Irritable bowel syndrome (IBS), defined clinically by chronic abdominal pain and altered bowel habits without an identifiable organic cause, affects up to 15% of the adult population. Although visceral hypersensitivity and abnormal gut motility are core abnormalities, several other factors participate in symptom generation in IBS, including genetic susceptibility, alterations in fecal microbiota, bacterial overgrowth, intestinal inflammation, dietary intolerance (including carbohydrate malabsorption), and gluten sensitivity. In addition, in a subset of patients with irritable bowel syndrome with diarrhea (IBS-D), the pathophysiology may include excess delivery of bile acids (BAs) into the colonic lumen, resulting in net fluid and electrolyte secretion. BA diarrhea (BAD) is a common contributing factor in as many as 25% to 50% of patients with IBS-D or functional diarrhea. BAD has an estimated prevalence of 1% among the adult population, hence afflicting as many as 10 million people in Western societies. There are at least three distinct categories of BAD: (1) type 1 BAD, a consequence of anatomical disruption from ileal resection, radiation injury, or disease (e.g., Crohn's disease), ultimately resulting in BA malabsorption (BAM); (2) type 2 BAD, a heterogeneous condition associated with increased BA production in subsets of patients with pediatric and adult NAFLD demonstrates altered enterohepatic BA homeostasis in NAFLD.
overlap with IBS-D or functional diarrhea; and (3) type 3 BAD, consisting of miscellaneous organic gastrointestinal disorders that affect BA absorption, including celiac disease, chronic pancreatitis, small intestinal bacterial overgrowth, and lymphocytic/microscopic colitis.\(^\text{(10,14)}\) Type 2 BAD has defined pathophysiology in which increased luminal colonic BA accelerates colonic transit and causes loose stools.\(^\text{(11)}\) Important pathophysiological consequences of type 2 BAD include increased intestinal permeability, increased fecal fat, and, in a subgroup with high total fecal BA output (>2,300 mM in 48 hours), increased representation of the primary BA, chenodeoxycholic acid (CDCA).\(^\text{(15)}\) Reflecting these pathophysiological associations, IBS patients with type 2 BAD usually respond to BA sequestrants, implicating aberrant BA regulation as an important target in the pathogenesis of a subset of IBS-D that may be amenable to pharmacologic intervention.\(^\text{(16)}\)

The burgeoning global epidemic of obesity has focused attention on its associated comorbidities, including NAFLD. There is considerable overlap in population prevalence of obesity and NAFLD (Fig. 1A).\(^\text{(17)}\) However, emerging studies also point to an overlap between obesity and IBS-D (Fig. 1A).\(^\text{(18)}\) Other studies have demonstrated a higher prevalence of NAFLD in patients with BAD,\(^\text{(19)}\) and yet other work has shown increased diarrhea symptoms in a subset of patients with NAFLD (Fig. 1).\(^\text{(20)}\) These factors, known pathophysiological links between altered BA metabolism and diarrhea, coupled with evidence linking aberrant

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**Fig. 1.** (A) The prevalence of obesity in the U.S. population is estimated at approximately 40% compared with NAFLD at 30% and IBS-D at 10%-15%. The estimated overlap between obesity and NAFLD is 75%-90%, between obesity and IBS-D is 10%-20%, and between IBS-D and NAFLD is 10%-20%. There is a presumed overlap of obesity, NAFLD, and IBS-D; these proportions are yet to be determined. (B) Data support that 25%-50% of patients diagnosed with IBS-D have BAD, and 10%-20% will have concurrent NAFLD. There is a presumed overlap of IBS-D, NAFLD, and BAD; these proportions are yet to be determined.
BA signaling to impaired metabolic homeostasis, have heightened awareness of shared pathophysiologic pathways in subsets of patients with both BAD and NAFLD. This association is reinforced by emerging data demonstrating the overlap of phenotypes linking obesity, NAFLD, IBS-D, and BAD (Fig. 1B) and by the findings with therapeutic agents targeting BAM in both BAD and NAFLD. Here we review aspects of BA pathophysiology and homeostatic signaling, with special emphasis on how disturbances in select signaling pathways may contribute to clinical manifestations, linking obesity phenotypes and BAD-related disorders.

Physiology of BA Metabolism and Derangements in BAD

Primary BAs (cholic acid [CA] and CDCA) are produced in the hepatocyte from enzymatic modification of cholesterol in a multistep process for which the rate-limiting step is cholesterol 7α-hydroxylase (CYP7A1) activity (Fig. 2). The classical pathway, occurring in the liver, is the dominant route for BA production in humans, as shown by the greater than 90% reduction in BA production in rare subjects with mutational CYP7A1 deletion. Affected individuals exhibit hypercholesterolemia and decreased (but not zero) hepatic CYP7A1 activity and increased 27α-hydroxylase (CYP27A1) activity. Those findings are reflected in the increased proportion of CDCA + lithocholic acid (LCA) (versus CA + deoxycholic acid [DCA]) found in CYP7A1 mutant patient stool samples, again suggesting that BA synthesis in those patients proceeds through the alternate pathway. The distinction between classical and alternate pathways of BA synthesis is also important in understanding the utility for intermediates in BA production as surrogate markers of CYP7A1 activity. Cholesterol catabolism through the classical (CYP7A1) pathway generates 7α-hydroxycholesterol and subsequently a stable steroid intermediate, 7α-hydroxy-4-cholesten-3-one (C4), the serum levels of which are a useful surrogate for CYP7A1 activity (Fig. 2). The alternate or acidic BA synthesis pathway, which is regulated by CYP27A1 activity, generates oxysterol intermediates, which undergo steroid side chain cleavage to produce cholanoic acids and, ultimately, CDCA.

Primary BAs undergo conjugation by cytosolic and peroxisomal BA transferases to glycine and taurine (in an approximately 70:30 ratio) and thereafter are exported across the canalicular membrane through bile salt export pump/adenosine triphosphate binding cassette subfamily B member 11 (Abcb11) (Fig. 2) and stored in the gallbladder, along with phospholipids and cholesterol. Following a meal, gallbladder contraction is induced by cholecystokinin secretion from duodenal L cells, promoting lipid emulsification, lipolysis, and dietary fat digestion. Active BA absorption occurs in the terminal ileum through the apical sodium-dependent bile salt transporter (ASBT), solute carrier family 10 member 2 (Slc10a2) (Fig. 2). Within the ileal enterocyte, BAs bind the farnesoid X receptor (FXR), which then promotes heterodimerization with the retinoid X receptor (RXR), activating the FXR/RXR complex. Furthermore, BAs that do not bind to the FXR and escape first-pass metabolism by the liver exert peripheral effects on adipose and muscle tissue, signaling through Takeda G protein-coupled receptor 5, to promote energy expenditure.
occurs by recycling of BA through the portal vein and hepatocyte reuptake. In IBS-D, BAD results from increased colonic BA content caused by decreased ileal production or secretion of FGF19 (and consequent de-repression of BA synthesis) rather than an impairment in ileal BA absorption. Reduced FGF19
levels impair negative feedback inhibition of hepatic BA biosynthesis, leading to increased hepatic BA synthesis and secretion and, consequently, increased intestinal BA content. Genetic variations in the pathways associated with BA metabolism may also play a role in BAD in IBS-D. Specifically, a variant (rs1761844) in KLB (encoding KLB) was associated with colonic transit time in patients with IBS-D, and other studies showed a variant in FGFR4 (rs1966265) was associated with fecal BA content in these patients. Other work has shown that, in addition to increased total fecal BA output, patients with BAD excreted greater than 10% fecal primary BA, again suggesting increased BA synthesis.

Ileal BA absorption and recycling is extremely efficient, with BA undergoing enterohepatic cycling at least 10 times daily and only 5% of luminal BAs reaching the colon. In the colon, primary conjugated BAs undergo microbial deconjugation, epimerization, and dehydroxylation into secondary BAs’ DCA, ursodeoxycholic acid (UDCA), and LCA, some of which are reabsorbed and recirculated back to the liver where they undergo uptake and reconjugation and secretion along with the primary BA. Colonic BAs influence fluid secretion by increasing cellular calcium and adenosine cyclic adenosine monophosphate, which in turn up-regulates epithelial chloride/bicarbonate secretion, thereby creating an active mechanism for fluid and electrolyte secretion and, consequently, diarrhea (Fig. 2).

Biomarker Development and Utility in Clinical Evaluation of BAD

Because BAD is a common condition and reflects increased fecal BA excretion, considerable efforts have been directed at the identification of clinical biomarkers to categorize subsets of BAD. The gold standard test for BAD in the United Kingdom, Canada, and other European countries is the selenium-75-labeled homocholic acid (75SeHCAT) retention test, with BAD defined by less than 10% retention and severe disease characterized by less than 5% retention. 75SeHCAT is a modified BA that mirrors the enterohepatic circulation of taurocholic acid. 75SeHCAT testing requires oral administration of a radiolabeled synthetic BA followed by gamma camera measurement of retention at baseline and 7 days after administration. Because 75SeHCAT testing is not available in the United States, 48-hour fecal BA excretion is the gold standard test. Fecal BA testing measures the total mass of BA excreted per day as a measure of increased BA production and has a diagnostic yield for BAD of 25.5% in functional diarrhea or IBS-D. A challenge of the 48-hour stool collection is a required adherence to a high dietary fat intake (100 g per day) for 4 days. A recent retrospective study of patients with IBS-D found that fecal BA excretion of less than 10% primary BAs had a 90% specificity to detect increased fecal weight and rapid colonic transit (both surrogate clinical markers of BAD) and that 45% of patients with chronic diarrhea exhibited elevated fecal primary BA abundance (>10%). These observations together suggest that measuring primary fecal BA in a single stool sample may be a useful and less cumbersome alternative to a 48-hour stool collection for identifying BAD.

Another approach for diagnosing BAD is to measure fasting serum C4, a surrogate for Cyp7a1 activity and a key intermediate in BA production. Increased serum levels of C4 signify and correlate with BA overproduction, and this approach has been validated to diagnose BAD when compared with 75SeHCAT testing and shown to be a reliable screening biomarker for BAD in patients with IBS-D. In addition, serum C4 levels were increased with BAD in patients with Crohn’s disease, suggesting that C4 may be a useful biomarker to screen for other diarrheal conditions resulting from BAM. Fasting serum FGF19 levels have also been evaluated as a potential biomarker for BAD, with levels less than 61.7 pg/mL exhibiting 83% sensitivity and 78% specificity to diagnose BAD when compared with the 48-hour BA excretion, and those specificity and sensitivity values were superior to fasting C4 levels. One caveat is that serum FGF19 concentrations rise after meals once secreted BAs reach the terminal ileum. Because of the pathogenic role of defective ileal FGF19 production in BAD, the proposal emerged that synthetic FXR agonists may have therapeutic benefit in patients with BAD by up-regulating expression of FGF19. Indeed, this expectation was confirmed in a small trial of the potent FXR agonist, obeticholic acid (OCA), in which improved diarrheal symptoms and stool form were observed in BAD.
Because of increased awareness of different pathophysiological mechanisms underlying IBS-D, testing to confirm the diagnosis of BAD has been recommended over empiric BA sequestrant therapy. The Canadian Association of Gastroenterology clinical practice guidelines recommend confirmatory testing with \(^{75}\)SeHCAT or C4 over initiating empiric BA sequestrant therapy. \(^{47}\) Individuals with a definitive diagnosis of BAD have been shown to have a response rate of over 70% to BA sequestrant therapy, as opposed to those with negative testing for BAD with only 25% response to therapy. \(^{48}\) Furthermore, confirmatory testing for BAD is likely cost-effective and reduces the need for excessive diagnostic evaluation in this subset of patients. \(^{49}\)

### Clinical Trials of Agents Modifying BA Metabolism in BAD and IBS

Cholestyramine is a BA sequestrant that reduces diarrhea in all types of BAD. In several case series, 71% to 93% of patients responded to cholestyramine. \(^{50-52}\) In IBS-D, as many as 96% have been reported to respond to empirical cholestyramine therapy, with a dose response based on severity of BAM (better response with more severe BAM). \(^{12}\) Colestipol is an alternative BA sequestrant that has been studied in the management of BAD, \(^{11}\) and colesevelam, yet another sequestrant, improved diarrhea in 83% of patients with BAD, \(^{53}\) with a trend toward slowing of 24-hour colonic transit time. \(^{54}\)

As previously mentioned, OCA is a potent synthetic FXR agonist that has been studied in limited patients with BAD. This agent improved clinical symptoms, with a reduction in weekly number of stools and mean stool form in patients with primary BAD and patients with secondary BAD with short ileal resections (< 45 cm). However, no improvement in symptoms was observed in patients with idiopathic chronic diarrhea in the absence of BAD. \(^{55}\)

An inhibitor of ileal BA transport, elobixibat, has also been studied in constipation-predominant disorders and is a locally acting inhibitor of ASBT. Blockade of ileal BA transport leads to increased BA concentration in the right colon and secretory and motor effects that benefit constipation. A secondary effect is increased serum C4, which correlates with colonic transit and stool form. \(^{56}\)

### Altered BA and FGF19 Signaling in Hepatic Triglyceride Metabolism and NAFLD

An important physiologic role of FGF19 is suggested by the predictable postprandial increase in circulating levels specific to dietary fat content, implying a role as an enteroendocrine system in regulating BA synthesis.

FGF19 signaling is restricted to the liver under physiologic (endocrine) concentrations through interactions between its receptor, the tyrosine kinase FGFR4, and its co-receptor, KLB (Fig. 2). \(^{58,59}\) As noted, rare genetic variants of KLB, which affect the stability of FGFR4, are associated with IBS-D \(^{33}\) and pediatric NAFLD. \(^{60}\) Although these genetic associations have yet to be linked with alterations in FGF19 levels, one would predict (in the event that FGF19 is actually taken up by hepatocytes) that defects in FGFR4/KLB should result in increased serum FGF19 levels (theoretically reflecting defective hepatic uptake). However, this prediction is at odds with findings from pediatric patients with NAFLD and advanced fibrosis in which hepatic messenger RNA expression of KLB directly correlated with serum FGF19 concentration. \(^{60}\) In addition, portal vein and peripheral arterial and venous FGF19 concentrations were comparable in subjects undergoing liver surgery, making it unlikely that the liver participates in clearance of FGF19. \(^{61}\) Among the pertinent phosphorylation targets of FGFR4 are the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin. However, the presence of the KLB co-receptor shifts signaling toward the mitogen-activated protein kinase/extracellular signal–related kinase signaling pathway for energy use. \(^{62}\) As a result, hepatic FGF19 signaling through FGFR4 increases fatty acid oxidation, decreases lipid biosynthesis (decreasing fatty acid synthase and stearoyl-coenzyme A desaturase), \(^{63}\) and
increases insulin sensitization.\(^{(64,65)}\) These observations reinforce the premise that FGF19 deficiency is associated with abnormal hepatic lipid metabolism. The related hypothesis that FGF19 deficiency is associated with NAFLD in humans is supported by studies showing either lower fasting levels of FGF19 or lower postprandial FGF19 integrated areas under the curve.\(^{(66-69)}\) Furthermore, this association was confirmed in a pediatric population, in whom an inverse association was observed between serum FGF19 levels and histologic severity of NAFLD (Table 1).\(^{(60,70)}\)

This inverse correlation between circulating FGF19 and NAFLD in humans remains even after adjusting for potentially relevant clinical confounders, such as body mass index, age, and gender.\(^{(60)}\) The hypothesis that FGF19 deficiency leads to worsening hepatic steatosis is further supported by a randomized trial with an FXR antagonist, UDCA, in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery.\(^{(71)}\) Obese patients pretreated for 3 weeks with UDCA exhibited lower serum concentrations of FGF19 and increased severity of hepatic steatosis, as detected on an intraoperative liver biopsy.

In summary, human data support a correlation between low serum FGF19 levels and hepatic steatosis. The most biologically plausible explanation of this relationship is that FGF19 deficiency precedes the development of steatosis, because this deficiency decreases hepatic triglyceride oxidation while simultaneously increasing de novo lipogenesis. Still, the reversal of causality (i.e., hepatic steatosis leads to low FGF19) remains a possibility; however, this is at odds with studies that have shown markedly elevated FGF19 levels in patients with alternative etiologies of liver disease, such as alcoholic hepatitis and cholestasis.\(^{(72)}\)

### Role of FGF15 in Mouse Models of NAFLD

The literature evaluating FGF15 in mice models of NAFLD illustrate the strong interaction among this FGF signaling pathway, genetics, dietary composition, and mitochondrial metabolism (Table 2). Many of the findings are consistent with the expected roles described previously, such as transgenic FGF19 expression protecting against hepatic steatosis\(^{(73)}\) and ileal FXR deletion (which reduces FGF15 production), worsening hepatic steatosis from high-fat feeding.\(^{(74)}\) On the other hand, although FGF15 knockout (KO) mice exhibit hepatic steatosis and insulin resistance, the severity of steatohepatitis was no different.\(^{(75)}\) Furthermore, hepatic steatosis induced by tetracycline administration was actually prevented by the antagonism of FGF15 signaling by using either Fgfr4 KO mice\(^{(63)}\)

### Table 1. Studies of FGF19 in Patients with NAFLD

| First Author (Reference) | NAFLD Diagnosis | N (Cases) | Fasting FGF19 (Median pg/mL) | P Value |
|--------------------------|-----------------|-----------|-----------------------------|---------|
| Eren\(^{(68)}\)           | Biopsy          | 91 (adults) | 130 (NAFLD) 210 (controls)  | <0.001  |
| Mouzaki\(^{(69)}\)        | Biopsy          | 21 (adults) | 57 (NASH) 101 (SS) 116 (controls) | 0.114   |
| Schreuder\(^{(66)}\)      | Ultrasound      | 20 (adults) | 180 (NAFLD) 260 (controls)  | 0.94    |
| Friedrich\(^{(67)}\)      | Ultrasound      | 26 (adults) | 116 (obese NAFLD) 128 (overweight) 178 (controls) | 0.01   |
| Nobili\(^{(70)}\)         | Biopsy          | 33 (pediatric) | 55 (NASH) 100 (SS) 175 (controls)  | <0.01 |
| Alisi\(^{(60)}\)          | Biopsy          | 84 (pediatric) | 41 (NASH) 80 (SS) 201 (controls)  | <0.001 |

Abbreviation: SS, simple steatosis.
or therapeutic administration of the FGFR4 extra-cellular domain.\(^{(76)}\) The role of extracellular FGFR4 in the prevention of tetracycline-induced hepatic steatosis is particularly intriguing, because this model induces hepatic steatosis through mitochondrial toxicity.\(^{(77)}\) An interesting potential translational application to consider would be other causes of microvesicular steatosis, such as Reye syndrome or acute fatty liver of pregnancy; however, this speculation will require formal experimental validation. Further mouse studies have highlighted alternative pathways for FGF19 signaling in metabolic regulation by demonstrating that liver-specific signaling is not required but rather that neuronal signaling mediates long-term metabolic effects on body weight and glycemic control.\(^{(78)}\)

### Clinical Trials of Agents Modifying Signaling Through the FGF19 Axis in NAFLD

The clinical use of recombinant FGF19 was initially perceived to be limited, given concerns with potential hepatocarcinogenicity caused by FGFR4/KLB receptor signaling through the signal transducer and activator of transcription 3 (STAT3) pathway.\(^{(79)}\) However, NGM282, a bioengineered mutant variant of FGF19, does not signal through STAT3 and has been demonstrated to be efficacious in reversing steatosis, inflammation and fibrosis, and is protective against hepatocellular cancer in a mouse model fed a high-fat/high-fructose diet.\(^{(80)}\) The phase 2 human study using parenteral injection of NGM282 successfully met its primary endpoint of a less than 5% loss in liver fat as measured by magnetic resonance proton density fat fraction in 74% and 78% of those treated with 3 mg and 6 mg, respectively (compared with only 9% in the placebo).\(^{(81)}\) These observed changes were associated with significant decreases in plasma C4 levels, suggesting that the mechanism of action involves altered BA synthesis. NGM282 treatment also led to increased serum low-density lipoprotein (LDL) cholesterol, primarily in large LDL particles.\(^{(81)}\)

Similarly, the potent FXR ligand, OCA, markedly increases FGF19 secretion.\(^{(82)}\) Both the FXR Ligand OCA in Nonalcoholic Steatohepatitis Treatment Trial (FLINT), a phase 2 study, and Randomized Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment (REGENERATE), a phase 3 study, met their primary endpoints by demonstrating both a statistically significant improvement in the NAFLD activity score on liver biopsy without worsening hepatic fibrosis (20% in placebo, 50% in the 25-mg group) and fibrosis improvement without worsening nonalcoholic steatohepatitis (NASH) (12% in placebo, 18% in the 10-mg group and 23% in the 25-mg group), respectively.\(^{(83,84)}\) The most common adverse effects were pruritus and increased serum LDL cholesterol, although there were no differences in cardiovascular event rates. Secondary analysis of the clinical parameters from the FLINT indicated significant interactions between weight loss and improvement in the NAFLD activity score and showed that patients who lost weight on OCA demonstrated increased LDL cholesterol and decreased high-density

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### TABLE 2. STUDIES OF FGF15/19 IN MOUSE MODELS OF NAFLD

| First Author (Reference) | Diet Intervention | Findings Related to FGF19 Axis |
|--------------------------|-------------------|--------------------------------|
| Schumacher\(^{(75)}\)    | High fat vs. chow | FGF15 KO                      |
| Schmitt\(^{(74)}\)       | 1% cholesterol vs. chow | Selective (ileal or hepatic) FXR KO |
| Chen\(^{(76)}\)          | Tetracycline      | FGF19 extracellular domain    |
| Fu\(^{(78)}\)            | High fat vs. chow in ob/ob mice | Transgenic expression FGF19 |
| Huang\(^{(63)}\)         | High fat vs. chow | FGF19 KO                      |

Abbreviation: ob/ob, obese.
lipoprotein cholesterol levels. These findings highlight the complexity of BA signaling, because hepatic FXR activation with OCA would be expected to decrease BA synthesis and in turn decrease cholesterol disposal (favoring LDL accumulation) while also decreasing hepatic triglyceride-rich lipoprotein production. It is clear that the signaling pathways involved in weight loss with OCA treatment are complex and remain incompletely understood; however, these promising results have opened the pipeline for other FXR agonists in the treatment for NAFLD.

In conclusion, the pathogenesis of BAD and NAFLD appear to share overlapping mechanisms and pathways (Table 3). Through a cognate FGFR4/KLB receptor in the liver, FGF19 activity not only regulates BA homeostasis but also plays a key role in lipid metabolism and insulin sensitivity. Thus, low serum levels of FGF19 have been implicated in the pathogenesis of BAD in IBS-D as well as NAFLD, and consequently, treatment paradigms that influence FGF19 homeostasis have shown benefit in small studies in both groups of disorders. Future studies will further elucidate the mechanisms and pathways involved and are expected to yield novel therapeutic targets and specific pharmacologic agents that may be useful to treat distinctive subsets of patients with both BAD and NAFLD.

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TABLE 3. OVERLAPPING ASSOCIATIONS OF IBS-D, BAD, AND NAFLD

|                      | IBS-D | BAD  | NAFLD |
|----------------------|-------|------|-------|
| FGF19 concentration  | ↓     | ↓    | ↓     |
| C4 concentration    | ↑     | ↑    | ↑     |
| 48-hour fecal bile acids | ±  | ↑    | ↑     |
| Associated variant FGFR4/KLB | + | +    | NS    |
| Response to FXR agonists | + | +    | +     |
| Obesity as risk factor | +   | +    | +     |

Abbreviations: ↑, increased concentration relative to controls; ↓, equivocal levels compared with controls; +, known association; NS, not studied.
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