
Fecal Microbiota Transplantation: Modulation of Metabolic and Inflammatory Intestinal Diseases

Transplante de Microbiota Fecal: Modulação de Doenças Metabólicas e Inflamatórias Intestinais

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ABSTRACT

Therapeutic properties of fermented feces for the treatment of common diseases, such as diarrhea, have been exploited for a long time. Recent studies have revealed that the benefit comes from the intestinal microbiota, which acts as a new metabolic and inflammatory modulating organ, showing favorable potential when well-regulated and unfavorable in the presence of dysbiosis. This review aims to evaluate the therapeutic modulation of this flora in endocrine and intestinal inflammatory diseases through transplantation. The study used PubMed, Cochrane, and Google Scholar as databases, without language restrictions, from 1989 onwards due to their historical relevance up to works from 2023. The descriptors used were "fecal microbiota transplantation," "metabolic diseases," "endocrine diseases" and "intestinal inflammatory diseases." It is observed that there is therapeutic benefit in regulating the microbiome of patients with obesity, metabolic syndrome, or intestinal inflammatory diseases, although the techniques for improvement are still under study. It is important that new studies be conducted to refine this process, as it shows great promise in modulating the enteroendocrine and inflammatory axes.

Keywords: Intestinal microbiota; Fecal transplant; Inflammation; Metabolism.

RESUMO

As propriedades terapêuticas das fezes fermentadas para o tratamento de doenças, como a diarreia, são exploradas há muito tempo. Estudos mais recentes revelam que o benefício é proveniente da microbiota intestinal, que atua como um novo órgão modulador metabólico e inflamatório, apresentando-se favorável quando bem regulado e desfavorável na presença da disbiose. Esta revisão tem como objetivo avaliar a modulação terapêutica desta flora em doenças endócrinas e inflamatórias intestinais por meio do transplante de microbiota fecal. O estudo utilizou como bases de dados PubMed, Cochrane e Google Scholar, sem restrições de idioma, a partir de 1989 devido à sua relevância histórica até trabalhos de 2023. Os descritores utilizados foram "transplante de microbiota fecal", "doenças metabólicas", "doenças endócrinas" e "doenças inflamatórias intestinais". Observa-se que há benefício terapêutico na regulação do microbioma de pacientes com obesidade, síndrome metabólica e doenças inflamatórias intestinais, embora as técnicas para melhora ainda estejam em estudo. É importante que novos estudos sejam realizados para refinar esse processo, já que se revela promissor na modulação dos eixos enteroendócrino e inflamatório.

Palavras-chave: Microbiota intestinal; Transplante fecal; Inflamação; Metabolismo.

INTRODUCTION

The microbiota has been extensively studied due to its potential role in modulating inflammation and metabolism in humans, and it can even be considered a new organ due to its important genetic information, mainly located in the gastrointestinal tract (BOKOLIYA et al., 2021; CHENG; FISCHER, 2023). The Human Microbiome Project has accumulated data on humans and mice, suggesting that dysbiosis, an imbalance in this system, is directly associated with the progression of inflammatory bowel diseases as well as autoimmune, neurological, and metabolic diseases (THE HUMAN MICROBIOME PROJECT CONSORTIUM, 2012).

Chronic dysbiosis is related to an increased expression of pro-inflammatory mediators, a characteristic of numerous chronic inflammatory diseases (WANG et al., 2022). It is worth noting that organs have an endocrine function in the production of organokines, molecules that mainly modulate inflammation and oxidative stress in the body. It is already known that they can be produced, especially by muscle, adipose tissue, bone, and liver (MINNITI et al., 2022). However, with the expansion of studies on these mediators, it has been discovered that the intestinal microbiota has the ability to release these compounds, which can recruit macrophages and trigger the inflammatory cascade (WANG et al., 2022).

Thus, the search for interventions targeting this intestinal community began. The use of probiotics and prebiotics has been studied and recommended, as well as medicinal plants with modulating capacity in inflammatory bowel diseases (IBD), but a need for different approaches has emerged (SIMON et al., 2021; LAURINDO et al., 2023). Therefore, fecal microbiota transplantation (FMT) has been under constant research, showing great potential in the future therapy of these chronic inflammatory pathologies (ZHENG et al., 2022).

This practice has its origins dating back over 3,000 years in India, with the preparation of cow dung for the treatment of diarrhea (ZHENG et al., 2022). In China, over 1,700 years ago, ancestors prepared the so-called "yellow soup," a broth made from dried and fermented feces of healthy individuals for patients with diarrhea, typically of infectious origin (ZHANG et al., 2012). Over time, there was the first report in the mid-1980s of a technique that predates Fecal Microbiota Transplantation (FMT) in a 45-year-old man with refractory ulcerative colitis, who showed improvement in his condition (BORODY et al., 1989).

Currently, the techniques have been refined. Donor patients undergo selection and preparation with an anti-inflammatory diet, and there is compatibility analysis with the recipient. The collected material is prepared for transplantation, a process that will be further explored in this article (WANG et al., 2019).

Given the aforementioned, as this ecosystem may have significant therapeutic potential, this study aims to explore fecal microbiota transplantation as a possible metabolic and inflammatory modulator in humans.

METHODOLOGY

This article presents bibliographic research on the impact of fecal microbiota transplantation on metabolic and inflammatory diseases.

The databases used were PubMed, Cochrane, and Google Scholar, with the following keywords: "fecal microbiota transplantation," "inflammatory bowel diseases," "ulcerative colitis," "Crohn's disease," and "metabolic diseases." Articles were selected without language restrictions from the period of 2010 to 2023, with only two articles from 1989 and 2001 included due to their relevance to the objective of this study.

DISCUSSION

FECAL MICROBIOTA TRANSPLANTATION TECHNIQUES

As seen previously, the use of feces for the treatment of certain diseases has been present since ancient times. With the need for improvement, studies have been conducted to refine the technique (CHANG; FISCHER, 2023).

There are various indications and contraindications for performing the procedure. Some of these include refractory *Clostridium difficile* infection, gastrointestinal diseases (such as Crohn's disease, ulcerative colitis, and irritable bowel syndrome), extraintestinal diseases (such as type 2 diabetes mellitus, metabolic syndrome, fatty liver, and obesity), as well as autoimmune and neurological disorders (MCCLAVE *et al.*, 2018; WANG *et al.*, 2019). Adverse effects may occur following FMT, including abdominal discomfort, nausea, vomiting, diarrhea, constipation, transient fever, and even more serious complications such as bacterial translocation and surgical perforation. Hence, there are challenges to be addressed and improved upon, considering that the technique can provide numerous benefits (WANG *et al.*, 2019).

Furthermore, some consensus statements indicate that when FMT is performed between close relatives, there is a higher chance of better adaptation and positive responses due to adaptive immunity in the intestinal mucosa. Donors should be between 18 and 65 years old, with no history of inflammatory bowel diseases and no use of medications that could interfere with the microbiota, such as antibiotics and probiotics, in the preceding 3 months before the procedure. They should also be proven to be free from communicable diseases. Therefore, tests should be conducted to exclude infections, as well as stool tests (WANG *et al.*, 2019; VINDIGNI *et al.*, 2017; BOKOLIYA *et al.*, 2021). "However, the process can be performed autologously for research purposes,

involving anti-inflammatory diets, collection of materials, and preparation (RINOTT *et al.*, 2021; CRAVEN *et al.*, 2020)

The FMT technique begins with the preparation of feces, which must be handled within 6 hours to avoid contamination. Approximately 50g of the material is processed with sodium chloride, and the mixture is filtered to eliminate larger particles. After this process, the filtrate is infused into 60ml syringes, and around 5 tubes of the material are inserted into the recipient's gastrointestinal tract. It is important that the recipient has been prepared to ensure better graft adherence, similar to preparations for endoscopic procedures, and is free of fecal materials that could interfere with the process (BLACKBURN *et al.*, 2015; WANG *et al.*, 2019; BOKOLIYA *et al.*, 2021).

Another possibility is the preparation of capsules for oral administration, which can also be composed of autologous or allogeneic microbiota, obtained through preparatory diets to obtain the raw material for the process (RINOTT *et al.*, 2021).

METABOLIC ASPECTS OF THE MICROBIOTA

The term "syndrome" refers to a set of signs and symptoms capable of characterizing a pathological process (LEE, 2022). Under this perspective, the term "metabolic syndrome" represents a multifactorial condition according to the guidelines of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), including central obesity, hypertension, altered glucose levels, triglycerides, and HDL cholesterol. At least three of these criteria must be present to characterize the syndrome (EXPERT PANEL ON DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD CHOLESTEROL IN ADULTS, 2001).

Obesity and type 2 diabetes mellitus (T2DM) are consistently associated with metabolic syndrome, and there has been an increasing prevalence of these diseases worldwide (LEE, 2022). In 2015, a global data collection on obesity revealed that there were a total of 604 million obese adults and 108 million obese children in 195 countries (SAKLAYEN, 2018). According to the International Diabetes Federation (IDF), there were over 415 million people with diabetes worldwide, and it is expected that this number will increase by approximately 50% by 2040, reaching a total of 642 million individuals (UNNIKRISHNAN *et al.*, 2017). In Brazil, the prevalence of obesity increased from 11.8% in 2006 to 18.9% in 2016, affecting almost one in every five Brazilians. The

medical diagnosis of diabetes increased from 5.5% in 2006 to 8.9% in 2016 (“VIGITEL BRASIL”, 2016).

Changes in the composition of the intestinal microbiota have been frequently associated with various aspects of metabolic syndrome (BAPTISTA et al., 2018; CARRILHO et al., 2018; WANG et al., 2022). This disorder can involve cases of hyperglycemia, as some bacteria in the intestinal microbiota are responsible for butyrate production. A reduction in the number of these microorganisms results in a decrease in butyrate production, which, through a complex process, leads to decreased glucose absorption by the tissues (LIANG et al., 2022; CUI et al., 2022).

A double-blind study involving 61 obese individuals with T2DM revealed that repeated FMT improved graft duration. Combining FMT with lifestyle changes created a favorable environment in the recipients' microbiota, leading to improvements in lipid profiles and liver diseases such as stiffness and steatosis (NG et al., 2021). Additionally, a review found that recipients of FMT with metabolic syndrome experienced increased insulin sensitivity and enhanced production of butyric acid by the gut microbiota (ILLIANO et al., 2020).

In a randomized study, obese patients were exposed to oral FMT, which demonstrated safety and efficacy with just a single dose for patients with severe obesity and metabolic syndrome. It was also observed that those who received fiber supplementation after FMT showed improved insulin sensitivity and better regulation of the enteroendocrine axis (MOCANU et al., 2021).

With emerging studies on metabolic modulation through the gut microbiome, it is evident that FMT holds therapeutic potential for patients with metabolic disorders.

MODULATION OF INFLAMMATORY BOWEL DISEASE

IBD is a condition characterized by chronic inflammation of the gastrointestinal tract. Its main features include abdominal colic, diarrhea or even dysentery, weight loss, vomiting, and fever. Additionally, complications outside the gastrointestinal tract, such as skin rashes, arthritis, and eye inflammation, can occur (FRANCO; MARQUES; GOMES, 2023).

Generally, IBD is divided into two main conditions: Crohn's disease (CD) and ulcerative colitis (UC). UC is characterized by inflammation limited to the rectum and colon, with mucosal inflammation causing symptoms such as edema, ulcers, bleeding,

and electrolyte loss. On the other hand, CD can affect any part of the gastrointestinal tract, presenting either continuous or non-continuous lesions (CONSENSUS GUIDELINES FOR MANAGEMENT OF INFLAMMATORY BOWEL DISEASE, 2010). CD involves inflammation that can lead to steatosis, fistulas, and affect all layers of the intestine due to its transmural nature, resulting in a cobblestone appearance in the mucosa during the later phase of the disease, frequently occurring in the terminal ileum region (MCDOWELL; FAROOQ; HASEEB, 2021).

Several factors associated with the etiology of IBD are mentioned, including genetic susceptibility, environmental factors, intestinal microbiota, and immune factors. It is believed that the combination of these components is responsible for its pathogenesis (ZHANG, 2014; LAURINDO et al., 2023).

As reported, the microbiota physiologically acts as an inflammatory mediator and can undergo alterations in conditions such as IBD, both in inflamed and healthy areas of the intestine. Furthermore, in such conditions, there is a reduction in the biodiversity of the gastrointestinal microbiome, directly affecting the symptoms experienced by individuals by leading to dysbiosis (JOOSSENS et al., 2011; WANG et al., 2022).

This dysregulation can have different outcomes. Patients with CD exhibit an increase in bacteria such as *Enterobacteriaceae*, *Pasteurellaceae*, *Veillonellaceae*, and *Fusobacteriaceae*, and a decrease in *Erysipelotrichales*, *Bacteroidales*, and *Clostridiales*, disrupting normal intestinal functioning (GEVERS et al., 2014). Sokol et al. (SOKOL et al., 2008) demonstrated a decrease in the bacterium *Faecalibacterium prausnitzii* in CD, which possesses anti-inflammatory effects by blocking factors involved in the inflammatory response, such as Nuclear Factor Kappa B (NF-Kb), and the secretion of Interleukin-8 (IL-8).

In UC, bacteria that produce hydrogen sulfide, toxic to the intestinal mucosa, contribute to inflammation. Additionally, there is lower colonization of *Bacteroides*, *Escherichia*, *Eubacterium*, *Lactobacillus*, *Ruminococcus*, and *Faecalibacterium prausnitzii*, which can help regulate an anti-inflammatory environment (Matsuoka and Kanai 2014). Moreover, the resident intestinal microbiota itself can promote pathogenic responses, such as *E. coli* and *Enterococcus faecalis*, which, after undergoing physiological changes in IBD, can invade the mucosa and interact with macrophages, activating a pro-inflammatory cytokine response (SARTOR; WU, 2017).

In a study, patients with IBD received FMT for 8 weeks, and after the treatment period, 83% showed improvement in disease activity, with the majority testing negative for *C. difficile* toxin (IANIRO et al., 2021). In a randomized trial involving UC patients who received FMT, significant disease remission was observed when combined with an anti-inflammatory diet (KEDIA et al., 2022). Xiang et al. (XIANG et al., 2020) analyzed DC patients who received FMT and also reported improvements in symptoms such as abdominal pain, diarrhea, and fever. Another study showed positive results for FMT in CD, utilizing two methods for the procedure, gastroscopy and colonoscopy. Both methods showed similar efficacy and safety outcomes (YANG et al., 2019).

CONCLUSION

The intestinal microbiome acts as an independent organ, generating numerous repercussions for the human body, which can be either positive or negative. With its capacity for inflammatory and metabolic modulation, this ecosystem is being explored in various studies that demonstrate its potential role in the prognosis and treatment of IBD and endocrine disorders, either as a possible adjunct or even a protagonist. Therefore, it is crucial to conduct more studies on this topic, with a thorough analysis of the FMT process and an improvement in the technique. This can lead to a significant change in the inflammatory landscape of these patients or even in other diseases.

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