fermentative treatment, by 18.3% ($p<0.001$), 37.8% ($p<0.001$), and 7.0% ($p=0.021$) respectively. After 6 months, the reductions were 26.3% ($p<0.001$), 45.4% ($p<0.001$), and 15.2% ($p<0.001$), and after 1 year, they were 31.0% ($p<0.001$), 46.5% ($p<0.001$), and 22.1% ($p<0.001$) respectively compared to baseline. After 1 year, total bilirubin levels remained 9.5% ($p=0.007$) higher in the control group, while conjugated ($p=0.077$) and unconjugated bilirubin ($p=0.094$) levels varied compared to the control group. Compared to Group I receiving standard treatment, total and unconjugated bilirubin levels decreased by 7.1% ($p=0.002$) and 7.4% ($p=0.009$) respectively after 6 months, and by 13.8% ($p<0.001$) and 15.8% ($p<0.001$) respectively after 1 year. The most significant reduction after fermentative treatment was observed in total bilirubin levels, while the unconjugated bilirubin fraction showed minimal changes.

Therefore, there are substantial alterations in the functional activity of the liver, bile ducts, and gallbladder in patients experiencing exacerbations with MS post-surgery. Our monitoring indicates that fermentative therapy does not yield significant benefits in the short term, with its most notable positive outcome observed within 1 year. The treatment administered to patients with echinococcosis and GSD leads to the restoration of the functional state of the liver, bile ducts, and gallbladder, contributing to the normalization of bile and pigment metabolism.

Assessment of cytokines and antimicrobial peptides after treatment during surgical diseases of the hepatobiliary organs.

As shown in the conducted research, patients with hemangiomas were under dynamic observation for 1 year even without treatment. Analyses conducted after 1 year indicate a tendency for a decrease in

the levels of IL-6 by 32.3% (p=0.126) and 26.0% (p=0.241) relative to the initial results in this group of patients.

Dynamic observations over 1 year in patients who underwent exinococcectomy show that in Group I patients receiving standard treatment, there is a tendency for a decrease in the involvement of IL-6 by 33.4% (p=0.374) compared to baseline levels after 3 months of surgery, but no significant changes were observed at 3 months and 1 year.

In Group I of patients with echinococcosis receiving standard treatment, TNF-α levels increased by 42.7% (p=0.008) compared to baseline after 3 months of standard treatment. The involvement of IL-6 and TNF-α is significantly higher compared to the control group, by 5.5 times (p<0.001) and 2.6 times (p=0.003) respectively after 1 year.

In patients with echinococcosis receiving treatment according to the respective scheme for correction of the hepatopancreatobiliary system alongside standard treatment in Group II, the involvement of IL-6 and TNF-α decreased by 44.1% (p=0.013) and 15.0% (p=0.444) respectively after 3 months of surgery, by 3.5 times (p=0.007) and 31.1% (p=0.037) respectively after 6 months, and by 5.0 times (p=0.007) and 2.0 times (p=0.013) respectively after 1 year compared to baseline. After 6 months of treatment, the involvement of IL-6 and TNF-α decreased by 3.2 times (p=0.001) and 31.0% (p=0.086) respectively, and after 1 year, it decreased by 4.6 times (p<0.001) and 2.1 times (p=0.013) respectively compared to patients receiving standard treatment.

In patients with cholelithiasis (GSD) in Group I, a significant reduction in the involvement of IL-6 and TNF-α by 41.8% (p=0.003) and 30.3% (p=0.068) respectively at 3 months, 32.3% (p=0.006) and 33.1% (p=0.028) respectively at 6 months, and 30.3% (p=0.006) and 28.5% (p=0.098) respectively at 1 year compared to baseline levels was observed.

In Group II of GSD patients receiving hepatoprotective therapy alongside standard treatment, IL-6 and TNF-α involvement decreased significantly by 37.1% (p=0.003) and 27.6% (p=0.073) respectively at 3 months, by 3.6 times (p<0.001) and 2.4 times (p<0.001) at 6 months, and by 4.4 times (p<0.001) and 2.9 times (p<0.001) respectively at 1

year compared to baseline. After 1 year, the levels were only slightly different from those in the control group.

During the study of antimicrobial peptides (AMPs), it was determined that the involvement of zonulin, calprotectin, and lactoferrin (LF) in the coprofiltrate of patients with hemangiomas did not significantly change over 1 year.

Research conducted on patients with echinococcosis in Group I showed a tendency for a decrease in the involvement of zonulin, calprotectin, and LF by 29.1% (p=0.176), 44.8% (p=0.128), and 2.5 times (p=0.018) respectively at 3 months, by 33.0% (p=0.310), 31.2% (p=0.310), and 2.1 times (p=0.028) respectively at 6 months, and by 35.5% (p=0.345), 29.7% (p=0.176), and 2 times (p=0.028) respectively at 1 year compared to baseline (Table, Figure.2).

Table. Changes in the level of antimicrobial peptides after treatment in patients with echinococcosis (M±m)

Parameters	Zonulin		Calprotektin	
Groups	I echinococcosis, n=13	II echinococcosis,, n=16	I echinococcosis,, n=13	II echinococcosis,, n=16
Before operation	1.83±0.34 (0.5-2.9)	1.62±0.14 (1.2-2.1)	89.6±15.4 (38.4-149.0)	82.4±12.1 (31.8-137.0)
After 3 month	1.3±0.2 (0.5-1.9) p_W=0.176	1.3±0.18 (0.6-2.2) p_W=0.176	49.5±8.0 (19.9-81.0) p_W=0.128	46.2±5.0 (22.6-58.4) p_W=0.045
After 6 month	1.23±0.24 (0.4-2.3) p_W=0.310	1.06±0.21 (0.6-2.2) p_W=0.028	61.6±12.3 (25.6-103.8) p_W=0.310	28.6±3.7 (11.7-37.4) p_W=0.028
After 1 year	1.18±0.26 (0.6-2.6) p_W=0.345	0.97±0.2 (0.3-1.8) p_W=0.090	63.0±12.7 (7.2-109.0) p_W=0.176	24.8±3.4 (11.2-36.0) p_W=0.028
Control group	0.93±0.12 (0.4-1.7)		19.8±2.0 (10.0-29.6)	

Note: pw – compare to before operation

In Group II of patients with echinococcosis, there was a significant decrease in the involvement of zonulin, calprotectin, and LF by 19.9% (p=0.176), 43.9% (p=0.043), and 2.6 times (p=0.028)

respectively at 3 months, by 34.6% (p=0.028), 2.9 times (p=0.028), and 11.0 times (p=0.018) respectively at 6 months, and by 40.1% (p=0.028), 3.3 times (p=0.028), and 24.3 times (p=0.018) respectively compared to baseline. The involvement of zonulin, calprotectin, and LF at 1 year after surgery was 4.7% (p=0.866), 25.4% (p=0.205), and 65.0% (p=0.127) higher compared to the control group.

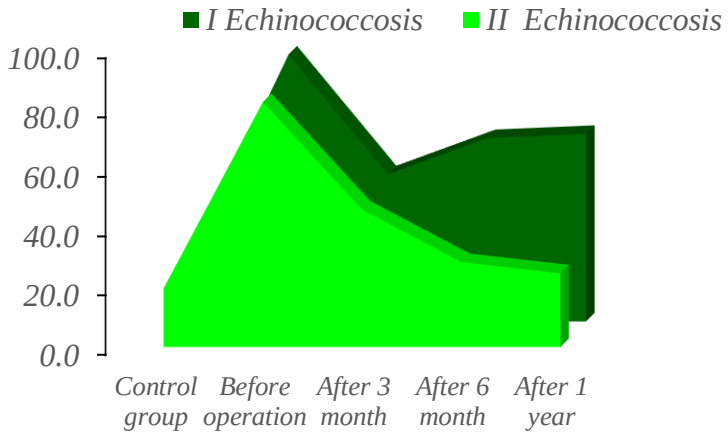

Figure 2. The dynamics of changes in calprotectin levels in patients with echinococcosis after surgery

The results indicate that the involvement of zonulin in patients with echinococcosis did not change significantly compared to those receiving standard treatment. However, there was a significant decrease in the involvement of calprotectin and LF, with a respective reduction of 2.2 times (p=0.041) and 4.9 times (p=0.002) at 6 months after treatment, and 2.5 times (p=0.035) and 11.4 times (p=0.002) at 1 year.

In Group I of patients with cholelithiasis (GSD), the involvement of zonulin, calprotectin, and LF decreased by 30.2% (p=0.062), 23.5% (p=0.328), and 19.6% (p=0.790) respectively at 3 months post-surgery, by 14.0% (p=0.477), 44.7% (p=0.016), and 3.1 times (p=0.004) respectively at 6 months, and by 22.1% (p=0.248), 30.7% (p=0.075), and 3.7 times (p=0.003) respectively at 1 year compared to

baseline results (Figure.3).

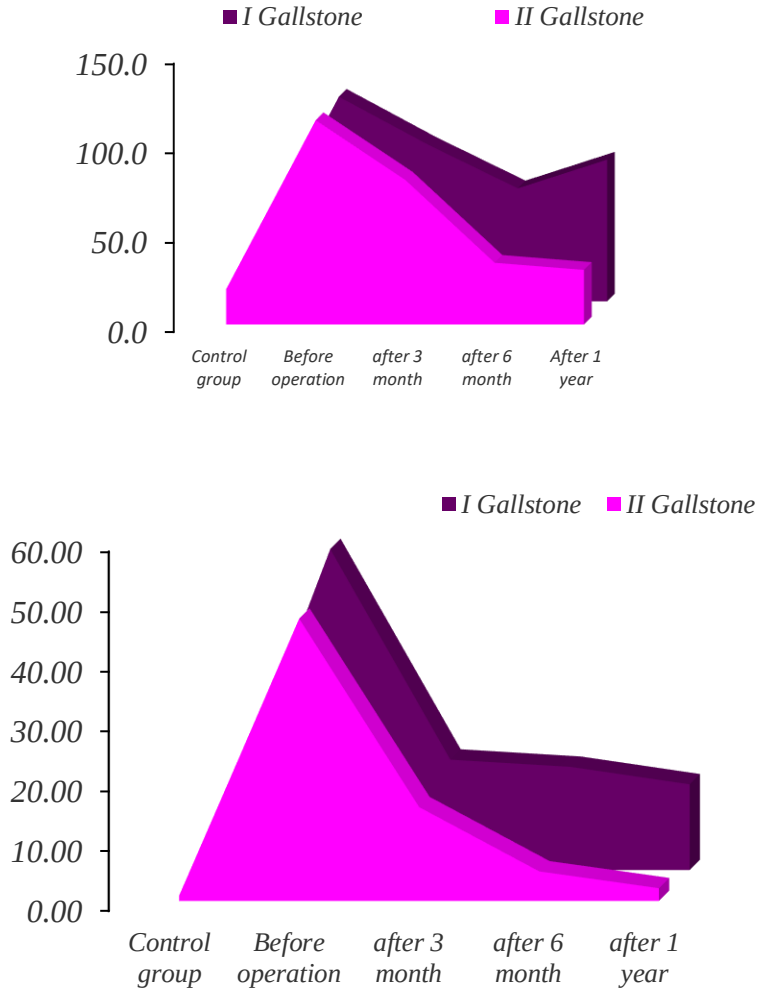

Figure 3. The dynamic changes in calprotectin and lactoferrin involvement in patients with gallstone disease after surgery.

In Group II of patients with cholelithiasis – gallstone disease (GSD), treatment resulted in a decrease in the involvement of zonulin, calprotectin, and LF at 3 months post-surgery by 19.6% (p=0.790), 29.1% (p=0.347), and 3.0 times (p=0.005) respectively. At 6 months,

there was a decrease by 31.4% (p=0.583), 3.3 times (p=0.002), and 9.5 times (p=0.002) respectively, while at 1 year, the decrease was by 34.7% (p=0.092), 3.7 times (p=0.005), and 22.0 times (p=0.002) respectively compared to baseline results.

Thus, the results obtained in the research may have significant scientific and practical importance in the development of additional diagnostic and prognostic measures, as well as in the selection of new treatment tactics for surgical diseases of the hepatobiliary system.

RESULTS

1. During the perioperative period, an increase in the activity of ALT, AST, γ-GT, and ALP enzymes, reflecting the functional activity of the liver and biliary tract, compared to the control group, indicates structural-functional impairments in the liver and biliary tract in patients with hydatidosis and cholelithiasis (GSD) exacerbating with MS [1, 8].
2. Investigation of cytokines and AMP during surgical hepatobiliary diseases is of significant practical importance in determining the progression of inflammatory processes in these patients. The involvement of IL-6 and TNF-α in patients with hydatidosis and GSD after surgery, with respective increases by 5.3 times and 2.3 times, 5.0 times and 3.5 times, demonstrates the significant importance of cytokines in the pathogenesis of MS [5, 6, 8].
3. For early diagnosis of MS associated with surgical diseases of hepatobiliary organs, the determination of zonulin, calprotectin, and lactoferrin involvement in coprofiltrate during the perioperative period in patients with hydatidosis and GSD is of great diagnostic importance, as their involvement increases by 2.0 times, 4.5 times, and 38.6 times, 2.2 times, 5.8 times, and 60.0 times compared to the control group [6, 7, 11].
4. Despite no significant changes in the activity of enzymes reflecting the functional activity of the liver, biliary tract, and pancreas 1 year after surgery in patients with hydatidosis and GSD under standard treatment, in the dynamics of complex treatment with hepatoprotectors, the activity of ALT, AST, γ-GT, ALP, α-amylase,

and lipase enzymes decreases significantly by 45.0%, 47.2%, 27.0%, 20.9%, 21.0%, and 21.9%, respectively, 2.2 times, 2.1 times, 41.8%, 37.1%, 44.6%, and 42.1%, while the activity of elastase-1 enzyme increases by 35.8% and 2.4 times [4, 5, 9].

5. In patients with hydatidosis and GSD, the levels of cytokines decrease significantly 1 year after surgery under the complex treatment with hepatoprotectors. The involvement of IL-6 and TNF-α cytokines decreases by 5.0 times and 2.0 times, respectively, 4.4 times and 2.9 times compared to baseline indicators before surgery [2, 5].

6. One year after surgery in patients with hydatidosis and GSD, the involvement of zonulin, calprotectin, and lactoferrin decreases significantly by 40.1%, 3.3 times, and 24.3 times, respectively, and by 34.7%, 3.7 times, and 22.0 times, respectively, compared to baseline indicators before surgery under complex treatment with hepatoprotectors [6, 7, 11].

PRACTICAL RECOMMENDATIONS

1. During surgical diseases of the hepatobiliary system, the analysis of antimicrobial peptides such as lactoferrin, zonulin, calprotectin, and inflammatory cytokines such as IL-6 and TNF-α is recommended alongside traditional biochemical tests due to their high informativeness in the early diagnosis of malabsorption syndrome.
2. For patients diagnosed with malabsorption syndrome, enzymatic therapy is recommended for the correction of the hepatobiliary system. This complex treatment normalizes the functional condition of the liver, bile ducts, and pancreas, improving the quality of life for patients.
3. In patients with malabsorption syndrome in the hepatobiliary system, immunocorrection alongside enzymatic therapy is recommended post-surgery to prevent the development of inflammation, aiming to optimize patient outcomes.

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12. Gasimova K.F. The outcome of the treating indigestion syndrome associated with gallstones, 3rd International Black Sea modern scientific research congress, Samsun, Turkiye, 2023, p.57

LIST OF ABBREVIATIONS

ALP – alkaline phosphatase

AMP – antimicrobial peptides

AsT – aspartate aminotransferase

İL – interleukins

HBZ – hepatobiliary zone diseases

KT – computer tomography

γ-QT – gamma-glutamiltransferase

MRT – Magnetic Resonance kholangiopankreatography

MS – Malabsorption Syndrome

GSD – gallstones disease

PXES – Postholesistectomic syndrome

TNF-α – tumor necrosis factor-α

USM – ultrasound

WHO – World Health Organization

The defense will be held on «10» june 2024 at «14^{00}» at the meeting of the Dissertation council ED 2.06 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Azerbaijan Medical University.

Address: AZ 1022, Baku city, A. Qasimzade street, 14 (conference hall)

Dissertation is accessible to the library of Azerbaijan Medical University.

Electronic version of the abstract is available on the official website of Azerbaijan Medical University (amu.edu.az).

Abstract was sent to the required addresses on «8» may 2024.

Signed for print: 06.05.2024

Paper format: 60 x 84 1/16

Volume: 39552

Number of hard copies: 20