Review Article

Gallstones

Gabriel E Njeze

Department of Surgery, Enugu State University of Technology Teaching Hospital, Park Lane, Enugu, Nigeria

Abstract

Gallstone disease is a worldwide medical problem, but the incidence rates show substantial geographical variation, with the lowest rates reported in African populations. Publications in English language on gallstones which were obtained from reprint requests and PubMed database formed the basis for this paper. Data extracted from these sources included authors, country, year of publication, age and sex of patients, pathogenesis, risk factors for development of gallstones, racial distribution, presenting symptoms, complications and treatment. Gallstones occur worldwide, however it is commonest among North American Indians and Hispanics but low in Asian and African populations. High biliary protein and lipid concentrations are risk factors for the formation of gallstones, while gallbladder sludge is thought to be the usual precursor of gallstones. Biliary calcium concentration plays a part in bilirubin precipitation and gallstone calcification. Treatment of gallstones should be reserved for those with symptomatic disease, while prophylactic cholecystectomy is recommended for specific groups like children, those with sickle cell disease and those undergoing weight-loss surgical treatments. Treatment should be undertaken for a little percentage of patients with gallstones, as majority of those who harbor them never develop symptoms. The group that should undergo cholecystectomy include those with symptomatic gallstones, sickle cell disease patients with gall stones, and patients with morbid obesity who are undergoing laparotomy for other reasons.

Keywords: Cholecystectomy, dissolution therapy, gallstones, risk factors

Address for correspondence:
Dr. Gabriel E Njeze,
Department of Surgery, Enugu State University Teaching Hospital,
Parklane, Enugu, Nigeria.
E-mail: iheaneboagu@yahoo.com

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Introduction

Gallstones are hardened deposits of the digestive fluid bile, that can form within the gallbladder. They vary in size and shape from as small as a grain of sand to as large as a golf ball.[1] Gallstones occur when there is an imbalance in the chemical constituents of bile that result in precipitation of one or more of the components.

Gallstone disease is often thought to be a major affliction in modern society.[2] However, gallstones must have been known to humans for many years, since they have been found in the gallbladders of Egyptian mummies dating back to 1000 BC.[3,4] This disease is however, a worldwide medical problem, even though there are geographical variations in gallstone prevalence[5-11] Gallstones are becoming increasingly common; they are seen in all age groups, but the incidence increases with age;[12] and about a quarter of women over 60 years will develop them.[13] In most cases they do not cause symptoms, and only 10% and 20% will eventually become symptomatic within 5 years and 20 years of diagnosis.[14,15] Thus the average risk of developing symptomatic disease is low, and approaches 2.0-2.6%/year.[15]

This article gives a clinically useful review of the literature on gallstones disease and focuses on current information about the pathogenesis, risk factors, investigations, and treatment of gallstones. The paper is intended to make readers aware of current thinking in this field.

Methods

Publications in English language on gallstones up to 2012 were obtained from both reprint requests and by searching PubMed database. Data extracted from these papers included authors, country, year of publication, age and sex of patients, pathogenesis, risk factors for development of gallstones, racial distribution, presenting symptoms, complications and treatment.

Pathogenesis

Gallstones are composed mainly of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein and other materials.[16-19] There are three types of gallstones[20] (i) Pure cholesterol stones, which contain at least 90% cholesterol, (ii) pigment stones either brown or black, which contain at least 90% bilirubin and (iii) mixed composition stones, which contain varying proportions of cholesterol, bilirubin and other substances such as calcium carbonate, calcium phosphate and calcium palmitate.[21] Brown pigment stones are mainly composed of calcium bilirubinate whereas black pigment

stones contain bilirubin, calcium and/or tribasic phosphate.[22] In Western societies[23] and in Pakistan[24] more than 70% of gallstones are composed primarily of cholesterol, either pure or mixed with pigment, mucoglycoprotein, and calcium carbonate.[25] Pure cholesterol crystals are quite soft, and protein contributes importantly to the strength of cholesterol stones.[26]

In the simplest sense, cholesterol gallstones form when the cholesterol concentration in bile exceeds the ability of bile to hold it in solution, so that crystals form and grow as stones.[27] Cholesterol is virtually insoluble in aqueous solution, but in bile it is made soluble by association with bile salts and phospholipids in the form of mixed micelles and vesicles.

Three types of abnormalities have been considered to be responsible for cholesterol gallstone formation. Cholesterol supersaturation, the essential requirement for cholesterol gallstone formation, might occur via excessive cholesterol biosynthesis, which is the main lithogenic mechanism in obese persons. In the non-obese, defective conversion of cholesterol to bile acids, due to a low or relatively low activity of cholesterol 7α hydroxylase, the rate limiting enzyme for bile acid biosynthesis and cholesterol elimination could result in excessive cholesterol secretion. Finally, interruption of the enterohepatic circulation of bile acids could increase bile saturation. Temporary interruption of the enterohepatic bile acid circulation during overnight fasting leads to a higher cholesterol/phospholipid ratio in the vesicles secreted by the liver. Estrogen treatment also reduces the synthesis of bile acid in women.[7]

Pigment stones occur when red blood cells are being destroyed, leading to excessive bilirubin in the bile. Black pigment stones are more common in patients with cirrhosis or chronic hemolytic conditions such as the thalassemias, hereditary spherocytosis, and sickle cell disease, in which bilirubin excretion is increased.[28,29] Primary bile-duct stones, defined as stones that originate in the bile ducts, are usually brown pigment stones associated with infection. Bacteria in the biliary system release β-glucuronidases, which hydrolyze glucuronic acid from conjugated bilirubin. The resulting unconjugated bilirubin precipitates as its calcium salts. Primary brown pigment stones of the bile ducts often occur in Asians, associated with decreased biliary secretory Immunogloblin A (IgA.)[30] About 15% of gallstones are calcified enough to be seen on a plain abdominal radiograph, and of these, two thirds are pigment stones.[31]

High biliary protein and lipid concentrations are risk factors for the formation of gallstones. Gallbladder sludge, i.e., thickened gallbladder mucoprotein with tiny entrapped cholesterol crystals is thought to be the usual precursor of gallstones.[32] Sludge can sometimes cause biliary pain, cholecystitis, or acute pancreatitis,[33] but sludge may also resolve without treatment. The sources of sludge are pregnancy,[34] prolonged total parenteral nutrition,[35] starvation, or rapid weight loss.[36,37] The antibiotic ceftriaxone can also precipitate in the gallbladder as sludge[38] and rarely, as gallstones.[39]

The biliary calcium concentration plays a part in bilirubin precipitation and gallstone calcification.[40,41] Many patients with gallstones have increased biliary calcium, with supersaturation of calcium carbonate.[42]

Impaired motility of the gallbladder as seen in patient with high spinal cord injury[43] or with the use of the somatostatin analogue octreotide, has been cited as another contributing factor in the development of gallstones.[43] In theory, microscopic cholesterol crystals would regularly be washed out of the gallbladder if its contractions were effective enough. Intestinal hypomotility has been recently recognised as a primary factor in cholesterol lithogenesis.[25] Fiber may protect against gallstone formation by speeding intestinal transit and reducing the generation of secondary bile acids such as deoxycholate[44-46] which has been associated with increased cholesterol saturation of the bile.[47,48]

Epidemiology of Gallstones

Epidemiological studies have suggested a marked variation in overall prevalence between different populations. Gallstone is one of the diseases prevalent in developed nations, but it is less prevalent in the developing populations that still consume traditional diets.[49] Its prevalence is especially high in the Scandinavian countries and Chile and among Native Americans.[50] Gallstones are more common in North America, Europe, and Australia, and are less prevalent in Africa, India, China, Japan, Kashmir, and Egypt.[2,7,51-57]

Factors influencing gallstone disease

Age

All epidemiological studies showed that increasing age was associated with an increased prevalence of gallstones. Gallstones are 4-10 times more frequent in older than younger subjects. Biliary cholesterol saturation increases with age, due to a decline in the activity of cholesterol 7α hydroxylase, the rate limiting enzyme for bile acid synthesis.[58] Deoxycholic acid proportion in bile increases with age through enhanced 7α dehydroxylation of the primary bile acids by the intestinal bacteria.[59]

Gender, parity, and oral contraceptives

In all populations of the world, regardless of overall gallstone prevalence, women during their fertile years are almost twice as likely as men to experience cholelithiasis. This preponderance persists to a lesser extent into the postmenopausal period, but the sex difference narrows with increasing age.[26] Increased levels of the hormone estrogen, as a result of pregnancy or hormone therapy, or the use of combined (estrogen-containing) forms of hormonal contraception, may increase cholesterol levels in bile and also decrease gallbladder movement, resulting in gallstone formation.[60]

Genetics

Both necropsy and population studies have clearly shown the existence of racial differences that cannot completely be

explained by environmental factors. Cholesterol gallstone prevalence varies widely, from extremely low (<5%) in Asian and African populations, to intermediate (10-30%) in European and Northern American populations, and to extremely high (30-70%) in populations of Native American ancestry (Pima Indians in Arizona, Mapuche Indians in Chile).[53]

The Pima tribe of Arizona has the highest gallstone prevalence in the world: More than 70% of Pima women older than 25 years had gallstones or a history of cholecystectomy. High rates of gallstone prevalence have been also reported in other North American Indian tribes, including the Chippewas, Navajo, Micmacs, and Cree-Ojibwas.[25] Certain Hispanic populations in the USA are above average risk for gallbladder disease. Some studies strongly support the existence of Amerindian lithogenic genes in Mexican-Americans.

Obesity and body fat distribution

Obesity is an important risk factor for gallstone disease, more so for women than for men. It raises the risk of cholesterol gallstones by increasing biliary secretion of cholesterol, as a result of an increase in 3-hydroxy-3-mthylglutaryl coenzyme A (HMGCoA) reductase activity. Epidemiological studies have found that the lithogenic risk of obesity is strongest in young women, and that slimness protects against cholelithiasis.[26]

Rapid weight loss

Rapid weight loss is associated with occurrence of sludge and gallstones in 10-25% of patients in a few weeks of initiating the slimming procedures.[61] If a person loses weight too quickly, the liver secretes extra cholesterol; in addition there is rapid mobilization of cholesterol from adipose tissue stores. In fasting associated with severely fat restricted diets, gallbladder contraction is reduced, and the accompanying gallbladder stasis favors gallstone formation. Enhancing gallbladder emptying by inclusion of a small amount of dietary fat inhibits gallstone formation in patients undergoing rapid weight loss.[62] Fasting in the short term increases the cholesterol saturation of gallbladder bile and in the longer term, causes gallbladder stasis which can lead to sludge, and eventually gallstone formation. Younger women with gallstones were shown to be more prone to skip breakfast than controls.[63] A shorter overnight fasting is protective against gallstones in both sexes.[64]

Diet

Nutritional exposure to western diet, i.e., increase intake of fat, refined carbohydrates and decrease in fibre content is a potent risk factor for development of gallstones.[65,66] Calcium intake seems to be inversely associated with gallstone prevalence.[67] Dietary calcium decreases cholesterol saturation of gallbladder bile by preventing the reabsorption of secondary bile acids in the colon. Vitamin C influences 7α hydroxylase activity in the bile and it was shown that ascorbic acid might reduce lithogenic risk in adults.[68] Coffee consumption seems to be inversely correlated with gallstone prevalence, due to an increased enterohepatic circulation of bile acids. Coffee components stimulate cholecystokinin release,[69] enhance gallbladder motility, inhibit gallbladder fluid absorption, decrease cholesterol crystallization in bile[70] and perhaps increase intestinal motility.[71,72]

Physical activity

Regular exercise, in addition to facilitating weight control, alone or in combination with dieting, improves several metabolic abnormalities related to both obesity and cholesterol gallstones. In contrast, sedentary behaviour, is positively associated with the risk of cholecystectomy.[17]

Drugs

All fibric acid derivatives increase biliary cholesterol saturation while lowering serum cholesterol. Clofibrate is a potent inhibitor of hepatic acyl-CoA cholesterol acyltransferase (ACAT). ACAT inhibition leads to an increased availability of free or unesterified cholesterol for secretion into bile, favouring gallstone formation.[24] Additionally, prolonged use of proton pump inhibitors has been shown to decrease gallbladder function, potentially leading to gallstone formation.[73] The lithogenic role of ceftriaxone, had earlier been mentioned.[36,37]

Diabetes

People with diabetes generally have high levels of fatty acids called triglycerides. These fatty acids may increase the risk of gallstones. Gallbladder function is impaired in the presence of diabetic neuropathy, and regulation of hyperglycaemia with insulin seems to raise the lithogenic index.[24] A lack of melatonin could significantly contribute to gallbladder stones, as melatonin inhibits cholesterol secretion from the gallbladder, enhances the conversion of cholesterol to bile, and is an antioxidant, which is able to reduce oxidative stress to the gallbladder.[74]

Clinical Presentations of Gallstone Disease

For practical purpose gallbladder disease can be equated with gallstones as these are present in the large majority of patients.[75] Most patients with gallstones have no symptoms.[25] These gallstones are called "silent stones" and may not require treatment.

Patients with symptomatic stones most often present with recurrent episodes of right-upper-quadrant or epigastric pain, probably related to the impaction of a stone in the cystic duct.[76] They may experience intense pain in the upper-right side of the abdomen, often accompanied by nausea and vomiting, that steadily increases for approximately 30 min to several hours. A patient may also experience referred pain between the shoulder blades or below the right shoulder region (Boas' sign). Often, attacks occur after a particularly fatty meal and almost always happen at night.[77]

Some patients with gallstones present with acute cholecystitis, and often secondary infection by intestinal microorganisms,

predominantly *Escherichia coli* and Bacteroides species. Inflammation of the gallbladder wall causes severe abdominal pain, especially in the right upper quadrant, with nausea, vomiting, fever, and leucocytosis.[27] This condition may remit temporarily without surgery, but it sometimes progresses to gangrene and perforation. Less commonly, gallstones can become lodged in the common bile duct (choledocholithiasis), sometimes with obstruction of the common bile duct and symptoms of cholestasis.[77] Obstruction leading to jaundice though commonly caused by a stone migrating into the common bile duct, can be due to compression of the common hepatic duct by a stone in the neck of the gall bladder or cystic duct (Mirrizi syndrome).[78] Infection in the bile ducts (cholangitis) can occur even with a seemingly minor degree of obstruction to bile flow. Stones in the common bile duct usually cause pain in the epigastrium or right upper quadrant, but may be painless. The passage of common-bile-duct stones can provoke acute pancreatitis, probably by transiently obstructing the main pancreatic duct where it passes near the common bile duct at the ampulla of Vater.[26] Gallstones may fistulate directly into the duodenum from the gallbladder during a period of silent inflammation.[79] This stone can impact in the duodenum leading to duodenal obstruction (Bouveret's syndrome) Alternatively, gallstones can impact at the narrowest portion of healthy small, bowel causing an obstruction termed gallstone ileus.[80,81]

The Diagnosis of Gallstone Disease

This disorder is usually diagnosed by history of recurrent episodes of right-upper-quadrant or epigastric pain, suggesting biliary colic and Boas' sign. There may be fever, tender right upper quadrant with or without Murphy's sign, tenderness when the hand taps the right costal arch (Ortner's sign).

The three primary methods used to diagnose gallbladder disease are ultrasonography, nuclear scanning (cholescintigraphy), and oral cholecystography. Today, ultrasonography is the method most often used to detect cholelithiasis and cholecystitis. Occasionally gallstones are diagnosed during plain X-rays. Ultrasonography has a specificity and sensitivity of 90-95%, and can detect stones as small as 2 mm in diameter.[26] It can demonstrate the presence of common-bile-duct stones, show bile-duct dilatation and detect thickening of the gallbladder wall.

In cholescintigraphy, a patient is injected with a small amount of non-harmful radioactive material that is absorbed by the gallbladder, which is stimulated to contract if intravenous injection of cholecystokinin is given in addition.[82] The short-lived isotope technetium-99 m, which is bound to one of several radioactive HIDA (iminodiacetic acids such as (hepatic iminodiacetic acid) or DISIDA (disopropyl iminodiacetic acid,) that are excreted into the bile ducts, can provide functional information about gallbladder contraction. It can detect total obstruction of the bile duct, but cannot provide anatomical information, and cannot identify gallstones. It permits the rapid assessment of gallbladder function in a patient with suspected acute cholecystitis. Gamma rays emitted by the tracer are used to make an image of the bile ducts and gallbladder. Failure of the tracer to enter the gallbladder suggests obstruction of the neck of the gallbladder, as occurs in acute cholecystitis. Cholescintigraphy has a sensitivity and specificity of about 95% for acute cholecystitis, in the setting of upper abdominal pain with signs of inflammation.

In oral cholecystography, an iodinated contrast agent such as iopanoic acid (Telepaque) is given orally the day before the examination.[83] The contrast agent is absorbed from the gut, taken up by the liver, conjugated with glucuronic acid, and secreted into bile, where it is concentrated in the gallbladder. It is still useful in patients who have suspected gallbladder symptoms but a negative or equivocal ultrasound examination. On oral cholecystography the gallbladder may be seen to contain stones, polyps, or sludge, or it may simply not be visualized because contrast material is reabsorbed through an inflamed gallbladder wall or because the cystic duct is obstructed.[84]

Treatment

Treatment of gallstones depends partly on whether they are causing symptoms or not. Recurrent episodes of upper abdominal pain related to gallstones are the most common indication for the treatment of gallstones.[80] Delaying elective cholecystectomy until repeated episodes of pain occur results in a minimal decrease in life expectancy.[85]

Prophylactic cholecystectomy for gallstones has been recommended in specific groups, such as children, because symptoms develop in almost all patients.[84] It has also been recommended in sickle cell disease patients with gallstones, because the symptoms of gallstones can mimic those of sickle cell crisis, and elective cholecystectomy is much safer than emergency cholecystectomy in this group.[86] Incidental cholecystectomy for cholelithiasis is often performed concomitantly with surgery for morbid obesity, in view of the high incidence of symptomatic gallstones during rapid weight loss.[87] Some surgeons have recommended incidental cholecystectomy for cholelithiasis in patients undergoing other abdominal surgery.[73]

Prophylactic cholecystectomy is also recommended in certain high-risk groups to prevent gallbladder cancer. These include native Americans who have gallstones,[88] patients in the general population with longstanding stone or stones greater than 3 cm in diameter[89] and patients with a calcified gallbladder wall, or "porcelain" gallbladder.[90]

Prophylactic cholecystectomy was recommended for diabetic patients with gallstones because of an increased risk of acute cholecystitis and increased mortality with emergency cholecystectomy. Recent studies show that diabetic patients have increased operative risk with elective as well as emergency gallbladder surgery[91] related to risk of cardiovascular disease and other coexisting conditions rather than to diabetes mellitus itself.[79] Most authorities do not recommend cholecystectomy in

diabetic patients without symptoms of gallstones.

Open cholecystectomy was formerly the gold standard of treatment for gallstones, until the advent of laparoscopic cholecystectomy.[92] Open cholecystectomy in an otherwise healthy, good-risk candidate requires hospital stay for some days, and has mortality of less than 1%.[93,94] The greatest drawbacks to open cholecystectomy are the resulting pain and weeks of disability.[26] Laparoscopic cholecystectomy has become widely used since it was first performed in 1988[95,96] with a complication rate probably at least as good as that of the open procedure.[97] However a patient who has undergone abdominal surgery a number of times may not be a suitable candidate for Laparoscopic cholecystectomy because of extensive adhesions around the gallbladder.[26] A patient who is medically too unstable to undergo open cholecystectomy is also not a good candidate for Laparoscopic cholecystectomy either. The evaluation and treatment of suspected stones in the common bile duct can be carried out by endoscopic retrograde cholangiopancreatography before laparoscopic cholecystectomy.[98] If common-bile-duct stones are unexpectedly found by cholangiography during laparoscopic cholecystectomy,[99] an open exploration of the common bile duct may be needed.

The laparoscopic procedure requires more operating time than the open procedure, but usually only one night in the hospital postoperatively; postoperative pain is greatly reduced, and the patients can usually return to work early, i.e., in one to 2 weeks, as compared with 4-6 weeks after open cholecystectomy.[100]

Attempts to use oral bile salts to dissolve gallstones began more than 30 years ago because of those who refuse or are poor risks for surgery.[101,102] Chenodeoxycholic acid (chenodiol) and ursodeoxycholic acid (ursodiol) are known to dissolve gallstones, but chenodiol causes diarrhoea and abnormal aminotransferase levels, while ursodiol does not. Therapy with bile salts is suitable for only a minority of patients with symptomatic cholesterol gallstones.[103] It is not suitable for patients with acute cholecystitis or stones in the common bile duct, who need urgent action. Candidates for treatment with bile salts should have a patent cystic duct and noncalcified cholesterol gallstones. Gallstones frequently recur after oral bile salts are stopped.

Contact dissolution therapy of cholesterol gallstones rapidly is possible by instilling solvents like the organic solvent methyl tert-butyl ether into the gallbladder through a percutaneous catheter placed through the liver.[104-107] Alternatively, a nasobiliary catheter can be endoscopically guided into the gallbladder can be used for instilling the organic solvent.[108] This is a technically difficult and hazardous procedure, and should be performed only by experienced doctors in hospitals where research on this treatment is being done. Serious side effects include severe burning pain.

Finally a mixture of plant terpenes may also be useful for dissolving radiolucent gallstones, particularly when used in combination with a bile acid.[109]

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