Fecal Microbiota Transplant

ABSTRACT

Aims: The fecal microbiota transplantation (FMT) may be a possible solution for symptoms reduction and improvement of the clinical condition in Inflammatory bowel diseases (IBDs), such as Ulcerative Colitis (UC) and Crohn's Disease (CD). In addition to being effective in other conditions associated with disequilibrium in gastrointestinal microbiota, such as recurrent *Clostridium difficile* infection (RCDI) and Metabolic Syndrome (MS). The aim of this study was to review the applicability of FMT: in UC, CD, RCDI and MS.
Study design: Minireview.
Place and Duration of Study: Faculty of Medical Sciences of São José dos Campos-Humanitas, between June 2021 and August 2022.
Methodology: A literature search was performed in the PubMed database for clinical trial studies and review articles, published in the last 10 (ten) years. The remission of clinical conditions was established as the primary outcome and exclusion criteria was not blind or incomplete blinding studies. Based on these studies, a review regarding the applications of FMT in patients with IBD, RCDI and MS, especially its therapeutic effects, was performed.
Results: In total, 53 (fifty-three) articles were selected. Studies have shown that FMT can be useful in the treatment of RCDI with cure rates ranging from 85% to 90% and represent a possible alternative to antibiotic therapy in cases of primary infection by *C. difficile*. FMT seems to be effective in inducing remission of UC, but its durability and long-term safety are still not well defined. Furthermore, in the treatment of Crohn's disease and metabolic syndrome, some studies show beneficial effects, but further studies are needed.
Conclusion: The studies are optimistic and, even if modest, suggest that FMT has the potential for treatment and/or remission of different inflammatory and infectious conditions.

Keywords: Fecal microbiota transplant, inflammatory bowel diseases, Clostridium difficile and microbiome.

1. INTRODUCTION

The gastrointestinal microbiota is a complex ecosystem composed of hundreds of thousands of microorganisms, including bacteria, viruses and fungi.1 These microorganisms participate in several metabolic and immunological interactions, contributing to the maintenance of health of the host.2 However, in situations of dysbiosis, that is, changes in the composition and function of the microbiota, its components can cause inflammatory gastrointestinal diseases.3

Feces largely reflect the individual's microbiome and its possible changes.4 Thus, in cases of dysbiosis, one of the options for restoring the healthy microbiome (eubiosis) is the transplantation of fecal microbiota (FMT), transferring the fecal content of a healthy organism (in eubiosis) to an organism with an altered microbiome, a possible cause of the disease.5

FMT is an emerging procedure in the treatment of Inflammatory Bowel Diseases (IBD) such as Ulcerative Colitis (UC) and Crohn's Disease (CD), besides *Clostridium difficile* infection,

demonstrating efficacy in the remission and/or improvement of clinical manifestations. In addition, FMT seems to promote detectable beneficial changes in the composition of the intestinal microbiota of patients with Metabolic Syndrome (MS).6,7,8,9
The first records of FMT are from the fourth century, in China, where it was used to treat patients with severe diarrhea.10 However, despite not being a current practice, there are still questions about the function and effectiveness of FMT in the treatment of different inflammatory and infectious diseases. Thus, the aim of this study was to review the applications of FMT in patients with IBD, recurrent *C. difficile* infection (RCDI) and MS, emphasizing the therapeutic effects obtained with this procedure.

2. Material and methods

A mini narrative review was conducted to update information on FMT area and explore the possibilities of using this practice in patients with IBD, RCDI and MS. A literature search was performed in the Pubmed Database for clinical trial studies and review articles published in the last 10 (ten) years. The keywords, single or associated, were fecal microbiota transplant, inflammatory bowel diseases, *Clostridium difficile*, ulcerative colitis, Crohn's disease and metabolic syndrome. The remission of clinical conditions was established as the primary outcome and exclusion criteria was not blind or incomplete blinding studies. In total, 53 (fifty-three) articles were selected.

3. Results and discussion

Fecal microbiota transplantation in the treatment of *Clostridium difficile* infection

C. difficile is a Gram-positive bacillus transmitted mainly by the fecal-oral route, whose clinical manifestation is characterized by three or more watery stools in 24 hours, for at least two consecutive days.11,12 Long-term use of antibiotics and consequent increase in the growth of antibiotic-resistant microorganisms is associated with the development of RCDI. Thus, in these cases, FMT has a great therapeutic potential, being used as an alternative therapy to antibiotic in cases of primary infection by *C. difficile* 13,14(figure 1).
Millan et al., in a single-center study, in which 20 patients with RCDI received FMT from universal donors via colonoscopy, observed that these individuals had a greater number of antibiotic-resistant microorganisms and that healthy fecal microbiota introduced through transplantation could eliminate these microorganisms, eradicate resistance genes, and restore antibiotic susceptibility.14
Youngster et al., studying different administration routes of FMT in RCDI patients, demonstrated, through a randomized-controlled trial, that the administration of fecal microbiota by nasogastric tube was as effective as administration via colonoscopy.15 The authors also demonstrated that the oral administration of frozen FMT capsules in a small group of patients with iRCDI, led to a clinical resolution of 90% of diarrheal conditions. Thus, the authors suggested the possibility of application in a wider population and in a safer way, although larger studies were needed to confirm the data.16
Likewise, Kao et al., studying patients aged 18 to 90 years, with at least three documented episodes of *C. difficile* infection, observed that the use of fresh stool was more effective compared to antibiotic therapy or placebo and that frozen stools transported by colonoscopy presented themselves as an alternative treatment to the use of fresh stools.17 Kelly et al., in a randomized, controlled and double-blind clinical trial, concluded that donor stools administered by colonoscopy seemed safer and more effective in preventing new episodes of *C. difficile* infection than FMT made from feces of infected patients themselves.18
Regarding FMT in patients with RCDI treated with vancomycin, a study conducted by Hota et al., compared 14 days of oral vancomycin followed by a single FMT via enema with only

oral vancomycin and concluded that there was no significant difference between them.19 However, another study performed by Hvas et al., compared the efficacy of FMT with fidaxomicin and vancomycin, in patients with RCDI, and concluded that clinical resolution rates were higher in patients who received FMT as treatment (92% vs 42% and 19% for fidaxomicin and vancomycin, respectively). 20

The applications of FMT in patients who underwent solid organ transplantation have also been studied. In an experience of Lin et al.,five of these patients with RCDI had a cure rate of 80% after one FMT, and 100% cure rate after two FMTs. 21

FMT also seems to be an effective treatment for elderly and very sick patients, with colonoscopy being the preferred infusion route. Concerns about the safety of this method is rare, even in patients with many comorbidities.22

The studies have shown that FMT seems to constitute a safe and effective approach in the management of RCDI.The cure rate of FMT in cases of RCDI can range from 85% to 90% and the phylogenetic diversity of the bacterial microbiome can be restored, even if the long-term effect is not yet known, nor how many procedures are need for the best result.23,24

Fecal microbiota transplant in the treatment of Ulcerative Colitis

UC is an inflammatory disease of the large intestine, especially from transverse colon, with unknown origin. It is featured by inflammation and ulceration at intestinal mucosa and submucosa.25

Very typical symptoms are diarrhea, generally with rectal bleeding and often abdominal pain. This disease has a high risk to symptomatic relapse and can persist for weeks or months. Further, UC, when extended, raises the risk of developing colon cancer, compared to not affected individuals.26

The innate and adaptive immunity of the host, under normal circumstances, is capable to prevent the invasion of harmful bacteria and to tolerate the normal microbiota. However, if the microbiota is not balanced and/or immunity is compromised, the intestinal mucosal immune response is overstimulated, which can lead to disease. The barrier function of the intestinal mucosa decreases as the intestinal microbiota is translocated, which causes further damage to the intestinal mucosa barrier, causing a vicious cycle and accentuating the intestinal inflammatory response.27,28

The treatment of UC with FMT aims to induce clinical remission through the progressive transformation of the inflamed mucous into normal, reestablishing the tissue's histological architecture, reducing morbidity and mortality and improving the quality of life of individuals who have this pathology.29(figure 1)

FMT can reduce permeability of the intestinal barrier and increase short chain fatty acids, which could help to keep the epithelial barrier intact. FMT can also restore immune dysbiosis because it can inhibit T cell and other leukocytes activity and reduce the production of inflammatory factors.30

Warren et al. studied the efficacy of UC regression, based on the use of FMT by endoscopic and capsule routes. Of the 30 patients undergoing FMT by endoscopy, 15 kept treatment using capsules, and in all patients, there was control of UC. Only four had adverse effects such as diarrhea, constipation and nausea, showing that FMT can be an innovative, safe and efficient alternative for the treatment of these IBD.31

Costello et al., in a systematic review and meta-analysis of four existing randomized clinical trials, concluded that, even without solid evidence, FMT seems to be effective in inducing UC remission, without signs of short-term insecurity.32

Fecal microbiota transplant in the treatment of Crohn’s Disease

CD is a chronic inflammatory condition with transmural involvement of the gastrointestinal tract, may occurring extraintestinal manifestations. Although treatment options have

expanded in recent years, they focus primarily on lowering the immune response, thus bringing notable risks associated with long-term immunosuppression.33

Its pathogenesis is not fully understood, but it is now recognized that it is related to an abnormal activation of the gastrointestinal immune system against microorganisms of the intestinal microbiota, in genetically susceptible hosts and under the influence of environmental factors.34

According to a recent meta-analysis, after minimizing publication bias, patients with inflammatory bowel disease who received FMT had a 36.2% remission rate: 22% for UC and 60.5% for CD.35 The central mechanism for the effectiveness of FMT is probably the construction of a community composed by intestinal bacterial strains and antimicrobial components, such as adhesins, immunomodulatory molecules, bacteriocins, etc., produced by them. Thus, pathogenic bacteria are prevented to adhere, making possible the rehabilitation of intestinal mucosa.36 (Figure 1)

Xiang et al. studied 174 patients with CD who received FMT by endoscopy, nasojejunal tube or colonic transendoscopic enteral tube. The median duration of follow-up was 43 months. The authors noted that 75.3% of patients showed a clinical response one month after FMT. Of these, 9.2% of patients presented sustained remission after a single FMT, while 10.7% of patients changed therapy due to loss of response. In total, 109 patients received multiple courses of FMT during follow-up. Of these, 58.7% showed clinical response with FMTs and 21.1%, sustained clinical remission. The overall average of FMT procedures was 3.5, and the average time between the first and second FMT was 123 days.37

Li et al., carrying out a study with sixty-nine patients with active CD, observed a significant benefit already in the first FMT. Four weeks after the first FMT, 63 patients demonstrated a clinical response and 47, clinical remission. In addition, 8.7% of patients showed partial improvement in the symptoms of CD. Just before these patients received the second FMT, 62.3% of them still maintained a clinical response, among which 43.5% still maintained clinical remission.38

Susking et al. selected nine families for a study about FMT in pediatric patients with active CD. These patients received the fecal transplant, whose donors were their parents. Two weeks after FMT, 7 of 9 patients were in clinical remission based on PCDAI score. After 6 and 12 weeks, 5 of 9 patients, who did not receive additional therapy, were still in remission. Only two subjects required additional standard medical therapies before the end of the study.39

Fecal microbiota transplant in the treatment of Metabolic Syndrome

MS is characterized by a set of symptoms strongly associated with the development of cardiovascular diseases, type 2 diabetes and nonalcoholic fatty liver disease, being characterized by insulin resistance, dyslipidemia, high blood pressure and increase of abdominal waist.40 It is believed that the gut microbiota plays a key role in maintaining the physiological function of the host, and dysbiosis caused by various factors leads to extensive physiological changes and increases the risk of MS. Studies have shown that it is possible that an increased frequency of the phylum Firmicutes, and reduced frequency of Bacteroidetes could be related to an obese phenotype. However, the underlying mechanisms by which gut microbiota affects host metabolism still need to be defined.41

It has been observed that FMT alters and increases the biodiversity of intestinal microbiota, modulates bacterial proportion, increases the release of glucagon like peptide 1 (GLP-1), modulates the paths of biliary acid and interferes with the production of short-chain fatty acids. It can also be responsible for complex effects like immune cells regulation, alteration of intestinal gluconeogenesis, reduction of tumor necrosis factors - alfa, change in the metabolism of lipids and glucose, among other mechanisms 35. Because of that, a hypothesis was raised that FMT might contribute to the treatment of MS/obesity by

increasing the insulin sensitivity, decreasing body fat and modulating the metabolism of lipids and cholesterol.42 (Figure 1).
Kotte et al. studied the effects of FMT in 38 men with MS - aleatory divided into a treatment group (26 men who received transplant from a healthy donor) and control group (12 men who received autologous fecal transplant). The authors observed that six weeks after the FMT there was an alteration in the composition of duodenal and fecal microbiota in the treatment group, associated with a better peripheral sensibility to insulin and a slightly, but significant, decrease in quantity of glycated hemoglobin, when compared to the control group.43 However, when the samples were collected and analyzed again, 18 weeks after the FMT, the microbiota composition had returned to the base composition, evidencing a short-term benefit, non-sustained in long-term.44
Allegretti et al., studying 11 obese men who received the FMT by oral capsules, with the dose reinforced twice every four weeks, observed significant change in the curve of glucose after 12 weeks, when compared to the placebo's group curve. It was also observed an alteration in the levels of insulin 6 weeks after the FMT.36 Therefore, the authors suggested that FMT might have preventive role in the development of MS in obese pacients.45
Studies have shown that FMT alters the receptors' microbiota making it similar to the donor's composition, but without any functional effect or metabolic change.44, 45, 46

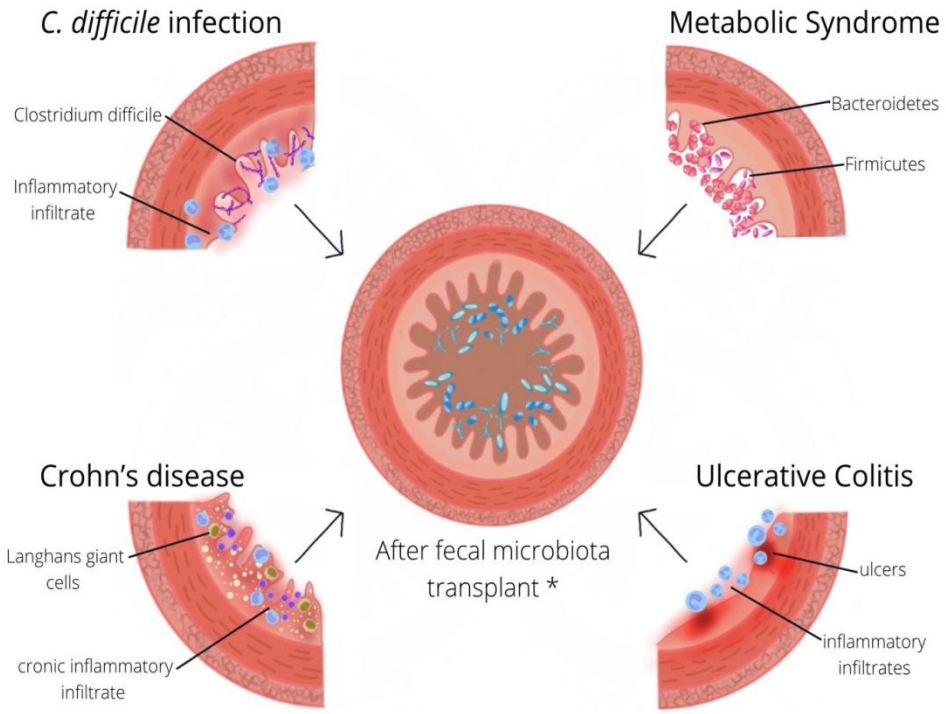

Figure 1: Mechanisms of successful treatment of recurrent *Clostridium difficile* infection (RCDI), Crohn's Disease (CD), Ulcerative Colitis (UC) and Metabolic Syndrome (MS) with fecal microbiota transplant (FMT). Improvement in symptoms after FMT has been associated with restoring the healthy microbiome (eubiosis) and reduction of inflammation and tissue damage.

4. Final considerations

The studies have shown that FMT can be useful in the treatment of RCDI with cure rates ranging from 85% to 90% and represent a possible alternative to antibiotic therapy in cases of primary infection by *C. difficile*. Regarding the treatment of UC, FMT seems to be effective in inducing remission, but its durability and long-term safety are still not well defined.31,32,46. Furthermore, the studies suggest that FMT in the treatment of CD and MS is still questionable, and further studies are needed to prove the feasibility of this procedure in these and other conditions.

It is important to highlight that all the studies have limitations and bias. It is observed, for example, that all studies were carried out in men and follow-up beyond 6 months is not yet available. Furthermore, none of the studies reported dietary control, a factor that directly affects the composition of the microbiota. For example, a diet rich in protein is associated with increased microbiota diversity47. This diversity makes communities more resilient, managing to build more resources, reducing the opportunity for bacterial invasion. This can be a barrier to the reversal of dysbiosis by FMT, as it offers more resistance to colonization.48 Another study pointed out the important role of the viral community in receiving treatment with FMT, as patients who did not respond to treatment had a greater difference in their viral communities when compared to their respective donors.49

It is also important to consider the limitations and the risks of the procedure. Risk of infection transmission after FMT has been of great concern, although it appears to be rare.50 Other adverse event, after nasoduodenal administration of FMT, could be aspiration pneumonia.51 As each procedure has its related complications, the best way of FMT administration must be verified for each patient and according to the professional experience.52

To provide long-term assessment for up to 10 years, aiming to answer the most pressing safety question regarding FMT, Gliklich et al. developed the FMT national registry, providing a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness.53

The present work has its own limitations, since it selected few studies, about four different conditions, emphasizing only the therapeutic results presented by them. Therefore, this study is insufficient as groundbreaking results. Further studies should be carried out to clarify the mechanisms, the best protocols and the real uses of the FMT.

5. Conclusion

The studies are optimistic and suggest that FMT has the potential for treatment and/or remission of different inflammatory and infectious conditions.

Competing interests

Authors have declared that no competing interests exist.

Authors' contributions

Mariana Araujo Mendes Silva designed the study and wrote the first draft of the manuscript. Mariana Dias Lopes Barud, Gabriel Vieira Barkett and Maria Eduarda Almeida managed the analyses of the study. Finally, Mariella Vieira Pereira Leão guided and proofread this review. All authors read and approved the final manuscript.

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