Serum Leptin Levels and Cognition in Parkinson's Disease Patients

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ABSTRACT

Introduction: To investigate the relationship between serum leptin levels and cognition in Parkinson's disease (PD) patients.

Methods: Thirty patients with idiopathic PD and 30 healthy controls were enrolled. At baseline, all patients had their standing height, weight, and waist circumference measurements taken using a standard scale. Their body mass index was then calculated. A fasting blood of 5 ml was obtained from each patient in the morning. ELISA was used to analyze leptin concentrations. The severity of PD was evaluated using the Hoehn and Yahr scale, and the clinical status of patients was evaluated using the Unified Parkinson's Disease Rating Scale. The cognitive status of whole patients was evaluated using a validated form of the Montreal Cognitive Assessment Scale in Turkey (MoCA-TR).

Results: The mean ages of the patients and controls were 59.37 ± 9.22 and 58.50 ± 9.85 years, while the mean leptin levels were 4.13 ± 3.61 and 3.12 ± 2.43 ng/mL, respectively. Leptin levels did not differ between PD patients and the controls. PD patients had significantly lower MoCA-TR scores than the controls ($p=0.028$). MoCA-TR scores were not correlated to leptin levels in PD patients.

Conclusion: In this study, we could not find a relationship between blood leptin levels of PD patients and cognition as assessed by MoCA-TR. Larger longitudinal studies are needed.

Keywords: Parkinson's disease, cognition, MoCA-TR, leptin

INTRODUCTION

There is some evidence about decreased neurotrophin production and signaling in the brain playing a role in the unknown mechanism of neurodegeneration in Parkinson's disease (PD) (1,2,3). Leptin is a growth factor that is synthesized and released from adipocytes and plays a principal role in food intake and body weight. There are leptin receptors in the hypothalamic, thalamic, and extra-thalamic brain regions, such as the cortex, hippocampus, brainstem, and cerebellum (1,4). Two functionally distinct groups of dopaminergic neurons are rich in leptin receptor expression in the brain (1,5,6): one is the medial group located in the ventral tegmental area, which is known to help food intake and reward pathways, while the other is the lateral group, namely the dopaminergic neurons of the substantia nigra pars compacta, which are involved in the modulation of peripheral motor control and, specifically, PD (1,5,6).

Learning and memory are functions of the hippocampus, and long-term potentiation, a type of plasticity, takes place in this area. Some studies have reported that the direct administration of leptin into the hippocampus improves learning and memory (7,8). Moreover, low leptin levels have been discovered in Alzheimer disease (AD) patients (9). There are some important pathways in the brain that utilize dopamine other than just the nigrostriatal and tubuloinfundibular pathway, namely the mesocortical and mesolimbic pathways that link the ventral tegmental area of the midbrain to the prefrontal cortex and to the limbic area, respectively. In PD, the nigrostriatal pathway and the other two abovementioned pathways can be affected. Although there are some studies in the literature about the relationship among weight loss, body fat mass, and satiety with blood leptin levels in PD patients (10,11,12), there is no study investigating the relationship between cognition and blood leptin levels in PD.

Therefore, in the present study, we aimed to investigate the relationship between blood leptin levels and the cognitive state of Turkish PD patients using the validated form of the Montreal Cognitive Assessment Scale in Turkey (MoCA-TR).

METHODS

Thirty patients with the diagnosis of idiopathic PD according to the United Kingdom PD society brain bank criteria (13) and 30 healthy controls with similar demographic features were enrolled into the study. The subjects were recruited from the outpatient clinic of movement disorders at Erenköy Education and Research Hospital for Neurological and Psychiatric Disorders in İstanbul, Turkey. PD patients were evaluated by the Unified Parkinson's disease rating scale (UPDRS) and the Hoehn and Yahr scale (HY) for the stage and the severity of the

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disease. The daily dose of dopaminergic medications taken by the patient was recorded as the L-dopa equivalent daily dose (LEDD, mg/day) (14). Patients who were unable to ambulate; those with systemic illnesses, such as diabetes, thyroid disease, and neoplasia; those with psychiatric diseases (psychosis and severe depression), which can interfere with the cognitive test performance; those using any medication that may affect body weight, namely some antidepressants, antipsychotics, antihistamines, corticosteroids, diabetes medications; and those who had major dietary restrictions were excluded. None of the patients presented with nausea or anorexia due to dopaminergic medication, and none changed their dietary habits throughout the whole study. None of the subjects had undergone surgical treatment for PD. The controls subjects did not have any past or present neurological, psychiatric, or metabolic disorders that are known to cause an impairment to cognition. Any subjects using medication that may affect body weight and that involved major dietary restrictions were excluded.

At baseline, all the patients had their standing height and weight measurements taken using a standard scale. Each patient's body mass index (BMI) was then calculated as the weight (in kilograms) divided by the square of their height (in meters) and classified as normal (<25), overweight (25–29), or obese (≥ 30). At baseline, the waist circumference (WC) (in centimeters) was measured at the level of maximum indentation over the abdomen.

On the day of the neurological examination and the body measurements, a 5 mL fasting blood sample was obtained from each patient between the times of 08.00 and 11.00 am. Serum was separated and stored at -80°C until analysis. Leptin concentrations were analyzed by DAsource ImmunoAssays Human Leptin ELISA kit (DAsource, Louvain-la-Neuve, Belgium) by an investigator who was blinded to the clinical criteria. This ELISA sandwiches human leptin between two monoclonal antibodies reacting against different epitopes on the leptin molecule.

The cognitive status of all the subjects was evaluated using the MoCA-TR scale. Selekler et al. (15) translated the MoCA-TR test in 2010 to Turkish, which had some cultural and linguistic changes from the original form. It was also validated with Parkinson's disease (PD) in Turkey (16). MoCA-TR is a 30 point scale in which a higher score indicates better cognition, and scores under 21 indicate a cognitive dysfunction in the Turkish PD population (16). PD patients were on dopaminergic treatment during the study and evaluated in their 'on' state.

This study was approved by the Institutional Review Board and informed written consent was obtained from all subjects.

Statistical Analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics, New York, USA) version 20. The independent sample t-test and Yates chi-square test were used for the between-group comparisons. Correlations between serum leptin and body weight, BMI, and UPDRS were performed using Spearman's rank correlation coefficient (r). All the p values were two-sided and the level of statistical significance was set at $p < 0.05$.

RESULTS

The mean age of the patients and controls were 59.37 ± 9.27 and 58.50 ± 9.85 , respectively. Five PD patients and eight controls were women (Table 1). The mean HY stage of the patients was 2.2 ± 0.9 . Ten patients were at Hoehn-Yahr stage 1, nine were at stage 2, eight were at stage 3, and three were at stage 4. The daily total dopaminergic dose of the patients was 777 ± 408 mg.

Although the WC of the patients were significantly higher than the controls ($p = 0.03$), there was not any statistically significant difference between BMI of PD patients and the controls ($p = 0.246$). Further, leptin levels did not differ between PD patients and the controls ($p = 0.209$), but PD patients had significantly lower MoCA-TR scores than the control subjects ($p = 0.037$).

In PD patients, leptin levels were significantly correlated with weight ($r = 0.417$, $p = 0.022$), waist circumference ($r = 0.522$, $p = 0.003$), and BMI ($r = 0.631$, $p = 0.001$) measurements (Table 2), but there was no correlation between MoCA-TR scores and leptin levels ($r = 0.020$, $p = 0.916$) (Table 2). There was no significant relationship between leptin levels and UPDRS III or the total scores ($r = -0.59$, $p = 0.750$; $r = -0.75$, $p = 0.69$), respectively. Also, the duration of the disease and the dose of dopaminergic treatment was not correlated with leptin levels ($r = 0.104$, $p = 0.585$ and $r = 0.19$, $p = 0.30$, respectively).

In the control group, there was no correlation of leptin levels with body composition measurements or MoCA-TR scores (Table 2).

DISCUSSION

In the present study, the blood leptin levels of PD patients were similar to normal controls, and they were not associated with cognition, as assessed by MoCA-TR, or the degree of motor or functional impairment, as assessed by UPDRS, or disease duration.

There are several reports in the literature evaluating leptin levels and its relationship with weight in PD patients (10,11,12,17). Lorefalt et al. (11) found that leptin was correlated with body fat mass both in PD patients and in the controls, and they found the lower leptin values in weight-losing PD patients could be related to their decreased body fat mass (11).

Table 1. Demographic features, leptin levels, MoCA-TR scores, and body measurements of PD patients and the healthy controls

(n=60)	Patients		Controls		p
	(n=30)		(n=30)		
	n	%	n	%	
Sex					
Female	5	16.7	8	26.7	a0.347
Male	25	83.3	22	73.3	
	Mean±SD		Mean±SD		
Age (years)	59.37±9.21		58.50±9.85		b0.726
Education (years)	7.87±3.92		9.47±4.62		b0.154
BW (kg)	80.10±13.86		76.63±11.66		b0.299
WC (cm)	104.83±10.59		98.47±11.57		b0.030*
BMI (kg/m²)	28.87±4.52		27.69±3.09		b0.246
HY score	2.2±0.9		-		-
LEDD (mg/day)	777±408		-		-
UPDRS III scores	13.63±8.15		-		-
UPDRS Total scores	28.26±18.49		-		-
Leptin (ng/mL)	4.13±3.61		3.12±2.43		b0.209
MoCA-TR scores	21.93±5.37		24.50±3.77		b0.037*

^aChi-square test, ^bIndependent groups t-test, * $p < 0.05$.

SD: standard deviation; BW: body weight; WC: waist circumference; BMI: body mass index; MoCA-TR: Turkish version of the Montreal cognitive assessment scale; UPDRS: the Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr; LEDD: L-dopa equivalent daily dose.

Table 2. The correlation of leptin levels with body measurements, UPDRS, and MoCA-TR in PD patients and controls

Subjects (n=60)		BW	WC	BMI	MoCA-TR	UPDRS III	UPDRS Total
Leptin levels of patients	r	0.417	0.522	0.631	0.020	-0.059	-0.075
(n=30)	p	0.022*	0.003**	0.001**	0.916	0.755	0.694
Leptin levels of controls	r	0.089	0.340	0.235	0.097		
(n=30)	p	0.639	0.066	0.210	0.610		
Spearman correlation analysis, *p<0.05, **p<0.01. BW: body weight; WC: waist circumference; BMI: body mass index; MoCA-TR: Turkish version of the Montreal cognitive assessment scale.							

Evidente et al. (12) found that mean serum leptin concentrations were lower in PD patients with weight loss than in weight stable patients, but this did not reach statistical significance. They concluded that unintended weight loss in PD patients is unlikely to be due to abnormal serum leptin concentrations (12). In our study, we could not find any statistically significant difference between the BMI of the patients and of the controls, but leptin levels were significantly correlated with weight, WC, and BMI in PD patients.

In two studies, it was shown that injecting leptin into the hippocampus directly improved learning and memory performance (8,18). In addition, the structure of some brain regions, such as the midbrain, the hippocampus, and the hindbrain, was shown to be altered by leptin (19,20,21,22). Also the neuroprotective actions of leptin have been reported in some studies (23,24). Paz-Filho et al. (25) reported that the substitution of leptin in a leptin-deficient child not only improved the metabolic parameters but also had a markedly positive effect on neurocognitive development (25). Because of these recent reports about leptin and its association with cognition, especially in AD, the absence of its beneficial effects in the central nervous system would suggest a predisposition to cognitive impairment (26). Although Power et al. (9) found lower serum leptin levels in patients with AD and vascular dementia, more recently Teunissen et al. (27) reported that serum leptin levels were not altered in a population of relatively young AD or vascular dementia patients (mean age 60) compared to healthy subjects and were not related to cognitive decline in that age group. In the sample we presented here, similarly, the blood leptin levels of PD patients were not lower than the control subjects and there was no statistically significant difference in blood leptin levels of PD patients and the controls.

Parkinson's disease patients had lower MoCA-TR scores than controls, but leptin levels were not associated with cognition. In two other prospective studies, higher leptin levels were associated with a lower risk of dementia or cognitive impairment (28,29). Al Hazzouri et al. (30) hypothesized that higher leptin would be associated with slower rates of cognitive decline in aging Mexican Americans and found that a higher baseline leptin level was associated with better cognitive function over time for females and males without central obesity, as measured by waist circumference. Leptin and insulin were found to have a modulation effect on the hippocampal function. The regulation of appetite and energy expenditure by leptin occurs by inhibiting serotonin synthesis and releasing it in brainstem neurons. This is suggested as leptin receptors were found also in brainstem serotonergic neurons. Leptin receptor mRNA expression has been demonstrated in substantia nigra (31). Leptin has been shown to increase tyrosine hydroxylase content and the regulation of dopamine transporter activity (32). Therefore, leptin was shown to be able to modulate the mesolimbic dopaminergic system (32,33).

To the best of our knowledge, there is no prior study in the literature investigating the relationship between leptin levels and cognition in PD pa-

tients. However, our study has some limitations. First, leptin levels may be subject to diurnal variation, although the blood samples were taken during fasting in the morning at the same time for all patients. Second, this is a cross sectional study with a small sample size. Third, our study group had a relatively low age and more than half of the patients were at a relatively early stage of the disease. Leptin levels might be lower in patients with more advanced PD and those with cognitive dysfunction.

In conclusion, cumulative data from our study and also from previous reports suggest that the relationship between leptin levels and cognition in neurodegenerative diseases such as AD and PD is still open to debate. We think that additional longitudinal studies in different larger populations need to be conducted to confirm the role of leptin as a biomarker or as a possible treatment regimen for neurodegenerative disorders in the future.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erenköy Research and Training Hospital for Neurological and Psychiatric Disorders.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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