PATHOGENESIS AND TREATMENT OF CHOLESTEROL GALLSTONE DISEASE

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Two primary defects may be the cause of cholesterol gallstone disease (CGD): **first**, the decrease of the absorption rate of cholesterol in the gallbladder (V_0Ch_{ABS}) and **second**, the decrease of the absorption rate of water in the gallbladder (V_0W_{ABS}) (Nakano K., Chijiiwa K. Gastroenterology. 1992; 102(4): A325). **These two primary defects interdepend**, i.e. the decrease of V_0Ch_{ABS} promotes the decrease of V_0W_{ABS} or the decrease of V_0W_{ABS} promotes the decrease of V_0Ch_{ABS}. It is possibly by two interdependent ways: **1)**. the decrease of V_0Ch_{ABS} → the increase of the cholesterol concentration in the gallbladder bile (Ch_{GB}) → the increase of CSI in the gallbladder bile (CSI_{GB}) at the normal total bile salts concentration in the gallbladder bile (TBS_{GB}) → the increase of vesicular cholesterol concentration (vCh_{GB}) → the increase of the precipitation rate of cholesterol monohydrate crystals (PR_{ChMC}) on the epithelial cells of mucous gallbladder → the decrease of V_0W_{ABS} → the decrease of the "passive" input of the hepatic bile inflow into the gallbladder (V_0HB_F) → the decrease of TBS_{GB}. **2)**. the decrease of V_0W_{ABS} → the decrease V_0HB_F → the decrease of TBS_{GB} → the increase of CSI_{GB} at the low TBS_{GB} → the increase of vCh_{GB} → the increase of PR_{ChMC} on the epithelial cells of mucous gallbladder → the decrease of V_0Ch_{ABS} → the increase Ch_{GB}. Hence, V_0Ch_{ABS} determine the Ch_{GB}, V_0W_{ABS} determine the TBS_{GB} .

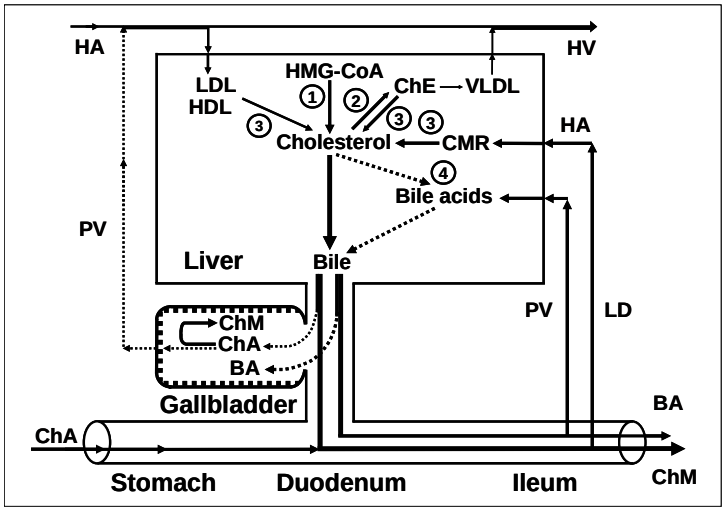

Fig. 1. Exchange of cholesterol and bile acids in patients with cholesterol gallstone disease.
1 = synthesis of cholesterol; **2** = synthesis of cholesterol esters for VLDL; **3** = hydrolysis of cholesterol esters entered the hepatocytes with HDL and LDL, and hydrolysis of cholesterol esters entered 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.

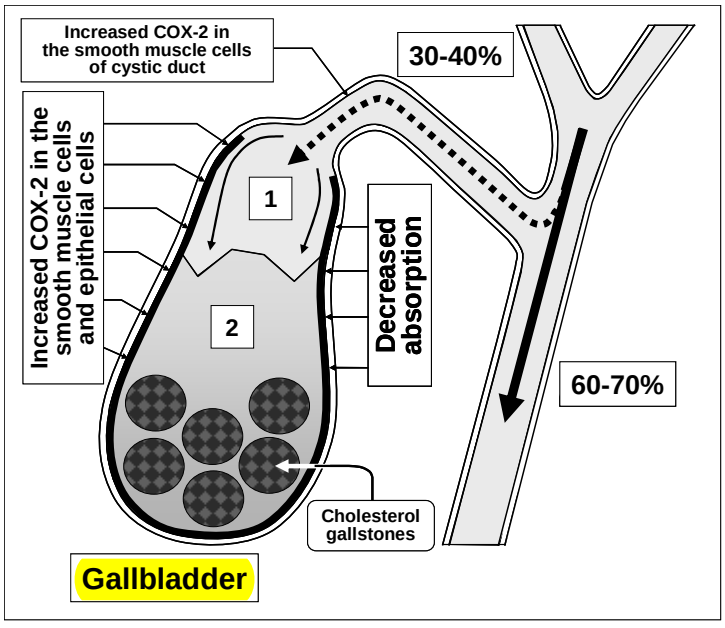

Fig. 2. "Active" and "passive" passage of hepatic bile into the gallbladder and into the duodenum in patients with cholesterol gallstone disease.
1 = unconcentrated hepatic bile;
2 = low concentrated gallbladder bile with gallstones.

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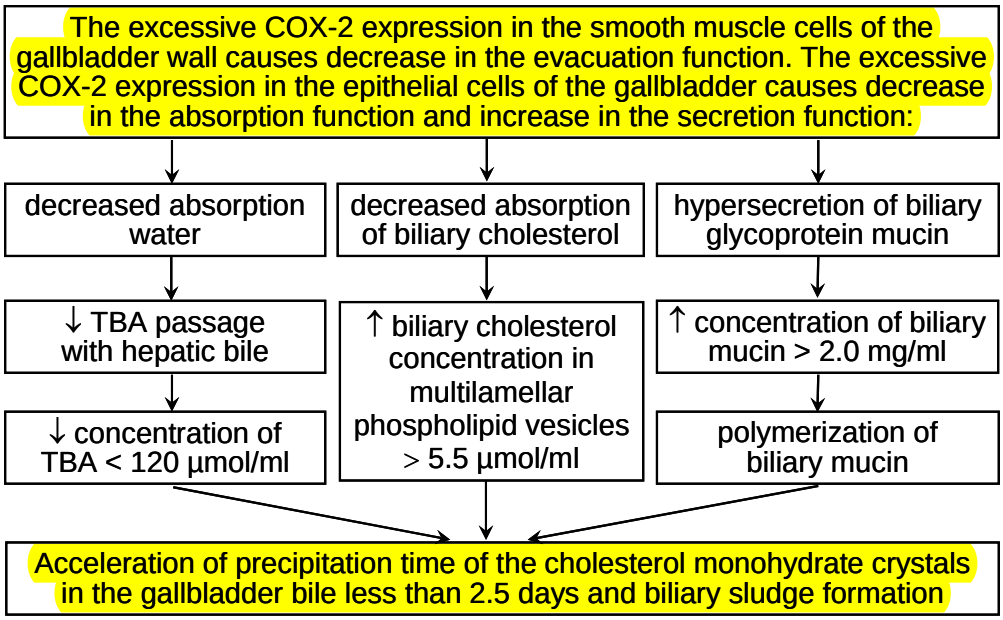

Fig. 3. Mechanism of lithogenic gallbladder bile formation in patients with cholesterol gallstone disease.

These two primary defects determine the secondary disturbances. The decrease of V_0W_{ABS} promotes the increase of the frequency of the gallbladder-independent enterohepatic circulation of bile salts (GB-ID EHC_{BS}). The increase of GB-ID EHC_{BS} promote the increase of the deoxycholic acid formation, the increase of the cumulative hydrophobicity index of bile salts (HI_{BS}), the fractional catabolic rates of bile salts (FCR_{BS}), the total bile salts concentration in the serum and the decrease of total pool size of bile salts (TPS_{BS}).

The increase of GB-ID EHC_{BS} and HI_{BS} promote the increase of the transit time of hydrophobic bile salts across the hepatocytes (LeSage G.D. et al. Gastroenterology. 1994; 106(4):A929), the increase of hydrophobic bile salts concentration in the hepatocytes (Honda A. et al. J. Gastroenterology. 1995; 30:61-66) and the increase of the different toxic effects of hydrophobic bile salts in the hepatocytes of peri-portal zones.

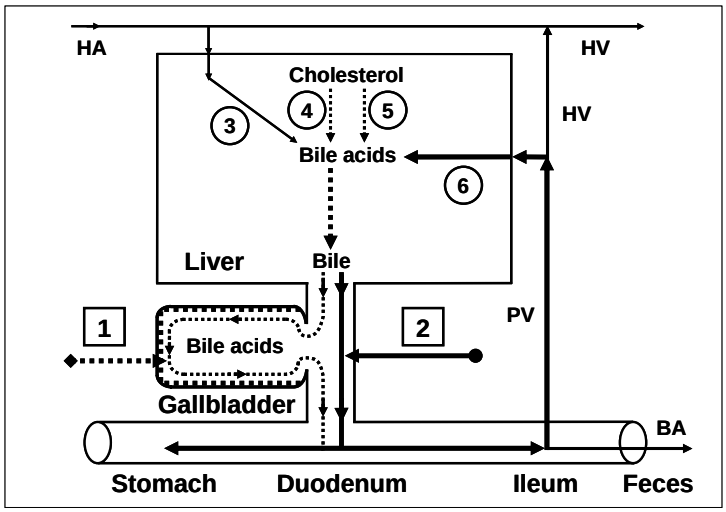

Fig. 4. Enterohepatic circulation of bile acids in patients with cholesterol gallstone disease.
1 = gallbladder-dependent enterohepatic circulation of bile acids; **2** = gallbladder-independent enterohepatic circulation of bile acids; **3** = bile acids entering the liver through the hepatic artery; **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.

Also, the increase of GB-ID EHC_{BS} may promote the increase of the catabolism rate of Ch-HDL in the liver and the decrease of Ch-HDL concentration in the serum. The increase of Ch-HDL catabolism in the liver may promote the increase of hepatic cholesterol secretion into the hepatic bile.

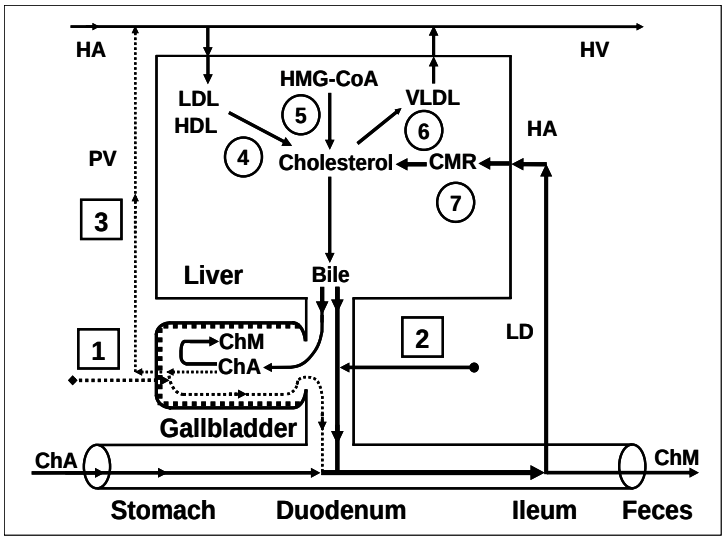

Fig. 5. **Exchange of cholesterol** in patients in patients with cholesterol gallstone disease. **1** = gallbladder-dependent output of biliary cholesterol; **2** = gallbladder-independent output of biliary cholesterol; **3** = gallbladder-hepatic circulation of biliary cholesterol; **4** = hydrolysis 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.

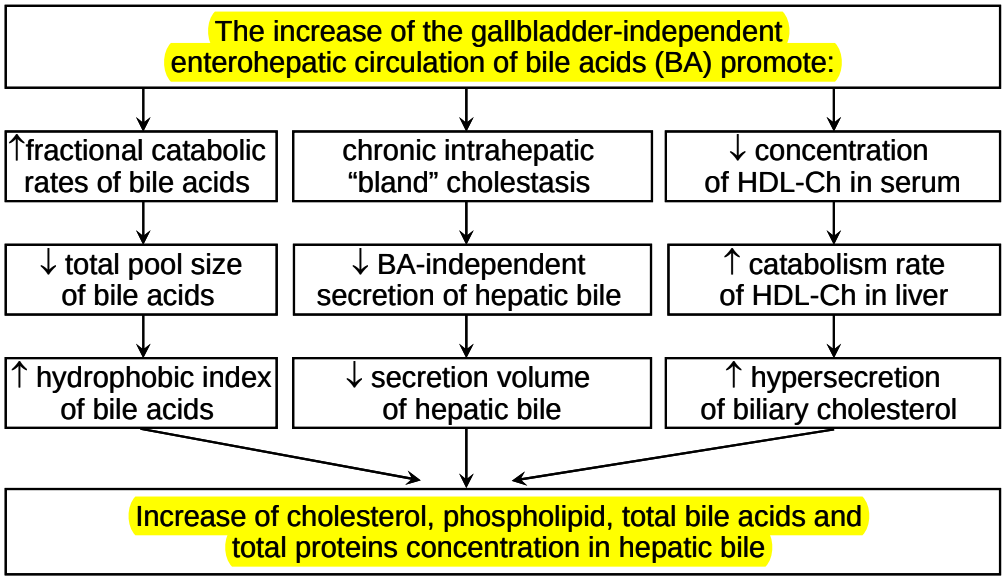

Fig. 6. Mechanism of lithogenic hepatic bile formation in patients with cholesterol gallstone disease.

The decrease of Ch-HDL concentration in the serum may promote the decrease of the removal of absorbed cholesterol from the gallbladder wall and the increase of the return back of absorbed cholesterol to the gallbladder bile. The part of absorbed cholesterol may be accumulated in the smooth muscle cells of gallbladder. The increase of bile salts concentration in the serum, the formation of the viscous "lithogenic" gallbladder bile in the paramucous layer (surface biliary sludge), the accumulation of cholesterol in the gallbladder wall may predisposes to the decrease of gallbladder motility.

Hence, the treatment of uncomplicated CGD must include the removal of the primary defects and the secondary disturbances: **1)**. The dissolution of cholesterol gallstones and cholesterol monohydrate crystals, the removal of surface biliary sludge and debris; **2)**. The sanitation of the gallbladder wall; **3)**. The restoration of the concentration function of the gallbladder; 4). The restoration of Ch-HDL concentration in the serum; 5). The stimulation of gallbladder motility.

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