

EDITORIAL

Fibroblast Growth Factor 19 in Alcohol-Associated Liver Disease: Bile Acids and Dysbiosis and Inflammation, Oh My!



Alcohol-associated liver disease (AALD) is the most common liver disease worldwide and presents as a spectrum of disorders ranging from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and liver failure.¹ Alcohol consumption skyrocketed during the coronavirus disease-2019 pandemic, and modeling has predicted that this will increase AALD-related morbidity and mortality.² It is imperative that research on AALD be performed to combat this increasing disease. Bidirectional gut–liver crosstalk is essential for physiological and pathologic functions and is regulated by the flow of various factors via portal vein and biliary system.³ Bile acids synthesized in the liver bind to the ileal farnesoid X receptor to induce fibroblast growth factor (FGF19 in human beings and *Fgf15* in mice) secretion that inhibits hepatic bile acid synthesis via FGF receptor 4/cholesterol 7 α -hydroxylase activation.⁴ Bile acids can influence gut microbial composition, and the microbiota in turn dictates bile acid conjugation.³ In AALD patients, circulating bile acid levels are increased⁵ along with microbial dysbiosis⁶; however, reports on FGF19 levels have been contradictory.^{5,7,8}

Key Findings

In this study by Ferrell et al⁹, FGF19 was overexpressed via FGF19–adeno-associated virus (AAV) infection in mice that were later subjected to a 10-day chronic + binge ethanol (ie, ETOH) diet or an isocaloric control feeding. FGF19-AAV increased FGF19 levels and suppressed endogenous *Fgf15* expression. FGF19-AAV exacerbated ETOH-induced liver weight but reduced white adipose tissue weight. Interestingly, FGF19-AAV activated canonical uncoupling protein 1–mediated metabolism in white adipose tissue, which may be one of the causes for the reduction in white adipose mass. ETOH increased serum levels of alanine aminotransferase and aspartate aminotransferase, as expected. Interestingly, FGF19-AAV further increased aspartate aminotransferase but not alanine aminotransferase serum levels in ETOH-fed mice. Regarding steatosis, ETOH feeding increased triglyceride levels, induced macrosteatosis, and dysregulated lipid metabolism. FGF19-AAV reduced liver cholesterol and enhanced serum cholesterol in control-fed mice, but had no effect on triglyceride levels, steatosis, or lipid metabolism. Although FGF19 plays a role in white adipose metabolism, it may have little to no effect on liver lipid metabolism.

When further evaluating liver damage, Ferrell et al noted that FGF19-AAV treatment and ETOH feeding had no impact on macrophages; however, ETOH-fed mice and FGF19-AAV-treated mice displayed a reduction in the density of

biliary epithelial cells. Interestingly, FGF19-AAV treatment in ETOH-fed mice increased the expression of various inflammatory genes, but ETOH feeding alone had no effect. FGF19-AAV may initiate inflammatory pathways via transcriptional regulation that could contribute to ETOH-induced inflammation, but this may be limited owing to the acute feeding model used.

FGF19 is a key determinant of bile acid synthesis, and thus the authors evaluated bile acid homeostasis. FGF19-AAV reduced the liver, gallbladder, intestinal, and overall bile acid pool regardless of diet. Mechanistically, serum 7 α -hydroxy-4-cholesten-3-one (C4), a biomarker of bile acid synthesis, was reduced in ETOH-fed mice and in FGF19-AAV-treated control-fed mice. Concurrently, hepatic expression of enzymes associated with bile acid synthesis were reduced in ETOH-fed mice and in FGF19-AAV-treated mice. Interestingly, FGF19-AAV decreased hepatic bile salt export pump expression in both control- and ETOH-fed mice, potentially as a compensatory mechanism. As expected, FGF19-AAV suppressed bile acid synthesis and the overall pool regardless of diet. ETOH feeding also impacted bile acid homeostasis.

The authors next examined how the gut and its microbiome were impacted in their model. Serum lipopolysaccharide levels were increased only in ETOH-fed mice treated with FGF19-AAV. Similarly, ileum gene expression of inflammatory markers was increased in ETOH-fed mice treated with FGF19-AAV. In the colon, gene expression of *chemokine ligand 2/3* was increased after ETOH feeding, whereas that of *tumor necrosis factor- α* and *interleukin-1 β* was increased in ETOH-fed mice treated with FGF19-AAV, and *nitric oxide synthase 2* was increased with FGF19-AAV treatment in both control- and ETOH-fed mice. Interestingly, colonic tight junction proteins were enhanced in ETOH-fed mice treated with FGF19-AAV, which may be a compensatory mechanism. Therefore, FGF19 may promote inflammatory markers in the ileum and colon. FGF19-AAV treatment reduced microbial α -diversity and richness at the phylum and species level, and altered β -diversity regardless of diet. Certain microbes are labeled as pathobionts, and thus the authors broke down their microbial evaluations to determine changes in harmful microbes. *Enterococcus* and the pathobiont *Enterococcus faecalis* were increased in FGF19-AAV control-fed mice, but reduced with ETOH feeding. Pathogenic *Clostridium perfringens*, *Escherichia coli*, and *Paraclostridium benzoelyticum* were induced by FGF19-AAV in both diets. *Parasutterella excrementihominis* was increased with FGF19-AAV treatment, and this pathobiont is associated with inflammatory bowel disease.¹⁰ *Faecalibaculum rodentium*, a beneficial microbe, was

reduced with FGF19-AAV treatment. The protective *Bacteroides acidifaciens* was increased with ETOH feeding but reduced with FGF19-AAV treatment. FGF19 overexpression in the presence of ETOH allows for the overgrowth of pathobionts, which may contribute to AALD progression.

What Did We Learn From This Novel Paradigm?

AALD is a complex disorder with varying injury symptoms and associated complications. Conflicting reports on changes in bile acid homeostasis and FGF19 signaling in AALD further complicate our understanding of this disease. Considering that an FGF19 analogue has been tested as a treatment for steatohepatitis,¹¹ it is appropriate to test artificial FGF19 overexpression in an AALD model to evaluate outcomes. In this model, Ferrell et al found significant perturbations in bile acid composition and conjugation associated with FGF19-AAV.

Their findings suggest that alterations in FGF19 signaling may contribute to AALD injury through changes in bile acid homeostasis and dysbiosis. Interesting protective effects in the white adipose tissue were noted, but more work in this area is needed. Although this acute ETOH feeding model did not inflict substantial damage in the liver, the introduction of FGF19 mimicked bile acid and microbiota alterations seen in AALD patients. Although FGF19-AAV is an artificial model, it enabled a better understanding of gut-liver communication via bile acids and the microbiota. Bile acid-based therapies are at the forefront of patient care and research for various liver disorders, and this study shows that bile acid-dependent dysbiosis and inflammatory signaling associated with these therapies should be evaluated. Further testing of FGF19 in different AALD models, ETOH feeding lengths, administrative routes, and approaches to alter this growth factor are necessary for future studies.

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Conflicts of interest

The author discloses no conflicts.

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