Chronic acalculous cholecystitis

Chronic acalculous cholecystitis is an inflammatory disease of gallbladder which affects the gallbladder wall and causes motoric-tonic dysfunctions of the biliary tract, which reveals as biliary pain (1-32). The motility dysfunction of the gallbladder can be caused by increased basal cystic duct resistance or cystic duct spasm, the muscle hypertrophy, and the chronic aseptic inflammation in the gallbladder wall.

Diagnostic criteria of the chronic acalculous cholecystitis

1. Recurrent episodes of moderate or hard biliary pain in the right hypochondrium or epigastrium, continuing for many hours. Biliary pains occur and intensify after intake of fatty and fried meals, eggs, sharp products, wine, and beer.
   In addition, biliary pain may occur with one or more of the following symptoms:
   a. nausea, vomiting, constant feeling of heaviness in the upper abdomen
   b. eructation, abdominal distension
   c. pain occurs after a meal
   d. pain occurs at night
2. Impaired gallbladder emptying.
3. According to ultrasound examination, thickening of the gallbladder wall up to 3-4 mm.

Causes of the gallbladder evacuation dysfunction, biliary pain and chronic 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. Contractile dyscoordination of the gallbladder and cystic duct (high degree of COX-2 expression in the smooth muscle cells of the gallbladder and cystic duct).
3. Increased basal cystic duct resistance (high degree of COX-2 expression in the smooth muscle cells of the cystic duct).

Mechanism of development of pathologic disorders

High degree of COX-2 expression in the smooth muscle cells of the gallbladder wall causes the decrease in the evacuation function of the gallbladder and "active" passage of the hepatic bile into the gallbladder (fig. 15). High COX-2 expression in the epithelial cells of the gallbladder mucosa causes decrease of the absorption function of the gallbladder (decrease of water and biliary cholesterol absorption) and "passive" passage of the hepatic bile into the gallbladder (fig. 15).

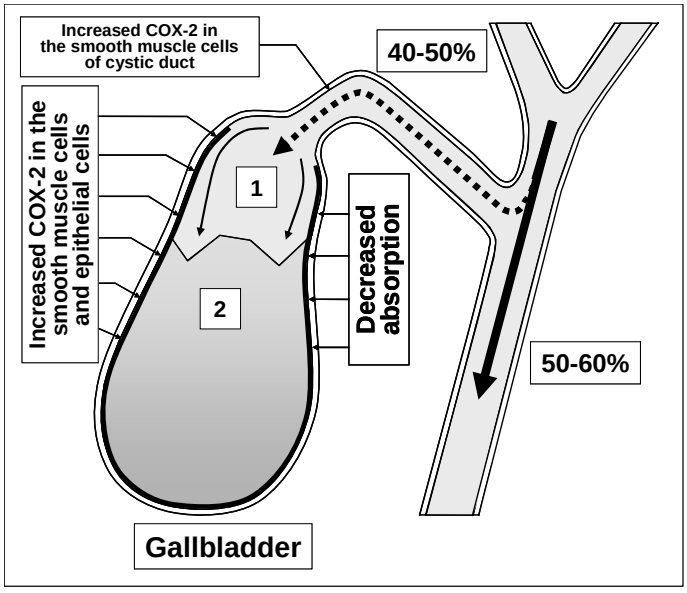

Fig. 15. "Active" and "passive" passage of hepatic bile into the gallbladder and into the duodenum in patients with chronic acalculous cholecystitis without biliary sludge.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile.

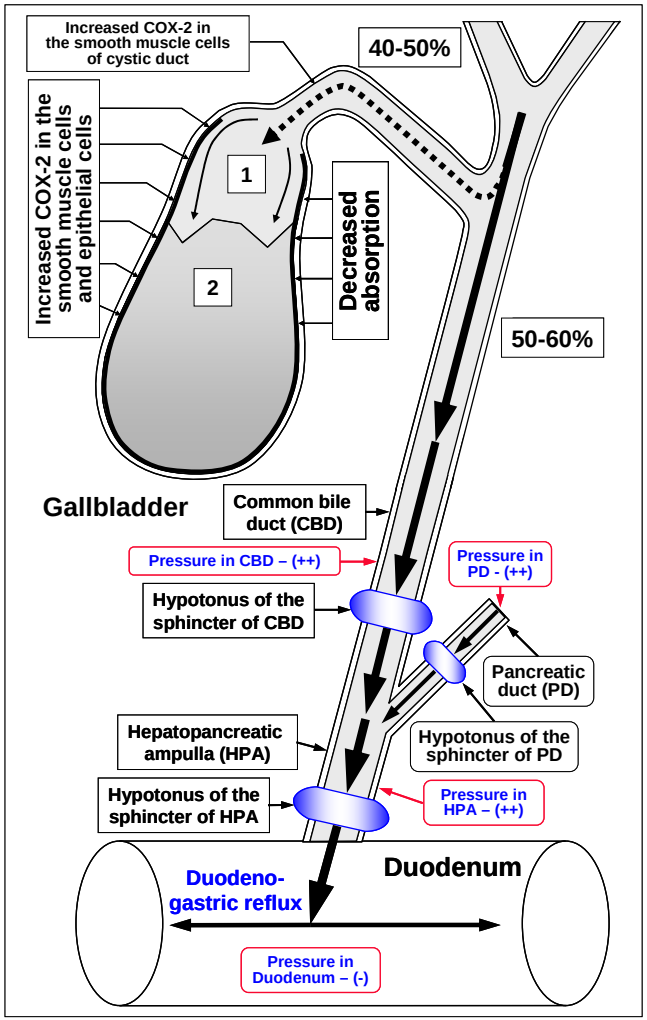

Fig. 15a. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis without biliary sludge, sphincter of Oddi hypomotility and duodenogastric reflux** (chronic bile reflux gastritis). **1** = unconcentrated hepatic bile; **2** = low concentrated GB.

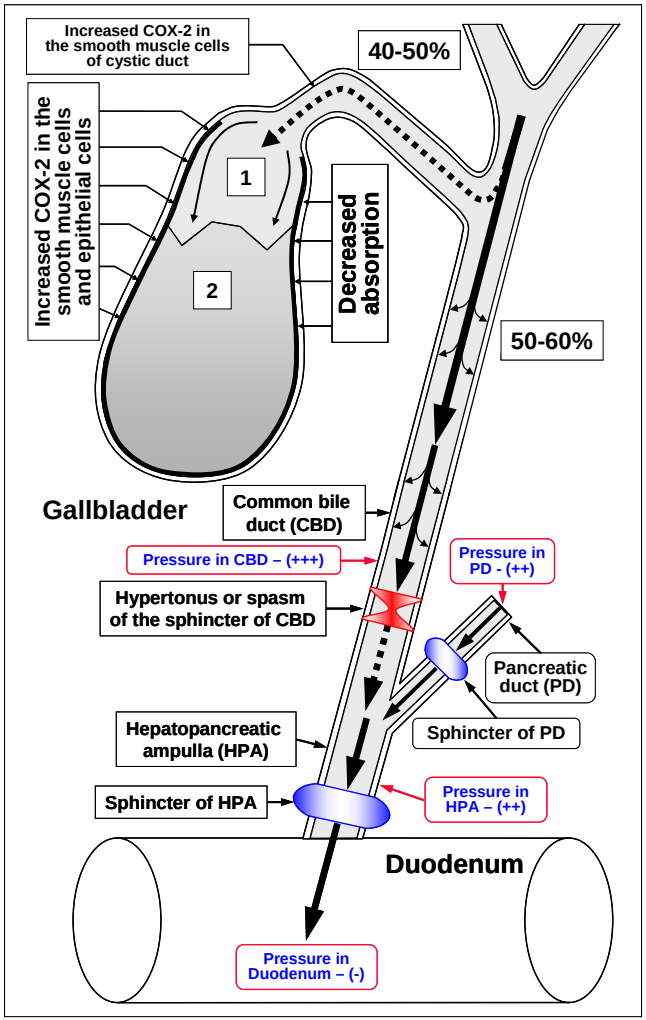

Fig. 15b. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis without biliary sludge and biliary type III of sphincter of Oddi dysfunction** (chronic spastic aseptic cholecystitis). **1** = unconcentrated hepatic bile; **2** = low concentrated gallbladder bile.

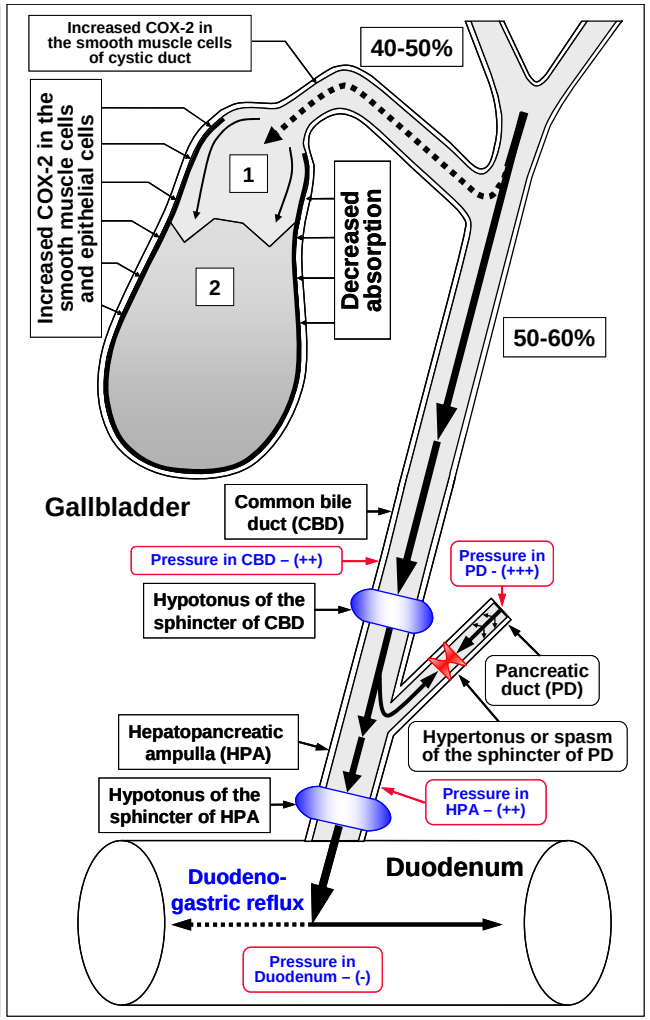

Fig. 15c. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis without biliary sludge and pancreatic type III of sphincter of Oddi dysfunction** (chronic spastic aseptic pancreatitis). **1** = unconcentrated hepatic bile; **2** = low concentrated GB.

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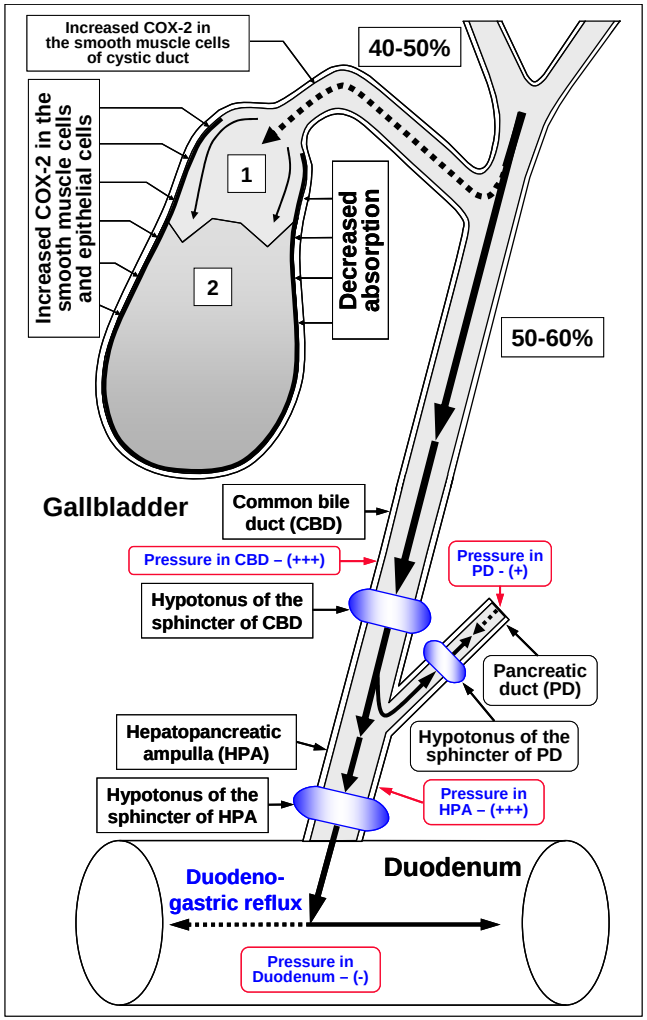

Fig. 15d. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis without biliary sludge, sphincter of Oddi hypomotility and biliopancreatic reflux** (chronic biliary pancreatitis)**. 1** = unconcentrated hepatic bile; **2** = low concentrated gallbladder bile.

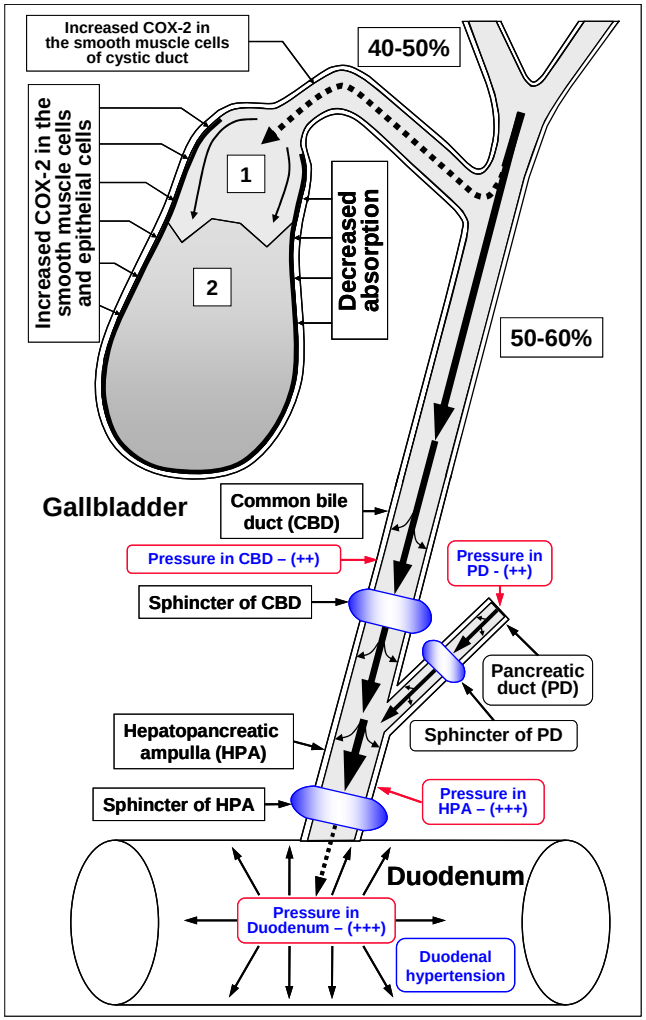

Fig. 15e. Passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis without biliary sludge and small intestinal bacterial overgrowth syndrome** (duodenal hypertension – the increase of intraluminal pressure in the duodenum). **1** = uncon hepatic bile; **2** = low concentrated gallbladder bile.

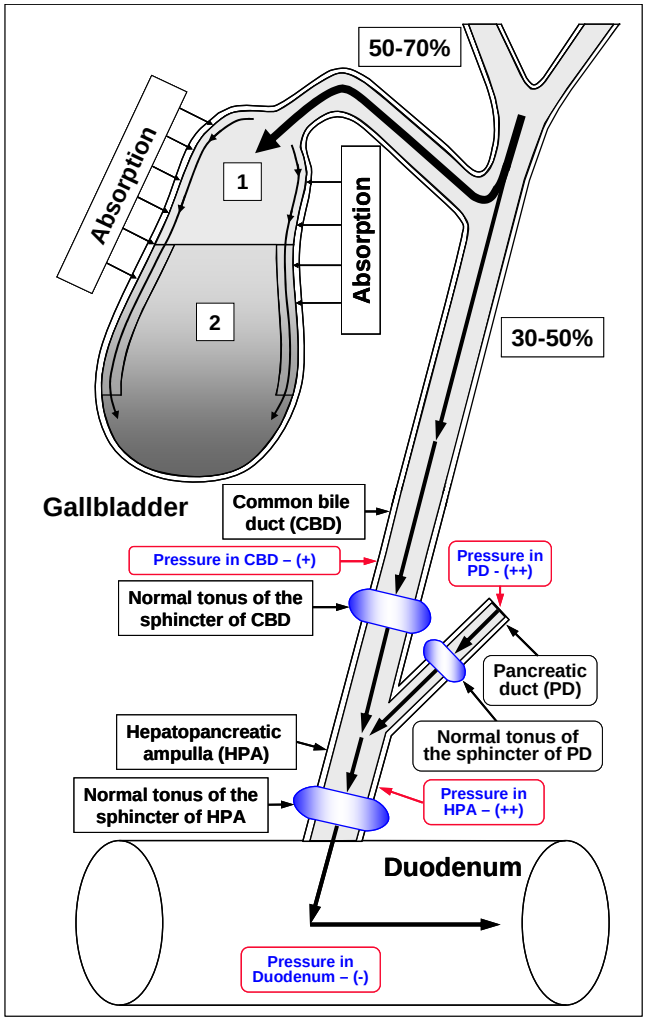

Fig. 15f. Passive passage of hepatic bile into the gallbladder and passive passage of hepatic bile and pancreatic juice into the duodenum lumen **in patients with chronic acalculous cholecystitis without biliary sludge after treatment with celecoxib and UDCA** (normal motility of the sphincter of Oddi). **1** = unconcentrated hepatic bile; **2** = normal concentrated gallbladder bile.

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This is accompanied by the decrease in concentration of total bile acids in the gallbladder bile and increase of concentration of biliary cholesterol in gallbladder bile, and causes disturbance in colloidal stability of the gallbladder bile and precipitation of cholesterol monohydrate crystals and calcium bilirubinate granules, i.e. formation of "lithogenic" gallbladder bile (fig. 16).

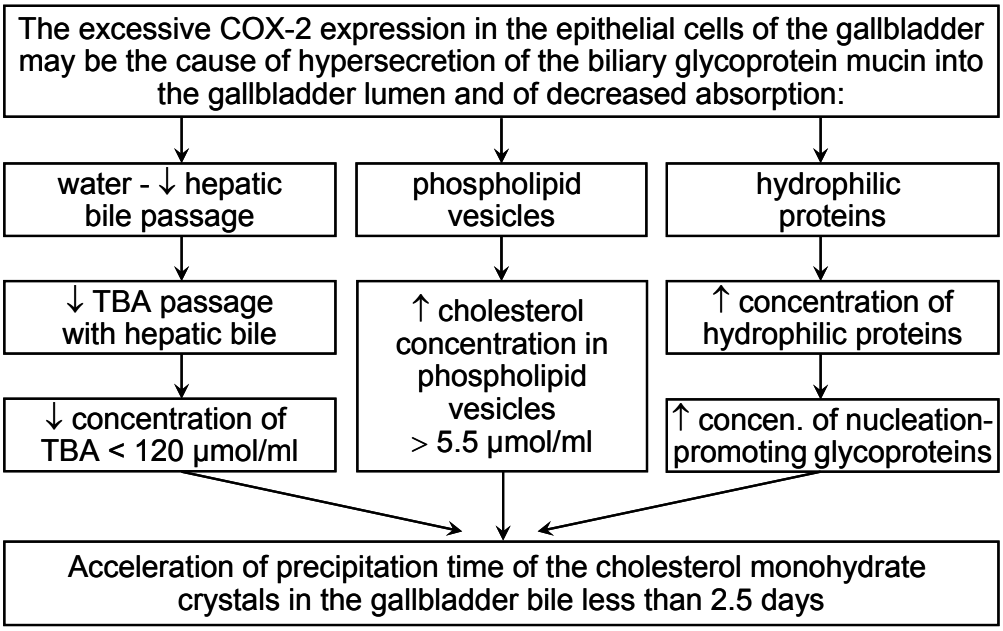

Fig. 16. Mechanism of lithogenic gallbladder bile formation in patients with chronic acalculous cholecystitis without biliary sludge.

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 the concentration of glycoprotein biliary mucin in the gallbladder bile is accompanied by increase of gallbladder bile viscosity.

The decrease in "active" and "passive" passage of the hepatic bile into the gallbladder causes increase of passage of hepatic bile into the duodenum and gallbladder-independent enterohepatic circulation of bile acids, biliary cholesterol and biliary bilirubin (fig. 17).

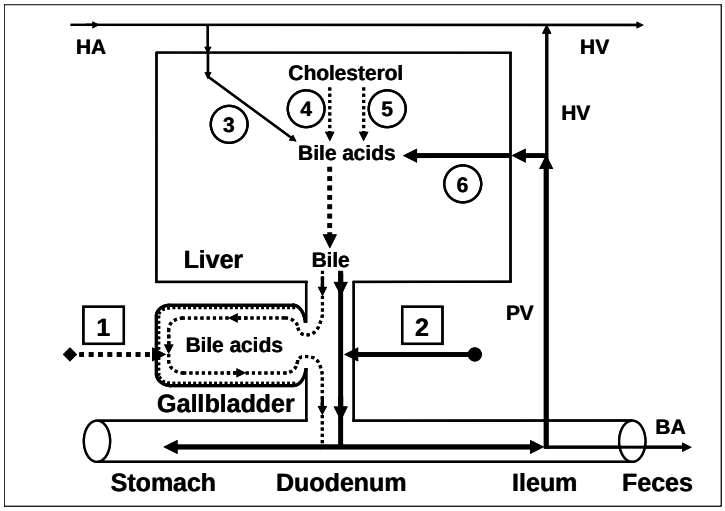

Fig. 17. Enterohepatic circulation of bile acids in patients with chronic acalculous cholecystitis without biliary sludge.
1 = gallbladder-dependent enterohepatic circulation of bile acids; **2** = gallbladder-independent enterohepatic circulation of bile acids; **3** = bile acids entering the liver 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.

The increase in the gallbladder-independent enterohepatic circulation of bile acids causes increase of concentration of bile acids in the hepatocytes and the decrease in the accumulation function and excretion function of the liver (i.e. formation of chronic "bland" intrahepatic cholestasis) (fig. 17).

The increase of the gallbladder-independent enterohepatic circulation of biliary cholesterol helps in increase of absorption of biliary cholesterol in the small intestine, the biliary cholesterol entering hepatocytes and hypersecretion of biliary cholesterol into hepatic bile (fig. 18).

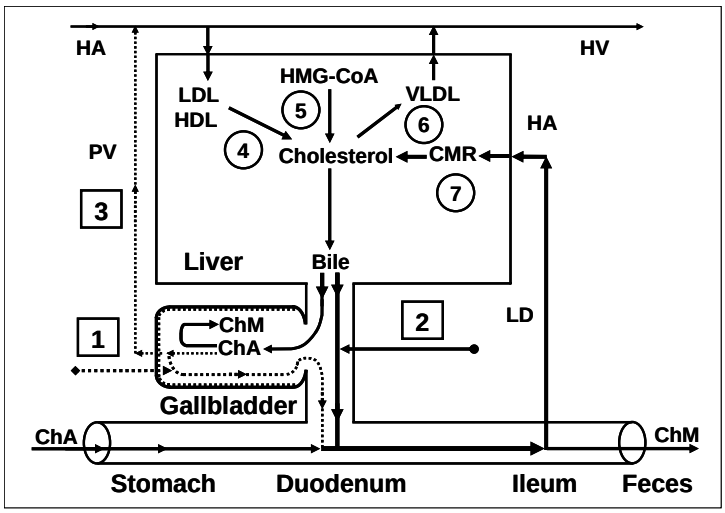

Fig. 18. Exchange of cholesterol in patients in patients with chronic acalculous cholecystitis without biliary sludge.
1 = gallbladder-dependent output of biliary cholesterol; **2** = gallbladder-independent output of biliary cholesterol; **3** = gallbladder-hepatic circulation of biliary cholesterol; **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.

These two factors contribute to the formation of the "lithogenic" hepatic bile (fig. 19).

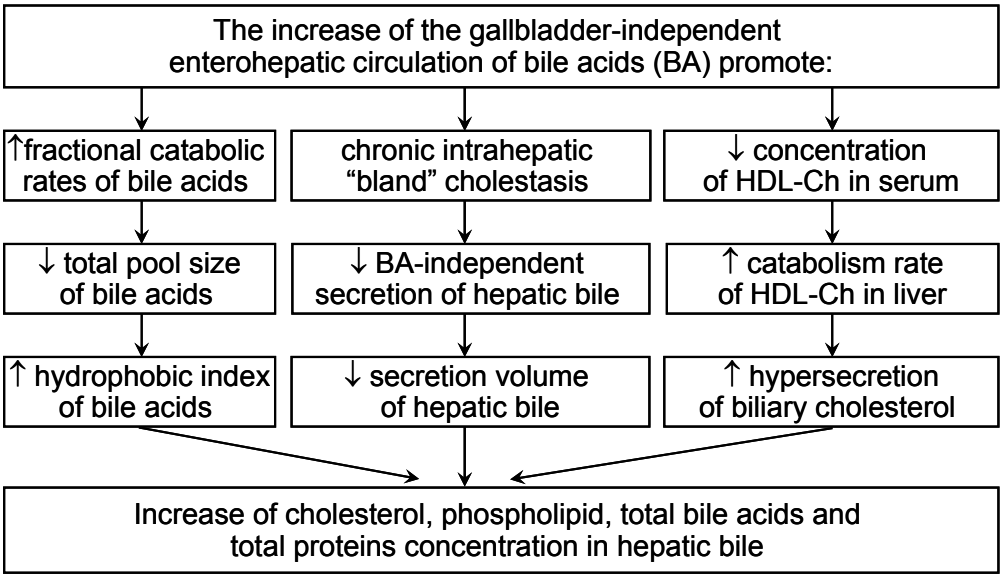

Fig. 19. Mechanism of lithogenic hepatic bile formation in patients with chronic acalculous cholecystitis without biliary sludge.

The 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 40% of patients with chronic acalculous cholecystitis without biliary sludge (fig. 20).

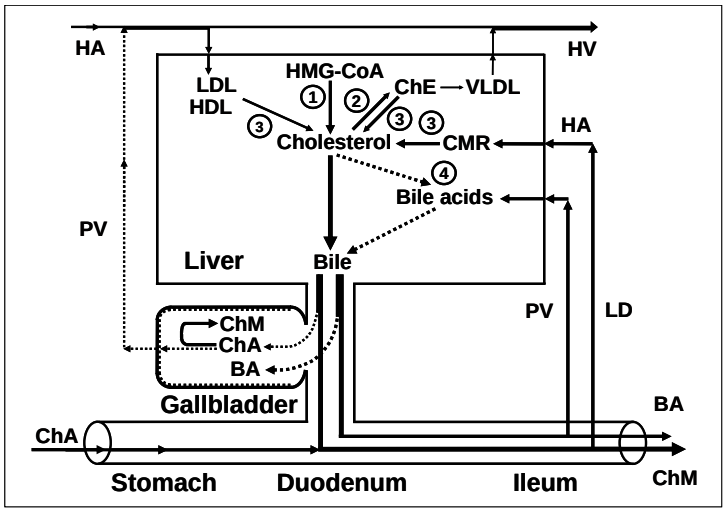

Fig. 20. Exchange of cholesterol and bile acids in patients with chronic acalculous cholecystitis without biliary sludge.
1 = synthesis of cholesterol;
2 = synthesis of cholesterol esters for VLDL;
3 = hydrolysis of cholesterol esters entered the hepatocytes with HDL and LDL, and hydrolysis of cholesterol 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.

Surplus COX-2 expression in the epithelial cells of the gallbladder mucosa causes hypersecretion of glycoprotein biliary mucin into the gallbladder bile. Increase in concentration of glycoprotein biliary mucin in gallbladder bile over 2 mg/ml causes its polymerization and formation of sites of the excessive viscosity. Precipitation of cholesterol monohydrate crystals and calcium bilirubinate granules in the sites of the excessive viscosity of polymerized glycoprotein biliary mucin contributes in formation of biliary sludge and transformation of chronic acalculous cholecystitis without biliary sludge into chronic acalculous cholecystitis with biliary sludge.

Pathogenetic treatment of patients with chronic acalculous cholecystitis without biliary sludge

Accordingly, treatment of the chronic acalculous cholecystitis without biliary sludge (with biliary pain) aiming for prophylactics of the chronic acalculous cholecystitis with biliary sludge, duodeno-gastral reflux, antral atrophic (bile acid-dependent) gastritis and 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 1 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 results 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 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 of glycoprotein mucin hypersecretion into the gallbladder lumen, decrease of concentration of glycoprotein biliary mucin in the 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 gallbladder and hepatic bile, disappearance of the chronic "bland" intrahepatic cholestasis (i.e. results in restoration of the accumulation and excretion functions of the liver) (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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