Epidemiology and natural history of common bile duct stones and prediction of disease

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Gallstones are extremely common in Western societies. Approximately l5% of Americans have gallstones, and approximately 650,000 to 700,000 cholecystectomies are performed every year.[1]. More than 98% of all biliary tract disorders are in some way related to gallstones. Symptoms and complications related to gallstones are among the most costly digestive disorders, at an estimated annual cost of almost $6.5 billion, exceeding the combined total for chronic liver disease and cirrhosis ($1.6 billion), chronic hepatitis C ($0.8 billion) and diseases of the pancreas ($2.2 billion).[2] Stones are most commonly found in the gallbladder, but gallstones can pass through the cystic duct to become intrahepatic or extrahepatic bile duct stones. Ten to fifteen percent of people with gallbladder stones will harbor concomitant common bile duct stones. In some situations, bile duct stones can develop as primary intrahepatic or extrahepatic stones without involving the gallbladder. Primary bile duct concretions are much more common in patients of Asian descent compared with those of European descent. In Western societies, gallstones are composed primarily of cholesterol.

EPIDEMIOLOGY OF CHOLESTEROL GALLSTONES

The epidemiology of cholesterol gallstones has been examined in multiple studies. Risk factors for gallstones include behavioral factors such as nutrition, obesity, weight loss, and physical activity as well as biologic factors such as increasing age, female sex, race, and serum lipid levels.

Race and genetic factors

The risk of cholesterol gallstones differs markedly by race, even after adjusting for other risk factors such as weight, diet, physical activity, and serum lipid levels.[1] Genetic factors are believed to account for much of this ethnic difference. The prevalence of gallstones is much higher in Native Americans, Chileans, and Hispanics than in age-matched white control subjects. For example, in Chile, the prevalence of gallstones is highest in persons of pure Native American ancestry.[3] The risk is intermediate in those of mixed Native American and Hispanic descent, and lowest in those with neither Native American nor Hispanic blood. In contrast, African Americans have a lower prevalence of gallstones than whites. In mice, the Lith1 and Lith2 genes have been associated with gallstone formation.[4] However, no human genes have been identified to date that are definitively linked to gallstones. Polymorphisms in the apolipoprotein E gene have been associated with gallstones in some populations, but this relationship is controversial.[5]

Female sex and pregnancy

The risk of gallstones is higher in women than in men at all ages, but the difference in risk is more pronounced at younger ages. Hormonal factors are felt to be largely responsible for this association. Much of the increased risk in young women is probably related to pregnancy and childbearing. The prevalence of gallstones increases with increasing parity. During pregnancy itself, gallstones form in 1% to 3% of women, and biliary sludge, a precursor to gallstones, forms in up to 30%.[6,7] Increased levels of serum estrogens during pregnancy promote secretion of bile supersaturated in cholesterol, whereas increased serum levels of progesterone may lead to gallbladder stasis, an additional risk factor for gallstone formation.[8]

Age

In all racial and ethnic groups studied, the risk of gallstones increases markedly with age. For example, gallbladder disease is found in 5% to 8% of young women but in 25% to 30% of women over the age of 50.[9] In men, the prevalence also increases with age, but the increase in risk begins later in life.[10]

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 0016-5107/2002/$35.00 + 0 **37/0/129005**

doi:10.1067/mge.2002.129005

Obesity, weight loss, and physical activity

Obesity is a strong risk factor for gallstones. The prevalence of gallstones increases steadily with increasing body mass index, and gallstones are found in up to 35% of women with a body mass index over 32 kg/m^2.[11] In the obese, excess amounts of cholesterol are secreted into bile, overwhelming the cholesterol-carrying capacity of bile.[12] Paradoxically, rapid weight loss is also a strong risk factor for gallstone formation.[13,14] Up to 25% of patients rapidly losing weight will eventually develop symptomatic gallstones and require cholecystectomy. The risk of gallstone formation is high regardless of the weight loss method. Thus, gallstone formation is common with either surgical weight loss procedures or caloric restriction. Weight fluctuation is an additional risk factor for gallstones.[15]

Other factors related to obesity and weight loss, including physical activity and diet, have also been studied as risk factors for gallstones. Increasing levels of both recreational and vigorous physical activity have been shown to reduce the risk of symptomatic gallstones and need for cholecystectomy, even after controlling for absolute weight and weight loss.[16,17] Dietary composition has not been clearly linked to gallstone formation.

Serum lipid levels

Because gallstones in Western countries are predominantly cholesterol, differences in serum levels of cholesterol and its metabolism have been studied as risk factors for gallstones. However, studies of this question have reached conflicting results. Most studies show that HDL cholesterol levels are inversely associated with gallstones, whereas serum triglyceride levels are positively associated with gallstones.[18,19] Total and LDL cholesterol levels appear to be associated with gallstones only weakly, if at all.[20]

Drugs and bacterial infection

Drugs such as ceftriaxone are secreted into bile and may precipitate with calcium, to form stones.[21] Other compounds, such as octreotide, may induce gallbladder stasis and increase cholesterol secretion in bile.[22] The role of biliary tract infection in gallstone pathogenesis is receiving renewed interest. Traditionally, bacterial infection was believed to be important only in the pathogenesis of mixed pigment (brown) stones. More recently, by using molecular genetic techniques, bacteria have been found in both mixed and pure (>90%) cholesterol stones, leading some to believe that bacteria may be important in cholesterol stone formation as well.[23] For example, the initial factor in brown pigment stone formation may be bacterial infection and subsequent bilirubin deconjugation. However, after initiation of the stone forming process, bile composition may change, with eventual formation of mixed or even pure cholesterol stones. Similarly, stones may act as foreign bodies and enhance bacterial colonization, resulting in precipitation of bilirubinate salts or remodeling of the existing stones.[24]

Natural history of gallstones

The majority of patients (60%-80%) with gallstones are asymptomatic.[9] In these patients, the reasons why symptoms develop are unknown. However, the risk of asymptomatic stones progressing to development of symptoms and complications is relatively small. Once gallstones start to cause biliary-specific symptoms, the risk of ongoing problems is high.

Previous studies following over 1307 patients with gallstones for up to 20 years have shown that 50% of patients remain asymptomatic, 30% have biliary colic develop, and 20% have further complications develop.[25,26] However, the patients in these studies, although asymptomatic at the time of entry to the follow-up study, had previously been hospitalized for symptoms related to gallbladder disease. In contrast, Gracie and Ransohoff[27] followed a cohort of 123 asymptomatic persons with gallstones for between 11 and 24 years. New-onset biliary colic developed at a rate of 2% per year for the first 5 years, but the cumulative incidence over time plateaued. The overall incidence of new biliary colic was 15% at 10 years and 18% at 15 and 20 years. Three patients (2%) had complications develop, all preceded by repeated attacks of biliary colic, and subsequently underwent uncomplicated cholecystectomy. No deaths related to gallbladder disease were reported. Similarly, the Italian Rome Group for Epidemiology and Prevention of Cholelithiasis study followed 161 patients with gallstones.[28] For initially asymptomatic patients, biliary colic developed in 11.9% at 2 years, 16.5% at 4 years, and 25.8% at 10 years. After 10 years, 3% of those who were initially asymptomatic had complications such as cholecystitis, pancreatitis, and biliary obstruction develop. One patient had an adenocarcinoma of the gallbladder develop.

A 20-year population-based survey of mortality in Pima Indians with and without gallstones has been reported.[29] The overall age- and sex-adjusted death rate was higher in those with a history of gallstones, with a ratio of 1.9. The death rate attributed to malignancies was 6.6 times higher in those with gallstones. Of the 20 fatal malignancies in patients with gallstones, 11 were cancers of the GI tract, of which six were malignancies of the gallbladder or bile ducts.

Once an episode of biliary colic has occurred, there is a high risk of repeated attacks of pain. Cohort studies following symptomatic gallstone patients indicate that 58% to 72% of patients have ongoing symptoms and complications.[25,30] More than 90% of complications, such as cholecystitis, cholangitis, and pancreatitis, are preceded by attacks of pain. The most serious complications are gangrene and perforation of the gallbladder, occurring in about 10% of cases of acute cholecystitis.

Choledocholithiasis

Choledocholithiasis, or stones in the common bile duct, can be classified as primary, forming initially in the bile ducts, or secondary, originating in the gallbladder and passing into the bile ducts. In Western countries, bile duct stones are most commonly secondary, and bile duct stones are found in 8% to 18% of patients with symptomatic gallstones. Co-existent gallbladder and common duct stones are correlated with increasing age, Asian descent, chronic inflammatory conditions (primary sclerosing cholangitis, acquired immunodeficiency syndrome, parasites), and possibly hypothyroidism.

Primary bile duct stones can also form, but their incidence in Western countries is low. Primary bile duct stones tend to be higher in bilirubin content, and lower in cholesterol content, than secondary stones. The pathogenesis of primary bile duct stones likely differs from that of secondary bile duct stones. Previous studies have implicated bacterial infection and biliary stasis as important factors in formation of primary duct stones.[31] Bacteria have been found in mixed pigment stones, and bile infection appears to precede stone formation.[32] Parasitic infection has also been associated with primary duct stones, primarily in Asia.

Primary intrahepatic stones, seen primarily in Southeast Asian countries, can lead to the syndrome of recurrent pyogenic cholangitis.[33] Primary intrahepatic stones are generally calcium bilirubinate or mixed stones, and contain less bilirubin and more cholesterol than pigment stones in the extrahepatic bile ducts. The pathogenesis of these stones is complex, and likely involves a combination of bile infection, malnutrition or dietary factors, biliary stasis, and possibly parasitic infestation. Hydrolysis of bilirubin by bacterial β-glucuronidase leads to formation of unconjugated bilirubin, which can precipitate as calcium bilirubinate. The β-glucuronidase enzyme often originates from *Escherichia coli* or other bacteria in the biliary tree. β-Glucuronidase can be inhibited by glucarolactone, whose levels are increased in patients with a low-protein and low-fat diet. It has therefore been suggested that dietary factors contribute to formation of intrahepatic stones. The role of infection by parasites such as *Ascaris lumbricoides* or *Clonorchis sinensis* has been controversial. Although these parasites are geographically widespread, primary intrahepatic stones are found primarily in southeast Asia. This suggests that factors in addition to parasitic infection are needed for these stones to form.

The natural history of secondary choledocholithiasis is not well defined, but complications appear to be more frequent and severe than with asymptomatic gallbladder stones. Secondary choledocholithiasis may be asymptomatic or associated with symptoms and complications similar to those seen with gallbladder stones. Bile duct stones may be discovered incidentally in the evaluation of suspected gallstones. Patients may become jaundiced with persistent obstruction; however, the biliary obstruction is usually incomplete.

Choledocholithiasis may also present with acute cholangitis, pancreatitis, or less commonly with hepatic abscesses. Common bile duct stones are covered by a biofilm of bacteria. The sessile adherent bacteria reside in a sealed off microenvironment and are quiescent. When the stone obstructs the bile duct or ampulla of Vater, cytokines of epithelial cell origin activate these bacteria to the planktonic and virulent forms. Obstruction by stones is often accompanied by bacterial sepsis because of the activation of the bacterial biofilm on stones. Malignant obstruction without stones is much less likely to result in sepsis. In patients with acute pancreatitis who also harbor gallbladder stones, the prevalence of common bile duct stones has been reported to be as high as 78% in those requiring urgent surgery. The majority of stones will pass spontaneously into the duodenum in a matter of hours, however.

With prolonged biliary obstruction, secondary biliary cirrhosis and portal hypertension may develop. The likelihood of developing cirrhosis depends on the duration and extent of obstruction. However, the average time for choledocholithiasis to lead to secondary biliary cirrhosis is approximately 5 years.[34] Thus, once discovered, common bile duct stones should be removed either endoscopically or surgically to prevent development of these complications. Even if the patient has cirrhosis, every effort should be made to relieve the obstruction because reversal of portal hypertension and secondary biliary cirrhosis may be possible.[35,36]

Predictors of choledocholithiasis

Several risk factors, including clinical, biochemical, and imaging variables, can help predict the presence of common bile duct stones.[37-39] Clinically, increasing age or a history of fever, cholangitis, or pancreatitis are risk factors for choledocholithiasis. Elevations of serum bilirubin, aspartate aminotransferase, or alkaline phosphatase are also independent positive predictors. However, US is not a sensitive or specific diagnostic tool for the presence or absence of common duct stones. A dilated common bile duct on US is a useful predictor.[37] Statistical models incorporating a combination of clinical, laboratory, and imaging variables are more accurate in predicting bile duct stones than any individual risk factor. Other imaging techniques, such as magnetic resonance cholangiography, CT cholangiography, or EUS, have been developed to detect common bile duct stones more accurately without the additional risks of ERCP.[40-42] In a patient with gallbladder stones being evaluated for elective cholecystectomy, or in a patient with known gallbladder stones presenting with acute pancreatitis, when and how the common bile duct should be imaged and the timing of therapeutic intervention remain areas of active investigation and are covered in detail in the next 4 articles in this supplement.

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