New Developments in Bile Acid Diarrhea

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Abstract: Bile acid diarrhea (BAD) is characterized by increased frequency of bowel movements, looser stool consistency, urgency, and need for proximity to toilet facilities owing to the severity of the diarrhea, when compared with or relative to irritable bowel syndrome with diarrhea. Consequently, BAD leads to decreased quality of life. The condition is often misdiagnosed as irritable bowel syndrome with diarrhea or functional diarrhea. Patients with BAD have accelerated colonic transit, increased intestinal or colonic mucosal permeability, and altered stool microbiome composition associated with reduced dehydroxylation of primary to secondary bile acids. The established diagnostic test, selenium-75 homocholic acid taurine retention, is not available in the United States. Therefore, 48-hour fecal bile acid excretion has been the gold standard for diagnosis. With recent validation of combined measurement of primary bile acids in a single, random stool in addition to fasting serum 7α-hydroxy-4-cholesten-3-one, a practical point-of-care diagnostic test will soon be available. Randomized controlled trials have documented superiority of colesevelam to placebo and, in a separate study, superiority of the glucagon-like peptide 1 agonist liraglutide compared with colesevelam. Novel experimental approaches for BAD include farnesoid X receptor agonists and fibroblast growth factor 19 analogs. This article updates information on the pathophysiology, mechanisms, manifestations, diagnosis, and treatment of BAD.

Keywords
Bile acid diarrhea, permeability, messenger RNA, sequestrants, fibroblast growth factor 19 analog

Bile acids (BAs) are actively absorbed in the ileum[1-3] by the apical sodium-dependent BA transporters in distal ileal mucosa,[4,5] and they are passively absorbed through the small intestinal[6] and colonic mucosa[7,8] along a concentration gradient. Bile acid diarrhea (BAD) results from delivery of excessive BAs to the colon (and this may result from malabsorption), excessive hepatic synthesis, or delivery to the small intestine that is not synchronized with the entry of food into the small intestine as may occur postcholecystectomy. BAD has been defined as BA sequestrant-responsive diarrhea in the presence of BA malabsorption (BAM), as can be measured by direct or indirect tests.[9] The mechanisms whereby BAs induce diarrhea include the effects on the surface epithelium (such as denudation of surface mucus and increased permeability resulting from detergent effects), as well as through binding to the G protein–

coupled BA receptor-1, also called Takeda G protein–coupled receptor 5 (TGR5), and inducing 3',5'-cyclic adenosine monophosphate (cAMP)-dependent changes of function. These mechanisms lead to increases in motility, visceral sensation, and fluid secretion. All BAs can bind to TGR5, and the most potent BA is lithocholic acid (LCA).[10-12] On the other hand, the di-alpha hydroxy BAs, chenodeoxycholic acid (CDCA) and deoxycholic acid (DCA), have significant detergent effects, which are not shared by cholic acid (CA) and LCA.[13]

This article summarizes the latest research on BAD, provides further understanding of its pathophysiology and mechanisms, and reviews validated simple diagnostic tests and novel treatments that have enhanced opportunities to diagnose and treat BAD.

Bile Acid Synthesis and Enterohepatic Circulation

The primary BAs, CA and CDCA, are synthesized from cholesterol and undergo conjugation with taurine and glycine in the liver. In this synthesis, the rate-limiting enzyme is cytochrome P450 7A1 isozyme (CYP7A1), and an intermediate is 7α-hydroxy-4-cholesten-3-one (C4). Up to 95% of primary BAs are actively reabsorbed by apical sodium-dependent BA transporters in terminal ileal enterocytes, and actively and passively absorbed BAs are transported to the liver via portal circulation. In the ileal enterocytes, BAs bind to the nuclear farnesoid X receptor (FXR) and induce synthesis of the enteroendocrine hormone fibroblast growth factor 19 (FGF19). FGF19 reaches the liver via portal circulation, binds to the fibroblast growth factor receptor 4 and Klotho B, inhibits CYP7A1, and reduces BA synthesis, providing a feedback regulation loop.[14] Thus, there is an inverse relationship between C4 and FGF19 (Spearman rank rs = −0.53; P=.01).[15,16] Patients with BAD have increased serum C4, which reflects excessive BA synthesis, and the increased synthesis of BAs overcomes the absorptive capacity of the ileum, reaching the colon and causing BAD and increased fecal BA excretion. Patients with type I BAD (secondary to ileal disease or resection) or type II BAD (idiopathic) also have decreased serum FGF19, the negative feedback regulator of BA synthesis.[15] The remaining 5% of BAs reach the colon, undergo deconjugation and dehydroxylation by bacterial enzymes to secondary BAs, DCA, and LCA, or epimerization to ursodeoxycholic acid, and are either passively absorbed in the colon or excreted in stool.[7]

Mechanisms of Bile Acid Diarrhea

Loss-of-function mutations in BA transporters, such as apical sodium-dependent BA transporters, have been identified as rare potential causes for BAD that may present in infancy.[17-19]

There is evidence of decreased FGF19 messenger RNA (mRNA) expression in ileal mucosa in patients who have reduced selenium-75 homocholic acid taurine (^{75}SeHCAT) retention (diagnostic of BAD) and lower serum FGF19 leading to reduced feedback inhibition of hepatic BA synthesis.[20] There is also evidence that patients with BAD (serum C4 ≥65.87 ng/mL) have significantly lower ileal FGF19 protein expression compared with patients with chronic diarrhea without evidence of BAD.[21]

Ileal and colonic mRNA expressions of several genes were compared in 10 patients with BAD, 34 with diarrhea-predominant irritable bowel syndrome (IBS-D), and 30 healthy volunteers. In the ileal mucosa of patients with BAD, there was downregulation of *SLC44A5* (a transporter of bile salts as well as glucose, other sugars, organic acids, metal ions, and amines).[22] This finding requires replication, and its biological significance is yet unclear. Expressions in ileal biopsies of other candidate genes (*FGF19, NR1H4* [gene for FXR], and *SLC10A2* [gene for apical sodium-dependent BA transporters]) were not different in BAD compared with IBS-D.[22] In contrast, ascending colon biopsies from patients with BAD showed upregulation in genes that reflect increased mucosal permeability to water (*CLDN2*), immune activation (controlling complement, chemokines, and interleukin-1 receptor antagonists), and cellular differentiation that are consistent with the detergent effects of BAs.[23] No differential expression of genes was documented in descending colon biopsies from the 2 groups.[22]

Pathophysiology of Bile Acid Diarrhea

Several pathophysiologic mechanisms may result from the effects of BAs in the colon, although these mechanisms may not be present in all patients. For example, colonic secretion of water and electrolytes may concur with increased colonic mucosal permeability, but they may be independent of effects on colonic motility.

Colonic Motility

BAs stimulate colonic motility mainly through TGR5.[24] Ileocolonic release of sodium chenodeoxycholate, 500 mg or 1000 mg, significantly accelerated overall and ascending colonic transit and was associated with increase in stool frequency and looser stool consistency.[25] Rectal administration of sodium chenodeoxycholate was associated with stimulation of colonic high amplitude propagating contractions.[26]

Fluid and Electrolyte Secretion in the Colon

BAs stimulate fluid and electrolyte secretion in the

colon[7,27] through a variety of mechanisms: stimulation of colonocyte intracellular mediators, mainly cAMP[28,29]; upregulating expression of colonic aquaporin channels[30]; increased serotonin-induced secretion[31]; neurocrine secretion through activation of TGR5 and submucosal cholinergic neurons[32]; and increased mucosal permeability.[23] There is also evidence that conjugated BAs can prevent water and sodium absorption and, at higher concentrations (≥5 mM), evoke secretion in human jejunum.[33] However, this effect was abolished in the presence of a polar lipid molecule, suggesting that the secretory effect occurs only after fat absorption has occurred.

Intestinal Permeability

Patients with BAD have increased intestinal permeability and an altered gut microbiome. In a Mayo Clinic prospective study, 44 patients with BAD had a significantly higher ^{13}C-mannitol excretion at 2 to 8 hours, 8 to 24 hours, and 2 to 24 hours than 161 patients with IBS-D without BAD.[34] Moreover, patients with BAD had a significantly lower microbial alpha diversity and a significantly different stool bacterial compositional profile than patients without BAD.[22] An important functional difference in the microbial functions is the reduced expression of thiol ligases that are associated with conversion of primary to secondary BAs, and this was associated with higher primary BA excretion in stool of patients with BAD.[22] These results are consistent with a previous study, involving 55 patients with IBS-D and 28 matched healthy controls, which hypothesized that altered BA metabolism in patients with IBS-D was associated with dysbiosis.[35]

Clinical Features of Bile Acid Diarrhea

There are 3 types of BAD: type I in patients with ileal disease or resection; type II, also called idiopathic BAD, in patients with functional diarrhea or IBS-D; and type III in patients with gastrointestinal conditions other than ileal disease.[36] Patients with hypertriglyceridemia[20] and patients on metformin treatment[37] may also develop BAD.

Epidemiology and Associated Diseases

A systematic review of the literature showed that the prevalence of BAD among patients with chronic functional diarrhea or IBS-D is estimated to be about 25% to 50%.[38] It is also estimated that the prevalence of BAD is about 1% of the general population. Diseases of the gastrointestinal tract, particularly Crohn's disease, ulcerative colitis, microscopic colitis, and celiac disease,[39] and intestinal neuroendocrine tumors[40] may all be associated with evidence of BAD, as documented in clinical practice medical records.

Symptoms

Diarrhea is the predominant symptom of BAD. In an online survey of patients in BAM Support UK, 91 of 100 respondents reported a diagnosis of BAD, either following a ^{75}SeHCAT scan (n=58) or clinically (n=33) based on symptoms alone or on response to a trial of BA binders. Among those patients, 38% had type II BAD and 37% had type III BAD. The most common symptoms were explosive, offensive smelling, or watery diarrhea (80%), urgency (85%), and abdominal bloating or swelling (54%). Moreover, 88% reported at least occasional stool incontinence or accidents, and 52% reported they felt the need to always be close to a toilet.[41] In the Mayo Clinic prospective study of 44 patients with BAD and 161 control patients with IBS-D, those with BAD had higher body mass index and more severe bowel dysfunction (urgency and frequency of bowel movements and loose stools).[42]

Quality of Life

Patients with BAD have lower quality of life. Among BAM Support UK participants, diarrhea symptoms affected the respondents' mental health, physical well-being, and ability to work. Greater than 80% reported sometimes or often having low self-esteem and/or feeling embarrassed, nervous to leave the home, isolated, depressed, or helpless. Furthermore, 44% reported inadequate support at work and changing jobs to reduce travel time.[41]

Patients with BAD surveyed in the Mayo Clinic study were more likely to worry about losing control of their bowels and to value proximity to a toilet than were patients with IBS-D. These symptoms were associated with depression based on the Hospital Anxiety and Depression Questionnaire.[42] Treatment of BAD with BA sequestrants resulted in significantly improved mean scores on the 36-Item Short Form Survey (SF-36) in the "Role limitation due to physical health" dimension and in the overall mental component summary.[43]

On the other hand, in a placebo-controlled randomized trial of colesevelam, quality of life assessed by some of the SF-36 items was improved, but the authors commented that the improvement seemed to be driven by diarrhea severity and diarrhea impact on everyday life, whereas general quality of life was mostly unchanged.[44] In the same study, physical and mental component scores and the general well-being item based on SF-36 (version 2) were largely unchanged from baseline to the end of 12 treatment days and at 6-month follow-up.[44]

Diagnosis of Bile Acid Diarrhea

The availability of diagnostic tests for BAD varies by country and health care centers.[45] The Table describes advantages and pitfalls of the different diagnostic tests.[14]

Table. Diagnostic Tests for BAD

Diagnostic test	^{75}SeHCAT	Fasting serum C4	Fasting serum FGF19	48-h fecal total BA	Primary BAs >4% + fecal total BAs	Fecal primary BAs >10%	Combined fecal primary BAs + fasting serum C4	Fecal total BAs
What it measures	Ileal capacity to reabsorb radio-labeled BA retention (%) on day 7	Hepatic BA synthesis	Feedback inhibition to hepatic BA synthesis	Total fecal BA excreted from the colon	Reflects direct (CDCA) or indirect secretory potential (CA via DCA) with total fecal BA excretion	BAs directly synthesized from the liver with secretory potential	Combining serum and stool biomarkers to simplify diagnosis of BAD	3α-hydroxy BAs measured by thio-NADH production during conversion to 3-keto steroids by 3-α-hydroxysteroid dehydrogenase
Diagnostic cutoffs	<5% (severe) <10% (moderate) <15% (mild)	≥52.5 ng/mL	≤61.7 pg/mL	≥2337 μmol/48 h	Primary BA >4% + fecal total BA >1000 μmol/48 h	>10% primary BA	Fecal sample primary BA >10% + fasting serum C4 ≥52.5 ng/mL	Fecal total BA 4.3 μmol/g
Sensitivity/ specificity for fecal weight >400 g/48 h	N/A	15%/86%	28%/75%	59%/92%	46%/97%	49%/91%	63%/90% relative to 48-h fecal total BA	57%/77% relative to ^{75}SeHCAT retention of ≤15%
Diet, radiation, and equipment required	γ camera + radiation; 7-day test	HPLC; before 9 AM	ELISA; before 9 AM	HPLC Requires 100-g high-fat diet × 4 days and 2-day stool collection			HPLC single stool sample; HPLC for C4 before 9 AM	IDK fecal BAs Photometric Kit (Immundiagnostik) single stool
Comment or pitfalls of testing	? best for type I BAD	Good as screening test	Good as screening test	Fecal BA reflects BA in colon	Identify additional patients	Identify additional patients	Potential for point-of-care testing	
Worldwide availability	Available in some European countries and in Canada, but not in the United States	Available through US commercial laboratories	Commercial ELISA kits	Available through select laboratories (eg, LSI Medience Corporation, Tokyo, Japan; Mayo Medical Laboratories, United States)			Commercially available	Commercial kit available (Ref: K7878W, BioHit Healthcare, United Kingdom)

Adapted with permission from Camilleri and Nurko.[14]

^{75}SeHCAT, selenium-75 homocholic acid taurine; BA, bile acid; BAD, bile acid diarrhea; C4, 7α-hydroxy-4-cholesten-3-one; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; ELISA, enzyme-linked immunosorbent assay; FGF19, fibroblast growth factor 19; HPLC, high-performance liquid chromatography; N/A, not available; thio-NADH, thionicotinamide-adenine dinucleotide, reduced.

Selenium-75 Homocholic Acid Taurine Test

The ^{75}SeHCAT test measures the retention of selenium-75 in the abdomen 7 days after oral ingestion of the radioisotopic-labeled BA. This test is considered the gold standard for diagnosis of BAD. A retention of less than 5% suggests severe BAD, of 5% to 10% suggests moderate BAD, and of 10% to 15% suggests mild BAD.[46] The ^{75}SeHCAT test is not available in the United States.

The 48-Hour Fecal Total Bile Acid Test

The 48-hour fecal total BA test measures the total BAs excreted and the percentage of primary BAs (CA +

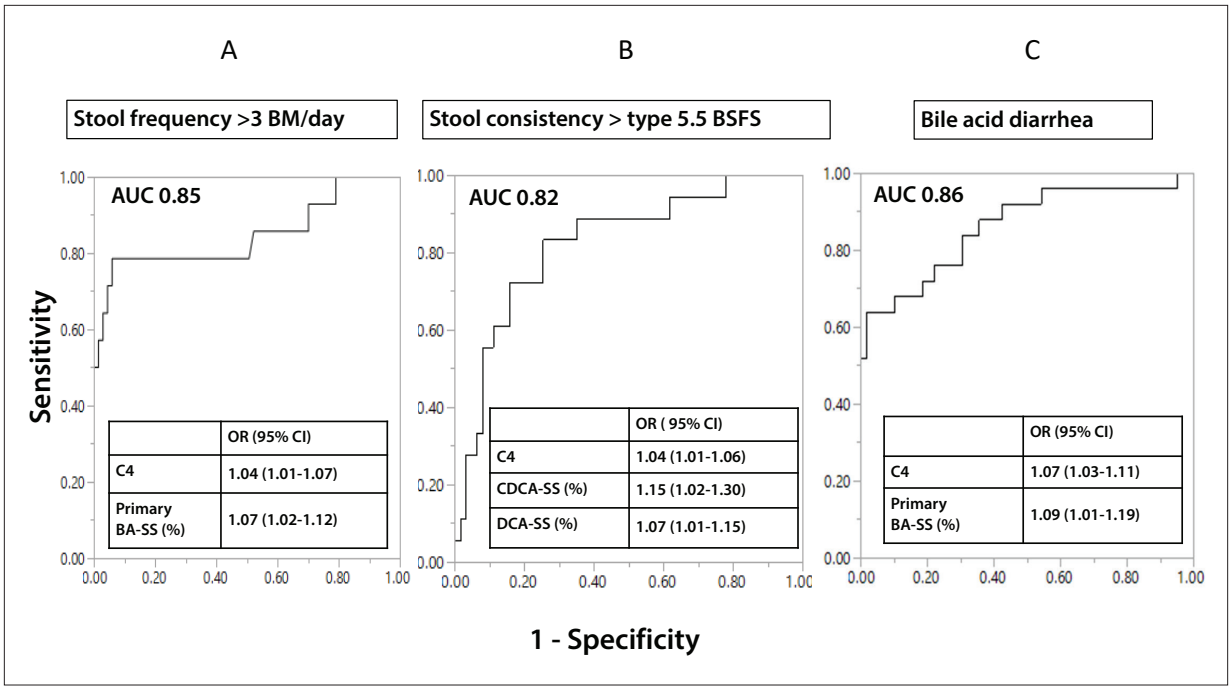

Figure. Receiver operating characteristic curve of combined factors and individual ORs (95% CI) of significant predictors of clinical markers of diarrhea based on stool frequency (**A**), stool consistency (**B**), and diagnosing bile acid diarrhea (**C**). Adapted with permission from Vijayvargiya et al.[54]

AUC, area under the curve; BA-SS, primary bile acid measured from the single stool sample; BM, bowel movement; BSFS, Bristol Stool Form Scale; C4, 7α-hydroxy-4-cholesten-3-one; CDCA-SS, chenodeoxycholic acid measured from single stool sample; DCA-SS, deoxycholic acid measured from single stool sample; OR, odds ratio.

CDCA) in stool that is collected during the last 2 days (48 hours) of a 4-day, high-fat diet (100 g/day). The cutoffs of total BAs greater than 2337 µmol/48 hours, primary BA greater than 10%, or fecal total BA of at least 1000 µmol/48 hours plus primary BA greater than 4% have shown good sensitivity and specificity to identify diarrhea defined as fecal weight greater than 400 g/48 hours.[47,48]

Fasting Serum C4

Serum C4, an intermediate in BA synthesis, is collected fasting before 9 AM owing to diurnal variation. The cutoff of 52.5 ng/mL has been shown to have a sensitivity of 29% and a specificity of 83% when compared with the 48-hour fecal BA test (using the extremely stringent cutoff of >2619 µmol/48 hours rather than the usual cutoff of >2337 µmol/48 hours) in 101 patients with IBS-D or chronic functional diarrhea.[49] It has a high negative predictive value (79%) when normal and, therefore, when assessed alone, it is most useful to exclude BAD.[49] Levels between 17 and 52 ng/mL should be followed by total 48-hour fecal total BA excretion or a therapeutic trial with a BA sequestrant. There are also data acquired in patients with type I or type III BAD (but excluding idiopathic BAD) suggesting sensitivity, specificity, positive predictive value, and negative predictive value of 90%, 79%, 73%, and 92%, respectively, for C4 greater than or equal to 48 ng/mL.[50] This suggests that the utility of the serum C4 may be greater with intestinal disease or resection.

Fasting Serum FGF19

Serum FGF19 is also collected before 9 AM after fasting.[51] The test performance was consistent with good specificity and negative predictive value, suggesting utility as a screening test to exclude BAD.[49]

Serum Lipidome

A single lipidome study of serum showed decanoylcarnitine, cholesterol ester (22:5), eicosatrienoic acid, L-alpha-lysophosphatidylinositol (18:0), and phosphatidylethanolamine (O-16:0/18:1) distinguished BAD (diagnosed with ^{75}SeHCAT retention) from controls with 78% sensitivity and 93% specificity.[52] Further experience with this test is awaited.

Single Stool Bile Acid Measurements

Measuring the concentration of fecal BAs in a single, random stool sample was tested in 113 patients with chronic diarrhea who had undergone ^{75}SeHCAT testing. Patients

who had severe BAD (^{75}SeHCAT retention <5%) had a significantly higher fecal BA concentration compared with patients who had moderate or mild BAD.[53] Different laboratories use different measurements for total BAs, including high-performance liquid chromatography–tandem mass spectrometry[47,48] or an enzymatic assay for 3 alpha-hydroxy BAs.[53]

Combined Fecal Primary BAs and Fasting Serum C4

The combination of fecal primary BAs and fasting serum C4 in a single stool sample was examined in 25 healthy volunteers, 59 patients with IBS-D, and 4 patients with terminal ileal resection. The combination was predictive of increased stool frequency (sensitivity 79%, specificity 94%) and BAD diagnosed by the 48-hour fecal total BA test (Figure).[54]

Treatment of Bile Acid Diarrhea

It is important to note that there are advantages of firm diagnosis over an empiric trial. In clinical practice cohorts, it has been demonstrated that when patients are formally diagnosed with BAD and treated with BA sequestrants, there is an approximately 70% likelihood of achieving clinical benefit in the gastrointestinal manifestations. In contrast, when patients with a negative diagnostic test are empirically treated with the same BA sequestrants, the response rate was approximately 35%.[55] A study conducted in the United Kingdom showed cost implications for missing the diagnosis of BAD. While ^{75}SeHCAT was found to be underused, late diagnosis was associated with treatment delay, whereas early diagnosis reduced cost and improved outcomes.[56]

Diet

A diet low with 20% energy from fat led to a significant reduction in abdominal pain, stool urgency, and nocturnal diarrhea in 116 patients with BAD based on ^{75}SeHCAT retention less than 20%.[57]

Bile Acid Sequestrants

BA sequestrants are used off-label for the treatment of BAD and include colesevelam, colestipol, and cholestyramine, which are available in either tablet or powder form. The latter is reported by many patients to lack palatability. Cholestyramine was associated with a 28.1% response rate in a treatment trial in 139 unselected patients.[58] Colesevelam tablets may have improved tolerability over the other BA sequestrants in powder formulation.[59]

Although previously validated in open-label trials (efficacy documented in a systematic review[59]) for effects on bowel function and improved quality of life,[43] there is also evidence of efficacy from a placebo-controlled trial.[44] In this placebo-controlled trial of colesevelam, the adjusted odds ratio for achieving remission was 9.1 (95% CI, 1.9-62.8) in the C4-defined BAD group and 11.1 (95% CI, 3.4-45.6) for the ^{75}SeHCAT-defined group.[44]

Colesevelam did not alter bacterial α/β-diversity, but patients who clinically responded to treatment had a significantly greater abundance of *Fusobacteria* and *Ruminococcus,* both of which aid in the conversion of primary to secondary BAs.[60]

BA sequestrants may interfere with the absorption of other medications and thus it is usually advisable to take other medications 2 hours before or 4 to 6 hours after the ingestion of the BA sequestrant. It is also important to note that the dosing schedule of a BA sequestrant for BAD has not been studied as well as that for the approved indication to reduce cholesterol, for which intake of the sequestrant with meals is recommended. In contrast, the antidiarrheal effect of the BA sequestrant relies on the binding of BAs in the colon rather than in the small intestine where binding of the BAs might interfere with absorption and therefore impair fat absorption. Thus, it is our practice to administer the BA sequestrant away from mealtimes, such as 2 hours after the intake of any meals or important medications, to avoid interference with absorption, and then give the second dose at bedtime to sequester BAs that may continue to undergo enteral hepatic circulation at nighttime in the absence of food. It is hypothesized that this approach may also reduce the total BA pool, reducing the potential for excessive BAs to reach the colon during other times of the day.

Newer Interventions

The FXR-FGF19 axis, which is pivotal in the pathophysiology of BAD, has been identified as a potential therapeutic target for BAD.

Obeticholic Acid

Obeticholic acid (6-ethyl chenodeoxycholic acid) is a first-in-class FXR agonist; it was demonstrated that this medication stimulates FGF19, reduces BA synthesis, and produces clinical benefits in BAD relative to a baseline run-in period.[61] This medication has been associated with significant pruritus when used in the treatment of metabolic dysfunction-associated steatotic liver disease.

Tropifexor

Tropifexor is an FXR agonist. A double-blind, randomized, crossover study of tropifexor 60 μg in 20 patients with BAD showed a significant increase in FGF19, decrease in serum C4, and increase in ascending colon half-emptying time. No changes in stool frequency or consistency were observed with a single daily administration.[62]

Aldafermin

Aldafermin, a 190 amino acid engineered peptide analog of human FGF19 with 95.4% homology, was compared with placebo in a 28-day, randomized, double-blinded, placebo-controlled (1:1 ratio) trial in idiopathic BAD based on serum C4 of at least 52 ng/mL or standard 48-hour fecal BA criteria. Aldafermin significantly decreased serum C4, fecal total BA, and percentage of secretory BA at days 14 and 28. There was numerically improved stool consistency in patients on aldafermin during days 15 to 28 (P=.082), particularly in week 4 of treatment (P=.047). Moreover, aldafermin caused greater increase in low-density lipoprotein cholesterol from baseline compared with the placebo group (P=.052).[63] Further studies in BAD are warranted.

Eluxadoline

Eluxadoline, a mixed μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist, reduced abdominal pain and improved stool consistency, urgency, and quality of life in 525 patients with IBS-D.[64] The efficacy of eluxadoline in patients with BAD was studied in a single-center, open-label study of 24 patients with IBS-D, 12 of whom had BAD. In this study, it was shown that eluxadoline improved stool consistency and decreased abdominal pain in patients with IBS-D regardless of BAD status.[65]

Liraglutide

Liraglutide, a glucagon-like peptide 1 agonist, was superior to colesevelam in reducing daily stool frequency by 25% after 6 weeks of treatment (77% of participants on liraglutide compared with 50% of participants on colesevelam), although no significant difference in the improvement in stool consistency was noted.[66,67]

Conclusion

BAD is a common gastrointestinal disorder that results from effects of increased BAs in the colon affecting permeability, transit, and microbiome changes. Stool and serum BA noninvasive tests are now widely available to facilitate diagnosis. They are affordable and have shown good sensitivity and specificity in diagnosis or screening to exclude BAD. While BA sequestrants are currently the mainstay of treatment for BAD, newer medications targeting the FXR-FGF19 axis have shown promising results.

Disclosures

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References

1. Lack L, Weiner IM. In vitro absorption of bile salts by small intestine of rats and guinea pigs. *Am J Physiol*. 1961;200:313-317.
2. Weiner IM, Lack L. Absorption of bile salts from the small intestine in vivo. *Am J Physiol*. 1962;202:155-157.
3. Schiff ER, Small NC, Dietschy JM. Characterization of the kinetics of the passive and active transport mechanisms for bile acid absorption in the small intestine and colon of the rat. *J Clin Invest*. 1972;51(6):1351-1362.
4. Wong MH, Oelkers P, Craddock AL, Dawson PA. Expression cloning and characterization of the hamster ileal sodium-dependent bile acid transporter. *J Biol Chem*. 1994;269(2):1340-1347.
5. Craddock AL, Love MW, Daniel RW, et al. Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter. *Am J Physiol*. 1998;274(1):G157-G169.
6. Krag E, Phillips SF. Active and passive bile acid absorption in man. Perfusion studies of the ileum and jejunum. *J Clin Invest*. 1974;53(6):1686-1694.
7. Mekhjian HS, Phillips SF, Hofmann AF. Colonic absorption of unconjugated bile acids: perfusion studies in man. *Dig Dis Sci*. 1979;24(7):545-550.
8. Camilleri M, Murphy R, Chadwick VS. Dose-related effects of chenodeoxycholic acid in the rabbit colon. *Dig Dis Sci*. 1980;25(6):433-438.
9. Schiller LR. BAM BAD. *Dig Dis Sci*. 2022;67(6):1930-1931.
10. Cai J, Rimal B, Jiang C, Chiang JYL, Patterson AD. Bile acid metabolism and signaling, the microbiota, and metabolic disease. *Pharmacol Ther*. 2022;237:108238.
11. Camilleri M, Vijayvargiya P. The role of bile acids in chronic diarrhea. *Am J Gastroenterol*. 2020;115(10):1596-1603.
12. Bunnett NW. Neuro-humoral signalling by bile acids and the TGR5 receptor in the gastrointestinal tract. *J Physiol*. 2014;592(14):2943-2950.
13. Chadwick VS, Gaginella TS, Carlson GL, Debongnie JC, Phillips SF, Hofmann AF. Effect of molecular structure on bile acid-induced alterations in absorptive function, permeability, and morphology in the perfused rabbit colon. *J Lab Clin Med*. 1979;94(5):661-674.
14. Camilleri M, Nurko S. Bile acid diarrhea in adults and adolescents. *Neurogastroenterol Motil*. 2022;34(4):e14287.
15. Walters JR, Tasleem AM, Omer OS, Brydon WG, Dew T, le Roux CW. A new mechanism for bile acid diarrhea: defective feedback inhibition of bile acid biosynthesis. *Clin Gastroenterol Hepatol*. 2009;7(11):1189-1194.
16. Wong BS, Camilleri M, Carlson P, et al. Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. *Clin Gastroenterol Hepatol*. 2012;10(9):1009-15.e3.
17. Oelkers P, Kirby LC, Heubi JE, Dawson PA. Primary bile acid malabsorption caused by mutations in the ileal sodium-dependent bile acid transporter gene (SLC10A2). *J Clin Invest*. 1997;99(8):1880-1887.
18. Ho RH, Leake BF, Urquhart BL, Gregor JC, Dawson PA, Kim RB. Functional characterization of genetic variants in the apical sodium-dependent bile acid transporter (ASBT; SLC10A2). *J Gastroenterol Hepatol*. 2011;26(12):1740-1748.
19. Qie D, Zhang Y, Gong X, et al. SLC10A2 deficiency-induced congenital chronic bile acid diarrhea and stunting. *Mol Genet Genomic Med*. 2021;9(8):e1740.
20. Johnston IM, Nolan JD, Pattni SS, et al. Characterizing factors associated with differences in FGF19 blood levels and synthesis in patients with primary bile acid diarrhea. *Am J Gastroenterol*. 2016;111(3):423-432.
21. Chang C, Jiang J, Sun R, Wang S, Chen H. Downregulation of serum and distal ileum fibroblast growth factor19 in bile acid diarrhoea patients. *Dig Dis Sci*. 2022;67(3):872-879.
22. Camilleri M, Carlson P, BouSaba J, et al. Comparison of biochemical, microbial and mucosal mRNA expression in bile acid diarrhoea and irritable bowel syndrome with diarrhoea. *Gut*. 2023;72(1):54-65.

23. Camilleri M. Bile acid detergency: permeability, inflammation, and effects of sulfation. *Am J Physiol Gastrointest Liver Physiol.* 2022;322(5):G480-G488.
24. Keely SJ, Urso A, Ilyaskin AV, et al. Contributions of bile acids to gastrointestinal physiology as receptor agonists and modifiers of ion channels. *Am J Physiol Gastrointest Liver Physiol*. 2022;322(2):G201-G222.
25. Odunsi-Shiyanbade ST, Camilleri M, McKinzie S, et al. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. *Clin Gastroenterol Hepatol*. 2010;8(2):159-165.
26. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. The proximal colonic motor response to rectal mechanical and chemical stimulation. *Am J Physiol Gastrointest Liver Physiol.* 2002;282(3):G443-G449.
27. Wingate DL, Krag E, Mekhjian HS, Phillips SF. Relationships between ion and water movement in the human jejunum, ileum and colon during perfusion with bile acids. *Clin Sci Mol Med*. 1973;45(5):593-606.
28. Conley DR, Coyne MJ, Bonorris GG, Chung A, Schoenfield LJ. Bile acid stimulation of colonic adenylate cyclase and secretion in the rabbit. *Am J Dig Dis*. 1976;21(6):453-458.
29. Coyne MJ, Bonorris GG, Chung A, Conley DR, Croke J, Schoenfield LJ. Inhibition by propranolol of bile acid stimulation of rabbit colonic adenylate cyclase in vitro. *Gastroenterology.* 1976;71(1):68-71.
30. Yde J, Borg J, Fenton RA, Moeller HB. Altered expression of aquaporin water channels in a rat model of chronic diarrhea due to bile acid malabsorption. *The FASEB Journal.* 2017;31(S1):703.14-703.14.
31. Zimmerman TW, Binder HJ. Serotonin-induced alteration of colonic electrolyte transport in the rat. *Gastroenterology*. 1984;86(2):310-317.
32. Duboc H, Tolstanova G, Yuan PQ, et al. Reduction of epithelial secretion in male rat distal colonic mucosa by bile acid receptor TGR5 agonist, INT-777: role of submucosal neurons. *Neurogastroenterol Motil*. 2016;28(11):1663-1676.
33. Wingate DL, Phillips SF, Hofmann AF. Effect of glycine-conjugated bile acids with and without lecithin on water and glucose absorption in perfused human jejunum. *J Clin Invest.* 1973;52(5):1230-1236.
34. Magnus Y, BouSaba J, Sannaa W, McKinzie S, Busciglio I, Camilleri M. Bile acid diarrhea is associated with increased intestinal permeability compared with irritable bowel syndrome-diarrhea. *Gastroenterology.* 2022;162(4):1343-1345.e1.
35. Wei W, Wang HF, Zhang Y, Zhang YL, Niu BY, Yao SK. Altered metabolism of bile acids correlates with clinical parameters and the gut microbiota in patients with diarrhea-predominant irritable bowel syndrome. *World J Gastroenterol*. 2020;26(45):7153-7172.
36. Fromm H, Malavolti M. Bile acid-induced diarrhoea. *Clin Gastroenterol*. 1986;15(3):567-582.
37. Scarpello JH, Hodgson E, Howlett HC. Effect of metformin on bile salt circulation and intestinal motility in type 2 diabetes mellitus. *Diabet Med.* 1998;15(8):651-656.
38. Valentin N, Camilleri M, Altayar O, et al. Biomarkers for bile acid diarrhoea in functional bowel disorder with diarrhoea: a systematic review and meta-analysis. *Gut.* 2016;65(12):1951-1959.
39. Vijayvargiya P, Gonzalez Izundegui D, Calderon G, et al. Increased fecal bile acid excretion in a significant subset of patients with other inflammatory diarrheal diseases. *Dig Dis Sci.* 2022;67(6):2413-2419.
40. Khanna L, Halfdanarson TR, Sonbol MB, Eiring R, Prond T, Camilleri M. Bile acid malabsorption in patients with neuroendocrine tumors. *Dig Dis Sci*. 2022;67(6):2517-2525.
41. Bannaga A, Kelman L, O'Connor M, Pitchford C, Walters JR, Arasaradnam RP. How bad is bile acid diarrhoea: an online survey of patient-reported symptoms and outcomes. *BMJ Open Gastroenterol.* 2017;4(1):e000116.
42. BouSaba J, Sannaa W, McKinzie S, et al. Impact of bile acid diarrhea in patients with diarrhea-predominant irritable bowel syndrome on symptoms and quality of life. *Clin Gastroenterol Hepatol.* 2022;20(9):2083-2090.e1.
43. Kumar A, Galbraith N, Al-Hassi HO, et al. The impact of treatment with bile acid sequestrants on quality of life in patients with bile acid diarrhoea. *BMC Gastroenterol.* 2022;22(1):325.
44. Borup C, Vinter-Jensen L, Jørgensen SPG, et al. Efficacy and safety of colesevelam for the treatment of bile acid diarrhoea: a double-blind, randomised, placebo-controlled, phase 4 clinical trial. *Lancet Gastroenterol Hepatol*. 2023;8(4):321-331.
45. Hughes LE, Ford C, Brookes MJ, Gama R. Bile acid diarrhoea: current and potential methods of diagnosis. *Ann Clin Biochem*. 2021;58(1):22-28.
46. Wedlake L, A'Hern R, Russell D, Thomas K, Walters JR, Andreyev HJ. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther.* 2009;30(7):707-717.
47. Vijayvargiya P, Camilleri M, Chedid V, et al. Analysis of fecal primary bile acids detects increased stool weight and colonic transit in patients with chronic functional diarrhea. *Clin Gastroenterol Hepatol*. 2019;17(5):922-929.e2.
48. Vijayvargiya P, Camilleri M, Burton D, Busciglio I, Lueke A, Donato LJ. Bile and fat excretion are biomarkers of clinically significant diarrhoea and constipation in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2019;49(6):744-758.
49. Vijayvargiya P, Camilleri M, Carlson P, et al. Performance characteristics of serum C4 and FGF19 measurements to exclude the diagnosis of bile acid diarrhoea in IBS-diarrhoea and functional diarrhoea. *Aliment Pharmacol Ther*. 2017;46(6):581-588.
50. Sauter GH, Münzing W, von Ritter C, Paumgartner G. Bile acid malabsorption as a cause of chronic diarrhea: diagnostic value of 7alpha-hydroxy-4-cholesten-3-one in serum. *Dig Dis Sci*. 1999;44(1):14-19.
51. Pattni SS, Brydon WG, Dew T, et al. Fibroblast growth factor 19 in patients with bile acid diarrhoea: a prospective comparison of FGF19 serum assay and SeHCAT retention. *Aliment Pharmacol Ther*. 2013;38(8):967-976.
52. Lewinska M, Kårhus ML, Ellegaard AG, et al. Serum lipidome unravels a diagnostic potential in bile acid diarrhoea [published online April 18, 2023]. *Gut.* doi:10.1136/gutjnl-2022-329213.
53. Kumar A, Al-Hassi HO, Jain M, et al. A single faecal bile acid stool test demonstrates potential efficacy in replacing SeHCAT testing for bile acid diarrhoea in selected patients. *Sci Rep*. 2022;12(1):8313.
54. Vijayvargiya P, Camilleri M, Taylor A, Busciglio I, Loftus EV Jr, Donato LJ. Combined fasting serum C4 and primary bile acids from a single stool sample to diagnose bile acid diarrhea. *Gastroenterology*. 2020;159(5):1952-1954.e2.
55. Vijayvargiya P, Gonzalez Izundegui D, Calderon G, Tawfic S, Batbold S, Camilleri M. Fecal bile acid testing in assessing patients with chronic unexplained diarrhea: implications for healthcare utilization. *Am J Gastroenterol*. 2020;115(7):1094-1102.
56. Fernandes DCR, Poon D, White LL, Andreyev HJN. What is the cost of delayed diagnosis of bile acid malabsorption and bile acid diarrhoea? *Frontline Gastroenterol*. 2019;10(1):72-76.
57. Jackson A, Lalji A, Kabir M, et al. The efficacy of a low-fat diet to manage the symptoms of bile acid malabsorption - outcomes in patients previously treated for cancer. *Clin Med (Lond).* 2017;17(5):412-418.
58. Costa S, Gattoni S, Nicolardi ML, et al. Prevalence and clinical features of bile acid diarrhea in patients with chronic diarrhea. *J Dig Dis.* 2021;22(2):108-112.
59. Wilcox C, Turner J, Green J. Systematic review: the management of chronic diarrhoea due to bile acid malabsorption. *Aliment Pharmacol Ther*. 2014;39(9):923-939.
60. Kumar A, Quraishi MN, Al-Hassi HO, et al. The analysis of gut microbiota in patients with bile acid diarrhoea treated with colesevelam. *Front Microbiol*. 2023;14:1134105.
61. Walters JR, Johnston IM, Nolan JD, Vassie C, Pruzanski ME, Shapiro DA. The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. *Aliment Pharmacol Ther*. 2015;41(1):54-64.
62. Camilleri M, Nord SL, Burton D, et al. Randomised clinical trial: significant biochemical and colonic transit effects of the farnesoid X receptor agonist tropifexor in patients with primary bile acid diarrhoea. *Aliment Pharmacol Ther*. 2020;52(5):808-820.
63. BouSaba J, Torres M, Dilmaghani S, Harmsen WS, Ling L, Camilleri M. Effects of FGF19 analogue aldafermin in patients with bile acid diarrhea: a randomized, placebo-control trial. *Gastroenterology.* 2023;165(2):499-501.e4.
64. Dove LS, Lembo A, Randall CW, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. *Gastroenterology*. 2013;145(2):329-38.e1.
65. Vijayvargiya P, Breen-Lyles M, Nord SL, et al. Safety and efficacy of eluxadoline in patients with irritable bowel syndrome-diarrhea with or without bile acid diarrhea: open-label study. *Dig Dis Sci.* 2022;67(8):3911-3921.
66. Kårhus ML, Brønden A, Forman JL, et al. Safety and efficacy of liraglutide versus colesevelam for the treatment of bile acid diarrhoea: a randomised, double-blind, active-comparator, non-inferiority clinical trial. *Lancet Gastroenterol Hepatol*. 2022;7(10):922-931.
67. Walters JRF. Treating bile acid diarrhoea with liraglutide. *Lancet Gastroenterol Hepatol*. 2022;7(10):897-899.