Normal Biliary Anatomy and Pathophysiology of Gallstones

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Embryology

During the fourth week of gestation, a bud arises off of the ventral wall of the primitive foregut, which eventually forms the duodenum. The liver diverticulum initially breaks into cranial and caudal portions—the cranial portion becoming the intrahepatic bile ducts and the caudal portion forming the gallbladder and cystic duct. The cranial diverticulum extends into the septum transversum mesenchyme and induces the formation of endothelium from the mesenchymal cells. The ductal cells then follow the development of the connective tissues of the portal venous system.

By the fifth week of intrauterine life, the cells between the liver bud and the remaining foregut proliferate and begin to form a primitive bile duct (Fig. 2.1). A distinct gallbladder bud forms off of this bile duct, and the connection between the two forms the cystic duct. The ventral pancreatic bud forms adjacent to these structures. By the sixth week, the ventral pancreatic duct rotates 180° posterior and medially to join the dorsal pancreatic bud. The duct of Wirsung (located in the ventral pancreatic bud) joins the common bile duct and empties into the duodenum via the ampulla of Vater. The duct of Santorini (located in the dorsal pancreatic bud) may fuse with the duct of Wirsung or may drain into the duodenum separately at the minor papilla, as seen in pancreas divisum [1, 2].

It is widely believed that the common bile duct becomes occluded with epithelial cell proliferation as it elongates, and by the end of the fifth week of development begins to recanalize moving distally toward the gallbladder, which remains solid until week 12. Failure of recanalization has been implicated in the pathogenesis of biliary atresia. However, some studies have failed to demonstrate the process of recanalization in human embryos [3]. As such, many aspects of biliary system development in utero remain unclear.

Anatomical Considerations

The biliary system functions to transport and store bile produced by hepatocytes in the liver. The gallbladder is the primary organ for bile storage, and it is located on the undersurface of the liver between segments IV and V (Fig. 2.2). Cantlie's line, which extends from the gallbladder fossa to the inferior vena cava, traditionally divides the liver into right and left lobes.

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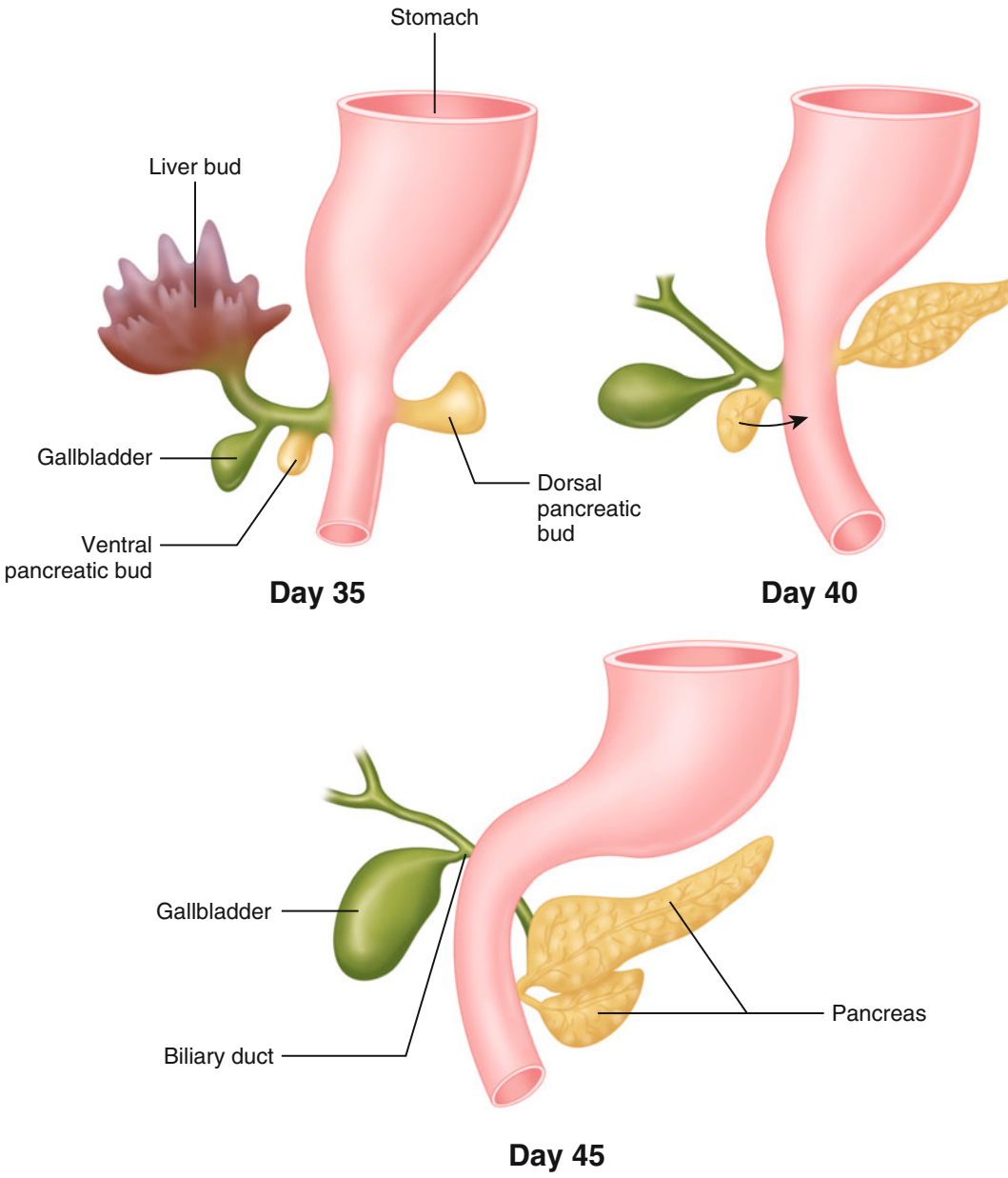

Fig. 2.1 Embryonic development of the bile ducts, gallbladder, and pancreas

The gallbladder is normally 7–10 cm in length and typically contains 30–60 mL of bile, although it is capable of storing up to 300 mL when maximally distended. The gallbladder is composed of a fundus, body, infundibulum, and neck. The fundus contains the majority of smooth muscle, which accounts for the organ's contractile function, while elastic tissue in the body affords distensibility. The infundibulum, often referred to as Hartmann's pouch, is an enlargement of the gallbladder between the body and neck. Dilatation of Hartmann's pouch may result from the presence of gallstones and can obscure the cystic duct and alter the anatomy during a laparoscopic cholecystectomy [4]. The infundibulum and gallbladder neck secrete

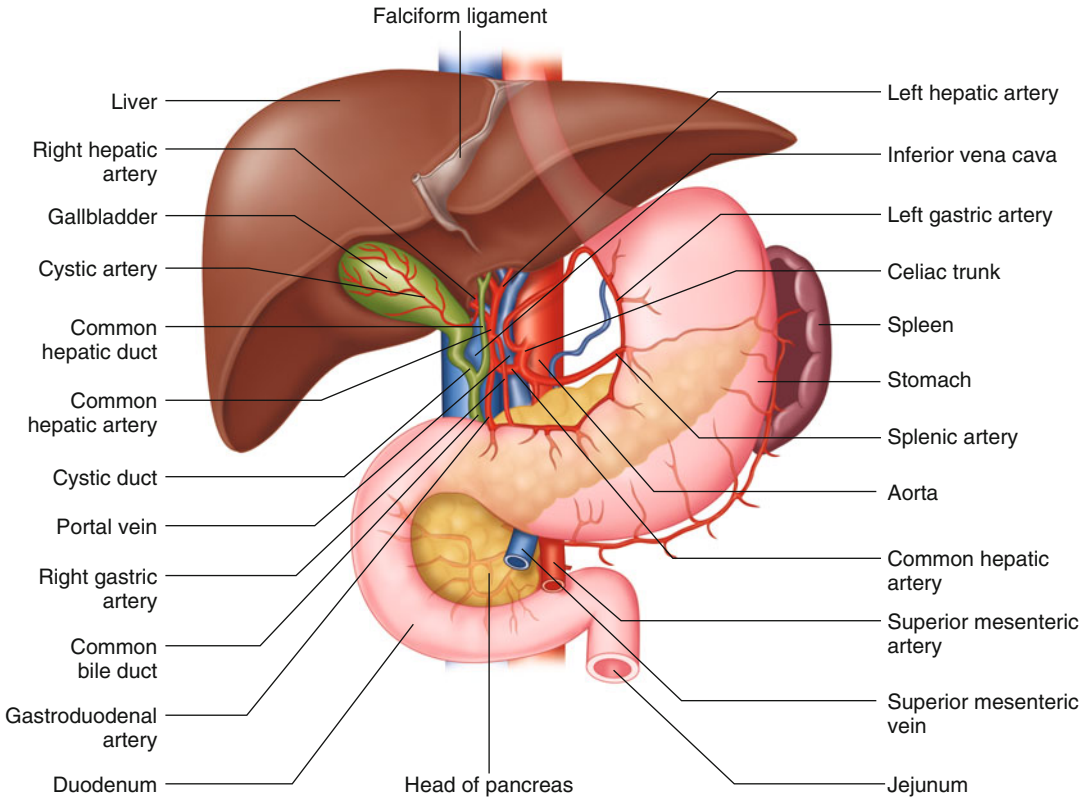

Fig. 2.2 Anatomy of the gallbladder and extrahepatic biliary system

mucus, which protects the gallbladder wall from the caustic nature of bile. The neck of the gallbladder is contiguous with the cystic duct, which joins the common hepatic duct to form the common bile duct. Within the neck of the gallbladder, the spiral valves of Heister act to prevent gallstones from falling into the common bile duct. The gallbladder is enveloped by a thin layer of visceral peritoneum, which is absent posteriorly where the gallbladder contacts the liver bed. Venous and lymphatic drainage of the gallbladder occurs here.

The junction of the right and left hepatic ducts forms the common hepatic duct. The common hepatic duct is about 1–4 cm in length and 4 mm wide. It lies anterior to the portal vein and just to the right of the common hepatic artery. The common bile duct is 7–11 cm long and 5–10 mm in diameter. It is divided into three portions: the supraduodenal, retroduodenal, and pancreatic portions. It courses in the hepatoduodenal ligament lateral to the proper hepatic artery and anterior to the portal vein. It then passes behind the first portion of the duodenum and moves laterally away from the portal vein and hepatic artery. The lowest portion of the common bile duct curves behind the head of the pancreas and can join the pancreatic duct before entering the second portion of the duodenum at the ampulla of Vater 10 cm distal to the pylorus (70 % of the time). In 20 % of cases, the common duct and pancreatic duct join within the duodenal wall, while in the remaining 10 % of patients these structures open into the duodenum separately. The sphincter of Oddi is composed of smooth muscle and surrounds the ampulla, maintaining continence of biliary drainage into the duodenum.

In contrast to the liver, which obtains a substantial portion of oxygen delivery from the portal venous system, the biliary system is supplied entirely by arterial blood flow. The inferior-most aspect of the common bile duct receives blood

from small vessels derived from the posterosuperior pancreaticoduodenal and the gastroduodenal arteries, which anastamose and travel along the medial and lateral walls of the duct (traditionally referred to as 3 o'clock and 9 o'clock). These vessels are at risk for disruption when dissecting close to the duct wall. The supraduodenal duct is perfused by the cystic artery, most commonly derived from the right hepatic artery. The common hepatic artery branches from the celiac axis to give off the proper hepatic artery which ascends alongside the anterior-medial aspect of the portal vein branches to form the right and left hepatic arteries. The right hepatic artery then dives beneath the common bile duct after which it gives off the cystic artery. The cystic artery is often found within the bounds of the triangle of Calot bordered by the cystic duct inferiorly, the common hepatic duct medially, and the liver margin superiorly. The cystic artery may often be found posterior to Calot's lymph node, which drains the gallbladder and is often enlarged in cholecystitis. Venous drainage of the biliary system follows the architecture of the bile ducts, with the veins generally coursing below the ducts [5].

The gallbladder is supplied by both sympathetic and parasympathetic innervation via the celiac plexus and the vagus nerve, respectively. At the level of T8 and T9, the preganglionic sympathetic chain receives afferent sensory information from the gallbladder, liver, and bile ducts, transmitting the pain of biliary colic. The parasympathetic supply of the gallbladder is derived from the hepatic branch of the vagus nerve. The cholinergic branches also release neurohormonal signals such as vasoactive intestinal peptide, somatostatin, and substance P, which act to modulate contraction and relaxation of the gallbladder wall and the secretion of bile.

Anatomic Variants

Common variations in biliary anatomy often contribute to inadvertent injuries during hepatobiliary surgery. The gallbladder itself can be buried within the parenchyma of the liver, referred to as an intrahepatic gallbladder. This can increase the risk of bleeding significantly, as injury to the liver parenchyma is more common during dissection. Duplication of the gallbladder, left-sided gallbladder, and congenital absence of the gallbladder are exceedingly rare conditions. Variation in the size of Hartmann's pouch can lead to obscuration of the cystic duct and increased incidence of common duct injury, as a short cystic duct may not be visible during lateral traction on the gallbladder [4].

Where the cystic duct emerges from the common bile duct is subject to great variability and is aberrant in 18–23 % of cases. Dissection of the cystic duct off of the common duct may increase the risk of injury to the latter. In 75 % of people, the cystic duct inserts into the middle one-third of the common bile duct, while it inserts into the distal third of the duct 10 % of the time. The typical pathway of cystic duct emergence is from the right lateral position; however, it may take other courses to join the gallbladder (Fig. 2.3). Around 1–2 % of patients have anomalous cysticohepatic ducts that empty into the cystic duct. Accessory bile ducts, observed in around 5 % of individuals, can arise from the right hepatic duct and insert directly into the cystic duct or join the common duct where it meets the cystic duct. This anomaly may lead to inadvertent clipping of the aberrant duct instead of the cystic duct during cholecystectomy [4].

Another common source of variation in biliary anatomy is the origin of the cystic artery and the presence of accessory hepatic arteries (Fig. 2.3). The cystic artery may have anterior or posterior branches to the gallbladder and are vulnerable to injury and subsequent bleeding if not recognized and ligated during cholecystectomy. In 90 % of patients, the cystic artery arises from the right hepatic artery; however, it can be seen arising from either the left or common hepatic, or the gastroduodenal artery (2–5 %). When this variant occurs, the cystic artery will cross anterior to the common duct. The cystic artery will course below the cystic duct in the event that it arises from the superior mesenteric artery. The right hepatic artery is often observed coursing behind the common duct and enters the liver high in Calot's triangle. The right hepatic artery may course very near the infundibulum of the gallbladder giving off a very short cystic artery, a

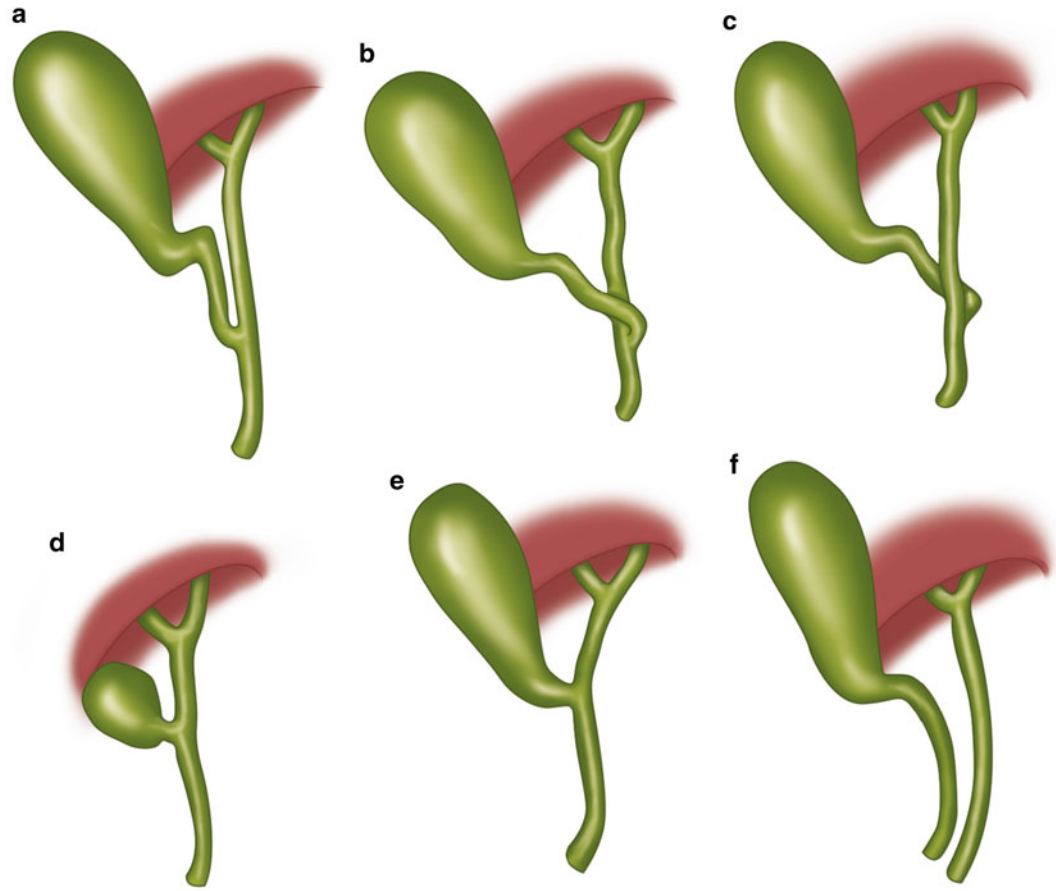

Fig. 2.3 Cystic duct variants. (**a**). Cystic duct lies parallel to the common bile duct (CBD). (**b**, **c**). Cystic duct crosses CBD and enters it on its left side. (**d**, **e**): Short cystic ducts. (**f**): Long cystic duct enters duodenum directly. There is no common bile duct, leaving only a common hepatic duct

variant referred to as Moynihan's or a caterpillar hump. The incidence of this variant may be as high as 50 % and can lead to the clipping of the right hepatic as it is mistaken for the cystic artery. In as many as 20 % of individuals, the right hepatic artery emerges from the superior mesentery artery. An accessory or second right hepatic artery emerging from the superior mesenteric artery is seen in 5 % of patients (Fig. 2.4) [6].

Physiology of the Biliary System

The liver normally produces about 500–1000 mL of bile daily. Bile travels from the hepatocytes into the surrounding biliary canaliculi, which converge to form bile ductules and then enter a portal triad composed of a hepatic artery, portal vein, and bile duct accompanied by lymphatics and vagus nerve branches. A hepatic lobule is composed of 4–6 portal triads. The bile ductules lie adjacent to the portal venule that communicates with the hepatic arteriole. The space of Disse separates hepatocytes from the sinusoidal space and facilitates the absorption of bile elements from the blood stream. After absorption, these elements are transported into the bile ductules and biliary tree, which is lined with tight junctions that prevent bile from refluxing back into the sinusoidal system. Bile flows retrograde through the common duct into the cystic duct to fill the gallbladder when pressure in the common bile duct increases due to tonic contraction of the sphincter of Oddi during fasting. The sphincter of

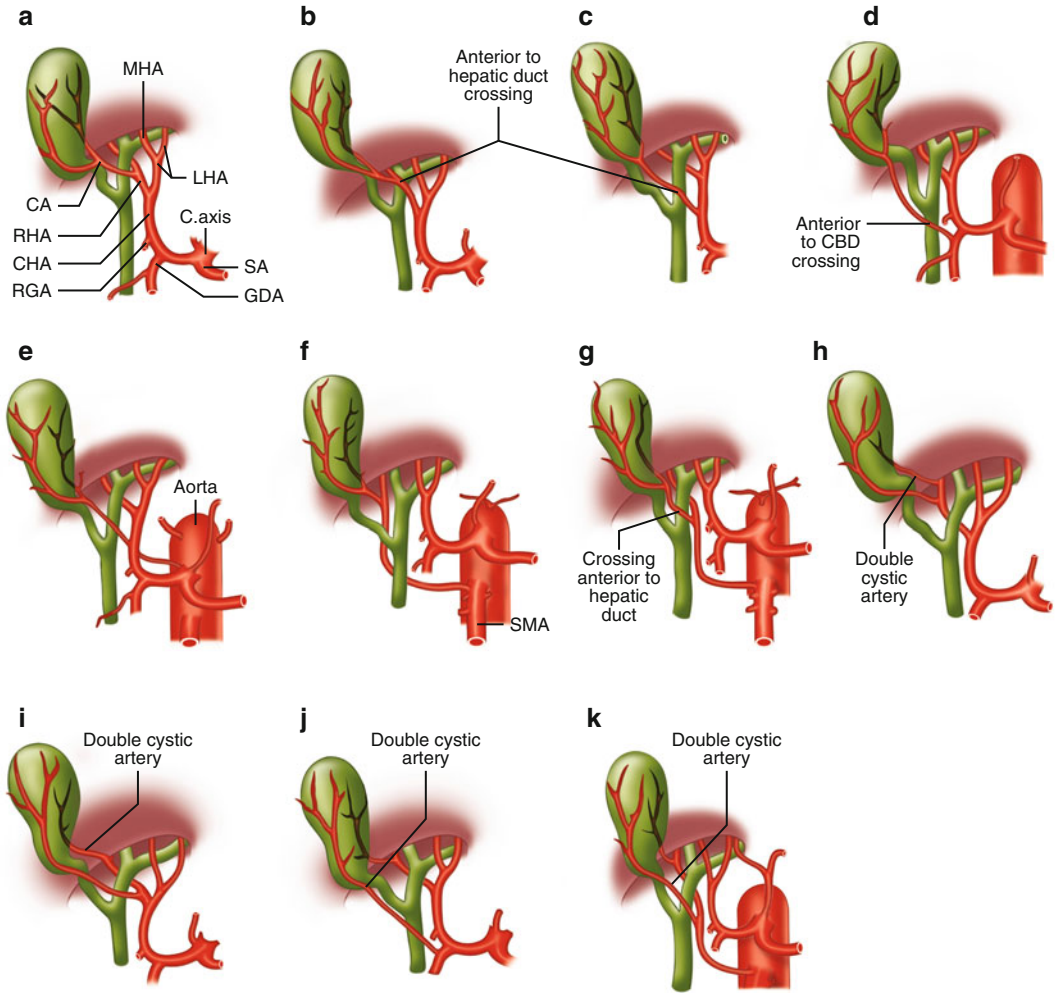

Fig. 2.4 Cystic artery anatomic variants. CA: Cystic artery. RHA: Right hepatic artery. CHA: Common hepatic artery. RGA: Right gastric artery. MHA: Middle hepatic artery. LHA: Left hepatic artery. C. axis: Celiac axis. SA: Splenic artery. GDA: Gastroduodenal artery. CBD: Common bile duct. SMA: Superior mesenteric artery

Oddi has a resting pressure of about 13 mmHg above the pressure measured in the duodenum. The interstitial cells of Cajal regulate its contraction, which occurs at a rate of 4 per minute.

Secretion of bile is stimulated through neurogenic, humoral, and chemical pathways. When a meal is consumed, vagal tone increases and sympathetic splanchnic tone decreases. Vagus nerve stimulation and distention of the gastric antrum cause gallbladder contraction and sphincter of Oddi relaxation. After eating, hydrochloric acid, proteins, and fatty acid entering the duodenum stimulate the release of secretin, which increases bile production. Cholecystokinin release causes gallbladder contraction and simultaneous relaxation of the sphincter of Oddi, allowing for ejection of 50–70 % of the gallbladder's contents. Vasoactive intestinal protein (VIP) and somatostatin decrease bile secretion and inhibit gallbladder contraction.

The two major functions of bile include excretion of cellular metabolites and toxins filtered out of blood by hepatocytes and emulsification of intestinal intraluminal fat to facilitate systemic absorption. Bile is composed of water, electrolytes, bile salts, bile pigment, and lipids, including cholesterol and phospholipid. Biliary pH is slightly alkaline, while concentrations of sodium, potassium, chloride, and calcium are similar to plasma. The two bile salts are cholate and chenodeoxycholate, which are derived from cholesterol

breakdown in the liver. Bile salts are conjugated with taurine or glycine and excreted by hepatocytes into bile through an ATP-dependent process. Bile salts facilitate the formation of micelles, which aid in the digestion and absorption of fats in the small intestine. Due to the amphipathic nature of bile salts, the hydrophilic regions aggregate and maintain contact with the surrounding environment, while the hydrophobic regions in the center of the micelle sequester fatty acids. Micelle formation is critical for the absorption of fat-soluble vitamins and many essential lipids. Bile salts also serve to eliminate cholesterol and other toxins from the body. Bile pigment, mainly bilirubin, is a breakdown product of hemoglobin and myoglobin from the destruction of red blood cells. It is transported from the bloodstream bound to albumin and enters the hepatocyte. Here, it is conjugated with glucuronic acid by the enzyme glucuronyltransferase, creating the water-soluble direct bilirubin. Direct bilirubin is then secreted into bile for excretion into the small intestine and colon. Colonic bacteria then deconjugate and metabolize bilirubin into urobilinogen, which is eliminated in stool or reabsorbed and ultimately eliminated in urine.

Approximately 95 % of bile salts are absorbed by the terminal ileum and colon and recycled through the mesenteric venous system back to the portal venous system in a process called the enterohepatic circulation. While the total amount of bile salt secretion into the gastrointestinal tract is about 12–36 g each day, the liver only produces 0.2–0.6 g of new bile salts each day, as the remaining is reclaimed through enterohepatic recycling. In the small intestine, bile salts are first unconjugated by bacterial bile salt hydrolase to form deoxycholate and lithocholate and then reabsorbed. Approximately 400–800 mg of bile salts reaches the colon each day and is ultimately excreted [7].

Natural History of Gallstone Formation

The production, storage, and secretion of bile are highly regulated. As such, any factor that disrupts this natural equilibration can induce gallstone formation, including increased saturation of bile with one of its components, altered concentrations of bile in the gallbladder, and gallbladder dysfunction.

To efficiently store bile produced by the liver, the gallbladder must first concentrate it approximately tenfold by absorbing water and sodium chloride. Additionally, the gallbladder secretes glycoproteins and hydrogen ions, which decreases the normally alkaline pH of bile and renders calcium more soluble. Concentrations of components in bile must be balanced to maintain a pure solution. Gallstones form when these concentrations are unbalanced. Cholesterol stones, the most common type of gallstones, are seen with excess cholesterol secretion that cannot be incorporated into micelles with bile salts. This leads to precipitation or nucleation of cholesterol salts and the formation of stones containing >70 % of cholesterol with some bilirubin and calcium. These stones are usually yellowish and range from hard to soft depending on the content of calcium. Pure cholesterol stones are rare and usually result in a single large stone.

In contrast, secretion of excess calcium-bilirubinate leads to the formation of black pigmented stones, which are usually small, brittle, and spiculated. This is often seen in hemolytic disorders such as sickle cell anemia and hereditary spherocytosis, where there is a large amount of conjugated bilirubin entering bile. A proportion of conjugated bilirubin will be deconjugated in the gallbladder by beta-glucuronidase produced by bacteria. In hemolytic states, this proportion is higher and a higher proportion of insoluble unconjugated bilirubin will precipitate with calcium to form black stones [7, 8]. This process is also observed in patients with Crohn's disease and cirrhosis. Patients with Crohn's disease have decreased absorptive capacity for bile salts, especially in the terminal ileum. As a result, they have a higher proportion of biliary calcium and unconjugated bilirubin. The cause of gallstones in cirrhosis may result from increased hemolysis due to hypersplenism or hepatocyte destruction and decrease the ability to conjugate bilirubin [9].

Brown gallstones form when there is dysfunction in gallbladder motility resulting in bile stasis and subsequent bacterial overgrowth. *E. coli*

produces beta-glucuronidase that deconjugates a higher proportion of the soluble direct bilirubin into indirect bilirubin, which then precipitates out of solution. Brown gallstones are often seen in developing countries with a higher incidence of parasitic infection causing biliary stasis. In the United States, biliary strictures can lead to brown stone formation in the gallbladder and common bile duct.

Conditions resulting in decreased gallbladder contractility induce biliary stasis and are implicated in stone formation. This is seen in biliary dyskinesia, prolonged fasting and iatrogenic causes including total parenteral nutrition and octreotide administration [10, 11].

There are several patient characteristics that are independent risk factors for the development of gallstones. Native North and South Americans are much more likely to develop gallstones than other populations. This is likely due to a combination of dietary and genetic factors. The incidence of cholelithiasis is 2–3 times higher in women and is expected to occur in as many as 50 % of women by age 75 compared to only 25 % of men. This is most likely due to the presence of estrogen, which increases the liver's removal of cholesterol from blood and deposits it into bile. Estrogen is also thought to promote the nucleation of cholesterol crystals out of micelles [12]. In fact, several studies have been performed to examine the relationship between gallstone formation and hormone replacement therapy with estrogen and progesterone in postmenopausal women. It appears that women who take hormone replacement therapy are 2–3 times more likely to develop gallstones and undergo cholecystectomy [13]. Additionally, pregnant patients are at increased risk for cholelithiasis due to the fact that estrogen increases cholesterol in bile and progesterone decreases gallbladder contractility [14].

Obesity, metabolic syndrome, and diabetes mellitus also increase the risk of gallstones. This is presumed to be secondary to increases in liver synthesis of cholesterol due to increased activity of HMG-CoA reductase activity. This causes an increase in the percentage of cholesterol in bile causing supersaturation and precipitation of stones [15]. Interestingly, rapid weight loss and bariatric surgery can also predispose patients to the development of gallstones. Rapid weight loss causes net excretion of cholesterol into bile, and fat-restricted diets can lead to decreased gallbladder contractility and stasis [16]. Diabetes is often associated with increased levels of cholesterol, although decreased intestinal and gallbladder motility due to autonomic dysfunction may also contribute to gallstone formation.

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