Managing Chronic Diarrhea From a Gut Microbiota-Bile Acid Perspective

Ling Zhao, PhD[1], Xiao-dong Fang, PhD[2], Wei Jia, PhD[1,3] and Zhao-xiang Bian, MD, PhD[1]

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As a significant cause of chronic diarrhea, disordered bile acid (BA) metabolic homeostasis with excessive BA loss from the colon results in electrolyte imbalance and accelerated motor activity in the colon lumen. BA-induced diarrhea frequently affects patients with Crohn disease or who have had a cholecystectomy and around 30% of patients with diarrhea-predominant irritable bowel syndrome (IBS-D) (1). Unlike diarrhea that is secondary to ileal or biliopancreatic problems, IBS-D comorbid with BA excretion irregularities is considered idiopathic. Pioneering researches with genetic or biochemical biomarkers have revealed that an excess of BA loss in feces of IBS-D or patients with functional diarrhea is associated with dysregulated BA synthesis or feedback control (2,3). However, the etiopathogenesis is not well understood, and there are no standard diagnostic methods nor satisfactory therapy for BA-induced diarrhea.

Past investigations of BA-induced diarrhea have focused on host metabolic processes, largely ignoring the impact of the gut microbiota. Gut microbiota, however, are an indispensable participant in BA metabolism known to convert primary BAs to secondary BAs in the gastrointestinal lumen and to mediate feedback control of BA synthesis (4). Recently, we discovered that, in a group of IBS-D patients with excessive BA excretion (BA^+IBS-D), a specific gut microbiota characterized by enrichment of BA-transforming *Clostridia* species was positively associated with patients' BA synthetic and excretive levels and was negatively correlated with their feedback hormone fibroblast growth factor 19 (FGF19) level (5). Moreover, we observed that fecal microbiota isolated from BA^+IBS-D patients and *Clostridium scindens*, a species identified as performing C7-dehydroxylation and epimerization, induced diarrhea-like behavior and BA metabolic phenotypes in mice that were similar to those in IBS-D subjects (5). Several *Clostridia*-derived BA metabolites (glycine or taurine-conjugated UDCA, UDCA and 7-KDCA) are also shown to inhibit intestinal FGF19/15 production *in vivo* and *in vitro*. These results point to a contribution of the *Clostridia*-rich microbiota in BA-induced diarrhea at least in IBS-D and, as such, suggest a potential significance of gut microbiota and its derived BAs in developing new strategies for managing chronic diarrhea (Figure 1).

It is necessary to enhance the accuracy and depth of gut microbial investigation of IBS-D. Our work using a BA excretion-based subgrouping strategy differentiates subgroups of IBS-D subjects based on microbial composition and microbial BA transformation. This differs significantly from previous case-control studies using undifferentiated IBS-D populations (6,7). Our results suggest that a BA excretion-based subgrouping strategy can fine-tune, promote, and improve understanding of gut microbiota distribution and function. Results from 2 other independent IBS studies support our suggestion. One study successfully revealed differences in fecal microbiomes in IBS people by considering the impact of BA malabsorption (BAM) (8). Specifically, the study found that there is no distinguishable signature in fecal microbiome across IBS subtypes, but there is an altered fecal microbiome in IBS patients with severe BAM. Similar to our work, BA excretion-based stratification was applied in this study when comparing fecal microbiomes in IBS subjects, but in contrast to our work, which found that abnormal BA excretion was identified among 24.5% of IBS-D patients, with a 90th percentile cutoff line of fecal total BA excretion level of healthy controls, this study recognized patients with BAM from IBS-D and mixed subtyped IBS population based on a 7-day retention of 75selenium-homotaurocholic acid (75SeHCAT). Another study, without considering BA excretion, reported that there is no distinct microbiome signature in an undifferentiatied IBS population compared with healthy controls nor is there a distinct microbiome signature in IBS subtypes (9). In other words, BA excretion levels are the critical factor distinguishing IBS subtypes. From these observations, we believe that a precise classification based on, or that includes, BA excretion is needed for meaningful, and potentially more productive, microbiome investigations of chronic diarrhea.

A featured microbiota-derived BA profile with increased proportions of serum glycoursodeoxycholic acid, glycochenodeoxycholic acid, and fecal chenodeoxycholic acid, cholic acid, ursodeoxycholic acid, and 7-ketodeoxycholic acid was detected in IBS-D patients with excessive BA loss, but without difference in other patients with IBS-D (5). The results point to gut microbiota and its derived BAs as the basis of a new diagnostic strategy. Currently, the diagnosis of BA-induced diarrhea relies

[1]Institute of Brain and Gut Research, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, China; [2]State Key Laboratory of Dampness Syndrome of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [3]Cancer Biology Program, University of Hawaii Cancer Center, Hawaii, USA. **Correspondence:** Zhao-xiang Bian, MD, PhD. E-mail: bzxiang@hkbu.edu.hk.

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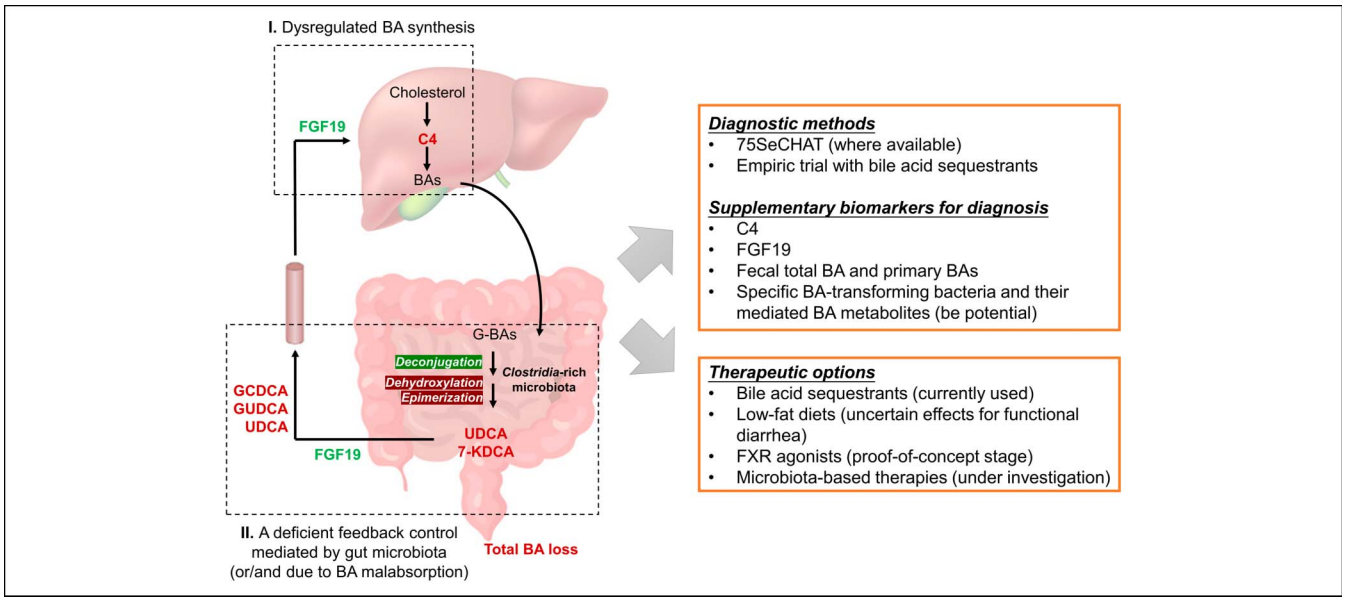

Figure 1. A summary of the pathogenic mechanisms (left panel) and management strategies (right panel) of BA diarrhea for IBS-D or functional diarrhea. Pioneering researches support a mechanistic hypothesis that an excess of BA loss in IBS-D or functional diarrheal patients is associated with dysregulated BA synthesis or intestinal BA malabsorption and is characterized by a decreased circulating level of intestine-released hormone FGF19 or/and an increased circulating level of hepatic BA synthetic intermediate 7α-hydroxy-4-cholesten-3-one (C4). Furthermore, a Clostridia-rich microbiota identified from the subgroup of IBS-D patients with excessive BA loss was found to suppress the intestinal expression of FGF19/15 via enhancing proportions of farnesoid X receptor-antagonistic secondary BAs. It suggests a contribution of BA-metabolizing dysbiosis in the pathogenesis of BA diarrhea. On the basis of previously known pathogenesis, diagnostic (e.g., 75SeCHAT) and therapeutic (e.g., BA sequestrants) options have been applied in current practices, and several concept-of-proof diagnostic biomarkers (e.g., C4, FGF19, and fecal total and primary BAs) and therapeutic methods (e.g., low-fat diets and FXR agonists) have being developed or are under evaluation. Furthermore, our microbiota-mediated testable mechanism suggests new microbiota-involved management hypotheses, including development of bacteria and bacteria-derived secondary BAs as supplementary diagnostic markers and adjustment of abnormal BA metabolism by targeting the gut microbiota. These hypotheses need to be further investigated. In the figure, biomarkers or bacterial action highlighted in red represent upregulation in patients with BA diarrheal IBS, whereas the one highlighted in green represents downregulation. BA, bile acid; FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; IBS-D, diarrhea-predominant irritable bowel syndrome; 75SeHCAT, 75selenium-homotaurocholic-acid.

on the test of 75SeHCAT in countries where it is available while empirical trials of BA sequestrants are generally used in other places where the 75SeHCAT test is not available (10). Specific biomarkers of BA synthesis and loss, including serum C4, FGF19, and fecal BAs, have been also used to support diagnosis in countries without 75SeHCAT testing capability. A recent systematic review has reported that 75SeHCAT has the highest diagnostic accuracy, followed by serum C4 assay, whereas the diagnostic accuracies of fecal BA and FGF19 assays are still under investigation (11). In practice, however, a combination of more than one test is generally used. From our work, we conclude that higher proportions of *Clostridia* species and their derived secondary BAs are the key mechanism of BA-induced diarrhea in IBS-D, and we suggest that testing for *Clostridia* species and certain secondary BA metabolites might improve diagnostic accuracy. Thus, assessments of the *Clostridia* species and BA levels in combination with serum C4 or/and FGF19 deserve to be considered new diagnostic methods (Figure 1). Future studies targeting the challenges, such as determining which combination of which types of *Clostridia* species and BAs is optimal, the accuracy and specificity of such combination, and any interference effects from racial, regional, and dietary differences will provide more data to develop specific diagnostic criteria.

The microbiota-driven mechanism also provides a theoretical basis for developing microbiota-targeted therapeutic strategies for chronic diarrhea. To date, several optional therapies targeting BA excessive secretion and intestinal malabsorption have been applied for BA-induced diarrhea, including (i) administration of BA sequestrants, (ii) low-fat diet, (iii) administration of farnesoid X receptor agonists, and (iv) bacteria modulation therapies. Of them, administration of BA sequestrants, such as cholestyramine, colestipol, and colesevelam, are the predominant choices for treatment, but they have disadvantages, the most serious of which is poor tolerance. All of the BA sequestrants, being nonspecific, are also capable of binding other fat-soluble compounds, which leads to deficiencies of fat-soluble nutrients. For patients with extensive ileal resection, a low-fat diet can prevent diarrheal symptoms, but its efficacy in functional diarrhea remains unclear. Recently, a proof-of-concept study found that a potent farnesoid X receptor agonist, obeticholic acid (at 25 mg administered orally, daily for 2 weeks), can improve BA synthesis and diarrheal phenotype in patients with ileal resections and can adjust BA synthesis in patients with idiopathic BA-induced diarrhea (12); however, its effectiveness needs to be further confirmed in large-scale clinical trials. As for microbiota-oriented therapies, including antibiotic and probiotic products, studies have reported these agents can improve IBS-D symptoms, but show no effect on gut microbiota and BAs (13,14). Based on our finding that *Clostridia* species modulating secondary BAs are the key factors in excessive BA synthesis and excretion, agents targeting these BA-transforming bacteria or their enzymes should be developed to adjust BA dysmetabolism and relieve diarrheal symptoms (Figure 1).

In summary, *Clostridia*-mediated mechanisms can help explain the etiopathogenesis of idiopathic BA diarrhea, and knowledge of these mechanisms can lead to developing successful

therapies for managing chronic diarrhea. Specifically, these results suggest that (i) a BA-based classification strategy might be needed for precisely investigating gut microbial function, (ii) combination testing with *Clostridia* species and BAs, with currently-used biochemical indices may enhance diagnostic accuracy, and (iii) targeting BA-transforming microbial taxa or reactions is a potential route for developing new remedies.

CONFLICTS OF INTEREST

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