Gallstones: Epidemiology, risk factors and prevention

AUTHORS: Nezam H Afdhal, MD, FRCPI, Salam F Zakko, MD, FACP, AGAF
SECTION EDITOR: Sanjiv Chopra, MD, MACP
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Sep 12, 2022.**

INTRODUCTION

Gallstones are highly prevalent and the majority are asymptomatic. However, symptoms due to gallstone disease are a leading gastrointestinal cause for hospitalization and health care utilization [1]. This topic will review the epidemiology, risk factors, and strategies for prevention of gallstones. The clinical presentation, diagnosis and management of gallstone disease are discussed in detail separately. (See "Overview of gallstone disease in adults" and "Approach to the management of gallstones".)

EPIDEMIOLOGY

Type and composition — Gallstones are composed of a mixture of cholesterol, calcium salts of bilirubinate or palmitate, proteins, and mucin. Based upon the predominant constituents, gallstones are broadly classified into the following (picture 1):

- **Cholesterol stones** – Cholesterol stones usually form in individuals with a genetic or environmental predisposition to bile that is supersaturated with cholesterol. Most "cholesterol" stones have a mixed composition with small amounts of calcium palmitate and bilirubinate salts.

- **Black pigment stones** – Black pigment stones result from hemolysis and consist primarily of calcium bilirubinate.

- **Brown pigment stones** – Brown pigment stones are associated with a bacterial infection or parasitic infestation of the biliary system. They are also often found in the bile ducts in association with prior biliary manipulation. They may also occur as de novo common bile duct stones following cholecystectomy.

Gallstones in an individual are usually homogeneous in composition.

Prevalence

- **Overall prevalence** – Gallstones are exceedingly rare in children except in the presence of hemolytic states. Prevalence of gallstone disease increases with age in both sexes, reaching a plateau after 50 and 60 years of age in females and males, respectively [2,3].

  The prevalence of cholelithiasis varies widely by geographic region and appears to be higher in White and Native American populations as compared with Eastern European, African American, and Japanese populations (table 1) [4-20]. The variation in the prevalence of gallstones may be attributable to both genetic and dietary factors.

  In North America, Native Americans appear to have high prevalence of cholelithiasis and gallbladder disease. As an example, in one study that includes 596 Pima Indians, 290 (49 percent) had gallstone disease. Gallstone disease was more prevalent in females as compared with males with a peak prevalence of 73 percent in females between the ages of 25 and 34 years [10]. Similar high rates have been found in multiple other Native American populations [11,12,21].

  In the United States, it is estimated that 6.3 million males and 14.2 million females aged 20 to 74 have gallstones or have undergone cholecystectomy for gallbladder disease [2]. These estimates were based upon a representative sample of more than 14,000 persons aged 20 to 74 who underwent abdominal ultrasonography to detect gallstones or had a history of cholecystectomy. Prevalence rates varied by ethnicity with the highest rates in Mexican American males and females (8.9 and 26.7 percent, respectively) and were lowest rates in non-Hispanic White American males and females (8.6 and 16.6 percent, respectively).

- **Prevalence by gallstone composition** – The prevalence of pigment stones is dependent primarily upon the frequency of hemolytic disorders. In industrialized countries, cholesterol gallstones account for approximately 75 percent of stones, black pigment stones for 20 percent, and brown pigment stones for 5 percent [15,22-25].

RISK FACTORS

Age and female sex — Increasing age and female sex are important risk factors for gallstones. The prevalence of gallstones is higher in females as compared with males in all age groups [9,10,15]. However, the differences in prevalence between females and males are greater in younger as compared with older adults. In a large cohort study of 46,139 individuals of whom 29,739 underwent abdominal ultrasound, the prevalence of gallstone disease was two to three times greater for females as compared with males prior to age 50 but less than twice the rate at ages over 50 years [15,26]. (See 'Epidemiology' above.)

Genetic susceptibility — Family history studies suggest that genetics has a significant role in the development of gallstones [27]. In one such study of 105 patients with gallstones using ultrasonography; cholelithiasis was found in 51 of 330 (15.5%) first-degree relatives, as compared to 12 of 330 (3.6%) of matched controls [28]. The risk of gallstones was higher in female relatives. Twin studies suggest that approximately 25 percent of the risk of gallstone disease is determined by an underlying genetic predisposition [29]. Mutations in the hepatic cholesterol transporter *ABCG8* confers most of the genetic risk of developing gallstones [30].

Pregnancy — Pregnancy is a risk factor for the development of cholesterol gallstones. Pregnancy is associated with both a qualitative change in bile composition and delayed gallbladder emptying, both of which promote stone formation. The risk increases with the frequency and number of pregnancies. (See "Gallstone diseases in pregnancy", section on 'Pathophysiology'.)

Diabetes mellitus — Diabetes mellitus is associated with an increased risk of cholesterol gallstones. As an example, a case control study compared 336 patients who had gallstones or had undergone cholecystectomy with 336 controls [31]. Diabetes mellitus was more prevalent in the patients with gallbladder disease (11.6 versus 4.8 percent). In another case control study, an increased prevalence of gallstones in diabetes could only be demonstrated in females (42 versus 26 percent in nondiabetic females) [32].

How diabetes mellitus predisposes to gallstones is not well understood. Hepatic insulin resistance appears to be important [33,34]. Other contributing factors may be hypertriglyceridemia and autonomic neuropathy leading to biliary stasis due to gallbladder hypomotility [35].

Dyslipidemia — Elevated non-high density lipoprotein (HDL) cholesterol may be a risk factor for gallstones. In a 2016 meta-analysis that included 2848 individuals with no gallstones at baseline, the cumulative incidence of gallstones after a mean follow-up of 12 years was 0.6

percent per year [36]. Non-HDL cholesterol was associated with an increased risk of gallstones (adjusted OR 1.2, 95%CI 1.07-1.32), however, there was significant statistical heterogeneity in the studies included. HDL cholesterol and triglyceride levels were not associated with the risk of gallstones in the meta-analysis.

Diet and lifestyle factors

Obesity — Obesity is an established risk factor for the development of cholesterol gallstones, presumably due to enhanced cholesterol synthesis and secretion (figure 1) [37-40]. The risk is particularly high in females, in those with Class 3 (morbid) obesity, and in younger age groups in which a threefold increase in risk has been reported [16,26,40-43]. Obesity is also associated with an increase in risk of symptomatic gallstones [43,44].

Rapid weight loss — High rates of gallstone formation have also been associated with rapid weight loss in patients on very low calorie diets (diets containing less than 800 kcal per day) or after gastric bypass [45-47]. In observational studies, gallstones have been reported a mean of 7.5 years after surgery [48]. (See "Bariatric operations: Late complications with subacute presentations".)

The mechanism by which this occurs is incompletely understood. One report evaluated changes in gallbladder bile during periods of weight loss [49]. Bile mucin content increased 18-fold and bile calcium concentration rose 40 percent. These factors may promote cholesterol nucleation and stone formation. In contrast to the general population in which the great majority of gallstones are asymptomatic, persons with weight-loss-related cholelithiasis are more likely to be symptomatic [43].

Medications — Several drugs can promote the formation of gallstones.

- **Fibrates** – The use of fibrates has been associated with an increase in lithogenicity of bile and increase in the risk of gallstones. Fibrates reduce bile acid secretion by inhibiting the rate limiting enzyme in bile acid synthesis, cholesterol 7-alpha-hydroxylase; this results in cholesterol supersaturated bile and stone precipitation [50]. In an observational study of 659 dyslipidemic patients treated with bezafibrate and ezetimibe, gallstones developed in 4 (0.6 percent) at 12 months [51]. In a population study that included 5466 individuals, the use of a fibrate (primarily fenofibrate) was an independently associated with an increased risk of gallstone formation (adjusted relative risk 1.7; 95% CI 1-2.7) [52].

- Ceftriaxone – Ceftriaxone can cause biliary sludge. Cholelithiasis has been reported with prolonged use (three weeks) at high doses. Biliary excretion accounts for up to 40 percent of ceftriaxone elimination and drug concentrations in bile can reach 200 times that of the

serum [53,54]. When supersaturated, ceftriaxone complexes with calcium and precipitates out of bile. This process is probably potentiated in intensive care unit patients who are not fed enterally and have bile stasis.

- **Somatostatin analogues** – Long-term administration of the somatostatin analogues in the treatment of acromegaly has been associated with gallstones [55-57]. Up to 25 percent of patients develop asymptomatic cholesterol gallstones or sludge during the first 18 months of therapy with octreotide [56,57]. Somatostatin use predisposes to gallstone formation by prolonging intestinal transit, impairing gallbladder emptying via reduced cholecystokinin release, and by inducing lithogenic changes in bile. (See "Treatment of acromegaly".)

- **Hormone replacement** – Estrogen therapy is associated with higher rates of gallstones and gallbladder disease. These associations have been noted both in females on menopausal hormone therapy and in men receiving estrogen therapy [58,59]. The risk of gallstones and gallstone disease in females on menopausal hormone therapy is discussed in detail separately. (See "Menopausal hormone therapy: Benefits and risks", section on 'Gallbladder disease'.)

- **Oral contraceptive** – Oral contraceptives have only a transient effect on gallstone formation. Females under the age of 40 years and those taking high-dose estrogen (>50 mcg) preparations have the greatest added risk [60,61]. In support of this hypothesis, a case control study found a slightly higher incidence of gallstones shortly after starting oral contraceptives, an effect which disappeared after 10 years [62]. A similar relationship was noted in a meta-analysis of epidemiologic studies [63].

Conditions associated with gallbladder stasis

Prolonged fasting/parenteral nutrition — Gallstones are a frequent complication of prolonged total parenteral nutrition [64,65]. As an example, one study of 84 patients with severe short bowel syndrome treated with total parenteral nutrition found asymptomatic gallstones in 44 percent [65]. Two factors are thought to contribute: biliary stasis due to lack of enteral stimulation; and, in patients with ileal resection, interruption of the enterohepatic circulation of bile acids results in a reduction in hepatic bile acid secretion and an altered composition of hepatic bile, which becomes supersaturated with respect to cholesterol.

Conditions that result in bile stasis are associated with a higher prevalence of gallstones. In the normal state, the gallbladder avidly absorbs water from bile. Thus, if bile remains within the gallbladder for a prolonged period, it can become overly concentrated with cholesterol, thereby

promoting stone formation. Prolonged fasting and the use of total parenteral nutrition both prevent normal enteral stimulation of gallbladder activity [64-66].

Spinal cord injury — Increased risk of gallstone disease in patients with spinal cord injury include decreased gallbladder motility leading to gallbladder stasis, decreased intestinal transit leading to an alteration in the enterohepatic circulation, and metabolic changes leading to abnormal biliary lipid secretion [66,67].

Additional risk factors predominantly for pigment stones

Cirrhosis — Cirrhosis is a risk factor for pigment gallstones. Only a small proportion of patients with cirrhosis have cholesterol stones. The increased risk of gallstone formation in these patients may be due to several factors, including reduced hepatic synthesis and transport of bile salts and nonconjugated bilirubin, high estrogen levels, and impaired gallbladder contraction in response to a meal [68-70]. The increased risk was illustrated in a combined cross-sectional and longitudinal study that included 1010 patients with cirrhosis [71]. The overall prevalence of gallstones was 29.5 percent. During an average follow-up of 50 months, 141 of 618 patients (23 percent) developed gallstones (which is approximately 10 times higher than would be expected in a general population). Multivariate analysis demonstrated that the risk was increased in patients with Child classes B and C cirrhosis (regardless of the cause), and in patients with a high body mass index.

Crohn disease/ileal resection — The prevalence of gallstones is increased in patients with Crohn disease [72-75]. In a population-based study, for example, gallstones were detected in 26 percent of patients with Crohn disease, which was approximately twice as frequent as the general population [72]. Gallstones in patients with ileal Crohn disease (or those who have undergone ileal resection) are frequently pigment based, reflecting an increased concentration of bilirubin conjugates, unconjugated bilirubin, and total calcium in the gallbladder bile due perhaps to altered enterohepatic cycling of bilirubin [73].

Hyperbilirubinemia — Elevations in serum bilirubin levels are associated with the risk of developing gallstones. In a population-based study that included 61,212 subjects, patients with mean bilirubin levels in the highest decile had an increased risk of symptomatic gallstone disease compared with patients who had lower mean bilirubin levels (hazard ratio 1.6, 95% CI 1.3-2.0) [76].

Disorders associated with hemolytic anemias (eg, hereditary spherocytosis, sickle cell disease, thalassemia and erythrocyte enzyme deficiencies) are associated with an increase the risk of gallstones due to increased efflux of bilirubin into bile. An increased risk of pigment stones has also been associated with decreased hepatic conjugation of bilirubin due to genetic variation in

the gene encoding the bilirubin-conjugating enzyme *UGT1A1* [77]. Biliary bilirubin and calcium can combine to form calcium bilirubinate salts, which may grow and become symptomatic as pigment gallstones or act as a nucleating factor for the precipitation of biliary cholesterol and formation of cholesterol stones. (See "Hepatic manifestations of sickle cell disease", section on 'Cholelithiasis' and "Diagnosis of thalassemia (adults and children)", section on 'Jaundice and pigment gallstones' and "Hereditary spherocytosis", section on 'Pigment gallstones'.)

PROTECTIVE FACTORS

Ascorbic acid — Vitamin C supplementation may have a protective effect on gallstones. The benefit of ascorbic acid may be related to its effects on cholesterol catabolism and conversion of cholesterol to bile acids [78]. In a population-based study that included 2129 subjects, the prevalence of gallstones detected by ultrasound was significantly lower in individuals who reported regular use of vitamin C as compared with those who did not (4.7 versus 8.2 percent, respectively) [79].

Dietary factors

- **Poly- and monounsaturated fats and nuts** – Mono- and polyunsaturated fats inhibit cholesterol gallstone formation and may reduce the risk of gallstone disease. In a cohort study of approximately 45,000 male health professionals [80], after 14 years of follow-up, the relative risk for gallstone disease was lower in those in the highest compared with the lowest quintile of polyunsaturated and monounsaturated fat consumption (RR 0.84, 95% CI 0.73-0.96 and 0.83, 95% CI 0.70-1.00), respectively.

  Daily consumption of nuts has been associated with a reduced risk of gallstone disease [81]. It is unclear of this reduction in risk is due to high monounsaturated and polyunsaturated fat content of nuts or due to the effect of other components present in nuts (eg, dietary fiber or vitamin E).

- **Coffee** – Coffee consumption has been associated with a decreased risk of developing gallstones [82,83]. The mechanism of benefit is not precisely known. Coffee has several effects on hepatobiliary processes involved in cholesterol gallstone formation. In a meta-analysis that included 227,749 participants, patients who drank coffee were less likely than those who did not to develop gallstones (relative risk [RR] 0.83; 95% CI 0.76 to 0.89) when prospective studies were examined [84]. There was a dose-response relationship, with the lowest risk seen among patients with the highest levels of coffee consumption (RR 0.75 for participants who consumed six cups per day; 95% CI 0.64-0.88).

- **Vegetable protein** – Limited evidence suggests that vegetable protein intake may be associated with a decrease in the risk of gallbladder disease, however existing studies are conflicting [85-87].

Physical activity — Physical activity is associated with a decreased risk of gallstone formation and symptomatic cholelithiasis. This was illustrated in a prospective cohort study of over 45,000 males, in which 828 subjects developed symptomatic gallstones during eight years of follow-up [88]. The males in the lowest quintile of physical activity had a relative risk of 1.72 between the ages of 40 and 64 and 1.33 above age 64 compared with those in the highest quintile. It was estimated that 34 percent of cases of symptomatic gallstones in males could be prevented by 30 minutes of endurance-type training five times per week.

The benefit of physical activity for the prevention of symptomatic cholelithiasis was also demonstrated in another cohort study that included 60,290 females between the ages of 40 to 65 who were followed for 10 years during which 3257 underwent cholecystectomy [89]. On multivariate analysis, the relative risk for females in the highest compared with the lowest quintile of physical activity was 0.69. In contrast, females who had a sedentary lifestyle were at increased risk of cholecystectomy (relative risk 1.42).

Statins — The effect of statins on decreasing the risk of gallstones has not been consistently demonstrated, however, statin use may reduce the risk of gallstone disease [90,91]. A case-control study compared 27,035 patients with gallstone disease requiring cholecystectomy with 106,531 matched controls [90]. Long-term statin use (>20 prescriptions filled) was associated with a decreased risk of gallstone disease requiring cholecystectomy (adjusted OR 0.64). The protective effect of statins started to be seen after approximately 1 to 1.5 years of statin use.

PREVENTION OF GALLSTONES

Dietary and lifestyle measures — Dietary and lifestyle recommendations to decrease the risk of gallstones aim to maintain ideal weight are in large part similar to recommendations for the general population and include the following (see "Healthy diet in adults"):

- Dietary measures include eating three well-balanced meals per day. Meals should be low in saturated fats and high in fiber and calcium to reduce biliary concentrations of hydrophobic lithogenic bile acids. Regular meal timing decreases the cholesterol saturation of gallbladder bile and reduces gallbladder stasis by promoting gallbladder emptying.

- Weight reduction in overweight and obese individuals to decrease the risk of gallstones but weight loss should be gradual (<1.5 kg per month) to reduce the risk of gallbladder sludge due to stasis. In individuals with rapid weight loss due to a very low calorie diet or following bariatric surgery, fat intake should be no lower than 7 to 10 grams per day to ensure good gallbladder contraction and bile cycling [92].

- Patients receiving total parenteral nutrition (TPN) should be periodically assessed for possible enteral feeding. Biliary sludge may resolve when a normal diet is reinstituted [64,93,94].

- Regular physical activity is important in maintaining a low body weight and may itself prevent gallstone formation. (See 'Physical activity' above.)

Ursodeoxycholic acid in selected patients — We reserve the use of ursodeoxycholic acid to prevent gallstones due to rapid weight loss in patients undergoing gastric bypass surgery without a prophylactic cholecystectomy [46,47,92,95]. Prophylaxis with ursodeoxycholic acid has been shown to be effective at reducing the risk of stone formation during rapid weight loss. In one trial of 1004 patients treated with a very low calorie diet, ultrasonography was performed at baseline and 8 and 16 weeks [47]. The incidence of gallstones was 28 percent in the placebo group compared with 8, 3, and 2 percent of those treated with 300, 600, and 1200 mg per day of ursodeoxycholic acid, respectively. Gallstones have been reported several years after bariatric surgery, but controlled studies on long-term use of ursodeoxycholic acid are lacking [48]. (See "Bariatric surgery: Postoperative and long-term management", section on 'Assessment and management of changes in comorbid diseases' and "Bariatric operations: Late complications with subacute presentations", section on 'Cholelithiasis'.)

Other interventions with unclear role — High doses of rapidly infused crystalline amino acids have been demonstrated to induce secretion of endogenous cholecystokinin and promote gallbladder emptying to prevent stasis in patients on TPN [96]. However, additional studies are needed to determine if these infusions can decrease the risk of gallstone formation.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gallstones".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Gallstones (The Basics)" and "Patient education: Choosing surgery to treat gallstones (The Basics)")
- Beyond the Basics topics (see "Patient education: Gallstones (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Gallstones are composed of a mixture of cholesterol, calcium salts of bilirubinate or palmitate, proteins, and mucin. Based upon the predominant constituents, gallstones are broadly classified into cholesterol, brown pigment, and black pigment stones. (See 'Type and composition' above.)
- The prevalence of cholelithiasis varies widely by geographic region and appears to be higher in White and Native American populations as compared with Eastern European, African American, and Japanese populations. Gallstones are exceedingly rare in children except in the presence of hemolytic states. Prevalence of gallstone disease increased with age in both sexes, reaching a plateau after 50 and 60 years of age in females and males, respectively. (See 'Prevalence' above.)
- Risk factors for gallstones include increasing age, female sex, pregnancy, diabetes mellitus, obesity, rapid weight loss, conditions associated with gallbladder hypomotility, and certain medications (table 2). Approximately 25 percent of the risk of gallstone disease is determined by an underlying genetic predisposition. Important risk factors for pigment stones include cirrhosis, Crohn disease/ileal resection, and hyperbilirubinemia. (See 'Risk factors' above.)

- Physical exercise and dietary factors (eg, ascorbic acid, mono- and polyunsaturated fats, coffee) may decrease the risk of gallstones. (See 'Protective factors' above.)

- Dietary and lifestyle recommendations to decrease the risk of gallstones aim to maintain ideal weight. Weight reduction in overweight and obese individuals should be gradual and patients receiving total parenteral nutrition should be periodically assessed for possible enteral feeding. We reserve the use of ursodeoxycholic acid to prevent gallstones due to rapid weight loss in patients undergoing gastric bypass surgery without a prophylactic cholecystectomy. (See 'Protective factors' above.)

REFERENCES

1. Peery AF, Crockett SD, Barritt AS, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology 2015; 149:1731.
2. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999; 117:632.
3. Aerts R, Penninckx F. The burden of gallstone disease in Europe. Aliment Pharmacol Ther 2003; 18 Suppl 3:49.
4. TORVIK A, HOIVIK B. Gallstones in an autopsy series. Incidence, complications, and correlations with carcinoma of the gallbladder. Acta Chir Scand 1960; 120:168.
5. Zahor A, Sternby NH, Kagan A, et al. Frequency of cholelithiasis in Prague and Malmö. An autopsy study. Scand J Gastroenterol 1974; 9:3.
6. Brett M, Barker DJ. The world distribution of gallstones. Int J Epidemiol 1976; 5:335.
7. Lindström CG. Frequency of gallstone disease in a well-defined Swedish population. A prospective necropsy study in Malmö. Scand J Gastroenterol 1977; 12:341.
8. Heaton KW, Braddon FE, Mountford RA, et al. Symptomatic and silent gall stones in the community. Gut 1991; 32:316.
9. Maurer KR, Everhart JE, Ezzati TM, et al. Prevalence of gallstone disease in Hispanic populations in the United States. Gastroenterology 1989; 96:487.
10. Sampliner RE, Bennett PH, Comess LJ, et al. Gallbladder disease in pima indians. Demonstration of high prevalence and early onset by cholecystography. N Engl J Med 1970; 283:1358.
11. Thistle JL, Eckhart KL Jr, Nensel RE, et al. Prevalence of gallbladder disease among

Chippewa Indians. Mayo Clin Proc 1971; 46:603.

12. Williams CN, Johnston JL, Weldon KL. Prevalence of gallstones and gallbladder disease in Canadian Micmac Indian women. Can Med Assoc J 1977; 117:758.
13. WILBUR RS, BOLT RJ. Incidence of gall bladder disease in normal men. Gastroenterology 1959; 36:251.
14. Williams CN, Johnston JL. Prevalence of gallstones and risk factors in Caucasian women in a rural Canadian community. Can Med Assoc J 1980; 122:664.
15. Attili AF, Carulli N, Roda E, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholelithiasis (M.I.COL.). Am J Epidemiol 1995; 141:158.
16. Barbara L, Sama C, Morselli-Labate AM, et al. A ten year incidence of gallstone disease: The Sirmione study. J Hepatol 1993; 18(Suppl 1):S43.
17. CUNNINGHAM JA, HARDENBERGH FE. Comparative incidence of choletithiasis in the Negro and white races; a study of 6185 autopsies. AMA Arch Intern Med 1956; 97:68.
18. NEWMAN HF, NORTHUP JD. The autopsy incidence of gallstones. Surg Gynecol Obstet 1959; 109:1.
19. Sichieri R, Everhart JE, Roth HP. Low incidence of hospitalization with gallbladder disease among blacks in the United States. Am J Epidemiol 1990; 131:826.
20. Nomura H, Kashiwagi S, Hayashi J, et al. Prevalence of gallstone disease in a general population of Okinawa, Japan. Am J Epidemiol 1988; 128:598.
21. Everhart JE, Yeh F, Lee ET, et al. Prevalence of gallbladder disease in American Indian populations: findings from the Strong Heart Study. Hepatology 2002; 35:1507.
22. Diehl AK. Epidemiology and natural history of gallstone disease. Gastroenterol Clin North Am 1991; 20:1.
23. Attili AF, Capocaccia R, Carulli N, et al. Factors associated with gallstone disease in the MICOL experience. Multicenter Italian Study on Epidemiology of Cholelithiasis. Hepatology 1997; 26:809.
24. Sherlock S, Dooley J. Diseases of the liver and biliary system, Blackwell Science, Oxford 200 2.
25. Trotman BW, Soloway RD. Pigment vs cholesterol cholelithiasis: clinical and epidemiological aspects. Am J Dig Dis 1975; 20:735.
26. The epidemiology of gallstone disease in Rome, Italy. Part I. Prevalence data in men. The Rome Group for Epidemiology and Prevention of Cholelithiasis (GREPCO). Hepatology 1988; 8:904.

27. Gilat T, Feldman C, Halpern Z, et al. An increased familial frequency of gallstones. Gastroenterology 1983; 84:242.
28. Sarin SK, Negi VS, Dewan R, et al. High familial prevalence of gallstones in the first-degree relatives of gallstone patients. Hepatology 1995; 22:138.
29. Katsika D, Grjibovski A, Einarsson C, et al. Genetic and environmental influences on symptomatic gallstone disease: a Swedish study of 43,141 twin pairs. Hepatology 2005; 41:1138.
30. Buch S, Schafmayer C, Völzke H, et al. A genome-wide association scan identifies the hepatic cholesterol transporter ABCG8 as a susceptibility factor for human gallstone disease. Nat Genet 2007; 39:995.
31. De Santis A, Attili AF, Ginanni Corradini S, et al. Gallstones and diabetes: a case-control study in a free-living population sample. Hepatology 1997; 25:787.
32. Chapman BA, Wilson IR, Frampton CM, et al. Prevalence of gallbladder disease in diabetes mellitus. Dig Dis Sci 1996; 41:2222.
33. Ruhl CE, Everhart JE. Association of diabetes, serum insulin, and C-peptide with gallbladder disease. Hepatology 2000; 31:299.
34. Biddinger SB, Haas JT, Yu BB, et al. Hepatic insulin resistance directly promotes formation of cholesterol gallstones. Nat Med 2008; 14:778.
35. Hahm JS, Park JY, Park KG, et al. Gallbladder motility in diabetes mellitus using real time ultrasonography. Am J Gastroenterol 1996; 91:2391.
36. Shabanzadeh DM, Sørensen LT, Jørgensen T. Determinants for gallstone formation - a new data cohort study and a systematic review with meta-analysis. Scand J Gastroenterol 2016; 51:1239.
37. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999; 341:427.
38. Friedman GD, Kannel WB, Dawber TR. The epidemiology of gallbladder disease: observations in the Framingham Study. J Chronic Dis 1966; 19:273.
39. Mabee TM, Meyer P, DenBesten L, Mason EE. The mechanism of increased gallstone formation in obese human subjects. Surgery 1976; 79:460.
40. Stampfer MJ, Maclure KM, Colditz GA, et al. Risk of symptomatic gallstones in women with severe obesity. Am J Clin Nutr 1992; 55:652.
41. Scragg RK, McMichael AJ, Baghurst PA. Diet, alcohol, and relative weight in gall stone disease: a case-control study. Br Med J (Clin Res Ed) 1984; 288:1113.
42. Jørgensen T. Prevalence of gallstones in a Danish population. Am J Epidemiol 1987; 126:912.

43. Amaral JF, Thompson WR. Gallbladder disease in the morbidly obese. Am J Surg 1985; 149:551.
44. Stender S, Nordestgaard BG, Tybjaerg-Hansen A. Elevated body mass index as a causal risk factor for symptomatic gallstone disease: a Mendelian randomization study. Hepatology 2013; 58:2133.
45. Liddle RA, Goldstein RB, Saxton J. Gallstone formation during weight-reduction dieting. Arch Intern Med 1989; 149:1750.
46. Broomfield PH, Chopra R, Sheinbaum RC, et al. Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. N Engl J Med 1988; 319:1567.
47. Shiffman ML, Kaplan GD, Brinkman-Kaplan V, Vickers FF. Prophylaxis against gallstone formation with ursodeoxycholic acid in patients participating in a very-low-calorie diet program. Ann Intern Med 1995; 122:899.
48. Csendes A, Csendes P, Orellana O, et al. Patients Remain at High Risk of Gallstones Development Late (10 y) After Sleeve Gastrectomy? Surg Laparosc Endosc Percutan Tech 2019; 29:451.
49. Shiffman ML, Sugerman HJ, Kellum JM, Moore EW. Changes in gallbladder bile composition following gallstone formation and weight reduction. Gastroenterology 1992; 103:214.
50. Ståhlberg D, Reihnér E, Rudling M, et al. Influence of bezafibrate on hepatic cholesterol metabolism in gallstone patients: reduced activity of cholesterol 7 alpha-hydroxylase. Hepatology 1995; 21:1025.
51. Teramoto T, Abe K, Taneyama T. Safety and efficacy of long-term combination therapy with bezafibrate and ezetimibe in patients with dyslipidemia in the prospective, observational J-COMPATIBLE study. Cardiovasc Diabetol 2013; 12:163.
52. Caroli-Bosc FX, Le Gall P, Pugliese P, et al. Role of fibrates and HMG-CoA reductase inhibitors in gallstone formation: epidemiological study in an unselected population. Dig Dis Sci 2001; 46:540.
53. Arvidsson A, Alván G, Angelin B, et al. Ceftriaxone: renal and biliary excretion and effect on the colon microflora. J Antimicrob Chemother 1982; 10:207.
54. Shiffman ML, Keith FB, Moore EW. Pathogenesis of ceftriaxone-associated biliary sludge. In vitro studies of calcium-ceftriaxone binding and solubility. Gastroenterology 1990; 99:1772.
55. Hussaini SH, Murphy GM, Kennedy C, et al. The role of bile composition and physical chemistry in the pathogenesis of octreotide-associated gallbladder stones. Gastroenterology 1994; 107:1503.

56. Ezzat S, Snyder PJ, Young WF, et al. Octreotide treatment of acromegaly. A randomized, multicenter study. Ann Intern Med 1992; 117:711.
57. Newman CB, Melmed S, Snyder PJ, et al. Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients--a clinical research center study. J Clin Endocrinol Metab 1995; 80:2768.
58. Henriksson P, Einarsson K, Eriksson A, et al. Estrogen-induced gallstone formation in males. Relation to changes in serum and biliary lipids during hormonal treatment of prostatic carcinoma. J Clin Invest 1989; 84:811.
59. Coronary Drug Project Research Group. Gallbladder disease as a side effect of drugs influencing lipid metabolism. Experience in the Coronary Drug Project. N Engl J Med 1977; 296:1185.
60. Strom BL, Tamragouri RN, Morse ML, et al. Oral contraceptives and other risk factors for gallbladder disease. Clin Pharmacol Ther 1986; 39:335.
61. Scragg RK, McMichael AJ, Seamark RF. Oral contraceptives, pregnancy, and endogenous oestrogen in gall stone disease--a case-control study. Br Med J (Clin Res Ed) 1984; 288:1795.
62. Thijs C, Leffers P, Knipschild P. Oral contraceptive use and the occurrence of gallstone disease--a case-control study. Prev Med 1993; 22:122.
63. Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. Am J Public Health 1993; 83:1113.
64. Quigley EM, Marsh MN, Shaffer JL, Markin RS. Hepatobiliary complications of total parenteral nutrition. Gastroenterology 1993; 104:286.
65. Nightingale JM, Lennard-Jones JE, Gertner DJ, et al. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gall stones in patients with a short bowel. Gut 1992; 33:1493.
66. Apstein MD, Dalecki-Chipperfield K. Spinal cord injury is a risk factor for gallstone disease. Gastroenterology 1987; 92:966.
67. Rotter KP, Larraín CG. Gallstones in spinal cord injury (SCI): a late medical complication? Spinal Cord 2003; 41:105.
68. Alvaro D, Angelico M, Gandin C, et al. Physico-chemical factors predisposing to pigment gallstone formation in liver cirrhosis. J Hepatol 1990; 10:228.
69. Stauber RE, Rosenblum E, Eagon PK, et al. The effect of portal-systemic shunting on hepatic sex hormone receptors in male rats. Gastroenterology 1991; 100:168.
70. Acalovschi M, Dumitraşcu DL, Csakany I. Gastric and gall bladder emptying of a mixed meal are not coordinated in liver cirrhosis--a simultaneous sonographic study. Gut 1997; 40:412.

71. Conte D, Fraquelli M, Fornari F, et al. Close relation between cirrhosis and gallstones: cross-sectional and longitudinal survey. Arch Intern Med 1999; 159:49.

72. Lapidus A, Bångstad M, Aström M, Muhrbeck O. The prevalence of gallstone disease in a defined cohort of patients with Crohn's disease. Am J Gastroenterol 1999; 94:1261.

73. Brink MA, Slors JF, Keulemans YC, et al. Enterohepatic cycling of bilirubin: a putative mechanism for pigment gallstone formation in ileal Crohn's disease. Gastroenterology 1999; 116:1420.

74. Fraquelli M, Losco A, Visentin S, et al. Gallstone disease and related risk factors in patients with Crohn disease: analysis of 330 consecutive cases. Arch Intern Med 2001; 161:2201.

75. Parente F, Pastore L, Bargiggia S, et al. Incidence and risk factors for gallstones in patients with inflammatory bowel disease: a large case-control study. Hepatology 2007; 45:1267.

76. Stender S, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Extreme bilirubin levels as a causal risk factor for symptomatic gallstone disease. JAMA Intern Med 2013; 173:1222.

77. Wasmuth HE, Keppeler H, Herrmann U, et al. Coinheritance of Gilbert syndrome-associated UGT1A1 mutation increases gallstone risk in cystic fibrosis. Hepatology 2006; 43:738.

78. Gustafsson U, Wang FH, Axelson M, et al. The effect of vitamin C in high doses on plasma and biliary lipid composition in patients with cholesterol gallstones: prolongation of the nucleation time. Eur J Clin Invest 1997; 27:387.

79. Walcher T, Haenle MM, Kron M, et al. Vitamin C supplement use may protect against gallstones: an observational study on a randomly selected population. BMC Gastroenterol 2009; 9:74.

80. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. The effect of long-term intake of cis unsaturated fats on the risk for gallstone disease in men: a prospective cohort study. Ann Intern Med 2004; 141:514.

81. Tsai CJ, Leitzmann MF, Hu FB, et al. A prospective cohort study of nut consumption and the risk of gallstone disease in men. Am J Epidemiol 2004; 160:961.

82. Leitzmann MF, Willett WC, Rimm EB, et al. A prospective study of coffee consumption and the risk of symptomatic gallstone disease in men. JAMA 1999; 281:2106.

83. Leitzmann MF, Stampfer MJ, Willett WC, et al. Coffee intake is associated with lower risk of symptomatic gallstone disease in women. Gastroenterology 2002; 123:1823.

84. Zhang YP, Li WQ, Sun YL, et al. Systematic review with meta-analysis: coffee consumption and the risk of gallstone disease. Aliment Pharmacol Ther 2015; 42:637.

85. Pixley F, Wilson D, McPherson K, Mann J. Effect of vegetarianism on development of gall stones in women. Br Med J (Clin Res Ed) 1985; 291:11.

86. Lander EM, Wertheim BC, Koch SM, et al. Vegetable protein intake is associated with lower gallbladder disease risk: Findings from the Women's Health Initiative prospective cohort. Prev Med 2016; 88:20.

87. Maclure KM, Hayes KC, Colditz GA, et al. Dietary predictors of symptom-associated gallstones in middle-aged women. Am J Clin Nutr 1990; 52:916.

88. Leitzmann MF, Giovannucci EL, Rimm EB, et al. The relation of physical activity to risk for symptomatic gallstone disease in men. Ann Intern Med 1998; 128:417.

89. Leitzmann MF, Rimm EB, Willett WC, et al. Recreational physical activity and the risk of cholecystectomy in women. N Engl J Med 1999; 341:777.

90. Bodmer M, Brauchli YB, Krähenbühl S, et al. Statin use and risk of gallstone disease followed by cholecystectomy. JAMA 2009; 302:2001.

91. Erichsen R, Frøslev T, Lash TL, et al. Long-term statin use and the risk of gallstone disease: A population-based case-control study. Am J Epidemiol 2011; 173:162.

92. European Association for the Study of the Liver (EASL). Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. J Hepatol 2016; 65:146.

93. Valdivieso V, Covarrubias C, Siegel F, Cruz F. Pregnancy and cholelithiasis: pathogenesis and natural course of gallstones diagnosed in early puerperium. Hepatology 1993; 17:1.

94. Marks JW, Stein T, Schoenfield LJ. Natural history and treatment with ursodiol of gallstones formed during rapid loss of weight in man. Dig Dis Sci 1994; 39:1981.

95. Sugerman HJ, Brewer WH, Shiffman ML, et al. A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. Am J Surg 1995; 169:91.

96. Zoli G, Ballinger A, Healy J, et al. Promotion of gallbladder emptying by intravenous aminoacids. Lancet 1993; 341:1240.

Topic 662 Version 27.0

GRAPHICS

Gallstones

Gallstones retrieved from six different patients. Note how gallstones are similar in the same patient but differ among patients.

(A-D) Cholesterol stones.

(E) Brown pigment stones.

(F) Black pigment stones.

Courtesy of Salam F Zakko, MD, FACP, AGAF.

Graphic 114842 Version 3.0

The prevalence of gallstone disease in selected populations

Population	Test	Age (years)	Female percent GSD	Male percent GSD
Mexican-American 1982-1984 (n = 1388)	Ultrasonography	20-39	13.8	2.6
		40-59	26.4	9.7
		60-74	44.4	15.5
Puerto Ricans 1982-1984 (n = 582)	Ultrasonography	20-39	9.0	2.0
		40-49	21.2	3.3
		60-74	12.1	11.1
Rome, Italy 1981-1982 (n = 2320)	Ultrasonography	20-29	2.5	2.3
		30-39	5.9	2.0
		40-49	10.9	6.7
		50-59	17.8	14.7
		>65	25	14.4
Bristol, England[1] 1987-1989 (n = 1896)	Ultrasonography	20-29	3.9	–
		30-39	6.4	–
		40-49	6.5	4.7
		50-59	14.2	22.4
		60-69	22.4	11.5
Pima Indians 1967-1968 (n = 596)	Oral cholecystogram	15-25	12.7	0
		25-34	73.2	4.4
		35-44	70.8	11.1
		45-54	75.8	31.9
		55-64	62.0	66.3
		>65	89.5	67.8
Okinawa, Japan[2] 1984 (n = 2727)	Ultrasonography	0-19	0	1.0
		20-29	3.0	1.0
		30-39	3.5	2.5
		40-49	3.0	2.0
		50-59	4.0	1.5

		60-69	9.0	4.5
		>70	9.5	15.0
United States[3] 1988-1991 (n = 14,000)	Ultrasonography	20-29	4.4	1.3
		30-39	5.2	1.1
		40-49	8.2	5.9
		50-59	11.9	7.3
		60-74	16.4	17.2
China[4] 2008 (n = 54,584)	Ultrasonography	20-29	1.1	1.2
		30-39	2.6	2.6
		40-49	3.6	5.1
		50-59	8.2	7.9
		60-69	8.8	8.0
		70+	12.2	10.7

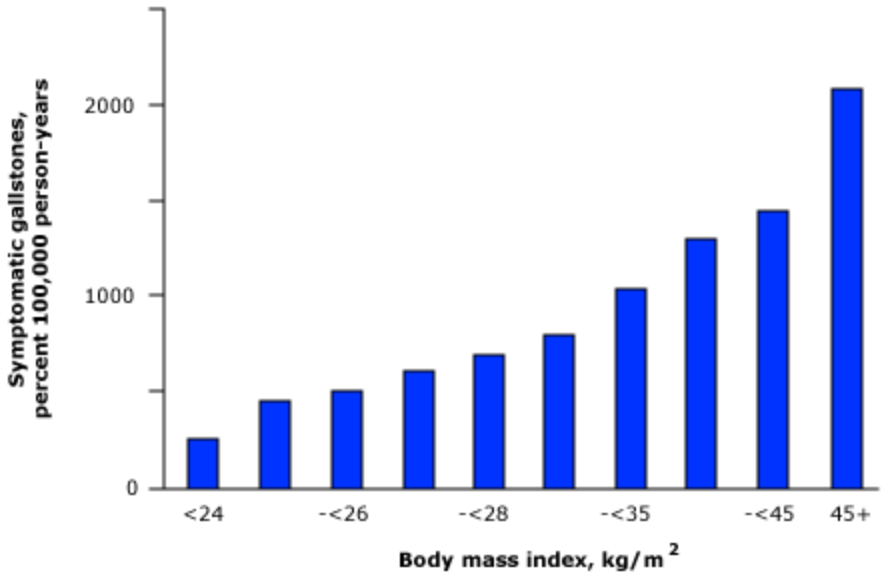
GSD: gallstone disease.

References:

1. *Adapted from: Heaton IW, Braddon FEM, Mountford RA, et al. Gut 1991; 32:316.*
2. *Adapted from: Nomura H, Kashiwagi S, Hayashi J, et al. Am J Epidemiol 1992; 136:787.*
3. *Adapted from: Everhart JE, Khare M, Hill M, Maurer KR. Gastroenterology 1999; 117:632.*
4. *Adapted from: Zeng Q, He Y, Qiang DC, Wu LX. Eur J Gastroenterol Hepatol 2012; 24:1459.*

Graphic 57092 Version 5.0

Relationship between body mass index (BMI) and gallstones



Relationship between the incidence of symptomatic gallstones (defined as cholecystectomy or newly diagnosed symptomatic unremoved gallstones) and BMI in the Nurse's Health Study.

Reproduced with permission from: the American Gastroenterological Association. Klein S, Wadden T, Sugerman HJ. AGA technical review on obesity. Gastroenterology 2002; 123:882.

Graphic 74965 Version 3.0

Major risk factors for the development of gallstones

Age
Female sex
Genetic
Pima Indians and certain other Native Americans
Chileans
Pregnancy
Obesity
Rapid weight loss
Very-low-calorie diet
Bariatric surgery
Cirrhosis
Hemolytic anemias
Hypertriglyceridemia
Medications
Estrogen and oral contraceptives
Clofibrate
Ceftriaxone
Octreotide
Terminal ileal resection
Gallbladder stasis
Diabetes mellitus
Total parenteral nutrition
Postvagotomy
Octreotide or somatostatinoma
Spinal cord injury
Reduced physical activity (at least in men)

Graphic 81139 Version 2.0

Contributor Disclosures

Nezam H Afdhal, MD, FRCPI No relevant financial relationship(s) with ineligible companies to disclose. **Salam F Zakko, MD, FACP, AGAF** No relevant financial relationship(s) with ineligible companies to disclose. **Sanjiv Chopra, MD, MACP** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→