Fecal Microbiota Transplantation in Non-Gastroenterological Diseases

Subjects: Infectious Diseases

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The gut microbiota has a critical function in human health, and its various disorders are associated with the development of particular diseases. Disruption of the gut microbiota may lead to both gastrointestinal and non-gastrointestinal diseases, such as cancer, metabolic syndrome, or neuropsychiatric diseases. In this context, it is not surprising that gut microbiota modification methods may constitute a therapy whose potential has not yet been fully investigated. In this regard, the most interesting method is thought to be fecal microbiota transplantation, which consists of the simultaneous replacement of the intestinal microbiota of a sick recipient with fecal material from a healthy donor.

fecal microbiota transplantation microbiota COVID-19

1. COVID-19

To the best of current knowledge, there have been no completed RCTs on the safety or efficacy of fecal microbiota transplantation (FMT) in patients with COVID-19. However, the first evidence that FMT may be beneficial for patients with COVID-19 was reported in two clinical cases by doctors from Imperial College London and the Medical University of Warsaw [1]. The first case involved an 80-year-old subject who had pneumonia and sepsis (blood poisoning) on top of recurrent *Clostridium difficile* infections: he was given remdesivir and plasma-containing antibodies to SARS-CoV-2 ('convalescent plasma'). Unexpectedly, his COVID-19 symptoms cleared up two days after the transplant without further worsening of his pneumonia [1]. The second case involved a 19-year-old individual with UC who was being treated with immunosuppressant drugs. He was admitted to the hospital because of recurrent *Clostridium difficile* infections. He was treated with antibiotics and given a stool transplant to prevent further recurrence. Fifteen hours later, he developed a suspected COVID-19 infection, which was confirmed by a positive swab test. Subsequently, other than two isolated episodes of fever, his COVID-19 symptoms cleared up. This second patient was not given any other medication to specifically treat his COVID-19 [1]. At present, Zhang et al. are investigating the effectiveness of washed microbiota transplantation in patients with COVID-19 for improving mortality rates, and quality of life of patients with COVID-19 [2].

2. Psoriasis

Psoriasis is a widespread inflammatory skin disease that is pathophysiologically similar to IBD. It has been found that patients with psoriasis exhibit abnormalities in gut microbiota, in particular, a reduction in the relative

abundance of *Akkermansia mucinophila* and a three-fold increase in the *Bacteroidetes*/*Firmicutes* ratio [3]. Effective psoriasis treatment is usually associated with a marked improvement in the composition of gut microbiota. The first clinical evidence for FMT efficacy in psoriasis was described in a 36-year-old Chinese male, who had suffered from psoriasis for 10 years and IBS for 15 years. FMT was initially performed by upper endoscopy, and repeated after 5 weeks via colonoscopy. Post-FMT, there was a reduction of serum TNF-α and intestinal symptoms, as well as an improvement of the Psoriasis Area and Severity Index (PASI), the Dermatology Life Quality Index (DLQI), and histological examination as compared to the baseline condition were observed [4]. A 6-month, double-blind, placebo-controlled RCT of the effectiveness and safety of FMT in patients with psoriatic arthritis is currently underway [5].

3. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease that causes severe neurological changes, for which there is an extant lack of highly effective treatment options. Many patients with multiple sclerosis have gastrointestinal symptoms and gut microbiota changes in comparison with healthy people [6]. In one experiment, the inflammatory response in mice with autoimmune encephalomyelitis (AE) decreased when bacterial strains producing butyrate were administered [7]. On the other hand, feces transplantation from patients with MS could precipitate an MS-like autoimmune disease in mice [8]. Li et al. tested FMT in mice with experimental AE, a mouse model of MS. FMT can rectify altered gut microbiota and led to a reduced activation of microglia and astrocytes, and conferred protection on the blood–brain barrier (BBB), myelin, and axons in experimental AEs [9]. The first case report in three people with MS described a short-term improvement of neurological symptoms after FMT for constipation [10]. A recent study suggested that FMT administered for over 10 years has a potential long-term benefit on MS disease progression [11]. This proof-of-concept research suggests that FMT might be an emerging treatment in relapsing-remitting MS. FMT interventions were associated with increased abundances of putative beneficial stool bacteria and short-chain-fatty-acid metabolites, which were associated with increased/improved serum brain-derived-neurotrophic-factor levels and gait/walking metrics [12]. The main limitation was the participation of only one patient, but the findings may constitute an important background for scientific rationale, and help design future RCTs assessing FMT in MS patients. Therefore, there is an extant view that MS can be treated by FMT, just as UC can.

4. Parkinson’s Disease (PD)

PD is an intractable neurodegenerative disease that is often associated with gastrointestinal disorders such as constipation, IBD, and IBS. PD patients also appear to have increased intestinal permeability [13] and small intestine bacterial overgrowth [14]. The gut microbiome of patients with PD is characterized by an overabundance of *Bacteroidetes*, *Faecalibacterium prausnitzii*, *Enterococci*, *Prevotella*, and *Clostridium*, particularly in severe cases [15][16]. Overall, more pro-inflammatory gut bacteria, such as LPS-producing *Proteobacteria*, and less anti-inflammatory butyrate-producing gut bacteria are found in PD patients [15][17].

In one experiment, the transplantation of microbiota from patients with PD in a mouse model led to a worsening of neurological manifestations, whereas gut microbiota depletion in the same model reduced neurological symptoms [18]. Another study showed that a PD mouse model had improved motor function, increased striatal neurotransmitters, and decreased neuroinflammation after receiving feces from healthy mice [17][18]. Furthermore, a healthy mouse donor FMT had neuroprotective effects in PD mice through the suppression of neuroinflammation and a reduction in TLR4/TNF-α signaling [19]. Zhou et al. demonstrated that intestinal microbiota may have a neuroprotective effect. FMT from normal mice with a fasting-mimicking diet to animals with PD has been shown to increase dopamine levels in substantia nigra [20].

The first case report assessing the effects of FMT in PD was described in a 71-year-old male patient who presented with 7 years of resting tremor. The patient successfully defecated within 5 min, and maintained daily unobstructed defecation until the end of the follow-up. The patient's tremor in the legs almost disappeared 1 week after FMT, but recurred in the right lower extremity 2 months after FMT [21]. Xue et al. reported data from the first pilot study for the efficacy and safety of FMT on 15 PD patients. FMT with a preference for colonic rather than the nasointestinal way can relieve the main PD symptoms. Moreover, 2/10 patients from the colonic FMT group in 2-year follow-up achieved satisfactory results. In the nasointestinal FMT group, all beneficial effects terminated after 3 months. FMT was safe, and only five mild and self-limiting adverse events occurred during the study [22]. Preliminary literature suggests that FMT may be a promising treatment option for PD. In summary, it should be noted that the available evidence is currently insufficient and is based on the scanty number of both experimental and RCTs, which necessitates further studies of FMT to assess the safety and the preferable methods of FMT [17].

5. Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a condition related to brain development that impacts how a person perceives and socializes with others, causing problems in social interaction and communication [23]. ASD is often associated with constipation, bloating, diarrhea, and changes in the gut microbiome [24][25]. Children with ASD usually have a reduced *Bacteroidetes*/*Firmicutes* ratio [26] and increased levels of the genus *Clostridium* [23]. Changes in the microbiome may interact with tryptophan metabolism and contribute to behavior change, but the evidence is inconsistent [27].

FMT from children with ASD to germ-free wild-type mice associated with the development of ASD-like symptoms displayed alternative splicing of ASD-relevant genes in their offspring [28]. Another study observed a reduction in oxidative stress markers, primarily glutathione and vitamin C, in the brains of ASD patients [29]. Probiotic/prebiotic treatments showed ameliorative effects; however, lactobacillus had the strongest [29].

A pilot open-label study investigated the effectiveness of FMT in 18 children (aged between 7 and 16 years old) with ASD after a 2-week course of antibiotic treatment. Parallel enhancement in ASD behavior scores and a decrease in intestinal symptoms (bloating, constipation, diarrhea) were observed, and the improvements persisted for more than 2 months after the FMT had been administered. In addition, there was engraftment of donor stool microbiota with an increase in both overall bacterial α-diversity, as well as an abundance of *Bifidobacteria*,

Prevotella, and *Desulfovibrio* which persisted for more than 2 months post-FMT [30]. These same benefits appeared to be maintained when participants were followed up for up to 2 years after FMT [31]. However, it was open-label, and there was no comparator arm of patients receiving placebo/autologous FMT, no controlling for diet or nutritional supplements, and a lack of information on adverse events in the long-term follow-up. An open-label randomized waitlist-controlled trial showed a significant improvement of the Childhood Autism Rating Scale in the FMT group, as compared to the waitlist group after the first procedure (10.8 vs. 0.8%, $p < 0.001$), and shifted the microbiome of ASD patients to a healthy state [32]. Although these observations point to a potential causal link between the microbiome and ASD, the results are preliminary and speculative.

6. Epilepsy

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes a loss of awareness [33]. In most cases, the etiology of the disease is unknown, but in some people epilepsy is caused by trauma, stroke, brain tumors, drug and alcohol abuse, or other causes [34]. The composition and distribution of gut microbiota profiles in patients with refractory epilepsy differ from healthy controls. Several studies reported an increased *Firmicutes/Bacteroides* ratio and α-diversity, as well as *Ruminococcus, Akkermansia, Neisseria, Coprococcus, Methanobrevibacter,* and *Roseburia*[35][36]. Moreover, the abundance of *Bifidobacterium* and *Lactobacillus* was associated with fewer seizures per year [35], and a ketogenic diet reduced the frequency of seizures by modulating the gut microbiota [37].

A recent study found that both chronic stress and microbiome transplanted from stressed to sham-stressed rats accelerated the progression and prolonged the duration of kindled seizures [38]. Olson et al. observed that the transplantation of ketogenic microbiota or the long-term administration of species *Akkermansia muciniphila, Parabacteroides merdae,* and *Parabacteroides distasonis* decreased the number of seizures in mice at a higher threshold [39]. He et al. reported a case report in which FMT was used to achieve a remission of intestinal and neurological symptoms in a girl with CD and a 17-year history of generalized epilepsy [40]. During the 20 months of follow-up, three rounds of FMT proved efficacious in preventing the relapse of seizures after withdrawing the sodium valproate [40].

7. Other Neurological Disorders

Vendrik et al. analyzed studies and case descriptions on FMT in neurological disorders in humans or animal models. From 541 identified studies, 34 were included in the analysis [17]. For stroke, Alzheimer's disease, and Guillain–Barré syndrome, only studies with animal models were identified. These studies suggested a potential beneficial effect of healthy donor FMT. In contrast, one study with an animal model for stroke showed increased mortality after FMT [17]. Only one study was identified for Guillain–Barré syndrome. It should be noted that it is not known whether the previous positive experimental results will be reflected in the treatment of patients. To date, several RCTs are scheduled, or are in the stage of active recruitment to validate the use of FMT for the treatment of the above-mentioned neurological disorders [22].

8. Metabolic Syndrome/Obesity

The development of metabolic syndrome is usually associated with changes in the gut microbiota. In recent times, one of the most essential aspects of obesity has been considered to be a modification in bacterial aches in the human gut [41][42]. Metagenomic studies and an analysis of 16S ribosomal DNA revealed significant differences in the composition of gut microbiota, and the number of genes when the feces of obese subjects and people of a healthy weight were compared [43]. Without diminishing the role of heredity and environmental factors, the gut microbiota makes a significant contribution to the development of metabolic disorders and obesity, modulating the cascade of host enzymatic reactions, interacting with receptors directly and/or using its own metabolites and signaling molecules [44].

It is obvious that maintaining homeostasis and normal metabolism is impossible without restoring the diversity of normal associations of gut microbiota. Despite the proven effect of diet, pre- and probiotics, further research is needed in order to develop differentiated regimens for the impact on gut microbiota, and thus achieve an improvement in metabolism and lose weight [45][46]. FMT may be considered as a potential therapeutic strategy for the treatment of obesity in the future. An early pilot study split 18 patients into two groups: patients who received allogeneic FMT from lean donors (*n* = 9) and obese patients who received autologous FMT (*n* = 9). The group receiving allogeneic FMT displayed improved insulin sensitivity after 6 weeks [47]. However, a subsequent larger study (*n* = 38) showed that allogeneic FMT (*n* = 26) failed to reduce insulin resistance, compared with autologous FMT (*n* = 12) after 18 weeks, and correlated to a lack of overall change in the composition of the intestinal microbiota [48]. FMT with oral capsules from lean donors to obese patients was tested in double-blind, placebo-controlled studies by Allegretti et al. It was shown that FMT did not affect the patient's body mass index (BMI) and area under the curve (AUC) of GLP1, but helped to reduce the concentration of taurocholic acid. Patients who received FMT had sustained shifts in microbiomes associated with obesity toward those of the donor [49]. The same group reported the secondary analysis of a previous RCT, with the analysis of post-prandial glucose and insulin levels. There was a significant change in glucose AUC at week 12, compared with the baseline, and in the insulin AUC at week 6 compared with the baseline in the FMT group versus placebo [50]. Weekly administration of FMT capsules in a double-blind randomized placebo-controlled study for adults with obesity resulted in gut microbiota engraftment in most recipients for at least 12 weeks. Despite the lack of metabolic parameters, changes such as insulin sensitivity, HbA1c, body weight, and body composition by DXA were assessed [51]. Zhang et al. have analyzed and compared data on the use of FMT in systemic review. Studies reported mixed results about improvement in metabolic parameters. Two studies reported improved peripheral insulin sensitivity at 6 weeks in patients receiving donor FMT versus patients receiving the placebo [52]. No differences in fasting plasma glucose, hepatic insulin sensitivity, BMI, or cholesterol markers were observed between the two groups across all included studies [52]. FMT has significantly increased the number of species such as *Roseburia intestinalis*, *Akkermansia muciniphila*, and *Clostridium* species. [52]. The most recent meta-analysis, with the inclusion of 6 RCTs and a total of 154 patients, evaluated the role of FMT from the lean donor(s) compared with any form of placebo (sham, saline, autologous FMT, or placebo capsules) for the treatment of obesity and metabolic syndrome. It was found that 6 weeks post-FMT, the level of HbA1c was significantly reduced. However, no difference was found for anthropometric parameters that characterize obesity at 6–12 weeks after the procedure [53].

It is believed that the responses of patients with metabolic syndrome to modification of the gut microbiome may depend on the microbiota's initial state and diet. Guirro et al. evaluated the effect of a hypercaloric diet on gut microbiota, and this was combined with antibiotic treatment to deplete the microbiota before FMT to verify its effects on gut microbiota-host homeostasis in rats. An HFD affected the gut microbiome and after the antibiotic therapy and subsequent use of FMT, the number of *Bacteroidetes*, *Firmicutes* was increased to the level that was before the antibiotic therapy [54]. The largest recent RCT included 90 participants to evaluate the efficacy and safety of diet-modulated autologous FMT for the treatment of weight regain after the weight-loss phase (DIRECT PLUS trial) [55]. The participants were randomly assigned to groups that received 100 capsules containing their own frozen fecal microbiota or placebo, until month 14. It was found that FMT administrated in the regain phase might preserve weight loss and glycemic control, and was associated with specific microbiome signatures [56]. A high-polyphenols, green plant-based or Mankai diet better optimized the microbiome for an autologous FMT procedure [56].

Preliminary studies showed a promising beneficial effect of FMT, manifested by improved insulin sensitivity, glycemic control, and reduced chronic systemic inflammation [57]. However, high-quality well-powered RCTs with longer follow-up are urgently needed to highlight the benefits of FMT as a viable option for patients with obesity and metabolic syndrome in the future.

9. Graft-Versus-Host Disease

Graft-versus-host disease (GvHD) is a syndrome characterized by inflammation in different organs. GvHD is commonly associated with bone marrow transplants and stem cell transplants. Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative strategy for patients with selected blood diseases. Complications from the procedure comprise most of all infections and GvHD, which are the major causes of morbidity and mortality (45% of attributable deaths) apart from relapse [58]. The first-line therapy in acute GvHD is systemic administration of high-dose glucocorticoids, but only 40–60% of patients respond to this treatment depending on the grade of severity of the disease [59]. At present, there is no established standard-of-care second-line therapy. The high mortality rate of steroid-refractory/dependent (sr/d) acute GvHD, especially in patients with grade III-IV lower gastrointestinal tract involvement, is a major drive for exploring novel therapeutic strategies [59][60]. As the patients with gut GvHD are often colonized with antibiotic-resistant bacteria (ARB), there are pioneer studies of experience performing FMT in patients with acute or chronic GvHD, co-colonized with ARB. These studies have shown a good efficacy of FMT in the treatment of GvHD and decolonization of the GI tract from ARB [58][59].

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