Highlighting the risk factors for recurrence of common bile duct stone

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Abstract

Background: A prevalent chronic condition is common bile duct stones (CBDS). Choledocholithiasis and cholelithiasis occur together in 5%–15% of cases of cholelithiasis. The most prevalent kind of treatment, endoscopic cholangiopancreatography with endoscopic sphincterotomy (ERCP), has a success rate of up to 95%, however recurrent choledocholithiasis occurs between 4% and 25% of the time.

Purpose of the review: to highlight the risk factors for recurrence CBDS after choledocholithiasis clearance. These highlights are extrapolated from recently published well respected studies and systematic reviews.

Conclusion: Stone-related factors, anatomical factors, congenital factors, intervention factors, and the frequency of stone recurrence are all carefully categorized as risk factors.

Keywords: risk factors, Gallstone formation, recurrence

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Introduction:

One of the most frequent and expensive digestive conditions requiring hospitalization is cholesterol gallstone disease [1]. Gallstones affect 10%–15% of adult Caucasian populations, and they can affect up to 70% of American Indian communities [1,8] Gallstones are, nevertheless, quite uncommon in Asian countries [9,10]. Gallbladder stones are typically asymptomatic, but 10% to 25% of those who have them may experience specific symptoms such characteristic pain and acute

inflammation of gallbladder, and 1% to 2% of them may experience major life-threatening consequences [2, 3].

Pain, jaundice, and occasionally cholangitis are the most common symptoms and main consequences that come from stones slipping into the common bile duct (CBD) and obstructing the passage of bile in the small intestine [4,5]. Whereas secondary choledocholithiasis is brought on by stones that have migrated from the gallbladder, primary CBD stones refers to stones generated de novo within the biliary tree [6].

The main treatment modality of gallstones is cholecystectomy. Of the total cholecystectomies performed each year, stones in the common bile duct affect 5–15% of patients [7]. To prevent cholecystitis, biliary colic, biliary pancreatic inflammation, or a recurrence of the CBD stone in symptomatic individuals, the primary goal is to secure complete clearance of the CBD [12,13]. On the other hand, there is still disagreement on the appropriate diagnostic and treatment approaches in asymptomatic individuals [11]. Nevertheless even after cholecystectomy, a sizable number of individuals continue to experience CBD stone recurrence. Recurrent bile duct stones are those that are discovered six months or longer following endoscopic retrograde cholangiopancreatography (ERCP) [13, 14, 15].

Anatomy of the biliary tract:

The biliary tract refers to the series of ducts via which the bile produced and expelled by the liver travels as it makes its way to the duodenum, the first section of the small intestine. The biliary tract, a typical feature of most mammals, has several small branches that converge to form the common bile duct, which is frequently referred to as the biliary tree. The portal triad is made up of the bile duct, the portal vein, and the branches of the hepatic artery. In the other two channels, bile flows in the opposite direction from the direction that the blood flows [16].

Usually referred to as the biliary system or tract, this system can also be referred to as "hepatobiliary" when only the liver and bile ducts are involved. Generally speaking, the term "biliary tract" refers to all of the ducts, organs, and structures involved in the generation, storage, and pouring of bile [16].

The biliary tract begins with bile canaliculi that connect to the Canals of Hering connect to the intrahepatic bile ductule (in portal tracts or triads) that connect to the interlobular bile ducts that connect to the left and right hepatic ducts.

The common hepatic duct, which is made up of the left and right bile ducts, joins with the gall bladder's cystic duct before leaving the liver. They come together to produce the pancreatic duct and common bile duct (CBD). Then enter the duodenum through the Vater's ampulla [16].

The gall bladder:

The gallbladder, a hollow cyst, is situated beneath the right lobe of the liver, which is grey-blue in life [8]. When completely inflated, adult gallbladders normally range in size from 7 to 10 centimetres (2.8 to 3.9 inches) in length and 4 centimetres (1.6 inches) in width. The gallbladder has a capacity of about 50 millilitres [17].

The fundus, body, and neck are the three components that make up the gallbladder. The globular base that is angled to face the abdominal wall is known as the fundus. The body is embedded in a groove on the surface of the liver's right lobe. The neck narrows to become continuous with the cystic duct, which forms the biliary tree's fusion with the hepatic duct [17].

Several layers make up the gallbladder wall. The deepest layer of the gallbladder wall is lined by a single layer of columnar cells that resemble the intestinal absorptive epithelium in appearance and feature a brush border known as microvilli. Lamina propria, a muscle layer, an outer perimuscular layer, and serosa are present below the lining epithelium. The muscularis mucosa is absent from the gallbladder, and the muscular fibres are not organised into discrete layers like they are in the intestinal system [17].

The mucosa is made up of a single layer of columnar cells with microvilli, which are tiny hair-like attachments on the cells. Rugae, or little outpouchings formed from the mucosa, are folded and corrugated [17].

Under the mucosa, there is a layer of muscles. This is made of smooth muscle, which does not have distinct layers and has fibres that randomly sit in longitudinal, oblique, and transverse directions. To release bile from the gallbladder, the muscle fibres in this area contract. The presence of Rokitansky-Aschoff sinuses, which are deep openings of the mucosa that can pass through the muscular layer and denote adenomyomatosis, is a unique characteristic of the gallbladder wall. An outer layer of connective and fat tissue covers the muscle layer [17].

Mechanism of bile formation:

The hepatocytes produce and exude bile, which is a physiologically necessary watery fluid. The majority of its ingredients are bile salts, along with phospholipids, cholesterol, electrolytes, conjugated bilirubin, and water [18]. Hepatocytes produce and secrete bile, which is then altered by the cholangiocytes that line the bile ducts.

In addition to having an intact biliary duct tree, active transport networks inside hepatocytes and cholangiocytes are necessary. Hepatocytes initially produce bile by secreting conjugated bilirubin, cholesterol, bile salts, phospholipids, ions, proteins, and water into their canaliculi, which are tiny tubules that connect nearby hepatocytes and eventually unite to create bile ducts [18]. The primary bile secretory mechanism is the canalicular membrane of the hepatocyte, which is made up of the cytoskeleton of the hepatocyte, carrier proteins, and intracellular organelles. Bile acids and ions are

transported via the carrier proteins contained in the canalicular membrane. Molecules are actively pumped into bile by transporter proteins embedded in the canalicular membrane using energy to overcome concentration gradients. Electrochemical and osmotic gradients are produced by this active transport. As a result, water follows conjugated bile salts when they enter the canaliculus due to an osmotic gradient. Passive diffusion of inorganic ions like sodium is made possible by the electrochemical gradient. The entry of conjugated bile salts into the biliary canaliculus is the most efficient bile formation promoter. A total of 600 ml of bile flow through the body each day, 75% of which comes from hepatocytes and 25% from cholangiocytes. About 225 ml per day of the hepatocyte portion of bile flow is dependent on bile salt, and the other half is independent of bile salt. Glutathione and bicarbonate are examples of osmotically active solutes that encourage bile salt-independent bile flow [19].

The bile is formed in two steps the transport through the hepatocyte to be expelled across the canalicular membrane facing the biliary compartment and the uptake of bile acids and ions from plasma across the basolateral (sinusoidal) membrane facing the body compartment [18].

An active transporter protein that keeps sodium and potassium gradients in place is the sodium-potassium ATPase on the basolateral membrane of the hepatocyte. An electrochemical gradient is produced because the cell loses three sodium ions while getting two potassium ions [18]. While the sodium gradient strengthens the sodium-dependent taurocholate cotransporter protein, the electrochemical gradient created across the hepatocyte membrane promotes the uptake of positively charged ions. This transporter permits conjugated bile acids to enter the system. The organic anion transporter protein, however, is not dependent on sodium for the importation of organic anions. The sodium-taurocholate cotransporting protein, ion exchangers that control pH like the sodium-hydrogen exchanger and the sodium-bicarbonate cotransporter, organic anion and cation transporters, and non-esterified fatty acid transporters are just a few of the transporters embedded in the basolateral surface of the hepatocyte [18].

The majority of the transporter proteins in the hepatocytes' canalicular membrane belong to the family of ATP-binding cassette proteins. Actively carrying chemicals and enzymes into the bile are these proteins. Bile salt export pump (BSEP), multispecific organic anion transporter (MRP2), multiple drug resistance 1 and 3 (MDR1 and MDR3), ATP dependent transporter of organic cations, ATP dependent phospholipid transporter (flippase), and canalicular bicarbonate transporter are some of the pump proteins that make up this system. In addition to enzymes like alkaline phosphatase, the canalicular membrane transporters aid in pumping chemicals into the bile against concentration gradients. Moreover, there are microfilaments that constrict in order to promote bile secretion through the canaliculi. The canalicular membrane only covers 1% of the hepatocyte's surface area [20].

The transport proteins anchored in the apical canalicular region of hepatocytes are the primary regulators of bile flow and bile composition. In order to pump organic solutes into bile despite

gradients of high concentrations of approximately 1:100 to 1:1000 compared to their concentration in plasma, the majority of these canalicular membrane transporters, which are members of the ABC superfamily, must use ATP [21].

They are composed of the P-glycoprotein MDR1 (ABCB1), which transports organic cations; Floppase MDR3 (ABCB4) transfers phosphatidylcholine to the canalicular membrane's outer domain; The MRP2 [multispecific organic anion transporter (ABCC2)] pumps a number of medications and other chemical conjugates as bilirubin digucuronide; the bile salt export pump, (BSEP, *ABCB11*) which is bile salts transporter; the breast cancer resistance protein (BCRP, ABCG2), hetermeric transporters (ABCG5 and ABCG8) excrete cholesterol and plant sterols into bile [18].

Phosphatidylcholine (PC) and cholesterol make up the majority of the lipid components in bile. Having values between 97 and 320 mg/dL and 140 to 810 mg/dL, respectively. Although the canalicular membrane also contains phosphatidylethanolamine, sphingomyelin, and phosphatidylserine, PC represents nearly all biliary phospholipids in bile A canalicular floppase (MDR3 in humans) is required for PC secretion, which also depends on bile salt excretion [18]

There are two hypothesized methods for how PC is expelled into bile. The first is that PC enters vesicles or cytosolic transport proteins that attach to the canalicular membrane, where it is subsequently flipped to the outer leaflet by MDR3. Bile salts discharged into the canalicular lumen may directly increase PC extraction because the accumulation of PC on the outer side of the canalicular membrane is intrinsically unstable. According to a different explanation, bile salts operate to destabilise PC microdomains that have accumulated on the outside leaflet, causing vesicles to first bud and then pinch off into bile. These hypotheses account for the findings that MDR3 and bile salts are essential for phospholipid excretion [18].

Although the mechanism by which the heteromeric ABC transporters ABCG5/G8 result in the extrusion of cholesterol is still unclear, evidence suggests that this process requires micelle-forming bile salts rather than other cholesterol receptors such high-density lipoprotein (HDL) [22].

Whereas Nieman-Pick-C2, a cholesterol-binding protein produced by the biliary system, enhances biliary cholesterol secretion by boosting ABCG5/G8-mediated cholesterol transport, Nieman-Pick C1-like 1 (NPC1L1) protein on the canalicular membrane inhibits cholesterol excretion in bile [14]. It is possible that hepatic NPC1L1 regulates cholesterol homeostasis by reducing NPC2 synthesis [24].

The most important risk factor for gallstone formation is thought to be increased biliary cholesterol release as well as cholesterol supersaturation of the bile. Almost 2/3 of the daily intestinal cholesterol input (800–1000 mg) in humans is eliminated through biliary cholesterol excretion, which is carried out by the canalicular transporters ABCG5/G8. An additional 300 mg is obtained through food [25].

Mechanism of gallstone formation:

Age, female gender, race, and lithogenic (LITH) genes are unmodifiable risk factors for gallstone disease. Modifiable risk factors include obesity, insulin resistance, physical inactivity, and other diseases. Gallstones are mostly made of cholesterol in 75–80% of instances in Western nations, and they are frequently linked to broader systemic problems, and the rest are pigment stones [26].

Gallstone development is not caused by a single risk factor; instead, interrelated disorders are critical in the development of cholesterol gallstones: Gallbladder dysmotility, genetic factors, hepatic hypersecretion of cholesterol, rapid phase transitions of cholesterol in bile, and altered gut microbiota are some of the other factors. Intestinal factors include cholesterol absorption, slow intestinal motility, and altered gut microbiota [27].

Risk factors for recurrence of CBD stones:

One of the common gastrointestinal disorders, CBD stones, is a chronic recurring hepatobiliary disease with abnormalities in cholesterol, bilirubin, and bile acid metabolism as its clinical clues [28].

Nowadays, endoscopic cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST) is a successful treatment modality commoly used for treatment of CBD stones. Success rates for ERCP cannulation and clearance rates both reach 98% [29.30]. The recurrence rate of common bile duct stones after endoscopic therapy, however, was shown to be 4%–25% in a wide number of cohort studies that followed patients after ERCP [31, 32].

1- Factors related to CBD stone characters:

- **stone size and number:**

According to a report, choledocholithiasis with a diameter more than 10 mm is at an increased risk of returning following ERCP. This is explained by the fact that the bile duct will dilate more noticeably the greater the stone diameter is. Cholestasis and bile duct bacterial infection are simple to develop when the normal bile duct motor function is compromised, which is an ideal circumstance for the development of bile pigment stones [33].

Presence of two or more stones in the CBD was thought to be a contributing factor to the recurrence [34]. Another study, however, revealed that the probability of residual bile duct stones after EST was determined by the number and size of the stones rather than the chance of bile duct stone recurrence. The number of stones identified, the diameter, and the chosen treatment plan may all have an impact on the different outcomes [35].

CBD stones size increases with multiple recurrence [36].

- **Chemical composition of stone:**

The chemical constitutions of bile under the physiological state is tightly controlled and balanced. Recurrent stones were all brown pigment stones, according to a research that followed patients following EST for up to 10 years. The presence of bacteria, cholestasis, and papillary stricture may be crucial [37].

Residual stone fragments missed by imaging during ERCP may be the initial nidus for formation of CBD stone and recurrence [38].

The most common form of choledocholithiasis is brown pigment stones, which is typically brought on by bacterial infection. They all have enteric bacterial infections, which are typically complicated with cholangitis. Cultivation of 38 brown pigment CBD stones revealed that 80.5% were bacteria positive. The most often found microbes were enterococci. At the same time, examination of the stone using electron microscopy revealed that 84.2% of the stones had bacterial infection. The growth of brown pigment stones and the presence of bacteria are closely related, according to the findings of bacteriological and morphological investigations [39].

Bacterial infection of bile contributes to stone formation by its ability to secrete certain hydrolytic enzymes as beta-glucuronidase, phospholipase A, and conjugated bile acid hydrolase [40].

Bacterial beta-glucuronidase deconjugates the conjugated bilirubin leading to calcium bilirubinate formation and precipitation, which results in biliary sludge and stone formation [41]. Escherichia coli (E-coli) were isolated from patients with CBD stones and a statistical correlation was found between presence of E-coli and brown pigment formation [42]. Clostridium perfringens secrete a more potent beta-glucorunidase, were also found to be associated with brown pigment stone formation [43].

2-Anatomical factors:

Common bile duct diameter:

Prolonged dilatation of CBD causes decrease in its smooth muscle tone. Subsequently, cholestasis and bacterial infection will occur leading to stone formation [44]. Certain cutoff diameter for recurrence of CBD stones is not established. Studies showed that diameter more than or equal to 10 mm is considered a risk [45,47]. Although, another studies believed that it was 15 mm [49,50].

Periampullary duodenal diverticulum (PAD):

Anatomically PAD is present 2 to 3 cm adjacent to duodenal papilla. According to its relation to the papilla, it is classified into three different types: type I papilla is located in the center of diverticulum, type II papilla is located on the margin of the diverticulum and type III papilla is located outside the diverticulum [49]. Most PAD cases occurred in patients older than 50 years

[51]. PAD is closely related to CBD stone formation [53]. PAD is enhancing CBD formation by unknown mechanisms. The possible explanation may be the following: PAD promotes bacterial spread to bile; food impacted in the PAD also enhances bacterial infection; PAD may compress the distal portion of CBD leading to cholestasis [54-56]. CBD recurrence is related to type I more than type II and type III [57].

The angle of CBD:

Anatomically, the CDB during its pathway to duodenum descents to the right causing an angle. This angulation affects the speed of bile drainage. There is no agreement between studies on the specific angle at which risk of CBD stone formation increases. Some studies reported ≤145° [58,59] and others reported ≤135° [60,61].

3-Congenital and non modifiable factors:

Sex:

Due to effect of estrogen and progesterone on gallbladder and bile secretion, cholelithiasis is prevalent in women more than men. Mainly due to cholesterol supersaturation and slower gallbladder empyting [62].

Moreover, gallstone development is recognised to be at risk during pregnancy [63,64]. However, the majority of research found no connection between sex and the recurrence of CBD stones [65,66].

Age:

Recurrence of CDB stones inceases with aging. Age was found to be the only independent risk factor for recurrence [67]. Aging is usually associated with CBD dilatation, PAD and CBD angulation. These factors may explain this association [68].

Genetic factors:

The Swedish Twin Registry study on 43 141 twin pairs born between 1900 and 1958 presented for the first time conclusive evidence for the role of genetic variables in humans [69]. Mutations in some genes involved in bile formation may be responsible for the formation of gallstones [70,71]. The ABCB4 gene is translated to a transporter protein . This protein is responsible for pumping the phosphatidylcholine into bile. Mutations affecting this gene can lead to disturbed bile constituents and promoting stone formation [72].

ABCG5/8 which encodes the cholesterol transporter in hepatocytes. A common genetic variant ABCG8D19H is documented to be associated with gallstone formation [70].

The gallstone risk factor ABCG8D19H, which is now known, can be used to predict the recurrence of CBD stones [73].

4-Inerventional factors:

Dietary factors and life style:

High caloric diet, cholesterol and fatty acids were documented to be associated with gallstone formation in different studies [74-76]. Also sedentary life and physical inactivity were associated with increased risk [77, 78]. Nevertheless, there were no studies on the relation of these risk factors on CBD stones recurrence.

Drugs:

A meta-analysis of randomized controlled trials conducted during weight loss, documented that ursodeoxycholic acid (UDCA) and/or higher dietary fat content appeared to protect against gallstone formation [79]. UDCA plays a role in prevention of CBD stones recurrence [80, 81].

Proton pump inhibitors (PPI) intake is reported to be a risk factor for recurrence of CBD stones after ERCP. The possible mechanism may be due to bacterial overgrowth. As PPI inhibit gastric acid secretion which is considered a physical barrier against infection [82].

Treatment modality used in CBD stone extraction:

Currently, ERCP is main treatment modality used in treatment of choledocholithiasis [83]. Less common procedures is still used in difficult cases as open common bile duct exploration (OCBDE), laparoscopic common bile duct exploration (LCBDE), extracorporeal shock wave lithotripsy (ESWL), laser lithotripsy and electrohydraulic lithotripsy (EHL) [84-86].

Endoscopic retrograde cholangiopancreatography with sphinecterotomy (ERCP+ EST) is the main procedure used. A prospective follow-up cohort study , comparing the early outcomes after EST and endoscopic papillary balloon dilatation (EPBD) revealed that EST is a risk factor for recurrence [87]. During EST the smooth muscle fibers of sphincter of Oddi is cut, disrupting its function. Food particles may enter the CDB and enhancing bacterial infection [88]. On the other hand, EPBD preserves 70% of sphincter of Oddi function [89,90].

Another modality in treatment of CBD stones removal is small incision EST combined with EPBD. This procedure is associated with less recurrence rate in comparison to conventional EST [91]. The smaller the papillary incision is, the lower the risk of recurrence will be [92].

Mechanical lithotripsy (EML) usage during ERCP, is a rescue maneuver in extraction of large stones. Nevertheless, EML is considered a risk factor for recurrence. During EML large stones are crushed and broken into smaller gravels which can be missed. These microstones form the initial nidus for formation of CBD stone [93].

Biliary endoprosthesis: biliary stent insertion for short term is associated with better clearance of CBD stones and lower rate of recurrence [94]. On the other hand, long term stent insertion is associated with stone recurrence due to formation of stent-stone complex [95].

Cholecystectomy: biliary stones are formed in the gallbladder then migrate to CBD causing obstruction. After extraction of CBD stone using ERCP, cholecystectomy should be performed to decrease recurrence [96,97]. However, postprandial gallbladder contraction sweeps the CBD and prevents gravels accumulation. A study on Asian population with CBD stone showed that a past history of cholecystectomy can increase the risk recurrence of choledocholithiasis after laparoscopic common bile duct exploration (LCBDE) [98]. Cholecystectomy in young age resulting in CBD dilatation, is considered a risk factor for recurrence [99].

Studies showed that early cholecystectomy (within one week) after ERCP removal of CBD stone removal, is associated with lower recurrence rate [100,101].

A meta-analysis comparing the LCBDE+ laparoscopic cholecystectomy (LC) and pre-EST+LC showed that LCBD E+LC is superior as regard perioperative complication and short- and long-term postoperative outcomes [102].

As regard EST vs OCBDE comparison, a study showed that EST is better in perioperative complication [103]. But there are no studies comparing both modalities in the recurrence risk.

History of biliary tract surgery as bile duct exploration and T- tube insertion can lead to biliary stricture and mucosal damage. These will increase the risk of stone formation and recurrence. Also, repeated ERCP causes more and more disruption in the function of sphincter of Oddi [93].

5- number of recurrence of CBD stones:

A large nationwide study on risk factor of CBD stones recurrence after ERCP+EST conducted in South Korea revealed that the recurrence rate was 11.3% for the first time, 23.4 % for the second and 33.4 % for the third time [104]. A similar result was shown in another study followed 477 patients with recurrent choledocholithiasis [33].

Conclusion:

Highlighting the risk factors for CBD stone recurrence is very important in follow up the patients with CBD stones. This enables clinicians and patients to adopt certain preventive measures to decrease complications.

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