Chronic acalculous cholecystitis with biliary sludge

Chronic acalculous cholecystitis with biliary sludge is an inflammatory disease, which affects the gallbladder wall and causes motoric-tonic dysfunction of the biliary tract, which is accompanied by appearance of hyperechogenic particles in the gallbladder lumen and reveals as biliary pain (1-10). The cause of the gallbladder motility disorders can be caused by increased basal cystic duct resistance or cystic duct spasm, muscle hypertrophy, and chronic aseptic inflammation in the gallbladder wall.

"Biliary sludge" is designated as any heterogeneity of gallbladder bile found with ultrasound examination (2-10). Biliary sludge is the result of precipitation of calcium bilirubinate granules, cholesterol monohydrate crystals and polymerized glycoprotein biliary mucin in gallbladder bile (2-10). Only cholesterol monohydrate crystals are the hyperehogenic particles without an acoustic shadow at sonography (2-5).

Biliary sludge is often found in women during pregnancy, in obese patients on a very-low-calorie diet (rapid weight loss), in patients with high spinal cord injuries, prolonged total parenteral nutrition, prolonged treatment with octreotide, and in patients after gastrectomy or colectomy (11-12).

According to the position in the gallbladder and the form biliary sludge is classified in diffused, surface, and precipitating (5). The dynamics of the transformation of biliary sludge into cholesterol gallstones has been shown as follows: diffused biliary sludge → precipitating biliary sludge → a cholesterol gallstone without acoustic shadow → a cholesterol gallstone with acoustic shadow (5). The transformation time of biliary sludge into cholesterol gallstones in the gallbladder makes up 3-36 months (12). Depending on cause the percentage of transformation may change from 5% to 50%.

Biliary sludge and cholesterol gallstones are formed in 25-50% of obese patients during very-low-calorie diet within 3-6 months, in 40% of obese patients within 6 months after surgery (12). Approximately 25% of obese patients who undergo strict dietary restriction develop gallstones, and as many as 50% of patients who undergo gastric bypass develop gallbladder sludge or gallstones within six months after surgery (12). As many as 40% of these patients will develop symptoms related to gallstones within the some six-month period (12). A decreased incidence in gallstone formation of 28% to 3% in obese patients on a very-low-calorie diet when they received 600 mg/day ursodeoxycholic acid (12). As many as 45% of adults will develop gallstones after 3 to 4 months of total parenteral nutrition (12).

The incidence of new sludge and stone formation during pregnancy is approximately 30% and 2%, respectively (12). After delivery, gallbladder motility returns to normal and biliary sludge disappears in 60% to 70% and stone disappears in 20% to 30% of women (12). In patients with biliary sludge who were followed prospectively, 8% were shown to develop asymptomatic gallstones and 6% developed symptomatic stones requiring cholecystectomy after 38 months (12). In 18% of the patients, the biliary sludge disappeared spontaneously; in the remaining 60%, the biliary sludge disappeared and subsequently reappeared (12).

Complications such as acute cholecystitis have been reported to occur in as many as 20% of patients with biliary sludge (12). It is clear from these and other studies that biliary sludge can be a precursor to stone formation and can be a source of potential complications (12).

Russian gastroenterologists single out 3 main types of biliary sludge, which have most clear ultrasound descriptions (11):

1. Microlithiasis is a presence of movable hyperechogenic single or multiple dot particles without acoustic shadow in the gallbladder lumen.
2. Echo unhomogeneous gallbladder bile includes movable clots of different densities without acoustic shadow in the gallbladder lumen.
3. Combination of "putty-like" bile with microlits. These microlits can be present simultaneously as in the "putty-like" bile, and as well as in the gallbladder lumen.

Diagnostic criteria of the chronic acalculous cholecystitis with biliary sludge

1. Biliary pains and feeling of discomfort in the right hypochondrium. Biliary pains may be in the right hypochondrium, frequently or occasionally, of different intensity and duration, no related or related to intake of fatty meals (1).
   In addition, biliary pain may occur with one or more of the following symptoms:
   a. regular or periodical feeling of bitter taste in the mouth
   b. nausea, heartburn, eructation, vomiting
   c. regular or periodical abdominal distension and borborygmus
   d. unstable stool with alternation of constipation or diarrhea
   e. pain occurs at night or after a meal
2. Impaired gallbladder emptying.
3. According to ultrasound examination, thickening of the gallbladder wall up to 3-6 mm.

Causes of the gallbladder evacuation dysfunction, biliary pain and chronic aseptic inflammation in the gallbladder wall

1. Pathology of the smooth muscle cells and epithelial cells in the gallbladder wall (high degree of COX-2 expression in the smooth muscle cells and epithelial cells of the gallbladder wall).
2. Hypersecretion of glycoprotein biliary mucin into gallbladder lumen and increase in concentration of glycoprotein biliary mucin in the gallbladder bile over point of polymerization (>2.0 mg/ml) (high degree of COX-2 expression in the epithelial cells of the gallbladder mucosa).
3. Contractile dyscoordination of the gallbladder and cystic duct (surplus degree of COX-2 expression in the smooth muscle cells of the gallbladder and cystic duct).
4. Increased basal cystic duct resistance (high degree of COX-2 expression in the smooth muscle cells of the cystic duct).
5. Increased basal common bile duct resistance (high degree of COX-2 expression in the smooth muscle cells of the sphincter of Oddi).

Mechanism of development of pathologic disorders

High degree of COX-2 expression in the smooth muscle cells of the gallbladder wall causes decrease in the evacuation function of the gallbladder and "active" passage of the hepatic bile into the gallbladder (fig. 21).

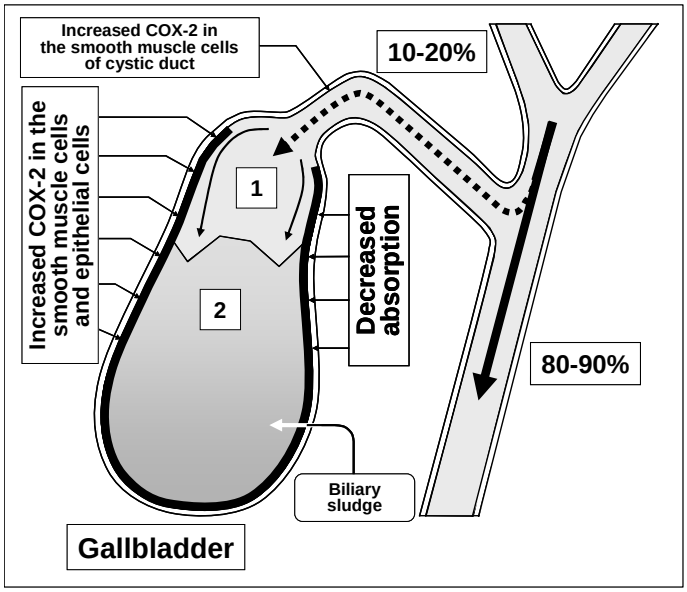

Fig. 21. "Active" and "passive" passage of hepatic bile into the gallbladder and into the duodenum in patients with chronic acalculous cholecystitis with biliary sludge.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.

Surplus COX-2 expression in the epithelial cells of the gallbladder mucosa causes decrease in the absorption function of the gallbladder (decrease of water and biliary cholesterol absorption) and "passive" passage of the hepatic bile into the gallbladder (fig. 21).

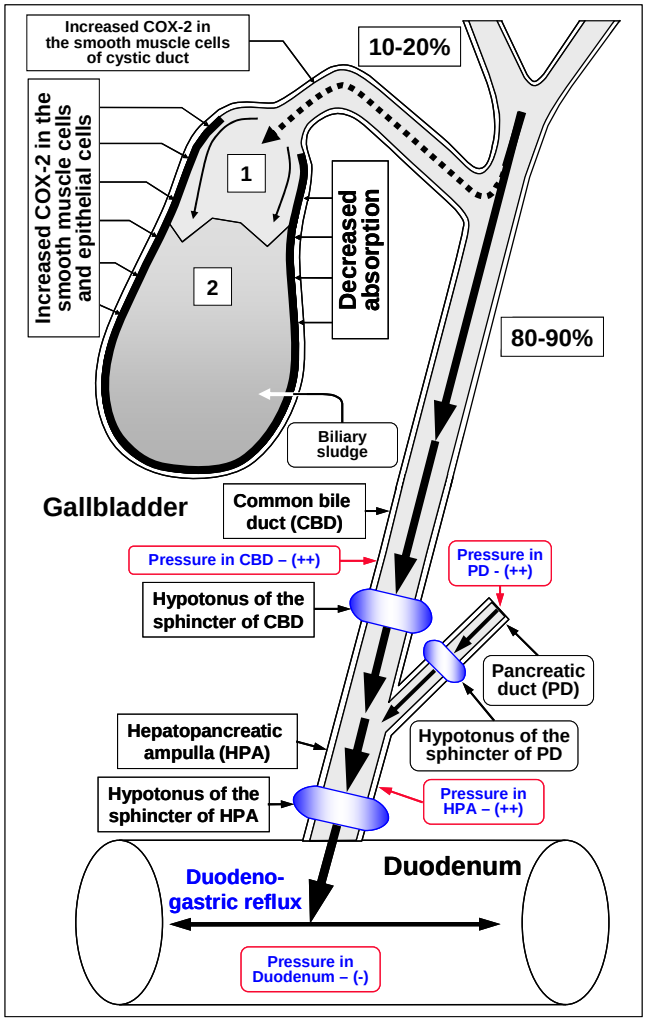

Fig. 21a. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis with biliary sludge, sphincter of Oddi hypomotility and duodenogastric reflux** (chronic bile reflux gastritis). **1** = unconcentrated hepatic bile; **2** = low concentrated GB.

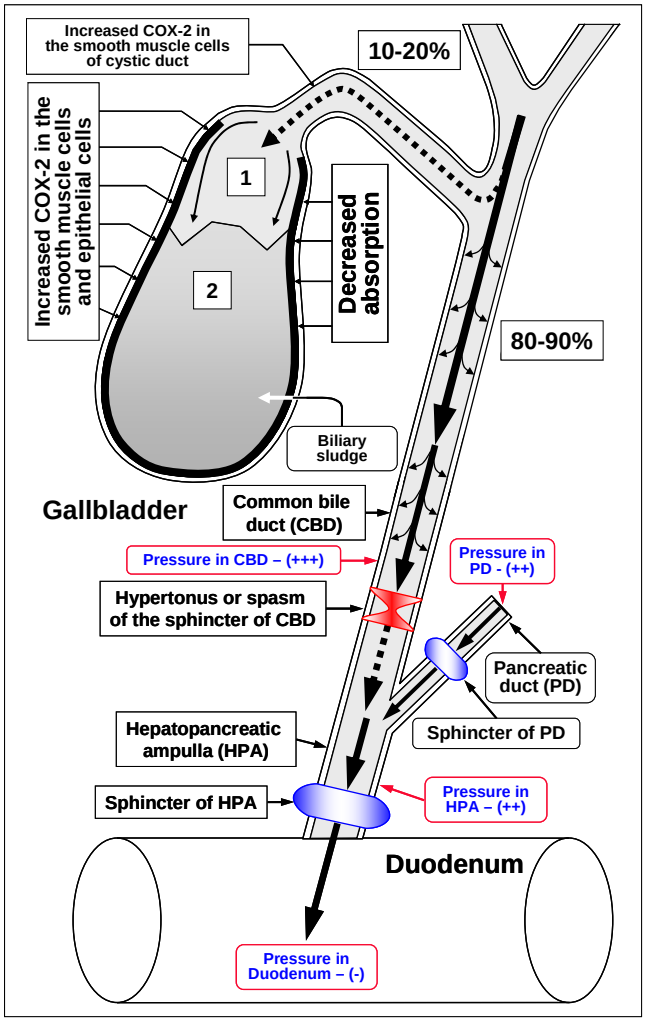

Fig. 21b. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis with biliary sludge and biliary type III of sphincter of Oddi dysfunction** (chronic spastic aseptic cholecystitis). **1** = unconcentrated hepatic bile; **2** = low concentrated gallbladder bile.

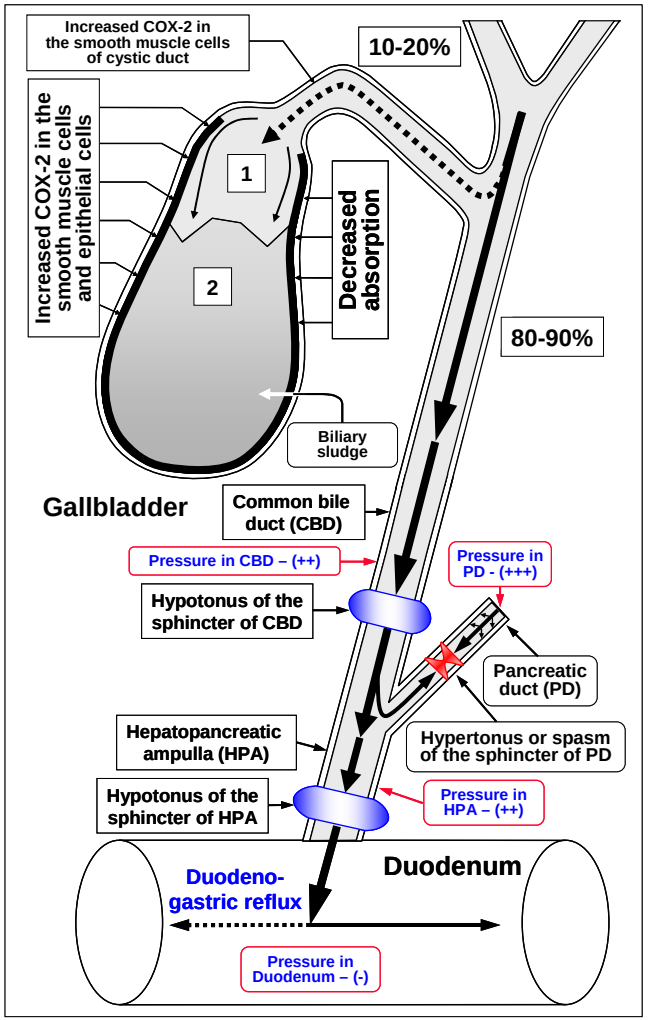

Fig. 21c. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis with biliary sludge and pancreatic type III of sphincter of Oddi dysfunction** (chronic spastic aseptic pancreatitis). **1** = unconcentrated hepatic bile; **2** = low concentrated GB.

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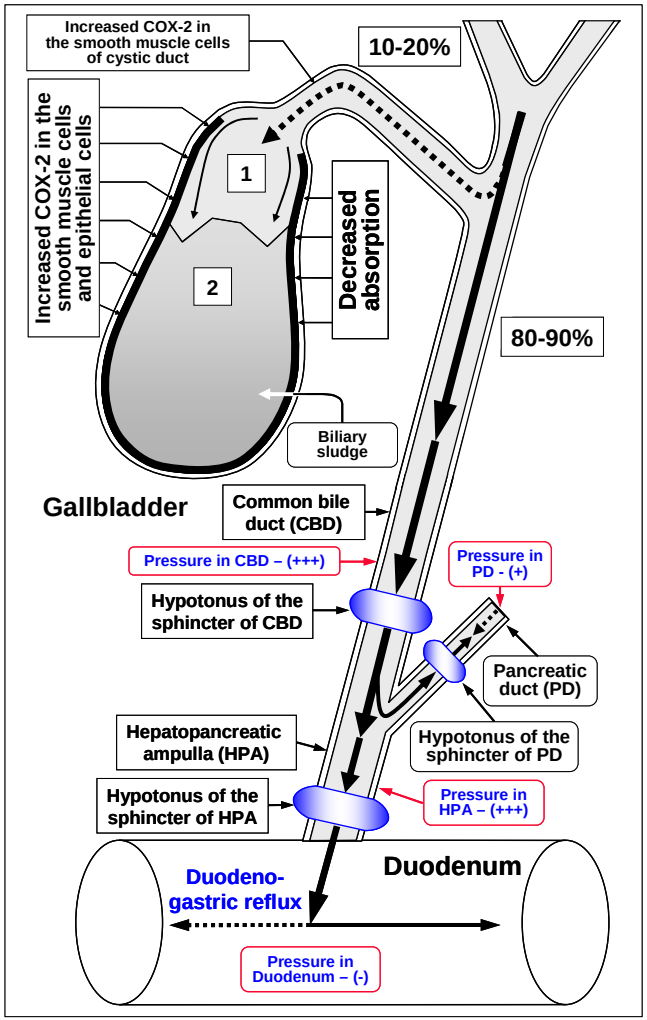

Fig. 21d. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis with biliary sludge, sphincter of Oddi hypomotility and biliopancreatic reflux** (chronic biliary pancreatitis)**. 1** = unconcentrated hepatic bile; **2** = low concentrated gallbladder bile.

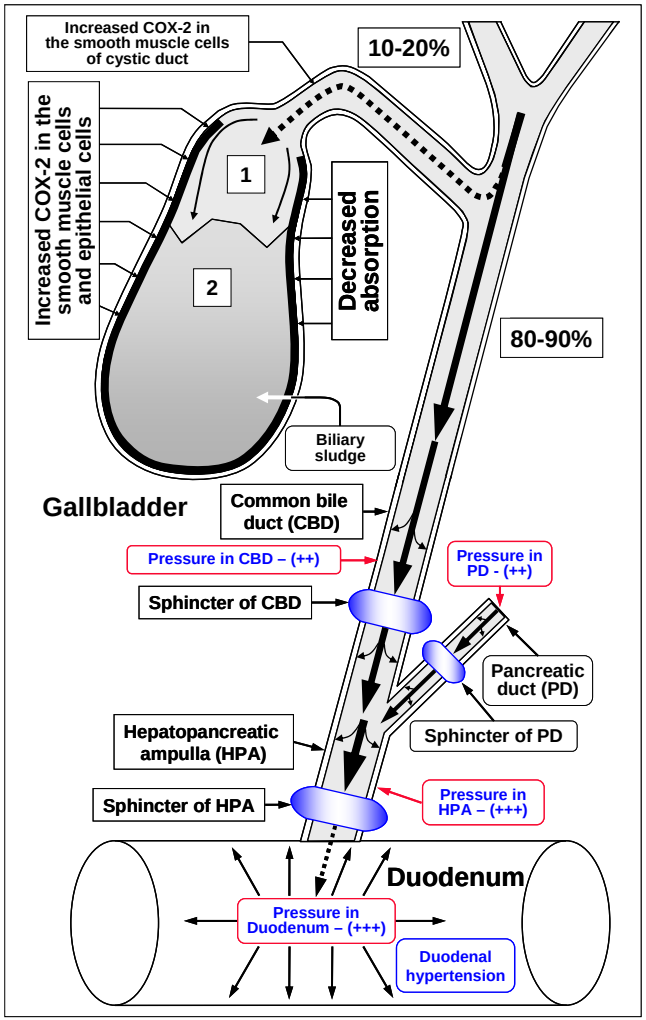

Fig. 21e. Passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis with biliary sludge and small intestinal bacterial overgrowth syndrome** (duodenal hypertension – the increase of intraluminal pressure in the duodenum). **1** = uncon hepatic bile; **2** = low concentrated gallbladder bile.

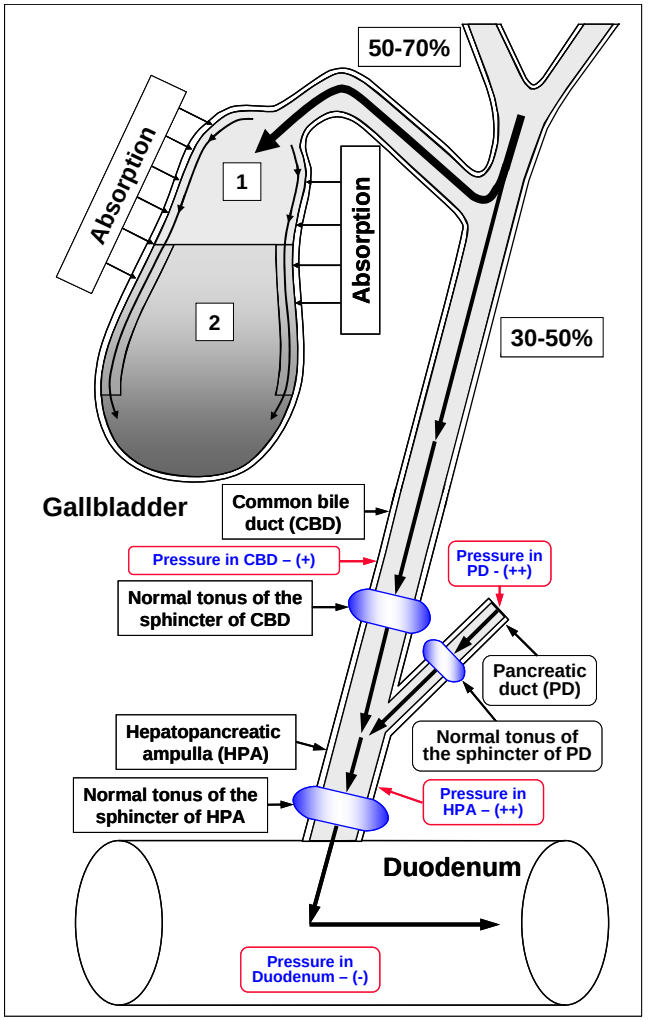

Fig. 21f. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis with biliary sludge after treatment with celecoxib and UDCA** (normal motility of the sphincter of Oddi). **1** = unconcentrated hepatic bile; **2** = normal concentrated gallbladder bile.

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This is accompanied by decrease in concentration of total bile acids in the gallbladder bile and increase in concentration of biliary cholesterol in the phospholipid vesicles, and causes disturbance in colloidal stability of the gallbladder bile and precipitation of cholesterol monohydrate crystals from unstable multilamellar aggregated phospholipid vesicles and calcium bilirubinate granules, i.e. formation of "lithogenic" gallbladder bile (fig. 22).

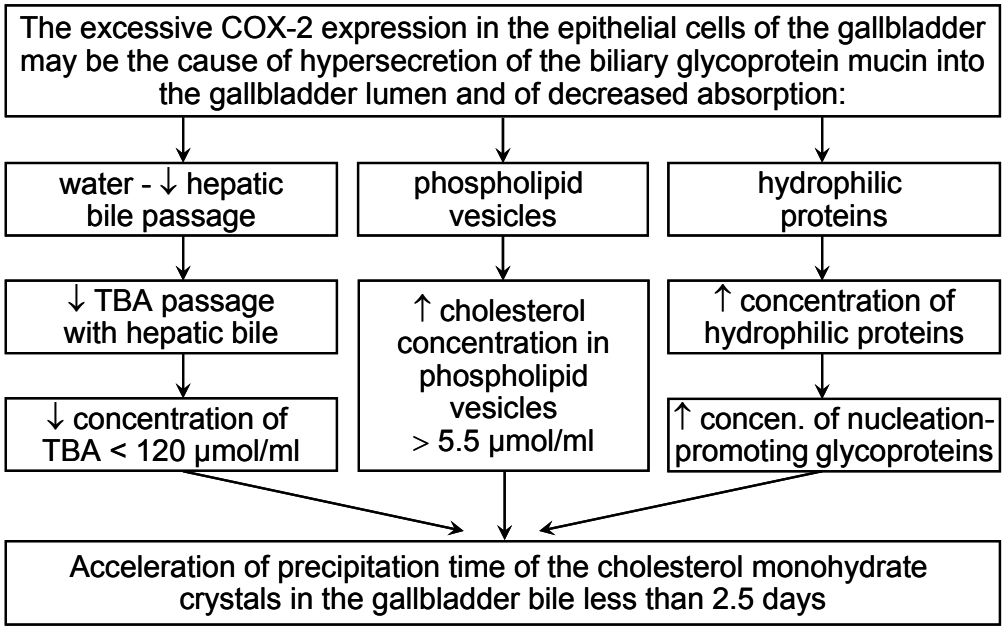

Fig. 22. Mechanism of lithogenic gallbladder bile formation in patients with chronic acalculous cholecystitis without biliary sludge.

High degree of COX-2 expression in the epithelial cells of the gallbladder mucosa causes hypersecretion of glycoprotein mucin into the gallbladder lumen and gallbladder bile. Increase in concentration of glycoprotein biliary mucin in the gallbladder bile over 2.0 mg/ml helps in its polymerization and formation of sites of the excessive viscosity and it is accompanied by rise of gallbladder bile viscosity. Precipitation of cholesterol monohydrate crystals and calcium bilirubinate granules in the sites of the excessive viscosity of polymerized glycoprotein biliary mucin causes formation of biliary sludge, increase its echogenicity and its reveal during ultrasonographic examination.

Decrease in "active" and "passive" passage of the hepatic bile into the gallbladder causes increase in passage of hepatic bile into the duodenum and gallbladder-independent enterohepatic circulation of bile acids, biliary cholesterol and biliary bilirubin (fig. 23).

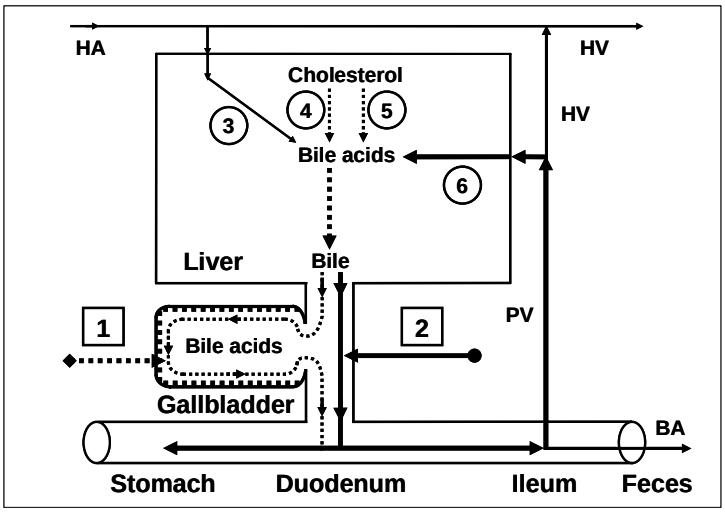

Fig. 23. Enterohepatic circulation of bile acids in patients with chronic acalculous cholecystitis with biliary sludge.
1 = gallbladder-dependent enterohepatic circulation of bile acids; **2** = gallbladder-independent enterohepatic circulation of bile acids; **3** = bile acids entering the liver through the hepatic artery; **4** = synthesis of cholic acid: cholesterol-7α-hydroxylase; **5** = synthesis of chenodeoxycholic acid: cholesterol-27-hydroxylase; **6** = bile acids entering the liver through the portal vein.
BA = bile acids;
HA = hepatic artery;
HV = hepatic vein; **PV** = portal vein.

Increase in the gallbladder-independent enterohepatic circulation of bile acids causes increase in concentration of bile acids in the hepatocytes and decrease in the accumulation function and excretion function of liver (i.e. formation of chronic "bland" intrahepatic cholestasis) (fig. 23).

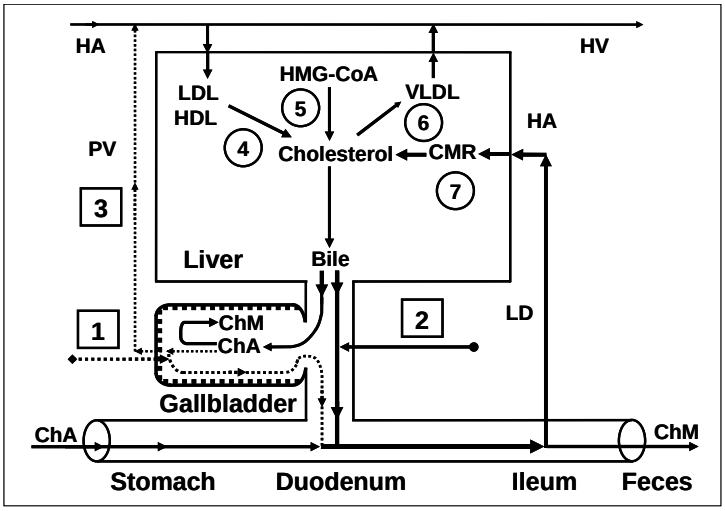

Fig. 24. Exchange of cholesterol in patients in patients with chronic acalculous cholecystitis with biliary sludge.
1 = gallbladder-dependent output of biliary cholesterol; **2** = gallbladder-independent output of biliary cholesterol; **3** = gallbladder-hepatic circulation of biliary cholesterol; **4** = hydrolysis of cholesterol esters entered the hepatocytes with HDL and LDL; **5** = synthesis of cholesterol; **6** = synthesis of cholesterol esters for VLDL; **7** = hydrolysis of cholesterol esters entered the hepatocytes with CMR.
ChA = cholesterol anhydrous; **ChM** = cholesterol monohydrate; **HA** = hepatic artery; **HV** = hepatic vein; **PV** = portal vein; **LD** = lymphatic duct.

Increase in the gallbladder-independent enterohepatic circulation of biliary cholesterol helps in increase in absorption of biliary cholesterol in the small intestine, the biliary cholesterol entering hepatocytes, and the hypersecretion biliary cholesterol into hepatic bile (fig. 24).

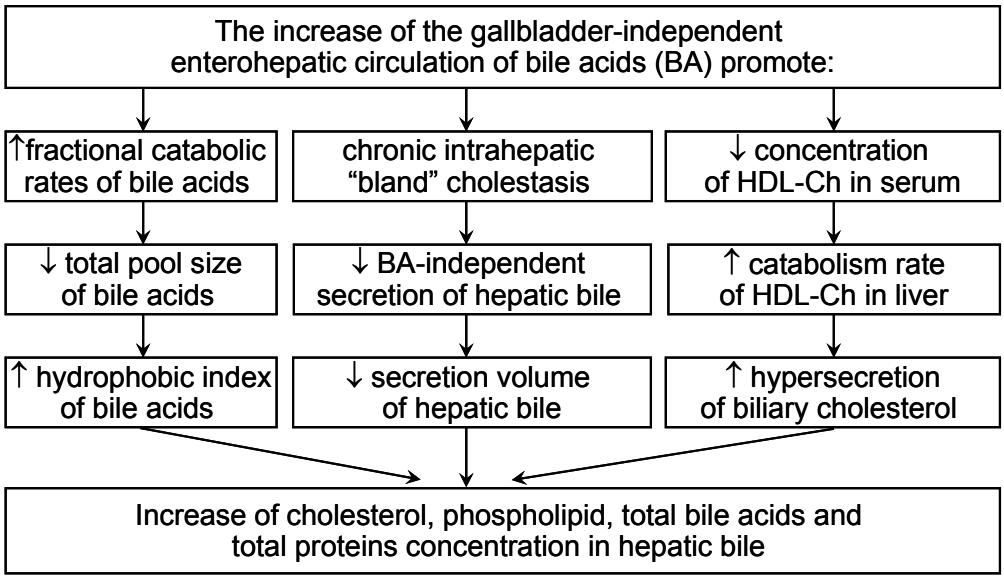

Fig. 25. Mechanism of lithogenic hepatic bile formation in patients with chronic acalculous cholecystitis with biliary sludge.

These two factors contribute to the formation of the "lithogenic" hepatic bile (fig. 25).

Decrease in the gallbladder-dependent output of biliary cholesterol and in the concentration of total bile acids in the gallbladder bile results in formation of the "lithogenic" gallbladder bile and precipitation of the cholesterol monohydrate crystals in the gallbladder lumen in 100% of patients with chronic acalculous cholecystitis with biliary sludge (fig. 26).

Long-term storage of biliary sludge and gallbladder hypomotility contributes to the gallstones formation in the gallbladder and transformation of chronic acalculous cholecystitis with biliary sludge into chronic calculous cholecystitis.

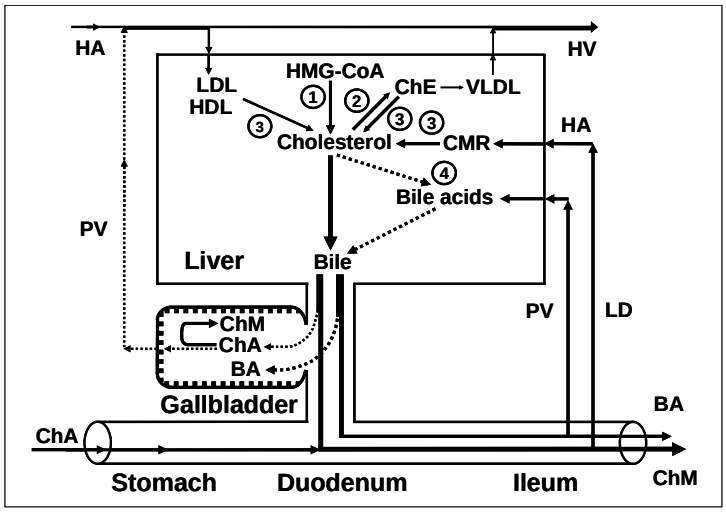

Fig. 26. Exchange of cholesterol and bile acids in patients with chronic acalculous cholecystitis with biliary sludge.
1 = synthesis of cholesterol;
2 = synthesis of cholesterol esters for VLDL;
3 = hydrolysis of cholesterol esters entered the hepatocytes with HDL and LDL, and hydrolysis of cholesterol esters entered the hepatocytes with CMR;
4 = synthesis of bile acids.
ChE = cholesterol esters; **ChA** = cholesterol anhydrous; **ChM** = cholesterol monohydrate; **BA** = bile acids; **HA** = hepatic artery; **HV** = hepatic vein; **PV** = portal vein; **LD** = lymphatic duct.

Pathogenetic treatment of patients with chronic acalculous cholecystitis with biliary sludge

Accordingly, treatment of the chronic acalculous cholecystitis with biliary sludge (with biliary pain) aiming for the prophylactics of the chronic calculous cholecystitis, duodeno-gastral reflux, antral atrophic (bile acid-dependent) gastritis and chronic biliary pancreatitis includes:

1. Celecoxib – 100 mg, 2 times a day after meal for 5-7 days, after which
2. Ursodeoxycholic acid – 750 mg, once a day (in the evening) for 2 month.

Celecoxib is a selective inhibitor of COX-2. Inhibiting COX-2 activity in the smooth muscle cells of the gallbladder wall and cystic duct it brings relief of the biliary pain within 3-5 days, restoration of the evacuation function of the gallbladder and the gallbladder-dependent output of the biliary cholesterol, "active" and "passive" passage of the hepatic bile into the gallbladder, and decrease in the gallbladder-independent enterohepatic circulation of bile acids, biliary cholesterol and biliary bilirubin.

Celecoxib, a selective inhibitor of COX-2, inhibiting COX-2 activity in the epithelial cells of the gallbladder mucosa causes inhibition in glycoprotein mucin hypersecretion into the gallbladder lumen, decrease in concentration of glycoprotein biliary mucin in gallbladder bile and gallbladder bile viscosity, which prevents formation of biliary sludge.

Low COX-2 activity in the epithelial cells of the gallbladder mucosa helps in restoration of the absorption function of the gallbladder (absorption of water and biliary cholesterol), which results in increase in concentration of total bile acids and decrease in concentration of biliary cholesterol in gallbladder bile.

Ursodeoxycholic acid (UDCA) is a hydrophilic hepatoprotective bile acid. It helps in dissolving the cholesterol monohydrate crystals in the gallbladder, decrease in lithogenicity of the gallbladder and hepatic bile, disappearance of the chronic "bland" intrahepatic cholestasis (i.e. results in the restoration of the excretion function of the liver) (1-66).

Celecoxib and ursodeoxycholic acid (UDCA), blocking main pathogenetic mechanisms of gallstones formation, contribute to elimination of biliary sludge in 100% of cases, and lower the repeated risk of biliary sludge formation, and, respectively, reduce risk of gallstone formation in the gallbladder (1-66).

Celecoxib is a selective inhibitor of COX-2. Inhibiting COX-2 activity in the smooth muscle cells of the biliary tract and the sphincter of Oddi it brings relief of the biliary pain within 3-5 days, restoration of the passage of the hepatic bile into the duodenum.

Celecoxib is a selective inhibitor of COX-2, inhibiting COX-2 activity in the epithelial cells of the biliary tract mucosa causes decrease in secretion of glycoprotein mucin into the biliary tract lumen, concentration of the glycoprotein biliary mucin in the hepatic bile and viscosity of hepatic bile, which prevents formation of biliary sludge and gallstones in the common hepatic duct and common bile duct. Low COX-2 activity in the epithelial cells and the smooth muscle cells of the biliary tract helps in lowering the risk of choledocholithiasis development.

Ursodeoxycholic acid (UDCA) is a hydrophilic hepatoprotective bile acid. It helps in dissolving the cholesterol monohydrate crystals in the biliary tract, decrease in lithogenicity of hepatic bile, disappearance of the chronic "bland" intrahepatic cholestasis (i.e. results in the restoration of the accumulation and excretion functions of liver), and in some patients helps in dissolving the biliary sludge in the biliary tract.

Ursodeoxycholic acid (UDCA) is a hydrophilic hepatoprotective bile acid, decreasing aggressive properties of bile, prevents development of chronic atrophic antral gastritis (duodenogastric reflux and bile reflux gastritis) and duodeno-gastroesophageal reflux (incompetence of Oddi's

sphincter), chronic biliary pancreatitis (biliopancreatic reflux) or chronic spastic aseptic pancreatitis (pancreatic type III of sphincter of Oddi dysfunction).

Celecoxib and Ursodeoxycholic acid (UDCA), pathogenetically blocking main mechanisms of gallstone formation, help in prophylactics of gallstone formation in the biliary tract, and lower the risk of development of choledocholithiasis and chronic biliary pancreatitis (1-66).

Effectiveness is 95%.

Remission period is 18-24 months.

Attention!!! Information for patients:

Before using this scheme of treatment please check the contraindications (below) and side effects of using pharmacological preparations of Celecoxib and ursodeoxycholic acid (UDCA), and obtain your doctor's permission.

Contraindications for Celecoxib:

- allergic reactions (nettle-rash, bronchial spasm) to acetylsalicylic acid or other NSAIDs (in anamnesis);
- 3rd trimester of pregnancy;
- high sensitivity to sulphonamides;
- high sensitivity to any component of the preparation.

Contraindications for ursodeoxycholic acid (UDCA):

- high sensitivity to the preparation;
- acute inflammatory diseases of the gallbladder and the bile ducts;
- ulcerative colitis;
- Crone's disease.

This web page does not bear any legal responsibility for usage of the treatment schemes, given here, without consulting your doctor.

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