Chapter 7
Pathophysiology of Bile Acid Regulation

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7.1 Introduction

Bile acids and their regulation has emerged as an important topic in understanding obesity, metabolic disorders, diabetes, and non-alcoholic fatty liver disease. Bile acids are steroid molecules that can act as important modulators. In this chapter we will review the normal physiology of bile acids and then summarize the pertinent bile acid signaling on medical conditions and co-morbidities.

7.2 Physiology of Bile Acid

Bile is an endogenous steroid produced from cholesterol and is secreted by hepatocytes. It has two major roles in human physiology, the first is absorption of lipids and the second is to allow for transport and excretion of toxins and cellular metabolites. The pathway of bile secretion starts in the biliary canaliculi. These coalesce into small bile ducts and subsequently portal triads. Four to six triads create a hepatic lobule, the smallest functional unit of the liver. Hepatocytes communicate with sinusoidal surfaces through the Space of Disse. Passage of bile salts through the space of Disse allows for hepatocyte uptake via sodium cotransport and sodium-independent pathways. Other organic anions are transported including unconjugated (indirect) bilirubin. With this communication the circulating components of bile are absorbed and secreted into the bile canaliculi. This step is the rate limiting step of bile salt excretion.

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Bile also contains proteins, pigments, and lipids. Major lipid components include cholesterol and phospholipids, which function to dispose of LDL and HDL but also to protect hepatocytes and cholangiocytes from bile toxicity. The source of cholesterol is hepatic synthesis and circulating lipoproteins. Although all the previously listed molecules play an important role in nutritional homeostasis, bile is a major route for toxin disposal. For example, bile pigments such as bilirubin are bound to albumin in the blood and transported to the liver and hepatocytes. There it is converted to conjugated (direct) bilirubin and excreted in both stool and urine.

Volume of biliary flow is an osmotic process and not affected by bile salts due to the formation of micelles, spherical pockets of bile salts that provide no osmotic activity. However, cations secreted into the biliary tree with the bile salt, which is an anion, provides osmotic pressure to draw in water and increase biliary flow. Some of the biliary flow is salt-independent, serving to expel toxins and metabolites, but more so flow is due to chemical, humoral, and neural stimuli. This includes vagal activity, secretin, and cholecystokinin (CCK). CCK specifically induces biliary tree secretion and gallbladder wall contraction increasing excretion of bile into the intestines.

Instead of a constant high rate of bile acid production, most bile is recycled through enterohepatic recirculation, terminal ileum reabsorption, and portal venous return. Approximately 0.2–06 yg/day of bile is produced by the liver daily with 95% of bile being recycled. Only 5% of bile salts are lost each day in the stool. If this amount increases bile has a powerful effect on the colonic lumen resulting in inflammation and diarrhea [1].

7.3 Pathophysiology of Bile Acid Regulation

7.3.1 Receptors and Signaling

Two major bile acid receptors that have a large role in metabolic disorders are farnesoid X receptor (FXR) and Takeda G protein-coupled receptor (TGR5). These receptors along with gut microbiota affect the synthesis, distribution, and metabolism of bile acids [2]. FXR is expressed in hepatocytes as well as enterocytes of the distal small intestine and colon, while TGR5 is expressed in enteroendocrine cells as well as bile duct epithelial cells and the gallbladder [3]. It should be noted prior to further description that these receptors have been most studied in mouse models and their translation into humans should be approached with care.

TGR5 has been suggested to play a role in the regulation of bile acids and regulation of energy expenditure potentially playing a role in the development of obesity. However, this mechanism is not fully understood. One study showed an increase in bile acid in TGR5-deficient mice that was potentiated by cholic acid (CA) feeding while another showed a decrease in bile acid pool in TGR5 deficient mice [4, 5]. Interestingly, a study by Watanabe et al. found that high-fat-diet-induced obesity

could be reversed by supplementing CA, which underwent transformation to a more biologically active form of deoxycholic acid (DCA) stimulating TGR5-mediated intracellular thyroid hormone activity [6]. Another study found that TGR5 helped regulate glucose homeostasis through increased energy expenditure in muscle and brown adipose tissue. It was also shown to increase glucose-like peptide (GLP)-1 release in intestinal L cells and alpha cells in the pancreas [7, 8]. FXR receptors appear to have an opposing effect on GLP-1 signaling to TGR5, with stimulation of FXR receptors leading to inhibition of GLP-1 synthesis [9]. Another molecule INT-777, a derivative of chenodeoxycholic acid (CDCA), a TGR5 agonist, was shown to ameliorate hepatic steatosis and adiposity along with improving insulin sensitivity in mice with high-fat-diet-induced obesity [8].

FXR has also shown somewhat conflicting results in mice models. In one study, FXR deficient mice on normal diets developed hyperglycemia and hypercholesterolemia [10]. By contrast other studies found that FXR-deficient mice bred to be genetically obese or fed with a high-fat diet were protected against obesity and had improved glucose hemostasis [11–13]. This is thought to be somewhat due to opposite actions of FXR in the liver and intestines. Hepatic expression of FXR has shown to protect against steatosis while intestinal deletion of FXR improved high-fat-diet-induced steatosis and obesity [14–16]. Increasing the complexity even further FXR agonism and antagonism can be beneficial for host metabolism and the full scope of FXR's role is not clear [15].

Overall, animal studies have suggested that bile acids affect metabolism and energy expenditure. As a result, numerous cross-sectional studies in humans have been performed with the goal of establishing connections between BMI, circulating bile acids, and insulin resistance. These studies have shown an increase in total bile acid levels in humans with obesity [17]. Patients who have insulin resistance have been shown to have enhanced bile acid synthesis and an increase in 12α-hydroxylated bile acids. This suggests that an increase in 12α-hydroxylated bile acids may negatively affect the function of insulin, like increased GLP-1. Other studies have shown that low levels of 12α-hydroxylated bile acids can improve glucose tolerance [18]. This interaction is thought to be due to Forkhead box protein (FOX)01, a transcription factor involved in gluconeogenesis that controls the production of 12α-hydroxylated bile acids through Cyp8b1 regulation [19]. In obese humans who have lost weight and improved their metabolic control through lifestyle modification, there was a shift in bile acid composition toward increased 12α-hydroxylated bile acids to non-12α-hydroxylated bile acids [20]. These same changes have not been seen in patients who have type 2 diabetes mellitus (T2DM) [17]. The only study so far with a positive effect of bile acids on energy expenditure examined CDCA. CDCA was shown to increase whole body energy expenditure and increase brown adipose tissue activity in 12 healthy women given a dose of 15 mg/kg body weight for 2 days [21].

One of the potential therapeutic targets for bile acids is depletion of bile acids as means of improving glycemic control. A meta-analysis examined 17 studies with colesevelam or colestimide, bile acid sequestrants, in 2950 patients. They showed

that those who that received either bile acid sequestrant had a lower hemoglobin A1c compared to the control group [22]. Another study compared colesevelam to placebo and found increased GLP-1 and GIP, as well as cholesterol and bile acid synthesis in those patients who were in the colesevelam group. This again suggests that depletion of human bile acids may improve obesity and metabolic syndrome. Metformin is another medication examined and was found to affect patient's gut microbiome [23]. The exact mechanism and downstream effect of this finding are currently being examined. Further studies will be needed to see what other effects medication can have on both bile acid synthesis and gut microbiome effects.

7.3.2 Obesity, Bariatric Surgery, and Diabetes

Bariatric surgery has been shown to be the most effective long-term treatment for morbid obesity with both decreases in body weight but also improving co-morbid complications for patients. Common procedures include Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG), and biliopancreatic diversion (BPD/DS). Interestingly the metabolic improvements (increased insulin sensitivity) occurs early after surgery, a few days, far before post-operative weight loss occurs [24]. This would suggest that it is more than just weight loss that leads to improvement in patient's metabolic profile after surgery.

One of the suggested mechanisms effecting this improvement is a change to bile acids [25]. In RYGB the patient's circulating bile acid pool is increased in both fasting and postprandial phases along with an elevation in the ratio of 12α-hydroxylated/non-12α-hydroxylated bile acids [17]. Similar changes to bile acid profile occurs in BPD/DS [26]. On the other hand VSG has a less consistent change to bile acid profiles with some studies showing unchanged, increased, or decreased bile acids [17]. This may be why VSG is less effective in improving glucose metabolism in comparison to RYGB and BPD/DS [27]. After RYGB, bile acids have been shown to have a positive correlation with several other metabolically active peptides. These include GLP-1, peptide YY, and adiponectin [26]. This could be secondary to bile acid–mediated TGR5 activation, however studies to support this conclusion are missing [28].

Additional studies have examined the mechanism for improved metabolic profile through bile acids after bariatric surgery. One study examined obese insulin-resistant patients after receiving tauroursodeoxycholic acid (TUDCA), which is typically increased after RYGB, and found that there was improved hepatic and peripheral insulin sensitivity [29]. This would suggest that increases in the bile acid TUDCA may play a role in improving patient's metabolic syndrome after RYGB. Similarly, murine models of RYGB and VSG confirmed increased circulating bile acids were associated with improved metabolic features [30]. While malabsorption and changes to bile acids may play a role in the metabolic benefits of bariatric surgery, consideration for whether or not calorie reduction plays a role is needed. One study found that calorie reduction does not affect the size of bile acid pool or composition in

humans [31]. Further studies need to be conducted to confirm this finding but at this time it does not appear that calorie reduction affects the size of the bile acid pool or its composition.

Another potential way that bariatric surgery improves metabolic features of obesity is changes to the gut microbiome. Several studies have shown that there is a shift in the gut microbiota 3 months after surgery and that these changes are still present 9 years later [32, 33]. Not only is there a change in the level of postprandial bile acid levels but there was also reduced fat gain in mice [32].

While it appears that changes to bile acids play a role in improvements after bariatric surgery, how specific receptors mediate this change remains less clear. One study examined mice lacking FXR and found that they had reduced weight loss and less glucose improvement after VSG, however in contrast mice with bile diversion to the ileum, a model of RYGB, showed reduced FXR signaling [34, 35]. These results at first glance appear to be contradictory but also suggest that the role of FXR signaling differs in restrictive and malabsorptive procedures. Two studies examining TGR5-deficient mice after VSG showed improved glucose metabolism, insulin signaling, and fat accumulation in the liver but body weight reduction was unclear [36, 37]. This helps show that TGR5 is involved in the beneficial aspects seen with VSG.

7.3.3 Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis

Non-alcoholic fatty liver disease (NAFLD), a chronic disease of the liver, represents another area where bile acids can play a role in both progression and improvement of this condition. Non-alcoholic steatohepatitis (NASH) represents a disease on the same spectrum as NAFLD and will be discussed together with it. Bile acids are seen to be elevated in both adult and pediatric patients with NAFLD/NASH with both increased fasting and postprandial serum bile acids. This correlates with the severity of NASH present in patients [38, 39]. The changes to the profile of serum bile acids is not entirely clear at this point. Some studies found that hepatic bile acids are increased in NASH, with prevailing CA, while other studies showed decreased CA levels [40, 41]. In either situation it suggests that the bile acid pathway is affected by liver disease leading to alternative pathways of bile acid production and potential therapeutic targets.

Changes to the gut microbiota may also play a role in NAFLD/NASH. Increased bile acid production may be due to changes from a strong FXR agonist, such as CDCA, to a weak agonist DCA [42]. Given these changes it stands to reason that modulation of intestinal microbiota may provide a therapeutic avenue for these patients. In fact, various studies have examined the FXR signaling pathway and have suggested that through modulation there was the potential to reverse insulin resistance and fatty liver disease [13, 16, 43]. Experiments examining FXR inhibition have utilized ileum bile acid transporter (IBAT) inhibitors. These result in

increased fecal excretion of bile acids, which cannot be fully compensated for with increased bile acid synthesis and was found to be protective against NAFLD in an experimental high-fat-diet-treated mouse model [44, 45].

At this time, there are no currently approved treatments for patients with NAFLD/NASH other than dietary and lifestyle modification. Some testing has been done with bile acid receptor modulation with limited results. Two randomized placebo-controlled trials using UDCA did not show overall improvement in inflammation associated with NAFLD but one study did show that high dose UDCA showed improvement in circulating markers of inflammation, fibrosis, and insulin resistance [46]. In contrast the semisynthetic bile acid, obeticholic acid (OCA), has shown some promise. OCA is 100 times more potent an FXR agonist in comparison to CDCA. In phase 2 and 3 trials, OCA improvements in insulin sensitivity and reduced body weight in those with NASH +/− DM was seen [47]. A multicenter double-blinded randomized placebo controlled phase 3a trial with OCA (FLINT) looked at 283 patients with NASH +/− DM and found that after 72 weeks of treatment NASH activity score and fibrosis improved. However, insulin sensitivity worsened with increased LDL and decreased HDL levels [48]. Unfortunately, these results were corroborated in healthy volunteers as well taking OCA [49]. Further studies are needed to determine ideal treatments for NAFLD/NASH patients but it appears that modulation of bile acid pathways may play a role in eventual therapeutic interventions.

7.4 Conclusion

Bile acids, once thought to only play a role in digestion and toxin excretion, appears to play a more expanded role than previously considered. TGR5 and FXR receptors seem to have a role in the results of bariatric surgery and may eventually be used as targets for NAFLD/NASH patient treatment. Clearly the full pathway for affecting this change has yet to be fully described but as our understanding of this complex system further improves, it should lead to targets to improve patient outcomes and care.

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