Editorial on Nutrition

The gut's feeling on bile acid signaling in NAFLD

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The gut to live axis plays a critical role in regulation of hepatic bile acid synthesis and metabolic homeostasis (1). Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease with a high prevalence of ~35% in adults. NAFLD can progress from simple steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma. NAFLD is associated with insulin resistance, obesity and type 2 diabetes. Bile acid-activated farnesoid X receptor (FXR) and G protein-coupled bile acid receptor-1 (Gpbar-1, aka TGR5) have been shown to regulate lipid, glucose and energy metabolism and activation of FXR by agonists have been shown to improve hepatic metabolism and metabolic disorder in several mouse models of NASH (2). However, the role of bile acid signaling in pathogenesis and treatment of NASH is not clear.

Jiao *et al*. reported recently that the serum bile acids concentrations and the percent of deoxycholic acid (DCA) were significantly increased while the percent of chenodeoxycholic acid (CDCA) was decreased, and the ratio of DCA + ursodeoxycholic acid (UDCA) to CDCA + cholic acid (CA) was increased in patients with NAFLD compared with healthy patients (3). However, they did not calculate the ratio of 12α-hydroxylated bile acids (CA and DCA) to non-12α-hydroxylated bile acids [CDCA and lithocholic acid (LCA)], which has been shown to increase significantly in NAFLD patients and is linked to insulin resistance in type 2 diabetic patients (4). Quantitative PCR analysis shows remarkably increase (10–20-fold) of mRNA levels of cholesterol 7α-hydroxylase (CYP7A1), sterol 12α-hydroxylase and other enzymes in bile acid synthesis. They suggested that bile acid synthesis was stimulated in NASH livers. Unexpectedly, expression of mRNA encoding for FXR and FXR-induced small heterodimer partner (SHP), a negative regulator of CYP7A1, was also increased in NASH livers compared to control livers (1). In the intestine, bile acids activate FXR to induce fibroblast growth factor 19 (FGF19), which is circulated to the liver to activate a hepatic FGF receptor 4 (FGFR4)/β-Klotho complex to inhibit *CYP7A1* gene transcription (1). However, they found that serum FGF19 concentrations were reduced in NASH patients compared to healthy control patients. They concluded that despite of increased hepatic FXR and SHP expression, hepatic bile acid synthesis was increased indicating that FXR/FGF19/FGFR4 signaling was impaired in NASH patients.

Bile acid homeostasis is maintained by bile acid synthesis in the liver, reabsorption in the intestine and fecal excretion (2). The total bile acid pool includes bile acids in the liver, gallbladder and intestine. Small amounts of bile acids are spilled over to blood circulation. It should be noted that increasing serum bile acids and *CYP7A1* mRNA expression does not necessarily indicate increase of bile acid synthesis as these authors suggested. They should have assayed 7α-hydroxy-4-cholesten-3-one (C4), a serum biomarker for bile acid synthesis. It is possible that hepatic inflammation may increase leakage of bile acids from liver into portal blood in NASH patients. These investigators also suggested that increased serum DCA might antagonize FXR activity to reduce FGF19 production and impair hepatic FGFR4 signaling and resulted in inducing *CYP7A1* and increasing

bile acid synthesis. These investigators thought that DCA is a FXR antagonist, in contrast to the fact that DCA is a potent FXR agonist. Bile acids activate FXR with the potency in the order of CDCA > DCA > CA > LCA, while bile acids activate TGR5 with the potency in the order of LCA > DCA > CDCA > CA. Known FXR antagonists are tauro-α-muricholic acid (TαMCA) and T-βMCA in mice and UDCA in humans (5).

In the colon, bile salt hydroxylase (BSH) activity in gut bacteria de-conjugates glycine and taurine conjugated-bile acids, and then gut bacteria 7α-dehydroxylase activity converts CA and CDCA to DCA and LCA, respectively. CDCA can be isomerized by 7α-hydroxysteroid dehydrogenase (7α-HSDH) to UDCA. To test the hypothesis that NAFLD patients have increased synthesis of DCA from CA, the gut microbiome from NAFLD and healthy control patients were analyzed by 16S rRNA sequencing. They found that the abundance of gut bacteria containing high BSH activity, including the genera *Bacteroides*, *Clostridium*, *Bifidobacterium* and *Lactobacillus*, were no difference between NAFLD and control patients. However, they did find significant increase of the abundance of bacteria metabolizing taurine including *Escherichia*, *Bilophila* and *Rhodobacter*. They then analyzed gut microbiome of HFD-fed rats and found significant increase of the genera expressing 7α-HSDH and taurine metabolizing bacteria compared to chow fed control rats. High fat diets are known to increase *Firmicutes* and decrease *Bacteroidetes*, and increases TCA and DCA to promote low abundant sulfate-reducing bacteria *Bilophila wadsworthia* and causes inflammation in mouse model of colitis (6). FXR and TGR5 agonists have been shown to protect against inflammation in diet-induced obese mice (DIO) (7).

The gut microbiota regulate bile acid metabolism, pool size and enterohepatic circulation of bile acids (2). Bile acid signaling via FXR and TGR5 regulates glucose, lipid and energy metabolism (8). Paradoxically, both activation and deficiency of intestinal FXR reduce weight and improve insulin sensitivity in mouse models of NAFLD (9,10). Inhibition of BSH activity increases T-MCAs to antagonize intestinal FXR activity to reduce ceramide synthesis, to stimulate bile acid synthesis to improve insulin resistance in DIO mice (9,11), whereas activation of intestinal FXR/FGF19 signaling promotes adipose tissue browning and energy metabolism to reduce weight and improve insulin sensitivity in DIO mice (10). High fat diets, circadian disruption, time of feeding/fasting, drugs and hormones can shape gut microbiota to alter bile acid composition and signaling and metabolic disorders such as NAFLD (8,12). NAFLD is a multifactorial metabolic disease. Increasing serum bile acid concentration and alteration of serum bile acid composition also have been observed after gastric-bypass surgery and linked to improved insulin resistance in overly obese patients (13). It is not clear whether increased serum bile acid concentration is the cause or consequence of NASH. However, clinical trials of bile acid derivative obeticholic acid have been shown to improve hepatic steatosis, reduce inflammation and the progression of NASH (14). The gut microbiome modulates host metabolism and pathogenesis of NASH, diabetes and obesity. Further study is needed to identify the metabolites and gut bacteria species responsible for altering bile acid metabolism and signaling in NAFLD.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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