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Parkinson's Disease and the faecal microbiota transplantation. Review of current knowledge

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Abstract

Introduction and Purpose

Parkinson's Disease (PD) is a chronic neurodegenerative disorder caused by dopamine deficiency due to neuronal degeneration, leading to motor and non-motor symptoms. Gastrointestinal symptoms are common and often precede motor symptoms. There is increasing evidence that imbalanced gut microbiota may influence the gut-brain axis and contribute to

motor and non-motor PD symptoms. Fecal microbiota transplantation (FMT) may have the potential to restore gut flora and improve PD symptoms. The study aims to explore the current knowledge on the impact of FMT on PD symptoms, acknowledging existing reviews and highlighting new studies not yet reviewed. Understanding the underlying causes of PD could lead to better treatment, diagnostics, and prevention.

State of knowledge

PD patients suffer from specific gut dysbiosis which leads to imbalance in the produced pro- and anti-inflammatory substances in the intestinal lumen resulting in aggreviation of α-synuclein in gut nervous cells which may hypothetically transfer via vagal nerve to CNS causing PD. In animal research FMT showed promising results in alleviating PD symptoms. Case reports showed reduction of both motor and non-motor dysfunctions, especially in constipation. DuPont et al. showed improvements in constipation, motor deficits, overall Parkinson's symptoms, and some non-motor disorders. Cheng et al. showed improvements in MDS-UPDRS, scores of GI tract symptoms scales, PD-related autonomic symptoms and the stool frequency. Bruggeman et al. showed better MDS-UPDRS part 3 scores and better colon transit, but no significant differencies in any other tested domains.

Conclusions

As there is yet no standarized protocol for FMT, all of the past research used different techniques and showed slightly different outcomes, but all have shown that FMT have some positive effects on PD symptoms.

Keywords: Parkinson's disease, faecal microbiota transplantation (FMT), brain-gut axis.

Introduction

Parkinson's Disease is a chronic neurodegenerative disease leading to disability. The underlying mechanism of PD is dopamine deficiency due to neuronal degeneration in the pars compacta of substantia nigra and other neural structures with aggregation of α-synuclein in Lewy bodies or Lewy neurites. This leads to the development of the variety of symptoms of which most common and recognizable are motor disorders such as bradykinesia, rigidity, postural instability, gait unsteadiness or tremor. [1,2]. The PD also presents with non-motor symptoms such as fatigue, behavioral changes or autonomic dysfunction. Some aspects of autonomic dysfunction such as constipation may be present long time before motor dysfunctions [3,4]. Constipation is very common in Parkinson's patients [5]. About 80% of PD patients may struggle with gastrointestinal symptoms (GIS) [1]. The number of reports of the influence of gut microbiota on the gut-brain axis is growing [6-9]. This circumstance may be a reason of the GI symptoms in PD itself, however some report the potential role of spreading the α-synuclein from the gut to the brain leading also to the development of motor disorders in PD [10]. Given that FMT can restore a disrupted gut bacterial flora [22], hypotheses have emerged about whether it might bring improvement in the context of reports on the disrupted gut-brain axis in Parkinson's disease

Aim of the study

Parkinson's Disease (PD) is a serious neurological condition. Currently we do not obtain full knowledge of its etiology and pathophysiology. Lewodopa supplementation is still the main management in PD patients, which is a symptomatic treatment. Complete understanding of its underlying causes can lead to developing better treatment, diagnostics and prevention. Aim of this study is to show the actual knowledge about influence of the faecal microbiota transplantation (FMT) on symptoms of PD patients. There are already some reviews in this topic, however lately there were published some new studies not included in any past review.

State of knowledge

Gut-brain axis in Parkinson's Disease

There are reports of gut dysbiosis in PD patients presenting with increased number of bacteria producing pro-inflamatory substances and decreased number of bacteria producing anti-inflammatory substances leading to increased intestinal permeability [11]. Prevotellaceae are underrepresented, while there is an increased presence of Lactobacillaceae, Verrucomicrobiaceae, Bradyrhizobiaceae, and Clostridiales incertae sedis IV in individuals with Parkinson's disease. Furthermore, a higher abundance of Enterobacteriaceae correlates with more severe axial motor symptoms [12]. The low levels of Prevotellaceae are associated with increased gut permeability as those bacteria take part in production of mucin in mucosal layer. Prevotellaceae also produce short-chain fatty acids (SCFA) taking role in promoting anti-inflamatory cytokines, scarity of which may lead to inflammation in intestinal walls and promoting α-synuclein aggregation [13,14].

The aggregation of α-synuclein is proven to be present outside of the Central Nervous System (CNS) in myenteric and submucosal plexuses and in mucosal nerve fibres [14]. Number of aggregations descend from upper parts of GI tract to rectum, correlating with the vagal innervation [15]. This phenomenon causes the emerge of hypotheses about the probable trans-synaptic transmission of α-synuclein to the CNS through the neurons of vagal nerve, what was proven in studies on mice [16]. There are studies on the influence of vagotomy on risk of developing PD in which it was proven that vagotomy did not have protective effect on developing PD [17]. However, in some studies, there is a difference in risk of developing PD between patients with truncal and selective vagotomy [18]. The bacterial imbalance may also affect the absorption of lewodopa or lead to its degradation in the intestines resulting in worse effectiveness of lewodopa on PD symptoms [19,20]. This reports of the microbiota influence on gut-brain axis in PD patients have lead to tests on effectiveness of FMT in PD patients on the intensity of their symptoms.

Faecal Microbiota Transplantation in Parkinson's Disease

Fecal microbiota transplantation (FMT) is a procedure where intestinal microbiota from a healthy donor is transferred to a patient to establish or reestablish a stable microbiome in recepient's gut [21]. FMT is registered as safe and effective treatment of severe and recurrent

Clostridioides difficile infection (CDI) [22]. It has the ability to rebuild disrupted microbiota and restore its stability and physiological metabolic activity [23,24]. Although its registration as treatment only in CDI, there are reports of FMT influence on other diseases, including neurodegenerative disorders [25].

The predominant part of reports on FMT proficiency in PD treatment come from studies on mice and case reports. Mice research show improvements in motor functioning, increased striatal neurotransmitters, increased dopaminergic neurons, decreased intestinal inflammation, reduced neuroinflammation. [26-29].

The outcome of FMT treatment in humans was mostly measured by score change of Unified Parkinson's Disease Rating Scale (UPDRS III) in which the higher the score the worse, other symptom specific scores were also used. First case report on FMT in PD patients was described by Huang et al., 2019 resulting in significant reduce in legs tremor, although it came back in the right lower extremity at 2 months after FMT, but with less intensity. [30] Segal et al., 2021 conducted case series of 6 PD patients, FMT infused via colonoscopy, resulted in improvement of PD motor and non-motor symptoms, including constipation in 5 of 6 patients [31]. Kuai et al., 2021 tested 11 patients resulting in lowering UPDRS significantly. The PAC-QOL score and Wexner constipation score improved [32]. Xue et al., 2020 tested 15 patients, 10 of them received FMT through colonoscopy, 5 via naso-jejunal tube. In a 3-month follow-up scores of PSQI, HAMD, HAMA, PDQ-39, NMSQ and UPDRS-III lowered significantly after the FMT. None of the patients that received the FMT via naso-jejunal tube showed satisfaction in results after the 3 months after the treatment. However, 2 of the patients who received FMT via colonoscopy had reported satisfactory improvement still after 24 months. Results between those 2 groups were significantly better in colonoscopy group than in the naso-jejunal group [33]. The results of these studies led to the need for a randomized, placebo-controlled trials to test this in a controlled environment.

Randomized, placebo-controlled trials

DuPont et al. carried out trial with 12 male and female patients with a history of constipation and mild to moderate PD who were given a capsule containing 60g feces lyophilized or placebo orally twice a week for 12 weeks. They were assessed at baseline, after 12 weeks of oral FMT and at 4-weeks, 6-, and 9-months post treatment. Patients were categorized randomly in two groups: FMT (n =8, in the end 7 patients were evaluated, because 1 was lost in the follow-up due to metastatic cancer) and placebo (n = 4). Participants assigned

to FMT reported more substantial subjective clinical improvements in constipation, falls, sleep disturbances, motor deficits, and overall Parkinson's symptoms between 4 and 16 weeks after starting the treatment. These improvements were not observed in the placebo group. Fecal microbiota transplantation showed not statistically significant reductions in the guts transit times compared to pre-treatment measurements. The motility index showed significant improvement with FMT treatment [34].

In the Cheng et al. study took part 54 participants with mild to moderate PD took part in the study, of which 27 patients were assigned in the FMT group and 27 in the placebo group randomly and completed the whole trial, both groups lost for one patient in the follow-up. The FMT (50g of stool) and placebo were both administered orally as capsules. The evaluation was performed at baseline and the 4th, 8th, and 12th weeks after the intervention. During the trial 6 events of adverse effects of no severe nature such as bloating, flatulence, diarrhea and nausea were observed (3 in FMT group and 3 in placebo group). Significantly larger decrease of the MDS-UPDRS total score was observed in the FMT arm at week 12. During the follow-up, the placebo arm showed a significant decrease in MDS-UPDRS total score only at week 4 compared to baseline and next its return to the baseline at week 12. Patients with FMT treatment also showed significant improvement in IBS-SSS, GSRS, IBS-QOL, PD-related autonomic symptoms, better quality of life regarding abdominal symptoms and the stool frequency [35].

The latest study, the GUT-PARFECT trial by Bruggeman et al. published in 2024, involved 46 patients with PD (22 in the test group and 24 in the placebo group). Clinical evaluations occurred at baseline, and 3, 6, and 12 months post-FMT. Complete data were available for 21 test group participants and 22 placebo group participants. Patients received 50g of stool from a healthy donor or their own stool (placebo) via nasojejunal tube. The healthy donor FMT group showed a significant MDS-UPDRS part 3 (motor scores) improvement with a decrease of 5.8 points (95% CI −11.4 to −0.2) compared to 2.7 points (−8.3 to 2.9) in the placebo group. This group also had improved colon transit but performed worse on the Parkinson's Fatigue Scale. Mild, transient gastrointestinal adverse events, like abdominal cramps and nausea, were reported in the first week post-treatment by 13 (59%) patients in the healthy donor FMT group and 6 (25%) in the placebo group but no severe adverse events related to the treatment were observed [36]. Placebo-controlled trials are shortly summarized in Table 1.

Table 1.

Study	Design	FMT	Evaluation	Results
DuPont et al. [34]	12 male and female patients, mild to moderate PD. FMT n=7, placebo n=4.	60g of healthy donor feces lyophilized and administered orally as capsule twice a week for 12 weeks (24 doses)	At baseline, after 12 weeks of oral FMT and at 4-weeks, 6-, and 9-months post treatment	Significant improvements: constipation, falls, sleep disturbances, motor deficits, and overall Parkinson's symptoms, motility index. Not statistically significant reductions in the gut transit times
Cheng et al. [35]	54 participants with mild to moderate PD. FMT n=27, placebo n=27.	50 g of feces from a healthy donor and placebo. A total of 16 capsules administered orally.	At baseline and the 4th, 8th, and 12th weeks after the intervention.	Significant improvements: MDS-UPDRS, IBS-SSS, GSRS, IBS-QOL, PD-related autonomic symptoms, better quality of life regarding abdominal symptoms and the stool frequency. 6 mild adverse effects events.
Bruggeman et al. [36]	46 patients with PD with mild to moderate PD. FMT n=22, placebo n=24.	50g of stool from a healthy donor or their own stool (placebo) via nasojejunal tube.	At baseline, and 3, 6, and 12 months post-FMT.	Significant improvements: MDS-UPDRS part 3 of 5.8 vs 2.7 points,

			better colon transit. **No** significant improvements in: PFS, MDS-UPDRS parts 1,2,4; LEDD, NMSS, PDQ-39, Wexner Constipation Scale, GDS, PAS, LARS, PDSS, MoCA. 19 mild, transient gastrointestinal adverse events.

PFS- Parkinson's Fatigue Scale, NMSS - Non Motor Symptoms Scale for Parkinson's Disease, PDQ-39- Parkinson's Disease Quality of Life Questionnaire, GDS- Geriatric Depression Scale, PAS- Parkinson Anxiety Scale, LARS- Lille Apathy Rating Scale, PDSS- Parkinson's Disease Sleep Scale, MoCA- Montreal Cognitive Assessment.

Conclusions

Despite the long history of neurodegenerative diseases such as PD, we still lack knowledge of the precised pathophysiology behind this disease and its treatment. Nowadays Parkinson's Disease treatment focus on symptom management. Lewodopa supplementation wear burden of some significant side effects, and its therapeutic effects can wear off in time. That is why the need of new treatment compatible with PD's pathophysiology grows big. Animal studies indicate that gut microbiota may play a role in PD pathophysiology through the gut-brain axis and in the levodopa metabolism. The microbiota transplantation is a procedure that can restore imbalanced gut microbiota. Although the FMT treatment has limited registered indications, the number of reports of its outcome in various disorders increases. The cited research show that there is some hope in alleviation of PD symptoms by FMT. Animal research showed inter alia better motor functioning, increased striatal neurotransmitters, decreased intestinal inflammation. This created a background to a creation of hypotheses if the same outcome may be acquired in humans. First case reports provided promising results in alleviating

PD symptoms. Some placebo-controlled studies also showed significant improvements, but the latest, the GUT-PARFECT trial showed no statistically significant improvements in most of assessed domains, except of the gut transit and the part 3 of UPDRS, meaning that the FMT had a significant improvement in motor symptoms. All the past studies used different methods resulting in slightly different outcomes, as there are no proven protocols. Some studies used oral administration of FMT in capsules, other via colonoscopy or naso-jejunal tube. All the past research showed some kind of improvements, that is why this field is yet to be investigated further to create precise protocols and perhaps to create a respectable line of treatment in the future.

Author's contribution

Conceptualization, Marcin Dudek, Magdalena Gajkiewicz Małgorzata Zając and Stanisław Anczyk; methodology, Tomasz Fura; software, Radosław Zaucha and Oliwia Iszczuk; check, Julia Silldorff Magdalena Gajkiewicz and Radosław Zaucha; formal analysis, Marcin Dudek, Zuzanna Felińska and Małgorzata Zając; investigation, Stanisław Anczyk Radosław Zaucha; resources, Marcin Dudek; data curation, Magdalena Gajkiewicz, Julia Silldorff; writing - rough preparation, Marcin Dudek; writing - review and editing, Tomasz Fura, Julia Silldorff, Magdalena Gajkiewicz, Małgorzata Zając; visualization, Zuzanna Felińska; supervision, Zuzanna Felińska; project administration, Marcin Dudek; receiving funding, not aplicable. All authors have read and agreed with the published version of the manuscript.

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The data presented in this study are availble upon requests from the correspondent author.

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