MECHANISM OF CHOLESTEROL GALLSTONE FORMATION

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SUMMARY
Cholesterol gallstone disease is now of exciting clinical and laboratory interest. However, the aetiology of cholesterol gallstone formation remains unclear.

Three concepts that may play an important role in cholesterol gallstone formation are discussed. Initially, researchers had accepted that cholesterol supersaturation of bile is a cause of gallstone formation. However, it is difficult to demonstrate consistent differences in the composition bile from patients with cholesterol gallstones and normal bile.

Two new concepts suggested may also play an important role in gallstone formation: The presence in gallbladder bile of nucleating promoting factors and nucleating-inhibiting factors which could be a protein. It has also been suggested that lipid absorption by gallbladder mucosa may influence biliary lipid composition and subsequent formation of gallstone.

INTRODUCTION
Disorder of the biliary tract are major medical and surgical problems in many countries. The most common of these is gallstone disease. For many years there was no therapeutic alternative, and during this time cholecystectomy had become the commonest elective abdominal operation performed in western countries. Indeed, some 10 to 20 percent of the population may expect to develop cholelithiasis at some time.

The purpose of the present review is to examine our current understanding of the mechanism of cholesterol gallstone formation. Three concepts need to be considered in discussing the cholesterol gallstone formation.

1. MICELLAR THEORY OF CHOLESTEROL SOLUBILITY
Cholesterol is insoluble in water and maintained in solution in human bile by formation of mixed micelles, which are aggregation of cholesterol, bile salts and phospholipid (lecithin). The amount of cholesterol that can be solubilised by mixed micelles depend on the relative molar concentrations of bile salts and lecithin. When more cholesterol is in bile the bile is called lithogenic or supersaturated bile.

The concept of lithogenic bile, or bile supersaturated with cholesterol, has dominated gallstone research since the initial model was proposed by Admirand and Small. They defined the upper limit of
cholesterol solubility which was subsequently modified by Holzbach et al.3. Admirand and Small studied patients with and without cholesterol gallstones and found that bile from all subjects with cholesterol gallstones was saturated with cholesterol and concluded that saturated bile is a prerequisite for cholesterol gallstone formation. This conclusion was supported by the finding that gallbladder and hepatic bile of gallstone patients contained excess cholesterol in relation to bile acids and lecithin. However, several investigators failed to show a clear distinction between the bile of patients with and without cholesterol gallstones.3,5 Supersaturated bile is therefore a risk factor for cholesterol stone formation but does not necessarily indicate that stones will form.

In the pathogenetic sequence of cholesterol cholelithiasis a prerequisite for cholesterol gallstone formation is the secretion of lithogenic bile followed by nucleation, crystal formation and growth of stone. These changes require time and thus retention of lithogenic bile within the gallbladder is necessary for these events to occur. Early studies have suggested that the gallbladder emptying and concentration ability in late pregnancy are impaired7, which is in agreement with the results of Potter. These observations were supported by the recent studies using real time ultrasonography8, which demonstrated incomplete emptying of the gallbladder in pregnancy. Nevertheless, progesterone, a known inhibitor of smooth muscle contraction,10 is a good candidate as an inhibitor of the gallbladder function during pregnancy.

The gallbladder may play an important role to determine the bile composition judging from the reports that bile composition is improved after cholecystectomy. Hepatic T-tube bile was found to be less saturated with cholesterol than hepatic bile obtained before surgery.11 However, others were unable to confirm any improvement in biliary lipid composition after cholecystectomy.12 These differing conclusions regarding the effect of cholecystectomy on biliary lipid composition may reflect differences in patient selection, where cholecystectomy improved the biliary lipid composition of the non-obese patients but not obese patients who have hypersecretion of cholesterol.13 Improvement of the biliary lipid composition after cholecystectomy in non-obese patients suggests that the gallbladder may play a role in the pathogenesis of gallstones.

Normal subjects without gallstones intermittently secrete supersaturated bile, which normally occurs during fasting.14 During the fasting period, most of the bile salt pool becomes sequestered in the gallbladder which interrupts the enterohepatic circulation and subsequently causes a reduction in hepatic secretion rate of bile acids. Similar results were obtained by several investigators as evidence of a connection between increased saturation of bile and interruption of the enterohepatic circulation.15 In addition, a number of patients with gallstones showed a reduced bile acid pool size as the result of increased frequency of the enterohepatic circulation.16

2. BILE PROTEINS

It is now clear that supersaturated bile alone does not explain the formation of cholesterol gallstones, as many normal individuals without stones have supersaturated bile.3 Holan et al. confirmed that saturation indices cannot discriminate between bile with and without cholesterol gallstones. They measured the nucleation time (the time taken for formation of cholesterol crystals) and found that bile of patients with stones formed crystal much quicker than those without stones. There was a correlation between saturation of bile and nucleation time for the patients without stones but not for the patients with stones. This study suggested that factors other than cholesterol saturation are involved in cholesterol stone formation. Subsequently, this was confirmed by others,17 suggesting that the in vitro observation of rapid onset time for cholesterol crystal nucleation could be accounted for by the presence in gallbladder bile of
excess nucleation-promoting factors or a decreased in nucleation-inhibiting factors. Recently, Holzbach et al. further reported that normal human gallbladder bile contains a protein fraction which delays the onset of nucleation of supersaturated native and model bile.

3. LIPID ABSORPTION BY THE GALLBLADDER

The gallbladder provides the physical conditions that may be favourable for stone formation, but may also influence biliary lipid composition by absorbing lipids from bile in the lumen of the gallbladder. Relatively little information is available to define lipid absorption by gallbladder epithelium although water and ion transport have been extensively studied. If, as it appears, a lipid transport system exists in the gallbladder, it is possible that primary lesion affecting this system may be involved in cholesterol gallstone formation, by altering the total amount of lipid that is solute in bile.

The human gallbladder mucosa is capable of absorbing cholestezol from bile. Cholesterol concentration in bile determines bile lithogenicity and stone formation, and thus the absorption of cholesterol could be a protective mechanism, preventing cholesterol crystallisation. This only can happen if the biliary phospholipids and bile salts are not absorbed to the same extent.

Recently there has been a suggestion that fatty acids may be a factor in cholesterol gallstone precipitation. They considered that the bile became lithogenic inside the gallbladder as a consequence of release of free fatty acids, as free fatty acids may compete with cholesterol in the solubilisation in biliary micelles. Additionally, free fatty acids have been found to damage the arterial lining by producing large cytoplasmic clefts and occasional blebbing and lysis of the arterial wall endothelial cell. They could therefore prove to be directly toxic to the gallbladder wall and produce cholecystitis. Consequently, study of fatty acid absorption and metabolism in the gallbladder is important to understand their possible role in the pathogenesis of gallbladder disease. Consequently, study of lipid absorption and metabolism in the gallbladder is important to understand their possible role in the pathogenesis of gallstones. Human gallbladder mucosa was shown to be able to absorb and metabolise oleic and palmitic acids.

Triglycerides and cholesteryl esters also can be absorbed by human gallbladder mucosa. Both types of lipid are present in human bile and are less polar than cholesterol. Thus, they may compete with cholesterol in the biliary micelles which may results in the preprecipitation of cholesterol.

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REFERENCES


