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Small intestinal bacterial overgrowth in Parkinson's disease

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ABSTRACT

Background: Recent studies reported a high prevalence of small intestinal bacterial overgrowth (SIBO) in Parkinson's disease (PD), and a possible association with gastrointestinal symptoms and worse motor function. We aimed to study the prevalence and the potential impact of SIBO on gastrointestinal symptoms, motor function, and quality of life in a large cohort of PD patients.
Methods: 103 Consecutive PD patients were assessed using the lactulose-hydrogen breath test; questionnaires of gastrointestinal symptoms and quality of life (PDQ-39); the Unified PD Rating Scale (UPDRS) including "on"-medication Part III (motor severity) score; and objective and quantitative measures of bradykinesia (Purdue Pegboard and timed test of gait). Patients and evaluating investigators were blind to SIBO status.
Results: 25.3% of PD patients were SIBO-positive. SIBO-positive patients had a shorter mean duration of PD (5.2 ± 4.1 vs. 8.1 ± 5.5 years, $P = 0.007$). After adjusting for disease duration, SIBO was significantly associated with lower constipation and tenesmus severity scores, but worse scores across a range of "on"-medication motor assessments (accounting for 4.2–9.0% of the variance in motor scores). There was no association between SIBO and motor fluctuations or PDQ-39 Summary Index scores.
Conclusions: This is the largest study to date on SIBO in PD. SIBO was detected in one quarter of patients, including patients recently diagnosed with the disease. SIBO was not associated with worse gastrointestinal symptoms, but independently predicted worse motor function. Properly designed treatment trials are needed to confirm a causal link between SIBO and worse motor function in PD.

1. Introduction

Gastrointestinal (GI) dysfunction is an important component of the spectrum of non-motor features in Parkinson's disease (PD) [1,2]. Symptoms include early satiety, nausea, abdominal bloating, pain, constipation, and weight loss. These symptoms are likely to be related to delayed gastric emptying, impaired gut motility and defecatory dysfunction [1,2]. It is now known that extra-nigral structures such as the enteric nervous system and the dorsal motor nucleus of the vagus nerve (which provides parasympathetic innervation to the GI tract from the esophagus to just before the splenic flexure of the colon) are affected due to the presence of alpha-synuclein aggregates from the early stages of the disease [1–3]. In addition, treatment of PD with dopaminergic drugs can also cause or exacerbate some GI symptoms.

An additional factor recently implicated in GI dysfunction in PD is small intestinal bacterial overgrowth (SIBO). Very little is known about small intestinal function in PD [4–6], and the literature on SIBO remains scarce [4–10]. The prevalence of SIBO in PD reported in recent studies ranged from 54% to 67% (in contrast, one large study of 294 older German adults without PD reported a 15.6% prevalence) [7–11]. These authors further

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suggested that SIBO could be associated with worse "on"-medication motor scores and more severe motor fluctuations [7,8]. It was postulated that impaired gut motility in PD leads to SIBO, which could in turn induce a secondary inflammatory response in the gut mucosa and thus impair levodopa absorption [7–9]. However, these studies were limited by relatively small sample sizes (15–51) [6–9] and the use of non-conventional measures of motor function [9,10].

This study aimed to investigate: (1) the prevalence of SIBO in a large cohort of patients with PD, and (2) the potential impact of SIBO on GI symptoms, motor function, and quality of life. We hypothesized that the presence of SIBO would be associated with worse GI symptoms, motor function and quality of life.

2. Patients and methods

2.1. Study population

Consecutive PD patients were recruited from the University of Malaya Neurology Clinic between July 2012 and March 2013. The study received ethics approval and informed consent was obtained from all patients. Patients were assigned a diagnosis of PD by a Movement Disorders neurologist (SYL) according to the Queen Square Brain Bank clinical diagnostic criteria. Exclusion criteria were: (1) age <18 years; (2) a history of gastric lesions or major abdominal/pelvic surgery; (3) prior eradication therapy for SIBO or *Helicobacter pylori*; (4) comorbidities that prevented reliable completion of study assessments; and (5) prior functional neurosurgery or treatment with apomorphine infusion. Patients were not recruited (or their recruitment delayed) if they had used antibiotics in the preceding four weeks; used anti-acid, prokinetic or laxative agents in the preceding two weeks; or were initiated on dopaminergic medications within the last three months (as these factors could potentially influence the results of SIBO testing and/or GI symptoms) [8,12,13].

2.2. Clinical evaluations

Subjects were evaluated on a single visit. Demographic and clinical data, including age, gender, race, body mass index (BMI), PD duration, pattern of PD medication use (including the use of anticholinergic agents) and daily levodopa equivalent units (LEU) were recorded. Regarding the age at PD onset, the proportion of subjects with onset <45 years was determined, since younger-onset patients have a relatively slower motor progression [14,15]. GI symptoms were evaluated using a questionnaire that has been used in previous clinical trials on SIBO and demonstrated improvement following eradication therapy [12]. The questionnaire evaluates ten GI symptoms, which are scored from 0 to 3 (higher scores indicating worse symptoms); the sum of these scores provides a Global Symptomatic Score (GSS). PD motor severity was assessed using the Unified PD Rating Scale (UPDRS) Part III and Hoehn and Yahr staging, during the subjects' usual "on"-medication state in the morning, by a clinician specializing in Movement Disorders (AHT). During their "on"-medication state, patients also underwent: (1) the Purdue Pegboard test (patients were instructed to insert as many pegs as possible in 30 s, first with the dominant hand, then with the non-dominant hand, followed by both hands simultaneously; the average of three trials was calculated); and (2) a timed gait test. Patients walked 14 m (7 m to and fro) as quickly as they could, followed by a second walk after 5 min. A walking aid could be used depending on individual preference. The time and number of steps taken to complete the walk were recorded, and the average of both trials was calculated. Quality of life was evaluated using the PDQ-39. Patients and research personnel performing the clinical assessments were blinded to the results of SIBO testing.

2.3. Lactulose-hydrogen breath testing (LHBT)

Bacteria are the sole producers of intestinal hydrogen, and the LHBT is based on bacterial metabolism of ingested lactulose into hydrogen [13,16–18]. Normally, the small bowel contains only small numbers of bacteria and ingested lactulose is metabolized when it reaches the dense population of bacteria in the colon, giving rise to a late peak in breath hydrogen content. In SIBO, small bowel bacterial metabolism of the lactulose produces an early rise of breath hydrogen [13,16–18].

An LHBT was performed on the same morning as the clinical evaluations, initiated at the same time (8:30 am) for each patient. Patients received carbohydrate-restricted meals and abstained from alcohol and carbonated drinks for 24 h prior to the breath test, and fasted for ≥10 h [13]. Smoking, physical exercise and food intake were not permitted during testing. After obtaining a baseline breath sample, patients ingested 10 g of lactulose and end-expiratory breath samples were collected every 15 min over 180 min and analyzed for hydrogen and methane [17] content using gas chromatography (Quintron Breath Test Analyzer, Quintron Instrument Company, Milwaukee, WI, USA). A positive test for SIBO was defined as a rise in the hydrogen level by >10 parts per million (ppm) or a rise in the methane level by >20 ppm above the basal level, on two consecutive readings within 90 min of lactulose administration [13,18,19]. Methane was also measured because if the gut harbors methanogenic species, hydrogen is converted into methane, producing a false-negative LHBT [17].

2.4. Statistical analysis

Data were analyzed using SPSS for Windows Version 20.0. Quantitative data were expressed as means and standard deviations. Chi-square and independent *t*-tests were used to compare differences between the SIBO-positive vs. SIBO-negative groups. Pearson correlation was used to examine the relationship between continuous variables. Hierarchical multiple regression analysis was used to explore the clinical correlates of SIBO; the dependent variables were the scores for GI symptoms, motor function, and PDQ-39. Independent variables were entered step-wise: PD duration (Model 1) followed by SIBO status (Model 2); thus, the effects of PD duration could be controlled for when examining the effects of SIBO on the outcomes of interest. The increment in the proportion of variance explained (R^2 change) by entering each independent variable was determined. Tests for multicollinearity, normality, and influential data points showed that the assumptions of the regressions were met. $P < 0.05$ was the threshold for significance.

3. Results

3.1. Study participants and LHBT results

103 Patients met the inclusion criteria and agreed to participate; demographic and clinical characteristics are presented in Table 1. The proportion of patients treated with antiparkinsonian medications were: levodopa 88.3%, dopamine agonists 48.5%, entacapone 29.1%, MAO-B inhibitor (selegiline) 23.3%, amantadine 10.7%, and anticholinergics 25.2%. Twenty six of the 103 patients (25.3%) were SIBO-positive. Forty patients did not demonstrate a significant rise in hydrogen and methane (>10 ppm and >20 ppm, respectively,

Table 1
Demographics and clinical characteristics.

Clinical characteristics	Overall ($n = 103$)	SIBO+ ($n = 26$)	SIBO− ($n = 77$)	*P* value
Age (years)	65.4 ± 8.5	67.2 ± 10.1	64.8 ± 8.0	0.210
Gender (% male)	60.2	61.5	59.7	0.871
Race (% Chinese/Indian/Malay/Other)	65.0/20.4/12.6/1.9	53.8/26.9/15.4/3.8	68.8/18.2/11.7/1.3	0.520
Smoking status (% Current smoker/Ex-smoker/Never-smoker)	1.0/20.8/78.2	0.0/15.4/84.6	1.3/22.1/74.0	0.632
BMI (kg/m^2)	23.7 ± 4.3	23.7 ± 4.4	23.6 ± 4.3	0.909
PD duration since diagnosis (years)	7.3 ± 5.3	5.2 ± 4.1 (range 0.5–24 years)	8.1 ± 5.5 (range 2–19 years)	0.007[a]
Age at PD onset <45 years (% yes)	7.8	3.8	9.1	0.388
Motor fluctuations present (% yes)	53.4	34.6	59.7	0.061
Unpredictable motor fluctuations present (% yes)	21.8	8.0	26.3	0.054
Total LEU (mg/day)	526.8 ± 412.7	368.5 ± 290.4	580.3 ± 435.3	0.007[a]
Use of levodopa (% yes)	88.3	88.5	88.3	0.984
Use of anticholinergic medication (% yes)	25.2	19.2	27.3	0.414

[a] Denotes statistically significant between-group differences.

over baseline in one or more breath samples) within 180 min of the LHBT [19].

3.2. Comparison between SIBO-positive vs. SIBO-negative patients

SIBO-positive patients had a shorter duration of PD (5.2 ± 4.1 vs. 8.1 ± 5.5 years, $P = 0.007$) and, correspondingly, a lower daily LEU (368.5 ± 290.4 vs. 580.3 ± 435.3, $P = 0.007$) (Table 1). There were no significant between-group differences in other variables (age, gender, race, smoking status, BMI, and use of anticholinergic medication). The results of univariate analyses for GI symptoms, motor function, and PDQ-39 are presented in Tables 2and 3.

3.3. GI symptom correlations

PD duration correlated with constipation severity (Pearson's $r = 0.236$, $P = 0.017$), but not with other GI symptoms. GI symptoms did not correlate with age, disease severity (Hoehn and Yahr stage and UPDRS Part III) or daily LEU. Among GI symptoms, strong correlations (Pearson's $r \geq 0.50$) were observed between constipation and tenesmus ($r = 0.609$, $P < 0.001$), and between upper abdominal pain and abdominal tenderness ($r = 0.571$, $P < 0.001$).

3.4. Hierarchical multiple regression analysis

As the SIBO-positive and SIBO-negative groups differed significantly in PD duration (a variable which could have a confounding effect on the outcomes of interest), hierarchical multiple regression analysis was used to examine the relationship between SIBO status, GI symptoms, motor function, and PDQ-39, after controlling for this (Table 4). Total LEU did not correlate with any of the motor scores (Pearson's r ranging from −0.043–0.143), and was not examined as a covariate. After adjusting for PD duration, SIBO did not contribute to the GSS. SIBO positivity was associated with lower constipation and tenesmus severity (R^2 change of 0.048 and 0.041). As expected, PD duration explained a significant amount of variance in all measures of motor function. After adjusting for this, SIBO positivity remained significantly associated with several measures of motor function, with worse UPDRS Part III scores (R^2 change of 0.042), less pegs on Pegboard tests (R^2 change of 0.090, 0.068 and 0.077 for the dominant hand, non-dominant hand, and both hands, respectively), and a longer completion time on gait test (R^2 change of 0.051). Nevertheless, PD duration was a more important predictor of these outcomes, with larger values of R^2 change (0.082–0.170). There was no association between SIBO status and the scores for UPDRS Part IV (total), UPDRS Part IVB Questions 36–39 (clinical fluctuations) and Part IVB Question 37 (unpredictable "off" periods). The PDQ-39 Summary Index score worsened with longer PD duration, but not with SIBO positivity.

4. Discussion

To our knowledge, this is the largest study to date on SIBO in PD. SIBO was present in one quarter of consecutive PD patients. SIBO positivity independently predicted worse motor function, but was not associated with dopa-related motor response complications or worse GI symptoms.

Our 25.3% prevalence of SIBO, assessed by the LHBT, was lower than that reported in recent studies (54–67%) [7–10], but higher than that reported by Davies et al. (which did not find any evidence of SIBO in all PD patients studied) [6]. There are numerous possible reasons for these differences. Only a minority of PD patients under our clinic follow-up were on anti-acid medications, and this was a specific exclusion criterion for recruitment into our study. These agents cause hypochlorhydria, which in turn may cause bacterial overgrowth in the stomach and upper small intestine [4,13,20–22]. Therefore, the inclusion of patients on proton pump inhibitor therapy in other studies (e.g., 39.6% of the cohort of Gabrielli et al.) may be an important factor [7,9,10]. The total LEUs in these studies were also higher (799.1 mg and 1380.5 mg/day, vs. 526.8 mg/day in the present study) [7,8], and there is some suggestion that dopaminergic medications can impair intestinal motility [23]. Other potentially relevant, but hitherto unstudied, factors are geographic effects, dietary factors including alcohol consumption, malnutrition, and possible alterations in gut and systemic immune function [17,20,21,24]. Importantly, breath tests for SIBO have not been standardized and protocols differ with respect to the substrate used, sampling intervals, and test interpretation [20]. Using the criterion of Dobbs et al. (>20 ppm rise in hydrogen in 120 min), however, SIBO prevalence in our cohort was still considerably lower (22.3% vs. 60.6–66.7%) [9,10]. The cut-off used to define a positive LHBT was not specified in the study by Fasano et al. [8].

Symptoms of SIBO may reflect the underlying disease leading to SIBO (e.g., gut hypomotility manifesting as constipation), or result from SIBO-related mucosal inflammation, malabsorption and luminal distention (manifesting as bloating, flatulence, abdominal discomfort or pain, diarrhoea, weight loss, and fatigue) [18,20,21]. However, SIBO is a heterogenous syndrome and it can be clinically

Table 2
Prevalence and severity of gastrointestinal symptoms.

Gastrointestinal symptoms	Overall cohort		SIBO+	SIBO−	*P* value	SIBO+	SIBO−	*P* value
	Prevalence (%)	Mean severity score	Prevalence (%)			Mean severity score		
Global symptomatic score	–	5.80 ± 4.21	–	–	–	4.38 ± 4.61	6.27 ± 3.99	0.048[a]
Diarrhoea	14.6	0.16 ± 0.39	11.5	15.6	0.733	0.15 ± 0.46	0.16 ± 0.37	0.964
Upper abdominal pain	30.1	0.43 ± 0.78	23.1	32.5	0.541	0.31 ± 0.68	0.47 ± 0.81	0.350
Lower abdominal pain	19.4	0.32 ± 0.73	26.9	16.9	0.465	0.38 ± 0.75	0.30 ± 0.73	0.625
Bloating	35.9	0.53 ± 0.79	19.2	41.6	0.093	0.31 ± 0.74	0.61 ± 0.80	0.089
Flatulence	72.8	1.06 ± 0.81	65.4	75.3	0.463	0.92 ± 0.84	1.11 ± 0.79	0.322
Abdominal tenderness	10.7	0.19 ± 0.58	7.7	11.7	0.708	0.12 ± 0.43	0.21 ± 0.62	0.470
Weight loss	40.8	0.62 ± 0.87	34.6	42.9	0.617	0.50 ± 0.86	0.66 ± 0.87	0.426
Nausea	24.3	0.34 ± 0.67	15.4	27.3	0.383	0.27 ± 0.67	0.37 ± 0.67	0.516
Constipation	73.8	1.30 ± 1.00	17.1	82.9	0.003[a]	0.85 ± 1.05	1.46 ± 0.94	0.006[a]
Tenesmus	52.4	0.94 ± 1.05	34.6	58.4	0.079	0.58 ± 0.95	1.07 ± 1.06	0.040[a]

Individual symptoms were scored as follows: 0 = absence of symptom; 1 = mild symptoms not interfering with daily activities; 2 = moderate symptoms interfering with but not preventing daily activities; or 3 = severe symptoms preventing performance of desired daily activities. The sum of these scores provides a Global Symptomatic Score (GSS) (range of scale 0–30).

[a] Denotes statistically significant between-group differences.

Table 3
Unified Parkinson's disease rating scale (UPDRS), timed tests of motor function, and health-related quality of life (PDQ-39).

Assessments ("on"-medication state)	Mean score and standard deviations		*P* value
	SIBO+ ($n = 26$)	SIBO− ($n = 77$)	
UPDRS Part I (0–16)[a]	3.60 ± 2.71	3.90 ± 2.80	0.645
UPDRS Part II (0–52)[a]	12.12 ± 7.65	14.38 ± 7.90	0.214
UPDRS Part III (0–108)[a]	32.37 ± 12.03	28.81 ± 11.61	0.185
UPDRS Part IV (0–23)[a]	2.76 ± 3.13	4.56 ± 3.44	0.022[e]
UPDRS Part IVB (Clinical fluctuations) (0–7)[a,c]	0.92 ± 1.26	1.75 ± 1.63	0.018[e]
UPDRS Part IVB (Unpredictable "off" periods) (0–1)[a,d]	0.08 ± 0.28	0.26 ± 0.44	0.022[e]
Total UPDRS (0–199)[a]	50.76 ± 21.36	51.33 ± 19.96	0.902
Hoehn and Yahr staging[a]	2.44 ± 0.70	2.40 ± 0.63	0.754
Purdue Pegboard (dominant hand)[b]	9.83 ± 3.05	11.40 ± 3.55	0.046[e]
Purdue Pegboard (non-dominant hand)[b]	9.44 ± 3.26	10.61 ± 3.20	0.110
Purdue Pegboard (both hands)[b]	6.50 ± 2.54	7.77 ± 3.07	0.061
Timed Gait (seconds)[a]	23.56 ± 22.74	17.86 ± 15.45	0.243
Timed Gait (steps)[a]	31.96 ± 17.64	29.61 ± 15.76	0.531
PDQ-39 Summary Index (0–100)[a]	25.71 ± 18.13	30.78 ± 19.60	0.248

[a] Higher scores on these scales indicate poorer function or quality of life.
[b] Lower scores indicate poorer function.
[c] Sum of scores for UPDRS Questions 36–39, which evaluate clinical fluctuations.
[d] UPDRS Question 37, which evaluates whether "off" periods are unpredictable.
[e] Denotes statistically significant between-group differences.

silent in otherwise healthy subjects [20,25]. In the present study, SIBO was not associated with a greater frequency or severity of GI symptoms. In accord with some studies, we found that constipation and tenesmus (both closely related symptoms) were more severe in patients with longer PD duration [2]. Interestingly, however, SIBO was associated with less severe constipation and tenesmus. This finding suggests that SIBO, once it has developed, may itself increase gut motility. This could be due to exposure of the intestinal wall to bacterial metabolites and toxins that stimulate intestinal motility [18]. Therefore, we hypothesize that SIBO effects may not always be detrimental and could possibly be of benefit in some patients suffering from severe constipation (a distressing symptom for many patients with PD). In this circumstance, the benefits of eradication therapy and the risk of aggravating constipation should be carefully considered. There has been interest in the possibility that SIBO could contribute to weight loss in PD, however, our finding that BMI did not differ according to SIBO status argues against this hypothesis. After adjusting for disease duration, SIBO positivity accounted for only 0.1% of the variance in BMI values (P = NS). Other investigators likewise did not find between-group differences in BMI [7,8].

In recent years, there has been considerable interest in the interplay between gut bacteria and PD, due to the potential role of eradication therapy in improving motor symptoms [7,8,26,27]. However, the association remains poorly understood. One study reported that SIBO occurred in patients with longer disease duration and worse "on"-medication UPDRS Part III scores [7]. In a selected cohort of patients with motor fluctuations ($n = 33$), SIBO was associated with unpredictable "off" periods [8]. SIBO was thus hypothesized to be a complication of GI dysfunction in patients with more advanced PD [7–9]. In contrast, SIBO was associated with a shorter duration of PD in our study and could be detected in patients with recently diagnosed PD (with correspondingly lower LEU requirements). After adjusting for disease duration, SIBO was an independent predictor of worse motor function. This finding was robust and statistically significant across a range of motor evaluations (UPDRS Part III, Pegboard and timed gait test).

It is possible that SIBO contributes to motor dysfunction by disrupting small intestinal integrity, with consequences on host immune function and/or levodopa absorption. Recently, a fundamental role of the GI system in the etiology and progression of PD has been hypothesized [1,2,4,28,29]. There is evidence to suggest that peripheral inflammatory states, including infections in the GI tract, can trigger microglial activation and exacerbate the ongoing neurodegenerative process in PD, leading to worse motor function [10,29]. The increased intestinal permeability seen with SIBO may promote translocation of bacteria and endotoxins across the intestinal epithelium, creating a proinflammatory environment [30]. Interestingly, a recent study involving newly-diagnosed PD patients found that intestinal permeability was markedly increased compared with healthy controls, and this was associated with more intense staining of *Escherichia coli* in the intestinal mucosa, and with systemic exposure to bacterial endotoxin [28]. These changes correlated with abnormal accumulation of alpha-synuclein in enteric neurons. Levodopa malabsorption could also be a factor, but one study found that eradication of SIBO did not affect levodopa pharmacokinetics [8]. Potential mechanisms include mucosal injury leading to ineffective drug absorption, competition between malabsorbed amino acid and bacterial degradation products with levodopa for the saturable active transport system in the small intestine, and drug metabolism by gut bacteria [31].

In the present study, 40 patients (i.e., 39% of the overall cohort) did not demonstrate a significant rise in breath hydrogen within 180 min [19]. As the prevalence of non-hydrogen producers was reported to be only around 2–20% [16,19,20], a possible explanation is that some of these patients might have had a prolonged oro-cecal transit time (OCTT) (in line with the findings of the two studies that have investigated this issue in PD) [5,6]. Davies et al. reported a prolonged OCTT (>180 min) in 10/15 (66.7%) elderly PD patients (and none was found to have SIBO), while Haboubi et al. found a mean OCTT of 194 min in 11 elderly PD patients (vs. 96 min in young healthy volunteers) (the patients in the study by Davies et al. appear to be comparable to our cohort with regards to PD status [mean PD duration six vs. 7.3 years; daily levodopa dose 450 vs. 527 mg/day]; these data were not reported by Haboubi and colleagues). Thus, SIBO in PD may not be explained by gut hypomotility alone [8,9], and other pathogenetic mechanisms, such as an impairment of local or systemic protective immune functions could play a role [13,20,21]. Interestingly, some investigators have reported significant reductions in circulating CD4+ T helper and B cells, suggesting some compromise in immune function, in PD patients [24,32].

Strengths of this study include recruitment of a relatively large number of subjects, across a broad range of disease severity. Patients underwent blinded evaluations, including objective and quantitative measures of motor function and a comprehensive survey of GI symptoms. The main weakness of the study is in the assessment of SIBO itself, since there is no gold standard way to diagnose SIBO and the accuracy of all current tests, including the LHBT (with a reported sensitivity of 52% and specificity of 86%), remains limited [16,17,20]. It is possible that a combination of tests, such as the LHBT plus a glucose breath test, could provide more accurate results [8], but so far this has not been routinely recommended, even in the research arena [13,16–18]. Although the most direct method is to perform colony counts of intestinal luminal contents, this technique is invasive and there are considerable shortcomings with the validity and reliability of culture methodology [4,13,16–18,20,21]. Furthermore, there is currently no methodology validated for culturing the mid- and distal small bowel, where SIBO is more likely to occur in patients with normal anatomy [18]. Modern molecular techniques may ultimately prove

Table 4
Hierarchical multiple regression analysis.

Dependent variable	Independent variable							
	Model 1 PD duration	Model 2 PD duration + SIBO status	Coefficients summary for Model 2					
			PD duration			SIBO		
	R^2 change	R^2 change	*B*	Standard error	Beta (β)	*B*	Standard error	Beta (β)
GI variables								
GSS	0.006	0.033	0.028	0.080	0.035	−1.810	0.973	−0.188
Diarrhoea	0.002	0.000	0.003	0.008	0.047	0.006	0.093	0.006
Upper abdominal pain	0.015	0.016	−0.022	0.015	−0.152	−0.229	0.181	−0.129
Lower abdominal pain	0.000	0.002	−0.001	0.014	−0.008	0.079	0.173	0.047
Bloating	0.000	0.028	−0.005	0.015	−0.037	−0.314	0.185	−0.173
Flatulence	0.005	0.007	0.008	0.016	0.054	−0.160	0.190	−0.086
Abdominal tenderness	0.016	0.002	0.012	0.011	0.116	−0.060	0.135	−0.046
Weight loss	0.024	0.002	0.024	0.017	0.145	−0.091	0.203	−0.046
Nausea	0.004	0.003	0.006	0.013	0.047	−0.083	0.157	−0.054
Constipation	0.055*	0.048*	0.034*	0.018	0.183*	−0.519*	0.225	−0.226*
Tenesmus	0.001	0.041*	−0.005	0.020	−0.024	−0.504*	0.244	−0.209*
Body Mass Index	0.044*	0.001	−0.176*	0.082	−0.220*	−0.387	1.004	−0.039
UPDRS and timed tests of motor function								
UPDRS Part III	0.082*	0.042*	0.740*	0.213	0.336*	5.670*	2.605	0.210*
UPDRS Part IV	0.152*	0.019	0.230*	0.061	0.357*	−1.128	0.741	−0.143
UPDRS Part IVB (Clinical fluctuations)[a]	0.106*	0.024	0.086*	0.029	0.289*	−0.581	0.351	−0.160
UPDRS Part IVB (Unpredictable "off" periods)[b]	0.029	0.024	0.010	0.008	0.133	−0.153	0.096	−0.161
Timed Gait (s)	0.113*	0.051*	1.289*	0.310	0.391*	9.359*	3.795	0.232*
Timed Gait (steps)	0.064*	0.016	0.858*	0.302	0.283*	4.778	3.695	0.129
Pegboard (dominant)	0.162*	0.090*	−0.310*	0.058	−0.474*	−2.458*	0.713	−0.308*
Pegboard (non-dominant)	0.170*	0.068*	−0.288*	0.054	−0.475*	−1.996*	0.666	−0.269*
Pegboard (both)	0.128*	0.077*	−0.237*	0.051	−0.424*	−1.943*	0.630	−0.284*
Quality of life								
PDQ-39 Summary Index	0.202*	0.000	1.612*	0.332	0.447*	0.497	4.055	0.011

The dependent variables for which SIBO made a significant difference are highlighted in bold (first column).
*Indicates significance ($P < 0.05$). R^2 change: incremental variance explained; *B*: unstandardized coefficient; Beta: standardized coefficient.
[a] Sum of scores for UPDRS Questions 36–39, which evaluate clinical fluctuations.
[b] UPDRS Question 37, which evaluates whether "off" periods are unpredictable.

to be the most precise method to define SIBO [17], but until better diagnostics are available, breath testing remains the predominant method [20,21], with the LHBT being the most widely used technique [16–18]. We also did not study SIBO prevalence in matched controls. Gabrielli et al. and Fasano et al. found an approximately three-to-seven-fold increased prevalence in PD patients, but Dobbs et al. reported a 67% LHBT positivity rate in both PD subjects and spousal controls; further study of this issue is needed [7–9].

In conclusion, SIBO was detected in one quarter of PD patients, and can occur early in the disease. SIBO was not associated with worse GI symptoms, but independently predicted worse motor function. Taken together with the findings of earlier studies, it may be worthwhile to screen for SIBO by non-invasive methods such as breath testing in patients who are not responding adequately to PD treatment. Properly designed treatment trials are needed to confirm a causal association between SIBO and worse motor function in PD.

Conflict of interest

The authors have no conflict of interest.

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