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Functional Disorders of the Biliary Tract and Cholelithiasis: Analysis of a Possible Relationship

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Aim: Diagnostic criteria for functional disorders of the biliary tract are presented in the materials of the Rome IV consensus, as well as expert councils of Russian and foreign specialists. Episodes of functional biliary pain are caused by a violation of bile outflow through the cystic duct and sphincter of Oddi. It has been suggested that there is a "biliary continuum" in which in some patients' biliary dysfunction is transformed into cholelithiasis.
Key points. Lithogenic bile is considered as the pathophysiological basis for the development of biliary dyskinesia and cholelithiasis. Lithogenic bile provokes inflammation of low grades in the mucous membrane of the biliary tract, decreased contractility of the gallbladder and impaired relaxation of the biliary sphincters, impaired physiological response to cholecystokinin. Changes in motility of the biliary tract may be associated with the influence of hydrophobic bile salts and impaired eicosanoid metabolism. Hyperplasia of the epithelium and muscle layer, hypersecretion of mucin and cholesterol precipitation further impair the outflow of bile. Experimental data and some clinical observations indicate the possibility of transformation of biliary dysfunction into cholelithiasis. Dysfunction of the sphincter of Oddi is one of the possible consequences of cholecystectomy and, in fact, acts as a variant of postcholecystectomy syndrome. The basis for the treatment of biliary dysfunctions are antispasmodics of different classes, which can be combined with ursodeoxycholic acid. The biliary tract-selective antispasmodic hymecromone has shown high effectiveness in relieving biliary pain, which also has a moderate choleretic effect and the ability to prevent the crystallization of cholesterol in bile and can be used both for functional diseases and for cholelithiasis. The domestic drug hymecromone "Odecromone" entered the pharmaceutical market.
Keywords: functional diseases of the biliary tract, lithogenic bile, dysfunction of the sphincter of Oddi, hymecromone
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Функциональные заболевания желчевыводящих путей и желчнокаменная болезнь: анализ возможной взаимосвязи

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Цель: Диагностические критерии функциональных заболеваний желчевыводящих путей представлены в материалах Римского консенсуса IV, а также экспертных советов российских и зарубежных специалистов. Приступы функциональной билиарной боли обусловлены нарушением оттока желчи через пузырный проток и сфинктер Одди. Выдвинуто предположение о наличии «билиарного континуума», в котором у части пациентов билиарная дисфункция трансформируется в желчнокаменную болезнь (ЖКБ).
Основные положения. В качестве патофизиологической основы развития билиарной дискинезии и ЖКБ рассматривается литогенная желчь. Она провоцирует воспаление низкой степени в слизистой оболочке желчных путей, снижение сократимости желчного пузыря и нарушение расслабления билиарных сфинктеров, нарушение физиологического ответа на холецистокинин. Изменение моторики желчных путей может быть связано с влиянием гидрофобных солей желчных кислот и нарушением обмена эйкозаноидов. Гиперплазия эпителия и мышечного слоя, гиперсекреция муцина и осаждение холестерина еще больше нарушают отток желчи. Данные экспериментов и некоторые клинические наблюдения указывают на возможность трансформации билиарной дисфункции в ЖКБ. Дисфункция сфинктера Одди представляет собой одно из возможных последствий холецистэктомии и, по сути, выступает как вариант «постхолецистэктомического синдрома». Основу лечения билиарных дисфункций представляют спазмолитики разных классов, которые можно комбинировать с урсодезоксихолевой кислотой. Высокую эффективность в купировании билиарной боли показал

селективный для желчных путей спазмолитик гимекромон, который также обладает умеренным холеретическим действием и способностью предупреждать кристаллизацию холестерина в желчи и может применяться как при функциональных заболеваниях, так и при ЖКБ. Отечественный препарат гимекромона «Одекромон®» вышел на фармацевтический рынок.

Заключение. Не вызывает сомнений актуальность дальнейшего изучения закономерностей развития билиарных дисфункций и ЖКБ. Изучение этой проблемы будет способствовать разработке эффективных профилактических подходов, в том числе в области нутрицевтики.

Ключевые слова: функциональные заболевания желчевыводящих путей, литогенная желчь, дисфункция сфинктера Одди, гимекромон

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Introduction

Dyskinesia of the gallbladder (GD) and of the sphincter of Oddi (DSO) are functional diseases. Their diagnostic criteria, presented in the materials of the Rome IV Consensus, as well as expert councils of Russian and foreign specialists, are based on the exclusion of organic lesions (severe biliary sludge, cholelithiasis, cholangitis, stenosis and tumors) and assessment of gallbladder emptying. With dysfunction of the sphincter of Oddi of the biliary type, ultrasound and biochemical markers of transient obstruction of the biliary tract can be determined, so the diagnosis of this disease requires a particularly responsible approach, using high-resolution imaging methods (magnetic resonance cholangiopancreatography and endoscopic ultrasound) [1–3].

The main clinical manifestation of GD and DSO is biliary pain, the characteristics of which are formulated on the basis of a large amount of data, which in most cases makes it easy to differentiate it from other abdominal pain. Key signs of biliary pain: 1) intensity exceeding 5 points on a visual analogue scale; 2) localization in the epigastric region and right hypochondrium; 3) occurrence regardless of body position and defecation; 4) ineffectiveness of antacids and antisecretory drugs; 5) lack of direct connection with food intake; 6) frequent occurrence at night; 7) the appearance of concomitant nausea and vomiting that does not relieve pain; 8) irradiation to the right shoulder and right arm. Biliary pain sharply decreases patients' quality of life, forcing them to see a doctor. With GD and DSO, classic biliary colic does not develop. The pathophysiology of functional biliary pain has not been sufficiently studied due to the impossibility of creating experimental models in animals and conducting the full range of necessary studies in humans. The origin of pain is due to impaired motility with transient biliary hypertension against the background of visceral hypersensitivity (disturbance along the "gastrointestinal tract — brain" axis) [3, 4].

Analysis of the tissues of the removed gallbladder and cystic bile in patients with functional biliary pain even back in the 1990s suggested that the high lithogenicity of bile initially disrupts the motility of the biliary tract and causes their subclinical inflammation through the following mechanism: hypersecretion of mucin + nucleation of cholesterol with the capture of its crystals by cells of the mucous membrane → microtraumatization + inflammation and narrowing of the ducts. Subsequently, bile microliths are formed. Thus, it has been suggested that there is a sequence of events in which biliary dysfunction in some patients is transformed into cholelithiasis. Pain can occur at any point along this continuum (Fig. 1) [5]. Attacks of functional biliary pain are caused by a disturbance of bile outflow through the Lütkens sphincter and the cystic duct or the sphincter of Oddi, which are the narrowest sections of the biliary system with a folded structure of the mucosa, predisposing to the retention of cholesterol crystals. Obstruction is caused by insufficient relaxation of these sphincters. However, a mechanical component cannot be excluded (obstruction by mucin clots and cholesterol crystals, ductal fibrosis) [6–8].

In patients with a preserved gallbladder, functional obstruction is accompanied by its impaired emptying, the "gold standard" for evaluation of which is bilioscintigraphy with cholecystokinin (CCK) stimulation. Under normal conditions, 45 minutes after the administration of CCK, the emptying fraction should exceed 35 %. In clinical practice, bilioscintigraphy and transcutaneous ultrasound cholecystography with stimulation with sorbitol or food are widely used. However, the results of the last two methods were not compared with the "gold standard".

The fraction of gallbladder emptying depends on two indicators — the magnitude of duct obstruction and a decrease in its contractility. A decrease in voiding fraction without biliary pain can be observed in functional dyspepsia, irritable bowel syndrome, pregnancy, celiac disease, total parenteral nutrition, oral contraceptives, and in patients with insulin resistance [9]. On the other hand, biliary pain also occurs in some patients with preserved

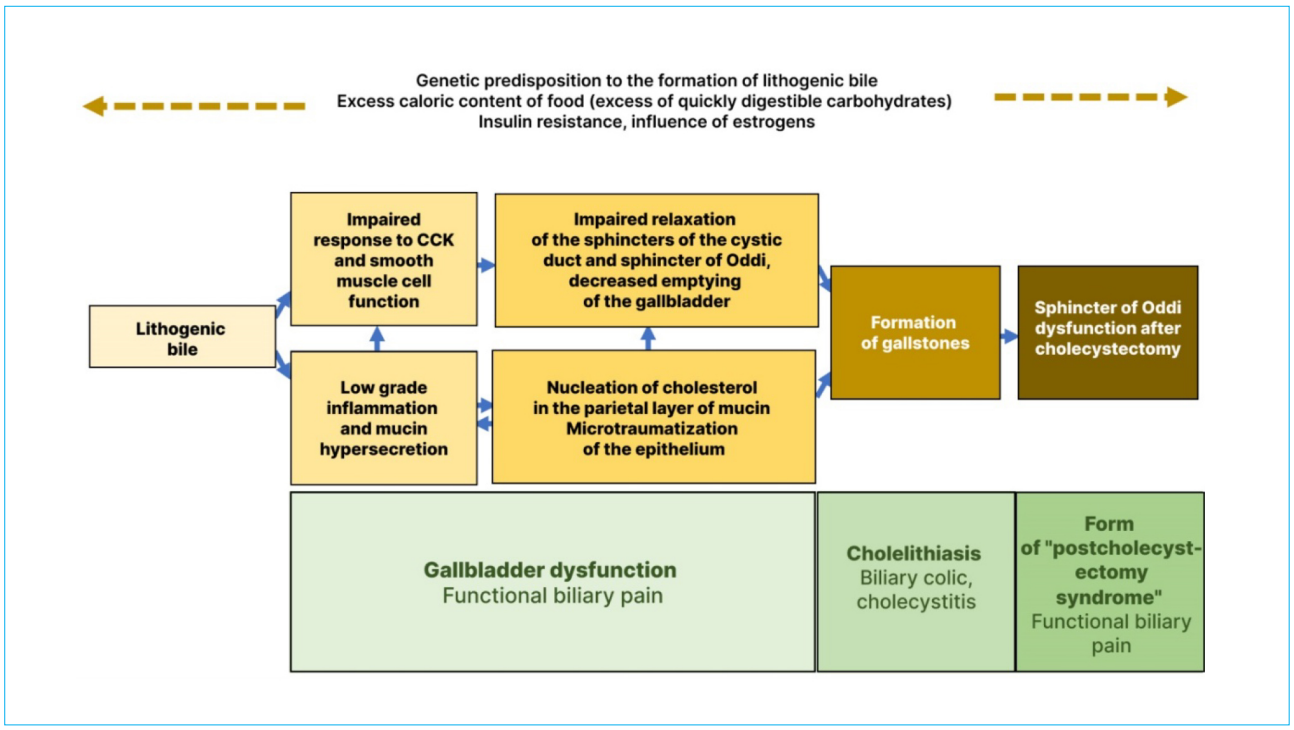

Figure 1. The hypothesis of the "continuum" of biliary disorders (the diagram reflects the main stages of the pathogenesis of diseases, the development of which is based on the high lithogenicity of bile; dyskinesia of the gallbladder can progress to the stage of cholelithiasis; after cholecystectomy, dyskinesia of the sphincter of Oddi occurs, which may be another cause of biliary pain)

Рисунок 1. Гипотеза «континуума» билиарных расстройств (схема отражает основные этапы патогенеза заболеваний, в основе развития которых лежит высокая литогенность желчи; дискинезия желчного пузыря может прогрессировать до стадии желчнокаменной болезни; после холецистэктомии возникает дискинезия сфинктера Одди, которая может быть еще одной причиной билиарной боли)

and even increased (> 85 %) emptying fraction. Morphologically, as a rule, signs of cholecystitis and cholesterosis are detected [10]. In addition to biliary pain, with biliary dyskinesia and cholelithiasis, symptoms of delayed gastric emptying (dyspepsia), gastroesophageal reflux (heartburn), and impaired intestinal motility (flatulence, stool disorder) may be observed.

Lithogenic bile and its effect on the development of biliary dysfunction

The term "lithogenic bile" refers to its persistent oversaturation with cholesterol, which is an important prerequisite for the precipitation of cholesterol monohydrate and the formation of cholesterol stones. Reduced levels of phospholipids and bile acids, impaired bladder emptying, and hypersecretion of mucin also contribute to the nucleation and crystallization of cholesterol. The leading pathophysiological defect in this case is hypersecretion of cholesterol by hepatocytes [11], and the promoters are the carriage of abnormal *Lith* genes, increased absorption of cholesterol in the intestine due to slow peristalsis and intestinal dysbiosis, as well as "external" lithogenic factors — hypercaloric nutrition, excess of easily digestible carbohydrates in the diet, metabolic disorders (obesity and insulin resistance), the influence of drugs (in particular estrogens) (Fig. 2). An increase in the activity of sterol regulatory element-binding protein 2 (SREBP-2) in the endoplasmic reticulum is important. SREBP-2 regulates the transcription and activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, an enzyme that synthesizes cholesterol. SREBP-2 activity and cholesterol production increase significantly under the influence of insulin-induced gene products (*INSIG1* and *INSIG2*), as well as under conditions of endoplasmic reticulum stress [12]. Such patients have Frederiksen type IIb and IV dyslipidemia (increased triglycerides ± low-density lipoproteins) [13]. With a defect in the LDL receptor genes, *APOB100R* and *APOE4*, dyslipidemia of types IIa, IIb, and III is observed.

As Figure 2 shows, the secretion of cholesterol into bile under physiological conditions is determined mainly by the activity of the hepatocyte apical membrane transporter ABCG5/G8, the rate of cholesterol synthesis (HMG-CoA reductase activity), the rate of synthesis of bile acids from cholesterol and, to a lesser extent, the rate of cholesterol

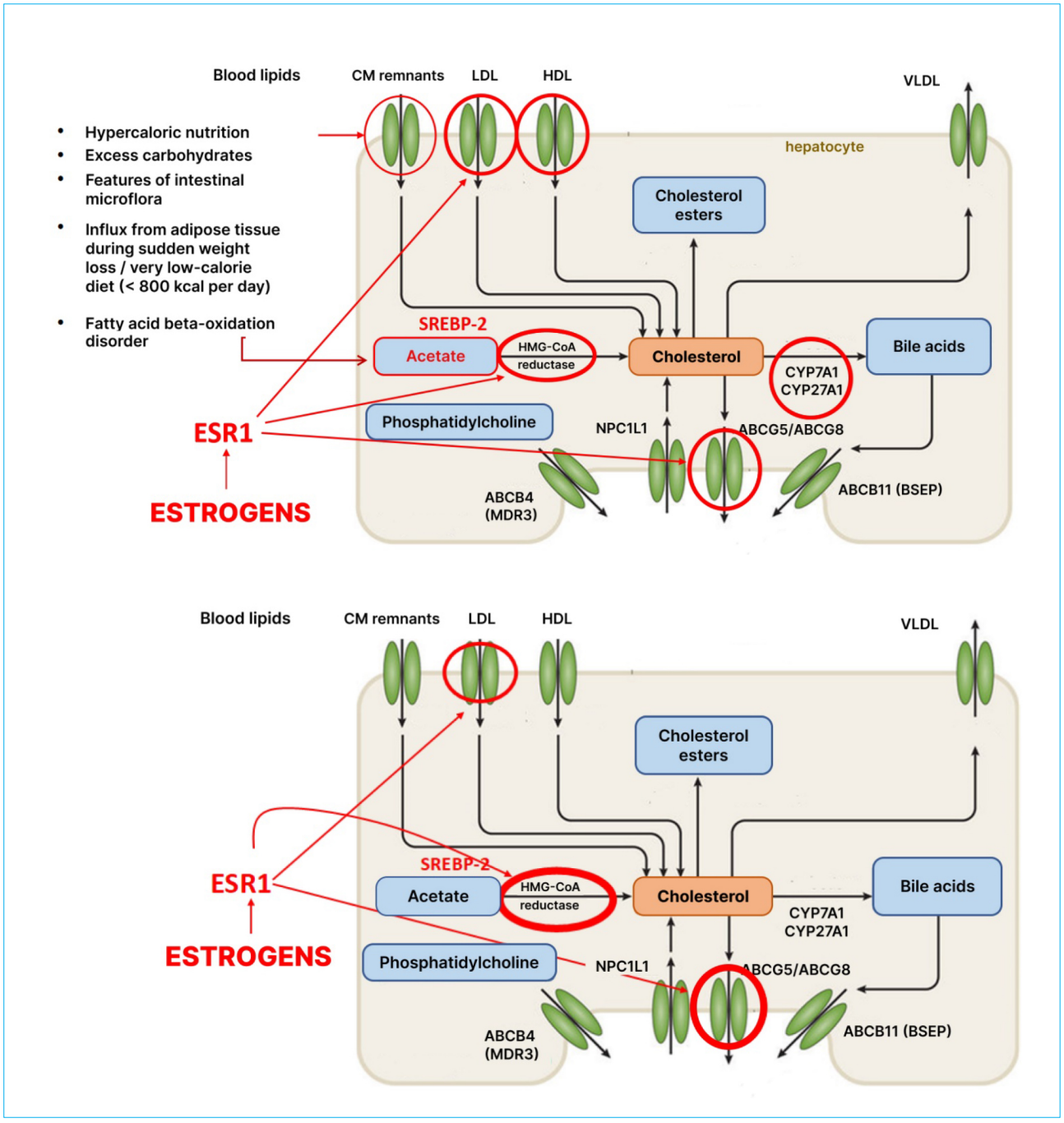

Figure 2. The mechanism of cholesterol transport by hepatocytes into bile, indicating the factors contributing to its hypersecretion: CM — chylomicron; LDL — low-density lipoprotein; HDL — high density lipoproteins; VLDL — very low density lipoproteins; SREBP-2 — sterol regulatory element binding protein-2; HMG-CoA reductase — 3-hydroxy-3-methylglutaryl coenzyme A reductase

Рисунок 2. Механизм транспорта холестерина гепатоцитами в желчь с указанием факторов, способствующих его гиперсекреции: СМ — хиломикрон; LDL — липопротеиды низкой плотности; HDL — липопротеиды высокой плотности; ЛПОНП — липопротеиды очень низкой плотности; SREBP-2 — белок-2, связывающий стерол-регуляторный элемент; HMG-CoA-редуктаза — 3-гидрокси-3-метилглютарил-кофермент А редуктаза

entry into the hepatocyte as part of LDL and HDL. Exogenous metabolic factors can promote the secretion of lithogenic bile, increasing the accumulation of acetate in hepatocytes, which is the substrate from which cholesterol is synthesized. Estrogens interact with estrogen receptor-1 (ESR1), which increases the activity of SREBP-2, HMG-CoA reductase, cholesterol synthesis and secretion into bile, as well as the transfer of cholesterol into the hepatocyte as part of LDL.

Lithogenic bile itself causes low grade inflammation. In animals carrying *Lith* genes, even before the stage of stone formation, granulocytic infiltration and fibrosis develop in the gallbladder wall, the density of Cajal cells and smooth muscle cells decreases with a decrease in the emptying fraction. It is lithogenic bile that is considered the most important cause of decreased contractility of the gallbladder and impaired relaxation of the biliary sphincters [14, 15]. Excessive consumption of carbohydrates and lithogenicity of bile result in a violation of spontaneous excitation of smooth myocytes, which ensures the tone of the gallbladder in the interprandial period, as well as sporadic cluster asynchronous and synchronous contractions in response to stimulation of CCK [16].

It has been established that lithogenic bile disrupts the physiological response to CCK. In the biliary tract, receptors for CCK are located on the presynaptic endings of vagus nerve motor neurons, as well as on the surface of smooth muscle cells. Oxidized forms of cholesterol (oxysterols), formed spontaneously or under the influence of microbiota, are embedded in the cell membrane, where, unlike cholesterol, they acquire an abnormal orientation and disrupt the sensitivity of receptors to ligands [17]. Type 1 CCK receptors are located in areas of the membrane rich in cholesterol, the so-called "rafts". Under normal conditions, the interaction of CCK with such a receptor with the participation of the caveolin protein results in the formation of caveolae, or membrane depressions with the immersion of the CCK-receptor complex in the cytoplasm. An excessive concentration of cholesterol in the membrane disrupts this process: the number of receptors returning to the membrane surface decreases (receptor turnover decreases) [18]. The permeability of calcium channels located in the "rafts" zone and mediating muscle contraction is also impaired. It should be noted that the functions of NO receptors localized outside the "rafts" and opioid receptors associated with another caveolar protein, clathrin, remain unchanged.

Impaired motility of the gallbladder and biliary sphincters can also be caused by hydrophobic bile acids interacting with a specific G-protein-coupled bile acid receptor 1 (GPBAR1). Taurochenodeoxycholate and taurolithocholate stimulate the opening of ATP-dependent potassium channels in cell membranes, causing their hyperpolarization [19]. The reason for the increased content of potentially toxic lithocholic acid in bile is its excessive formation from chenodeoxycholic acid in the intestine, as well as impaired detoxification (sulfation) in the liver. The importance of lithocholic acid in the pathogenesis of biliary dyskinesias has not been sufficiently studied [20].

Lithogenic bile promotes the accumulation of cholesterol monohydrate in the parietal layer of mucus, damage to the epithelium of the biliary tract and the development of low-grade inflammation in the lamina propria with the participation of eosinophils, neutrophils and lymphocytes. Consequently, hyperplasia of the epithelium and muscle layer further impairs the outflow of bile [14, 21]. Excessive cholesterol content in the cell membrane leads to spontaneous activation of phospholipase A and changes in the balance of eicosanoids, which prolongs subclinical inflammation up to the development of cholecystitis. It was found that in smooth muscle cells of the gallbladder taken from patients with cholesterol cholecystolithiasis, the antioxidant effect of prostaglandin PGE2 is significantly weakened. After removal of excess cholesterol from plasma membranes, it is restored [22]. Eicosanoids play an important role in regulating contraction of smooth muscle cells. PGE2, PGF2 not only enhance the effect of CCK, but also independently stimulate contraction of the gallbladder [14, 23]. In patients with lithogenic bile, the production of these prostaglandins decreases, but the production of PGI2, which is an antagonist of CCK, increases. Estrogens exacerbate eicosanoid imbalances [22].

Mechanisms of evolution of biliary dysfunction in cholelithiasis

In the materials of the Rome IV Consensus, gallbladder dyskinesia (GD) is presented as a disease with a favorable prognosis. At the same time, it has been suggested that GD serves as a background for the development of cholelithiasis [23]. And although large-scale studies have not been conducted on this problem, the similarity of risk factors, pathophysiological mechanisms and symptoms makes this possibility very likely. Experiments have shown that the formation of cholesterol stones is preceded by GD [24]. Biliary dysfunction usually manifests itself between the ages of 10 and 17 years in overweight patients, more often in girls. The formation of gallstones in this group is observed already at the age of 20–30 years [23, 24].

In the pathogenesis of cholelithiasis, genetic predisposition plays a significant role. The genes responsible for the formation of cholesterol stones encode the structure of carriers of cholesterol and phospholipids into bile (*ABCG8, ABCG5, ABCB4, ABCB11*), apolipoproteins ApoB100 and ApoE4, as well as mucin. It is the carriers of abnormal genes that are most prone to the formation of lithogenic bile [25]. In recent publications, special attention has been paid to mutations of the *Lith13* gene, which encodes the structure of the CCK receptor type 1. In carriers of mutations of this gene, the emptying fraction of the gallbladder decreases, and cholesterol sludge and stones form. Dysfunction of

the CCK type 1 receptor slows down transit through the small intestine, thereby increasing cholesterol absorption [11]. A change in the balance of eicosanoids also serves as a pathogenetic link between GD and cholelithiasis. An important role is played by dietary stereotypes (increased calorie content, excessive consumption of easily digestible carbohydrates) [20].

"Postcholecystectomy syndrome" as a link in the "continuum" of biliary disorders

Hundreds of thousands of cholecystectomies are performed annually around the world. In some countries, they are also performed for gallbladder dyskinesia. In 15–30 % of cases, after removal of the gallbladder, previously existing symptoms (abdominal pain, dyspeptic disorders) not only persist, but even intensify or appear for the first time. Since the middle of the last century, this situation has been referred to as "postcholecystectomy syndrome" (PCS). This collective concept unites heterogeneous pathological conditions, namely: complications and defects of surgical intervention (residual common bile duct stones, inflammation of the bile duct stump, bilomas, strictures, etc.), unrecognized diseases, the symptoms of which were mistakenly regarded as a manifestation of cholelithiasis (gastroesophageal reflux disease, peptic ulcer disease, functional diseases of the stomach and intestines, diverticular disease, chronic pancreatitis). This also includes disorders directly caused by cholecystectomy: 1) loss of a bile reservoir → disruption of the "physiology" of bile secretion → DSO; 2) increased duodenogastric reflux → reflux gastropathy, "alkaline" reflux esophagitis; 3) change in the circulation of bile acids → diarrhea. Thus, PCS is a stage diagnosis that requires further full specification [1].

The term "dyskinesia of the sphincter of Oddi of the biliary type" refers to incomplete opening of the sphincter with impaired bile secretion, which is accompanied by biliary pain, transient hyperfermentemia, and dilation of the common bile duct. According to the 2012 Milwaukee Classification, there are three types of DSO. In the materials of the Rome IV Consensus (2016), the classification of biliary disorders has been revised (Table).

The appearance or intensification of symptoms of DSO after cholecystectomy is due to an increase in the volume load on the sphincter of Oddi [1].

Modern approaches to the prevention and treatment of functional biliary disorders

Preventive measures are aimed at normalizing the motility of the biliary tract and reducing the lithogenicity of bile. An important role is played by limiting the consumption of quickly digestible carbohydrates (glucose, fructose, sugar). Simple carbohydrates serve as a source of cholesterol production, and also indirectly contribute to the development of bacterial overgrowth in the intestines with a change in the ratio of primary and secondary bile acids in bile. Diets high in fiber and calcium help reduce the content of hydrophobic bile acids in bile. Regular meals reduce bile stagnation. Adequate intake of vitamin C is necessary for the synthesis of bile acids from cholesterol. Hyperglycemia, hyperinsulinemia and stress (sympathetic stimulation) contribute to inhibition of the reactivity of smooth muscle cells of the biliary tract. Addressing these factors is essential. In the presence of anxiety and depression, appropriate examination is indicated. During periods of exacerbation, it is advisable to limit the consumption of animal fats, fried foods, extractive nutrients, herbs, seasonings and spices, marinades. For two hours after eating, prolonged bending and horizontal body positions should be avoided.

The first-line pharmaceuticals for patients with GD and DSO are antispasmodics that eliminate "functional biliary obstruction".

Ursodeoxycholic acid (UDCA) for the treatment of biliary tract dysfunctions is usually used in combination with antispasmodics, when they are insufficiently effective. UDCA helps reduce the lithogenicity of bile and has an anti-inflammatory and antioxidant effect on the epithelium of the biliary tract. Prokinetics can be used to relieve symptoms caused by impaired motility of the stomach and initial parts of the small intestine. With a clearly substantiated diagnosis and often recurrent pain, in which a neuropathic component or connection with central sensitization can be assumed, the prescription of tricyclic antidepressants is justified. If there is a substantiated diagnosis of sphincter of Oddi dysfunction and there is no effect of conservative therapy, it is advisable to consider endoscopic papillosphincterotomy of the biliary portion of the sphincter of Oddi [1].

When choosing an antispasmodic for the treatment of diseases of the biliary tract, one should focus on the mechanism of action and the point of application of the antispasmodic effect, giving preference to drugs with a selective effect. To correct DSO, the calcium channel blocker nifedipine and the NO donor nitrosorbide sublingually have been proposed; however, when taking them, there is a risk of developing severe arterial hypotension. The anticholinergic blocker hyoscine butylbromide and trimebutine, which act on enkephalin receptors of the gastrointestinal tract, can be used both to relieve an attack of biliary pain and for a course of treatment. For the treatment of DSO, trimebutine is effective, as well as the sodium channel blocker of smooth muscle cells of the digestive tract mebeverine hydrochloride, the phosphodiesterase-4 inhibitor drotaverine hydrochloride, the calcium channel blocker pinaveria bromide, an extract from the

Table. Classification of sphincter of Oddi dyskinesias
Таблица. Классификация дискинезий сфинктера Одди

Milwaukee classification (Rome criteria III) ***Милуокская классификация (Римские критерии III)***	**Rome criteria IV** ***Римские критерии IV***
Sphincter of Oddi dysfunction type I (biliary pain, hyperfermentemia, persistent dilatation of the ducts) *Дисфункция сфинктера Одди I типа (билиарная боль, гиперферментемия, стойкое расширение протоков)*	Папиллостеноз (органическое патологическое состояние) *Papillostenosis (organic pathological condition)*
Sphincter of Oddi dysfunction type II (biliary pain, hyperenzymemia, transient dilatation of the ducts) *Дисфункция сфинктера Одди II типа (билиарная боль, гиперферментемия, преходящее расширение протоков)*	Dysfunction of the sphincter of Oddi of the biliary or pancreatic type (hypersensitivity, spasm or compensated stenosis) *Дисфункция сфинктера Одди по билиарному или панкреатическому типу (гиперчувствительность, спазм или компенсированный стеноз)*
Sphincter of Oddi dysfunction type III (biliary pain) *Дисфункция сфинктера Одди III типа (билиарная боль)*	Functional biliary pain (hypersensitivity) *Функциональная билиарная боль (гиперчувствительность)*

leaves of the artichoke (the drug is contraindicated in cholelithiasis due to stimulation of the contractile activity of the gallbladder) [1].

One of the most widely used drugs in Russia and Europe for the relief of biliary pain is hymecromone, a myotropic antispasmodic with high selectivity of action on the biliary tract. In terms of its chemical structure, hymecromone is an analogue of umbelliferone, a substance with an antispasmodic effect, which is found in many plants that have a beneficial effect on digestion (coriander, anise, chamomile, lovage). Experiments have established that the mechanism of the antispasmodic action of hymecromone is explained by an increase in the content of cyclic mononucleotides and NO in smooth myocytes, as well as by blockade of Na^+ channels. The high biliary selectivity of hymecromone when taken orally is explained by the peculiarities of its pharmacokinetics. Absorbed in the small intestine, the drug enters the portal bloodstream. Further, similar to unconjugated bilirubin, it is taken up by hepatocytes with the participation of the organic anions transporting pump (OATP) of the basolateral membrane. In the hepatocyte, hymecromone is conjugated with glucuronic acid, after which it is excreted into bile with the participation of the canalicular multispecific organic anion transporter 1 (cMOAT). Thus, hymecromone accumulates and acts primarily in bile. No more than 3 % of the dose taken enters the systemic circulation. In addition to antispasmodic, hymecromone has anti-inflammatory and choleretic effects due to the secretion of electrolytes without stimulation of the synthesis of bile acids [26, 27]. Hymecromone reduces bile stagnation, prevents the crystallization of cholesterol and thereby the development of cholelithiasis. During therapy with hymecromone, the activity of leucine aminopeptidase in portions of bile B and C decreased, and the number of cholesterol crystals decreased [35].

Hymecromone ("Odekromone®") can be prescribed "on demand" at 200–400 mg orally when symptoms appear, but hymecromone is predominantly prescribed as a course of treatment at 200–400 mg 3 times a day half an hour before meals for 2–3 weeks, repeated courses.

The effectiveness of hymecromone in the treatment of biliary pain has been confirmed in clinical and experimental studies. In patients with sphincter of Oddi dysfunction, hymecromone caused a significant decrease in intraductal pressure by increasing the opening time of the sphincter of Oddi ($p < 0.001$). In clinical studies with manometry, the increase in pressure in the common bile duct during the administration of morphine could be stopped by the administration of hymecromone [28]. In a study of 123 patients with biliary dysfunction, cholelithiasis and dyspepsia (mean age — 60.3 ± 14.2 years), patients were randomized to receive hymecromone 1200 mg daily or placebo for 14 days. In the group of patients receiving hymecromone, a more pronounced and lasting reduction in the symptoms of dyspepsia and biliary pain was achieved (reduction in severity by 70.3 and 43.8 %, respectively). Treatment with hymecromone was well tolerated by patients and was assessed by researchers as effective in 88.5 % of patients [29]. When comparing the effectiveness of two different dosages of hymecromone (600 and 1200 mg per day) in the treatment of patients diagnosed with PCS, after a course of therapy with hymecromone at a higher dose, the clinical effect lasted longer — for an average of 3 months. In this group, there was a more pronounced reduction in pain ($p < 0.01$), normalization of stool frequency and consistency (χ^2; $p = 0.015$); significant decrease

in the diameter of the common bile duct. In the group using hymecromone at a dose of 1200 mg per day, a higher proportion of patients (81.3 %) were satisfied with the results of treatment compared to the group receiving the drug at a dose of 600 mg per day (55.5 %). According to the RAPID questionnaire, patients receiving 1200 mg of hymecromone per day maintained a statistically significant reduction in the impact of pain on daily activities 3 months after the end of therapy (χ^2; $p = 0.014$) [30].

Hymecromone is recommended in combination with UDCA in conservative litholysis regimens for the treatment of biliary sludge and cholelithiasis. A comparative study assessed the clinical benefits of combined therapy with UDCA and an antispasmodic for biliary sludge. There was a more pronounced decrease in the severity of biliary dyspepsia (pain in the right hypochondrium, bitterness in the mouth, nausea) with combination therapy of UDCA and hymecromone compared with UDCA monotherapy. According to ultrasound data, in both groups there was a decrease in the severity of sludge, with a transition to the stage of a suspension of echo-dense particles in 33 % of cases. Among the remaining patients, there was an improvement in the characteristics of the contents of the gallbladder (reduction in the number of clots, suspension, layer of echogenic bile) in 62 % in the combination therapy group and 48 % in the UDCA monotherapy group. During treatment, no significant changes in biochemical blood test parameters were registered, which indicates the safety of the therapy. Thus, the addition of hymecromone to UDCA therapy for stage 2 biliary sludge increased the effectiveness of litholytic therapy by 14 % [31, 32].

Gimecromone does not enhance the contractile function of the gallbladder, which makes it safe for cholelithiasis [27]. In patients with cholelithiasis and chronic calculous cholecystitis without "biliary colic", but with pain in the epigastrium and right hypochondrium, the use of hymecromone at a dose of 600 mg per day helped relieve pain in 60 % of patients by day 7; in 30 % — by day 14, in 10 % the pain was relieved after increasing the dose of hymecromone to 1200 mg per day [33]. Thus, the use of hymecromone at a dose of 1200 mg per day has a higher potential in relieving pain not only in PCS, but also in chronic calculous cholecystitis [30, 33].

As shown by the results of a prospective multicenter observational study conducted in 60 research centers in four cities of the Republic of Kazakhstan with the participation of 877 patients, hymecromone demonstrates fairly high effectiveness in patients with various diseases of the biliary tract in everyday clinical practice. Most often, doctors prescribed hymecromone for functional disorders of the biliary tract (65.3 %), including in patients with chronic acalculous cholecystitis with dysfunction of the biliary tract, less often in patients with uncomplicated cholelithiasis, biliary sludge and functional disorder of the sphincter of Oddi after cholecystectomy (as a variant of PCS), choosing a dose of 1200 mg per day.

The use of hymecromone, which has a selective antispasmodic effect on the biliary tract in combination with a moderate choleretic effect, provides greater satisfaction with treatment when prescribing a dose of 1200 mg per day, especially with a more pronounced effect of pain on daily activities. The results of this study also showed the possibility of prescribing hymecromone in repeated courses and in combination with ursodeoxycholic acid.

Conclusion

Considering the commonality of the pathophysiological mechanisms underlying biliary dysfunctions and cholelithiasis, there is no doubt about the relevance of further studying the patterns of development and the relationship of these diseases. Studying this problem will contribute to the development of effective preventive approaches, including in the field of nutraceuticals. Understanding the mechanisms of motility disorders and the development of subclinical inflammation at the stage of gallbladder dysfunction opens up the possibility of developing more optimal methods for treating biliary pain, preventing progression with the development of cholelithiasis and, accordingly, reducing the frequency of cholecystectomy. Hymecromone, due to the selectivity of its antispasmodic effect, the presence of a moderate choleretic effect and the ability to prevent the crystallization of cholesterol in bile, may be the drug of choice for the treatment of functional diseases of the biliary tract.

In November 2023, the pharmaceutical company Sotex launched a new drug with an active ingredient, Odecromone, which is a complete alternative to its Western analogue, that is currently not easy to find in pharmacies. Odecromone has an identical composition, including the substance, as well as similar packaging — 20, 50 and 100 tablets, familiar to patients.

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