

## Review on Cholelithiasis or Gallstones (*Hissat-e-Marara*)

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### **Abstract**

Gallstones or cholelithiasis are a major public health problem in Europe and other developing countries like India, it affect up to 20% of the population. Gallstone disease is the most common gastrointestinal disorder for which patients are admitted to hospitals in European countries. The interdisciplinary care for patients with gallstone disease has advanced considerably during recent decades thanks to a growing insight into the pathophysiological mechanisms and remarkable technical developments in endoscopic and surgical procedures. In contrast, primary prevention for this common disease is still in its infancy. Gallstone disease (GD) is a chronic recurrent hepatobiliary disease, the basis for which is the impaired metabolism of cholesterol, bilirubin and bile acids, which is characterized by the formation of gallstones in the hepatic bile duct, common bile duct, or gallbladder. GD is one of the most prevalent gastrointestinal diseases with a substantial burden to health care systems. GD can result in serious outcomes, such as acute gallstone pancreatitis and gallbladder cancer. The epidemiology, pathogenesis and treatment of GD are discussed in this review. According to doctrine of Unani Medicine disease occurs in the gall bladder is due to Su-e-Mizaj, Su-e-Tarkeeb or Taffarruq-e-Itteshal. Unani Scholars also described about Amraz-e-Marara, under the caption of Amraz-e-Kabid, they also mentioned that inflammation and Hissat occurs in the mararaa is due to Ghaleez wa fasid ghiza, ehtebas ghair tabayi. This is connected with a change in lifestyle: reduction of motor activity, reduction of the physical load and changes to diets. One of the important benefits of early screening for gallstone disease is that ultrasonography can detect asymptomatic cases, which results in early treatment and the prevention of serious outcomes. The pathogenesis of GD is suggested to be multifactorial and probably develops from complex interactions between many genetic and environmental factors. It suggests that corticosteroids and oral contraceptives, which contain hormones related to steroid hormones, may be regarded as a model system of cholelithiasis

development in man. The achievement in the study of the physiology of bile formation and the pathogenesis of GD has allowed expanding indications for therapeutic treatment of GD.

**Keywords:** Cholelithiasis, Hissat-e-Marara, Amraz-e-Kabid, Su-e-Mizaj, Unani Medicine

## Introduction

It is a flask (pear) shaped blind-ending diverticulum or hollow viscus (sac), with a muscular wall. In life, it is grey-blue in colour, situated obliquely in a non peritoneal fossa on the under surface of the right lobe of the liver. It extends from the right end of porta hepatis to the inferior border of liver. It is 7 - 10cm (3 to 4 inches) long, 3-4 cm broad at its widest part and about 30 to 50ml in capacity<sup>1</sup>. The gallbladder is divided into the following regions: funds, body and neck. The portion of body that joins the neck is referred to the infundibulum; sometimes there is a small bulge in this region, known as Hartmann pouch<sup>1</sup>. Neck continues as cystic duct and is marked by a constriction. The gallbladder varies in size and shape. The fundus may be elongated and highly mobile. Rarely, the fundus is folded back upon the body of the gallbladder and is called Phrygian cap, on ultrasound this may be wrongly interpreted as an apparent septum within the gallbladder.

Gall bladder: It is a flask (pear) shaped blind-ending diverticulum or hollow viscus (sac), with a muscular wall. In life, it is grey-blue in colour, situated obliquely in a non peritoneal fossa on the under surface of the right lobe of the liver. It extends from the right end of porta hepatis to the inferior border of liver. It is 7 - 10cm (3 to 4 inches) long, 3-4 cm broad at its widest part and about 30 to 50ml in capacity<sup>1</sup>. The gallbladder is divided into the following regions: funds, body and neck. The portion of body that joins the neck is referred to the infundibulum; sometimes there is a small bulge in this region, known as Hartmann pouch<sup>1</sup>. Neck continues as cystic duct and is marked by a constriction. The gallbladder varies in size and shape. The fundus may be elongated and highly mobile. Rarely, the fundus is folded back upon the body of the gallbladder and is called Phrygian cap, on ultrasound this may be wrongly interpreted as an apparent septum within the gallbladder.<sup>[1]</sup>

**FUNCTION:** Reservoir of bile, concentrates bile (5to10 times), bile helps in emulsion cation and absorption of fats, bile helps in eliminating bilirubin, a product of haemoglobin metabolism.

## HISTOLOGY

Gallbladder following layers present:

**Mucosa layer-**The lining epithelium presents single layer of tall columnar cells having basal nuclei and lightly stained cytoplasm with occasional small apicalvacuoles<sup>[2]</sup>. Ultra structurally these cells have numerous apical microvilli with filamentous glycocalyx and core rootlets.<sup>[3]</sup> Epithelium also shows pencil cells (smaller, darkly stainingcolumnar cells) and basal cells and myoepithelial cells are absent. The lamina propria contains loose connectivetissue, fenestrated capillaries, small vessels, nerves, some diffuse lymphatic tissue and a scattering of IgA containing plasma cells<sup>[4]</sup>.

Muscularis mucosa is absent. The mucosa exhibits numerous interlacing tiny temporary irregular folds which are varying in size and shape gives honeycomb appearance and disappears when the gallbladder is distended with bile. In the neck of the gallbladder, these folds (containing smooth muscle) coalesce to form the spiral valves of Heister, where gallstones are commonly gets stuck. Sub mucosa layer is absent.

**Muscle layer-** Large amount of elastic fibers are intermingled with the smooth muscle fibers which are arranged in circular, longitudinal and in oblique manner so this layer is also called fibromuscular layer.

**Serosa layer-** Covers its entire surface except the hepatic, where an adventitia attaches it to the liver. The gallbladder has a wide layer of perimuscular loose connective tissue which contain blood vessels, lymphatic and nerves.

### History of Gallbladder

**Roman anatomist Galen** – He identified the gall bladder and spleen as the two crucial subsidiary organs of the liver. All three organs worked together to produce and store three of the four humors of the body: blood (liver), yellow bile (gall bladder) and black bile (spleen).

**Berengario** - Suggested that the gallbladder regulated the emotions by being a repository for gall. Harvey described the liver as a "noble organ" in 1653 and the spleen as an "ignoble organ" the gall bladder as "a very long pear compressed from base into neck".

### Society and Culture

To have 'gall' is associated with bold behaviour, whereas to have 'bile' is associated with bitterness<sup>5</sup>. In the China, the gallbladder is associated with courage and a plethora of related idioms, including using terms such as "a body completely of gall to describe a brave person, and "single gallbladder hero" to describe a lone hero.<sup>[5]</sup>

### Comparative Anatomy

Most vertebrates have gallbladders, where as invertebrates do not. However, its precise form and the arrangement of the bile ducts may vary considerably. Several species of mammals (including horses, deer, rats, and various laminiis)<sup>[6]</sup> and several species of birds lack a gallbladder all together, as do lampreys<sup>[7]</sup>.

### Review of Literature

**Cholelithiasis:** Gallstones are hard; pebble like deposits in the gallbladder. The word cholelithiasis derived from greek word (chol = bile + lith = stone + iasis = process). Gallstones generally form because the bile is saturated with either cholesterol or bilirubin then bile undergoes supersaturation, nucleation and precipitation of cholesterol monohydrate crystals and growth to stone-size aggregates<sup>[8]</sup>. Initially there is always the formation of a biliary sludge which contains mucus gel, hydrophobic bile pigment, cholesterollecithin liquid crystals and solid cholesterol monohydrate crystals. The basic constituents being cholesterol, calcium bilirubinate and calcium carbonate.

On the basis of their composition, gallstones can be divided into the following types:

**Pure gallstones (10%)** - Cholesterol stones- are single, large ( 2- 3 cm long), spheroidal to oval in shape and vary from light yellow to dark green or brown to bluish white in color, each often having a tiny, dark, central spot. To be classified as such, they must be at least 80% cholesterol by weight or 70%, according to the Japanese- classification system<sup>[9]</sup>. In the literature the reported incidence of this type of stone varies between 5.43 % to 17.3%. Pigment stones- are multiple, small (2-5 mm) and brown to jet black (dark) in color and comprise bilirubin and calcium salts that are found in bile. They contain less than 20% of cholesterol or 30%, according to the Japanese-classification system<sup>[10]</sup> In the literature the reported incidence of this type of stone varies between 1.62 % to 20%.

**Mixed gallstones (80%)**-These are typically consists of 20–80% cholesterol or 30–70%, according to the Japanese- classification system<sup>[10]</sup>, calcium carbonate, calcium bilirubinate, palmitate phosphate and other bile pigments. Because of their calcium content, they are often radiographically visible. These are usually multiple, faceted, laminated and vary in size & numbers. In the literature the reported incidence of this type of stone varies between 59 % to 90.8%.

**Combined gallstones (10%)** -These are characteristically large and single. They may have a pure nucleus with a mixed shell or the reverse. Barrel stones, a type of combined stone, are usually two in number, large and faceted on one surface and the thick walled gallbladder is closely wrapped around them. In the literature the reported incidence of this type of stone varies between 0.54% to 25% .

### **Pathophysiology**

Cholesterol gallstones develop when bile contains too much cholesterol and not enough bile salts. Besides a high concentration of cholesterol, two other factors are important in causing gallstones. The first is how often and how well the gallbladder contracts. Incomplete and infrequent emptying of the gallbladder may cause the bile to become over concentrated and contribute to gallstone formation. This can be caused by high resistance to the flow of bile out of the gallbladder due to the complicated internal geometry of the cystic duct <sup>[11]</sup>. The second factor is the presence of proteins in the liver and bile that either promote or inhibit cholesterol crystallization into gallstones.

In addition, 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. Sequential cholecystographic studies and carbon-14 dating suggest that gallbladder stone grow at a rate of approximately 1-2 mm/ year and that they are usually present for 5-20 years before they are removed <sup>[9]</sup>.

**Number of stones:** Gallstones are present in single, double and multiple numbers. In the available literature the incidence of single stone varied from % to 39.6% cases, double stones in 8.8% cases and multiple stones from 51.6% to 93% cases. <sup>[12]</sup>

**Sex ratio:** All the available studies suggest that the females are more prone to gallstone than males. In the review male and female ratio (M: F) range between 1:1:4 to 1:7:3 <sup>[13]</sup>

**Size:** The maximum gallstone size of 4.0 cm was observed in cases of malignancy (Narang et al 2014). Mathur et al 2012 has reported the gallstone size to be 2.147 cm in cases with carcinoma, followed by hyperplasia 1.187 cm, metaplasia 1.145 cm and cholecystitis 1.136cm <sup>[14]</sup>

**Volume:** The average volume of the gallstone was 2.664 ml in cholecystitis, 3.742 ml in hyperplasia, 4.532ml in metaplasia and 19.178 ml in carcinoma as reported by Mathur et al <sup>[15]</sup>

**Age:** Stones are found in patients with age range between 23 to 76 years. <sup>[16]</sup>

### **Management**

**Medical Treatment** Cholesterol gallstones can sometimes be dissolved by oral ursodeoxycholic acid, but it may be necessary for the patient to take this medication for up to two years.

Gallstones may recur, however, once the drug is stopped. Obstruction of the common bile duct with Gallstones can sometimes be relieved by endoscopic retrograde sphincterotomy (ERS) following endoscopic retrograde cholangiopancreatography (ERCP). Gallstones can be broken up using a procedure called extracorporeal shock wave lithotripsy (often simply called "lithotripsy"), which is a method of concentrating ultrasonic shock waves onto the stones to break them into tiny pieces. They are then passed safely in the feces. However, this form of treatment is suitable only when there is a small number of gallstones. <sup>[17]</sup>

## Surgical Treatment

Cholecystectomy (gallbladder removal) has a 99% chance of eliminating the recurrence of cholelithiasis. Surgery is only indicated in symptomatic patients. The lack of a gallbladder may have no negative consequences in many people. However, there is a portion of the population — between 10 and 15% — who develop a condition called post cholecystectomy syndrome <sup>[18]</sup> which may cause gastrointestinal distress and persistent pain in the upper right abdomen, as well as a 10% risk of developing chronic diarrhoea.<sup>[19]</sup>

There are two surgical options for cholecystectomy:

**Open cholecystectomy** is performed via an abdominal incision (laparotomy) below the lower right ribs. Recovery typically requires 3–5 days of hospitalization, with a return to normal diet a week after release and to normal activity several weeks after release.<sup>[20]</sup>

**Laparoscopic cholecystectomy**, introduced in the 1980 is performed via three to four small puncture holes for a camera and instruments. Post-operative care typically includes a same-day release or a one night hospital stay, followed by a few days of home rest and pain medication. Laparoscopic cholecystectomy patients can, in general, resume normal diet and light activity a week after release, with some decreased energy level and minor residual pain continuing for a month or two. Studies have shown that this procedure is as effective as the more invasive open cholecystectomy, provided the stones are accurately located by cholangiogram prior to the procedure so that they can all be removed. <sup>[21]</sup>

## Usul-e-Ilaj of Hissat-e-Marara

- Removed the root cause of disease
- Avoid from fatty, oily and Ghizae Kasif
- Use warm water for drinking purpose
- Be regular aerobic exercise
- At the time of pain used Arque Mako and arque Kasni 6 Tola each with Roghan-e-Arandi and Roghan-e-Zaitoon
- Dry Hammam is effective
- Correct the sue Mizaj of Kabid
- Islahe Jigar
- Use of hepatoprotective and Mufatit-e-Hissat Drugs <sup>[22]</sup>

## Conclusion

Cholangitis is a serious complication of gallstones, with significant morbidity and mortality, especially in the elderly. First line treatment should include general supportive measures including adequate intravenous hydration and antibiotics, which are required in the first hour after hospital admission in case of sepsis. Considering the polymicrobial content of infected bile, broad spectrum antibiotics should be applied. The choice of antibiotic coverage depends on cholangitis severity and local antimicrobial resistance patterns. Enteric gram-negative bacteria are usually cultured from bile of patients with acute cholangitis, especially E. coli

and *Klebsiella* species. Nevertheless, the microbiological profile has changed in the last decades, due to increased instrumentation of the bile ducts and frequent use of antibiotics in the population. Polymicrobial bile cultures are often found. Anaerobic bacteria are usually isolated in conjunction with aerobic bacteria, rather than a sole isolate from bile, and often in the setting of previous bile duct instrumentation and a more severe clinical condition. There is a clear difference between results of bile cultures compared to associated blood cultures. Bile cultures are positive in 80–100%, and blood cultures in 20–60% of patients with cholangitis. *Streptococcus* and *Enterococcus* species are infrequently and anaerobic bacteria are rarely cultured from blood. One of the main goals of antibiotics is to control bacteremia and sepsis. Most antibiotics (with the exception of quinolones) are not or are less well excreted into bile in case of biliary obstruction. Empirical antibiotic therapy that includes coverage of the aerobic gram-negative bacteria and anaerobic bacteria should be considered until the results of bile cultures and blood cultures are available. The duration of antibiotic therapy will depend on severity of the clinical condition at presentation, whether blood cultures were positive and recovery after biliary drainage. Most cholangitis patients will respond satisfactorily to initial conservative therapy with broad spectrum antibiotics. Although these patients could get elective biliary decompression and stone removal, it appears wise to achieve biliary decompression in all cholangitis patients at the earliest time point possible, preferably within 24 h, since up to 20% of patients will run a progressive course with severe deterioration. Urgent decompression should be considered in case of severe cholangitis not responding to fluid resuscitation and intravenous antibiotics. Consensus criteria for defining severity of cholangitis have been published.

#### **Conflict of interest**

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