Original Article

# Gastrointestinal dysfunction in Parkinson's Disease: absence of anti-gliadin antibodies

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**Background and Objectives:** Parkinson disease (PD), which is a neurodegenerative disorder, includes several gastrointestinal symptoms that are similar to those of Celiac disease (CD). However, the presence of celiac antibodies in PD patients has not yet been studied. Our aim in this study is to compare anti-transglutaminase (ATA) and antigliadin antibodies (AGA) as well as gastrointestinal symptoms and nutrition habits between patients with Parkinson's disease (PD) and healthy controls. **Methods and Study Design:** Serum AGA IgG and IgA and the ATA antibodies IgA and IgG were studied in 102 PD patients and 91 healthy controls. Gastrointestinal symptoms, specifically constipation, were investigated using the gastrointestinal system rating scale (GSRS) and the constipation rating scale (CRS). Dietary habits were also investigated and compared between the groups. **Results:** No significant differences were found between the two groups in terms of celiac antibodies. As expected, the hypokinetic GSRS and CRS scores were significantly higher in the PD group ($p$<0.001). Dietary habits, especially carbohydrate-rich diets, had a negative impact on gastrointestinal symptoms in the PD patients. **Conclusions:** Studies have suggested a connection between PD and CD, which infers a probable non-celiac gluten intolerance and the need to offer PD patients an elimination diet. However, the results of our study did not support any link between celiac antibodies and PD. Notwithstanding, the negative impact of a carbohydrate-rich diet in PD patients still leaves a question regarding gluten sensitivity in these patients.

**Key Words: Parkinson's, constipation, gastrointestinal symptom, celiac antibodies, diet**

## INTRODUCTION

Celiac disease (CD), which is regarded as a multisystemic autoimmune disease, has several neurological manifestations.[1] Until now, several neurological diseases and symptoms, including headache and migraine, ataxia, chronic neuropathies, and cognitive impairment, have been found to be related to CD.[2] The enteric nervous system is thought to be responsible for the extraintestinal manifestations of CD.[3] Parkinson's disease (PD) is a common neurodegenerative condition that exhibits both motor and non-motor symptoms. Gastrointestinal (GI) problems are one of the most common non-motor system symptoms in patients with PD, with up to 30% of these patients suffering from GIS symptoms, among which nausea, vomiting, and constipation are the most common. Gastrointestinal symptoms in PD could be related to the dysregulation of the gut–brain–microbiota axis. Furthermore, the hypothesis that the pathological impairment in PD spreads from the gut to the brain bears some similarities to CD, which presents with extraintestinal symptoms that emanate from the enteric nervous system.[4] Based on both the clinical and pathogenetic similarities with CD, we investigated the presence of celiac disease-related antibodies in a PD population (Figure 1). We also studied the PD patients' gastrointestinal symptoms and related demographic features, including nutrition habits, and compared them with those of the healthy controls.

## METHODS

This study was designed as a prospective, cross-sectional, case-controlled study. The patient selection, clinical evaluations, and laboratory analyses were conducted between September 2020 and March 2021.The study participants were comprised of two groups, namely, the PD group and the healthy control group. The PD group consisted of PD patients who had been diagnosed with idiopathic PD in movement disorder and neurology outpatient clinics. The inclusion and exclusion criteria for the PD group were based on the MDS clinical diagnostic criteria.[5] The healthy control group comprised of voluntary partners of the patients from our neurology outpatient clinic. These individuals were required to be 18 years of age or older and not have any GIS-related complaints that could indicate serious disease. People with CD, severe GIS-related

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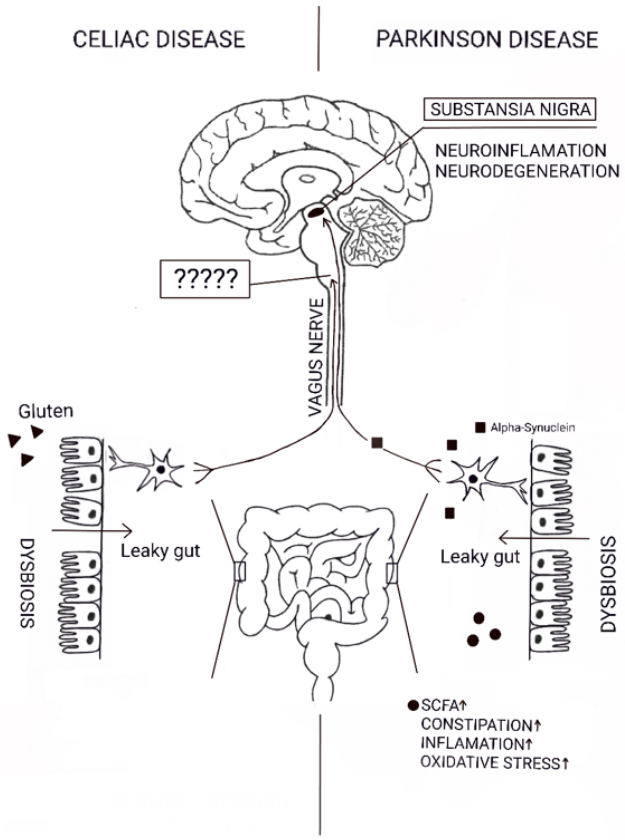


**Figure 1.** The study hypothesis discusses the potential association between PD and CD

diseases, stroke, head trauma, brain tumors, similar neurodegenerative diseases such as Alzheimer's disease, and/or serious medical diseases were not included in the study. The study sample included 193 participants, of which 102 had PD, and 91 were healthy controls.

A 5 mL blood sample was obtained from each participant using a yellow-capped gel biochemistry tube, which was subsequently delivered to the laboratory within 30 min, where it was centrifuged at 10,000 rpm for 10 min. Following centrifugation, the remaining serum was transferred to sterile gel-free tubes and stored in a −80°C cabinet for a maximum period of two months until analysis. The sample was analyzed using the ELISA and IFA method on a EUROIMMUN Analyzer I device. The levels of the serum antigliadin antibodies (AGA) IgG and IgA and anti-transglutaminase (ATG) antibodies IgA and IgG were studied.

Age, gender, education level, family history of PD, smoking habits, dietary habits, complaints of constipation, and daily water consumption (more or less than 1.5 L) of each participant were evaluated using a sociodemographic form, prepared by the researchers. In terms of diet, the participants were asked to choose between four nutrition groups: carbohydrate-weighted (CH), carbohydrate–vegetable mixed (CHvg), vegetables–fruits (VgFr), and protein-weighted (Prt). Carbohydrate weighted meals included foods like pasta, rice, and wheat products the most. Meat, poultry, and fish were included in protein-weighted meals. Meat and carbohydrates intake were low in vegetable-fruit weighted meals, which prioritized fruits and vegetables. A carbohydrate-vegetable mixed diet provided equal amounts of carbohydrates and vegetables. Patients were given an explanation of these four popular diet styles in Turkey and instructed to select one that best suited their eating habits. The levodopa equivalent doses of the dopaminergic treatments used by the PD patients were calculated and added to the form.[6] The Unified Parkinson's Disease Rating Scale (UPDRS) and Parkinson's Disease Non-Motor Symptom Scale Form (NMSS) were used to evaluate the participants in the PD group.[7,8]

The Gastrointestinal System Symptom Rating Scale (GSRS) and Constipation Rating Scale (CRS) were applied to all the participants to assess their gastrointestinal symptoms. The GSRS is a disease-specific, interview-based rating scale that consists of 15 items grouped into five symptom clusters, namely, reflux, abdominal pain, indigestion, diarrhea, and constipation. Each question can be scored between 1 and 7 (1=no disturbance and 7=very severe disturbance). The analysis was performed using three subcategories: upper GSRS (abdominal pain, borborygmus, abdominal distention, increased flatus, heartburn, acid reflux, sucking sensation, nausea and vomiting, increased eructation), hyperkinetic GSRS (increased passage of stools, urgent need for defecation, soft stools), and hypokinetic GSRS (decreased passage of stools, hard stools, feeling of incomplete evacuation) scores. The total GSRS score was also calculated (Table 1). The questionnaire had previously been validated and applied to the assessment of gastrointestinal symptoms in CD.[9] The CRS is a self-assessment scale that consists of 28 items, which are grouped as anxiety (11 items), physical discomfort (4 items), psychosocial discomfort (8 items), and satisfaction (5 items).[10]

**Table 1.** Parkinson's disease and control groups' demographics, disease-related characteristics, and celiac antibodies

| | Parkinson's disease group (n= 102) Mean (SD) or n (%) | Control group (n= 91) Mean (SD) or n (%) | *p*-value† |
|---|---|---|---|
| Age | 62.9 ± 11.2 | 56.8 ± 9.5 | <0.001 |
| Gender | | | 0.187 |
| Male | 52 (51%) | 55 (60.4%) | |
| Female | 50 (49%) | 36 (39.6%) | |
| Dietary habits | | | 0.779 |
| Carbohydrate-rich diet | 32 (31.4%) | 60 (31.1%) | |
| Carbohydrate and vegetable diet | 42 (41.2%) | 83 (43%) | |
| Vegetable and fruit diet | 20 (19.6%) | 38 (19.7%) | |
| Protein-rich diet | 8 (7.8%) | 12 (6.2%) | |
| Water consumption | | | 0.206 |
| 1.5 L and more | 39 (38.2%) | 43 (47.3%) | |
| Less than 1.5 L | 63 (61.8%) | 48 (52.7%) | |
| İndividuals with constipation | 68 (66.7%) | 35 (38.5%) | <0.001 |
| Gliadin A antibody (+) | 1 | 0 | |
| Gliadin G antibody (+) | 2 | 1 | |
| Transglutaminase A (+) | 1 | 0 | |
| Transglutaminase G (+) | 0 | 0 | |
| Disease duration (years) | 5.2 ± 4.1 | | |
| Disease subtypes | | | |
| Akinetic rigid type | 60 (58.8%) | | |
| Tremor dominant type | 42 (41.2%) | | |
| UPDRS (total) | 58.9 ± 30.9 | | |
| NMSS | 12.4 ± 4.1 | | |
| Levodopa equivalent daily dosage (mg) | 713.9 ± 437.7 | | |

SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale; NMSS: Nonmotor symptom Rating Scale. System Rating Scale; GIS: Gastrointestinal System

†*p*-values were determined through independent samples test, Mann–Whitney U test, or Spearman's chi square test

**p*-values <0.05

The data were analyzed using IBM SPSS version 23. Compliance with the normal distribution was examined by applying the Kolmogorov–Smirnov and Shapiro–Wilk tests. Chi-square and Fisher's exact tests were used to compare the categorical variables according to the groups. An independent two-sample t-test was used to compare the normally distributed data according to the paired groups, and a Mann–Whitney U test was employed to compare the non-normally distributed data. A one-way analysis of variance was conducted to compare the normally distributed data in groups of three or more, and multiple comparisons were performed using Duncan's test. The Kruskal–Wallis test was used to compare the data that were not normally distributed according to groups of three or more, while Spearman's rho correlation coefficient was applied to examine the relationship between the data that were not normally distributed. The analysis results relating to the quantitative data were presented as mean ± standard deviation and median (minimum–maximum) and the categorical data as frequency (percentage). The significance level was taken as $p<0.050$.

Approval was obtained from the Ethics Committee (decision number 2020/514/160/21, dated 06/26/2020). After informing them about the study, signed informed consent forms were obtained from all the participants who had agreed to participate in the study.

## RESULTS

The demographic features of the participants in the PD and control groups and the clinical assessments of the PD participants are summarized in Table 1. The mean age of the PD group (50 male, 52 female) was 62.9±11.2 years, while the mean age of the controls (36 male, 55 female) was 56.8±9.5 years. The mean age of the PD group was significantly higher than that of the control group ($p<0.001$). A family history of PD was more common in the PD group (PD group: 26%, control group: 6%; $p<0.001$). The participants in the control group were more likely to smoke than those in the PD group (PD group: 35%, control group: 47%, $p<0.001$). Dietary habits and water consumption were similar between the PD and control groups. The mean UPDRS score of the PD group was 58.9 ± 30.9, and the mean disease duration was 5.2 ± 4.1 years. The total UPDRS and NMSS scores for the PD group were 58.9 ± 30.9 and 12.4 ± 4.1, respectively. In addition, disease subtype of 58.8% of PD participants were akinetic rigid, and the rest (41.2%) were tremor dominant. The PD participants were using 713.9 ± 437.7 mg levodopa equivalent anti-PD treatments.

There was a nonsignificant difference between the two groups in terms of the presence of celiac antibodies. One Parkinson patient was antigliadin Ig A antibody positive whereas none of the control patients had antigliadin Ig A antibody. Two PD patients and one control group participant had antigliadin Ig G antibody. Only one PD patient had Transglutaminase Ig A antibody; neither PD patients nor control group had Transglutaminase Ig G antibody (Table 1). Although the total, upper, and hyperkinetic GSRS scores were statistically similar between the two groups ($p$=0.119, 0,08 and 0,525), the hypoactive GSRS and CSS scores were found to be significantly higher in

**Table 2.** Comparison of gastrointestinal symptom-related scales between participants with Parkinson's disease and healthy controls

| | PD group | | Control group | | Test statistics | *p* |
|---|---|---|---|---|---|---|
| | Median ± SD | Mean (min-max) | Median ± SD | Mean (min–max) | | |
| CRS | 43.5 ± 41.4 | 39.0 (0.0–142.0) | 22.7 ± 32.4 | 0.0 (0.0–114.0) | U = 3200 | <0.001 |
| GSRS total | 32.6 ± 12.7 | 33.0 (15.0–66.0) | 30.2 ± 12.1 | 28.0 (15.0–83.0) | U = 4037.5 | 0.119 |
| Upper GSRS | 16.1 ± 7.6 | 14.0 (8.0–41.0) | 17.8 ± 7.6 | 17.0 (8.0–44.0) | U = 3964 | 0.080 |
| Hypokinetic GSRS | 11.8 ± 7.1 | 14.0 (3.0–21.0) | 7.1 ± 5.5 | 3.0 (3.0–24.0) | U = 2848 | <0.001 |
| Hyperkinetic GSRS | 4.8 ± 1.6 | 4.0 (3.0–12.0) | 5.1 ± 2.5 | 4.0 (4.0–21.0) | U = 4445 | 0.525 |

CRS: Constipation Rating Scale; GSRS: Gastrointestinal System Rating Scale; GIS: Gastrointestinal System

**Table 3.** The correlation of the clinical assessment scales with age, disease duration, and LEDD in the participants with Parkinson's disease

| | Age | Disease duration | LEDD |
|---|---|---|---|
| UPDRS (total) | | | |
| *r* | 0.478 | 0.368 | 0.462 |
| *p* | <0.001 | <0.001 | <0.001 |
| NMSS | | | |
| *r* | 0.357 | 0.263 | 0.334 |
| *p* | <0.001 | <0.001 | <0.001 |
| CRS | | | |
| *r* | 0.259 | 0.242 | 0.257 |
| *p* | 0.009 | 0.014 | 0.009 |
| GSRS total | | | |
| *r* | 0.282 | 0.203 | 0.274 |
| *p* | 0.004 | 0.041 | 0.005 |
| Upper GISRS | | | |
| *r* | 0.203 | 0.142 | 0.265 |
| *p* | 0.040 | 0.155 | 0.007 |
| Hypokinetic GSRS | | | |
| *r* | 0.227 | 0.209 | 0.199 |
| *p* | 0.022 | 0.035 | 0.045 |
| Hyperkinetic GSRS | | | |
| *r* | −0.001 | 0.003 | 0.022 |
| *p* | 0.993 | 0.976 | 0.829 |

CRS: Constipation Rating Scale; GSRS: Gastrointestinal System Rating Scale; GIS: Gastrointestinal System; LEDD: Levodopa equivalent daily

the PD group, as expected ($p<0.001$) (Table 2). We found a positive correlation between the total UPDRS, NMSS, CRS, GISRS, and hypokinetic GISRS and age, disease duration, and levodopa equivalent daily dose (LEDD). The upper GISRS scores had a positive correlation with age and LEDD; however, no correlation was found between the hyperkinetic GISRS score and age, disease duration, and LEDD (Table 3). The total GISRS scores were higher among the participants with CH-rich diets. The upper GISRS scores were also higher among the participants who preferred CH-rich diets compared to protein-rich diets. The participants who preferred CH-rich diets had higher hypokinetic GISRS and CRS scores compared with those who consumed vegetable- and protein-rich diets. Participants who consumed less than 1.5 L of water a day also had higher GISRS, hypokinetic and hyperkinetic GISRS, and CRS scores (Table 4).

## DISCUSSION

Gastrointestinal problems are common in PD patients and related to both motor and nonmotor symptoms.[4] GIS symptoms in PD patients include drooling, dental problems, diminished taste, swallowing disorders, impaired gastric emptying that causes postprandial bloating or abdominal discomfort, weight loss, and constipation.[11] The gastric symptoms seen in PD have similarities with those of CD and gluten sensitivity. To date, the most common neurological symptoms seen in CD patients have been reported as ataxia, polyneuropathy, and epilepsy.[12] Although the GIS symptoms between patients with PD and those with CD are similar, the prevalence of celiac antibodies in patients with PD has not previously been studied. There is only one case in the literature in which a patient had PD symptoms and celiac disease, and the patient's PD symptoms improved after starting a gluten-restricted diet.[13] Studies have suggested a connection between PD and celiac disease, which highlights the possi-

**Table 4.** The relationship between the scales applied in the Parkinson's disease group and diet and water consumption

| | GSRS total | Upper GIS GSRS | Hypokinetic GSRS | Hyperkinetic GSRS | CRS |
|---|---|---|---|---|---|
| Nutrition | | | | | |
| Carbohydrate-rich diet | 40.3 ± 12.3 | 19.5 ± 8.7 | 15.9 ± 5.5 | 4.9 ± 1.6 | 69.0 ± 38.1 |
| | 40.0 (15.0–66.0) | 16.5 (8.0–41.0) | 17.5 (3.0–21.0) | 4.0 (4.0–10.0) | 71.0 (0.0–142.0) |
| Carbohydrate and vegetables-rich diet | 31.6 ± 11.7 | 15.2 ± 6.6 | 12.1 ± 6.9 | 4.4 ± 0.9 | 42.4 ± 37.8 |
| | 33.0 (15.0–59.0) | 13.0 (8.0–34.0) | 14.5 (3.0–21.0) | 4.0 (3.0–8.0) | 38.0 (0.0–119.0) |
| Vegetables and fruits-rich diet | 26.3 ± 10.4 | 14.4 ± 6.9 | 6.9 ± 5.6 | 5.1 ± 2.3 | 17.1 ± 34.9 |
| | 25.0 (15.0–48.0) | 11.5 (8.0–30.0) | 4.0 (3.0–20.0) | 4.0 (4.0–12.0) | 0.0 (0.0–138.0) |
| Protein-rich diet | 22.9 ± 7.0 | 11.9 ± 5.3 | 5.9 ± 6.4 | 5.1 ± 2.1 | 13.1 ± 25.5 |
| | 21.5 (15.0–33.0) | 11.0 (8.0–24.0) | 3.0 (3.0–21.0) | 4.0 (4.0–9.0) | 0.0 (0.0–67.0) |
| Test statistics | $x^2$= 22.306 | $x^2$=10.599 | $x^2$= 25.377 | $x^2$= 1.363 | $x^2$= 28.174 |
| *p* | <0.001 | 0.014 | <0.001 | 0.714 | <0.001 |
| Water consumption | | | | | |
| <1.5 liters | 35.7 ± 12.1 | 16.9 ± 7.4 | 13.9 ± 6.7 | 5.0 ± 1.7 | 54.6 ± 40.2 |
| | 36.0 (15.0–62.0) | 15.0 (8.0–37.0) | 17.0 (3.0–21.0) | 4.0 (4.0–12.0) | 57.0 (0.0–142.0) |
| >1.5 liters | 27.6 ± 12.2 | 14.9 ± 7.9 | 8.4 ± 6.5 | 4.4 ± 1.3 | 25.5 ± 37.2 |
| | 25.0 (15.0–66.0) | 12.0 (8.0–41.0) | 5.0 (3.0–21.0) | 4.0 (3.0–10.0) | 0.0 (0.0–119.0) |
| Test statistics | U = 743.0 | U = 971.0 | U = 656.5 | U = 989.0 | U = 702.0 |
| *p* | 0.001 | 0.075 | <0.001 | 0.036 | <0.001 |

CRS: Constipation Rating Scale; GSRS: Gastrointestinal System Rating Scale; GIS: Gastrointestinal System

bility of non-celiac gluten intolerance in patients with PD and the potential value in offering these patients an elimination diet.[14] Our study is the first to investigate the possible presence of celiac antibodies in the PD population. In terms of celiac antibody positivity, the PD group was found to be similar to the normal population at a rate of 1–2% for both groups. The serological diagnosis of CD has improved in recent years. AGA was the first serological marker in the diagnosis of CD, but it has low specificity. ATG antibodies, especially the IgA type, have 96% sensitivity for the diagnosis of CD. We therefore studied both the AGA and ATG antibodies in the participants in our study; however, we found no significant difference between the control and PD groups. Notwithstanding, to increase the diagnostic accuracy of intestinal biopsies in seronegative patients, an HLA DQ2/DQ8 investigation is advised.[3] We may therefore have missed these seronegative patients. Although we could not demonstrate a higher celiac antibody prevalence among the participants with PD in our study, the results could not exclude gluten sensitivity because the participants were not offered the option of starting an elimination diet. The potential role of gluten in neurodegeneration has been suggested previously, and a sequence homology between wheat, tissue TG, and alpha-synuclein may play a role in the pathogenesis of PD. Nevertheless, the role of gluten in the pathogenesis of PD remains unresolved.[15]

We also investigated GIS issues among the participants with PD using GISRS and CRS (Table 3). The constipation complaints and CRS scores were higher in the PD group compared with the healthy controls, but the total GIRS scores of the two groups were similar. This result contradicts a study by Kenna and colleagues, who found a higher total GISRS score among the patients with PD in their study; however the hyperactive and hypoactive GISRS scores were similar to the results of our study.[16] This difference could be explained by a higher upper gastrointestinal symptom issue in their patient cohort or in our control group.

Both higher dose drug usage and disease severity could be factors in GIS symptoms related to PD. In this study, the GISRS and CRS scores had positive correlations with age, disease duration, and LEDD (Table 4). These results were compatible with those of Kenna and colleagues. They analyzed the correlation of each anti-PD drug with GISRS scores. Although LEDD correlated with total GISRS, neither levodopa, nor dopamine agonist, COMT inhibitor, or MAO B inhibitor usage correlated with the GISRS scores, which shows that it is not the drugs used in PD treatment, but the disease severity related to LEDD that is important in the GIS symptoms in PD patients.[16]

In our study, we also evaluated the nutrition habits of the PD and control group participants a similarity between the PD group and the control group in terms of nutrition and water consumption were noted (Table 1). However, the CRS scores of the PD group increased with an increase in the amount of CH in the diet and a decrease in water consumption. The participants with PD who had CH-rich nutrition habits had worse total, hypokinetic, and upper GISRS scores (Table 4). As a result, not only constipation-like symptoms, but also the upper GISRS scores were higher among the participants with PD who consumed more CH. In a study conducted in Ghana, the rate of constipation in patients with PD was found to be lower than that indicated in the literature, and it was shown that the population living in Ghana consumed large amounts of fruits and vegetables.[17] Accordingly, nutrition habits, especially in relation to CH consumption, could be an important factor in PD patients with GIS symptoms. One potential disadvantage of our study is that we did not assess the individuals' nutritional habits using an objective, accurate scale. However, there are no guidelines for eval-

uating and screening nutritional status in people with Parkinson's disease.[18]

The relationship between CH consumption and GIS symptoms may indicate a link between seronegative non-celiac gluten sensitivity (NCGS) and PD. However, a detailed investigation involving, for example, a gluten challenge is needed to exclude NCGS in these patients. NCGS is a controversial diagnosis, and the absence of sensitive and specific biomarkers for NCGS make the identification of NCGS cases challenging. A definite diagnostic approach to NCGS is not yet available, and studies are needed to clarify the relationship between NCGS and PD.

Although a direct relationship between gluten antibodies and PD could not be demonstrated in this study, we found that constipation and the GIS symptoms seen in PD were associated with dietary patterns. We also revealed that, CH-dominated diet in particular, and low water consumption could worsen GIS-related symptoms. These results suggested that the relationship between gluten sensitivity and PD should be investigated by examining more specific celiac antibody subtypes. These findings should be evaluated along with motor symptoms during clinical follow-ups of PD patients, and recommendations should be provided to patients on their medical and nutritional habits. Since GIS-related non-motor symptoms are difficult to manage in patients with PD, we recommend that, based on the results of this study, researchers should gain a better understanding of the pathophysiology of PD related with gluten, investigate the celiac antibody subgroups in more detail, and develop comprehensive nutritional scales to assess nutrition habits in PD.

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**AUTHOR DISCLOSURES**

The author declares no conflict of interest.

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