Bile Acids:
Beyond Fat Digestion
by Carrie Decker, ND

Although our discovery of the distinct constituents of bile goes back to the mid-19th century,[1] record of their first use therapeutically dates far earlier than this. Bile from many different animals and even human sources at times of battle have a record in traditional Chinese medicine (TCM) beginning in the Zhou dynasty from 1046-256 BCE.[2] In TCM, bile acids have an array of uses, including the treatment of gallstones (still a common use for bile acids, in particular ursodeoxycholic acid[3,4]), infectious skin diseases or burns, vision and eye conditions, respiratory infections, and even coma and epilepsy. Ox bile was one of the first forms of bile to be used in TCM and contains many of the same bile acids found in human bile.[2]

In addition to their well-known role in the digestion of dietary fats, bile acids influence the balance of flora in the gut,[5] gastrointestinal motility,[6] immune system function,[7] and bind with numerous receptors distributed throughout the human body.[8] Lower levels of bile acids in the gut are associated with an overgrowth of *Clostridium difficile* and *Helicobacter pylori*,[9,10] constipation,[11] and increased bacterial translocation.[12] Given their origination in the liver, it may not come as a surprise that bile acids also have a significant impact on metabolism[13] and liver/gallbladder health,[14] reviewed herein.

Bile Acid Metabolism and Receptor Interactions

The human bile salt pool is primarily comprised of cholic acid (CA), chenodeoxycholic acid (CDCA), and deoxycholic acids (DCA), with smaller amounts of lithocholic acid (LCA) and ursodeoxycholic acid (UDCA).[15,16] The primary bile acids CA and CDCA are produced in the hepatocyte from cholesterol by the classic or alternative pathways involving multiple cytochrome P450 (CYP450) enzymes.[17] They are then conjugated with glycine or taurine (increasing their water solubility) prior to being excreted from the hepatocyte across the canalicular membrane via transporters also associated with Phase III detoxification: bile salt export protein (BSEP) and multidrug resistance-associated protein-2 (MRP2).[18]

In the digestive tract, enzymes produced by certain microbes in the gut deconjugate and dehydroxylate these bile acids, forming the secondary bile acids DCA (from CA) and LCA (from CDCA).[19] Deconjugated bile acids are more hydrophobic and have greater detergent action, which increases their ability to facilitate solubilization and absorption of dietary lipids, fat soluble vitamins, and break down bacterial membranes.[20,21] DCA is a particularly strong antimicrobial agent, having 10 times the antimicrobial activity of CA, its precursor.[22]

Bile acids have a multitude of effects throughout the body due to their interactions with the nuclear receptors farnesoid X receptor (FXR),[23] pregnane X receptor (PXR),[24] and the vitamin D receptor, as well as multiple G-protein coupled receptors (GPCRs), which are found on the cell membrane.[7] In the hepatocyte, the majority of the actions of bile acids are mediated by FXR, which also plays a role in the synthesis, transport, and enterohepatic circulation of the bile acids themselves. Interactions of bile acids with FXR in the hepatocyte serves a self-regulatory role, protecting the cell from damage that can take place when an excessive amount of bile exists (such as occurs with cholestasis) by increasing transcription of efflux transporters[25] and reducing bile acid synthesis,[26] which both help lower the intracellular bile acid concentration.

In addition to protecting hepatocytes in the setting of cholestasis,[27] activation of FXR by bile acids induces genes involved in the different phases of detoxification,[28] protecting the cells of the liver from drug and xenobiotic toxicity.[29,30] This is one reason why supplemental bile acids are a life-saving intervention for individuals with bile acid synthesis disorders,[31] as they help protect the liver by increasing bile acid-dependent bile flow and toxin transport out of the hepatocyte. For individuals with bile acid synthesis disorders, CA is the primary bile acid used as a therapy.[32]

FXR is known to be expressed in the liver, pancreas, ileum, kidney, and adrenal glands, and at lower levels in the heart, central nervous system, adipose tissue, and arterial walls.[15] The ability of the different bile acids to activate FXR varies, with CDCA being the strongest activator and CA the weakest. Animal and in vitro studies suggest that activation of FXR by bile acids decreases plasma triglycerides, cholesterol, and hepatic steatosis; reduces gluconeogenesis; and increases insulin sensitivity, glucose transporter type 4 (GLUT4) transcription, and

glycogen synthesis.[33-37] Stimulation of the ileal enterocytes with bile acids also activates FXR and increases secretion of fibroblast growth factor 19 (FGF19), which has insulin-sensitizing and hypolipidemic effects.[38]

Interactions of bile acids with TGR5, a cellular membrane GPCR, is another major route via which their metabolic actions are exerted. TGR5 is *not* expressed in the hepatocyte but is expressed in brown adipose tissue, pancreatic beta cells, intestinal neuroendocrine cells, the biliary tract, as well as Kupffer cells and liver endothelial cells.[39] Interactions of bile acids with TGR5 increases cyclic-AMP synthesis, which impacts energy production and increases insulin secretion by pancreatic beta cells;[40] and increases production of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY),[41] which play important roles in appetite and blood sugar regulation.

Metabolic Disease

The effect of bile acids on blood sugar, cholesterol, appetite, and even weight via their interactions with FXR and TGR5 have been demonstrated in numerous animal and human studies.

In animals, enhanced expression of the primary CYP450 enzyme regulating bile acid synthesis enlarged the bile acid pool and led to increased hepatic cholesterol catabolism and decreased expression of several genes involved in lipogenesis and glucogenesis.[42] Despite being subject to high-fat diet (HFD) feeding, these mice were resistant to HFD-induced obesity, fatty liver changes, and insulin resistance, and had increased whole body energy expenditure.

Supplementation of CA along with HFD feeding was shown to prevent the increases in weight and adipose mass seen in mice fed a HFD alone, also preventing brown adipose tissue (BAT) whitening (which has negative metabolic effects).[43] In mice initially fed a HFD for 120 days, the addition of CA to the diet also returned their body weight to that of the typical chow-fed mice within 30 days. Similar effects of weight normalization, in addition to improved glucose tolerance, were also seen in mice fed CDCA along with HFD feeding.[44] In both of these studies, it was shown that these effects were at least in part due to increased expression of cyclic-AMP-dependent type 2 iodothyronine deiodinase (D2) in the BAT. D2 converts thyroxine (T4) to triiodothyronine (T3) within the cells of the BAT,[45] mediated by TGR5. In the investigation using CA as an intervention,[44] it was noted that serum levels of T3 and T4 in the mice did not change. Both CA and CDCA have also been shown to induce mitochondrial uncoupling protein 1 (UCP1),[46,47] which is known to regulate BAT-mediated thermogenesis.

Several studies suggest that the weight loss and improved glycemic control seen with bariatric surgery, or other weight-loss procedures such as gallbladder bile diversion to the ileum, may be due to altered bile acid availability.[48,49] In patients post-gastric bypass, total bile acid levels, as well as the bile acid subfractions, were significantly higher than overweight controls.[50,51] Total bile acid levels and their subfractions were inversely correlated with 2-hour post-prandial glucose and triglyceride levels as well as thyroid stimulating hormone, and positively correlated with adiponectin and GLP-1 levels.[51]

Multiple studies have also shown altered bile acid homeostasis in individuals with type 2 diabetes (T2D).[52,53] Serum fasting levels of CDCA and FGF19 (a marker commonly used to assess for FXR activation) have been shown to be independently related and significantly lower in individuals with impaired glucose tolerance and T2D.[54,55] Interestingly, serum levels of FGF19 have also been observed to be lower in patients with overt and subclinical hypothyroidism,[56] which may contribute to metabolic changes seen in this setting as well.

As a therapy, there are currently only a few human studies investigating the impact of bile acids on metabolic health and weight. In one study of healthy females, short-term oral supplementation with CDCA at a dose of 15 mg/kg/day was shown to be bioavailable and significantly increase BAT activity as well as whole body energy expenditure without any deleterious effects such as diarrhea.[57] In obese individuals with T2D, rectal administration of taurocholic acid dose-dependently increased secretion of GLP-1, PYY, and insulin, simultaneously decreasing plasma glucose,[58] while in healthy volunteers, in addition to stimulating GLP-1 and PYY, it dose-dependently increased the sensation of fullness.[59] Tauroursodeoxycholic acid (UDCA conjugated with taurine), taken orally at a dose of 1,750 mg/day, was shown to significantly improve hepatic and muscle insulin sensitivity compared to placebo in obese individuals after four weeks of supplementation.[60]

One additional item worthy of note in a discussion of bile acids and metabolic disease is the use of probiotic bacteria to modify the balance of bile acids. Known as bile salt hydrolase (BSH)-active bacteria, these bacteria produce the enzyme BSH that deconjugates bile acids, reducing the absorption of cholesterol and increasing FXR activation, as the deconjugated bile acids are strong activators of FXR.[61] Human studies using the BSH-active probiotic strain *Lactobacillus reuteri* NCIMB 30242 have shown that, indeed, such a probiotic is capable of improving not only the balance and levels of cholesterol,[62,63] but also improves symptoms of irritable bowel syndrome,[64] which may be somewhat attributable to the antimicrobial effects of the secondary bile acids in addition to other well-known properties of *Lactobacillus* spp. bacteria.

Fatty Liver Disease

Given that the main uses of bile acids in modern medicine are for the

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dissolution of cholesterol gallstones and as a treatment for cholestatic disease,[65-67] it should not come as a surprise that bile acids have other potential applications in the setting of liver and gallbladder disease. Although UDCA is the primary bile acid indicated for uncomplicated cholelithiasis, at one time, CDCA, found in both human and ox bile, was also a common intervention.[68] CDCA was abandoned as a primary intervention with UDCA taking its place due to the reduced occurrence of side effects, such as diarrhea, and lower dose required for resolution of gallstones.[69]

Although the condition of non-alcoholic fatty liver disease (NAFLD), frequently seen in conjunction with obesity and T2D, is primarily attributed to increased triglyceride accumulation in the cells of the liver, it also is associated with dysbiosis, intestinal inflammation, and increased gut permeability.[70,71] In addition to the antimicrobial, insulin-sensitizing, and triglyceride-reducing effects that bile acids have,[72,73] activation of FXR by bile acids also supports intestinal barrier integrity and reduces bacterial translocation, positioning bile acids as a very promising agent for the treatment of this condition, which to date has no recommended pharmaceutical intervention. Activation of FXR by bile acids may reduce hepatic inflammation and injury associated with alcoholic liver disease as well,[74,75] mediated by many of the same mechanisms. Both FXR and TRG5 play a role in protecting the liver from fibrosis,[76] the end stage of both NAFLD and alcoholic liver disease.

In animals fed a HFD, increased bile acid synthesis prevented fatty liver changes, suggesting similar effects also may be seen in humans.[42] Obeticholic acid (OCA) is a synthetic variant of CDCA, produced by the addition of an ethyl group, which increases its binding affinity for FXR approximately 100-fold.[77] It also is a TRG5 activator, much like CDCA.[78] Cellular studies comparing CDCA to OCA have shown that they have similar effects of increasing the transport of bile acids out of the hepatocyte (protecting it in cholestasis)[79] and reducing the production of proinflammatory mediators such as tumor necrosis factor alpha.[80] OCA has been shown in clinical studies to be beneficial at very low doses (typically 5 to 25 mg) for liver disease including non-alcoholic steatohepatitis, the more severe form of NAFLD,[81] also possibly supporting weight loss in this population as well.[82] Occasionally, the side effect of pruritis may occur with this and other FXR agonists. Given their similar mechanism of action, natural forms of the bile acids also may be of benefit in NAFLD.

Clearly, although bile acids have a long history of use medicinally, we are only starting to understand their broad therapeutic application. Unfortunately, we will likely only see such research with regards to their more potent, synthetic derivatives – which neglects the importance that a blend of bile acids, similar in composition to what is naturally produced by our body, may offer as a natural therapy. Often, lower doses of such substances gently stimulate the body rather than pushing a single pathway very strongly, leading to great potential for their systemic healing action.

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