ARTÍCULO ORIGINAL

Gac Méd Caracas 2024;132(4):910-924
DOI: 10.47307/GMC.2024.132.4.5

Optimization of therapeutic management for heartburn

Optimización del manejo terapéutico para la pirosis

Feruzakhan Tajibaeva[1, a], Eliza Bekeshova[2, b], Mayramkan Zhumanalieva[3, b], Gulzat Aripova[4, b], Diloramkhan Abdurashitova[5, b]

SUMMARY

One of the most common symptoms of gastrointestinal tract diseases is heartburn caused by biliary reflux. This symptom is prevalent in East Asian countries due to the predominance of spicy, fried foods with high fat content. **Purpose:** *enhance the condition and quality of life for patients by focusing on optimizing treatment protocols and interventions. This involved a detailed examination of current treatment methods and exploring improvements to increase their effectiveness and efficiency.* **Method:** *133 patients with symptoms of heartburn on the background of various diseases of the biliary system, in combination with other symptoms of the gastrointestinal tract, were selected to examine the subject. Individual schemes of complex treatment of heartburn in patients with alkaline reflux are developed, including prokinetic (Itomed) drugs in combination with ursodeoxycholic acid (Ursosan). The patients were divided into two groups: the first received Itomed, and the second received a combination of Itomed and Ursosan.* **Results:** *During the study, it was established that 82 % of patients responded positively to therapy with the prokinetic Itomed. In addition, patients receiving a combination of the drugs itoprid and ursodeoxycholic acid had a 92 % reduction in heartburn symptoms. Patients with alkaline reflux who suffered from biliary dyskinesia had a 98 % positive effect. Notably, treatment with Itomed in combination with Ursosan, which has a cytoprotective effect, reduces the inflammatory process of the mucous membrane of the upper digestive tract, which improves the digestive process, preventing the development of reflux, which substantially improves the general condition.*

Keywords: *Duodenal reflux, alkaline reflux, prokinetics, Itomed, ursodeoxycholic acid, Ursosan.*

DOI: https://doi.org/10.47307/GMC.2024.132.4.5

ORCID: 0000-0002-6735-7384[1]
ORCID: 0009-0000-4172-7511[2]
ORCID: 0009-0008-1156-4027[3]
ORCID: 0009-0004-2156-8575[4]
ORCID: 0009-0003-3595-6184[5]

[a]Department of Clinical Disciplines 1, Osh State University, 723500, Osh, Kyrgyz Republic.
[b]Department of Internal Diseases with a Course in Family Medicine, Osh State University, 723500, Osh, Kyrgyz Republic

*Corresponding author: Feruzakhan Tajibaeva
E-mail: tajibaevaferuzakhan@gmail.com

Recibido: 24 de julio 2024
Aceptado: 4 de septiembre 2024

RESUMEN

Uno de los síntomas más comunes entre las enfermedades del tracto gastrointestinal es la acidez estomacal causada por el reflujo biliar. El síntoma es sustancialmente común en los países del este de Asia debido al predominio de alimentos fritos y picantes con altos niveles de contenido de grasa. **Objetivo:** *Se prestó mucha atención a este tema para mejorar la condición y calidad de vida de los pacientes, y se trabajó en el campo de la optimización del tratamiento, que era el*

objetivo del estudio. **Método:** *Para examinarlos se seleccionaron 133 pacientes con síntomas de acidez estomacal en el contexto de diversas enfermedades del sistema biliar, en combinación con otros síntomas del tracto gastrointestinal. Se han desarrollado esquemas individuales de tratamiento complejo para la acidez estomacal en pacientes con reflujo alcalino, que incluyen fármacos procinéticos (Itomed) en combinación con ácido ursodesoxicólico (Ursosan). Los pacientes se dividieron en 2 grupos: el primero recibió Itomed, el segundo recibió una combinación de Itomed y Ursosan*. **Resultados:** *Durante el estudio se estableció que el 82 % de los pacientes respondieron positivamente a la terapia con el procinético Itomed. Además, los pacientes que recibieron una combinación de los medicamentos itoprid y ácido ursodesoxicólico tuvieron una reducción del 92 % en los síntomas de acidez estomacal. Los pacientes con reflujo alcalino que padecían discinesia biliar tuvieron un efecto positivo del 98 %. En particular, el tratamiento con Itomed en combinación con Ursosan, que tienen un efecto citoprotector, reduce el proceso inflamatorio de la mucosa del tracto digestivo superior, lo que mejora el proceso digestivo, previniendo el desarrollo de reflujo, lo que mejora sustancialmente el estado general*.

Palabras clave: *Reflujo duodenal, reflujo alcalino, procinéticos, Itomed, ácido ursodesoxicólico, Ursosan*.

INTRODUCTION

The annual increase in the number of heartburn patients worldwide has led to attention being drawn to the subject and a large number of studies being conducted to optimize the treatment tactics of this condition (1). Dunn et al. (2) suggested that many patients with heartburn have a disruption of the peristalsis of the upper digestive tract, which leads to an increase in the occurrence of not acidic but mixed (with the presence of bile) reflux. In 1978, Pellegrini et al. (3) proposed the term "alkaline reflux" as an alternative to the concept of "acid reflux". "Pure" alkaline reflux occurs exclusively in patients who have undergone gastric resection surgery. In contrast, other types of refluxes have a mixed content but with a predominance of an acidic or alkaline component. In the literature, several terms that describe the composition of reflux from the duodenum to the stomach and esophagus can be identified: alkaline reflux, biliary reflux, and duodenal reflux. However, these three terms can be considered synonymous since the contents of the duodenum contain bile, pancreatic, and duodenal juice, which, when mixed, have an alkaline environment. Therefore, "duodenal reflux" is considered a more complete term that characterizes this pathological process (4,5). Such a symptom as bitterness in the mouth, which patients with heartburn note, has long been considered a sign only of liver and gallbladder diseases; however, it was established that this sign is characteristic of "high" biliary reflux, which reaches the oral cavity (6,7).

Duodenal reflux is a disorder of the digestive system characterized by the discharge of bile, pancreatic products, and duodenal contents into the upper gastrointestinal tract (stomach, esophagus) and inflammation (8). This disorder may be accompanied by symptoms of heartburn, burning in the chest area, bitterness in the mouth, flatulence, nausea, abdominal discomfort, a feeling of a lump and soreness in the throat. Reflux can also cause coughing. In practice, especially in the conditions of an oriental mentality, with a predominance of fatty and fried foods in the diet, practitioners are more faced with alkaline reflux. Therefore, examining the problems of "high" reflux was initiated, with the rational development of programs for treating patients with heartburn against the background of the pathology of the hepatobiliary system.

It is necessary to regulate the function of the excretory system of the gallbladder, peristalsis of the stomach, duodenum, and small and large intestines to prevent duodenal reflux. These data confirm the expediency of treating biliary reflux by using ursodeoxycholic acid (UDCA) to improve the function of the hepatobiliary system and prokinetics to normalize the motor evacuation function of the upper gastrointestinal tract (9-12). This combination allows UDCA to accelerate the excretion of toxic hydrophobic acids into the intestine and improve the composition of bile by increasing the number of hydrophilic bile acids, which reduces the harmful effects on the mucous membrane of the esophagus and stomach. UDCA is also involved in forming the cytoprotective properties of the drug by changing

the phospholipid layer of the cell membrane, which substantially increases its resistance to the aggressive action of hydrophobic bile acids (13-15). Thus, if epithelial apoptosis is eliminated, which is also caused by hydrophobic acids, it is possible to substantially reduce the signs of damage to the mucous membrane of the esophagus and stomach, which are well visualized by fibrogastroduodenoscopy (FGDS) (16-18).

In addition, the choleretic property of UDCA is notable, which improves the rheology of bile, leading to the normalization of its discharge from the gallbladder (11). The drug regulates the supply of bile in response to food stimulation, which leads to the proper functioning of the gallbladder without chaotic bile release between meals, reducing the risk of biliary reflux and its complications. In addition, bile has the property of regulating intestinal microbiota and participating in the normalization of gastrointestinal peristalsis, which leads to a decrease in complaints of flatulence, playing an important role in increasing intra-abdominal pressure and, as a result, the development of biliary reflux. The recommended UDCA (Ursosan) dose for treating patients with duodenal reflux is 500 mg/day for taking the drug after dinner (one tablet each).

The study aims to determine the formation and optimization of rational therapy for heartburn on the background of duodenal reflux using prokinetic and UDCA drugs. For that purpose, it was 1. Identify the frequency of detection of patients with alkaline reflux; 2. Assess the effectiveness of prokinetics in high duodenal reflux; and 3. Evaluate the effectiveness of combined therapy with UDCA and prokinetics in biliary reflux.

MATERIALS AND METHODS

Before starting the study, a detailed examination of alkaline reflux, its treatment, and prevention was conducted. The effect of the drugs used in this experiment has also been investigated in detail. The study was based on two levels of interaction with patients.

An empirical randomized trial was conducted during the first stage, and several tests and interviews of patients were performed, including consent to participate in the study, according to the standards of the Helsinki Declaration (19). The analysis included patients with isolated alkaline reflux. One hundred thirty-three patients with gastrointestinal tract diseases and disorders of the biliary system were interviewed and selected: chronic cholecystitis, biliary dyskinesia (BD), and post-cholecystectomy syndrome (PCS). Of them, 125 people had classic symptoms of heartburn, and eight people had other signs of reflux disease in the form of burning behind the sternum, pain, and a lump in the throat. The most significant number of patients examined were patients with chronic cholecystitis, n=54; patients with BD, n=47; and patients with PCS were in the number of n=32. As shown in Figure 1, the patients were divided into groups in percentage terms. The majority of patients had chronic cholecystitis, which was 41 %. 35 % were patients with BD, and 24 % had a resected gallbladder.

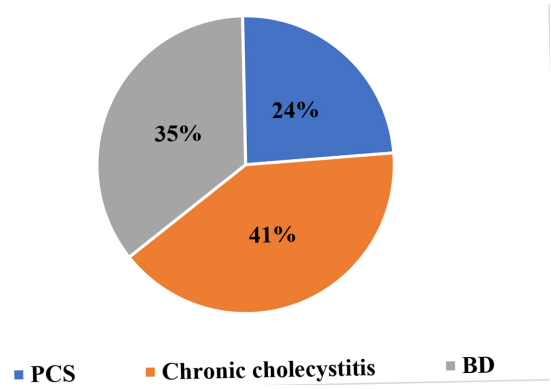

Figure 1. Distribution of patients by groups
Source: compiled by the author.

Patients were asked to undergo testing, which noted symptoms of heartburn, burning behind the sternum, flatulence, abdominal discomfort, bitterness in the mouth, soreness, and a lump in the throat. They were also interviewed for self-help with heartburn. The main groups of relief of heartburn symptoms were identified: antacids, proton pump inhibitors (PPIs), prokinetics, enzymatic drugs, and histamine blockers. It is important for patients with

alkaline reflux to carefully follow the prescribed treatment, including itoprid hydrochloride and ursodeoxycholic acid (UDCA). Itoprid (Itopride hydrochloride 50 mg) improves the motility of the digestive tract, which helps to speed up the evacuation of stomach contents and bile, reducing the risk of reflux. UDCA improves the rheological properties of bile, reduces the toxicity of bile acids, and helps reduce the concentration of bile in the gallbladder, which also helps reduce the symptoms of reflux. In addition to medication, proper nutrition plays a significant role. Eating small meals several times daily is recommended to avoid stomach overflow, which can contribute to reflux. Fatty and fried foods should be avoided, as they can slow down stomach emptying and worsen symptoms. Reducing caffeine and alcohol intake is also important, as these foods can exacerbate the symptoms of alkaline reflux and negatively affect the overall health of the gastrointestinal tract.

The second stage of the experiment was the appointment of drugs of the prokinetics itopride hydrochloride (Itomed) and a combination of drugs Itomed+Ursosan for one month. The patients were randomly divided into two groups:

The first group – patients received Itomed as the main type of therapy at a dosage of one table of 50 mg, three times a day, for one month. Seventy-nine people were monitored and treated in this group.

The second group, consisting of 54 people, received Itomed combined with Ursodeoxycholic acid (UDCA) (Ursosan forte 500 mg), one tablet in the evening for one month. Ursodeoxycholic acid is a hepatoprotective active substance with cholelitholytic, choleretic, hypocholesterolemic and immunomodulatory effects.

An analysis of data on the detection of heartburn in patients with various nosological pathologies of the biliary system was also conducted. A percentage ratio for heartburn in patients with PCS, BD, and chronic cholecystitis was compiled. The survey data that patients underwent in the initial symptom testing were analyzed. All complaints of burning behind the sternum, heartburn, bitterness in the mouth, flatulence, abdominal discomfort, pain, and a lump in the throat were divided into groups as a percentage. Data on the distribution of patients into groups with nosological diseases and taking groups of drugs were also considered. The following groups were also created: patients with PCS taking only prokinetics, patients with PCS taking a combination of prokinetics and UDCA, patients with BD taking prokinetics, patients with BD taking prokinetics+UDCA, patients with chronic cholecystitis taking prokinetics and patients with chronic cholecystitis taking a combination of prokinetics+UDCA.

After a study of these groups of patients, the data was analyzed as a percentage ratio before and after treatment. The reduction or complete absence of heartburn symptoms in each group of subjects was considered.

RESULTS

Risk factors for alkaline reflux

Based on the studied data, biliary reflux is identified as a chronic recurrent disease. It is characterized by impaired evacuation and the stomach and esophagus motor function. This condition involves spontaneous or frequent regurgitation of duodenal contents, pancreatic juice, and bile into the stomach and esophagus. Inflammation, including catarrhal and ulcerative signs, results from irritation of the mucous membrane of the upper digestive tract (20). The main symptoms of alkaline reflux are heartburn, burning behind the sternum, pain in the epigastric region, bitterness in the mouth, nausea, vomiting with bile contents, and a lump and sore throat, sometimes respiratory manifestations in the form of coughing.

Alkaline reflux often occurs due to impaired gastric and duodenal motility, neuroendocrine regulation, gastroduodenal hormone imbalances, chronic diseases of the upper digestive tract, infectious diseases, and gastric, duodenal, and gallbladder surgery (20). Digestive hormones, such as gastrin, secretin, cholecystokinin, and motilin, affect gastric motility and hydrochloric acid production (21). Impaired gastric and esophageal motility is associated with increased nitric oxide levels and opening of the pyloric sphincter, which is important in the development of reflux. Surgical interventions, such as gastroenterostomy, enterostomy, gastric resection, sleeve gastrectomy, and pyloroplasty,

also contribute to the formation of alkaline reflux (22). Loss of gallbladder function after cholecystectomy can also contribute to the development of reflux disease. The inflammatory process in alkaline reflux is caused by the contents of the reflux, where lysozolicytin and bile acids disrupt the barrier function of the gastric mucosa, increasing the permeability of epithelial cells to toxic substances (23, 24).

Pancreatic juice is also toxic to the mucous membrane of the stomach and esophagus. Pancreatic enzymes have a high activity of the metalloenzyme phospholipase A2, which has a toxic effect on the membrane structures of lysophosphatidylcholine. All these etiological factors lead to an inflammatory process of the gastric mucosa – gastritis. Using FGDS, signs of edema, hyperemia, erosions, and ulcers of the gastric mucosa are identified in patients. Given that the stomach acidity is substantially reduced due to the intake of the alkaline contents of the duodenum into the stomach, this affects the active reproduction of bacteria, which enter the stomach and esophagus in large numbers. These factors disrupt the stomach and esophagus microflora, inevitably leading to an aggravation of gastritis symptoms. Notably, there are risk factors that additionally affect the occurrence of biliary reflux (25, 26). These factors include gender. It was identified that women suffer from alkaline reflux more often than men. The age-related risk factor is important in the elderly and young people, compared with middle-aged people who suffer from reflux less often (27). According to the type of constitution, the incidence of reflux in people of small stature is lower than in tall and slender people. However, people suffering from abdominal obesity have a higher risk of developing reflux disease, regardless of body mass index. Eating sugary foods and dishes made from coarse or whole grains can be highlighted as bad habits in food preferences. Products with a pronounced sweet component enhance the production of the hormones cholecystokinin and glucagon and stimulate hydrochloric acid release, which in combination leads to inhibition of gastric peristalsis and contractility of the pyloric sphincter (28). Consuming fried, fatty, and spicy foods will lead to similar changes (29). In turn, whole grains and products containing coarse grains contribute to a slower evacuation of the chyme by stretching and relaxing the stomach, which leads to bile staying in its cavity and an increase in the inflammatory process.

Alcohol consumption and smoking have a negative effect on the occurrence of reflux. These bad habits traumatize the stomach and esophagus mucous membranes and reduce the tone of the pyloric sphincter, which leads to the abandonment of duodenal contents. It was determined that people suffering from gallbladder diseases have a higher incidence of alkaline reflux than those without (30-32). With polyposis of the gallbladder and the presence of gallstone disease, the release of bile into the digestive tract substantially increases due to decreased speed and amount of water absorbed in the gallbladder (33). However, people who have undergone cholecystectomy are also susceptible to the development of reflux disease due to the continuous supply of bile into the duodenum (34). Notably, due to increased pressure in the bile duct, the release of bile into the intestine increases, leading to a disruption of normal peristalsis and the formation of bile regurgitation in the pylorus. There is also a link between cholecystectomy and impaired Oddi sphincter function, which increases the risks of biliary reflux. In addition, patients suffering from diabetes mellitus are more prone to alkaline reflux due to an imbalance of the autonomic nervous system and a decrease in blood supply to the gastric mucosa, which leads to a chain reaction of reflux in the form of slowing down peristalsis, stretching of the stomach, pyloric sphincter, and abandonment of the contents of the duodenum (35-37).

Identifying *Helicobacter pylori* is also important since exposure to the bacterium also negatively affects the development of symptoms, complications risks, and treatment inhibition. Therefore, it is necessary to eradicate the bacterium. The patient's psychological state also plays a role in the prevalence and occurrence of reflux disease. Thus, people who do not suffer from psychological disorders are less susceptible to the formation of alkaline reflux. When diagnosing, the following data should be considered: complaints, family and medical history, and the results of additional examination methods (FGDS, pH-impedance measurement, pH-metry, manometry, and, in some cases, contrast fluoroscopy). With improper

monitoring and treatment of heartburn, the risk of gastric adenocarcinoma and Barrett's esophagus is substantially increased. Reflux disease treatment aims to improve the patient's condition by eliminating complaints and symptoms, regenerating the esophagus and stomach mucous membrane, and preventing complications such as Barrett's esophagus and adenocarcinoma.

First of all, it is necessary to ensure proper training of the patient on non-drug modification of reflux disease, with normalization and organization of 6 meals a day with a decrease in portion sizes and intervals between meals, avoiding late dinners and taking a lying position after meals, eliminating foods that cause exacerbation. Normalization of the way of life with decreased physical activity, avoidance of physical lab or the body tilted forward, and organization of sleep with a raised head end. It was giving up bad habits: smoking and drinking alcohol, weight loss, treatment of chronic diseases, and exclusion of drugs that affect the slowing down of the motor function of the digestive tract. For treating duodeno-gastroesophageal reflux, three groups of drugs are used: PPIs, prokinetics, and UDCA drugs. The appointment of PPIs reduces the amount of gastric juice produced and the rate of secretion of hydrochloric acid, which reduces the harmful effect on the stomach and esophagus mucous membrane (38). However, if reflux has an alkaline or mixed component, combination therapy with the appointment of prokinetics, UDCA drugs, antacids, and esophagus protectors is considered. The use of prokinetics is due to the pathogenetic treatment of biliary reflux because this group of drugs improves the peristalsis of the esophagus, stomach, duodenum, and lower digestive system, enhances the tone of the esophageal, pyloric sphincters, Oddi sphincter, reduce the regurgitation of bile, pancreatic enzymes into the stomach and gastric juice with the contents of the duodenum into the esophagus (39).

A commonly used drug among the selective prokinetics of the second generation is Itomed, which has two mechanisms of action. The therapeutic effect of itopride hydrochloride is that it blocks the action of dopamine D2 receptors and anticholine esterase, which slow down food movement through the stomach and intestines — blocking dopamine receptors by Itomed increases the motility of smooth muscles in the stomach and intestines, improving their contractility and accelerating food passage through the digestive tube. Itopride hydrochloride also stimulates muscarinic receptors by releasing acetylcholine, which in turn leads to the normalization of motility and peristalsis of the digestive system. It has minimal toxic effects on the liver. It is also well tolerated by patients with minimal side effects. In addition, apart from the speed and durability of the drug, its advantage is the possibility of long-term use. The usual therapeutic dose of itopride hydrochloride is 50 mg 3 times a day, 30 minutes before meals, for one month.

The use of UDCA is also due to its effect on the pathogenesis of alkaline reflux. The drug has cytoprotective, choleretic, and cholelitic effects. Ursosan is a modern drug used to treat alkaline reflux. UDCA improves the properties of bile by replacing its toxic components with non-toxic ones, which leads to a decrease in the aggressive effect of the reflux contents on the mucous membranes of the stomach and esophagus. The cytoprotective effect of Ursosan consists of the stabilization of the phospholipid bilayer of cell membranes, preventing the leakage of cellular contents and maintaining membrane integrity which leads to a faster excretion of bile acids into the intestine, reducing the damaging factor of the gastric mucosa and esophagus. The choleretic effect of the drug is due to a decrease in the lithogenic properties of bile, which leads to its normal supply from the gallbladder to the duodenum. In addition, during digestion, UDCA helps regulate the emptying of the gallbladder, which leads to the normalization of the production and response of the gallbladder to food intake, thus preventing exacerbations of reflux disease. Bile also improves the intestinal microbiome, stimulating the peristalsis of the lower part of the digestive tract, which substantially reduces the symptoms of bloating, playing an important role in alkaline reflux. The standard dose of UDCA is 500 mg per day after lunch and dinner.

Results of an empirical randomized trial

This study monitored 133 people with alkaline reflux who received a prokinetic and a combination of UDCA+prokinetics. One hundred

twenty-five people suffered from heartburn, and 8 had other reflux symptoms. Figure 2 shows the percentage of heartburn frequency in various nosologies of the biliary system. Thus, heartburn bothered 46 out of 47 patients with BD, which was 98 %. In 54 patients with chronic cholecystitis, heartburn was observed in 51 patients, which was 94 %. Of the 32 patients with PCS, 28 people complained of heartburn, which was 89 % of the cases.

A total of 125 patients with heartburn were identified, but eight more people had non-classical manifestations of alkaline reflux in the form of burning behind the sternum. However, they were all included in the trial. These data confirm the extensive prevalence of alkaline reflux among patients suffering from diseases of the biliary system. Figure 3 shows the usual symptoms of biliary reflux. Thus, heartburn takes the first place, with a frequency of up to 94 %, followed by burning behind the sternum at 87 %. Next comes the bitterness in the mouth of 76 % and flatulence – 56 %. Nausea was manifested in 50 % of patients. Such manifestations of high

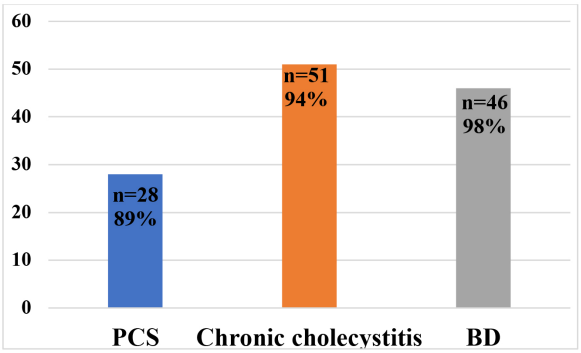

Figure 2. The frequency of heartburn detection in different groups. PCS: Post-cholecystectomy syndrome; BD: Biliary dyskinesia. Source: compiled by the author.

duodenal reflux as a lump in the throat and sore throat amounted to 33 % and 23 %, respectively, which at the primary level prompted patients to consult otorhinolaryngologists, suspecting pathology of the upper respiratory tract. 23 % of patients complained of discomfort in the epigastric region. These data are valuable for

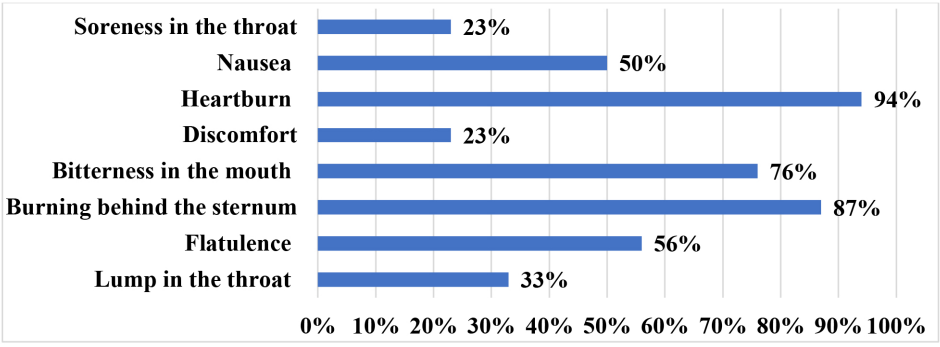

Figure 3. Symptoms of biliary reflux (% of patients with these symptoms at the moment of consultation). *Source: compiled by the author.*

practitioners in the differential diagnosis and prevention of alkaline reflux.

When interviewing patients for taking medications and other substances to relieve the condition, 72 patients replied that they were taking antacids, which was 34 %, as shown in Figure 4.

Traditional PPIs were used in 12 patients, and the percentage reached 6 %. 8 patients took the usual prokinetics (4 %). The use of enzymatic drugs was detected in 8 patients (4 %), and 11 patients took histamine blockers (5 %). As for the alternative therapies, soda remains relevant,

which was used by 36 people (17 %), carbonated drinks – by 26 people (12 %), carrots – by 24 people (11 %), and mineral water – by 15 people (7 %). This indicates that a large percentage of patients use outdated methods, and practitioners should pay special attention to patient awareness

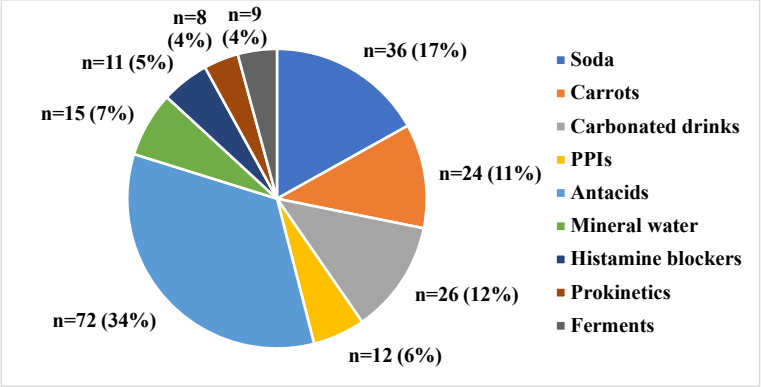

Figure 4. Drugs used by patients to relieve the condition. *Source: compiled by the author.*

in the treatment and prevention of biliary reflux and its complications.

Figure 5 shows the examined patients divided into 2 groups. The first group included 79 patients who took Itomed in isolation at a dose of 50 mg, 1 tablet 3 times a day, 20 minutes before meals for 1 month. The second group, 54 in number, took combination therapy with itopride hydrochloride in the same dosage and drugs in a

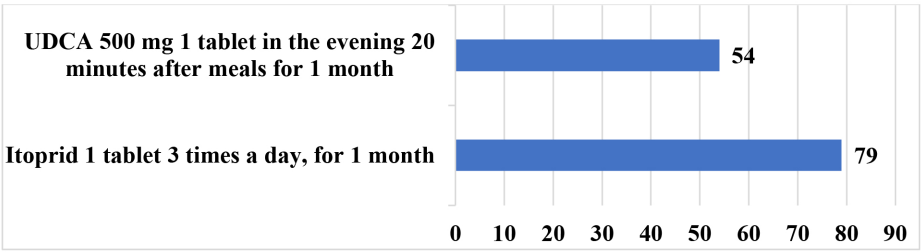

Figure 5. Distribution of patients by therapeutic groups. Source: compiled by the author.

dosage of 500 mg, 1 tablet in the evening after meals, for 1 month.

In Figure 6, patients were divided into 6 groups: patients with PCS who took Itomed-8 people; patients with PCS who received the combination of Itomed + UDCA-24 people; patients with chronic cholecystitis who took Itome-34 people; patients with chronic cholecystitis who received Itomed + UDCA; patients with BD who took

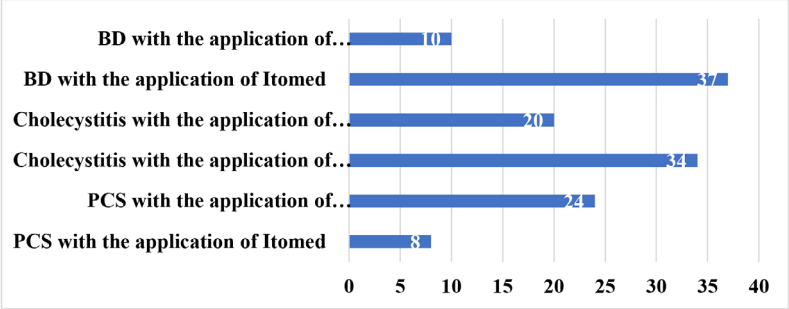

Figure 6. Distribution of drugs by groups. *Source: compiled by the author.*

Itomed-37 people; patients with BD who took Itomed + UDHC-10 people.

According to the study, as shown in Figure 7, during the use of itopride in isolated form, there was a decrease in heartburn in 65 out of 79 patients, which was 82 %. When using itopride in combination with UDCA preparations, the disappearance of heartburn was noted in 50 out of 54 patients with high duodenal reflux, which was 92 %. Moreover, in patients with BD, the disappearance of heartburn was noted in almost 100 % of the cases. There was a substantial decrease in heartburn in patients in the group taking combination therapy with Itomed and Ursosan. Thus, in 37 patients with BD who took itoprid in isolation, a decrease in heartburn was noted in 32 people, which was 88 %. Combined therapy with itoprid and UDCA in 10 patients with BD decreased the symptom of heartburn in 9 patients, which amounted to 98 %. In the 34 patients with chronic cholecystitis, the manifestations of duodenal reflux taking itoprid decreased in 27 people, which amounted to 80 %. In addition to that, using the combination therapy with UDCA in 20 patients with chronic cholecystitis, heartburn decreased in 19 people, which amounted to 95 %. 6 out of 8 patients with PCS noted a decrease in heartburn on the background of isolated itoprid therapy, which amounted to 87 %. In 24 patients with PCS with combined therapy with itoprid and UDCA, the

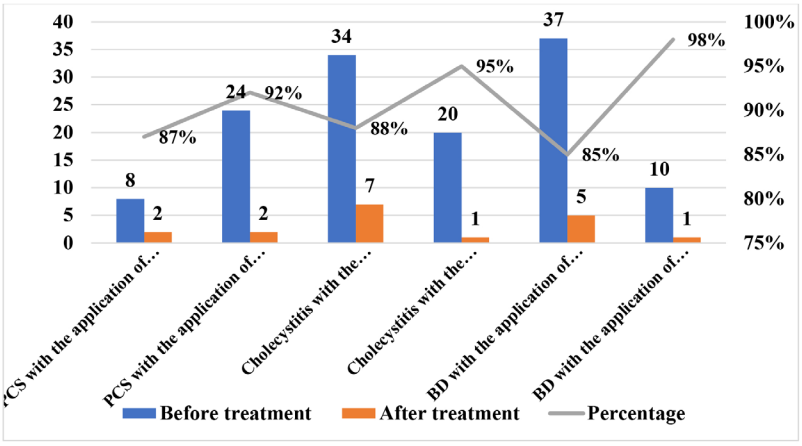

Figure 7. The results of reducing heartburn in groups. *Source: compiled by the author.*

manifestations of duodenal reflux decreased to 2 patients, which makes the success rate 92 %.

The use of individual schemes of complex treatment of heartburn in patients with alkaline reflux, including Itomed and Ursosan, which provide a cytoprotective effect against the esophagus mucous membrane, prevents the occurrence of pathological reflux and improves the quality of digestive processes. The dynamics of the effectiveness of the use of itoprid and the

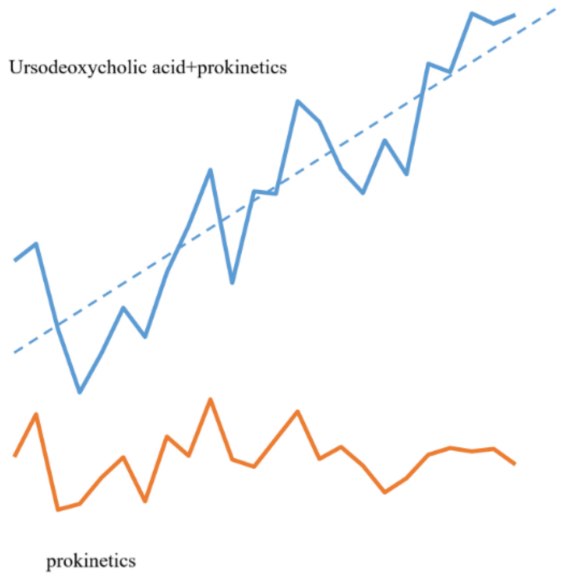

Figure 8. Distribution of results into two groups. *Source: compiled by the author.*

combination therapy of UDCA with itoprid are presented in Figure 8.

Against the background of taking drugs, Itomed and Ursosan, bile secretion improves upon food intake into the body, which leads to the normal participation of bile in the food processing process and prevents the release of bile between meals, which reduces the likelihood of alkaline reflux. Bile also affects the microbiotic flora of the intestine and participates in the motor-evacuation process of the intestine, which positively affects the severity of flatulence by reducing intra-abdominal pressure (17,21,40). Considering these data, it is necessary to highlight the importance of simultaneous use of UDCA and prokinetics.

As a result, it was determined that this chronic disease is characterized by impaired gastric and esophageal motility, which leads to frequent regurgitation of the duodenal contents, pancreatic juice and bile. This causes irritation of the mucous membrane of the upper digestive tract, manifested by heartburn, pain behind the sternum, epigastric pain, bitterness in the mouth, nausea, vomiting of bile and a feeling of a lump in the throat. The main factors are peristalsis disorders, hormone imbalances, chronic and infectious diseases, as well as surgical interventions on the stomach, duodenum, and gallbladder. Digestive system hormones and disorders of nitric oxide production also play an important role in the development of this disease.

DISCUSSION

Biliary reflux is a disease in which the contents of the duodenum, containing bile and pancreatic juice, return to the stomach or, together with the contents of the stomach, are thrown into the esophagus, causing irritation and inflammation of the mucous membrane of the stomach or esophagus. This condition disrupts the upper digestive tract's motor-evacuation function, the stomach's hormonal background, the duodenum, and operations in the upper gastrointestinal region (41,42). In this regard, this study was conducted to determine the optimal treatment option for heartburn in alkaline reflux and to develop preventive measures to prevent complications, such as erosive and ulcerative conditions of the stomach and esophagus, Barrett's esophagus, and stomach and esophageal cancer. For this purpose, patients with pathology of the biliary system were selected: patients with chronic cholecystitis, PCS, and BD. The patients were divided into two groups. One group received itopride hydrochloride, and the other – a combination of itopride hydrochloride and UDCA. Babak (4) also resorted to the same goals and conclusions in his study, where alkaline

reflux, its pathogenesis, and treatment with PPIs, prokinetics, and UDCA were investigated.

Prokinetics is a group of drugs that includes the examined itopride hydrochlodide (Itomed), which affects the contractility of the digestive system, improving the peristalsis of the stomach, duodenum, gallbladder, and lower intestine (43). This allows for accelerating the evacuation of chyme from the stomach and bile from the gallbladder, which will help prevent reflux into the upper parts of the digestive system and reduce the risks of heartburn in reflux disease and the number of relapses. As for UDCA, it is a drug that improves the rheological properties of bile, replaces toxic bile acids with less aggressive ones, reduces the concentration of bile in the gallbladder, which allows bile to enter the intestine in a dosed manner and at the right time, reduces the risk of formation of gallbladder concretions, which also reduces the incidence of biliary reflux, relapses, and its complications.

This study demonstrated that patients receiving monotherapy with prokinetic itopride hydrochloride had a less therapeutic response than patients taking a combination of Itomed and Ursosan. Thus, patients taking monotherapy with itopride hydrochloride noted a decrease in signs of heartburn by 82 %. 92 % of patients receiving a combination of itoprid and UDCA noted an improvement in their condition with regard to heartburn. The distribution by nosological units identified the following result: in the groups receiving monotherapy with Itomed with BD, heartburn persisted in only 12 % of the subjects, 20 % of patients with chronic cholecystitis noted signs of alkaline reflux, and 13 % of patients with PCS also did not notice improvement. These data are similar to Shcherbinina (14), who reported the effect of Itomed on biliary reflux was examined, which confirms the importance of using prokinetics. However, in the groups of patients receiving a combination of UDCA and itopride hydrochloride, the distribution was as follows: patients with PCS complained of heartburn in 8 % of cases, patients with chronic cholecystitis had no positive effect in 5 % of cases, and those with BD had reflux manifestations only in 2 % of cases. Similar results were demonstrated in the study conducted by Tikhonov et al. (15), where the issue of treating patients with alkaline reflux combined with obesity was investigated. The use of UDCA with prokinetics gave a positive result. This means that the effectiveness of combined treatment with prokinetics and UDCA has been proven with regard to alkaline reflux. However, the study did not consider the data of additional research methods, which is an important criterion for diagnosing the stage of damage to the mucous membranes of the upper part of the digestive tract and evaluating the effect of drugs on the healing of tissues affected by alkaline reflux.

By FGDS, it is possible to identify the percentage of damage to the mucous membrane of the esophagus and stomach in the studied groups, the stage of the disease, and to note an improvement in the condition and the transition to milder stages. In addition, gastric pH would show the state of gastric acidity before and after treatment, which would help to analyze and optimize treatment by prescribing individual therapy regimens. In addition, the study did not use first-line drugs – PPIs, which are the main drug in the treatment of acid reflux, but this allowed for a more accurate assessment of the effect of using prokinetics and UDCA. Similar results were obtained in an empirical study by Zviahintseva and Sharhorod (44), where 39 patients were examined and treated. During the therapy, PPIs were used in the standard therapeutic dose, UDCA – 500 mg, 2 times a day, itopride hydrochloride – 30 mg, 3 times a day. The observation took place over a month. During this period, 81 % of patients did not complain of heartburn and in 17 %, the frequency of symptoms of biliary reflux decreased to 2 times a week, 2 % of patients noted a slight improvement in bitterness in the mouth, and in 12 % of patient's complaints of belching with air decreased slightly. Notably, in this study, the appointment of a combination of UDCA and prokinetics was advisable since the drugs reduce the rheology, speed, and amount of bile excreted into the intestine, positively affect the mucous membrane of the stomach and esophagus, improve the motor evacuation function of the upper digestive tract.

Alkaline reflux was examined in detail by Shi et al. (45). Their study showed all aspects of this condition, describing the pathogenesis, risk factors, complications, diagnosis, and treatment in detail. The conclusions made in this review showed that combination therapy is the most effective than treatment with

monopreparations. However, the researchers considered using a broader combination of PPIs, prokinetics, UDCA, antacids, and lipid-lowering agents, such as cholestyramine. Thus, one of the additional drugs for the treatment of biliary reflux is hydrotalcite, which has a protective property for the esophagus and stomach mucous membrane and, to some extent, neutralizes the toxic effect of bile acids, reducing the symptoms of heartburn and abdominal discomfort. In turn, cholestyramine was used as a bile adsorbent since this drug reacts with bile acids in the intestine and forms a strong complex excreted with feces. A smaller amount of bile acids is returned to the liver through the intestinal-hepatic system, which leads to a slight decrease in bile production and, as a result, reduces the toxic effect of bile on the mucous membranes of the stomach and esophagus due to a smaller amount of bile in the reflux (46,47). This means that the use of second-line drugs can also lead to a positive result in the treatment of alkaline reflux. The data provided by the researchers are similar in the combination of UDCA drugs and prokinetics but differ in the use of second-line drugs, which offers great opportunities to identify new drugs effective in alkaline reflux.

Johncilla et al. (48) investigated the diagnosis and treatment of alkaline gastritis in detail. It was concluded that the most effective integrated approach is lifestyle modification, organization of eating behavior, and combination therapy. Three main groups were identified from the drugs: PPIs, prokinetics, and UDCA; it was determined that itopride hydrochloride should be used at a dose of 150 mg per day, divided into 3 doses, UDCA – 250 mg per day once a night, rebamipide – 100 mg 3 times a day, during up to two months. The importance of the finding of *H. Pylori* is notable since the latter causes an additional negative effect on the course and outcome of biliary gastritis and increases the risks of complications and delays in the recovery process (49).

Many scientists and research groups have evaluated the treatment of heartburn in biliary reflux. The importance of these studies lies in the search for effective treatment drugs with the most significant clinical effect, the minimum number of side effects, and high safety, which will reduce the frequency of relapses, the risks of degeneration of reflux disease into a carcinomatous process, and also improve the quality of life of patients. An individual approach to each patient's treatment should be applied, and combination therapy should be used to achieve the best result. The use of individual schemes of complex treatment of heartburn in patients with alkaline reflux, including Itomed and Ursosan, which substantially reduce the clinical manifestations of biliary reflux, improve the condition of the gastric mucosa, esophagus with the help of cytoprotective effect, improve the digestive process and prevents the occurrence of reflux. It is recommended that Itomed be prescribed for alkaline reflux in a dose of 50 mg 3 times a day 30 minutes before meals. For the combination therapy in the form of Itomed and Ursosan, it is recommended to prescribe Itomed at a dose of 50mg 1 tablet 3 times a day before meals for 20 minutes and Ursosan – 500 mg 1 tablet once in the evening after meals after 30 minutes for 1 month, respectively. However, further research should be directed at empirical studies to identify modern treatment regimens for heartburn in biliary reflux in practice. In addition, the option of surgical treatment should be considered, if conservative therapy is ineffective in more severe cases.

The discussion on biliary reflux highlights that this condition involves the return of duodenal contents, including bile and pancreatic juice, to the stomach or esophagus, leading to irritation and inflammation of the mucous membranes. The key factors contributing to biliary reflux include disruptions in the motor-evacuation function of the upper digestive tract, hormonal imbalances, and surgical interventions in the gastrointestinal region. Prokinetics, such as itopride hydrochloride (Itomed), enhance the contractility of the digestive system, improving peristalsis in the stomach, duodenum, gallbladder, and lower intestine. This improvement facilitates the evacuation of chyme and bile, potentially reducing the risk of reflux and heartburn. On the other hand, UDCA improves bile rheology, replaces toxic bile acids with less aggressive ones, and decreases bile concentration in the gallbladder. This regulation allows bile to enter the intestine in a controlled manner, reduces the risk of gallstone formation, and helps mitigate the effects of biliary reflux.

The study on biliary reflux presents valuable insights but is not without its limitations. One

significant limitation is the relatively small sample size, which may affect the generalizability of the findings. A larger cohort would provide more robust data and enhance the conclusions' reliability. Additionally, the study's timeframe was limited, restricting the ability to assess long-term outcomes and the sustainability of the treatment effects over an extended period. Future research should address these limitations by incorporating larger sample sizes and extending the duration of the study. This approach would allow for a more comprehensive evaluation of the treatment's effectiveness and long-term impact on patients with biliary reflux. Further studies could also explore the influence of different variables, such as diet and lifestyle, on the efficacy of the treatments and their impact on reducing complications associated with alkaline reflux.

CONCLUSIONS

The study confirmed that biliary reflux is increasingly common in global clinical practice but has not been thoroughly investigated. The disease develops due to the throwing of duodenogastric contents into the stomach and esophagus due to a disruption of the peristalsis of the upper digestive tract, an imbalance in hormonal regulation of the stomach and duodenum, the consequences of previous surgical interventions on the stomach, gallbladder. The development of reflux disease is affected by the inflammatory process, which occurs due to the action of the contents of the reflux on the mucous membrane of the stomach and esophagus.

It was established that among the common factors, the presence of chronic gallbladder diseases, diabetes, psychological disorders, abdominal obesity, sex, age, body constitution, existing bad habits, and eating disorders, the presence of *Helicobacter pylori* should be highlighted. The importance of monitoring, treatment, and prevention of alkaline reflux to reduce the risks of complications in the form of Barrett's esophagus and gastric adenocarcinoma, the esophagus is notable. In the group of patients with PCS who took itoprid, the disappearance of heartburn was noted in 87 %, and in patients with PCS who received itoprid and UDCA as treatment, a decrease in heartburn was achieved by 92 %. A group of patients with chronic cholecystitis with the use of itoprid noted a reduction in heartburn to 80 %, and patients with chronic cholecystitis with oral administration of itoprid in combination with UDCA preparations had a substantial decrease in heartburn to 95 %. Similar results of reducing duodenal reflux were observed in subjects with BD with isolated itoprid therapy, up to 88 %. Combining itoprid and UDCA in patients with BD decreased heartburn in 98 % of cases. This clinical study has similarities with literature data, which indicates the acceptability of using the combination of Itomed and Ursosan for treating biliary reflux and heartburn symptoms, compared with monotherapy with prokinetics. However, itopride hydrochloride also resulted in a good positive trend in the study group of patients.

In further studies, it is worth identifying drugs that will help improve the quality of life of patients with biliary reflux, reduce the number of relapses, and reduce the risk of complications. The limitations that block the receipt of research data may be patients' concomitant diseases and the use of a large number of drugs that may distort the clinical effect of the drug under study.

REFERENCES

1. Maev IV, Dicheva DT, Andreev DN. Approaches to individualization of treatment of gastroesophageal reflux disease. Eff Pharmacother. Gastroenterology. 2012;4:8-22.
2. Dunn LJ, Burt AD, Hayes N, Griffin SM. Columnar metaplasia in the esophageal remnant after esophagectomy: A common occurrence and valuable insight into the development of Barrett's esophagus. Ann Surg. 2016;264(6):1016-1021.
3. Pellegrini CA, DeMeester TR, Wernly JA, Johnson LF, Skinner DB. Alkaline gastroesophageal reflux. Am J Surg. 1978;135(2):177-184.
4. Babak OYa. Bile reflux: Modern view in pathogenesis and treatment. Mod Gastroenterol. 2003;11(1):28-30.
5. Mabrut JY, Collard JM, Baulieux J. Duodenogastric and gastroesophageal bile reflux. J Chir. 2006;143(6):355-365.
6. Dixon MF, Neville PM, Mapstone NP, Moayyedi P, Axon ATR. Bile reflux gastritis and Barrett's oesophagus: further evidence of a role for duodenogastro-oesophageal reflux? Gut. 2001;49:359-363.

7. Souza RF. The role of acid and bile reflux in oesophagitis and Barrett's metaplasia. Biochem Soc Trans. 2010;38(2):348-352.
8. Tarnawski A, Ahluwalia A, Jones MK. Gastric cytoprotection beyond prostaglandins: Cellular and molecular mechanisms of gastroprotective and ulcer healing actions of antacids. Curr Pharm Des. 2013;19(1):126-132.
9. Minushkin ON. Ursodeoxycholic acid (UDCA) in clinical practice. Med Counc. 2010;1-2:10-11.
10. Nadinskaya MY. Exploring the use of ursodeoxycholic acid in hepatology from the perspective of evidence-based medicine. Consi Med. 2003;5(6):318-322.
11. Bueverov AO. Possibilities of clinical application of ursodeoxycholic acid. Consil Med. 2005;7(6):460-463.
12. Okada K, Shoda J, Taguchi K, Maher JM, Ishizaki K, Inoue Y, et al. Ursodeoxycholic acid stimulates Nrf2-mediated hepatocellular transport, detoxification, and antioxidative stress systems in mice. Am J Physiol Gastrointest Liver Physiol. 2008;295(4):G735-G747.
13. Maev IV, Gulenchenko YS, Andreev DN, Kaziulin AN, Dicheva DT. Duodenogastroesophageal reflux: Clinical significance and approaches to therapy. Consil Med. 2014;16(8):5-8.
14. Shcherbinina MB. Itomed®: Rational treatment of gastrointestinal dyskinesias. Policlin. 2012;4:52-54.
15. Tikhonov SV, Simanenkov VI, Bakulina NV, Vorzheinova VA, Papin KV, Rodionova NV, et al. Multitarget therapy in patients with GERD and obesity. Med Alphabet. 2021;1(6):8-13.
16. Aziz M, Haghbin H, Gangwani MK, Weissman S, Patel AR, Randhawa MK, et al. Erythromycin Improves the Quality of Esophagogastroduodenoscopy in Upper Gastrointestinal Bleeding: A Network Meta-Analysis. Dig Dis Sci. 2023;68(4):1435-1446.
17. Amaral JD, Viana RJS, Ramalho RM, Steer CJ, Rodrigues CMP. Bile acids: Regulation of apoptosis by ursodeoxycholic acid. J Lipid Res. 2009;50(9):1721-1734.
18. Gubergrits NB, Fomenko PG. The modern prokinetic itopride in the treatment of dyspepsia. Intern Med J. 2009;3(15).
19. WMA declaration of Helsinki – Ethical principles for medical research involving human subjects. 1964. Available at: https://web.archive.org/web/20110830192613/http://www.wma.net/en/30publications/10policies/b3/index.html
20. Aliiev RB. Features of the endocrine activity of fat tissue in metabolism disorders. Bull Med Bio Res. 2023;5(1):26-32.
21. Camilleri M. Gastrointestinal hormones and regulation of gastric emptying. Curr Opin Endocrinol Diabetes Obes. 2019;26(1):3-10.
22. Shi Y, Wei Y, Zhang T, Zhang J, Wang Y, Ding S. Deoxycholic acid could induce apoptosis and trigger gastric carcinogenesis on gastric epithelial cells by quantitative proteomic analysis. Gastroenterol Res Pract. 2016;2016:9638963.
23. Tarnawski A, Ahluwalia A, Jones MK. Gastric cytoprotection beyond prostaglandins: Cellular and molecular mechanisms of gastroprotective and ulcer healing actions of antacids. Curr Pharm Des. 2013;19(1):126-132.
24. Li T, Guo H, Li H, Jiang Y, Zhuang K, Lei C, et al. MicroRNA-92a-1-5p increases CDX2 by targeting FOXD1 in bile acids-induced gastric intestinal metaplasia. Gut. 2019;68(10):1751-1763.
25. Naylor A, Axon A. Role of bacterial overgrowth in the stomach as an additional risk factor for gastritis. Can J Gastroenterol Hepatol. 2003;17:350347.
26. Zholdasbekova A, Biyashev KB, Biyashev BK, Sarybaeva DA, Zhumanov KT. Method for producing attenuated Salmonella strain. J Pharm Sci Res. 2018;10(1):162-163.
27. Li D, Zhang J, Yao WZ, Zhang DL, Feng CC, He Q, et al. The relationship between gastric cancer, its precancerous lesions and bile reflux: A retrospective study. J Dig Dis. 2020;21(4):222-229.
28. Gürler EB, Özbeyli D, Buzcu H, Bayraktar S, Carus İ, Dağ B, et al. Natural sweetener agave inhibits gastric emptying in rats by a cholecystokinin-2- and glucagon like peptide-1 receptor-dependent mechanism. Food Funct. 2017;8(2):741-745.
29. Fass OZ, Mashimo H. The effect of bariatric surgery and endoscopic procedures on gastroesophageal reflux disease. J Neurogastroenterol Motil. 2021;27(1):35-45.
30. Stathopoulos P, Zundt B, Spelsberg FW, Kolligs L, Diebold J, Göke B, et al. Relation of gallbladder function and helicobacter pylori infection to gastric mucosa inflammation in patients with symptomatic cholecystolithiasis. Digestion. 2006;73(2-3):69-74.
31. Zhang R, Luo H, Pan Y, Zhao L, Dong J, Liu Z, et al. Rate of duodenal-biliary reflux increases in patients with recurrent common bile duct stones: Evidence from barium meal examination. Gastrointest Endosc. 2015;82(4):660-665.
32. Bogoyavlenskiy A, Alexyuk M, Alexyuk P, Amanbayeva M, Anarkulova E, Imangazy A, Bektuganova A, Berezin V. Metagenomic Exploration of Koumiss from Kazakhstan. Microbiol Resour Announce. 2022;11(1):e01082-21.
33. Housset C, Chrétien Y, Debray D, Chignard N. Functions of the gallbladder. Compr Physiol. 2016;6(3).
34. Gilani SNS, Bass GA, Kharytaniuk N, Downes MR, Caffrey EF, Tobbia I, et al. Gastroesophageal

mucosal injury after cholecystectomy: An indication for surveillance? J Am Coll Surg. 2017;224(3):319-326.

35. Watkins CC, Sawa A, Jaffrey S, Blackshaw S, Barrow RK, Snyder SH, et al. Insulin restores neuronal nitric oxide synthase expression and function that is lost in diabetic gastropathy. J Clin Invest. 2000;106(3):373-384.
36. Krishnasamy S, Abell TL. Diabetic gastroparesis: Principles and current trends in management. Diabetes Ther. 2018;9(1):1-42.
37. Svyatova G, Berezina G, Danyarova L, Kuanyshbekova R, Urazbayeva G. Genetic predisposition to gestational diabetes mellitus in the Kazakh population. Diabetes Metab Syndr Clin Res Rev. 2022;16(12):102675.
38. Fernandez AM, Chan WW. Update on extraesophageal manifestations of gastroesophageal reflux. Curr Opin Gastroenterol. 2024;40(4):305-313.
39. Scarpellini E, Vos R, Blondeau K, Boecxstaens V, Farré R, Gasbarrini A, et al. The effects of itoprid on esophageal motility and lower esophageal sprinter function in man. Aliment Pharmacol Ther. 2011;33(1):99-105.
40. Kawiorski W, Herman RM, Legutko J. Current diagnosis of gastroduodenal reflux and biliary gastritis. Przegl Lek. 2001;58(2):90-94.
41. Pizza F, D'Antonio D, Lucido FS, Tolone S, Dell'Isola C, Gambardella C. Postoperative clinical-endoscopic follow-up for GERD and gastritis after one anastomosis gastric bypass for morbid obesity: How, when, and why. Obes Surg. 2020;30:4391-4400.
42. Bongiovanni A, Parisi GF, Scuderi MG, Licari A, Brambilla I, Marseglia GL, Leonardi S. Gastro-esophageal reflux and respiratory diseases: Does a real link exist? Minerva Pediatr. 2019;71(6):515-523.
43. Alexyuk P, Bogoyavlenskiy A, Alexyuk M, Akanova K, Moldakhanov Y, Berezin V. Isolation and Characterization of Lytic Bacteriophages Active against Clinical Strains of E. coli and Development of a Phage Antimicrobial Cocktail. Viruses. 2022;14(11):2381.
44. Zviahintseva TD, Sharhorod II. Gastroesophageal reflux disease and alkaline reflux: The mechanisms of the development and therapeutic approach. Gastroenterol. 2021;(4.62):21-25.
45. Shi X, Chen Z, Yang Y, Yan S. Bile reflux gastritis: Insights into pathogenesis, relevant factors, carcinomatous risk, diagnosis, and management. Gastroenterol Res Pract. 2022;264:25-51.
46. Saribayeva DA, Biyashev KB, Valdovska A, Sansyzbai AR, Biyashev BK. Study antagonistic activity, the level of resistance to hydrochloric acid and bile probiotic strain *Escherichia coli*. J Pure Appl Microbiol. 2015;9(1):573-578.
47. Tamm T, Zulfiharov I, Mamontov I, Kramarenko K, Zakharchuk O, Reshetniak O, Ustinov A. Peculiarities of Liver Histostructure and Choledochous Duct in Partially Restored Bile Duct. Surg East Eur. 2021;10(4):452-459.
48. Johncilla M, Elsoukkary S, Jessurun J. The significance of focally enhanced gastritis in haematopoietic stem cell transplant recipients. Histopathol. 2021:79(4):599-606.
49. Stefaniwsky AB, Tint GS, Speck J, Shefer S, Salen G. Ursodeoxycholic acid treatment of bile reflux gastritis. Gastroenterol. 1985;89(5):1000-1004.