

Leading article

Gall stones and gall bladder motility

In recent years, studies of gall stone pathogenesis have been focussing on the role of gall bladder motility. This has been fuelled by the advent of both ultrasonographic^{1,2} and radionuclide techniques³ for measuring gall bladder motility and by the realization that many people have cholesterol supersaturated bile but do not have gall stones.⁴ Furthermore, in patients who have had gall stones dissolved by oral bile acid therapy recurrence is not inevitable, despite the persistence of cholesterol supersaturated bile.^{5,6} These findings indicate that factors other than cholesterol supersaturation of bile, such as impaired gall bladder motility, are necessary for stone formation. Cholesterol crystal nucleating inhibitors⁷ and promoters⁸ are also implicated. As crystal nucleation and growth take time, however, an inert gall bladder with stagnant bile is the ideal location for these processes. Secretion of mucin by the gall bladder mucosa is also thought to contribute to crystal nucleation.⁹ Thus gall bladder stasis, by allowing prolonged contact between bile and the mucosa, could further contribute to stone formation.

Physiology of gall bladder motility

Under normal conditions, eating is the main stimulus to gall bladder emptying. Meals containing fat, especially polyunsaturated fat, are the most powerful stimuli but protein and carbohydrate meals also result in some emptying.¹⁰⁻¹² After a liquid meal containing fat, a minimum gall bladder volume of about 5-10 ml is reached in 30-45 minutes, after which refilling occurs.¹³ After a mixed solid-liquid meal, however, it may take up to 4 hours for the gall bladder to reach its minimum volume.¹⁴ Fifteen percent of gall bladder contents empty before gastric emptying begins and refilling begins after expulsion of about 85% of solid gastric contents.^{15,16} During fasting, the gall bladder undergoes periodic emptying of about 10% of its volume every 1-2 hours.^{14,17} Sham feeding induces expulsion of up to 65% of the gall bladder contents.^{18,19} Short time-sequence studies, with ultrasound imaging of the gall bladder every 2 minutes, indicate that there are frequent small 'bellows-like' evacuations and refilling during both fasting and meal stimulated contraction.^{17,20}

Vagal cholinergic and cholecystokinin (CCK) mediated hormonal mechanisms are the most important controls of gall bladder emptying under physiological conditions. Cholinergic blockade with atropine increases the fasting volume of the gall bladder, suggesting that cholinergic mechanisms have a role in maintaining fasting tone²¹; it also reduces emptying after solid and liquid meals and in response to CCK.^{22,23} The cephalic phase of gall bladder emptying depends on a cholinergic mechanism, as atropine abolishes gall bladder emptying in response to sham feeding.²⁴ Specific CCK antagonists similarly increase resting gall bladder volume and abolish postprandial contraction.²⁵ CCK is released from the upper small intestine²⁶ and exists in a number of different molecular forms.^{27,28} Sulphation of the C-terminal is important for receptor binding.²⁹ Recent studies have provided some insights into the interaction of CCK and cholinergic mechanisms in promoting gall bladder emptying under physiological conditions. In humans it seems that

normal CCK induced postprandial gall bladder emptying relies on a cholinergic mechanism.^{22,23,30}

The periodic evacuations of the gall bladder that occur during fasting coincide with phase II of the duodenal migrating motor complexes and phase III of antral complexes.³¹⁻³⁴ Studies in animals using retrograde neural tracers have shown that long neural projections exist between the duodenum and gall bladder.³⁵ These are probably involved in the coordinated motility patterns of the gall bladder and intestine during fasting.

With recent advances in biochemical purification techniques and recombinant DNA technology, there has been a proliferation of newly identified peptides. While there is considerable information on the pharmacological role of these peptides investigation of their physiological role, which is more difficult, has lagged behind. Thus many peptides modulate gall bladder motility under experimental or pathological conditions, but their physiological role remains uncertain. Somatostatin in humans produces an increase in resting gall bladder volume and prevents contraction in response to sham feeding, test meals, cholinergic stimulation, and CCK infusion.^{36,37} Whether motilin is involved in the migrating motor complex associated gall bladder evacuations during fasting remains controversial,^{38,39} although it is accepted that this hormone does not act directly on the gall bladder muscle.⁴⁰ Human and animal studies show that neurotensin,⁴¹ gastrin releasing peptide,⁴² substance P,⁴³ and neuropeptide Y⁴⁴ can promote gall bladder contraction whereas pancreatic polypeptide,⁴⁵ peptide YY,⁴⁶ vasoactive intestinal polypeptide,⁴⁷ and calcitonin gene related peptide⁴⁸ promote relaxation. Many of these peptides exert their effect indirectly by release of other peptides or neurological pathways.

Role of impaired gall bladder motility in the pathogenesis of gall stones

Impaired emptying after a fatty meal has been shown in patients with gall stones by both radionuclide and ultrasound techniques.^{13,49-52} Gall bladder contraction in response to intravenous administration of CCK in patients with stones is less than that occurring in normal subjects.^{13,53} In studies of large numbers of gall stone patients, contraction is impaired at the time of study only in a 'subgroup' of about 50% and many have normal emptying in response to both a fatty meal and intravenous CCK.^{13,53,54} The impairment of gall bladder emptying is not the result of the physical presence of gall stones as the defect does not correlate with the size or number of stones,⁵³ and furthermore stone clearance with lithotripsy does not reverse the motility defect.⁵⁵

In a number of patient groups with either temporary or permanent impairment of gall bladder motility, there is an increased predisposition to stone formation. Patients receiving total parenteral nutrition do not empty their gall bladders regularly,¹⁴ and have a high incidence not only of biliary tract sludge but also of gall stones.^{56,57} Similarly, patients who have undergone major abdominal surgery necessitating a fast of at least 48 hours show an increased incidence of gall stones.⁵⁸ Although gall bladder motility was not measured in this latter

study, it is likely that stasis and sludge formation associated with prolonged postoperative fasting contributed to the stone formation.^{59,60} Women who have had several pregnancies have an increased prevalence of gall stones^{61,62}; in the third trimester of pregnancy as the serum progesterone concentration rises,⁶³ the fasting gall bladder volume is increased and emptying is impaired.^{63,64} Although bile tends to become cholesterol supersaturated in the last trimester of pregnancy,⁶⁵ gall bladder stasis may also be a factor in the development of pregnancy related gall stones.

Patients with sickle cell anaemia produce excessive amounts of bilirubin because of long term haemolysis and have a high prevalence of pigment gall stones.⁶⁶ They also have impaired gall bladder emptying, although this, and biliary bilirubin concentrations are similar in sickle cell anaemia patients with and without gallstones.⁶⁷ Thus, impairment of postprandial gall bladder emptying cannot fully explain why only 50% of those with sickle haemoglobinopathy develop stones. Those with gall stones tend to have more severe and complicated crises than those who are stone free.⁶⁷ Perhaps the prolonged fasting associated with more severe crises leads to further gall bladder stasis and predisposes to stone formation in this group.

Giving somatostatin or its long acting analogue, octreotide, to humans results in gall bladder dilatation and impaired postprandial emptying.^{36,68} The gall bladder inertia associated with somatostatin excess may well explain the high prevalence of stones in patients with somatostatinomas.⁶⁹ Furthermore, patients with acromegaly who receive long term treatment with octreotide have an increased prevalence of gall stones.^{70,71}

Whether there is an increased incidence of gall stones in diabetic patients^{72,73} and in those who have had vagotomies^{74,75} is controversial. The impaired gall bladder motility in these patient groups may contribute to stone pathogenesis.⁷⁶⁻⁷⁸ Finally, patients with spinal cord injuries have both impaired postprandial gall bladder emptying and a high prevalence of gall stones.^{79,80}

Although various changes in bile composition also occur in most of these patient groups, impaired gall bladder motility is a common feature, suggesting that bile cholesterol supersaturation (or increased bilirubin concentrations) and impaired emptying are interdependent rather than independent risk factors for stone formation.

The questions remain whether impaired gall bladder motility in gall stone disease occurs secondary to changes in bile composition or gall bladder inflammation, or whether the impaired motility is a separate factor in the pathogenesis? It is not yet possible to give a definite answer. In animals, feeding a lithogenic diet induces cholesterol supersaturation of bile and impairment of gall bladder emptying before stone formation, indicating that there is a close association between the two factors.⁸¹⁻⁸³ In humans, *in vitro* gall bladder muscle contraction in response to CCK or acetylcholine is less in those with biliary cholesterol excess than in those with pigment stones.⁸⁴ Non-dietary induction of biliary cholesterol supersaturation in the prairie dog by the plant steroid diosgenin, which promotes biliary excretion of cholesterol from endogenous pools, does not impair gall bladder contraction, however, and stones and crystals are less likely to form in this situation.⁸⁵ Furthermore, some workers have failed to show a decrease in gall bladder smooth muscle contraction in animals fed a high cholesterol lithogenic diet.⁸⁶ Thus, it is not possible to say that the impaired gall motility occurs solely as a consequence of the changed bile composition. The fact that impaired release into plasma and raised duodenal levels of CCK have been noted in gall stone patients provides further evidence that the impaired contractility is related to factors apart from altered bile composition.^{87,88}

From a therapeutic viewpoint, the cause of impaired gall

bladder motility is of little relevance since in animals improving gall bladder emptying prevents stone formation.⁸⁹⁻⁹¹ Furthermore, in humans receiving total parenteral nutrition, daily administration of intravenous CCK empties the gall bladder and prevents sludge formation.⁹² In humans therefore it is likely that correcting impaired emptying will prevent stone formation irrespective of the aetiology of the motility defect.

Therapeutic implications and opportunities

Pharmacological agents that modulate gall bladder motility may be valuable in two circumstances. Agents that dilate the gall bladder and lower intraluminal pressure, especially during periods of biliary colic, may help relieve the associated pain. On the other hand, gall bladder prokinetic agents may be useful in preventing bile stagnation and stone formation.

In a double-blind controlled study, non-steroidal anti-inflammatory drugs relieved biliary pain better than opiates.⁹³ Furthermore, these agents are able to prevent progression of simple biliary colic to cholecystitis.⁹⁴ Indomethacin decreased *in vivo* gall bladder pressure in humans with acute cholecystitis⁹⁵ and also lowered the resting tone of gall bladder strips *in vitro* from patients with acute cholecystitis.⁹⁶ These effects of indomethacin may explain its success in treating biliary pain. No formal assessment of other agents that dilate the gall bladder, such as CCK antagonists, have been reported but these agents may prove useful in relieving biliary pain. It is possible, however, that these agents might promote the formation of an empyema by dilating the gall bladder, so it is important that their use is fully assessed at the outset.

A number of agents have a prokinetic effect on the gall bladder including erythromycin,⁹⁷ cisapride,^{98,99} and cholestyramine.¹⁰⁰ In contrast to its effect on acutely inflamed gall bladders, indomethacin has a prokinetic effect on uninflamed gall bladders which presumably contain lithogenic bile.¹⁰¹ The prevention of stone formation in animals⁸⁹⁻⁹¹ and sludge in humans⁹² by promoting gall bladder emptying raises the possibility that oral prokinetic agents may prevent stone formation in humans. Prevention of stone formation by non-steroidal anti-inflammatory drugs¹⁰² may be the result of a prokinetic effect.¹⁰¹ Erythromycin and its 'motilide' analogues are prokinetic agents and may well find a role in preventing stone formation in high risk groups such as dieting obese people, acromegalics taking octreotide, or those who have had their stones removed or dissolved by bile acids, MTBE, cholecystolithotomy, or extracorporeal shock wave lithotripsy. Furthermore, these agents may have a role to play in clearing the gall bladder of gall stone fragments after lithotripsy and percutaneous contact dissolution.

Conclusion

Gall bladder motility is an important factor in stone pathogenesis but its cause is unknown in most cases. Improving motility in animals prevents gallstones and in humans prevents sludge formation. The recent description of orally administered gall bladder prokinetic agents, particularly erythromycin and its analogues, raises the possibility that these agents may be of value in preventing gall stones in high risk groups.

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