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Faecal microbiota transplant – prospects and safety

Transplantacja mikroflory jelitowej – perspektywy i bezpieczeństwo

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SUMMARY

The intestinal microbiota, either directly or indirectly, plays an important role in maintaining the homeostasis of the body. The intestine microorganisms are significant due to the role they play in stimulating the development of the immune system, protecting against pathogens, and also managing metabolic and nutrient processing.

The effectiveness of probiotics and prebiotics in various gastrointestinal diseases has been repeatedly confirmed. However, increasing interest in faecal transplantation has also been observed. Its efficacy in the treatment of pseudomembranous colitis has been repeatedly demonstrated. More often this method is discussed regarding the possibility of using it in other diseases linked with dysbiosis. Faecal microbiota transplantation, because of its rapid efficacy, minimal risk and adverse effects, relatively low cost, and the ability to re-establish the correct intestinal microbiota profile, could be an alternative treatment method in several other diseases.

This paper will introduce the latest therapeutic aspects of microbiota transplantation, including its implications in the treatment of gastrointestinal diseases.

Key words: faecal microbiota transplantation, intestinal microbiota, *Clostridium difficile* infections.

STRESZCZENIE

Mikrobiota przewodu pokarmowego, zarówno bezpośrednio, jak i pośrednio, wpływa na zachowanie homeostazy w organizmie człowieka. Mikroorganizmy jelitowe są szczególnie istotne ze względu na ich udział w rozwoju układu immunologicznego, ochronę przed patogenami, jak również funkcje metaboliczne i troficzne. Pomimo że skuteczność probiotyków oraz prebiotyków w łagodzeniu objawów szeregu chorób gastroenterologicznych została wielokrotnie potwierdzona, to w dalszym ciągu rośnie zainteresowanie metodą transplantacji kału. Skuteczność tej terapii potwierdzono przede wszystkim w leczeniu rzekomobłoniastego zapalenia jelita grubego. Coraz częściej dyskutuje się o możliwości zastosowania tej metody w leczeniu innych chorób przebiegających z dysbiozą jelitową. Transplantacja mikroflory kałowej, z uwagi na szybki efekt terapeutyczny, minimalne ryzyko działań niepożądanych, stosunkowo niski koszt i zdolność do modulowania składu mikroflory jelitowej wydaje się wartościową, alternatywną metodę leczenia w przypadku wybranych chorób przewodu pokarmowego.

Celem pracy było przedstawienie tematu transplantacji kału, w tym jego zastosowanie w leczeniu innych chorób gastroenterologicznych.

Słowa kluczowe: transplantacja mikroflory jelitowej, mikrobiota jelitowa, zakażenia *Clostridium difficile*.

Numerous researchers have demonstrated that improper microbial colonization of the intestine is a risk factor for many diseases (e.g. atopic diseases, NEC, obesity, type 2 diabetes, colorectal cancer, and inflammatory bowel diseases) [1, 2, 3, 4, 5]. This wide-ranging influence of the indigenous bacteria on the human body was the driving force behind creating a large international study in 2007 called the Human Microbiome Project. Research was initiated to understand the genomes of microorganisms and their broad impact on physiological processes, and to explore the relationship between disease and changes in the human microbiome [6]. The development of culture-independent molecular techniques has provided new insights into the composition and diversity of the intestinal microbiota. Both endogenous and exogenous factors, including e.g. antibiotics, other drugs, stress, smoking, and genetic factors may cause disturbances in the composition of intestinal microbiota. In some cases the re-establishment of a proper microbiota profile may take from several months to even years. A commonly known and well-documented way to modify the intestine microbiota is pre- and probiotic administration. Despite numerous publications documenting the positive effects of probiotics, they also have a major disadvantage – they do not colonize the intestine permanently. Their adhesion to the intestinal epithelium is temporary, and after cessation of the supplementation the probiotic strains are not detected in the patient's stool. Researchers started to look for new therapeutic approaches that would be able to modulate and make permanent changes in the gut microbiota profile. These criteria match the faecal transplantation procedure – an old therapy with a new potential. This method has been popular

in the effective treatment of *Clostridium difficile* infections (CDI), including recurrent cases. *Clostridium difficile* infections is a condition that is very hard to cure and may result in medical conditions ranging from diarrhoea to pseudomembranous colitis. If this method is effective in this case, why not apply it to other diseases linked with gut disturbances?

Faecal microbiota transplant (FMT) consists in single or multiple infusions of a faecal suspension from a healthy individual into the gastrointestinal (GI) tract of the recipient. The stool is a biologically active substance comprised of a plurality of living microorganisms which are in continuous interaction with human cells. This is a specific cross-talk process. A faecal suspension can supply up to 1000–1500 different bacteria species. For a comparison, standard probiotic preparations contain only one to a few species of *Lactobacillus* and/or *Bifidobacterium.* An advantage of FMT is that bacteria from the sample are living, do not require culture, and are already adapted to the intestinal environment. There are several routes for transplant administration, and each may be appropriate under a particular set of individual patient circumstances. The most common way of administering faecal microbiota is to supply it during colonoscopy, but it is also possible to infuse it during gastroscopy [7, 8] enemas (including self-administered) [9], via nasogastric or nasoenteric tubes [10], and gastroduodenoscopy [11]. Positive results and very high tolerance among patients has been achieved with oral capsules containing intestinal microbiota. Researchers reported 100% efficiency with one oral procedure in impeding cycles in patients with recurrent *Clostridium difficile* infections (RCDI) [12]. However, the optimal route of administration still remains uncertain.

The first report of faecal transplantation in the treatment of GI-associated diseases appeared in China in the 4th century. Ge Hong, a local physician, prescribed treatment with an oral supply of faecal suspensions in patients with food poisoning and severe diarrhoea. This was considered a medical miracle and was published in the first handbook of emergency medicine, "Handy Therapy for Emergencies". The next mention of the same therapeutic method was in the 16th century. Li Shizhen, in the most well-known book of traditional Chinese medicine, "Compendium of Materia Medica", described his therapeutic recommendations involving the administration of fermented or fresh faecal suspensions, as well as dry or infant faeces. Through this approach he achieved positive therapeutic effects in cases of abdominal diseases, including severe diarrhoea, fever, pain, vomiting, and constipation [13]. The first medical publication about FMT was published in a revered journal in 1958. *Eiseman et al.* described four cases of pseudomembranous colitis found as *Micrococcus pyogenes* (*Staphylococcus aureus*) aetiology, in which faecal transplantation by enema brought about an improvement in the clinical course, and a decrease of the above-mentioned bacteria [14]. Significant interest in this area increased after studies proving the effectiveness of the therapy in recurrent *C. difficile* infections, which is an important medical problem worldwide with high morbidity and mortality rates. Over the past two decades the amount of CDI grew to epidemic proportions. In the USA in 2010 there were 500 000 cases of CDI, and it is estimated that mortality is approximately 20 000 per year [15]. Overgrowth of the microorganism in the intestines is due to qualitative and quantitative imbalance in the gut's microbial ecosystem caused by using broad-spectrum antibiotics. It is believed that even a single dose of each antibiotic in patients with risk factors can lead to CDI. Particularly vulnerable are elderly people, >65 years. Other risk factors include low serum albumin concentration, recent abdominal surgery, prolonged hospitalization, or a stay in an intensive care unit [16]. In the case of a CDI, the first line of treatment is to discontinue ongoing antibiotic therapy, if possible, and replacing it with metronidazole, vancomycin or fidaxomycin. Appropriate choices between antibiotics depend on the severity of the infection [17, 18]. Unfortunately, CDI tends to recur, and the reoccurrence rate amounts to 15–35% [19]. Every further relapse increases the risk of a second and subsequent infection by 45% and 65%, respectively [20]. If CDI recurs three or more times, alternative therapy, including FMT should be considered. For this reason it is extremely desirable to search for a method which, beyond treatment, is also able to prevent the recurrence of the disease. The first described use of FMT for the treatment of CDI was in 1983 by *Schwan et al*. [21]. Consequently, the faecal transplantation in CDI and pseudomembranous colitis captured the attention of scientists. In patients with recurrent CDI, a decrease in microbiota diversity and reduction of *Bacteroidetes* and *Firmicutes* phyla in the stool was observed, compared with patients with only 1 episode of CDI [22]. Studies using molecular techniques showed that the intestinal microbiota profile in recipients after FMT is similar to the profile of the donors, and is dominated mainly by *Bateroidestes.* What is interesting is that these beneficial changes remain several weeks after transplantation. For comparison, after the administration of oral probiotics, in 10–14 days the probiotic strains present during preparation are not found in the stool [23]. *Grehan et al*. studied 10 patients who underwent FMT (infused into the caecum and colon) and their healthy donors [24]. Stool samples from recipients were collected prior to treatment, then the first stool after FMT, and 4, 8, and 24 weeks after transplantation. The composition of the intestinal microbiota in recipients consisted mainly of bacteria that occurred in donors, and was stable even 24 weeks after transplantation, with small changes occurring as the microbiota stabilized. Similar results were obtained by *Khoruts et al.* [25]. Fourteen days after transplantation the gut microbiota profile closely resembled that of the donor. It was an observed trend in patients with CDI. After the transplantation their stool is dominated by *Bacteroides* spp., which was originally lacking [24, 25, 26]. In one multicentre long-term follow-up study on the influence of FMT in patients with RCDI, the research demonstrated a very high cure rate of 98%, which is an excellent and promising result [27]. It seems that the achievement of a therapeutic effect is not influenced by the route of FMT, but this requires further studies. In research conducted by *van Nood et al.* in patients with RCDI a solution of donor faeces was infused into the duodenum via a nasoduodenal tube [28].

The researchers, as in the previous studies, observed an increased amount of *Bacteroidetes* after the FMT. In addition they observed increased numbers of clostridium clusters IV and XIVa and a decrease in the *Proteobacteria* species. Patients showed increased faecal bacterial diversity, similar to that in healthy donors. In the study, the group with FMT obtained better treatment outcomes in recurrent CDI compared to groups without faecal infusions.

The successes with FMT in CDI therapy suggest that it can also be useful in treating other GI and non-GI diseases with altered gut microbiota. Recent studies have documented a connection between intestine microbiota composition and several diseases. Beyond the best documented beneficial impact of faecal transplantation in CDI and RCDI [29, 30], more often this subject is taken up regarding antibiotic-associated diarrhoea [31], inflammatory bowel diseases, irritable bowel syndrome, metabolic syndrome, neurodevelopmental disorders, autoimmune diseases, allergic diseases, and others [32]. A systematic review comprising 17 studies and 41 patients with ulcerative colitis or Crohn's disease who underwent FMT found a reduction or complete resolution of symptoms in 76% of patients. Faecal microbiota transplantation was administered via colonoscopy/enema, or via enteral tube. Additionally, the cessation of IBD medications in 76%, and disease remission in 63% of patients was reported [33]. Another review paper that summarizes the data of 3 studies comprising 9 patients with refractory IBD (8 patients with ulcerative colitis and 1 with Crohn's disease) treated with faecal enemas described remission of the disease in all 9 patients [34]. Currently, there is growing interest in FMT in non-GI diseases, including, i.e. obesity [35], insulin resistance, metabolic syndrome [36], Parkinson's disease [37], chronic fatigue syndrome [38], multiple sclerosis [39], myoclonus dystonia [40], and childhood regressive autism [41].

Despite the positive effects and over 1700 years of FMT's tradition, it is still required to standardize the transplantation protocol and select a suitable donor. The stool, as a biological material, should be tested for potential infectious agents. Detailed screening is extremely important and desirable in order to reduce the risk of infections and adverse reactions. The American Gastroenterological Association has proposed guidelines for FMT [42]. Each donor should be screened for infectious diseases via both blood and stool testing. The donor stool should be screened for *C. difficile* A/B toxin (PCR is preferred to enzyme immunoassay), intestinal parasites such as *Giardia* (antigen test), *Cryptosporidium* (antigen test), *Isospora* and *Cyclospora* (acid fast stain) and other ova and parasites, enteric bacterial pathogens by routine bacterial culture (e.g. *C. difficile*, Shiga toxin-producing *Escherichia coli*, *Yersinia*, *Aeromonas*, *Klebiesiella*, *Campylobacter jejuni*, *Salmonella*, *Shigella*), *Helicobacter pylori* (stool antigen) and *Rotavirus*. Donor blood is screened for hepatitis A (IgM), B (hepatitis B surface antigen, anti-hepatitis B core [IgG and IgM], anti-hepatitis B surface antigen) and C (HCV antibody) viruses, HIV, CMV (IgM, IgG), EBV (IgM, IgG), and syphilis. Recipients should be screened via blood testing for infectious diseases to document any pre-existing infections, for HIV types 1 and 2, hepatitis A, B, C and syphilis. Depending on the circumstances, screening of individual patients and donors may require modification, including additional testing, to those above. Besides laboratory tests each donor candidate has to answer questions about his or her medical history. The most important are:

— Has the donor received antibiotics within past 3 months?

— Has the donor been incarcerated, or had any tattoos or body piercings within the past 6 months?

— Has the donor engaged in high-risk sexual behaviours within the past 3 months?

— Does the donor have a history of chronic diarrhoea, constipation, IBD, IBS, colorectal polyps or cancer, morbid obesity, metabolic syndrome, atopy, or chronic fatigue syndrome?

An affirmative answer to any of the above questions may be a reason to exclude such a person as a potential donor. If the recipient has any known allergy, the donor must avoid the allergen for several days before the procedure. It is also very important that donor should remain on a standard. There are no studies that clearly suggest whether a related or unrelated donor is better. Nevertheless, data showed that FMT using a stool from a standard donor gave satisfactory results in curing a disease [27, 43].

Standard practice for FMT is the use of a fresh stool that has been passed within 8 hours, certainly within 24 hours, and preferably within 6 hours. It should not be frozen, although a study has been conducted using frozen stool in patients with RCDI and it found that cure rates were similar, with 92% for fresh stool and 90% for frozen stool. Nonetheless, additional studies are necessary to determine the effectiveness of frozen versus fresh stool [27, 43]. Donors may collect the stool sample in their home. Preparation of the suspension for FMT is a multistep procedure. A specimen of stool weighing 50 to 60 g is added to 250 to 300 mL of saline solution, respectively. It is suspended using a blender, or manually through stirring or shaking. The most desirable diluent is a saline solution, although others, like water and milk, have been successfully used [44]. Once the suspension has been achieved with the diluent, the mixture is filtered through a coffee filter or gauze pad, or strained through a kitchen-type steel strainer to remove larger particulate matter that may obstruct the nasoenteric tube or endoscope. Then the suspension is drawn up into 60 mL syringes; upper tract FMT requires between 60 and 75 mL, and colonic FMT uses about 300 mL. The finished stool mixture should be used immediately. Only one, multicentre long-term follow-up study has been conducted, in which 97% of the patients with RCDI who received FMT would undergo FMT again if necessary, and 53% of patients reported that they would choose FMT before choosing an antibiotic treatment [27]. To assess safety we need to cite the same study. The 77 patients who had undergone FMT were followed for 3 months, and in 4 of the patients an autoimmune disease (rheumatoid arthritis, Sjögren syndrome, idiopathic thrombocytopenic purpura, and peripheral neuropathy) developed after some time following the FMT. Although transitory GI symptoms or a disruption

in bowel habits is not unusual in patients directly following an FMT, a correlation has not been found between the new autoimmune diseases and FMT [27].

Microbiota transplantation due to high therapeutic potential is listed in the top 10 medical innovations for 2014. As we know more and more about our microbiome and its link with the homeostasis of a body it seems that much attention should be paid to the FMT issue. It is also supported by the fact that intestinal dysbiosis is a risk factor for several diseases. Well-documented positive results for the treatment of RCDI suggest that FMT may play a role in treating a variety of other GI and non-GI diseases wherein altered gut microbiota is observed. Nevertheless, well-designed randomized controlled trials are required to validate the FMT protocol, including investigating the optimal route of administration, amount of suspension, frequency, and to determine the safety and long-term efficacy of FMT. It should be emphasized that the easiest therapeutic methods (e.g. FMT) are often the best.

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