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CHOLELITHIASIS: AN OVERVIEW ON PRE-DISPOSING FACTORS, PATHOGENESIS AND MANAGEMENT IN CLINICAL CARE SETTING

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ABSTRACT

Cholelithiasis is one of the most common disorders and a major source of abdominal morbidity around the world. The presence of one or more gallstones in the bile duct is known as cholelithiasis. Gallstone disease is spreading globally as a result of dietary changes, lifestyle changes associated with excessive junk food consumption, and an increase in sedentary behaviour. Gallstone disease is more common in women due to hormonal imbalances. Obesity, diabetes mellitus, and hormonal imbalance are all risk factors for gallstone formation. Cholelithiasis is a serious medical condition that necessitates surgery. However, the technique of therapy has evolved drastically, and laparoscopic cholecystectomy is now gaining popularity. The review focuses on pre-disposing factors, pathogenesis, and management of Cholelithiasis patients.

KEYWORDS: Gallstones, Cholelithiasis, Pre-disposing, Cholecystectomy.

INTRODUCTION

The gallbladder is a tiny organ that situated underneath the liver. Bile is a digestive fluid that is stored in the gallbladder and discharged into the small intestine.[1] The presence of one or more gallstones in the common bile duct is defined as cholelithiasis, often known as gallstone disease. Gallstones are solidified deposits of bile that come in a variety of sizes and shapes.[2]

Gallstones can be as minute as a flake of grit or as large as a tennis ball, and patients may have one enormous gallstone, hundreds of minor stones, or a combination of both.[3] Gallstones form when the chemical contents of bile are out of balance, causing one or more of the components to precipitate.[4]

Gallstones, referred known as cholelithiasis, are stones made up of cholesterol, bilirubin, and bile that form in the gallbladder. In most instance, these stones are asymptomatic, and they are discovered by chance. Patients with symptoms include right upper stomach pain, nausea, vomiting, and pain in the epigastrium that extends to the right scapula or mid-back after eating oily or spicy meals. Gallstone complications include cholecystitis, cholangitis, choledocholithiasis, gallstone pancreatitis, and cholangiocarcinoma in rare circumstances. Patients with chronic gallstones may experience gallbladder fibrosis and loss of motor function, culminating in cholecystitis, or gallbladder inflammation.[5] Acute or chronic cholecystitis can occur, with recurring episodes of acute inflammation leading to chronic cholecystitis, the most prevalent condition linked with gallstones. 90 percent to 95 percent of chronic cholecystitis patients are caused by cholelithiasis. Insufficient evidence suggests that those with chronic cholecystitis are more likely to acquire gallbladder cancer, presumably because both illnesses are associated with inflammation.[6,7]

EPIDEMIOLOGY

Gallstone disease was formerly thought to be a Western condition.[5] It is believed that 20–25 million adults in the United States are affected.[8] Eighty percent of people with gallstones who develop symptoms have biliary colic.[9] Gallstone disease and associated consequences (cholecystitis, pancreatitis, and cholangitis) are the leading causes of gastrointestinal morbidity and hospitalization.[10] Gallstone disease is more common in older people and women. Clinically, the incidence of gallstone disease has increased over the last decade, coinciding with an increase in calorie and fat consumption, a decrease in fiber intake, and an increase in the prevalence of the population's sedentary lifestyle.[11] According to specialists, the obesity phenomenon has likely intensified the rise in gallstones. Cholelithiasis is rather prevalent, affecting roughly 6% of men and 9% of women. Gallstones are uncommon in Africa and Asia.

Gallstones are prevalent, with prevalence rates ranging from 60% to 70% in American Indians and 10% to 15% in white adults in affluent countries. Cholelithiasis is the most prevalent inpatient diagnosis among patients with gastrointestinal and liver diseases.[12,13] It is

also one of the most expensive digestive disorders for the healthcare system, as well as the leading cause of death from gastrointestinal nonmalignant disease.[14] Certain gallstone risk factors are unchangeable: feminine gender, advancing age, and ethnicity/family pedigree. Obesity, metabolic syndrome, rapid weight loss, some disorders (cirrhosis and Crohn disease), gallbladder stasis (from spinal cord damage or medicines like somatostatin), and lifestyle are all controllable. Gallstones triggered by cholesterol are becoming more prevalent, along with other metabolic disorders such as insulin resistance and type 2 diabetes, enlargement of visceral adiposity as a result of overweight and obesity, and metabolic syndrome.[15]

TYPES OF CHOLELITHIASIS

Gallstones are mostly made up of cholesterol, bilirubin, and calcium salts, with trace amounts of protein and other substances.[16]

Gallstones are classified into three categories.[17]

(i) Pure cholesterol stones consisting at least 90% cholesterol

(ii) Pigment stones, either brown or black, containing at least 90% bilirubin

(iii) Stones of mixed composition,

They contain different amounts of cholesterol, bilirubin, and other ingredients such as calcium carbonate, calcium phosphate, and calcium palmitate.[2] Brown pigment stones are mostly calcium bilirubinate, whereas black pigment stones are constituted of bilirubin, calcium, and/or tribasic phosphate.[18] Pure cholesterol crystals are fairly soft, and protein exerts a crucial role in the strength of cholesterol stones.[19]

Types of stone	Cholesterol Gallstones	Black pigment gallstone	Brown pigment gallstone
Colour	Yellow to dark green	Black	Brown
Shape	Oval in shape with dark central spot	Various shapes	Various shapes rounded to faceted
Cholesterol Content	70%	30%	43%
Composition	Cholesterol (50-100%)	Calcium Bilirubinate polymer	Unconjugated bilirubin, calcium soaps of fatty acids, cholesterol & mucin
Location	Gallbladder ±Common duct (~10%)	Gallbladder ±common duct	Bile duct
Detection	Ultrasonography	ultrasonography	Cholangiography
Clinical Association	Metabolic: family history, obesity, female sex, aging	Increased or altered bilirubin excretion in	Infection, inflammation, infestation

	excessive cholesterol	hemolysis, cirrhosis, cystic fibrosis, crohns disease, advanced age	
Clinical Disease	Gilbert syndrome, Sickle cell disease, cystic fibrosis	Diabetic mellitus	Bacterial-infection, Parasitic infection

PRE-DISPOSING FACTOR

Risk factors for Cholelithiasis can be classified as genetic or environmental, and further classified as modifiable and non-modifiable.[20,21,22]

Age	Gallstones are 4-10 times more common in elderly adults than in younger generations. Due to a decrease in the activity of cholesterol 7 hydroxylase, the rate-limiting enzyme for bile acid secretion, biliary cholesterol saturation increased with age.[23]
Gender	Gallstones generally two to three times more common among females during their reproductive years than in males, due to the high of oestrogen, which elevates biliary cholesterol synthesis.[24]
Obesity and body fat distribution	Obesity is a major risk factor for gallstone disease, particularly in women. It stimulates cholesterol biliary secretion, which increases the chance of cholesterol gallstones. Obesity's lithogenic high mortality in young women, as according epidemiological studies.[19]
Rapid weight loss	If a person loses weight too quickly, the liver secretes more cholesterol and cholesterol from adipose tissue deposits is immediately mobilized. In fasting associated with severely fat restricted diets, gallbladder contraction is reduced, and gallstones are more likely in those who are overweight or obese.[25]
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.[26,27]
Physical activity	Regular exercise, alone or in combination with dieting, improves several metabolic abnormalities linked to obesity and cholesterol gallstones, in addition to facilitating weight control. Sedentary behaviour, on the other hand, is linked with an increased risk of cholecystectomy.[28]
Drugs	All fibric acid derivatives lower serum cholesterol while enhancing biliary cholesterol saturation. Clofibrate affects the acyl-CoA cholesterol acyltransferase activity in the liver (ACAT). Moreover, long-term usage of proton pump inhibitors has been linked to decreased gallbladder function, which might lead to gallstone formation. Ceftriaxone's lithogenic effects had earlier been mentioned.[29,30,31,32]
Diabetes	Triglycerides, a subtype of fatty acid, are observed in individuals with diabetes. Gallstones may be aggravated by these fatty acids. Gallbladder function is altered in diabetic neuropathy, and insulin-induced hyperglycemia tends to increase the lithogenic index.[29]
Acute Cholecystitis	The risk factors for cholecystitis are considered to be identical to those for cholelithiasis.[20,21]
Acute Acalculous Cholecystitis (AAC)	Serious illness (e.g., major surgery, burns, sepsis, or trauma), chronic fasting, or total parenteral nutrition, where all predispose to hepatic stasis, shock, vasculitis, and a history of immunological weakness, have all been risk factors for AAC.[21]

CLINICAL PRESENTATION

- Gallstones cause no symptoms in the majority of patients. These gallstones are termed as "silent stones," and usually don't have to be treated.[33]
- Typical gall stone symptoms of biliary colic (intermittent episodes of prolonged, severe, right upper quadrant (RUQ) abdominal pain usually combined with nausea and vomiting), normal physical examination findings, and normal laboratory test results were common among patients with gallstone disease. Diaphoresis, nausea, and vomiting are all possible complications.[34]
- Gallbladder contraction is frequently triggered by high - calorie foods. The soreness generally starts within an hour of consuming a fatty meal, is severe and dull, and can remain anywhere from 1 to 5 hours.[34]
- Fever, sensitive right upper quadrant with or without Murphy's sign, and soreness while tapping the right costal arch (Ortner's sign) are all common symptoms.

PATHOGENESIS

Gallstones impaction in the bladder neck, Hartmann's pouch, or the cystic duct is the most prevalent cause of cholelithiasis; however, gallstones are not always present in cholecystitis.[38] The gallbladder expands, the walls tighten, the blood supply reduces, and an effusion may occur.[36,38] Cholelithiasis can be acute or chronic, with chronic cholelithiasis growing as a result of repeated occurrences of acute inflammation. Various microorganisms, including those that release gas, can infect the gallbladder and cause infection. Necrosis and gangrene can develop in an inflamed gallbladder, which can lead to clinical sepsis if left untreated.[35,36,38] Failure to treat cholelithiasis effectively can lead to gallbladder perforation, a rare but potentially fatal complication.[36,38,40] Gallstone can develop as a result of cholelithiasis.

PATHOPHYSIOLOGY

Gallstones block the cystic duct with hard, pebble-like formations. The presence of biliary sludge, a viscous mixture of glycoproteins, calcium deposits, and cholesterol crystals in the gallbladder or bile ducts, often precedes the production of gallstones.[38] Hypersaturation is induced primarily by hypersecretion of cholesterol due to abnormal hepatic cholesterol metabolism, which results in a cholesterol concentration greater than its solubility percentage.[35,37] In the bile, a biased balance of pronucleating (crystallization-promoting) and antinucleating (crystallization-inhibiting) proteins can also speed up cholesterol

crystallisation.[35-38] Mucin seems to be a glycoprotein combination released by biliary epithelial cells that acts as a pronucleating protein. Mucin breakdown by lysosomal enzymes is slowed.[37]

Gallstone development is further encouraged by a loss of gallbladder muscular-wall mobility and excessive sphincteric contraction.[35] Hypomotility causes bile stasis and a reduction in reservoir function.[37,38] As a result of insufficient filling, a greater proportion of hepatic bile is redirected to the small bile duct.[35,38] Bilirubin, a substance formed as a byproduct of the normal breakdown of RBCs, is sometimes seen in gallstones. The reasons might include biliary tract infection and increased enterohepatic cycling.[35,37,39] In Asia and Africa, pigment stones are more common.[37,39]

COMPLICATION

- Choledocholithiasis is a complication of gallstones. When gallstones obstruct the common bile duct, the transport of bile from the liver to the intestine is delayed. As blood pressure rises, liver enzymes rise, inducing jaundice.
- Pancreatitis
- Gall bladder cancer
- Acute cholecyctitis.[34]

DIAGNOSIS

Recurrent incidents of right-upper-quadrant or epigastric pain, which suggests biliary colic and Boas' sign, are commonly used to identify this condition. Ultrasonography, nuclear scanning (cholescintigraphy), and oral cholecystography are the three basic techniques used to confirm the diagnosis of cholelithiasis, cholecystitis, and other gallbladder illnesses.[19] The most common imaging studies used to diagnose cholelithiasis and cholecystitis are ultrasonography and cholescintigraphy.[41] Stones, thickening of the gallbladder wall, pericholecystic fluid, and Murphy's sign (pain) on contact with the ultrasonographic probe are all positive findings on ultrasonography.[41] In more than 90% of patients, ultrasonography performed during fasting indicates the proper diagnosis, whereas bile-duct stones may be undetected in 50% of cases.[37] The excess of alanine aminotransferase levels higher than 2.5 times above normal is the most accurate indicator of gallstones as the causation of acute pancreatitis.[43]

Abdominal radiography and computed tomography were sometimes effective since only 10% of gallstones are calcified and so visible as radiopaque masses in the right upper quadrant. For the diagnosis of choledocholithiasis, magnetic-resonance-cholangio-pancreatography (MRCP) has rapidly remained common[42], and its accuracy is identical to that of ERCP.

TREATMENT

Gallstones are treated appropriately depending on whether or not they are generating symptoms. The most prevalent reason for gallstone treatment is recurrent episodes of upper abdominal pain linked to gallstones.[44] The purpose of symptomatic treatment for cholelithiasis is to remove stones from the gallbladder or bile ducts.

The basic treatments for GD are.

- Endoscopic Cholecystectomy
- Litholytic Therapy (Lt)
- Extracorporeal Shock Wave Lithotripsy (Eswl)
- Eswl + Litholytic Therapy
- Percutaneous Trans hepatic Lt

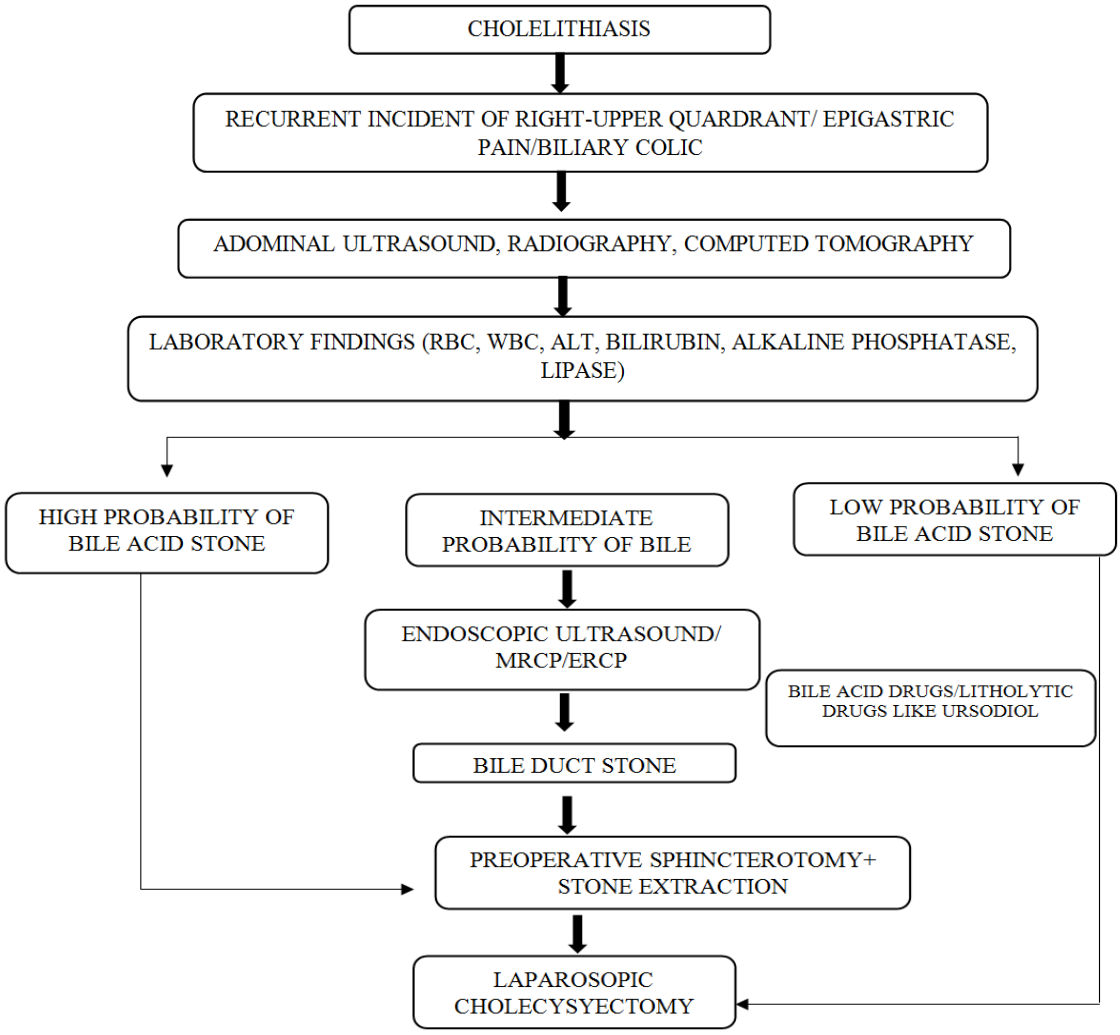
OPEN/ LAPAROSCOPIC CHOLECYSTECTOMY

Until the development of laparoscopic cholecystectomy[45], open cholecystectomy was the gold standard of gallstone treatment. In a healthy, low-risk candidate, an open cholecystectomy needs a few days in the hospital and has a mortality rate of less than 1%.[46] The most significant disadvantages of open cholecystectomy are the discomfort and weeks of impairment that follow.[47] Laparoscopic cholecystectomy has become widely used, with a complication rate that is probably at least as excellent as the open technique.[48] However, due to significant adhesions around the gallbladder, a patient who has had several abdominal surgeries may not be a good candidate for laparoscopic cholecystectomy. A patient who is medically unfit for open cholecystectomy is unlikely to be a good candidate for laparoscopic cholecystectomy. Endoscopic retrograde cholangiopancreatography can be used to evaluate and treat potential stones in the common bile duct before laparoscopic cholecystectomy.[49] If cholangiography reveals common-bile-duct stones during laparoscopic cholecystectomy, an open examination of the common bile duct may be required.[50]

BILE ACIDS DRUGS

Gallstones are treated using litholytic medicines. litholytic drugs that contain chenodeoxycholic and ursodeoxycholic (UDCA). They're more efficient and have almost no adverse effects. The medication eliminates bile acid deficiency, inhibits hepatic cholesterol synthesis and release into the bile, and reduces intestinal absorption, resulting in a lower bile cholesterol level and stone breakdown.[51] Gallstones can be dissolved by chenodeoxycholic acid (chenodiol) and ursodeoxycholic acid (ursodiol), although chenodiol causes diarrhoea and abnormal aminotransferase levels, whilst ursodiol does not. Only a small percentage of patients with symptomatic cholesterol gallstones can benefit from bile salt therapy. It is not recommended for patients who have acute cholecystitis or stones in the common bile duct and require immediate treatment. This is a common misunderstanding. Candidates for bile salt treatment must have a patent cystic duct and noncalcified cholesterol gallstones. Gallstones typically reappear after stopping oral bile salts.[52]

TREATMENT ALOGORITHAM OF PATIENTS WITH CHOLELITHIASIS



CONCLUSION

Gallstones can cause Cholelithiasis, which can be accompanied with or without notable symptoms. Gallstone disease is more commonly encountered in females, and quick and systematic diagnostic procedures, including history-taking, physical examination, laboratory tests, and imaging tests, should be conducted properly to decide the management and prevent false positive events. Multiple gallstones requires surgical intervention, which is generally accomplished with laparoscopic cholecystectomy, which has fewer complications than open cholecystectomy.

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