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Fecal microbiota transplantation for irritable bowel syndrome: Current evidence and perspectives

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Abstract

In this editorial we comment on the article by Halkjaer SI published in the recent issue of the World journal of Gastroenterology 2023; **29**(20):3185-3202. We focus specifically on the mechanisms underlying the effects of fecal microbiota transplantation (FMT) for irritable bowel syndrome (IBS), the factors which affect the outcomes of FMT in IBS patients, and challenges. FMT has emerged as a efficacious intervention for Clostridium difficile infection (CDI) and holds promise as a therapeutic modality for IBS. The utilization of FMT in the treatment of IBS has undergone scrutiny in numerous randomized controlled trials (RCTs), yielding divergent outcomes. The current frontier in this field seeks to elucidate these variations, underscore the existing knowledge gaps that necessitate exploration, and provide a guideline for successful FMT implementation in IBS patients. At the same time, the application of FMT as a treatment for IBS confronts several challenges.

Key words: Fecal microbiota transplantation; Irritable bowel syndrome; Microbiota; Randomized controlled trial; Meta-analysis

Core tip: Fecal microbiota transplantation (FMT) has emerged as a efficacious intervention for Clostridium difficile infection (CDI) and holds promise as a therapeutic modality for irritable bowel syndrome (IBS). The utilization of FMT in the treatment of IBS has undergone scrutiny in numerous randomized controlled trials (RCTs), yielding divergent outcomes. The current frontier in this field seeks to elucidate these variations, underscore the existing knowledge gaps that necessitate exploration, and provide a guideline for successful FMT implementation in IBS patients. At the same time, the application of FMT as a treatment for IBS confronts several challenges.

Introduction

The transplantation of the intestinal microbiome through feces obtained from a healthy individual with normal bowel function, commonly termed fecal microbiota transplantation (FMT), has historical roots dating back to the fourth century when the Chinese physician Ge Hong pioneered its application in addressing severe diarrhea and malaria [1]. In contemporary medical contexts, FMT has emerged as a efficacious intervention for Clostridium difficile infection (CDI) and holds promise as a therapeutic modality for various conditions, including irritable bowel syndrome (IBS) [2-4]. The utilization of FMT in the treatment of IBS has undergone scrutiny in numerous randomized controlled trials (RCTs), yielding divergent outcomes [5-10]. The current frontier in this field seeks to elucidate these variations, underscore the existing knowledge gaps that necessitate exploration, and provide a guideline for successful FMT implementation in IBS patients.

Halkjaer *et al*. conducted a comprehensive meta-analysis to evaluate the efficacy and safety of FMT in the treatment of IBS [11]. The study revealed that, compared to a placebo, FMT yielded no statistically significant benefits in alleviating IBS symptoms at three months post-treatment (RR 1.19, 95% CI: 0.68-2.10). Additionally, FMT exhibited no discernible enhancement in the quality of life for individuals with IBS (MD -6.30, 95% CI: -13.39-0.79). Notably, a subgroup analysis indicated a noteworthy amelioration of symptoms with endoscopic FMT delivery, whereas capsules did not elicit a comparable effect. Adverse events were documented in 97 participants within the FMT group, contrasting with 45 participants in the placebo group (RR 1.17, 95% CI: 0.63-2.15). The incongruent findings across the included studies can be attributed to variations in the selection of IBS patient subtypes, the frequency and route of transplant delivery, FMT-content, pre-treatment protocols, and the number of donors.

While the studies included in the analysis did not report major adverse effects linked directly to FMT, it is imperative to maintain a low threshold for toxicity evaluation, especially in non-life-threatening conditions. It becomes incongruent when proponents selectively reference murine transplant experiments highlighting the role of the microbiota in IBS pathogenesis while neglecting analogous studies suggesting the potential transferability of phenotypes. Consequently, the risks associated with FMT extend beyond infection or

transmission of antibiotic-resistant organisms, encompassing the theoretical transfer of inflammatory, metabolic, and even behavioral phenotypes from donor to recipient. Although meticulous donor selection can mitigate these risks, certain microbiotas may harbor latent dangers associated with the future onset of colon cancer. Then I will provide a detailed introduction to the mechanisms, the influencing factors, and challenges of FMT for IBS.

Mechanisms of FMT for IBS

Enteroendocrine cells, mast cells, and fecal Short Chain Fatty Acids (SCFAs) in individuals with IBS exhibit distinctions from those in healthy subjects, and these variances are thought to be pivotal in the pathophysiology of IBS [12-14]. Butyrate, an SCFA, serves as an energy source for colonic epithelial cells, modulates immune responses, mitigates oxidative stress, reduces intestinal motility, and decreases cell permeability. Notably, butyrate also regulates colonic hypersensitivity, and its intake has been associated with diminished abdominal pain in IBS patients. While it is premature to definitively delineate the mechanisms underpinning the effects of FMT, available data propose that the amelioration of IBS symptoms through FMT may be attributed to alterations in enteroendocrine cells, mast cells, and SCFAs including butyrate.

The majority of bodily serotonin is situated in the gut, with only 10% residing in the enteric nervous system (ENS), and the remaining portion contained in the enterochromaffin (EC) cells dispersed among the gastrointestinal epithelial cells. Serotonin plays a crucial role in gastric emptying and intestinal peristalsis [15]. Additionally, serotonin activates the sensory nerve endings of submucosal ENS, transmitting gut sensations to the central nervous system (CNS). Upon exerting its effects at serotonin receptors, serotonin is transported into intestinal epithelial cells by the serotonin-selective reuptake transporter (SERT), where it undergoes degradation. In individuals with IBS, reported lower densities of EC cells and diminished SERT immunointensity in the gut suggest impaired serotonin uptake and degradation . Specific bacteria, such as Corynebacterium, Streptococcus, and Enterococcus spp., alongside indigenous spore-forming bacteria, have been identified as serotonin producers. Furthermore, Clostridium ramosum regulates serotonin release from EC cells. The altered intestinal bacterial composition induced by FMT may influence the

serotonin-regulating system.

The influencing factors of FMT for IBS

FMT donor selection

Considerable variability in the outcomes of FMT for IBS has been noted among studies, a phenomenon largely ascribed to differences in donor selection. The designation "superdonor" is bestowed upon a donor eliciting a robust response to FMT [16]. Attempts to predict superdonors have involved pooling feces from multiple donors to augment the chances of patients receiving superdonor feces. However, this strategy proved unsuccessful, likely due to the dilution of superdonor feces and subsequent inadequate dosing for recipients. The divergent outcomes in RCTs of FMT in IBS can be predominantly traced to variations in donor selection criteria. Notably, the RCT conducted by El-Salhy *et al*., which demonstrated positive FMT responses, established the strict selection of superdonor [17]. But some RCTs omitted these criteria for donor selection. The temporal stability of the donor's intestinal bacterial composition is another pivotal consideration when selecting a superdonor.

Clinical criteria for superdonor selection have been grounded in factors known to impact the intestinal microbiota, including age (> 50 years), smoking habits, birth by cesarean section, formula feeding during infancy, antibiotic use, nonantibiotic drug consumption, and lifestyle factors such as regular exercise and diet. Genetic considerations also underscore the need for superdonors to be non-first-degree relatives of recipients. The superdonor identified in El-Salhy *et al*.'s RCT adhered to a profile of a healthy young male with a normal body mass index, born vaginally, breastfed, non-smoking, medication-free, with infrequent antibiotic use, regular exercise, and a healthy diet. Fecal microbiota analysis of this donor revealed high microbial diversity, with deviations in bacterial composition from the norm of 165 healthy subjects, predominantly in the Firmicutes phylum. This included increased abundance of beneficial bacteria including Lactobacillus, Streptococcus, and Ruminococcaceae spp. Importantly, the composition of fecal microbiota from the superdonor can remain stable for over 18 months. Despite efforts to ensure

superdonor presence by pooling feces from multiple donors, this strategy yielded no response or only transient improvement.

IBS patient inclusion

Caution must be exercised in generalizing the outcomes of RCTs of FMT for IBS, as the patient cohorts included in these trials represent specific subsets of the IBS population. Notably, five RCTs exclusively enrolled patients with diarrhea-predominant IBS (IBS-D), mixed-diarrhea-and-constipation IBS (IBS-M), or IBS unclassified (IBS-U). In contrast, three other RCTs encompassed all IBS subtypes, encompassing IBS-D, constipation-predominant IBS (IBS-C), IBS-M, and IBS-U. Additionally, the RCT conducted by El-Salhy *et al* found that the patients who live with IBS patients for two days may exhibit moderate to severe IBS symptoms, even if they completely follow the National Institute for Health and Care Excellence (NICE) dietary regimen [17]. The RCT by Holster *et al* specifically included patients characterized by low levels of fecal butyrate-producing bacteria [8]. Furthermore, Holvoet *et al* exclusively enrolled refractory IBS patients with severe bloating who are ineffective in conventional therapies for at least 3 days [10]. These variations in patient selection criteria underscore the need for cautious interpretation and application of the outcomes of FMT trials to the broader spectrum of individuals with IBS.

Route of administration and dose of FMT

FMT can be performed through upper gastrointestinal pathways including gastroscope and nasojejunal tube, as well as lower gastrointestinal pathways including colonoscope. Both routes of administration have demonstrated efficacy. But a noteworthy placebo effect was observed in 43%-44% and 23.6%-26% of patients who received FMT in the large and small intestine, respectively [8, 10]. This placebo effect might be more pronounced in patients receiving FMT in the colon, potentially attributable to the favorable impact of bowel preparation for colonoscopy on IBS symptoms. In contrast to its success in treating CDI, the administration of FMT via capsule ingestion proved ineffective in IBS. Possible factors contributing to this ineffectiveness include donor selection, a low transplant dose, or the pooling of donors.

The dose of the fecal transplant appears to influence FMT outcomes, suggesting a dose-dependent response. Notably, 70% of patients unresponsive to a 30 g FMT dose exhibited a

positive response to a 60 g FMT dose. The majority of included studies utilized a dose of at least 30 g [8, 10]. Concurrently, further investigations are imperative to assess the comparative efficacy of single versus repeated FMT administrations.

Challenges of FMT for IBS

Although FMT is a promising treatment for gastrointestinal and nongastrointestinal diseases, the application of FMT as a treatment for IBS confronts several challenges. Firstly, the absence of a definitive microbial signature and the diverse dysbiosis patterns in IBS. Pathobiont proliferation, commensal loss, and reduced microbial diversity contribute to the complexity of the condition in IBS. At the same time, some factors such as infection, inflammation, dietary influences, xenobiotics, genetics, and familial transmission exert dynamic effects on the composition of the intestinal microbial community.

Secondly, the lack of a universally defined normal microbiome limits the application of FMT. FMT has many complex mechanisms of action, including direct effects on the host, reinstatement of missing network interactions, and microbiome modulation. However, it is crucial to acknowledge that FMT is not a curative measure, as its benefits persist for a median duration of four months and gradually diminish over a year.

Thirdly, FMT responsiveness varies in IBS patients, with distinct and stable subsets of responders and non-responders. While initial responders often regain a positive response after re-FMT, those who failed to respond initially generally continue to exhibit disappointing outcomes with subsequent FMT attempts from different donors. This raises the prospect that disruptions in the microbiota may offer a pathway for stratifying IBS patients. While symptoms play a central role in IBS diagnosis, their questionable value in stratification is evident as patients categorized as IBS-C, IBS-D, or IBS-M may transition between these patterns over time. Additionally, microbiota studies do not support stratification based on constipation or diarrhea. Integrating microbiota analysis including microbiome composition and functional analysis before and after FMT into the design and monitoring of future FMT trials for IBS appears reasonable. This does not imply exclusive responsiveness in those with disturbed microbiota but holds the potential to predict varying degrees of responsiveness, offering a refined rationale for patient selection and valuable data for result interpretation.

Fourth, the risks of FMT should also be evaluated. Improving the screening of FMT donors including testing the donor stool for beta-lactase extended-spectrum beta-lactamase (ESBL), E. *coli*, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) would reduce the risks of infection by known agents. Moreover, restricting the selection of patients with IBS for FMT to those without systemic disease, immune deficiency, treatment with immune-modulating medication, and severe illness would reduce the risks.

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