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EXPLORING THE MICROBIOTA-INTESTINE-BRAIN AXIS IN PARKINSON'S DISEASE AND THE POTENTIAL OF FECAL MICROBIOTA TRANSPLANTATION (FMT) THERAPY

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Abstract: Objective: To evaluate the relationship between the gut microbiota and the progression of Parkinson's Disease, focusing on the potential improvements provided by TMF, as well as discussing the applicability of this approach as a therapeutic intervention for PD patients. **Methodology:** Narrative bibliographic review, developed according to the criteria of the PVO strategy. The searches were carried out in the PubMed database. The search terms included "Parkinson's disease", "Fecal microbiota transplant" and their combinations. A total of 17 articles published between 2019 and 2024 were selected for detailed analysis. **Discussion:** In PD, BMT can reduce the activation of microglia and astrocytes, as well as decrease the levels of pro-inflammatory cytokines such as TNF-α and IL-6, preserving dopaminergic neurons and improving motor deficits. In addition, TMF also interferes with pathological mechanisms, such as the aggregation of α-synuclein (αSyn), potentially interrupting the action of endotoxin-producing gram-negative bacteria. This modulation, in turn, reduces the production of bacterial enzymes that degrade levodopa, increasing its bioavailability and efficacy. Therefore, this interaction reinforces the potential of TMF as an adjunct in the management of PD. **Final considerations:** Beneficial changes in the microbiota include an increase in anti-inflammatory taxa, such as *Faecalibacterium* and *Bifidobacterium*, and a reduction in pathogens, such as *Escherichia-Shigella* , resulting in improvements in motor and non-motor symptoms, such as constipation and depression. Despite the advances provided by TMF, future studies should include rigorously controlled clinical trials, with randomization and standardization, to validate its efficacy and safety, as well as elucidating the mechanisms of interaction between bacterial metabolites and neuroinflammation.

Keywords: Parkinson's Disease, Intestinal Microbiota, Fecal Microbiota Transplant.

INTRODUCTION

Parkinson's Disease (PD), one of today's most prevalent and progressive neurodegenerative disorders, is mainly characterized by the loss of dopaminergic neurons in the nigrostriatal pathways, which results in significant challenges in the clinical management and quality of life of patients. This condition contributes considerably to the global burden of mortality and morbidity, generating important implications for medical and social care. Although it was developed from a neurological perspective, PD has robust connections with the gastrointestinal (GI) system, which plays a crucial role in its pathogenesis. Evidence suggests that dysfunctions in the GI tract can serve as an entry route for pathogens that spread to the central nervous system (CNS). In this context, the brain-intestine axis emerges as an essential modulator of neurobiological processes, mediated by bidirectional communications involving the vagus nerve and humoral mechanisms, consolidating its relevance in the course of PD (Kang *et al.,* 2021; Rahul *et al.,* 2021).

In recent years, the role of the gut microbiota in the pathogenesis of PD and other intestinal and extraintestinal conditions has received increasing attention. It is believed that modulating the microbiota could open up new therapeutic possibilities (Wanyi *et al.,* 2024). Among the emerging approaches, fecal microbiota transplantation (FMT) has emerged as a promising strategy. This technique consists of administering fecal material from a donor into the intestinal tract of a recipient, via routes such as nasogastric tube, oral capsules or colonoscopy. Studies indicate that TMF has significant therapeutic potential, particularly given the high prevalence of gastrointestinal symptoms associated with PD (Kang *et al.,* 2021).

Currently, treatment options for PD focus mainly on pharmacotherapy based on doses of dopamine. These interventions often result in complications such as tremors, dyskinesia and psychosis. In addition, they show resistance to dopamine over time, which reduces their effectiveness and limits management possibilities. These therapies also have no significant impact on the progression of the disease, highlighting the need for innovative strategies. In this context, TMF has emerged as an alternative with the potential to revolutionize the treatment of PD, offering an approach that transcends the limits of conventional dopaminotherapy (Matheson *et al.,* 2023; Rahul *et al.,* 2021).

However, despite the encouraging prospects of interventions such as diet, probiotics and fecal microbiota transplantation, relevant gaps remain in the understanding of the underlying mechanisms, especially with regard to the interaction between bacterial metabolites and neuroinflammation (Jia *et al.,* 2024; Czarnik *et al.,* 2024). In addition, controversies about the long-term efficacy and safety of these approaches have yet to be resolved. Thus, this study aims to evaluate the relationship between the gut microbiota and the progression of Parkinson's Disease, focusing on the potential improvements provided by fecal microbiota transplantation, as well as discussing the applicability of this approach as a therapeutic intervention for PD patients.

METHODOLOGY

This is a narrative literature review developed according to the criteria of the PVO strategy, which stands for: population or research problem, variables and outcome. This strategy was used to develop the guiding question: "How can fecal microbiota transplantation influence the progression and symptoms of Parkinson's Disease, considering the impact on the microbiota-intestine-brain axis?". The searches were carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases. The sear-

ch terms were used in combination with the Boolean operators "AND" and "OR", using the following search strategy: ((Parkinson's disease) OR (PD)) AND ((Fecal microbiota transplant) OR (FMT)). From this search, 1668 articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles published between 2019 and 2024 and which addressed the themes proposed for this research, such as review-type studies, meta-analysis, observational studies, experimental studies and clinical trials. The exclusion criteria were: duplicate articles, articles available in abstract form, articles that did not directly address the proposal studied and articles that did not meet the other inclusion criteria. After applying the inclusion and exclusion criteria, 17 articles were selected from the PubMed database to make up the collection of this study.

DISCUSSION

The microbiota-gut-brain axis is a bidirectional communication pathway that connects the Central Nervous System (CNS) to the Enteric Nervous System (ENS), regulating neuronal, hormonal and immunological interactions. The modulation of this axis by the gut microbiome influences crucial processes such as digestion, metabolism and immune regulation. Changes in the composition of the microbiota, caused by diet, genetics and environmental exposures, can compromise intestinal integrity, leading to inflammatory conditions such as irritable bowel syndrome (IBS) and inflammatory bowel diseases, and predisposing to the development of neurological diseases (Hang *et al.,* 2022).

In Parkinson's disease (PD), evidence associates intestinal dysbiosis with increased intestinal permeability, favoring bacterial translocation and triggering systemic inflammation. This process results in oxidative stress in the ENS and the accumulation of alpha-synuclein (αSyn), a protein associated with the pathogenesis of PD. Studies indicate that αSyn can be transported from the intestine to the CNS via the vagus nerve, contributing to the progression of neurodegeneration (Chui *et al.,* 2024; Yang *et al.,* 2024). The more pro-inflammatory composition of the microbiota of PD patients reinforces its role in symptom severity (Yang *et al.,* 2024).

However, gaps persist in the understanding of the microbiota-gut-brain axis, hindering more effective therapeutic interventions. The absence of longitudinal studies limits the identification of causal relationships between dysbiosis and PD, while the heterogeneity of disease subtypes, such as "gut first" and "brain first", points to the need for personalized approaches (Xue *et al.*, 2020). In addition, the precise mechanisms of αSyn transport and the interaction between neurotransmitters and the microbiome are still poorly understood (Vendrik *et al.,* 2023).

Recent research explores the potential of fecal microbiota transplantation (FMT) as a therapy to restore intestinal homeostasis in PD. Originally tested for Clostridium difficile infections, TMF has also shown efficacy in inflammatory bowel diseases and chronic constipation. In PD, preclinical studies show that TMF can reduce the activation of microglia and astrocytes, as well as decreasing levels of pro-inflammatory cytokines such as TNF-α and IL-6, preserving dopaminergic neurons and improving motor deficits (Chan *et al.*, 2022).

TMF also interferes with pathological mechanisms such as αSyn aggregation, potentially interrupting the action of endotoxin-producing gram-negative bacteria. Beneficial changes in the microbiota include an increase in anti-inflammatory taxa, such as *Faecalibacterium* and *Bifidobacterium*, and a reduction in pathogens, such as *Escherichia-Shigella*, or that improve motor and non-motor symptoms, such as constipation and depression (Fang *et al.,* 2024).

Despite the progress made, the application of FMT still faces challenges in clinical practice. Methodological heterogeneity in the studies, the absence of rigorous controls and the lack of standardization in the protocols make it difficult to draw definitive conclusions. In addition, the long-term effects on the microbiota and the progression of PD remain uncertain, requiring studies of a larger scale and duration (Mao *et al.*, 2023).

Another relevant aspect is the impact of TMF on the efficacy of drugs such as Levodopa. Modulation of the microbiota reduces the production of bacterial enzymes that degrade the drug, increasing its bioavailability and efficacy (Vendrik *et al.,* 2020). This interaction reinforces the potential of TMF as an adjunct in the management of PD, integrating with neuroprotective approaches based on modulating the microbiota-intestine-brain axis (Kuai *et al.*, 2021).

Although current pharmacotherapy for PD is limited, TMF represents a promising strategy. Future studies should include rigorously controlled clinical trials, with randomization and standardization, to validate its efficacy and safety. In addition, it is essential to understand the mechanisms underlying the relationship between gut microbiota and neurodegeneration, as well as to identify strategies to ensure the durability of the effects of TMF and its applicability at different stages of PD (Lorente-Picón; Laguna, 2021; DuPont *et al.*, 2023).

FINAL CONSIDERATIONS

Therefore, PD still faces significant management challenges due to the limited efficacy and adverse effects of conventional therapies. In this context, TMF has emerged as a promising approach with the potential to improve motor and non-motor symptoms by restoring healthy gut microbiota and modulating the microbiota-gut-brain axis. Studies suggest that TMF can act as a neuroprotectant, positively influencing systemic inflammation and brain function, and has already demonstrated safety in conditions related to intestinal dysbiosis, such as *Clostridium difficile* infections. However, challenges remain, including the identification of the most specific bacterial strains, the methodological variability of the available studies and the need to understand the durability of the effects and the need for repeat treatments. Rigorous clinical trials, with randomization, use of placebo and standardization of protocols, are crucial to validate TMF as a safe and effective therapeutic intervention, allowing it to be used on a large scale for the treatment of PD.

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