PROGRESS REPORT

Interactions between gall bladder bile and mucosa; relevance to gall stone formation

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Over 300 years ago, Diemerbroek appreciated that bile enters the gall bladder to 'acquire greater strength and digestive power',¹ and since then many studies have increased our knowledge of its functions. Understanding the gall bladder and its interaction with the biliary contents is important, because the gall bladder plays a crucial role in the formation of gall stones; most gall stones develop within the gall bladder, and removal of the gall bladder cures the tendency to form further stones in most, though not all, instances. Although cholesterol saturated bile originating in the liver (so called 'lithogenic' bile) is a prerequisite for gall stone development,² lithogenic bile is also frequently found in normal individuals.³ Consequently there must be other factors within the bile or mucosa of the gall bladder which determine why gall stones develop in some patients with lithogenic bile but not others.

One of these factors may be the concentration of calcium within the gall bladder bile. Studies have now shown that gall bladder bile from patients with either cholesterol or pigment stones is frequently super saturated with calcium and thus liable to calcium precipitation.⁴ Most gall stones contain a central core of calcium salts^{5,6} around which layers of either cholesterol or calcium bilirubinate are deposited as the stone enlarges.⁵ This suggests that calcium precipitation may be the critical initiating factor for gall stone development. Supporting evidence for this is seen in studies which show that feeding modest amounts of calcium to animals increases the biliary calcium concentration and also promotes the risk of gall stone formation.⁷ The concentration of calcium within the gall bladder lumen appears to be the critical determinant, and lowering the intraluminal calcium concentration by using amiloride (which reduces the concentrating ability of the gall bladder mucosa)^{8,9} reduces the incidence of stone formation in these animals.⁹ As well as being physically incorporated into gall stones during their formation, biliary calcium ions also reduce the solubility of biliary cholesterol,¹⁰ making cholesterol crystal formation (nucleation) and deposition into stones more likely. Biliary calcium ions also stimulate mucus glycoprotein secretion by the gall bladder mucosa¹¹ and this effect can be blocked by calcium antagonists. Other studies have suggested that the mucus glycoproteins found in bile may be responsible for the precipitation of biliary calcium^{12,13}; thus the calcium

within the gall bladder bile, by stimulating mucus production, may be indirectly responsible for its own precipitation.

Mucus itself has long been recognised as a factor that plays a role in gall stone development.¹⁴ In animals fed a lithogenic diet, mucus hypersecretion by the mucosa precedes cholesterol crystal and stone formation,¹⁵ and patients with gall stones have increased levels of mucus degradation products in bile compared with non-lithogenic controls.¹⁶ Secretion of mucus by the gall bladder mucosa into the bile, as previously mentioned, may be stimulated by calcium ions,¹¹ but also by prostaglandins.^{14,17,18}

The prostaglandins may also be of relevance to the formation of gall stones. As well as being potent mucus secretagogues, they have other important effects on gall bladder mucosal function¹⁹; they reduce sodium and water absorption by the mucosa²⁰ and initiate fluid and electrolyte secretion into the gall bladder lumen,²¹ both of which will tend to result in a less concentrated gall bladder bile. They also stimulate gall bladder motility.²² Normally, there is a basal release of prostaglandins by the gall bladder mucosa and this can be enhanced by luminal lysophosphatidyl choline, gall bladder distension or experimental cholecystitis.²³ Cholesterol given to animals (which causes gall stones to form) results in an increased synthesis of prostaglandins by the gall bladder mucosa¹⁸ and subsequently of mucus secretion into the bile.¹⁵ Recent studies have suggested that treatment with non-steroidal anti-inflammatory drugs (NSAID's - which are prostaglandin antagonists) may inhibit cholesterol precipitation and crystal formation in man,²⁴ and may also prevent stone formation in the gall bladders of animals²⁵ and man²⁶ at high risk of cholelithiasis. The link between prostaglandins and gall stone formation may be through mucus secretion, and NSAID's may protect against gall stone formation by blocking prostaglandin induced mucus release and consequent biliary calcium precipitation.

Between periods of digestion the resting gall bladder stores bile, and concentrates the stored bile through the active absorption of sodium (Na⁺) and the passive absorption of water.²⁷ In chronic cholecystitis, however, as gall bladders become progressively more diseased, there is a corresponding reduction in concentrating ability by the mucosa.^{28,29} This is the result of a 'functional' failure of electrolyte and water

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Accepted for publication
10 August 1989

absorption³⁰ and also an active fluid and Na⁺ secretion.³¹ It is likely that the fluid secretion in these inflamed gall bladders is mediated by prostaglandins, as it can be reversed to the more usual absorption by NSAIDs.^{31,32} The effects of prostaglandins, on motility and fluid absorption in the human gall bladder, are believed to be mediated through intramural nerves,³³ and there is some evidence that endogenous opiates may act as a feedback control by blocking the prostaglandin effects.³⁴

Although prostaglandins are involved in mediating physiological and pathophysiological changes in the gall bladder, the lipid content of the bile may also be an important determinant of gall bladder function. Studies have now shown that during the early stages of cholesterol gall stone formation, before gall stones have actually formed, there is an increase in water and electrolyte absorption by the gall bladder.³⁵ Further studies have suggested that it is the increased lipid content of the bile during this early phase of lithogenesis which determines these alterations in ion transport across the gall bladder mucosa.³⁶ Lithogenic bile contains increased amounts of cholesterol and phospholipids, and consequently has a higher phospholipid to bile salt ratio,^{35,36} which significantly alters ionic mucosal transport.³⁶ The gall bladder mucosae of animals³⁷ and man^{38,39} also normally absorb cholesterol from the bile and will absorb more cholesterol from biles containing larger amounts of cholesterol.³⁸ When inflamed, however, there is a secretion of cholesterol from the mucosa into the gall bladder lumen.³⁸ Changes in mucosal cell membrane cholesterol content as a result of increased cholesterol absorption from lithogenic biles³⁹ will be associated with changes in cellular membrane fluidity and function⁴⁰ that may be responsible for the alterations in mucosal function seen in the early stages of gall stone formation.

The gall bladder, however, has evolved several of its own defence mechanisms against gall stones forming, which revolve around its ability to absorb and secrete various substances. First, the mucosa acidifies bile by secreting hydrogen ions (H⁺)⁴¹ which causes a fall in biliary pH that will reduce the likelihood of calcium precipitation within the gall bladder lumen⁴¹ and thus the initiation of gall stones. Biliary acidification appears to be extremely important in preventing calcium precipitation⁴² and one study has suggested that gall stone formation in some patients may be caused by a specific defective mucosal H⁺ secretion in spite of a relatively normal gall bladder concentrating ability.⁴³ Second, the gall bladder absorbs large amounts (50%) of calcium from the bile,⁴⁴ which reduces the intraluminal free Ca⁺⁺ content and thus the risk of calcium precipitation within bile, by mucin or other nucleating factors. Third, during periods of digestion, there is active secretion of electrolytes and water into the gall bladder lumen.⁴⁵ The hormone secretin may be partly responsible for this secretory effect,⁴⁶ which will have an intermittent diluting effect on the biliary contents and may also help to 'wash out' particulate matter and 'sludge' from the gall bladder which may otherwise act as a nidus for stone formation. Lastly, antinucleating factors that inhibit chole-

sterol⁴⁷ and calcium⁴² precipitation, are found in the bile (although it is not clear whether the gall bladder mucosa or liver actually secretes them) and may also help to reduce the risk of gall stones developing.

Gall stones are still a major cause of morbidity in man. In the United Kingdom, about 20% of the population may expect to develop cholelithiasis at some time⁴⁸ and cholecystectomy is now the most common elective abdominal operation performed in Western countries. In high risk patients, therapeutic manipulation of the mucosal or biliary factors that predispose to gall stone formation (such as mucosal prostaglandins, biliary mucus, calcium content and pH) may eventually allow the possibility of prevention of gall stone formation.

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