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A SCIENTIFIC REVIEW ON: GALL STONES- A COSTLY DIGESTIVE DISEASE

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ABSTRACT

The gallbladder is a small, pear-shaped hollow organ, located just below the liver on the right side of the body. The gallbladder forms a reservoir to store bile, also known as "gall," which is linked to the origin of its name. The main function of the gallbladder is to store and concentrate bile (which is produced in the liver) as well as to release bile into the digestive system. Gallstones are small, hard stones that develop due to the accumulation of digestive fluids (bile) in your gallbladder. They are usually caused by high levels of cholesterol, cirrhosis of liver, rapid weight loss or pregnancy. Gallstones, stone-like objects often made of cholesterol or bilirubin can develop in the gallbladder or bile ducts. These stones can cause Sudden; rapid abdominal pain is a common symptom, lasting for several minutes to a few hours. Other symptoms include Nausea and Diarrhoea. In the United States, an estimated 20 million people have gallstones, termed Cholelithiasis, with women being two to three times more likely to have them compared with men. Cholelithiasis is a costly digestive disease for the healthcare system; the pain associated with it is a common reason for emergency department visits. Patients with chronic Cholelithiasis may develop cholecystitis, which can be acute or chronic. Gallstones are most commonly diagnosed using ultrasound. Treatment depends on patient symptoms, other comorbidities, and overall health. Treatment for Cholelithiasis may involve surgery or medical management with oral bile acids. Typically, patients with asymptomatic Cholelithiasis do not warrant therapy unless an issue arises. Expectant management is recommended for asymptomatic stones; recommended treatments for symptomatic stones include laparoscopic cholecystectomy or, sometimes, stone dissolution using Ursodeoxycholic acid (UA).

Key Words: Eudragit S 100, Eudragit RS 100, Ethyl Cellulose, Floating Microballons, Hydroxy Propyl Methyl Cellulose (HPMC), Ursodeoxycholic acid (UDCA).

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INTRODUCTION

The gallbladder is a small, pear-shaped hollow organ, located just below the liver on the right side of the body. The gallbladder forms a reservoir to store bile, also known as "gall," which is linked to the origin of its name. It is a muscular organ that contracts when bile is needed, forcing the bile through the cystic duct. The main function of the gallbladder is to store and concentrate bile (which is produced in the liver) as well as to release bile into the digestive system¹.

What is Bile?

Bile is a greenish-brown alkaline fluid (consisting of waste products, cholesterol, and bile salts). Bile is not a digestive enzyme, but, the bile salt functions in a similar manner, in that it emulsifies large fat droplets. Bile's primary function in the digestive system is to breakdown fats. Bile is secreted from the gallbladder (where it is stored) then enters the small intestine in response to a hormone called cholecystokinin (which gets released when food enters the small intestine from the stomach). Once bile enters the duodenum (the first section of the small intestine) it goes to work breaking down ingested fat, as well as fat-soluble vitamins, improving the ingested solubility of digested fat, facilitating its absorption².

There are several important functions of the biliary system, including:

- To drain the liver's waste products into the first section of the small intestine (called the duodenum)
- To secrete bile (in a controlled release fashion) which aids in digestion of fats during digestion

Bile has two primary functions, including:

1. To carry away waste
2. To break down fats

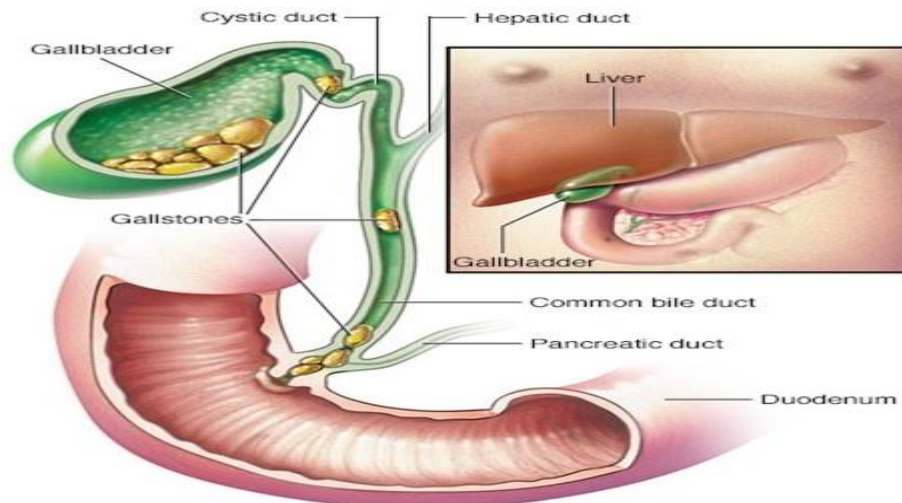


Figure 1: anatomical features of gall bladder and formation of gall stones

What are common issues that affect the gallbladder?

Several conditions can cause problems in your gallbladder. The most common condition is gallstones. Gallstones are typically harmless but can sometimes lead to disease states. Gallbladder issues include:

- **Gallstones:** Gallstones are pebble-like objects made of bile material that develop in the gallbladder or bile ducts. They can be as tiny as grains of sand to as large as golf balls. They're usually harmless but can cause pain, nausea or inflammation.
- **Cholecystitis:** Cholecystitis is inflammation of your gallbladder. It can occur when a gallstone blocks bile from exiting your gallbladder. Cholecystitis causes fever and pain and usually requires surgery.
- **Gallstone pancreatitis:** Gallstone pancreatitis is inflammation of your pancreas. It occurs when a gallstone travels down the common bile duct and blocks the pancreatic duct at a common point just before draining into the small intestine.
- **Gallbladder cancer:** Gallbladder cancer is rare. You might feel pain in the right upper quadrant of the abdomen. But, it is far more likely for this pain to occur due to another condition³.

This review focuses on the problems that gallstones cause and their optimal treatment based on current evidence. Gallstones or Cholelithiasis is a costly digestive disease for the healthcare system; the pain associated with it is a common reason for emergency department visits.

What are Gallbladder Stones?

Gallstones are small, hard stones that develop due to the accumulation of digestive fluids (bile) in your gallbladder. They are usually caused by **high levels of cholesterol, cirrhosis of liver, rapid weight loss or pregnancy**. Gallstones, stone-like objects often made of cholesterol or bilirubin can develop in the gallbladder or bile ducts. These stones can cause **Sudden; rapid abdominal pain is a common symptom**, lasting for several minutes to a few hours. Other symptoms include **Nausea and Diarrhoea**. These gallstones may go on further to develop complications such as cholecystitis, cholangitis, choledocholithiasis, gallstone pancreatitis, and rarely cholangiocarcinoma².

Who gets gallstones?

Gallstones occur when there is an imbalance in the chemical constituents of bile that results in precipitation of one or more of the components. Gallstones are seen in all age groups but the incidence increases with age. The old age "fat and fertile, female and forty" tells only part of the story. Estrogen does cause more cholesterol to be excreted into bile, and obesity (body mass index >30). Most gallstones form when there's too much cholesterol in the bile. 80 percent of gallstones are made of cholesterol. The other 20 percent of gallstones are made of calcium salts and bilirubin⁴.

Fatty meals are a common trigger for gallbladder contraction. The pain usually starts within an hour after a fatty meal and is often described as intense and dull, and may last from 1 to 5 hours. However, an association with meals is not universal, and in a significant proportion of patients.

ETIOLOGY

There are three main pathways in the formation of gallstones:

Cholesterol super saturation: Normally, bile can dissolve the amount of cholesterol excreted by the liver. But if the liver produces more cholesterol than bile can dissolve, the excess cholesterol may precipitate as crystals. Crystals are trapped in gallbladder mucus, producing gallbladder sludge. With time, the crystals may grow to form stones and occlude the ducts which ultimately produce the gallstone disease.

Excess bilirubin: Bilirubin, a yellow pigment derived from the breakdown of red blood cells, is secreted into bile by liver cells. Certain hematologic conditions cause the liver to make too much bilirubin through the processing of breakdown of hemoglobin. This excess bilirubin may also cause gallstone formation.

Gallbladder hypo motility or impaired contractility: If the gallbladder does not empty effectively, bile may become concentrated and form gallstones.

Depending on the etiology, gallstones have different compositions. Patients with Crohn's disease and those with ileum disease (or resection) are not able to reabsorb bile salts and this increases the risk of gallstones⁵.

Cholelithiasis is a complication of gallstones when stones obstruct the common bile duct it impedes the flow of bile from the liver to the intestine. Pressure rises resulting in elevation of liver enzymes and jaundice. Cholangitis is triggered by the colonization of bacteria and overgrowth in static bile above an obstructing common duct stone. This produces purulent inflammation of the liver and biliary tree. Charcot's triad consists of severe RUQ tenderness with fever and jaundice and is classic for cholangitis. Surgical removal of the stone obstruction with intravenous antibiotics is required to treat this condition⁶.

Types of gallstones

There are two Types of gallstones in the gallbladder include:

Cholesterol gallstones. The most common type of gallstone, called a cholesterol gallstone, often appears yellow in color. These gallstones are composed mainly of undissolved cholesterol, but may contain other components.

Pigment gallstones. Bilirubin calcium salt is predominant; approximately 2% of all gallstones are black and brown pigment stones. These can be found in individuals with high hemoglobin turnover. The pigment consists of mostly bilirubin. Patients with cirrhosis, ileal diseases, sickle cell anemia, and cystic fibrosis are at risk of developing black pigment stones. Brown pigments are mainly found in the Southeast Asian population and are not common in the United States. Risk factors for brown pigment stones are intraductal stasis and chronic colonization of bile with bacteria⁷.



Figure 2: Types of gall stones

What are the symptoms of gallstones?

Gallstones may become lodges in the neck of the gall bladder or in the bile ducts. When the gallbladder is plugged in this way, bile can't exit. This may lead to the gallbladder becoming inflamed or distended and this can lead to cause pain in the upper right abdomen. Patient may also experience with these general symptoms.

- Severe stomach pain
- Nausea and vomiting
- Jaundice, a yellowish tint to skin and eyes
- Dark urine
- Clay colored stools
- Burping and indigestion/diarrhea.

Acute Cholecystitis: *Acute cholecystitis* is a sudden inflammation of the gallbladder that develops over hours, typically because a gallstone impedes the cystic duct. Symptoms include right upper quadrant pain and tenderness; patients may also present with fever, chills, nausea, and vomiting. The majority of patients ($\geq 95\%$) with acute cholecystitis have cholelithiasis.⁵ Risk factors for cholecystitis are considered to be analogous to the risk factors for cholelithiasis.

In older patients, symptoms of cholecystitis may be vague (e.g., anorexia, vomiting, malaise, weakness), and fever may be absent. Although acute cholecystitis resolves spontaneously in 85% of patients without therapy, localized perforation or another problem develops in 10%.⁵ Acute cholecystitis may also be confused with other illnesses, such as peptic ulcer disease, irritable bowel syndrome, and cardiac disease.¹ Chronic and acute pancreatitis can also imitate cholecystitis⁸.

Chronic Cholecystitis: *Chronic cholecystitis* is a long-standing inflammation of the gallbladder. Repeated episodes of acute cholecystitis may result in chronic cholecystitis and may cause thickening and shrinking of the gallbladder wall, resulting in a failure to store bile. The major symptom of chronic cholecystitis is usually intermittent pain. Upper abdominal pain, often localized to the right upper quadrant, is the most common symptom⁹.

Acute Acalculous Cholecystitis (AAC): AAC is an inflammatory disease of the gallbladder without evidence of gallstones or obstruction of the cystic ducts. An estimated 2% to 15% of cases of cholecystitis are a calculous and typically arise in very sick hospitalized patients. The precise causal mechanism is not clear.²⁹ A calculous cholecystitis is correlated with a greater mortality rate, estimated at 45%, due in part to serious underlying medical conditions and delayed diagnosis. It accounts for 5% to 10% of cholecystectomies done for acute cholecystitis¹⁰.

DIAGNOSIS

Tests performed to diagnose gallbladder conditions (gallstones) may include:

- Liver enzyme tests are blood tests which may be elevated when severe inflammation is present, may also indicate the possibility of gallstones)
- A complete metabolic panel (CMP) blood test may show an elevation in bilirubin levels when there is an obstructed bile duct.
- A complete blood count (CBC) blood test may indicate acute cholecystitis when the white blood cells are elevated
- Ultrasound (test of choice for cholecystitis, can accurately show if there are signs of inflammation and/or if gallstones exist) ⁷
- Computed tomography (CT) scan—a detailed X-ray image of the gallbladder
- Magnetic resonance imaging (MRI)/Magnetic resonance cholangio pancreatography (MRCP) is often done during an emergency examination when a person complains of unexplained abdominal pain.⁷ the bile ducts are examined with magnetic resonance imaging (MRI), a test that uses a large magnet, radio waves, and a computer to produce very clear images of parts of the body. Unlike ERCP, MRCP can only diagnose common bile duct stones. It cannot remove them. However, MRCP's advantage over ERCP is that it is the safer alternative, so often physicians will opt for MRCP initially.
- X-rays of the abdomen
- Endoscopic retrograde cholangio-pancreatography (ERCP) involves endoscopy. A tube with a camera that is inserted into the throat and down the esophagus into the stomach then into the small intestine, a dye is injected into the gallbladder ducts, liver, and pancreas so the organs can be clearly viewed on an X-ray.
- A hepatobiliary iminodiacetic acid (HIDA) scan with cholecystikinin (CCK) is a test involving the administration of cholecystikinin to stimulate the gallbladder. Next, images are taken of the gallbladder before and after the CCK is given to evaluate how well the gallbladder contracts¹¹.

Endoscopic ultrasound (EUS): This procedure combines endoscopy with ultrasound (there's a probe at the tip of the scope). Like ERCP, this scope is passed through the mouth and advanced to the common bile duct and gallbladder region. It visualizes the common bile duct well. Similar to MRCP, gallstones are identified but not removed during this procedure. If common bile duct stones are demonstrated by EUS (or MRCP), then an ERCP will generally follow to remove them.

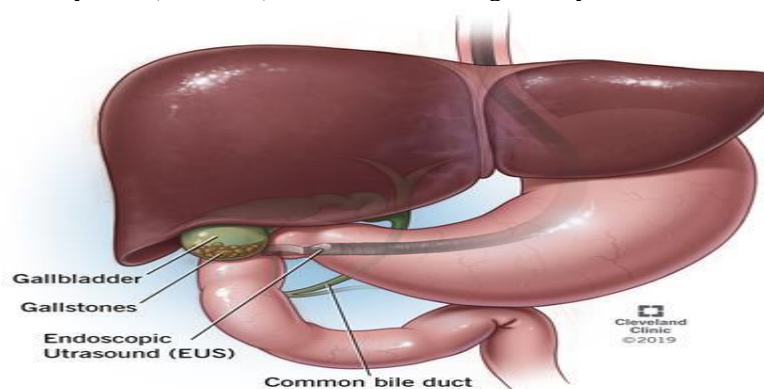


Figure 3: Endoscopic ultrasound passes through the mouth to the common bile duct and gall bladder.

Endoscopic retrograde cholangio pancreatography (ERCP): This is both a test and a possible treatment for common bile duct stones. When used as a test, an endoscope — a flexible tube with a light and a camera attached — is inserted into the patient's mouth, down the throat, and into the stomach and small intestine. A dye is injected to allow the bile ducts to stand out. If there are gallstones in the bile duct, they can be removed by the endoscope. This scope cannot remove stones contained within the gallbladder¹².

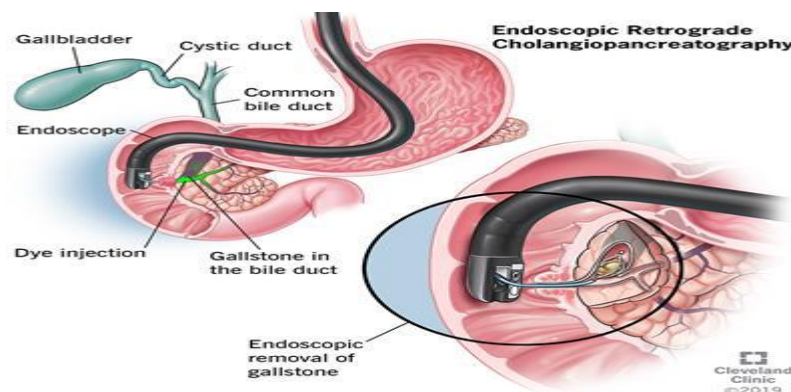


Figure 4: Endoscopic retrograde cholangio pancreatography (ERCP) can diagnose and sometimes treat gallstones.

What are the risk factors for the gallstones?**Lifestyle risk factors**

- Being overweight or obese
- Eating diet that's high in fat or cholesterol or low in fiber
- Having rapid weight loss in a short period of time.
- Having diabetes mellitus

Uncontrolled risk factors

- Being female
- Having family history of gallstones
- Being 40 years or older.

Medical risk factors

- Being pregnant
- Having cirrhosis
- Taking certain medications for lowering cholesterol
- Taking medicaments that have high estrogen content.
- Have diabetes.
- Have Crohn's disease
- Take drugs that lower cholesterol.
- Take various medicines including oral contraceptives.

What are the complications of untreated gallstones?

- Pancreatitis, an inflammation of pancreas
- Bile duct stones
- Acute cholecystitis
- Gallbladder emphysema, necrosis
- Cholangitis, a bile duct infection
- Jaundice, a yellowish tint to skin and eyes
- Sepsis, a blood infection
- Gallbladder cancer
- Cholecystoenteric fistula

Why to get Gall stones treated early?

- Avoid Inflammation of the gallbladder
- Avoid blockage of the bile duct
- Prevent jaundice infection
- Untreated Gallstones can lead to complications including Gallbladder cancer¹³.

TREATMENT

Typically, patients with asymptomatic Cholelithiasis do not warrant therapy unless an issue arises. Expectant management is recommended for asymptomatic stones; recommended treatments for symptomatic stones include laparoscopic cholecystectomy or, sometimes, stone dissolution using Ursodeoxycholic acid (UA).

Management of gallstones can be divided into two categories:

1. Asymptomatic gallstones
2. Symptomatic gallstones.

Asymptomatic gallstones require the patient to be counseled regarding symptoms of biliary colic and when to seek medical attention and can be treated acutely with oral or parenteral analgesics. Today, laparoscopic cholecystectomy is the standard of care and most patients are managed as outpatients.

Patients with symptoms and workup consistent with acute cholecystitis will require admission to hospital, surgical consult and intravenous antibiotics. Patients with choledocholithiasis or gallstone pancreatitis will also require admission to hospital, gastrointestinal (GI) consultation and ERCP or MRCP. Patients with acute ascending cholangitis are usually ill-appearing and septic. They often also require aggressive resuscitation and ICU-level care in addition to surgical intervention to drain an infection in the biliary tract.

Oral Bile Agents: For patients who decline surgery or for those who may be at higher surgical risk because of other comorbidities or advanced age, clinicians may elect to use oral bile acids.^{1,2} It is important to note that medical management of gallstones with pharmacologic therapies has diminished in the past few years.¹ Medical therapy that is used alone or in combination may include oral bile salt therapy, such as Ursodeoxycholic acid (UA), which is often used for x-ray-negative cholesterol gallstones in patients with normal gallbladder function.¹ In addition to Ursodeoxycholic acid (UA), another available oral bile agent is chenodeoxycholic acid (Chenodiol). Extracorporeal shockwave lithotripsy may also be used, particularly in patients with noncalcified cholesterol gallstones who have normal gallbladder function^{14, 15}.

Surgery:**What is a laparoscopic cholecystectomy?**

Laparoscopic cholecystectomy is known as a minimally invasive procedure because it uses several small incisions instead of one large one. A laparoscope is a narrow tube with a camera. This surgical tool is inserted through one incision. The camera allows your doctor to see your gallbladder on a TV screen. Your gallbladder is then removed through another small incision^{16, 17}.

Traditional Ayurvedic treatment

There is a scientific report and clinically effective with an advanced Ayurvedic product like i glow (the main ingredients of i glow was Kashmir Saffron, Black grape seed extract, Lutin extract from marigold flower, Plant collagen, Liquorice extract, Co enzyme

10 and Kojic acid) is from Indus Viva Health Sciences, Bangalore and this company was certified by AYUSH department of India and USFDA, which was an Ayurvedic liquid preparation meant for oral use and which was symptomatically relieved from gall stones of my grandmother in Telangana, India as a natural liver detoxifier^{18, 19}.



Figure 5: Composition of Advanced Ayurvedic Product of i glow from Indus Viva

Can children get gallstones?

Gallstones can happen to both children and adults. It is most common to see gallstones in middle-aged adults. However, adults are not the only ones who experience gallstones. One challenge with gallstones in children is identifying symptoms. Young children may have difficulty expressing where the pain is located. If you child has any unusual symptoms or abdominal pain, call your doctor²⁰.

Why are some people unhappy about gallstones surgery?

Gallstones only cause severe abdominal pain and the complications listed above. Symptoms such as abdominal tightness, bloating, indigestion, heartburn, constipation and increased frequency of stools are very common in the general population and are not related to gallstones. Mostly when the patients / treating doctors try to correlate these symptoms with gallstones it leads to unhappiness as these symptoms may not get relieved by a cholecystectomy²¹.

CONCLUSION

Gallbladder disease is a common occurrence in the U.S. Fortunately; most cases can be effectively treated without complications. These gallstones may go on further to develop complications such as cholecystitis, cholangitis, choledocholithiasis, gallstone pancreatitis, and rarely cholangiocarcinoma. Gallstone formation occurs secondary to obesity, sedentary lifestyle, fatty food consumption and constipation. People from some parts of India such as cow belt (UP, Bihar and West Bengal) area have an especially high incidence of stones. Multiple pregnancies can predispose to gallstones as well. Gallstones cause sudden onset severe pain in the upper abdomen or right half of abdomen which starts after food intake or in the night /early morning hours. Pain radiates to right shoulder or back, it is moderate to severe and stops within ½ hr to 6 hrs. If pain lasts more than 24 hrs complications of gallstones such as gallbladder infection (acute cholecystitis) pancreatitis/ bile duct-liver infection (cholangitis) / gangrene or perforation are to be suspected. People who are overweight — especially women — are more likely to develop gallstones. This is because people who are overweight may have more cholesterol in their bile. More cholesterol in your bile can cause gallstones. People who are overweight may also have bigger gallbladders that don't work as well. Losing weight too quickly may raise your chances of forming gallstones as well. But slowly losing weight may help you prevent them. Moreover, pharmacists can remind patients to discuss their concerns with their primary healthcare provider regarding how to reduce their risk via proper diet, losing weight if warranted, controlling associated diseases, and implementing strategies to reduce other modifiable risk factors for gallbladder disease. Typically, patients with asymptomatic Cholelithiasis do not warrant therapy unless an issue arises. Expectant management is recommended for asymptomatic stones; recommended treatments for symptomatic stones include laparoscopic cholecystectomy or, sometimes, stone dissolution using Ursodeoxycholic acid (UA).

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