Cholesterol gallstone disease

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With a prevalence of 10–15% in adults in Europe and the USA, gallstones are the most common digestive disease needing admission to hospital in the West. The interplay between interprandial and postprandial physiological responses to endogenous and dietary lipids underscores the importance of coordinated hepatobiliary and gastrointestinal functions to prevent crystallisation and precipitation of excess biliary cholesterol. Indeed, identifying the metabolic and transcriptional pathways that drive the regulation of biliary lipid secretion has been a major achievement in the field. We highlight scientific advances in protein and gene regulation of cholesterol absorption, synthesis, and catabolism, and biliary lipid secretion with respect to the pathogenesis of cholesterol gallstone disease. We discuss the physical-chemical mechanisms of gallstone formation in bile and the active role of the gallbladder and the intestine. We also discuss gaps in our knowledge of the pathogenesis of gallstone formation and the potential for gene targeting in therapy.

Introduction

Gallstones are abnormal masses of a solid mixture of cholesterol crystals, mucin, calcium bilirubinate, and proteins that have affected people for centuries:[1] multiple gallstones were found in a mummified Egyptian priestess,[2] but the disease was first described in 1507 by a Florentine pathologist, Antonio Benivenius.[3] The Swiss medic Paracelsus viewed gallstones as a consequence of "tartaric" disease.[4] With a prevalence of 10–15% in adults in Europe and the USA, gallstone disease is one of the most common and most expensive to treat of digestive disorders that need admission to hospital.[5,6] Every year in the USA, more than one million people are newly diagnosed with gallstones, and about 700 000 individuals have cholecystectomies.[7] In 1882, in the first open cholecystectomy Langenbuch successfully removed the gallbladder of a 43-year-old man who had had gallstones for 16 years.[8] This technique remained the gold standard therapy for symptomatic gallstones for over a century, although medical treatment with bile acids was first described in the late 19th century.[9,10] After a report of complete dissolution of gallstones by bile acids in 1937,[11] oral bile acid litholysis with chenodeoxycholic acid as a method for removing cholesterol gallstones emerged in the 1970s,[12] and litholysis with ursodeoxycholic acid in the 1980s.[13] Extracorporeal shockwave lithotripsy plus oral bile acids for symptomatic gallstones was introduced first in 1986 in Munich.[14] Later, several studies proved that gallstones recur in 30–50% of cases, 5 years after bile salts therapy or lithotripsy.[15,16] In 1987, Mouret[17] undertook the first laparoscopic cholecystectomy, which is today the treatment of choice for symptomatic gallstones.

In the human gallbladder, three types of gallstones exist, depending on the major constituents: pure cholesterol, pure pigment, and mixed (small amounts of calcium and bilirubin salts). Pigment stones appear in two major forms: black and brown. Whereas black pigment stones result from haemolysis and consist primarily of calcium bilirubinate, brown pigment stones are associated with infections of the biliary tract (bacterial and helminthic) and are more frequent in Asia or occur after cholecystectomy as de novo common bile duct stones.[18] Cholesterol gallstone disease results from a complex interaction of genetic and environmental risk factors. Discoveries linking gene transcription, protein function, lipid metabolism, and regulation of biliary lipid secretion in the formation of cholesterol gallstones provide the impetus to review our understanding of the disease.

Pathobiology

In Western societies, cholesterol gallstones account for 80–90% of the gallstones found at cholecystectomy.[19] Precipitation of excess cholesterol in bile as solid crystals is a prerequisite for cholesterol gallstone formation.[20,21] Cholesterol gallstones are composed mainly of cholesterol crystals (70%) held together in an organic matrix of glycoproteins, calcium salts, and bile pigments (figure 1). Patients present with single or multiple gallstones of different sizes, shapes (spherical or oval), and surfaces (smooth or morular). Both anhydrous[22,23] or monohydrate[24] cholesterol crystals occur in human bile from cholesterol gallstone patients[25] (figure 2).

Cholesterol is only slightly soluble in aqueous media, but is made soluble in bile through mixed micelles by bile salts and phospholipids, mainly phosphatidylcholine, whose concentrations determine the degree of cholesterol saturation.[26] The description of the ternary phase diagram by Admirand and Small[27] (figure 3) and later by Wang and Carey[28,29] has clarified the importance of the relative amounts of bile salts and phospholipids needed to solubilise biliary cholesterol.

In supersaturated bile, phospholipids solubilise cholesterol into vesicles. Monohydrate crystals can precipitate from these cholesterol-enriched vesicles,[30] become entrapped in gallbladder mucin gel together with bilirubinate (biliary sludge),[31] and ultimately agglomerate into a macroscopic gallstone.[32] However, supersaturated gallbladder bile with cholesterol crystals occurs frequently in healthy individuals,[33] suggesting that microcrystals can be flushed into the duodenum during normal postprandial gallbladder contraction. In patients who form gallstones, pro-nucleating factors such as biliary glycoproteins and mucin,[34] as well as impaired gallbladder

motility[35] allow these microcrystals to be retained and to eventually grow over months or years into macroscopic gallstones.

Role of the liver and biliary lipid secretion

Bile is composed mainly of water (>90%)[36] and is the primary excretory route for organic compounds such as cholesterol, lipid hormones, and drugs with low water solubility. The hepatocyte is the major site for cholesterol synthesis and peripheral uptake, and excess cholesterol is directly secreted into bile or converted into bile salts.[37]

Cholesterol and phosphatidylcholine are mainly secreted in bile as small unilamellar vesicles (40–200 nm in diameter) that form on the external hemileaflet of the canalicular membrane.[38] Because of their detergent properties, bile salts secreted from hepatocytes within the canalicular lumen directly convert vesicles into smaller (40–100 Å in diameter) structures called micelles.[39] Thus, "mixed" micelles containing bile salts and phospholipids and unilamellar vesicles are the physiological carriers of cholesterol in bile.

Biliary lipid secretion is regulated by an elaborate network of ATP-binding cassette (ABC) transporters on the hepatocyte canalicular membrane. The ABC transporter (ABCB11), known as the bile salt export pump (BSEP), serves as the major canalicular bile salt export pump in mammalian liver.[40] The human multidrug resistant 3 p-glycoprotein, also known as ABCB4 (corresponding to the murine Mdr2 p-glycoprotein), functions as a "flippase", translocating phosphatidylcholine molecules from the inner to the outer leaflet of the canalicular membrane.[41] Finally, the ABC transporters ABCG5 and ABCG8 pump cholesterol into bile[42] (figure 4).

Two nuclear receptors in hepatocytes, the bile acid receptor or farnesoid X receptor[43–45] (FXR) and the oxysterol receptors or liver X receptors[46,47] (LXRs) play important roles in transcriptional regulation of the genes encoding these proteins. The expression of *ABCB11*[48] and *ABCB4*[49] is under FXR control, while *ABCG5* and *ABCG8* are target genes of LXRs.[50]

The relevance of these transcriptional activations for cholesterol gallstone disease has been highlighted in a mouse model. After one week on a lithogenic diet, cholesterol gallstones formed in the gallbladder of FXR-null mice, due to decreased biliary bile salt and phospholipid concentrations, associated with reduced expression of *ABCB11* and *ABCB4*. Treatment of gallstone-susceptible (C57L) mice with synthetic FXR ligands prevented cholesterol precipitation and gallstone formation due to the FXR-induced expression of *ABCB11* and *ABCB4*, which was associated with higher biliary concentrations of bile salts and phospholipids, and a subsequent lowering of the cholesterol saturation in bile compared to untreated animals.[51] By contrast, activation of LXR by synthetic ligands rendered gallstone-resistant (AKR) mice prone to gallstone formation because of LXR-induced expression of *ABCG5* and *ABCG8*, which increased biliary cholesterol secretion and saturation.[52] The relevance of these intriguing observations in mice to human gallstone disease is not yet clear.

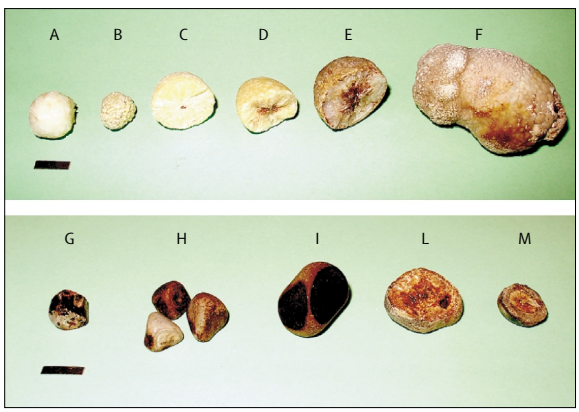

***Figure 1*: Morphological variability of human gallbladder stones**
Top: Pure spherical or oval shaped cholesterol stones with smooth (A) or morular (B) surface, and a small (C), medium (D) or large (E) dark pigment nucleus on the cut surface. F is a very large, almost pure, cholesterol stone, which is a conglomeration of stones. Bottom: Cholesterol stones with spherical (G), multifaceted (H, I) surface and a largely pigment nucleus (L), or with a small cholesterol nucleus (M) surrounded by a pigment thick layer on the cut surface. Black horizontal line=1 cm.

Through the quantitative trait loci approach, Paigen has identified genetic defects and described several *lith* genes in mice that are susceptible to cholesterol gallstones.[53–56] Description of candidate *lith* genes in the mouse[56] will eventually help in the identification of the human *LITH* genes. Several family and twin studies, including haplotype analysis, have indicated the role of few genes (*ABCG5*, *ABCG8*, *FXR*, *LDLR*, *CYP7A1*, *Apolipoprotein B-100*, *APOE*, *CCKAR*) as common genetic determinants for cholesterol gallstone diseases in

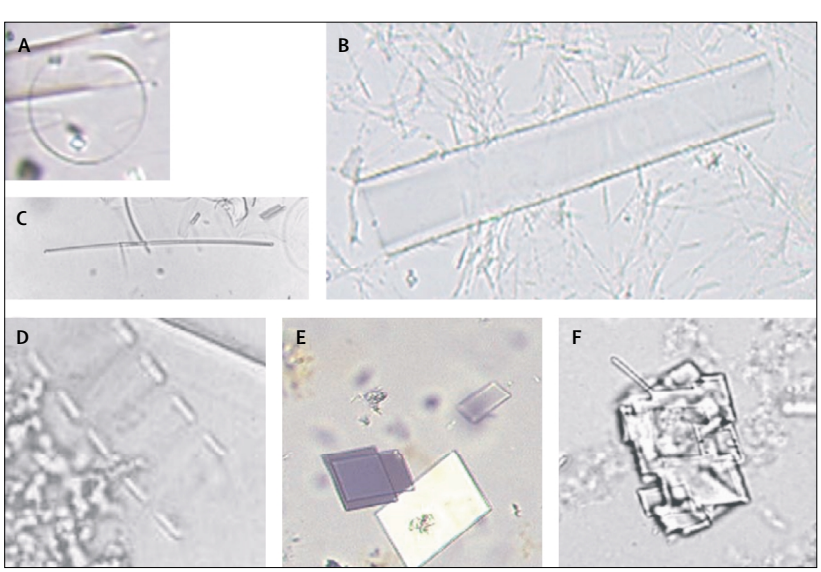

***Figure 2*: Morphological variation in cholesterol crystals seen through light microscopy**
Mainly "anhydrous": arcs (A), tubules with "double track" appearance (B), needles (C), spirals-ribbons (D). Monohydrate: mature rhomboid plates (birefringent at polarised microscopy) (E), and thick intertwined plates (F). Magnification ×200.

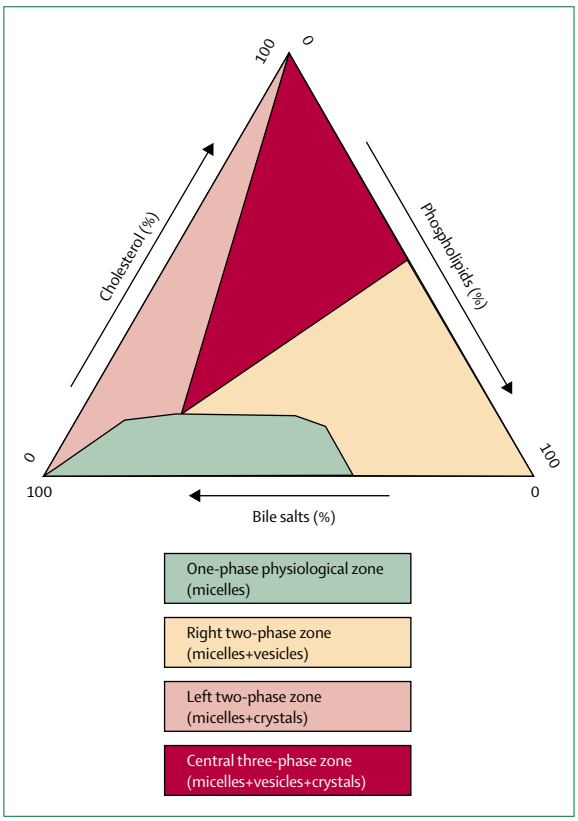

Figure 3: **Schematic representation of the ternary bile salt-cholesterol-phospholipid phase diagram, that describes the different pathways of cholesterol solubilisation or precipitation, or both, in bile.**
The three axes of the triangle represent the concentrations of the three lipids. The triangle has been adapted from refs 27–29 for a putative bile of total lipid concentration 72 g/L, pH 7, and temperature 37°C. Cholesterol precipitates quickly with excess bile salts; at increasing amounts of phospholipids, cholesterol can reside in vesicles with phospholipids and crystal formation is slower or absent. Depicted are the one-phase zone in green (only micelles), and three zones with cholesterol supersaturation: a left two-phase zone (containing micelles, vesicles, and cholesterol crystals), and a right two-phase zone (containing micelles and vesicles). Bile from cholesterol gallstone patients plots within the orange and red zones. If the hydrophilic bile salt ursodeoxycholate is present, the yellow zone expands to the left at the expense of the crystals containing orange and red zones. Thus, a cholesterol-supersaturated bile of pathophysiological importance might lie in the three-phase zone (with crystals) if enriched with hydrophobic bile salts (ie, deoxycholate), but in the right two-phase zone (without crystals) if enriched with hydrophilic bile salts (ie, ursodeoxycholate).[143] This partly explains why ursodeoxycholate prevents cholesterol crystallisation and gallstone formation and is effective for oral litholysis in a subgroup of cholesterol gallstone patients.

humans.[57,58] The precise understanding of the ultimate role of such genes as well as their functions is an active research field.

Role of gallbladder dysfunction in gallstone disease

Hepatic bile is concentrated in the gallbladder during fasting and emptied into the duodenum in response to feeding (figure 4). Gallbladder-induced bile flow into the intestine facilitates digestion and absorption of lipids and lipid-soluble vitamins, and protects against intestinal bacterial overgrowth.[39] Meal-induced release of cholecystokinin (CCK) from the duodenum is the principal factor driving gallbladder smooth muscle contraction, accounting for 70–80% of the decrease of fasting gallbladder volume. A subgroup of cholesterol gallstone patients ("bad contractors") have severely decreased or even absent postprandial gallbladder emptying, whereas patients whose gallbladders empty ("good contractors") mostly have increased fasting and residual gallbladder volumes compared with controls.[35,59]

Whether gallbladder dysmotility is a primary factor in cholesterol gallstone disease or secondary to inflammation[60] and excess cholesterol accumulation in gallbladder smooth muscle is debatable.[61] However, gallbladder motility is often impaired in many high-risk situations for gallstone formation, such as pregnancy, obesity and rapid weight loss in obese patients, diabetes mellitus, and total parenteral nutrition.[62] Also, impaired gallbladder motility is an independent risk factor for gallstone recurrence after successful extracorporeal shockwave lithotripsy.[63,64] Furthermore, acromegalics are at high risk for gallstone formation during treatment with the somatostatin analogue octreotide, which suppresses postprandial CCK release and gallbladder contractility.[65] Genetic deletion of the CCK-1 receptors in the mouse induces gallbladder stasis, increasing the risk of gallstone formation.[66] A primary role for gallbladder motility in gallstone formation is also indirectly supported by the observation that daily CCK injection during total parenteral nutrition[67] or inclusion of dietary fat to enhance CCK release during rapid weight loss restores gallbladder contractility and can prevent gallstone formation.[68]

Role of the intestine and the enterohepatic circulation

Bile salts secreted into the duodenum are reabsorbed in the distal ileum and transported back to the liver where they are secreted into bile—the so-called entero-hepatic circulation[39] (figure 4). The circulating bile salt pool comprises primary and secondary bile salts. Primary bile salts (cholate and chenodeoxycholate) are synthesised de novo from cholesterol and secondary, more hydrophobic, bile salts (deoxycholate and lithocholate) are produced in the colon by bacterial 7α-dehydroxylation of primary bile salts.[37] Slow intestinal transit can increase the rates of deoxycholic acid formation; indeed, impaired intestinal motility as well as increased biliary deoxycholate levels are found in some patients with cholesterol gallstone disease.[25,69]

Evidence for a causal relation between impaired intestinal motility, deoxycholate formation and bile lithogenicity comes from studies in humans[70] and mice.[71] First, patients with cholesterol gallstones have increased amounts of Gram-positive anaerobic bacteria and increased 7α-dehydroxylating activity in their caecum, with subsequent higher levels of biliary deoxycholate compared with controls.[72] Second, treatment with

octreotide (a known risk factor for cholesterol gallstone disease) prolongs colonic transit, biliary deoxycholate concentration, and biliary cholesterol precipitation.[73] Moreover, antibiotic treatment decreases faecal 7α-dehydroxylation activity, and lowers biliary deoxycholate and cholesterol concentration.[74] Animals susceptible to cholesterol gallstone formation have high levels of biliary deoxycholate, associated with cholesterol supersaturation and gallstone formation.[75]

Altered gallbladder and intestinal motility can have a role in gallstone formation. Normally, a 20–30% fall in fasting gallbladder volume occurs in the fasting state, just before phase III (ie, intense, regular coordinated contractions) of the intestinal migrating motor complex (MMC, see figure 4), associated with a rise in plasma motilin concentrations.[76,77] Gallstone patients have less frequent MMC cycles, absent fasting gallbladder emptying, and abnormal pattern of motilin release compared with controls.[78] Indeed, more frequent food consumption and avoidance of long fasting periods seems to protect against gallstones.[79]

Intestinal absorption of dietary cholesterol can also contribute to stone formation. Animal studies indicate that high cholesterol absorption efficiency and subsequent rapid biliary secretion of cholesterol promote cholesterol gallstone disease.[80] Also, delayed or impaired small intestinal transit time has been associated with enhanced intestinal cholesterol absorption, biliary cholesterol secretion and gallstone prevalence.[66] However, conflicting data exist from research in human beings, with some studies showing that high dietary cholesterol either increases[81–83] or has no effect on cholesterol saturation of bile.[84]

The role of chronic intestinal infection as a potential factor in cholesterol gallstone pathogenesis has been proposed. Distal intestinal infection with a variety of enterohepatic *Helicobacter* species, but not *Helicobacter pylori*,[85] are essential to nucleate cholesterol supersaturated bile in a well-established murine model of cholesterol gallstone formation.[86] Of note, *Helicobacter* species have been identified in the bile and gallbladder tissue from Chilean patients with chronic cholecystitis.[87] Given the potential therapeutic implications of these data, further studies should investigate whether chronic enteritis has a direct pathogenic role in patients with cholesterol gallstone disease. Patients with Crohn's disease, as well those who underwent bowel resection or total colectomy, have cholesterol supersaturated bile which is prone to cholesterol crystal precipitation and cholesterol gallstone formation.[88] Impaired bile acid entero-hepatic circulation and metabolism have been postulated as the cause. However, the link between bowel disease and resection with cholesterol gallstones has been fully explained; Crohn's disease might also lead to impaired enterohepatic cycling of bilirubin, increased biliary bilirubin levels, and formation of pigment, rather than cholesterol gallstones.[89]

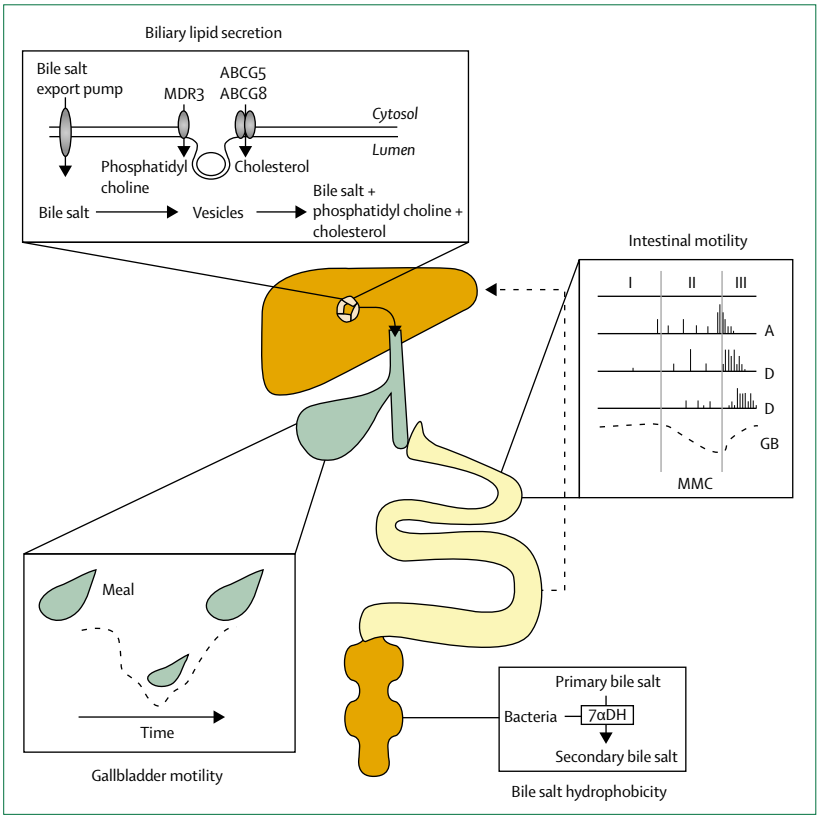

***Figure 4*: Role of the liver, gallbladder, intestine, and the entero-hepatic circulation in cholesterol gallstone disease**

The four boxes represent key physiological events in cholesterol gallstone prevention. Box A shows the pathways of biliary lipid secretion and nascent bile formation in the liver; Box B shows a schematic of normal time-dependent changes in gallbladder volumes before and after a meal; C shows the rhythmic cycles of gastric and small intestinal motility synchronised with periodic fluctuations of fasting gallbladder volume (20–30% decrease of maximal fasting gallbladder volume occurs during end-phase II of the migrating motor complex, MMC). D represents hydrophobic secondary bile salts (deoxycholate and lithocholate), produced in the colon by bacterial 7α-dehydroxylation of the primary bile salts (cholate and chenodeoxycholate, respectively). The broken line represents the entero-hepatic circulation of bile salts: after their secretion in bile and appearance in the duodenum, bile salts are reabsorbed in the ileum into the portal vein circulation and re-uptaken from the liver. 7αDH=7α-dehydroxylation.

Epidemiology

The major risk factors for cholesterol gallstone disease are age, female gender and parity.[90] The prevalence of gallstone disease is very high in some ethnic groups: 73% of female Pima Indians aged 25 years and older, studied by cholecystography;[91] 29·5% of men and 64·1% of women aged 47 years and older studied by ultrasonography.[92] In South America, a high prevalence of gallstones (35·2%) is present in Chilean Mapuche Indians, who migrated from Asia.[93] In the NHANES III study,[5] the first large epidemiological ultrasonographic US survey on gallstone disease, the overall prevalence was 7·9% (men) and 16·6% (women) with progressive increase after age 20 years. The prevalence rates showed ethnic differences: higher for Mexican Americans (8·9% in men, 26·7% in women), intermediate for non-Hispanic white (8·6% in men, 16·6% in women), and low for African-Americans (5·3% in men, 13·9% in women). Overall prevalence rates in Europe, from large ultrasonographic surveys in adults

aged 30–69 years, are similar.[94] By contrast, gallstones are virtually absent in children and adolescents aged 6–19 years (they were present in only two females of 1570 asymptomatic individuals of both sexes).[95] The overall prevalence of gallstone disease is lower in Asians (overall ranging from 3% to 15%) and almost absent (less than 5%) in Africans.[93,96]

Epidemiological surveys and family clustering point to a critical role of genetic susceptibility for gallstones.[97,98] A single gene defect has been identified in a subgroup of cholesterol gallstone patients. A mutation in the gene encoding the hepatocanalicular phosphatidylcholine transporter (ABCB4) leads to extremely low levels of biliary phosphatidylcholine, resulting in enhanced cholesterol precipitation and formation of crystals and gallstones.[99,100]

Risk factors

Several risk factors are involved in gallstone formation (panel), such as having given birth, oestrogen-replacement therapy, oral-contraceptive use, and rapid weight loss.[101–104] Similar to atherosclerosis, the risk of cholesterol gallstone disease increases with age, obesity, type 2 diabetes, dyslipidaemia (hypertriglyceridaemia and low HDL [high density lipoprotein] serum cholesterol), hyperinsulinaemia, and sedentary life-style.[96,105] All these conditions are risk factors for the metabolic syndrome, of which cholesterol gallstone disease is deemed as just another complication.[106,107]

The consumption of the high calorie diet that is more common in the West is clearly a key factor in cholesterol gallstone disease. Indeed, gallstone composition has changed over the past decades in East Asian countries, with a prominent increase in the prevalence of cholesterol gallstones, possibly because dietary habits have become more unhealthy.[108,109] However, there is still little agreement about the risk of specific dietary components for gallstones.[110] The difficulty in estimating the ingestion of specific dietary constituents by individuals could account for the large variability in data for humans.[105]

Studies on the association between total fat intake and risk of cholesterol gallstone disease have reported either positive[111] or non-significant[112] conclusions. A high intake of cis-unsaturated fats was associated with a lower risk for gallstone disease in men.[113] Additional dietary factors associated with gallstone disease are cholesterol, highly refined carbohydrates, alcohol, and dietary fibre.[81–84,105,114]

***Panel*: Major risk factors for cholesterol gallstones**

Independent
- Increasing age
- Female gender
- Race
- Family history

Dietary
- High calorie
- Low fibre
- Low cis-unsaturated fats
- High refined carbohydrates

Life style
- Low grade physical activity
- Prolonged fasting
- Rapid weight loss
- Pregnancy and parity
- Oral contraceptives

Associated conditions
- Metabolic syndrome
- Obesity
- Hyperinsulinism
- Oestrogen replacement therapy
- Gallbladder or intestinal stasis, or both

Natural history and clinical features

Gallstones are often discovered incidentally during abdominal ultrasonography and remain asymptomatic in nearly 80% of cases.[115] After diagnosis, the risk of developing pain or complications is low; 1–4% per year, with only 10% and 20% of patients developing symptoms within 5 years and 20 years, respectively.[116]

The typical symptom of cholesterol gallstone disease is a steady pain called biliary "colic". The pain is usually severe, intermittent, starts abruptly without fluctuations, and reaches a peak within 1 h in two-thirds of patients. The symptoms tend to resolve gradually over 1–5 h, and those lasting for longer (more than 5 h) should raise suspicion of complications (ie, acute cholecystitis). The visceral pain is caused by the impaction of the stone in the cystic duct or ampulla of Vater, with distension of the gallbladder or the biliary tract, or both, and activation of visceral sensory neurons.[117] The pain is relieved if the stone returns into the gallbladder lumen, passes through the ampulla into the duodenum, or migrates back to the common bile duct. The pain is not exclusively postprandial, referred in the right upper quadrant or in the epigastrium (representative dermatomes T8/9), sometimes radiating to the right scapula or shoulder, or both, or infrequently (7%) to the retrosternal area. The pain can be accompanied with vomiting. More than 90% of patients presenting with their first attack of biliary colic have recurrent pain within 10 years (two-thirds within 2 years).[118] Although the "uncomplicated" biliary colic is not followed by persistent symptoms after the acute attack, symptomatic cholesterol gallstone disease can be alleviated with narcotic analgesics or non-steroidal anti-inflammatory drugs.

Patients with cholesterol gallstone disease may also be seen for gallstone complications, such as cholecystitis, choledocholithiasis, ascending bacterial cholangitis, or pancreatitis. The presence of persisting pain and vomiting, the association of fever, and leucocytosis may help the physician in the differential diagnosis between uncomplicated and complicated biliary pain. Empyema,

abscess formation, or perforation of the gallbladder are also complications of cholesterol gallstone disease. Whereas most gallbladder cancers (70 to 90%) are associated with gallstones, gallbladder cancer is uncommon in the USA (yearly incidence of over 5000) and the Western world.[119] History of gallstones seems to be the highest risk factor for gallbladder cancer with a pooled relative risk of 4·9, followed by obesity, multiparity, and chronic infections.[120]

Diagnosis

Figure 5 shows a flow chart of the diagnosis and treatment of cholesterol gallstone disease. Ultrasonography of the right upper quadrant is the best method of diagnosing gallstone disease.[121] It is a non invasive, safe, and a widely available, low-cost procedure with more than 95% sensitivity and specificity for the detection of gallbladder stones (>1·5 mm diameter in size). In a longitudinal subcostal scan, the gallbladder is seen below the liver as an anechoic area, in which the stones appear as multiple, mobile echogenic foci with posterior acoustic shadowing (indicated by a dark area behind the gallstones in the fat adjacent to the gallbladder).[110]

Ultrasonography provides information about the size of the gallbladder, the presence of a thickened gallbladder wall, and pericholecystic fluid (signs of acute cholecystitis), the size of the common bile duct and hepatic duct, and the status of both liver and pancreas parenchyma. Functional ultrasonography provides additional information about time-dependent changes of both fasting and postprandial gallbladder volume,[122,123] as markers of gallbladder emptying and cystic duct patency.

Since only 10% of gallstones are calcified, ultrasonography is the first-line technique for gallstone detection, and abdominal radiography or CT have a secondary role. Abdominal ultrasonography, by contrast, has limited value in the diagnosis of choledocholithiasis; small bile duct stones are more difficult to detect because of their localisation and the presence of intestinal gas. Dilatation of the common bile duct at ultrasonography as well as liver function analysis—such as serum bilirubin concentration and alkaline phosphatase levels—will help in the diagnosis of choledocholithiasis.

Common bile duct stones can transiently obstruct the pancreatic duct, which in turn leads to a raised serum amylase level. If the obstruction is prolonged, some patients develop severe gallstone pancreatitis, which can be life-threatening. CT should be used if biliary pancreatitis or common bile duct stone obstruction are suspected. However, if acute cholecystitis with blockage of the cystic duct by a gallstone is suspected, cholecystosintigraphy (HIDA scanning) has 95% sensitivity and specificity for diagnosis.[124] On the other hand, endoscopic retrograde cholangiopancreatography (ERCP)[125] has both diagnostic and therapeutic value for visualisation and extraction of the impacted stones. Finally, magnetic resonance cholangiopancreatography (MRCP) has been used for diagnosing choledocholithiasis.

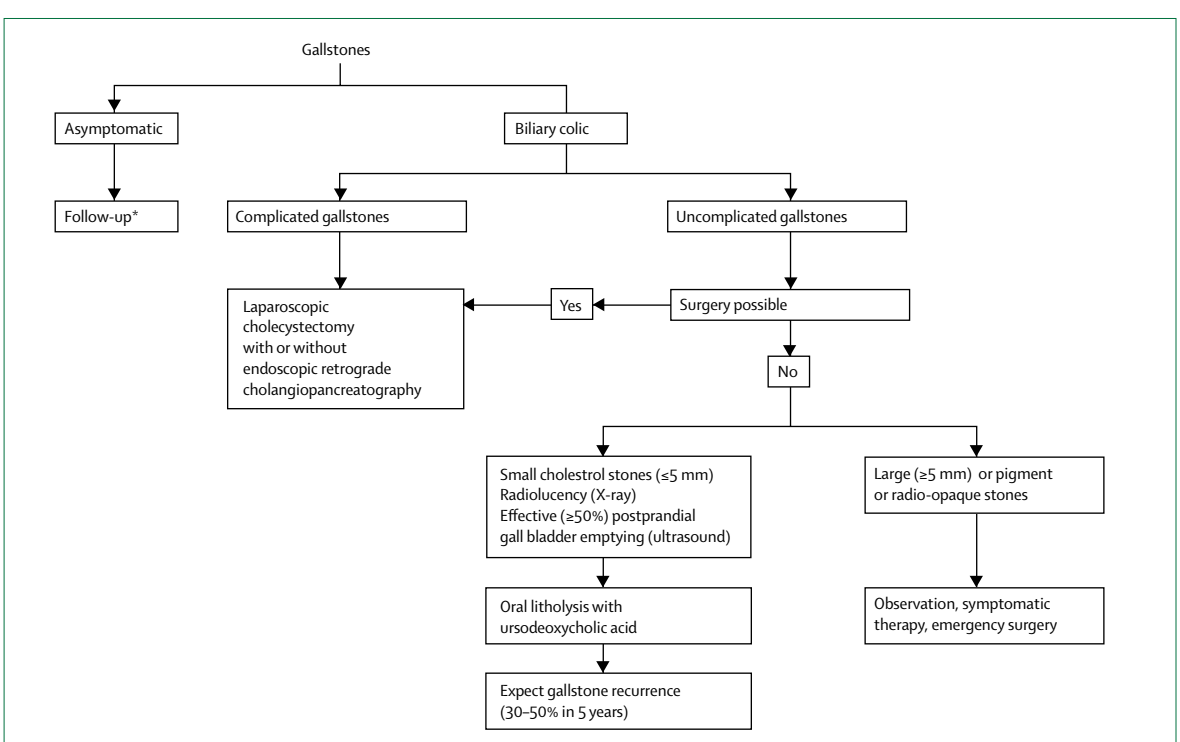

***Figure 5*: Algorithm for the management of cholesterol gallstone disease**
*See the text for exceptions.

The accuracy of MRCP is similar to ERCP. However, MRCP is not available in all medical centres and does not provide the therapeutic option of ERCP for the endoscopical extraction of stones.[126] MRCP might play a role in the preoperative screening of patients undergoing laparoscopic cholecystectomy for gallstones, in whom choledocholithiasis is suspected. In this situation some surgeons prefer laparoscopic cholecystectomy and ERCP.

Therapeutic guidelines

Treatment of asymptomatic gallstone patients is not routinely recommended, because of the overall low risk of biliary colic, complications, and gallbladder cancer.[20,110,127] However, prophylactic cholecystectomy includes patients at high risk of becoming symptomatic, such as children[128] (for their long-term exposure to the physical presence of stones) or gallstone patients undergoing surgery for morbid obesity[129] (who are likely to become symptomatic during rapid weight loss). Prophylactic cholecystectomy should also be offered to patients with increased risk for gallbladder cancer, such as patients with large stones[130] (≥3 cm in diameter) or a "porcelain" gallbladder,[131] or Native Americans with gallstones, whose risk of cancer is 3–5%.[132] Prophylactic cholecystectomy has also been proposed in patients with small gallstones (≤5 mm in size) and associated gallbladder dysmotility, conditions that increase the risk of pancreatitis.[133] Although small gallstones, sludge, and microlithiasis are definitively major aetiological factors for acute pancreatitis,[134,135] prospective studies are needed to evaluate costs and risk-related benefits of prophylactic cholecystectomy, since no data exist for incidence and occurrence of pancreatitis in patients with small gallstone.

Symptomatic gallstone patients, by contrast, do need treatment. Apart from the analgesic therapy of biliary colic, further steps include the medical or surgical option, or both together. Most patients with symptomatic gallbladder stones are treated by elective laparoscopic cholecystectomy, which provides a permanent "cure" for nearly all individuals. The US National Institutes of Health consensus conference concluded that laparoscopic cholecystectomy is safe and cost effective compared with open cholecystectomy.[7] Results of case control studies have indicated that cholecystectomy could increase the risk for colon cancer in the long term; putative mechanisms include changes in bile flow and biliary lipid composition. A large retrospective study comparing a cholecystectomy group with a control cohort has better addressed this important issue.[136] Despite a non-causal short-term (2 years) significant elevation of rates of cancers of the colon, pancreas, liver, and stomach after cholecystectomy, there was no long-term increase of such neoplasms (including colon cancer). Further epidemiological studies are needed to clarify this critical issue.

Of the non-surgical therapeutic approaches for cholesterol gallstone disease, the "contact" method for stone dissolution by methyl tert-butyl ether through percutaneous puncture of the gallbladder or extracorporeal shockwave lithotripsy have been abandoned.[14,137–139] Oral litholysis with ursodeoxycholic acid might still be appropriate for a subset of patients who do not want or are unfit for surgery, with small (≤5 mm in size) radiolucent cholesterol stones in a functioning gallbladder.[140] Ursodeoxycholic acid could prevent gallstone formation in obese patients during rapid weight loss,[141] but it is debatable whether ursodeoxycholic acid would also decrease the incidence of biliary symptoms in gallstone patients awaiting elective cholecystectomy.[118,142] Gallstone recurrence after medical treatment together with cost-benefit analysis are the main reasons why laparoscopic cholecystectomy has become the standard treatment of symptomatic gallbladder stones today.

Conclusions

Cholesterol gallstone disease is a prevalent and costly disease. It has emerged as a complex disorder, involving the liver, gallbladder, and intestine. Studies in mouse models has helped identify several genes underlying susceptibility to cholesterol gallstones. In spite of numerous well-defined risk factors for cholesterol gallstones, genetic determinants in humans remain unclear. The growing global epidemic of obesity and metabolic syndrome will probably increase rates of gallstone disease worldwide.

Conflict of interest statement

We declare that we have no conflict of interest.

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