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REVIEW ARTICLE

Efficacy and Safety of Fecal Microbiota Transplantation for Parkinson's Disease: A Systematic Review

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ABSTRACT

Background: Fecal microbiota transplantation (FMT) is a procedure that involves transferring fecal material from a healthy donor to a patient to restore intestinal balance. Gut dysbiosis in Parkinson's disease (PD) worsens motor and gastrointestinal symptoms. Studies suggest that FMT may alleviate these symptoms by improving gut health and reducing neuroinflammation. **Methods:** This review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane guidelines. A literature search was performed on Cochrane Library, PubMed, and Scopus databases. Articles were screened for inclusion using the Rayyan® platform, based on predefined eligibility criteria, with any conflicts resolved by consensus. **Results:** Out of 760 records, four studies met the inclusion criteria. FMT demonstrated variable outcomes, with symptom improvement ranging from 45% to 70% for gastrointestinal disturbances and motor function. Adverse events were minimal, primarily involving mild gastrointestinal discomfort. FMT was effective in restoring gut microbiome balance and reducing neuroinflammation. However, heterogeneity in patient populations, FMT protocols, and study designs complicated the standardization of outcomes. **Conclusion:** FMT offers a promising therapeutic approach for PD, particularly in improving gastrointestinal and motor symptoms. The variability in patient populations, FMT protocols, and study designs highlights the need for standardized methodologies and more extensive clinical trials. Optimizing FMT administration and exploring its role as an adjunctive treatment alongside conventional therapies could enhance patient outcomes and provide an innovative strategy for managing PD.

Descriptors: Neurology; Fecal Microbiota Transplantation; Parkinson's Disease; Cognition; Evidence-Based Medicine.

Eficácia e Segurança do Transplante de Microbiota Fecal para a Doença de Parkinson: Uma Revisão Sistemática

RESUMO

Contexto: O transplante de microbiota fecal (TMF) é um procedimento que envolve a transferência de material fecal de um doador saudável para um paciente, com o objetivo de restaurar o equilíbrio intestinal. A disbiose intestinal na doença de Parkinson (DP) agrava os sintomas motores e gastrointestinais. Estudos sugerem que o TMF pode aliviar esses sintomas, melhorando a saúde intestinal e reduzindo a neuroinflamação. **Métodos:** Esta revisão seguiu as diretrizes PRISMA e Cochrane. Uma busca bibliográfica foi realizada nas bases de dados Cochrane Library, PubMed e Scopus. Os artigos foram selecionados para inclusão usando a plataforma Rayyan®, com base em critérios de elegibilidade predefinidos, com quaisquer conflitos resolvidos por consenso. **Resultados:** De 760 registros, quatro estudos preencheram os critérios de inclusão. O TMF demonstrou desfechos variáveis, com melhora dos sintomas variando de 45% a 70% para distúrbios gastrointestinais e função motora. Os eventos adversos foram mínimos, envolvendo principalmente desconforto gastrointestinal leve. O TMF foi eficaz na restauração do equilíbrio da microbiota intestinal e na redução da neuroinflamação. No entanto, a heterogeneidade nas populações de pacientes, nos protocolos de TMF e nos desenhos de estudo complicaram a padronização dos desfechos. **Conclusão:** O TMF oferece uma abordagem terapêutica promissora para a DP, particularmente na melhora dos sintomas gastrointestinais e motores. A variabilidade nas populações de pacientes, nos protocolos de TMF e nos desenhos de estudo destacam a necessidade de metodologias padronizadas e de ensaios

clínicos mais abrangentes. Otimizar a administração do TMF e explorar seu papel como tratamento adjuvante às terapias convencionais podem melhorar os desfechos dos pacientes e fornecer uma estratégia inovadora para o manejo da DP.

Descritores: Neurologia; Transplante de Microbiota Fecal; Doença de Parkinson; Cognição; Medicina Baseada em Evidências.

INTRODUCTION

Fecal microbiota transplantation (FMT) has been considered a possible treatment alternative for Parkinson's disease (PD), which involves introducing processed fecal material from a healthy donor into the gastrointestinal tract of a recipient. This approach aims to restore the balance of the intestinal microbiota by reintroducing a new, diverse community with new commensal microorganisms, which may be insufficient or modified in the recipient.[1] Several studies suggest an important role of the intestinal flora in the pathophysiology of neurological disorders.[2]

Dysregulation of the intestinal microbiome has emerged as a significant factor in the pathophysiology of PD, a progressive neurodegenerative disease that predominantly affects older adults.[3] Recent studies have shown that the gut-brain axis plays a significant role in the development and progression of neurological diseases such as PD, suggesting that changes in the composition of the intestinal flora, such as dysbiosis, may influence motor and non-motor symptoms, which are commonly observed in these patients.[3,4] This imbalance can exacerbate symptoms of constipation and other gastrointestinal disorders.[3]

In addition, PD has a strong correlation with the aggregation of alpha-synuclein, a primary component of Lewy bodies.[2] This pathology extends beyond the central nervous system, impacting peripheral autonomic circuits, such as the enteric nervous system. In PD, Lewy pathology extends from the esophagus to the rectum, affecting the myenteric and submucosal plexuses.[5]

Research suggests that the enteric nervous system and the vagus nerve are involved early in the progression of PD, even before the onset of motor symptoms.[2] Because traditional therapeutic approaches have focused primarily on alleviating motor symptoms, emerging evidence pointing to the importance of gut health has prompted the exploration of alternative treatment strategies.[6]

Preclinical studies have demonstrated promising effects of FMT on PD symptoms in animals, including improvements in motor functions and, in addition, reduction of neuroinflammation.[3] However, despite these encouraging results, there is still a need for systematic clinical evaluations to infer the safety and efficacy of FMT in humans.[7]

This study aims to conduct a systematic review to evaluate the safety profile of FMT in patients diagnosed with PD and their clinical outcomes.

Through a rigorous evaluation, we aim to contribute valuable insights into the potential of FMT as an adjunctive treatment option in the management of the multifaceted symptoms of PD, especially in patients with early gastrointestinal disorders. Furthermore, the management of these symptoms may increase the efficacy of standard PD treatment.

METHODS

This systematic review was performed and reported following the recommendations of the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines.[8,9]

Eligibility criteria

This study included observational studies that evaluated the safety and efficacy of FMT in the treatment of PD. Studies were excluded if they met any of the following exclusion criteria: (1) did not include patients diagnosed with PD; (2) used treatment methods other than FMT or did not compare microbiota transplantation with no treatment or placebo; (3) were single-arm studies without a comparative group; or (4) were non-English publications, reviews, letters to the editor, or conference abstracts.

Research strategy and data extraction

A comprehensive search was conducted in the PubMed, Cochrane, and Scopus databases, using the PICO framework (P: patients with PD; I: FMT; C: placebo or no treatment; O: clinical outcomes and safety), from inception to September 2024 with the following research strategy: ("microbiota transplantation" OR "microbiota transplant" OR "fecal transplant" OR "fecal transplantation" OR "faecal microbiota" OR "faecal transplantation") AND ("Parkinson disease" OR "Parkinson's disease"). The references of all included studies were manually searched to find additional studies. Two authors (KAMM and MMC) independently screened and extracted the data based on predefined search criteria.

Endpoints

Efficacy outcomes included the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score, the Montreal Cognitive Assessment (MoCA) score, and changes in Levodopa Equivalent Daily Dose (LEDD) over the follow-up period. These measures were assessed at different time points across studies, ranging from 1 to 12 months, depending on the study design. Safety outcomes focused on the incidence of adverse events (AEs).

Selection

For the selection, the Rayyan® Platform (https://www.rayyan.ai/) was used. The results of the articles from the search strategies were added to the platform, and five contributors were invited to blindly select them by reading titles and abstracts. All reviewers were allowed to review for conflicts. After resolving the conflicts, the articles included blindly were read in full, and, subsequently, the final inclusion of the articles was carried out in October/2024.

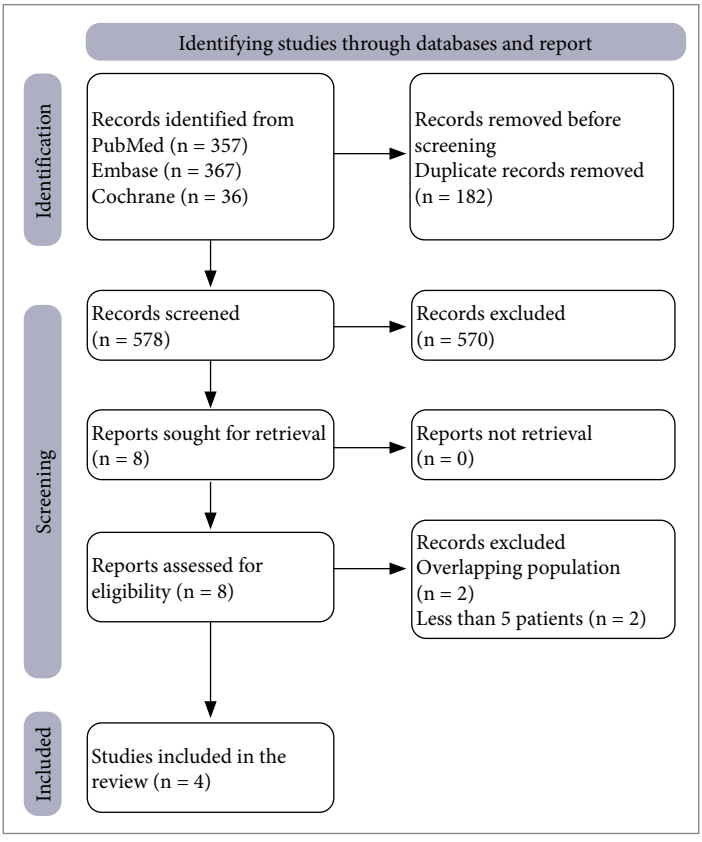
Quality assessment

Quality assessment of randomized controlled trials (RCTs) was performed using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).[10,11] In this tool, studies are scored as high, low, or unclear risk of bias in five domains: selection, performance, detection, attrition, and reporting biases. Two authors independently performed the quality assessment of the included studies (PSO and MOB), and any conflict was resolved by a third author (KAMM).

RESULTS

Study selection

A total of 760 records were identified from PubMed (n = 357), Scopus (n = 367), and Cochrane (n = 36). After removing 182 duplicates, 578 records remained for title and abstract screening. Among these, eight articles were selected for full-text evaluation. Reasons for exclusion included: studies with overlapping populations (n = 2) and studies with fewer than five patients (n = 2). Ultimately, four studies met our inclusion criteria and were included in the present analysis (Fig. 1).[3,6,7,12]



Source: Elaborated by the authors.

Figure 1. PRISMA flow diagram.

Baseline characteristics of the included studies and patients

Collectively, these studies involved 84 patients with PD undergoing FMT, with follow-up durations ranging from 3 to 12 months. The studies included one pilot study and three randomized, placebo-controlled trials.[3,6,7,12] Details and main features outlined by the studies are represented in Tables 1 and 2.

Table 1. Summary of the baseline characteristics of the included studies.

Study	Design	Country	Follow up (months)	Number of patients	Age (years)	Male/female	PD disease duration (years)
Cheng et al.[3]	Randomized, single-blinded, placebo-controlled trial	China	3	FMT, 27	Mean 60·52 (8·68)	15/12	Mean 6·74 (4·00)
				Placebo, 27	Mean 62·63 (8·41)	17/10	Mean 5·85 (4·35)
Bruggeman et al.[6]	Double-blind and placebo-controlled phase 2 trial	Belgium	12	FMT, 22	Mean 61 (1.1)	15/7	Mean 4.2 (0.7)
				Placebo, 24	Mean 60.5 (0.7)	14/10	Mean 4.4 (0.7)
				Placebo, 4	Median 68 (56–74)	4/0	Median 3 (2–10)
Scheperjans et al.[7]	Double-blind and placebo-controlled trial	Finland	12	FMT, 30	Median 66 (59.25-69.75)	16/14	Median 5.91 (3.86–7.57)
				Placebo, 15	Median 65 (52.5-70)	9/6	Median 6.96 (2.5–8.78)
Dupont et al.[12]	Double-blind placebo-controlled pilot study	United States	1, 3, 4, e 9	FMT, 8	Median 68.5 (61–75)	5/3	Median 2 (1–3)
				Placebo, 4	Median 68 (56–74)	4/0	Median 3 (2–10)

Source: Elaborated by the authors.

Table 2. Main outcomes and AEs of the included studies.

Study	MDS-UPDRS (baseline)	LEDD (baseline)	MoCA score (baseline)	Intervention	MDS-UPDRS total (outcome)	LEED (outcome)	MoCA (outcome)	AEs
Cheng et al.[3]	FMT 1, 11·11 (4·42) 2, 12·04 (4·78) 3, 24·74 (10·58) 4, 3·44 (3·26) Total, 51·33 (16·92)	NR	19.41 (5.23)	16 FMT capsules orally once a week for 3 consecutive weeks	1, 43.33 (16.49) 2, 42.85 (15.93) 3, 41.93 (19.44)	NR	1, 21.22 (4.85) 2, 22.74 (4.83) 3, 23.3 (4.37)	Patients with any AE, 3, flatulence, 1, nausea, 1, diarrhea, 1
	Placebo 1, 12·11 (4·89) 2,14·74 (4·89) 3, 29·59 (13·07) 4,3·70 (3·20) Total, 60·15 (17·74)	NR	19.30 (5.55)	Placebo	1, 55.52 (19.16) 2, 53.26 (17.84) 3, 57.3 (15.27)	NR	1, 21.11 (4.5) 2, 21.22 (4.8) 3, 20.93 (5.2)	Patients with any AE, 3, bloating, 1, flatulence, 2
Bruggeman et al.[6]	FMT 1, 11.0 (1.3) 2, 10.7 (1.3) 3, 40.3 (2.7) 4, 2.2 (0.6) Total, 63.9 (4.2)	383 (53)	27.6 (0.3)	Single FMT; nasojejunal route	3,62.7 (4.3) 6, 62.7 (4.4) 12, 60.1 (4.6)	3, 398.8 (57.2) 6, 399.5 (57.0) 12, 429.1 (59.0)	6, 28.4 (0.3) 12, 28.2 (0.2)	Abdominal cramps and nausea, 13

Continue...

Table 2. Continution...

Study	MDS-UPDRS (baseline)	LEDD (baseline)	MoCA score (baseline)	Intervention	MDS-UPDRS total (outcome)	LEED (outcome)	MoCA (outcome)	AEs
Bruggeman et al.[6]	Placebo 1, 10.6 (1.3) 2, 8.0 (1.2) 3, 37.1 (2.5) 4, 2.6 (0.5) Total, 58.2 (4.0)	431 (51)	28.2 (0.3)	Own stool	3, 53.3 (4.1) 6, 53.3 (4.1) 12, 51.2 (4.2)	3, 429.7 (54.7) 6, 442.1 (54.5) 12, 455.9 (56.5)	6, 28.7 (0.3) 12, 28.9 (0.2)	Abdominal cramps and nausea, 6
	Placebo 3. 26 (18–42) Total. 47 (26–69)	645 (400–792)	27.5 (26–29)	Placebo	NR	NR	NR	Patients with any AE, 4, abdominal pain/ cramps/discomfort, 1, worsening constipation, 2, diarrhea, 0, nausea, 0, melena, 0
Scheperjans et al.[7]	TMF 1. 9 (6–14) 2. 9 (7.25–15) 3 desligados. 29.5 (21.75-37.75) 3 ligados. 18.5 (13.75-23.75) 4.3 (0-5.75)	670 (405–1031.12)	26 (25-27)	Single-dose FMT via colonoscopy	NR	6, 33.34 (−23.54 to 90.21) 12, 87.63 (31.09 to 144.18)	6, 0.24 (−0.58 to 1.06) 12, 0.52 (−0.29 to 1.32)	Gl AEs, 16, new or worsening of depression, 3, new or worsening of dyskinesia, 1, new or worsening of OFF symptoms, 8, bone fractures, 1, AEs are probably or definitely related to the intervention, 12serious AEs, 3, total number of AEs, 105
	Placebo 1. 9 (7.5–10.5) 2. 10 (6.5–13.5) 3 off. 20 (18.5–31.5) 3 on. 14 (11.5–21.5) 4. 1 (0–3)	712 (400–946.74)	25 (23-28.5)	180 mL of sterile physiological Saline and 20 mL of 85% glycerol	NR	6, 164.28 (84.80 to 243.76) 12, 179.86 (100.84 to 258.89)	6, 1.40 (0.31 to 2.49) 12, 1.49 (0.39 to 2.58)	Gl AEs, 1, new or worsening of depression, 0, new or worsening of dyskinesia, 1, new or worsening of off symptoms, 6, bone fractures, 1, AEs probably or definitely related to intervention, 1, serious AEs, 0, total number of AEs, 50
Dupont et al.[12]	TMF 3. 16 (13–21) Total. 24 (19–32)	446 (114–900)	28 (28–30)	Oral capsules (60 g) of donor feces twice a week for 12 weeks (24 doses)	NR	NR	NR	Patients with any AE, 7, bloating/flatulence, 2, abdominal pain/ cramps/discomfort, 3, worsening constipation, 1, diarrhea, 2, nausea, 1, melena, 1
	Placebo 3. 26 (18–42) Total. 47 (26–69)	645 (400–792)	27.5 (26–29)	Placebo	NR	NR	NR	Patients with any AE, 4, abdominal pain/ cramps/discomfort,1, worsening constipation, 2, diarrhea, 0, nausea, 0, melena, 0

Source: Elaborated by the authors. NR = not related.

Participants

The four studies included patients with mild to moderate PD (Hoehn-Yahr stage 1 to 3). Regarding the mean disease duration, two studies used mean (SD), ranging from 4.2 (0.7) to 6.74 (4.00) in the FMT group and from 4.4 (0.7) to 5.85 (4.35) in the

placebo group.[3,6] The other two studies used median (interquartile range [IQR]), ranging from 2 (1–3) to 6.96 (2.5–8.78) in the FMT group and from 3 (2–10) to 5.91 (3.86–7.57) in the placebo group.[7,12]

Cheng et al.[3] included patients aged between 30 and 85 years, with a mean participant age of 61.57 years. DuPont et al.[12] included patients aged 55 to 80 years, with a median age of 68.5 and 68 in both groups. Bruggeman et al.[6] included patients with an age limit of 65 years and an age of motor symptom onset above 50 years, with a mean age of 61 (1.1) and 60.5 (0.7). Scheperjans et al.[7] specified age only by median (IQR), which was 65 (52.5–70) in the FMT group and 66 (59.25–69.75) in the placebo group.

Regarding constipation, each study defined it differently. Cheng et al.[3] reported that 85.19% of patients in the FMT group had constipation compared to 88.89% in the placebo group. Bruggeman et al.[6] defined constipation according to the Rome IV criteria, showing that 14 (63.3%) patients in the FMT group had constipation compared to 15 (62.5%) in the placebo group. Scheperjans et al.[7] used the Wexner constipation score and median (IQR) to define this complaint, reporting a score of 6 (4–9) in the FMT group and 7 (3.25–10.75) in the placebo group. Lastly, DuPont et al.[12] included only PD patients who reported constipation, characterized by a history of passing hard stools with difficulty and having a maximum of three bowel movements per week. All studies included both men and women. However, in all of them, male patients were predominant.[3,6,7,12]

Interventions

All groups compared FMT with a placebo. Scheperjans et al.[7] used sterile saline solution plus glycerol. DuPont[12] and Cheng[3] did not specify the placebo used. Bruggeman et al.[6] used placebo FMT (own stool).

Administration

FMT administration methods varied across the studies. Bruggeman et al.[6] employed a nasojejunal route for single-dose FMT, while Cheng et al.[3] and DuPont et al.[12] utilized oral capsules. The protocol in Cheng et al.[3] involved 16 capsules weekly for 3 weeks, while DuPont et al.[12] used donor feces capsules administered twice weekly. Scheperjans et al.[7] used rectal infusions of donor microbiota as the delivery method.

Dose and frequency

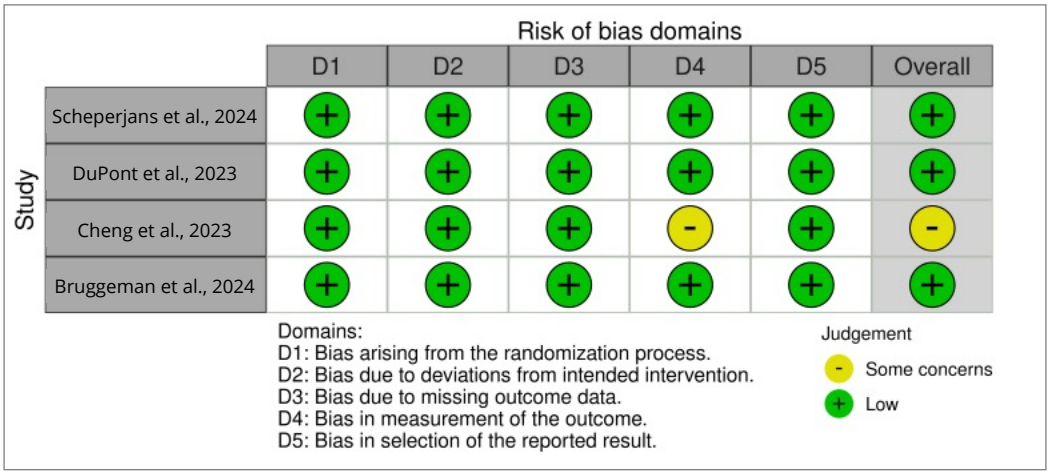
Scherperjans et al.[7] performed FMT, without prior antibiotic treatment, through a single dose by colonoscopy. DuPont et al.[12] administered 60 g of donor feces twice a week for 12 weeks (totaling 24 doses) in lyophilized capsules. In Cheng et al.,[3] 16 oral capsules of FMT or placebo were used, taken on an empty stomach for three consecutive weeks. Bruggeman et al.[6] performed the infusion of 200 mL of FMT solution, containing 50 g of fecal product, via a tube with placement guided by the Cortrak Enteral Access System.

AEs

The AEs reported in the analyzed studies were predominantly gastrointestinal and more frequent in the FMT groups compared to the placebo groups. Scheperjans et al.[7] recorded 50 AEs in the placebo group and 105 in the FMT group, the latter presenting considerably more frequent gastrointestinal symptoms (16 of 30 patients; 53%). Most events were mild or moderate in severity, with only one severe case of anxiety, which was deemed unlikely to be related to the intervention. DuPont et al.[12] reported that seven out of eight patients (88%) in the FMT group and four out of four patients (100%) in the placebo group experienced gastrointestinal symptoms, which were more common in the FMT group. All events were transient and classified as mild (47%) or moderate (38%), with no need to discontinue treatment. Cheng[3] reported a total of six AEs, three in the FMT group (diarrhea, flatulence, and nausea) and three in the placebo group (one bloating and two flatulence). Bruggeman et al.[6] had no severe AEs, but mild and transient gastrointestinal events occurred in 13 out of 22 patients (59%) in the healthy donor FMT group and in six out of 24 patients (25%) in the placebo group, mostly within the first week after treatment. None of the studies identified significant laboratory abnormalities related to treatment safety.

Risk of bias assessment

Studies were generally assessed as having a low risk of bias across most domains, except for the measurement of outcomes, which presented some concerns in one study due to methodological imprecision (Fig. 2).[3] This study was rated as having a moderate overall risk of bias. In contrast, three studies were consistently rated as having a low risk of bias across all evaluated domains, ensuring high reliability of their findings.[6,7,12]



Source: Elaborated by the authors.

Figure 2. Risk of bias assessment of the included studies. RoB2 assessment tool for randomized studies.

Potential bias/limitations

DuPont's et al.[12] study has several limitations, including a small sample size, a short treatment duration, and the absence of block randomization and subgroup allocation. Moreover, the lack of dietary control among participants may have affected the results. Although the authors did not consider the absence of a control group without PD a limitation, the assessment of patients in the "off" state could have been influenced by the duration of dopaminergic medication withdrawal.

In Cheng et al.,[3] the lack of blinding of the investigator and the small sample size may have influenced allocation biases; the differences in baseline MDS-UPDRS scores between groups suggest differences in disease severity; the 3-month follow-up period limits the assessment of long-term effects.

Sheperjans et al.[7] already presented a limited sample size, which resulted in reduced statistical power and a wide confidence interval. Additionally, adjustments to participants' medication to minimize dropouts may have affected the results. Furthermore, there is a possibility that the placebo procedure was not a true inert control, considering that important changes in the composition of the intestinal flora were observed in the placebo group.

In Bruggeman et al.,[6] the lack of criteria that prioritize patient inclusion, the application of a single dose, and the small sample size may have limited the analysis of non-motor symptoms.

Primary outcomes

Motor improvement

In the study by Bruggeman et al.,[6] there was a significant improvement in motor function in the FMT group, with a mean reduction of 5.8 points (95%CI −11.4 to −0.2) in the MDS-UPDRS motor score, without medication after 12 months, compared to the placebo group 2.7 points (95%CI −8.3 to 2.9) ($p = 0.0235$). Cheng et al.[3] had a significantly greater reduction in the MDS-UPDRS score in the FMT group at 12 weeks (group × time effect = -6.56; 95% CI −12.98 to −0.13; $p < 0.05$). DuPont et al.[12] observed motor improvement without medication in the FMT group with a 12.5% reduction. Scheperjans et al.[7] found no significant difference in MDS-UPDRS between groups at 6 months.

Secondary outcomes

Non-motor symptoms improvement

In Sheperjans et al.,[7] after 12 months, the score on the Non-Motor Symptom Scale increased significantly in the FMT group, and at 6 months, the time of the Timed Up and Go test (without medication) increased significantly in the same group. The daily dose of levodopa was higher in the placebo group. Cheng et al.[3] indicated that FMT therapy may improve cognition in PD patients, based on improvements in the MMSE and MoCA scales. According to Bruggeman et al.,6 no significant benefits of FMT were found in several parameters, including cognition.

Evaluation for gastrointestinal disorders

In Cheng et al.,[3] the improvement in gastrointestinal symptoms was observed in both groups, including improvement in constipation, reduction in abdominal pain and flatulence, and better quality of life. In Scheperjans et al.,[7] there was a significant increase in complete and spontaneous evacuations in the FMT group. DuPont et al.[12] identified a significant improvement in the

motility index with FMT treatment ($p = 0.0374$). However, Bruggeman et al.[6] found no significant differences between groups in the Wexner Constipation Scale scores.

Alterations in gut microbiota

Cheng et al.[3] identified significant differences in alpha and beta diversity between PD individuals and donors, with lower abundances of several bacterial genera in PD patients, but no significant microbial diversity changes after 3 weeks of intervention. Scheperjans et al.[7] showed a significant increase in beta diversity in the FMT group compared to placebo (0.36-0.43 vs. 0.26-0.32), with greater changes at 30 days. However, after 12 months, the difference between the groups was not significant. The long-term dysbiosis status was also analyzed in this study, with significant changes from dysbiotic to non-dysbiotic after FMT at 1 month in 24% of patients, decreasing to 3% at 12 months. In the placebo group, an increase from 13% to 33% at 12 months was observed. DuPont et al.[12] found beta diversity significantly differed between groups starting at week 6 ($p = 0.008$) and week 13 ($p = 0.0008$). Bruggeman et al.[6] did not specify gut microbiota alterations.

DISCUSSION

A prevalent symptom, often pre-motor, that is associated with rapid progression in PD is intestinal dysfunction.[7,13] Studies show that the intestinal microbiota influences PD symptoms and may be related to dopamine dysregulation.[14-17] Given this, interventions targeting intestinal microbiota, such as FMT, have been the subject of research, which are still limited, but have demonstrated important results in neuroprotection and symptom improvement.[7,13]

The study by DuPont et al.[12] demonstrated that PD patients in the FMT group had greater beta variation of the microbiome compared to placebo. Although the exact mechanisms by which this microbiota may improve PD remain unclear, the effects associated with FMT resulted in improved intestinal motility, protection and reduction of malodorous gas production, and pro-inflammatory reduction, suggesting potential benefits in several PD parameters.[12]

Chronic constipation is frequently associated with PD and has been linked to intestinal dysbiosis.[18,19] However, alterations in intestinal motility may also impact the microbiota.[20,21] Research indicates that FMT can mitigate intestinal dysbiosis by increasing the abundance of Firmicutes and Clostridiales, suggesting that a reduction in Firmicutes may contribute to constipation in PD.[22,23]

In this way, increased proportions of this phylum were identified in the study by DuPont et al.,[12] in patients treated with FMT compared to placebo, demonstrating its therapeutic potential by improving the motility index and intestinal transit time. Thus, it is suggested that the intestinal microbiome has a primary role related to constipation in PD. Kuai et al.[24] also obtained similar results with only one dose of FMT in the same context. In addition, there were also subjective improvements, evidenced by visual analog scales, reinforcing the need to evaluate non-motor symptoms in PD.[12,24]

Research also indicates that PD may favor Clostridiales contamination due to intestinal dyskinesia, and FMT may play an important role in its treatment.[25,26] Evaluating the presence of this bacterium when enrolling patients in the study is necessary because its presence can alter the results.[12]

The use of probiotics as a more conservative approach has also been explored to improve chronic constipation related to neurodegenerative diseases.[15] A meta-analysis by Xiang et al.[27] revealed that although probiotics enrich cognitive function in patients with Alzheimer's disease (AD), their benefits in PD are more closely related to gastrointestinal response. These effects, by reducing inflammation, may indirectly slow disease progression. However, FMT has demonstrated a mutual interaction in PD between gastrointestinal and neurological benefits, suggesting greater therapeutic potential.[27]

Hongliang et al.[16] demonstrated that FMT outperformed conventional treatments (behavioral modification, probiotics, laxatives, macrogol rescue therapy, and education) in individuals with slow transit constipation, although this did not include patients with PD.[16] On the other hand, Tamtaji et al.[28] compared probiotics to placebo in PD patients and identified a significant reduction ($p = 0.01$) in the MDS-UPDRS score, indicating positive effects of this therapy on clinical symptoms of the disease.[28] Direct comparative studies between FMT and probiotics are needed to determine which approach is more effective, but suggest that FMT may be as efficient as probiotics and could potentially offer additional advantages in managing neuromotor symptoms.[19]

Application of FMT is considerably invasive and expensive due to its methods, such as colonoscopy or endoscopy. Cheng et al.[3] present an innovative, safe, and economical option with oral capsules. They observed good efficacy in restoring intestinal microecology, tolerability, and improvement of gastrointestinal symptoms, cognitive function, and quality of life in PD patients, suggesting that the microbiota may also serve as a biomarker in estimating the response to FMT in PD.[3]

Bruggeman et al.[6] have explored nasojejunal administration. Although more invasive than oral capsules, it is an alternative for PD patients, and its application may also influence the composition of the small intestine microbiota compared to colonoscopy.[29,30] However, its complex technique demonstrates challenges, as observed in intolerance or failure by some study candidates.[6]

An important key highlighted in all studies was the use of FMT through donors, with selection criteria showing significant differences. Costello et al.,[31] who used FMT to treat ulcerative colitis, demonstrated that patients who received FMT from healthy donors had better results than those who received autologous transplants, highlighting the importance of taking care of the donor's microbiota in influencing the results.[31]

Bruggeman et al.[6] present a similar comparison using autologous FMT with greater gastrointestinal benefits at 6 months and motor benefits mainly after 12 months.[6] Holster et al.[32] observed that even autologous FMT associated with intestinal cleansing promoted relevant changes in the microbiota and mucosa in 2 to 8 weeks, suggesting that autologous transplants may not act as true pharmacological placebos.[32]

Sheperjans et al.[7] compared a single dose of colonic FMT with an anaerobic preparation, against a placebo solution containing saline and glycerol as a cryoprotectant. However, their results revealed an initial transient increase in β-diversity after FMT, indicating an immediate effect of the transplant, but this increase was not maintained after 12 months of follow-up, suggesting instability and continuity of the baseline microbiota. This initial improvement may be related to factors beyond changes in microbiota composition, such as host factors including diet, inflammation, and antibiotic therapy, as well as the protocol design, along with potential donor-dependent effects that may alter outcomes in the recipient group.

This study also observed a significant improvement in the placebo group compared to FMT, with fewer adverse effects, but still requiring higher doses of levodopa throughout the treatment.[7] This reinforces the importance of further exploring modified FMT approaches, along with study design, and the need for studies that correlate long-lasting engraftment with clinical benefit.

Dietary intake is an important determinant of the gut microbiota composition and can significantly influence the outcomes of FMT. Several PD trials did not control any pattern in participants' diets, introducing variability in the microbial response, affecting endpoints, and possibly being a confounding factor during studies. Trials noticed the absence of control in diets as a limitation and a potential concern in their repeat-dose pilot trial.[12] Similar concerns have been observed by methodological reviewers, considering nutritional components should be harmonized to reduce the confounding effects and improve the results when replicating tests in later interventions.[1,2]

Placebos are a key methodological challenge in FMT, considering the variation between studies: autologous stool,[6] sterile saline with glycerol,[7] unspecified oral capsules.[3,12] Evidence indicates that these placebo methods may induce microbiota shifts and unintended biological activity, reinforcing the necessity of a consensus on the most appropriate placebo formulation, to ensure reliable evaluation of therapeutic efficacy and control of FMT in Brazil.[27]

Donor selection in FMT is a crucial, but challenging determinant of its efficacy. Considering that all the international trials selected healthy patients as volunteers, the criteria were substantially different between them, ranging from simple health assessments to rigorous microbiota tests.[3,6,7,12] In general, the healthy donor microbiota should also be explored, considering that the presence of bacteria such as Clostridiales and Firmicutes can influence the outcomes.

A study showed that stool from healthy donors, when compared to autologous material, was not significantly superior in irritable bowel syndrome.[32] However, the fecal material was administered after bowel cleansing, which may have affected its results.[32] Brazilian studies emphasize the necessity of harmonized protocols to select donors in studies and in clinical practice, to ensure safety and minimize the heterogeneity across PD populations, suggesting rigorous clinical and laboratory criteria[26] and standardizing donor selection using a hospital stool bank.[25]

The preparation of the fecal material and its administration remain just as heterogeneous as the other aspects mentioned. International studies tested different approaches: oral capsules,[3] nasojejunal infusions,[6] and colonoscopy,[7] and each of the trials exhibited different levels of efficacy and tolerability, further challenging the creation of standards and protocols. In addition, other factors seemed to influence in sample quality, such as anaerobic versus aerobic processing, dose volume, cryoprotectant amounts, and none of these factors have been harmonized yet.

In Brazil, the treatment for patients with PD is limited to supportive therapies. Available medications in the Brazilian Unified Health System (Sistema Único de Saúde [SUS]) include levodopa, dopaminergic antagonists, and MAO-B and COMT inhibitors.[33] Non-pharmacological measures, including physical, speech, and occupational therapy, are also available to improve quality of life. However, these therapies are limited, and the wait times are long. For patients in advanced stages, deep brain stimulation may be an alternative, but it is limited due to its high cost and complexity.

In this context, FMT represents a cost-effective alternative for reducing disease symptoms, with less complexity, hospitalization, and prolonged use of medications, acting on underexplored targets of the gut-brain axis. However, its inclusion still depends on the consolidation of new studies and protocols that truly demonstrate its efficacy and safety. In Brazil, there is a lack of studies evaluating FMT for patients with PD. However, recent Brazilian studies have shown positive results from this therapy for patients with recurrent or refractory Clostridiodes difficile infection, which, as seen before, is indirectly correlated and may contribute to future research in this area in the country.[25,26]

Strengths and limitations

The greatest strength of this article is that it presents a robust methodology with recent articles in full, allowing a significant update on the subject and potential innovations in this line of treatment. Regarding limitations, the number of articles interferes with adequate quantification on the subject, as well as the quality of the studies with potential biases, as demonstrated in the results, which contributes to this assessment.

CONCLUSION

It is seen that FMT has potential to improve motor symptoms and quality of life of patients with PD, including gastrointestinal symptoms. However, further studies are needed to determine the ideal dosage, frequency, and route to address the symptomatic effects of the disease. In addition, it is important to define the criteria for selection and preparation of donors to allow a more accurate comparison between studies.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantial scientific and intellectual contributions to the study: Martins KAM, Faria IC. **Conception and design:** Martins KAM, Faria IC. **Data analysis and interpretation:** Martins KAM, Faria IC. **Writing of the article:** Martins KAM, Faria IC, Corcinio MM, Oliveira PS, Nogueira GF, Bittarães AJSO, Braga MO. **Final approval:** Martins KAM.

DATA AVAILABILITY STATEMENT

All data were analysed in the present article.

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