

A Brief Review on Cholelithiasis

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ABSTRACT:

Cholelithiasis is one of the most prevalent diseases in gastroenterology. There are many factors in cholelithiasis such as genetic, lack of physical activity, obesity, dietary, age, and other comorbidities. Commonly, cholelithiasis occurs asymptotically; however Murphy's sign is one of the most frequent pathognomonic findings in abdominal examination. Ultrasonography is known as the gold standard imaging examination in diagnosing cholelithiasis. The management of cholelithiasis can be divided into two categories, such as medical treatment and surgical management, which depends on the patient's condition. Therefore, this review has intended to provide a compiled up-to-date information on etiology, epidemiology, formation of gallstones, pathophysiology, signs and symptoms, risk factors, factors influencing gallstone formation, complications, diagnosis and management of Cholelithiasis.

KEY WORDS:

Cholelithiasis, ultrasonography; urxodeoxycholic acid; laparoscopic cholecystectomy.

I. INTRODUCTION:

Cholelithiasis or gall stone is the presence of hardened deposits of digestive fluid that is formed in the gall bladder. The gallbladder is a small organ located just beneath the liver. It holds the digestive fluid known as bile, which will be released into the small intestine. Cholelithiasis affects approximately 5.3 – 25% of the population, according to clinical survey reports from Europe, North and South America, and Asia. Commonly, this disorder occurs asymptotically, and only 20% of people with cholelithiasis experience pain and complications. The most common risk factor and is also related to metabolic syndrome events. Pimple et al stated that cholelithiasis is commonly found in females in the 4th to 5th decade of life, with abdominal pain being the most typical symptom.

There are some other risk factors of cholelithiasis, such as genetics, the lack of physical activity which is also associated with metabolic syndrome, obesity which is related to the increase of cholesterol gallstones formation, dietary factors, and other comorbidities. This review explains briefly about cholelithiasis.

ETIOLOGY:

Gallstones usually form from sluggish emptying of bile from the gallbladder. When bile is not fully drained from the gallbladder, it can precipitate as sludge, which in turn can develop into gallstones. Biliary obstruction from various causes such as strictures in the bile duct or neoplasms may also lead to gallstones. The most common cause of cholelithiasis is the precipitation of cholesterol from cholesterol – rich bile. The second most common form of gallstones is pigmented gallstones. These form from the breakdown of red blood cells and they are black. The third type of gallstones is mixed pigmented stones, a combination of calcium substrate such as calcium carbonate or calcium phosphate, cholesterol, and bile. The fourth type of stone is calcium stones. These may be due to the precipitation of serum calcium in patients with hypercalcemia. Often these patients will have concurrent kidney stones.

EPIDEMIOLOGY:

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

FORMATION OF GALLSTONES:

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 condition cause the liver to make too much bilirubin through the processing of breakdown of haemoglobin. 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.

The three most common types of gallstones are cholesterol gallstones, black pigment gallstones and brown pigment stones. 90% of gallstones are cholesterol gallstones.

PATHOPHYSIOLOGY:

Gallstones occur when substance in the bile reach their limits of solubility. As bile becomes concentrated in the gallbladder, it becomes supersaturated with these substances, which in time precipitate into small crystals. These crystals, in turn, become stuck in the gallbladder mucus, resulting in gallbladder sludge. Over time, these crystals grow and form large stones. Complications caused by gallstones are a direct consequence of occlusion of the hepatic and biliary tree by sludge and stones.

SIGNS AND SYMPTOMS:

Gallstones generally don't cause symptoms unless they get stuck and create a blockage. This blockage causes symptoms, most commonly upper abdominal pain and nausea. These may come and go, or they may come and stay. You might develop other symptoms if the blockage is severe or lasts a long time, like:

- Sweating.
- Fever.
- Fast heart rate.

- Abdominal swelling.
- Tenderness.
- Yellow tint to skin.
- Yellow tint to eyes.
- Dark coloured stool.
- Light coloured urine.

Gallstone symptoms are not different in women or people Assigned Female at Birth (AFAB). But people AFAB may be more likely to experience referred pain – pain that you feel in a different place from where it started. So, they may be more likely to experience gallstone pain in their arm, shoulder, chest or back. People AFAB are also more prone to chronic pain.

RISK FACTORS:

- In pregnancy, progesterone decreases the contractility of the gallbladder leading to stasis
- Age
- Obesity
- Genetics
- Certain medications (estrogens, fibrates, somatostatin analogs)
- Stasis of the gallbladder
- Female gender
- Metabolic syndrome
- Rapid weight loss
- Prolonged fasting
- Bariatric surgery
- Crohn disease, ileal resection.

FACTORS INFLUENCING GALLSTONE FORMATION:

Dysfunction of the gallbladder or other parts of the bile – secretion pathway can result in gallstone formation. Given that the bile – secretion pathway is a complex process, there are many reasons for the formation of gallstones. Evidence suggests that gallstones are related to age, gender, female physiological status, obesity, cardiovascular disease, micro biome, sugar metabolism, and various environmental exposures. Based on large no.of studies, the interaction of five main factors were proposed. The pathogenesis of cholesterol gallstone disease is precipitated by: genetic factors; excessive cholesterol secretion by the liver (leading to super saturation of cholesterol in gallbladder bile); rapid phase change by accelerating the growth of cholesterol crystals and solid cholesterol crystals; impairment of gallbladder motility; and intestinal factors. Intestinal factors can be further broken down into two categories: increased cholesterol absorption from the small intestine to the liver,

eventually resulting in increased bile secretion, and micro biota that inhibit the intestinal tract.

These factors will increase the production or growth of cholesterol crystals, eventually leading to the formation of stones.

- Age
- Obesity
- Gender
- Genetics
- CVD
- Microbiome
- Estrogen
- Sugar Metabolism

COMPLICATIONS:

- Cholecystitis (gallbladder inflammation)
- Pancreatitis (pancreas inflammation)
- Cholangitis (bile duct inflammation)
- Hepatitis (liver inflammation)
- Jaundice (bile in bloodstream)
- Septicaemia (an infection in bloodstream)
- Bile duct stones
- Gallbladder empyema, necrosis
- Gallbladder cancer
- Cholecystoenteric fistula.

DIFFERENTIAL DIAGNOSIS:

- Acute pancreatitis
- Appendicitis
- Bile duct strictures
- Bile duct tumours
- Diabetic ketoacidosis
- Emergent treatment of gastroenteritis
- Oesophageal spasm
- Gallbladder cancer
- Gastroesophageal reflux disease (GERD)
- Hepatitis
- Irritable bowel syndrome
- Pancreatic cancer
- Pancreatitis (acute or chronic)
- Peptic ulcer disease.

DIAGNOSIS:

Diagnosis of cholelithiasis is established by performing history taking physical examination, blood examination, and ultrasonography.

LAB TESTS

A healthcare professional may take a blood sample from you and send the sample to a lab to test. The blood test can show signs of infection or inflammation of the bile ducts, gallbladder, pancreas or liver.

IMAGING TESTS

Health care professionals use imaging tests to find gall stones a technician performs these tests in your doctor's office, an out patients enter, or a hospital .A radiologist reads and reports on the images. You usually don't need anaesthesia or a medicine to keep you clam for most of these tests. However, a doctor may give you anaesthesia or a medicine to keep u clam for endoscopic retrograde cholangiopancreatography (ERCP)

ULTRA SOUND

Ultra sound is the best imaging tests for finding gall stones. Ultra sound uses a device called a transducer, which bounces safe, painless sound waves off your organs to create an image or picture of their structure. If u have gall stones, they will be seen in the image. Sometimes, health care professionals find silent gall stones when you don't have any symptoms.

COMPUTED TOMOGRAPHY (CT-SCAN)

CT- scans use a combination of x-rays and computer technology to create images of your pancreas, gallbladder, and bile ducts. CT scans can show gall stones, or complications such as infections and blockage of the gallbladder or bile ducts. However, CT- scans also can miss gall stones that you may have.

MAGNETIC RESONANCE IMAGING (MRI)

MRI machines use radio waves and magnets to produce detailed images of your organs and soft tissues without x- rays. MRIs can show gall stones in the ducts of the biliary tract.

CHOLESCINTIGRAPHY

Cholescintigraphy also called a hydroxyl iminodiacetic acid scan, HIDA scan, or Hepatobiliary scan-uses a safe radioactive material to produce pictures of your biliary tract. You" II lie on a table while a health care professional injects a small amount of the radioactive material into a vein in your arm. The health care professional may also inject a substance that causes your gallbladder to squeeze. A special camera takes pictures of the radioactive material as it moves through your biliary tract. Doctors use cholescintigraphy to diagnose abnormal contractions of your gall bladder or a blockage in the bile ducts.

ENDOSCOPIC RETROGRADE

CHOLANGIOPANCREATOGRAPHY (ERCP)

ERCP combines upper gastro endoscopy and x-rays to treat problems of your bile and pancreatic ducts. ERCP helps the health care professional locate the affected bile duct and the gall stones. This test is

more invasive or involves more instruments inside your body than other tests. Doctors use it selectively, usually to remove a gallstone that is stuck in the common bile duct.

MANAGEMENT

MEDICAL DISSOLUTION OF GALL STONES

Ursodeoxycholic acid (Ursodiol) is a gallstone dissolution agent. In humans, long-term administration of ursodeoxycholic acid reduces cholesterol saturation of bile both by reducing liver cholesterol secretion and by reducing the detergent effect of bile salts in the gallbladder (thereby preserving vesicles that have a high cholesterol-carrying capacity). Desaturation of bile prevents crystals from forming and, in fact, may allow gradual extraction of cholesterol from existing stones. In patients with established cholesterol gallstones, treatment with ursodeoxycholic acid at a dose of 8-10 mg/kg/d PO divided bid/tid may result in gradual gallstone dissolution. This intervention typically requires 6-18 months and is successful only with small, purely cholesterol stones. Patients remain at risk for gallstone complications until dissolution is completed; the recurrence rate is 50% within 5 years. Moreover, after discontinuation of treatment, most patients form new gallstones over the subsequent 5-10 years.

CHOLECYSTECTOMY

Removal of the gallbladder (cholecystectomy) is generally indicated in patients who have experienced symptoms or complications of gallstones, unless the patient's age and general health make the risk of surgery prohibitive. In some cases of gallbladder empyema, temporary drainage of pus from the gallbladder may be preferred to allow stabilization and to permit later cholecystectomy under elective circumstances. In patients with gallbladder stones who are suspected to have concurrent common bile duct stones, the surgeon can perform intraoperative cholangiography at the time of cholecystectomy. The common bile duct can be explored using a choledochoscope. If common duct stones are found, they can usually be extracted intraoperatively. Alternatively, the surgeon can create a fistula between the distal bile duct and the adjacent duodenum, allowing stones to pass harmlessly into the intestine.

OPEN VERSUS LAPAROSCOPIC CHOLECYSTECTOMY

The first cholecystectomy was performed in the late 1800s. The open approach pioneered by

Langenbuch remained the standard of care until the late 1910s, when laparoscopic cholecystectomy was introduced. Laparoscopic cholecystectomy was the vanguard of the minimally invasive revolution, which has effected nearly all areas of modern surgical practice. Currently, open cholecystectomy is mainly reserved for special situations; the traditional open approach to cholecystectomy employed a large right subcostal incision. In contrast, laparoscopic cholecystectomy employs four very small incisions. Recovery time and postoperative pain are diminished markedly by the laparoscopic approach.

In its 2010 guidelines for the clinical application of laparoscopic biliary tract surgery, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) states that patients with symptomatic cholelithiasis are eligible for laparoscopic surgery. Cholelithiasis patients whose laparoscopic cholecystectomy was uncomplicated may be sent home the same day if postoperative pain and nausea are well controlled. Patients older than 50 years may be at greater risk of readmission. During laparoscopic cholecystectomy, a surgeon must retrieve stones that might escape through a perforated gallbladder. Conversion to an open procedure might be required in certain cases in patients, in whom gallstones have been lost in the peritoneal cavity; the current recommendation is to follow up with ultrasonography examinations for 12 months. Most complications (usually, abscess formation around the stone) occur within this time frame. The most dreaded and morbid complication of cholecystectomy is damage to the common bile duct. Bile duct injuries increased in incidence with the advent of laparoscopic cholecystectomy, but the incidence of this complication has since declined as experience and training in minimally invasive surgery have improved.

CHOLECYSTOSTOMY

A cholecystostomy is a minor procedure that creates an opening into your gallbladder. "Cholecyst" – means gallbladder and "ostomy" – means a surgically created opening in your gallbladder is a small, hollow organ that stores bile for your digestive system. A health care provider might have to create an opening in your gallbladder to treat gallbladder disease like infection, inflammation or gallstones.

II. CONCLUSION

In conclusion, cholelithiasis refers to the formation of gallstones and may present with or

without any obvious symptoms. Because cholelithiasis is a multi-factorial, prompt and structured diagnostic approaches including history taking, physical examination, laboratory tests, and imaging tests, should be performed to decided properly and minimize false - positive events.

REFERENCES

- [1]. Stinton LM, Myers RP, Shaffer EA (2010) Epidemiology of gallstones, *Gastroenterol clin north Am* 39(2):157-169.
- [2]. Pimpale R, Katakwar P, Akhtar M (2019) Cholelithiasis: causative factors, clinical manifestations and management. *Int Surg J* 6 (6):2133-2138.
- [3]. Chen Y, Kong J, Wu S (2015) Cholesterol gallstone disease: focusing on the rolr of gallbladder *Laboratory Investigation* 95: 124-131.
- [4]. Gore JM, (2013) Cholelithiasis. *JAAPA* 26 (12):54-55.
- [5]. Reshetnyak VI, (2012) Concept of the pathogenesis and treatment of cholelithiasis. *World J Hepatol* 4 (2):18-34.
- [6]. European Association for the Study of the Liver (2016) EASL clinical practice guidelines on the prevention, diagnosis and treatment of gallstones. *Journal of Hepatology* 65:146-181.
- [7]. Gutt C, Schlafer S, Lammert F (2020) The treatment of gallstone disease. *Dtsch Arztebl Int* 117(9):148-158.
- [8]. Parra-Landazury, N.M.; Cordova -Gallardo, J; Mendez-Sanchez, N. Obesity and Gallstones, *Visc. Med.* 2021, 37, 394-402.
- [9]. Schwab, M.E.; Braun, H.J.; Feldstein, V.A.; Nijagal, A. The natural history of fetal gallstones: A case searies and updated literature review. *J. Matern. Fetal Neonatal Med.* 2020, 35, 4755-4762.
- [10]. Sun, H.; Warren, J.; Yip, J.; Ji, Y.; Hao, S.; Han, W.; Ding, Y. Factors Influencing Gallstone Formation: A Review of tge Literature. *Biomolecules* 2022, 12, 550.
- [11]. Di Ciaula, A.; Wang, D.Q.; Portincasa, P. An update on the pathogenesis of cholesterol gallstone disease. *Curr. Opin. Gastroenterol.* 2018, 34, 71-80.
- [12]. Di Ciaula A, Portincasa P. Recent advances in understanding and managing cholesterol gallstones. *F1000Res.* 2018;7
- [13]. Rebholz C, Krawczyk M, Lammert F. Genetics of gallstone disease. *Eur J Clin Invest.* 2018 Jul;48(7):e12935.
- [14]. Chung Ay, Duke Mc. Acute Biliary Disease. *Surg Clin North Am.* 2018 oct;98(5):877-894.
- [15]. Yeh DD, Chang Y, Tabrizi MB, Yu L, Cropano C, Fagenholz P, King DR, Kaadarani HMA, de Moya M, Velmahos G. Derivation and validation of a practical Bedside Dcore for the diagnosis of cholecystitis. *Am J Emerg Med.* 2019 Jan ;37(1):61-66.