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ORIGINAL ARTICLE

Relationship between subjective sleep quality and serum ghrelin levels in Parkinson's disease

Alper Ayaslı[1], Yıldız Değirmenci[2], Davran Fat[3], Mehmet Ali Sungur[4]

[1]Department of Neurology, Atatürk State Hospital, Düzce, Türkiye
[2]Department of Neurology, Medicana Zincirlikuyu Hospital, İstanbul, Türkiye
[3]Department of Biochemistry, Düzce University Faculty of Medicine, Düzce, Türkiye
[4]Department of Biostatistics, Düzce University Faculty of Medicine, Düzce, Türkiye

ABSTRACT

Objectives: This study aimed to investigate the relationship between serum ghrelin levels and subjective sleep quality in patients with Parkinson's disease (PD).

Patients and methods: This prospective case-control study was conducted between July 2020 and September 2021. Sixty-three patients (39 males, 24 females; mean age: 64.8±12.8; range, 52 to 76 years) diagnosed with idiopathic PD and 59 healthy participants (34 males, 25 females; mean age: 63.9±6.2 years; range, 57 to 59 years) were included in the study. The patients' modified Hoehn and Yahr and Unified Parkinson's Disease Rating Scale scores were determined. Subjective sleep quality of study groups was evaluated with the Pittsburgh Sleep Quality Index, and serum fasting ghrelin levels were measured.

Results: The patient and control groups did not show any significant differences in terms of sociodemographic characteristics. The Pittsburgh Sleep Quality Index values of the patient group were higher compared to the control group ($p \leq 0.001$). There was no significant difference between serum ghrelin levels ($p=0.329$).

Conclusion: A significant relationship was not identified between subjective sleep quality and serum ghrelin levels in PD, and ghrelin did not support the diagnosis of PD. Further studies with larger samples that account for the variability in food intake and the timing of serum ghrelin measurements are needed.

Keywords: Ghrelin, Parkinson's disease, sleep quality.

Idiopathic Parkinson's disease (IPD) is a progressive chronic neurodegenerative disease characterized by the gradual loss of dopaminergic neurons in the substantia nigra pars compacta.[1] It is the second most common neurodegenerative disease following Alzheimer's disease, with a prevalence of 160 per 100,000 individuals and an incidence of 20 per 100,000 individuals.[2] The pathophysiology underlying IPD includes environmental and genetic factors, mitochondrial dysfunction, oxidative stress, excitotoxicity, apoptosis, and inflammation. Intraneuronal Lewy bodies are the pathological hallmarks of the disease.[3] While it often manifests in individuals in their 50s and 60s, earlier-onset cases were reported.[2] Major motor features include bradykinesia, resting tremor, rigidity, and postural instability. However, nonmotor symptoms such as gastric motility issues, autonomic dysfunctions, cognitive impairment, mood disorders, and sleep disturbances are likely to occur during the course of the disease.[2]

Common sleep disorders in IPD encompass parasomnias, including insomnia, daytime sleepiness disorders, respiratory disorders related to sleep, circadian rhythm disorders (e.g., delayed sleep phase disorder and advanced sleep phase disorder), movement disorders related to sleep,

Correspondence: Alper Ayaslı, MD. Atatürk Devlet Hastanesi Nöroloji Kliniği, 81010 Düzce, Türkiye
E-mail: draayasli@gmail.com
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and REM (rapid eye movement) sleep behavioral disorders.[4,5]

Ghrelin is known as the hunger hormone, produced by gastric oxyntic A-like cells, and serves as an endogenous ligand for the growth hormone secretagogue receptor. The association between serum ghrelin levels and gastrointestinal system diseases, metabolism, feeding disorders, mood disorders, sleep health, and neurodegenerative diseases, including Parkinson's disease (PD), garnered significant interest. Ghrelin serum levels exhibit a dynamic pattern: they increase during fasting, decrease with food intake, and then slowly rise again.[6-11] It is thought that ghrelin increases the release of growth hormone-releasing hormone, which, in turn, increases non-REM sleep Stage 2 and affects sleep.[12] Although this suggests that IPD patients may have a relationship with sleep quality, based on our literature review, the relationship between serum ghrelin levels and sleep health in patients with IPD appears to be underestimated. From this perspective, this study aimed to investigate the association between serum ghrelin levels and subjective sleep quality in patients with IPD.

PATIENTS AND METHODS

This prospective case-control study was conducted in the Düzce University Faculty of Medicine, Department of Neurology, between July 2020 and September 2021. A total of 63 patients (39 males, 24 females; mean age: 64.8±12.8; range, 52 to 76 years) diagnosed with IPD according to the United Kingdom Brain Bank Criteria[13] in the PD in the Düzce University Faculty of Medicine, Department of Neurology, along with 59 healthy participants (34 males, 25 females; mean age: 63.9±6.2 years; range, 57 to 59 years), were enrolled in the study. Exclusion criteria included patients under 18 years of age, those without a diagnosis of IPD, patients with mental retardation, dementia, psychiatric diseases, existing sleep disorders, and alcohol and substance addictions. The control group consisted of randomly enrolled, healthy, and age-matched volunteers. Sociodemographic characteristics, including sex, age, body mass index (BMI), education, occupation, dominant hand, chronic illnesses, and medical history were recorded for both groups. Disease characteristics (disease stage, onset of symptoms, initial symptom, and antiparkinsonian treatments) of the patients were documented. The modified Hoehn and Yahr score and Unified Parkinson's Disease Rating Scale (UPDRS) scores were also recorded. The local ethical committee of Düzce University Non-Interventional Health Research Ethics Committee approved the study (date: 06.07.2020, no: 2020/145). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The Hoehn and Yahr scale, developed by Hoehn and Yahr[14] in 1967, was used to determine the stage of IPD. This scale, which is generally used to indicate the extent and progression of the disease, defines five stages.[14]

The UPDRS consists of four main categories, totaling 42 questions. Scores are measured through examination, with higher scores indicating a higher disease severity level.[15] The Turkish version's validity and reliability were confirmed by Akbostancı et al.[16] These categories include mental, behavioral, and emotional state (0-16), activities of daily living (0-104), motor rating (0-56), and complications of treatment in the previous week (0-23).

Subjective sleep quality of patients and healthy volunteers was evaluated using the Pittsburgh Sleep Quality Index (PSQI). Developed by Buysse et al.,[17] this 19-item scale assesses sleep quality and disturbances in the previous month. Parameters such as subjective sleep quality, sleep latency, sleep duration, habitual sleep activity, sleep disturbance, use of sleep medication, and daily dysfunction are evaluated. Scores range from 0 to 21, with a total score greater than 5 indicating poor sleep quality.[17] Its Turkish validity and reliability were confirmed by Agargun.[18] Subjective sleep quality of the study groups was assessed using PSQI scores.

Biochemical analysis of fasting ghrelin levels was performed on blood samples drawn into a gel biochemistry tube after 8 h of fasting. Serum samples were obtained by centrifuging blood samples at 4000 rpm for 10 min. Serum samples were stored at −80°C until the day of analysis. Fasting ghrelin levels in serum samples were measured with the ghrelin. ELISA (enzyme-linked immunosorbent assay) kit according to the manufacturer's instructions (Sunred-HUMAN (GHRL) 201-12-5583; Shanghai Sunred Biological (SRB) Technology Co., Ltd., Shanghai, China). Briefly, serum samples and reagents in the study kit were brought to room temperature

before measurement. Samples and reagents were loaded on plates precoated with ghrelin antibody according to the manufacturer's instructions. The optical density formed at the end of the reaction was measured in an ELISA reader device at a wavelength of 450 nm. The ghrelin concentration in the patient and control group samples was calculated using the formula obtained from the standard curve drawn with the concentration and absorbance values of the standards.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were specified with the mean ± standard deviation (SD) or median, interquartile range (IOR), and minimum-maximum by data range. Categorical variables were expressed as frequency and percentage. The range of numerical variables was assessed with the Kolmogorov-Smirnov test, and group comparisons were made using the independent sample t-test and the Mann-Whitney U test. Categorical variables were analyzed with the Pearson chi-square or Fisher-Freeman-Halton tests. Correlation analyses were performed using Spearman correlation analysis. The strength of the correlation coefficient was interpreted as weak if between 0.2 and 0.4, moderate if between 0.4 and 0.6, strong if between 0.6 and 0.8, and very strong if between 0.8 and 1.0.[19] The significance level was accepted as $p<0.05$.

RESULTS

The two groups had a similar sex distribution ($p=0.607$). Both groups had a similar age range ($p=0.630$). Sociodemographic characteristics such as place of residence, education, dominant hand, and BMI of the patient and control groups were also similar. However, the marital status of the two control groups was different from each other. The most common marital status in both groups was married, whereas divorced status was higher in the patient group (Table 1).

While there was a significant difference between the PSQI values of the patient and control groups participating in the study ($p\leq0.001$), there was

TABLE 1
Descriptive features of the patient and control groups

	Patient group (n=63)						Control group (n=59)						
	n	%	Mean±SD	Median	IQR	Min-Max	n	%	Mean±SD	Median	IQR	Min-Max	*p*
Age (year)			64.8±12.8						63.9±6.2				0.607†
Sex													0.630*
Male	39	61.9					34	57.6					
Female	24	38.1					25	42.4					
Where they live													0.466*
City center	34	54.0					28	47.5					
Countryside	15	23.8					20	33.9					
Seashore	14	22.2					111	18.6					
Marital status													**0.007#**
Single	0	0.0					1	1.7					
Married	47	74.6					54	91.5					
Widow	16	25.4					4	6.8					
Education													0.772*
Be illiterate	5	7.9					7	11.9					
Be literate	9	14.3					8	13.6					
Elementary	38	60.3					30	50.8					
High school	6	9.5					9	15.3					
University	5	7.9					5	8.5					
Dominant hand													0.905*
Right	57	90.5					53	89.8					
Left	6	9.5					6	10.2					
BMI				28.2						30			>0.05
PSQI				8	6	1-18				3	5	0-11	**<0.001‡**
Ghrelin				1055	583	572-3997				944	602	554-3913	0.329$

SD: Standard deviation; IQR: Inter quartile range; BMI: Body mass index; PSQI: Pittsburgh sleep quality index; †: Independent samples t test; ‡: Mann-Whitney U test; *: Pearson chi-square; #: Fisher-Freeman-Halton.

TABLE 2
Comparison between UPDRS nonmotor and motor scores of IPD patients, PSQI scores, and serum hunger ghrelin levels

	Ghrelin	PSQI
UPDRS non-motor		
r	0.229	**0.516**
p	0.071	**<0.001**
n	63	63
UPDRS motor		
r	−0.204	0.160
p	0.109	0.212
n	63	63

UPDRS: Unified Parkinson's Disease Rating Scale; IPD: Idiopathic Parkinson's disease; PSQI: Pittsburgh Sleep Qality Index.

TABLE 3
Beginning period of disease's symptoms and correlation with other variables

	Disease period
PSQI	
r	0.197
p	0.121
n	63
Ghrelin	
r	0.129
p	0.313
n	63
UPDRS non-motor	
r	0.361
p	0.004
n	63
UPDRS motor	
r	0.420
p	0.001
n	63
H&Y	
r	0.523
p	<0.001
n	63

PSQI: Pittsburgh Sleep Quality Index; UPDRS: Unified Parkinson's disease rating scale; H&Y: Modified Hoehn & Yahr Staging Scale.

no significant difference between serum ghrelin levels (p=0.329; Table 1).

A slight positive correlation was found between PSQI and UPDRS nonmotor scores of IPD patients (p<0.001, r=0.517; Table 2).

When the PSQI scores of the patients were compared with the serum fasting ghrelin levels, no significant correlation was found (p=0.707, r=0.048). No significant correlation was found between the onset of the disease and PSQI values and serum ghrelin levels (p>0.05). There was a statistically significant correlation between the onset of the disease and UPDRS nonmotor (p=0.004), UPDRS motor (p=0.001), and modified Hoehn and Yahr (p<0.001) scores (Table 3).

There was no statistically significant correlation between the presence of additional diseases and serum ghrelin levels and PSQI scores in the patient group (p=0.144 and p=0.147, respectively; Table 4).

DISCUSSION

In this study, the sleep quality of the patient group was found to be significantly lower compared to the control group. However, no significant difference was found between serum ghrelin levels. A slight positive correlation was observed between PSQI and UPDRS nonmotor scores. There was no significant correlation between the onset of the disease and sleep quality and serum ghrelin levels, but there was a correlation between the onset of the disease and motor and nonmotor symptoms. No significant correlation was found between the presence of comorbidities and serum ghrelin levels and PSQI scores.

Sleep quality, which is the result of the very complex and synchronized operation of multiple brain regions and neurotransmitters, is affected by medical agents used for motor and nonmotor symptoms of IPD, nocturnal akinesia symptoms,

TABLE 4
Comparison with using ghrelin and PSQI, between who had comorbid disease and who don't had comorbid disease amongst IPD patients and control group (n=63)

	No comorbid disease (n=16)			Have comorbid disease (n=47)			
	Median	IQR	Min-Max	Median	IQR	Min-Max	*p*
PSQI	6.5	5	3-16	9	6	1-18	0.147
Ghrelin	1045	539	606-1576	1073	636	572-3997	0.144

PSQI: Pittsburgh sleep quality Index; IPD: Idiopathic Parkinson's disease; IQR: Interquartile range.

accompanying comorbidities, patient lifestyles, and some genetic factors.[20,21] It is known that ghrelin is related to the sleep process, and ghrelin levels are lower in patients with PD compared to the normal population.[9] Ghrelin was discovered 20 years ago by Kojima et al.[26] in 1990. Ghrelin, previously defined as the endogenous ligand of the secretory receptor of growth hormone, is a 28 amino acid structure produced from X/A-like cells in the stomach.[7] Ghrelin is an orexigenic substance that has a prokinetic effect in the gastrointestinal system and also affects higher brain functions.[8] It was discovered that it significantly increases the secretion of growth hormone from the anterior pituitary. Furthermore, it stimulates food intake and weight gain by activating neuropeptide Y neurons at the arcuate nucleus of the hypothalamus. For these reasons, it is commonly referred to as the hunger hormone.[22] Although the expectation of a change in eating behavior after lowering the ghrelin level led to the idea that obesity could be treated in this way, it was later observed that the results were contradictory.[23] Studies in rodents demonstrated that ghrelin receptors were also located in the myenteric plexus, dorsal vagal complex, and different brain parts and that ghrelin was involved not only in eating behavior but also in many higher brain functions such as memory, reward, mood, and sleep.[24] In recent years, many scientific studies examined the relationship between ghrelin and metabolic diseases, sleep disorders, psychiatric diseases, rheumatological diseases, and neurodegenerative diseases.[24]

It was shown that calorie restriction reduced the incidence of all degenerative diseases, and ghrelin was effective in this context.[25] The relationship between ghrelin and neurodegenerative diseases such as IPD was investigated in many studies.[10] It was shown that the ghrelin receptor (GHS-R1a) was localized in a wide range of different dopaminergic pathways and that ghrelin played an important role in dopamine metabolism.[24] Recent studies showed that ghrelin promoted dopamine discharge in the striatum and that ghrelin had protective effects on nigral dopaminergic neurons in IPD.[6] The known effect of ghrelin on gastric motility, its relationship with the vagal system, and its reduction in gastric motility in early-stage IPD support early Lewy body neuropathology in the dorsal motor nucleus of the vagus nerve and indicate that ghrelin synthesis is impaired in REM sleep behavior disorder. All these suggest that, when measured at the right time and with the right method, ghrelin can be a good biomarker that can be used in the diagnosis of PD and in determining sleep quality.[24-26]

In a study conducted in healthy volunteers, it was shown that serum fasting ghrelin levels followed a dynamic pattern that increased physiologically during fasting, decreased with food intake, and then increased slowly, and total fasting ghrelin levels of females were higher compared to males.[9] In the same study, although there was no significant difference between IPD stages, serum total ghrelin levels and active ghrelin levels were shown to be lower than in healthy volunteers. This suggests that postprandial ghrelin responses may also be impaired in PD.[9] In our study, it was determined that total fasting ghrelin levels did not show a significant decrease in IPD cases.

Ghrelin has an important place in sleep physiology.[10] It was reported that ghrelin positively affected sleep quality, sleep restriction increased ghrelin levels, as well as other metabolic effects, and unhealthy and insufficient sleep led to obesity by directing the patient to a carbohydrate diet.[27-29] It was emphasized that disruption of the ghrelin metabolism in IPD may lead to sleep disorders.[8,10,11] However, in our study, no significant relationship could be demonstrated between PSQI scores and ghrelin levels in the patient and control groups.

In our study, the PSQI score of the patient group was found to be higher than the control group, and a significant and moderate correlation ($r=0.517$) was found between PSQI scores and UPDRS nonmotor scores. These scores are consistent with the literature.[29,30]

Conflicting results were reported in the literature regarding the relationship between dopaminergic treatments and sleep health.[30,31] Happe et al.[31] stated that there was no relationship between dopaminergic drugs used in patients with PD and sleep quality. Zoccolella et al.[32] stated that higher doses of dopaminergic therapy were a risk factor for sleep health. Corcuff et al.[33] showed that levodopa and other treatments did not make a difference in ghrelin levels. In our study, PSQI scores and ghrelin levels were found to be lower in patients using dopamine agonists ($p<0.05$), but other treatments did not have a significant effect.

Limitations of this study included the timing of ghrelin measurement and the number of patients with PD enrolled in the study, which may have been insufficient to accurately reflect changes in

ghrelin concentration. Additionally, ghrelin can be affected by the variety of foods consumed, the amount of calories, and time of the last food eaten. We could not provide the same calories to the patient and control groups at the same time.

In conclusion, no statistically significant relationship could be demonstrated between fasting serum ghrelin levels of patients with PD and their sleep quality. Due to the dynamic physiology of ghrelin, which is affected by conditions such as hunger and satiety, in addition to studies investigating fasting serum ghrelin levels of patients with the same last meal times and calorie intake, studies with a greater number of patients and their ghrelin levels at different postprandial times are needed. Future studies are expected to approach the sensitivity and specificity of ghrelin, a potential peripheral clinical biomarker for the diagnosis and treatment for IPD and sleep quality. Furthermore, sex and BMI differences between the patient and control groups should be considered, and food intake variation and the timing of serum ghrelin measurement should be standardized.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, control/supervision: Y.D.; Design: A.A.; Data collection and/or processing, materials: A.A., F.D.; Analysis and/or interpretation, references and fundings: A.A., M.A.S.; Literature review, writing the article: A.A.; Critical review: A.A., Y.D.

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