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Review

Gallstone disease: From genes to evidence-based therapy☆

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The number of gallstone patients is increasing in ageing populations with a high prevalence of metabolic syndrome and obesity. Recently variants of hepatic ATP binding cassette transporters have been identified as genetic susceptibility factors for gallstone disease, pointing to novel means for risk assessment and prevention. Although laparoscopic cholecystectomy is the mainstay of therapy for symptomatic gallbladder stones, the clinical management of gallstone disease is changing rapidly, with an increase in day case surgery and the advent of transluminal endoscopic surgery. Here, we summarize the molecular and genetic mechanisms of gallstone formation as well as the current evidence-based algorithms for diagnosis and therapy of gallbladder and bile duct stones.

***Keywords*: ABC transporter; Association study; Bile duct stone; Cholelithiasis; Cholecystectomy; Gallbladder stone; Gallstone formation; Polymorphism; Prevention**

1. Introduction

In Europe, 10–20% of the population carry gallbladder stones [1,2]. Many gallstones are silent, but symptoms and severe complications ensue in more than 40% of patients above the age of 40 years, necessitating laparoscopic cholecystectomy [2]. In a recent study from Germany [2], the highest prevalence rate of gallstones was observed in women between 70 and 79 years of age: 57% had either a history of cholecystectomy or current sonographic evidence for gallstones. The prevalence of cholelithiasis is even higher in most Hispanic populations of Central and South America, and in American Hispanics with Native American ancestry [3–6]. Native populations from North and South America represent the groups at highest risk in the world. In these populations, gallstone disease appears earlier in life [4,7], reaching prevalence rates at the age of 50 years over 50% and 70% in male and women, respectively [6,8,9]. Overall, gallstone disease represents a serious burden for our healthcare systems: Each year, an estimated 700,000 cholecystectomies are performed in the US, more than 190,000 in Germany, and more than 40,000 in Chile [1,10,11].

2. Molecular mechanisms

2.1. Cholesterol stones

Gallstones are classified as cholesterol and pigment stones. More than 90% of gallstones consist mainly of cholesterol and are formed within the gallbladder [12]. Cholesterol stones form mainly if bile contains more cholesterol than can be solubilized by mixed micelles of bile salts and phosphatidylcholine (lecithin). Additional factors such as biliary mucin and impaired

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Abbreviations: ABC, ATP-binding cassette; ERC, endoscopic retrograde cholangiography; ESWL, extracorporeal shock-wave lithotripsy; FXR, farneosid X receptor; GT, glutamyltransferase; MRC, magnetic resonance cholangiography; RCT, randomised controlled trial; UDCA, ursodeoxycholic acid.

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gallbladder motility allow cholesterol microcrystals to be retained and to grow into macroscopic gallstones [13,14]. Whether gallbladder hypomotility is a primary defect or secondary to excess cholesterol accumulation in gallbladder smooth muscle is debatable [14]. Recent studies in mouse models [15] indicate that cholesterol monohydrate crystals induce expression of inflammatory cytokines in a T-cell-dependent fashion. There appears to be a link between gallstones and intestinal hypomotility, since gallstone patients display slower intestinal transit [16], thereby increasing bacterial formation of the secondary bile salt deoxycholate in the colon, which in turn, increases biliary cholesterol secretion and saturation [17].

In principle, cholesterol supersaturation of gallbladder bile can result from hepatic hypersecretion of cholesterol, or from hyposecretion of bile salts or lecithin. The open question as to which defect might be primary in gallstone pathogenesis has driven genetic studies in animal models [18–20] and, more recently, in humans. A large study within the framework of the Swedish Twin Registry provided conclusive evidence for a role of genetic factors in gallstone pathogenesis [21]. Based on data from 43,141 twin pairs, concordance rates were significantly higher in monozygotic compared with dizygotic twins, and we calculated that genetic factors accounted for 25% (95% confidence interval 9–40%) of the phenotypic variation among the twins [21]. A similar analysis in 358 families in Wisconsin, each of which contained at least two obese siblings, determined that the heritability of symptomatic gallstones is $29 \pm 14\%$ [22], which is similar to the figure obtained in the Swedish twin study.

Data from several large epidemiological studies in the US, Europe, China and Japan implicate chronic overnutrition with refined carbohydrates and triglycerides as well as depletion of dietary fiber as environmental risk factors for cholesterol gallstones [23]. Hence, gallstone disease is likely to result from the complex interaction of genetic factors, high-carbohydrate, high-fat and low-fiber diets [24–28], and other not fully defined environmental factors including scarce [2,29,30] and postmenopausal estrogen therapy [31]. This hypothesis is supported by the profound increases of cholesterol gallstone prevalence rates in Native Americans, post-war European countries and current urban centers in East Asia, all of which are associated with the introduction of high-caloric "Westernized" diets [23]. Similar to atherosclerosis, the risk of cholesterol gallstone disease increases with obesity, type 2 diabetes, insulin resistance and dyslipidaemia (hypertriglyceridaemia and low-serum HDL cholesterol levels) [14]. These conditions are associated with the metabolic syndrome, of which cholesterol gallstone disease is deemed to be yet another "fellow traveller" [32,33].

In spite of a large number of candidate gallstone genes identified in mouse models, common genetic factors that contribute to gallstone formation in humans have remained elusive until now [34]. Recently, the first genome wide association study in a large cohort of gallstone patients from Germany [35] and a linkage study in affected sib pairs [36] identified a common variant (p.D19H) of the hepato-canalicular cholesterol transporter *ABCG5/ABG8* as genetic risk factor for gallstones. Of note, this variant was also a susceptibility factor for gallstones in Chilean Hispanics [35]. Hepatocytes express specific transport proteins for biliary lipids – known as ATP-binding cassette (ABC) transporters – at the canalicular membrane domain. The ABCB11 transporter is the bile salt export pump, ABCB4 is the transporter for phosphatidylcholine, and ABCG5/ABCG8 form obligate heterodimers for biliary cholesterol secretion [37]. The p.D19H variant confers odds ratios of 2–3 and 7 for heterozygous and homozygous carriers, respectively, and 8–11% of the total gallstone risk can be attributed to this variant [35,36]. These studies identify the first common susceptibility factor for cholesterol gallstones in humans. Carriers of the lithogenic *ABCG8* variant 19H display lower serum plant sterol levels (sitosterol, lathosterol) and higher levels of cholesterol precursors (cholesterol, lathosterol) [38,39], indicating decreased cholesterol absorption and a reciprocally increased cholesterol biosynthesis. This might be clinically relevant, since we would predict that HMG-CoA reductase inhibitors could be particularly effective in lowering serum cholesterol concentrations [40] and biliary cholesterol levels in patients carrying the *ABCG8* 19H variant. Of note, a genome wide scan in experimental crosses of inbred strains identified the orthologous mouse gene as gallstone susceptibility gene [41], demonstrating that identical genes affect gallstone formation in both mice and men.

Since only 10% of the total gallstone risk is due to the *ABCG8* 19H variant, other genetic factors have yet to be discovered. Evidence for a single gene defect that causes gallstone formation in a defined subgroup – young patients with a recurring form of cholelithiasis – was provided by Rosmorduc et al. [42]. The group performed a mutation search in the *ABCB4* gene in patients with cholesterol gallbladder stones and intrahepatic sludge or microlithiasis, recurrence of biliary symptoms after cholecystectomy, positive family history, and mild chronic cholestasis and/or intrahepatic cholestasis of pregnancy; point mutations were identified in 18 out of 32 patients (56%) [42]. These findings are clinically relevant, since asymptomatic carriers might benefit from prevention with ursodeoxycholic acid (UDCA) [42]. Hence, genetic testing for *ABCB4* mutations may already be useful in young patients (onset of symptoms <40 years) with a positive family history, cholesterol gallbladder stones and intrahepatic sludge or microlithiasis, or recurrence of biliary symptoms after cholecystectomy [42], albeit the diverse spectrum of mutations makes the analysis laborious. The pathophysiological