Bile Metabolism and Lithogenesis

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KEYWORDS

• Gallstones • Gallbladder • Cholelithiasis • Bile • Bile acids

KEY POINTS

- Bile acids play a prominent role in expression of genes involved in their own uptake and secretion within the enterohepatic circulation.
- Bile acids serve as ligands for the nuclear receptor farnesoid X receptor and transmembrane protein TGR5, through which they exert their regulatory effects in hepatic and extrahepatic tissues.
- Cholelithiasis is a disease associated with the metabolic syndrome and is the result of both modifiable and nonmodifiable risk factors.
- Different types of gallstones (cholesterol, black pigment, brown pigment stones) are associated with separate risk factors and disease processes.
- Disease states and therapies can alter bile metabolism, leading to an increased risk of gallstone formation.

INTRODUCTION

Gallstone disease affects 20 to 25 million adults in the United States.[1,2] Although most patients remain asymptomatic, some patients do eventually progress to symptomatic or complicated disease, leading to more than 750,000 cholecystectomies in the United States every year.[3] Of all hospital admissions in 2009, cholelithiasis and cholecystitis were the second most common discharge diagnoses among patients admitted with gastrointestinal illnesses.[4] Cholelithiasis poses a significant economic burden in this country, with direct and indirect costs totaling $6.2 billion annually.[2,5] As our population continues to age and the obesity epidemic persists, the incidence of gallstone disease is increasing. A thorough understanding of the underlying physiology of bile metabolism and lithogenesis is necessary to provide optimal management of these patients and for developing new strategies to prevent gallstone formation.

BILE METABOLISM

The synthesis of bile acids, the formation of bile, the enterohepatic circulation, and the modifications of bile acids throughout their lifespan all contribute in the metabolism of

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bile. In recent years, many advances have been made in the understanding of the widespread activities of bile acids on a cellular and molecular level.

Function of Bile Acids

Bile acids function as the detergent component of bile, emulsifying dietary fats, fat-soluble vitamins, and drugs to allow intestinal absorption. Bile acids and phosphatidylcholine maintain the solubility of cholesterol in bile; the excretion of bile acids is the primary pathway for cholesterol catabolism, accounting for 50% of the daily turnover.[6] Recently, many studies have shown that bile acids have other important physiologic activities beyond fat digestion, including regulation of their own synthesis, endocrine and paracrine functions.[7–9] Bile acids serve as ligands for nuclear receptors, mainly farnesoid X receptor (FXR) and pregnane X receptor, which are involved in carbohydrate, triglyceride, and sterol metabolism.[10–13] Bile acids have also been shown to interact with cell surface receptors, namely TGR5, and be involved in energy expenditure, lipid metabolism, glucose homeostasis, and inflammatory/immune responses.[14] TGR5 receptors are located in brown adipose tissue, skeletal muscle, nervous system tissue, immune tissue, and colonic tissue, demonstrating the widespread effects of bile acids beyond the biliary system.[15,16] The molecular structure of TGR5 consists of a unique ligand-binding pocket for bile acids, making this receptor a potential drug target for new pharmaceuticals developed to treat metabolic syndrome.[17]

Bile Composition

The liver produces 600 to 750 mL of bile daily. The major lipid components of bile include bile acids (72%), phospholipids (24%), and cholesterol (4%).[18] The bile acid pool consists of primary bile acids (cholic acid and chenodeoxycholic acid) and secondary bile acids (deoxycholic acid and lithocholic acid). Primary bile acids are those that are produced de novo by the liver, and secondary bile acids are primary bile acids that have undergone deconjugation by intestinal bacteria. Phospholipids in healthy individuals consist mainly of phosphatidylcholine (>95%). These proportions are altered in chronic cholestatic conditions, such as primary sclerosis cholangitis or primary biliary cirrhosis.

Bile Acid Synthesis

Bile acids, the main lipid component of bile, are formed in the perivenous hepatocytes. Formation of all bile acids begins with a steroid nucleus, to which subsequent modifications are made. The amphipathic nature of bile salts is caused by the combination of hydrophilic hydroxyl groups and hydrophobic methyl groups, which are oriented opposite each other around the steroid nucleus.[16]

There are 2 pathways by which bile acid biosynthesis occurs: the classic or neutral pathway and the alternative or acidic pathway. The classic pathway begins with hydroxylation of the steroid nucleus, which is the rate-limiting step controlled by cholesterol 7α-hydroxylase (CYP7A1).[19] This enzyme is only found in hepatocytes; thus, the classic pathway only takes place in the liver. This pathway is regulated by a negative feedback loop with bile acids inhibiting CYP7A1 activity and expression.[7]

The alternative pathway is controlled by oxysterol 7α-hydroxylases (CYP7B1), which are constitutively expressed in extrahepatic tissue, such as macrophages, kidney, and vascular endothelium. These enzymes oxidize cholesterol to oxysterols in the peripheral tissues, which are then transported to the liver for final modification to form primary bile acids.[20] Normally, the alternative pathway contributes approximately 10% to overall daily bile acid synthesis; however, this pathway may become more prominent in patients with liver disease.[16]