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Short Communications

The impact of an active lifestyle on markers of intestinal inflammation in Parkinson's disease: Preliminary findings

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ABSTRACT

Alterations in the gut microbiota leading to intestinal inflammation and decreased levels of Short Chain Fatty Acids (SCFA) has been observed in Parkinson's disease (PD).
Objective: The aim of this study was to compare these factors between physically active and less active people with PD.
Methods: Stool, plasma samples and clinical data were collected from 35 people with PD (20 men and 15 women, mean age 66 years). Their level of physical activity was retrospectively assessed using the International Physical Activity Questionnaire (IPAQ). Participants were divided into two groups based on their physical activity level: Active and Inactive. Both SCFA and calprotectin, a marker of intestinal inflammation, were respectively measured by GC–MS and ELISA, according to standardized, validated protocols.
Results: Age, disease stage (Hoen & Yahr) and Montreal Cognitive Assessments (MoCA) were similar between groups. Acetate, propionate, and butyrate levels were significantly higher in the Active group than in the Inactive group. In addition, fecal calprotectin was significantly lower in the Active group than in the Inactive group. The constipation values were significantly lower in the Active group.
Conclusion: Our results suggest that an active lifestyle with regular physical activity is beneficial in patients with PD, through increased production of SCFA by the gut microbiome, and reduced intestinal inflammation and constipation.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by intraneuronal accumulation of aggregated alpha-synuclein amyloids (i.e. Lewy bodies), low-grade neuroinflammation and selective neuronal dysfunction, neurodegeneration of dopaminergic neurons in different areas of the nervous system, as well as the development of motor and non-motor symptoms [1,2]. Important non-motor features include gastrointestinal disturbances such as constipation and motility disorders, which often precede motor PD symptoms [3]. These elements suggest an early involvement of the gastrointestinal tract in the development of PD. Recently, disturbances of the gut/brain axis were proposed to play a role in the pathophysiology of neurodegenerative diseases such as PD [4]. It was recently shown that pharmacological treatment against PD cause alterations of the gut microbial ecology, small intestine bacterial overgrowth (SIBO) and motility [5]. Hence, impairments in the gut microbial ecology are proposed to decrease the numbers of short-chain fatty acid (SCFA)-producing bacteria [6], and to increase intestinal permeability and promote a low-grade inflammatory state [6]. SCFAs (acetic, propionic, and butyric acid) are the main product of bacterial fiber fermentation in the gut [7]. They were suggested to reduce neurodegeneration by normalizing the integrity of the epithelial barrier and ultimately low-grade systemic inflammation [5]. Interestingly, people with PD display higher levels of calprotectin in their stools than healthy individuals [8]. High calprotectin levels and impaired SCFA production were proposed as indicators of gut permeability and inflammation in PD [6].

However, the factors responsible for these effects remain unclear. Recent data suggested that regular physical activity promotes significant changes in the gut microbiota that may reduce inflammation in the intestine [9,10] Interestingly, physical activity reduced fecal calprotectin levels in healthy individuals [9,5]. In addition, an active lifestyle

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appears to increase the concentration of SCFAs in active and healthy individuals [9]. Considering these elements, we hypothesized that patients with PD who are physically active would show lower fecal calprotectin levels and a favorable SCFA profile compared to sedentary people with PD. The main aim of this study was to investigate the impact of a physically active lifestyle on SCFA production and fecal calprotectin [6]. We also took this opportunity to determine whether active people with PD showed less constipation than inactive individuals. If confirmed, the present results would suggest that regular physical activity normalizes gut microbial ecology and SCFA production while decreasing fecal calprotectin levels. These effects could, in turn, have a positive impact on reducing gut permeability and inflammation in active PD patients.

2. Methods

Physically active participants with PD were recruited with the help of NeuroMotrix, an organization that provides physical activity classes for people with neurological disorders. Participants were also recruited with the help of the Parkinson Quebec Network. Patients with a neurological disorder other than PD, or individuals with significant psychotic disorders such as hallucinations or delirium, as well as patients diagnosed with inflammatory bowel disease, were excluded from the present study. Prior to participation in the study, written informed consent was obtained from all participants in accordance with the General Data Protection Regulation. The study protocol was approved by the Ethics Committee of the University of Québec in Montreal (2023–5329). Participants were then asked to complete the International Physical Activity Questionnaire (IPAQ) [11]. The International Physical Activity Questionnaires (IPAQ) is a commonly used tool assessing physical activity intensity as well as the time people spend sitting as part of their daily life. It provides both an estimate of total physical activity in MET minutes/week and the time individuals spend sitting. The IPAQ is commonly used for estimating physical activity in participants with and without pathologies. Gilby and his colleagues tested the reliability of the IPAQ questionnaire in twenty-four participants with Parkinson's disease. The group compared the IPAQ data with a body-worn accelerometer (used to measure physical activity) and validated the use of the questionnaire (Gilby and al., 2023). The validity of the IPAQ questionnaire was also confirmed in another study testing 872 participants with Parkinson's disease using the IPAQ (Chouhfeh and al., 2017). In our study, the IPAQ was used to categorize the participants' level of physical activity into one of two different groups (*Active* or *Inactive)*. The *Inactive* group consisted of participants who had an IPAQ score < 3 METs, and the *Active* group included participants with an IPAQ score ≥ 6 METs [11]. If participants fulfilled the above criteria, they were included in one of the two experimental groups. Then, stool and blood samples were collected from included participants and stored on the same day, before they come to the Laboratory of Physiology and Exercise at Université du Québec à Montréal. They were instructed to collect stool samples after fasting for at least 10 h, at the time of the first bowel movement of the day, beginning at 4 am. An exception was made for participants with constipation problems. For these exceptions, participants were required to collect their samples in fasting conditions after dinner. Blood samples were collected early in the morning in the fasting condition. It was carried out this way to prevent participants remaining in fasting condition for too long a period. They were then offered an orange juice and cookies. According to the instructions provided, they placed a sterile disposable paper under the toilet seat in the center of the bowl to collect the stool sample. They then transferred the stool sample (5 to 10 g) with a sterile plastic spoon into a sterile container, which was immediately stored in the refrigerator. Upon arrival at the laboratory, the stool samples were immediately stored in a freezer at −80 °C.

A blood sample was collected via an intravenous catheter into screw-capped tubes and stored at 4 °C until centrifuged at 1800 g for 10 min. Serum samples were then collected and stored at −80 °C until the analyses were performed. Anthropometric parameters were then checked using the InBody230 device to provide an in-depth assessment of body composition by analyzing body fat percentage, body mass index, muscle mass and basal metabolic rate of each body region (right arm, left arm, right leg, left leg) [12]. In addition, three self-assessment questionnaires were completed:

(1) The Montreal Cognitive Assessment Scale (MoCa), which relates to cognitive function (simple, short assessment with several tasks to be completed by the patient). The items assessed were divided into six subsections: Memory, Executive Functions, Attention, Concentration, Language, and Temporal and Spatial Orientation. The total score was calculated based on 30 points, with a low score representing the threshold for the detection of cognitive decline [13].
(2) Rome IV defines constipation as the presence of two or more symptoms (straining to defecate, hard stools, feeling of incomplete evacuation, feeling of anorectal obstruction, fewer than three bowel movements per week) [14].
(3) The Cleveland Constipation Scoring System (CSS) was used to assess the severity of constipation. The CSS is one of the most used instruments to assess the prevalence and severity of constipation. The questionnaire included scores for different variables such as: Frequency of bowel movements, Difficulty (painful voiding effort), Completeness (feeling of incomplete evacuation), Abdominal pain, Time (minutes on the toilet per attempt), Type of assistance with defecation, Failure (unsuccessful voiding attempts per 24 h) and History (duration of constipation). A score of less than 15 was defined as mild constipation and a CCS score of 15 or more was defined as severe constipation [15]. Here, the raw scores were used to determine the degree of constipation of each participant.

All samples were stored in our laboratory freezer at −80 degrees. Once data collection was completed, we submitted the fecal and plasma samples for analysis at the same time. Quantitative analyzes of SCFA were carried out at the Institute of Nutrition and Functional Foods (INAF, Université Laval) using gas chromatography. All individuals involved in the analysis were blinded to avoid any bias from the research professional performing the assay. Serum samples were thawed and centrifuged for 2 min at 18,000 *g* at 4 °C. Two aliquots of serum were acidified with 10 % H_3PO_4 to reach a pH of approximately 2 and deproteinized with 5 % v/v sulfosalicylic acid at a concentration of 500 mg/mL [16]. The samples were then centrifuged at 18,000 *g* for 5 min at 4 °C and the supernatant was transferred to a glass vial. An equal volume of methyl *tert*-butyl ether was added to extract the SCFAs by shaking for 2 min. The extracts were centrifuged at 5,500 *g* for 10 min at 4 °C to separate the organic and aqueous phases. The system was controlled by GC solution software. Two microliters of the organic phase were injected into a Nukol capillary GC column (30 m × 0.25 mm i.d., 0.25 μM film thickness, Supelco analytical) in split mode, and hydrogen was used as the carrier gas. On the day of fecal fermentation, fecal samples were thawed, suspended in 5 mL of ultrapure water, and homogenized with a BeadRuptor (Omni, Kennesaw, Georgia) at 4.0 m/s for 2 min. The fecal suspension was then centrifuged at 5,500 °C *g* and 4 °C for 30 min to remove larger solid particles [16]. The fecal suspension was then centrifuged at 5,500 °C g and 4 °C for 30 min to remove larger solid particles [16]. The samples were then lipophysed. This is a low pressure cold drying procedure, i.e. this means that the samples were refrozen and then dehydrated to remove water and reduce the moisture content [16]. The injector and detector were set to 250 °C. The oven temperature was initially programmed to 60 °C and then increased to 200 °C at 12 °C/min, and the temperature was maintained for 7 min [16]. SCFA analyzes stool and serum (with acetic acid, propionic acid, butyric acid) were performed using a GC-FID system (Simadzu) consisting of a GC

2010 gas chromatograph and an AOC-20 s autosampler, an AOC-20i autoinjector and a flame ionization detector [16]. The SCFA analyzes were performed in duplicate. Results were averaged and expressed as μmol/g dry stool. Data was processed using Skyline21.1.30 software.

Quantitative analysis of fecal calprotectin was performed at the Maisonneuve-Rosemont Hospital (HMR) laboratory. Samples were kept at 4 °C for at least 12 h, shaken vigorously until the sample was completely in suspension and then pretreated with preparation and extraction tubes. Then, the samples were mixed for 30 sec by vortex and homogenized for 25 min. The homogenate (1 mL) was transferred to a tube and centrifuged at 10,000 g for 20 min. Finally, the supernatant was collected and frozen at − 20 °C. The supernatants were thawed and the evaluation of calprotectin in stool samples was performed by enzymatic immunoassays (ELISA) using IDK ® commercial kits. First, we used a two-sample modified Welch's to confirm that the level of physical activity differed between the groups. The same test was performed to ensure that both groups had similar age, gender, disease stage and disease duration, sociodemographic characteristics, and anthropometric measurements. Since three different, yet related SCFAs were investigated, we used a Bonferroni correction to adjust the final p value for multiple comparisons. All statistical tests were two-sided, and statistical significance was set at $p < 0.05$. Finally, used a Spearman's Rank correlation test to examine the relationship between levels of stool and blood SCFAs on the entire sample size. Statistical analyzes were performed using SPSS software (Statistical Package for Social Sciences, version 27.0).

3. Results

To achieve the aim of this study, and control for major confounding factors, patients were carefully selected so that baseline demographic and clinical characteristics such as age, disease stage, cognitive status, disease duration were similar between groups, except the L-dopa dose (MP treatment) (Table 1). Most participants in the *Inactive* group reported taking medications for high blood pressure and cholesterol.

Forty participants were eligible to take part after the first assessment was completed. Three participants were excluded because their energy consumption was between 3 and 5.9 METs, and 2 participants dropped out for unrelated personal reasons. A total of 35 participants (20 men and 15 women, mean age 66 years) were included in the final analysis.

Table 1
Descriptive characteristics of the participants (n = 35).

Groupes	*Active* (n = 20)	*Inactive* (n = 15)	P-value (Power)
Mean age [range]	66 ± 7.9 [54–80]	65 ± 7.3 [54–73]	0,14
Sex (males/females)	15/5	5/10	
Time since diagnosis (years)	4.5 ± 3	4,2 ± 3	0,24
Hoen and Yahr scale (ON period)			0,12
• **Stage I**	n = 2	n = 4	
• **Stage II**	n = 15	n = 8	
• **Stage III**	n = 3	n = 3	
MDS UPDRS — part III	22.2 [12 –30]	22.8 [18 –30]	0.17
MoCa	25 ± 6	25 ± 4	0.77
Medication			
• **LEDD (mg)**	527 ± 211.5	221 ± 110	0,003

LEDD = Levodopa Equivalent Daily Dose, MoCA = Montreal Cognitive Assessment,

Thirty-four of them were receiving anti-PD treatment and one was not receiving any medication. In most cases, the diagnosis occured within the last 5 years, and most were at stage 2 (n = 23). The sociodemographic characteristics of the participants are presented in Table 1. See (Table 2).

As for dietary habits, the results of the surveys did not reveal any major differences between the active and inactive groups. Fifty percent of both groups eat a healthy diet and avoid dairy products, cereals, gluten and red meat, while the other fifty percent do not follow a special diet and eat ready meals or frozen food without restrictions.

Levels of physical activity were different between the *Active vs.* the *Inactive* groups (Table 3), this for all types of physical activities (transportation, leisure-time, intense/moderate activity, and walking).

Results showed that fecal concentrations of acetic acid ($p = 0.03$), propionic acid ($p = 0.006$) and butyric acid ($p = 0.003$) were significantly higher in the Active groups compared to the Inactive group (Fig. 1). In addition, plasma concentrations of acetic acid ($p = 0.004$), propionic acid ($p = 0.002$) and butyric acid ($p = 0.03$) were also significantly higher in the Active group compared to the Inactive group (Fig. 1). At the same time, the mean fecal calprotectin level was lower in the ACTIVE group compared to the Inactive group ($p = 0.009$). Values below the reference limit (50 μg/g) were found in samples from twelve (60 %) of the twenty Active participants (Fraga et al., 2012). In these cases, values were set to 50 μg/g. In contrast, values above 50 μg/g were found in the samples of nine (50 %) of the fourteen Inactive participants, and values above 100 μg/g (Fraga., 2012) were found in the samples of four Inactive participants (Fig. 1).

Table 3 shows that the *Inactive* group suffered significantly more from constipation compared to the *Active* group (Table 3). When scores from the Constipation Scoring System (CSS) and ROME V were compared between groups.

4. Discussion

In the present study, we compared the concentrations of calprotectin levels, and different SCFAs between active and less active people with PD. Our results show that acetate, propionate and butyrate concentrations in stool and plasma were significantly higher in the *Active* group than in the more sedentary group. In addition, calprotectin levels were significantly lower in the *Active* group than in the less active group. These results support the hypothesis that an active lifestyle may help regulate intestinal microbial metabolite production and gastrointestinal inflammation by increasing SCFAs profiles and reducing calprotectin levels in PD. Our results also show lower levels of constipation in the *Active* group.

There is now ample evidence that physical activity is beneficial for people with Parkinson's disease [17,18,19]. The increase in SCFA profiles observed in our study is consistent with previous studies in athletes [19,20] and healthy, active older adults [21]. For example, Dalton and

Table 2
IPAQ score.

	Active (n = 20)	*Inactive* (n = 15)	p-value (Power)
Transportation (Mets. Minutes/week)	1039	206	
Leisure-time (Mets. Minutes/week)	3459	833	
Intense/Moderate (Mets. Minutes/week)	2345	830	
Walking (Mets. Minutes/week)	2044	466	
Total sedentary time (Hours/week)	136	210	
Total AP (day)	6 ± 0.8	3 ± 1.5	
Total IPAQ score (Mets. Minutes/week)	8440	1914	0,04

PA: Physical Activity; Mets. Minutes/week: Metabolic Equivalent Tasks. Minutes/week.

Table 3
Gastric characteristics of the participants (n = 35).

	Active (n = 20) %	*Inactive* (n = 15) %	*p* value
CSS total Score			
Constipation	10	90	0,001
Rome IV			
Functional constipation	70	100	
Fecal incontinence	5	45	
Bloating	60	90	

CSS: Constipation Scoring System.

colleagues (2019) showed an increase in SCFA levels in response to regular voluntary physical activity [22]. We observed that the plasma to fecal ratio of each SCFA type was positively affected by an active lifestyle, contradicting the idea that higher blood levels of SCFAs may be associated with worsening Parkinson's disease. Dysregulation of fatty acid metabolism in PD has been shown to be short-lived, and these abnormalities also occur in early and late stages of PD, suggesting that gut dysbiosis is associated with PD progression. Our results agree with several studies that have found low levels of SCFA in feces and plasma in patients with Parkinson's disease. Only a few studies reported discrepant results suggesting that these patients had higher than normal plasma SCFA concentrations. For example, Shen and colleagues showed that plasma acetic acid was elevated in PD patients, although this level did not correlate with the severity of motor symptoms. They also showed that key cognitive symptoms were associated with higher plasma concentrations of butyric acid and valeric acid [28]. However, our results are consistent with the majority consensus that SCFA concentrations are generally low in Parkinson's disease, which means that an active lifestyle improves the plasma and fecal levels of SCFAs, which our study showed and confirmed.

To our knowledge, the current study is the first one to show that an active lifestyle has a positive impact on calprotectin and SCFA fecal levels in people with PD. The decrease in calprotectin levels observed in the current study is consistent with studies in patients with inflammatory diseases who have undergone an exercise program [30]. The literature suggests that calprotectin and SCFAs are among the most reliable indicators of a dysregulated and inflammatory gut environment in PD [6]. Our results provide key data confirming the important role of regular physical activity to improve intestinal inflammation and the production of metabolic products (SCFA), as well as possibly reducing constipation in people with PD.

Constipation is one of the most common non-motor symptoms of PD and it is demonstrated to even precede motor features [31]. The present results seem to suggest that people with PD who suffer from constipation could benefit from an active lifestyle which includes exercise. Our results are consistent with previous results which showed a correlation between the severity of constipation and the results from the 6-minute walk test: the less the patients with PD walked, the more constipated they were [32].

Although the results of the current study strongly suggest that physical activity may contribute to reducing inflammation, it should be kept in mind that this is a preliminary study with several limitations. First, it is a cross-sectional study with a small sample. This prevented us to control for types of physical activity nor for the diet of participants. Third, disease stage was limited to between 1 and 3 on the Hoen and Yahr, so participants were either at an early or intermediate stage. Finally, there were more women in the sedentary group than in the active group. Houser and colleagues (2018) analyzed proteins related to immunity and angiogenesis in the stool of people with PD and found that women with PD had higher immune factors than control women (33). However, we found no evidence of sex-specific differences in SCFA or calprotectin concentrations, even in PD. Future longitudinal studies of gut inflammation in PD using different approaches and larger sample sizes in conjunction with a well-controlled training program will expand our knowledge and provide a deeper understanding of how gut microbes and their metabolites interact with the host and impact disease etiology, symptoms, and progression of PD. not forgetting to take into account potential confounding factors such as diet, which could provide new targets along the gut-brain axis for more effective disease-modifying treatment of this disorder.

In conclusion, the result of this preliminary study suggests that an active lifestyle that includes regular physical activity is beneficial through increased production of short-chain fatty acids by the gut microbiome, reduced intestinal inflammation and constipation in patients with PD.

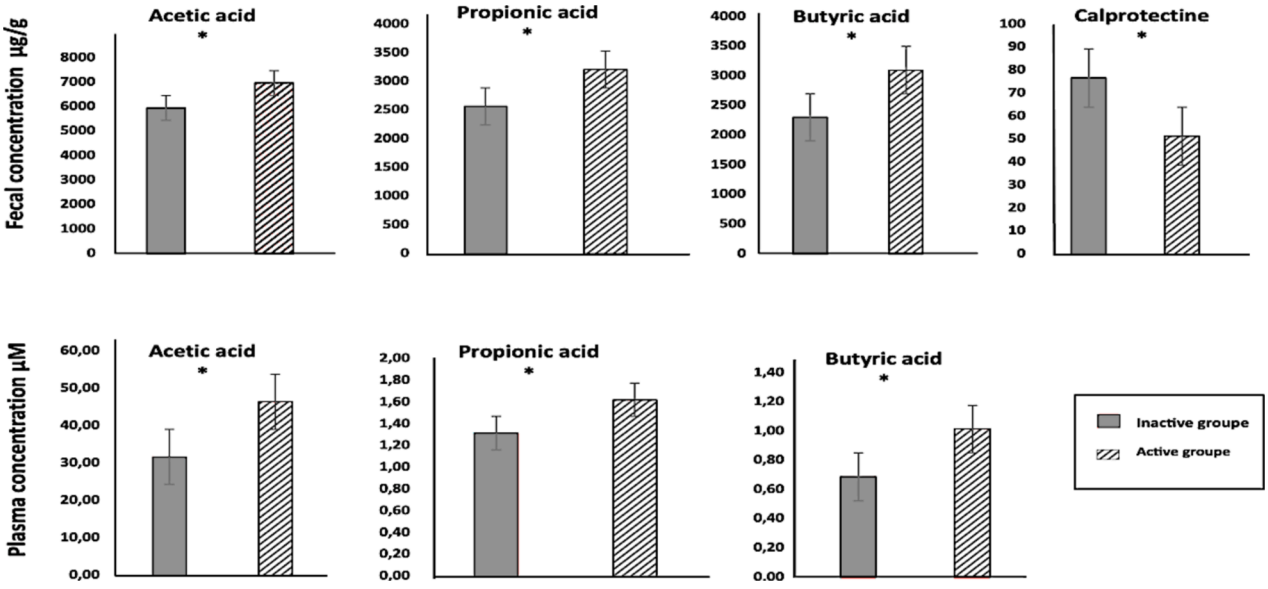

Fig. 1. Comparison of SCFA and calprotectin levels in people with PD: mean ± standard error for fecal and plasma levels of acetic acid, propionic acid, butyric acid, and fecal calprotectin in people with PD by MP. *p < 0.05 (1- β < 0.80). The Spearman rank correlation between the *Active* group and the *Inactive* group was negative, respectively.

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The authors have no funding to declare.

CRediT authorship contribution statement

Nesrine Chtioui: Writing – review & editing, Writing – original draft, Methodology. **Christian Duval:** Validation, Supervision, Project administration. **David H. St-Pierre:** Validation, Resources, Formal analysis.

7. Data availability

Data supporting the results of this study may be made available upon request to researchers based on research purposes and ethical considerations from the respective institutions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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