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FECAL MICROBIOTA TRANSPLANTATION IN GASTROINTESTINAL AND EXTRAINTESTINAL DISORDERS

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Abstract: Gut microbiota has a significant influence on human health and is also involved in the pathogenesis of several disorders. The reconstitution of the healthy gut microbiota is an essential aim in the treatment of disorders associated with microbiota imbalance. Fecal microbiota transplantation (FMT) is the infusion of faces from healthy donors to patients, with the aim of curing a particular disease. This treatment is highly effective in the cure of recurrent *Clostridioides difficile* infection and has been increasingly evaluated in other disorders associated with microbial dysbiosis.

Over time, different FMT working protocols have been investigated and, until now, methodology has not yet been standardized. Future efforts to improve the therapeutic effect of FMT will include the definition of specific protocols for each disease, the application of metagenomic techniques for the assessment of gut microbiota composition into daily practice, and the development of well-designed studies.

Keywords: Fecal microbiota transplantation, Gut microbiota modulation, *Clostridioides difficile* infection, Metabolic syndrome, Diabetes, Ulcerative colitis, inflammatory bowel disease, Irritable bowel syndrome, Autism, Allergy, Cancer.

INTRODUCTION: THE ROLE OF GUT MICROBIOTA IN HEALTH AND DISEASE

A large number of microorganisms inhabit the inner and in the outer compartments of our body. The majority of them are localized into our gastrointestinal tract, making up the gut microbiota[1,2]. The gut microbiota is far from being a simple collection of microbes, the gut microbiota is a complex, dynamic entity which is equivalent to an additional organ within the human body[3].

Gut microbiota composition is still not very clear. Bacteria are the most largely known constituents of human gut microbiota. Bacteroidetes and Firmicutes are the most represented phyla[4]. Other microbial constituents are Archaea, Viruses, Fungi and Protozoa[5,6]. Most of the microbial community living in our gut is not cultivable through standard microbiological procedures. The use of culture-independent diagnostic tools, including metagenomics, is conferring a fundamental improvement to our understanding of gut microbiota composition in health and disease[7].

The gut microbiota is responsible for several important tasks within the human body, including contributing to the development and control of both local and systemic immunity, the regulation of various metabolic pathways and barrier function against foreign agents throughout our intestine[8]. Different lines of evidence suggest that impairment of gut microbiota homeostasis can lead to the development of many digestive and extra-digestive disorders, including irritable bowel syndrome (IBS) and other functional gastrointestinal diseases[9], inflammatory bowel disease (IBD)[10], colon cancer[11], gastrointestinal infections[12], non-alcoholic fatty liver disease and other liver diseases[13,14], diabetes, obesity and metabolic syndrome[15,16], autism[17] and allergies[18]. In principle, restoration of a healthy gut microbiota is a reliable approach for the management of gut microbiota-related diseases[19]. Antibiotics, probiotics and prebiotics are, at present, the most popular therapeutic options in this regard for the reestablishment of healthy microbiota. Fecal microbiota transplantation (FMT) has proven undoubted efficacy in the management of recurrent *C. difficile* infection (CDI), and it is also considered as a promising therapeutic avenue for other diseases associated with gut microbiota imbalance.

FECAL MICROBIOTA TRANSPLANTATION: THE STORY SO FAR

FMT is the infusion of stools from a healthy donor to a patient in order to heal a particular disorder. The use of FMT in medical and veterinary field was sporadically described since ancient times[20,21]. The first mainstream documentation of FMT in clinical practice dates back 1958, when Eiseman and his surgical team from Colorado successfully attempted feces enemas as rescue treatment for the management of patients with pseudomembranous colitis[22]. Since this initial experience, many FMT studies for the control of recurrent CDI have been reported[23]. The recent debate relating to consideration of FMT as a tissue transplant, instead of a simple infusion of feces, has provided the rational to evaluate FMT efficacy in other gut microbiota-related diseases, with encouraging outcomes[24,25].

FECAL MICROBIOTA TRANSPLANTATION: PROCEDURAL PROTOCOL

Donor Selection

Differently from other organ transplants (such as liver or kidney transplant), fecal microbiota transplantation does not need any immune match between recipient and donor. However, a thorough pre-procedural screening is necessary to avoid dissemination of diseases from the donors to the recipients. In the past, donors were selected among patients' family members, companions or friends, to limit the "yuck factor", that is the disgust of the recipient towards stool transfer. However, due to the increasing request for FMT in patients with recurrent CDI, and the need for standardization, universal donors are now recommended as first choice[26]. As first step, medical history of candidates is collected, generally through questionnaires. Nowadays, concerning FMT for CDI, absolute or relative contraindications which exclude candidates from donating feces are constituted by communicable diseases (such as pulmonary infections), infection or recent exposure to viral hepatitis, syphilis, human immunodeficiency virus (HIV) infections; drug dependence, sexual promiscuity, jail history, recent tattoos, piercings, or travel to countries characterized by endemic diarrheal diseases; risk factors for Creutzfeldt-Jakob disease, history of digestive cancers or polyps, IBD, IBS/functional gastrointestinal diseases, of other disorders potentially associated to gut microbiota imbalance (metabolic syndrome, autoimmune and atopic illnesses), and of principal abdominal surgical interventions; use of certain drugs (immunosuppressants, chemotherapy drugs, antibiotics) within the prior 3 months[26,27]. The second step consists of blood and stool screening for, respectively: hepatitis A, B, C, HIV, syphilis; *C. difficile* toxin, stool culture, parasitological exams, and others[26,27]. This preliminary evaluation appears to be appropriate for the management of patients with CDI[28]. Nonetheless, when FMT is applied to other diseases, such as IBD, donor's microbiota composition seems to extensively affect results[29]. This necessitates a thorough characterization of gut microbiota of donors and recipients as an essential step in the donor selection procedure.

Changes in Donor Recruitment at the Time of COVID-19 Pandemic

In the last few months, the outbreak of Coronavirus disease 2019 (COVID-19) has imposed the FMT workflow rearrangement, including protocols for the recruitment of donors[30].

First, anamnestic questionnaire was expanded with some specific questions to investigate COVID-19 characteristics symptoms, such as fever, cough, dyspnea, chills, anosmia or ageusia or muscle pain, not explainable by alternative diagnosis, or potential history of exposure to subject with infection. Moreover, the nasopharyngeal swab and RT-PCR assay for SARS-CoV-2 have been added to the panel of laboratory testing and to the checks to be done the day of each donation[30,31]. If candidate donors result positive to one of the questionnaire items or to nasopharyngeal swab, they were excluded.

Preparation of Recipients and Fecal Material

Usually, recipients undergo bowel preparation 24 hours before the transplant, to wash out the gut. If feces are administered by upper route, patients are usually given proton-pump inhibitors, prior to FMT administration, to prevent microbiota damage by gastric acid. Before the transplant, feces are diluted in saline or water, and the resulting suspension is filtered to get rid of rough residuals. If the material is to be frozen, glycerol is added up to 10%, as cryopreservant. The fecal material should be infused within 6 hours from the donation or defrosting[32,33]. Frozen feces and fresh feces have been utilized with similar results[34]. A single FMT infusion usually can cure mild CDI, but severe CDI may require sequential FMT infusions[35]. Also, long-standing diseases (e.g., IBS, metabolic syndrome, IBD) may need multiple infusions in order to obtain similar results.

Route of Administration

Many routes have been investigated for the introduction of feces: gastroscopy, nasogastric/nasojejunal tube, colonoscopy, enemas[36]. Upper route seems to return lower eradication rates than lower delivery routes[23]. Cheapness and ease of administration represent the main benefits of enema. However, colonoscopy has also a diagnostic value, enabling a better estimation of disease extent/severity[37,38]. FMT through naso-jejunal tube has been investigated in obese patients, with interesting but preliminary results[39].

FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF DIGESTIVE AND EXTRADIGESTIVE DISEASES

C. Difficile Infection

Usually, CDI develops after massive antibiotic treatment regimens, often among fragile patients. In hospital settings it happens commonly after antibiotic treatment and subsequent impairment of physiologic gut microbiota composition[22]. Recurrent CDI is the major indication for FMT, with high rates (around 90%) of therapeutic success, and a very high safety profile[24]. Indeed, FMT shows meaningful efficacy in the eradication of recurrent CDI[40]. Moreover, FMT has been shown to be effective in decreasing sepsis occurrence, length of stay and mortality rates related to CDI when compared to antibiotic treatment[41]. Moreover, despite the increase of CDI through the years, FMT may be also capable of reducing the frequency of surgery due to complicated infections[42].

Inflammatory Bowel Disease (IBD)

Dysbiosis of gut microbiota is a fundamental step in the development of IBD[43,44]. Lower diversity and higher instability, as well as a decrease of Firmicutes and Bacteroides and expansion of Enterobacteriaceae and Actinobacteria characterize the gut microbiota composition of IBD subjects[44]. To date, some controlled experiences of FMT for IBD have been described[45].

FMT has proven effective in inducing short term ulcerative colitis remission compared to placebo[46]. However, available reports show high methodological heterogeneity in terms of procedural protocol and outcomes[46,47]. For example, improvement in Mayo scores following FMT have been reported and linked to sustained modulation of the recipient's microbiota toward donor profiles[29]. In contrast, present evidence is poor and unconvincing in Crohn's disease[48,49]. Although FMT appears to be safe in CDI, some adverse events, such as high fever, transient relapse of the disease or infections, have been described in patients with IBD, highlighting the need for additional/refinement control measures when developing FMT protocols for non-CDI indications[34,45,46,50-52].

Functional Gastrointestinal Diseases

Gut microbiota has been suggested to play a role in the pathogenesis of IBS through many pathways, such as gut barrier disruption, modulation of gut-brain axis and other neuro-enteric avenues[53]. In patients with constipation-type IBS, a reduction in *Roseburia-E. rectale* group bacteria (butyrate producers), and a rise of sulphate-reducing bacteria have been described[54]. In a mixed cohort of subjects with IBD or IBS, FMT has been reported to relieve disease symptoms in 52% of cases[55]. FMT also ameliorated symptoms in 45 subjects suffering from chronic constipation[56]. In contrast, a recent systematic review and meta-analysis or randomized controlled trials showed no overall benefit of FMT compared to placebo in the amelioration of symptoms in patients suffering from IBS. However, compared trials involved different FMT protocols and the lower gastrointestinal route of delivery seems to be superior and beneficial for patients[57].

Obesity and Metabolic Diseases

Numerous lines of evidence highlight gut microbiota impairment in the development of obesity. As demonstrated in various mouse models, the gut microbiota can gain energy from dietary intake, and also non absorbable polysaccharides can be split by microbiota-derived lytic enzymes[58]. Subsequent to transfer of conventional mice-derived gut microbiota, an increase of insulin resistance and body fat percentage, independent of food intake, has been reported[59,60]. In a small randomized controlled trial, insulin sensitivity and quantity of bacteria linked to butyrate production were greatly raised in 18 subjects suffering from metabolic syndrome who received FMT from lean donors[38]. Another study[61] assessed a similar result in reducing insulin resistance, even though the metabolic change was not maintained at long term.

Neurological, Neuropsychiatric and Immune Disorders

Mouse models propose a connection between neurological disorders and gut microbiota alterations[62-64]. The alleviation of symptoms in multiple sclerosis[65] and Parkinson's disease[66] after FMT has been described, but data are weak and fragmented. An open-label trial performed on 18 children affected by autism assessed an improvement of gastrointestinal and behavioral symptoms together with a partial engraftment of donors' microbiota after 8 weeks subsequent to the FMT[67]. Preliminary data suggests that FMT may improve anxiety and depression due to the increase of intestinal microbiota diversity[68]. Furthermore, FMT was examined in 34 subjects with chronic fatigue syndrome (CFS), with continuous amelioration of symptoms in 14 of them[69]. FMT has shown some efficacy also in immune diseases. An increase in platelet counts has been reported in subjects with immune thrombocytopenic purpura (ITP) undergoing FMT for ulcerative colitis[70].

Cancer

FMT seems a promising avant-garde strategy in the oncologic field, as clinical and translational evidence for gut microbiota modulation in cancer therapies is coming up[71]. For instance, as the response to immune checkpoint inhibitors in melanoma murine models appears to be related to the abundance of certain strains in intestinal microbial community[72], and as the

FMT in mice from responders to melanoma increased the effect of immunotherapy[73], FMT from individuals with "responder-like" fecal microbiota is being tested in oncologic patients under treatment with checkpoint inhibitors[74]. Moreover, FMT was reported to be capable of reverting cisplatin-induced dysbiosis and intestinal injury in mice[75], as well as to abrogate colitis caused by immune checkpoint inhibitors in humans[76]. Likewise, a pilot study[77] reported the efficacy and safety of FMT in treating steroid-resistant or steroid-dependent gut acute graft-versus-host disease occurred after stem cell transplantation for acute myeloid leukemia in a small number of patients. These preliminary data pave the way for a possible solution of treatment-induced dysbiosis-related side effects in oncological patients.

Multi-Drug Resistant Organisms

As FMT can eradicate and prevent further episodes of CDI[78], some authors applied this principle to gut colonizing drug-resistant bacteria with remarkable results. Indeed, a few case series and a case report assessed a successful outcome in decolonizing or preventing further infections in patients with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, *Klebsiella pneumoniae* MBL$^+$ and *Escherichia coli* ESBL$^+$[79-81]. Furthermore, in a study[82] conducted on 20 hematological patients colonized with one or more antibiotic resistant strains, single or multiple FMT fulfilled a 75% eradication rate in absence of severe adverse events.

Hepatic Encephalopathy

Another condition which has been largely related to intestinal microbiota alteration is portosystemic encephalopathy in hepatopatic patients, whose therapy with lactulose and rifaximin may be associated with modulation of microbial composition and metabolic function[83]. A randomized trial in cirrhotic patients with recurrent encephalopathy demonstrated that FMT from a selected donor with antibiotic pre-treatment was associated with lower recurrent episodes of encephalopathy and improved of cognitive symptoms when compared to standard of care therapy[84].

CONCLUSIONS

Gut microbiota have a core role in our health as well in the onset of many disorders. The improvement of our knowledge on gut microbiota composition and functions is leading us to the detection of new therapeutic paths for the handling of gut microbiota-related diseases. FMT induces a constant modulation of gut microbiota, and has shown uncontested effectiveness on recurrent CDI, as well as positive results on metabolic diseases. Anyway, data are already few and fragmentary. Additionally, a satisfactory safety profile has not been achieved in all patients.

The development of a standardized protocol for each disease, as well as a thorough evaluation of gut microbiota constitution of donors and recipients will possibly improve outcomes, enabling the spread of FMT in clinical practice.

Conflict of interest

The authors declare that they have no conflict of interests.

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