URIC ACID: THE ROLE IN THE PATHOPHYSIOLOGY AND THE PREDICTION IN THE DIAGNOSIS OF PARKINSON'S DISEASE: A TURKISH-BASED STUDY

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Background and purpose – Oxidative stress has been associated as an essential contributor to the development of neurodegenerative diseases. Recent developments in the field of Parkinson's Disease (PD) pathophysiology have led to a renewed interest in this field. As an antioxidant, uric acid (UA) has arisen as a potential neuroprotectant. Higher concentrations of UA are linked to reducing the risk of the development of the disease and preventing its progression. However, the expositions are unsatisfactory because the outcomes of these reports have not been consistent. This study is set out to assess the association of whether lower UA concentrations increased the PD risk by investigating its relationship with patients' demographic and clinical data, and to determine whether previous studies are compatible with the Turkish-sampled population. Furthermore, we aimed to determine UA's probability of being an early-stage diagnostic marker.
Methods – A total of 305 patients and 100 healthy controls were included. Serum UA levels of patients and controls were compared with clinical features. We classified the patients into three motor subtypes and determined the disease severity by modified Hoehn&Yahr Staging Scale (mH&Y) and Unified Parkinson's Disease Rating Scale (UPDRS). Standardized Mini-Mental State Examination (MMSE-TR) was assessed for cognition.
Results – There were not any significant differences of age and sex between patients and controls (p=0.030, p=0.132). The mean UA was 5.06±1.33 mg/dL in patients and 5.46±1.44 in controls, and a statistical significance was detected (p=0.022). The mean MMSE-TR

A HÚGYSAVNAK A PARKINSON-KÓR KÓRÉLATTANÁBAN ÉS A DIAGNÓZIS ELŐREJELZÉSÉBEN BETÖLTÖTT SZEREPE – TÖRÖK POPULÁCIÓN ALAPULÓ VIZSGÁLAT

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Háttér és cél – Az oxidatív stressz lényegesen hozzájárul a neurodegeneratív betegségek kialakulásához. A Parkinson-kór (PD) kórélattanában a közelmúltban bekövetkezett fejlemények nyomán ismét megnőtt a téma iránti érdeklődés. A közelmúltban derült fény a húgysav potenciális idegvédő szerepére is. Elképzelhető, hogy a magasabb húgysav-koncentrációk csökkentik a Parkinson-kór kialakulásának kockázatát és megelőzik annak progresszióját. Mindazonáltal, ez a felvetés egyelőre nem bizonyított, mivel e korábbi vizsgálatok eredményei ellentmondásosak. A jelen vizsgálat célja, hogy a betegek demográfiai és klinikai adatai közötti kapcsolat elemzésével megvizsgálja, létezik-e összefüggés az alacsonyabb szérumhúgysav-koncentrációk és a PD megnövekedett kockázata között, és meghatározza, hogy a korábbi vizsgálatok eredményei megegyeznek-e a török populációból származó betegek adataival. További cél volt annak meghatározása, hogy használható-e a húgysavszint a korai stádiumú betegség diagnosztikai markereként.
Módszerek – 305 beteget és 100 egészséges kontrollt vontunk be a vizsgálatba. A betegek és a kontrollok szérumhúgysav-koncentrációit összevetettük klinikai adataikkal. A betegeket három motoros alcsoportra osztottuk, és betegségük súlyosságát módosított Hoehn & Yahr értékelő skálával (mH&Y), valamint egységes Parkinson-kór értékelési skálával (UPDRS) határoztuk meg. A kognitív működést standardizált Mini-Mentál Teszttel (MMSE-TR) értékeltük.
Eredmények – A beteg- és a kontrollcsoport tagjainak életkora, nemi összetétele nem különbözött szignifikánsan (p = 0,030, p = 0,132). A betegek átlagos szérumhúgy-

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were 24.83±4.35 in patients and 27.09±2.13 in controls, and statictical significance was revealed (p=0.001). The mean duration of the disease was 6.31±4.16 years, mean UPDRS scores were 59.74±22.33, and mH&Y scores were 2.29±0.91. In binary comparisons, patients with tremor-dominant motor subtype had lower UA concentrations than controls (p=0.014). ROC curve analysis revealed UA's cut-off as ≤9.15, the specificity was 99.3, the sensitivity was 10.0, and the area under the curve was 0.576 (p<0.005). Regression analysis revealed age as an independent risk factor on UA values. Oxidative stress might be a factor in the development of PD, and UA may be a possible prospective protecting factor in the clinical course of the disease. However, it does not affect the severity.

Conclusion – Our results support that lower uric acid concentrations are associated with PD; however, it is not a powerful indicator for predicting PD risk. As we reveal more about UA and its effect in further investigations, its significant role will become well-defined.

Keywords: *Parkinson's disease, uric acid, biomarker, neuroinflammation, oxidative stress*

savszintje 5,06 ± 1,33 mg/dl, a kontrolloké 5,46 ± 1,44 volt; az eltérés statisztikailag szignifikáns (p = 0,022). Az átlagos MMSE-TR-pontszám a betegek körében 24,83 ± 4,35, a kontrollok körében 27,09 ± 2,13 volt; az eltérés statisztikailag szignifikáns (p = 0,001). A betegség fennállásának átlagos időtartama 6,31 ± 4,16 év, az UPDRS-skála átlagos pontszáma 59,74 ± 22,33, az átlagos mH&Y-pontszám 2,29 ± 0,91 volt. A bináris összehasonlítás szerint a tremordomináns motoros alcsoportba tartozó PD-betegeknek alacsonyabb volt a húgysavszintje, mint a kontrolloknak (p = 0,014). A ROC-görbe elemzése ≤9,15 mg/dl-es vágópontot határozott meg, a specificitás 99,3, a szenzitivitás 10,0, a görbe alatti terület pedig 0,576 (p < 0,005) volt. A regresszióanalízis feltárta, hogy az életkor a húgysavszint független kockázati tényezője. Az oxidatív stressz közreműködhet a PD kialakulásában, a húgysavszint pedig védőfaktorként működhet a betegség klinikai lefolyása során, habár a betegségsúlyosságot nem befolyásolja.

Következtetés – Eredményeink alátámasztják, hogy PD esetén alacsonyabb a húgysavszint, azonban az a PD betegségkockázatának nem eléggé erős indikátora. Ahogy a további kutatások réven egyre többet tudunk meg a húgysavszint hatásáról, annak szignifikáns hatásai is jobban körvonalazódnak majd.

Kulcsszavak: *Parkinson-kór, húgysav, biomarker, neuroinflammatio, oxidatív stressz*

Parkinson's disease (PD) decreases life quality through its motor and non-motor manifestations, and in the pathophysiology, neurodegeneration in substantia nigra, accumulation of Lewy body, mitochondrial dysfunction, and neuroinflammation are well-defined mechanisms[1–5]. Lately, dopaminergic neurons in substantia nigra have been proven to be sensitive to oxidation, consequently, oxidative stress has risen as a prominent cause in disease development[1, 6]. Oxidative stress decreases dopamine levels in basal ganglia by increasing the enzymatic and nonenzymatic activity, reduces the calcium concentrations via L-type calcium channel receptors, and induces genetic modifications that affects uric acid (UA) concentrations[2]. Consistent with this knowledge, pathological reports showing the aggregation of reactive oxygen species (ROS) in basal ganglia revealed the misfolding of the proteins, impairment in the cell-cycle, apoptosis, and the excessive release of neurotransmitters[2].

Throughout these discoveries, researchers have shown an increased interest in the importance of antioxidants[1]. Uric acid is a modifiable factor that eliminates free oxygen radicals by its antioxidant effect. Its elevated levels are associated with lowering the risk of the development of PD, decelerating the disease progression and cognitive impairment in the course of the disease[1, 6, 7]. The latest studies on this topic have also suggested an inverse correlation between UA concentrations and the existence of non-motor manifestations[3]. Such expositions are unsatisfactory because the outcomes of these reports have not been consistent[7]. Lately, decreased UA concentrations have been associated to predict the PD risk[8]. This study aims to contribute to this growing area of research by exploring whether higher serum UA concentrations decreased the PD risk through investigating the patients' demographic and clinical data, and determining whether previous studies are compatible with the Turkish-sampled population. We also aimed to determine the probability of uric acid being a diagnostic marker at the early-period of the disease.

Methods

This cross-sectional study evaluated 572 individuals between January 2018 and January 2020 retrospectively at Erenkoy Mental Health&Neurological Disorders, and Fatih Sultan Mehmet Research& Training Hospital, Neurology Departments, Movement Disorders clinics in Istanbul, Turkey. The individuals were examined by two neurologists

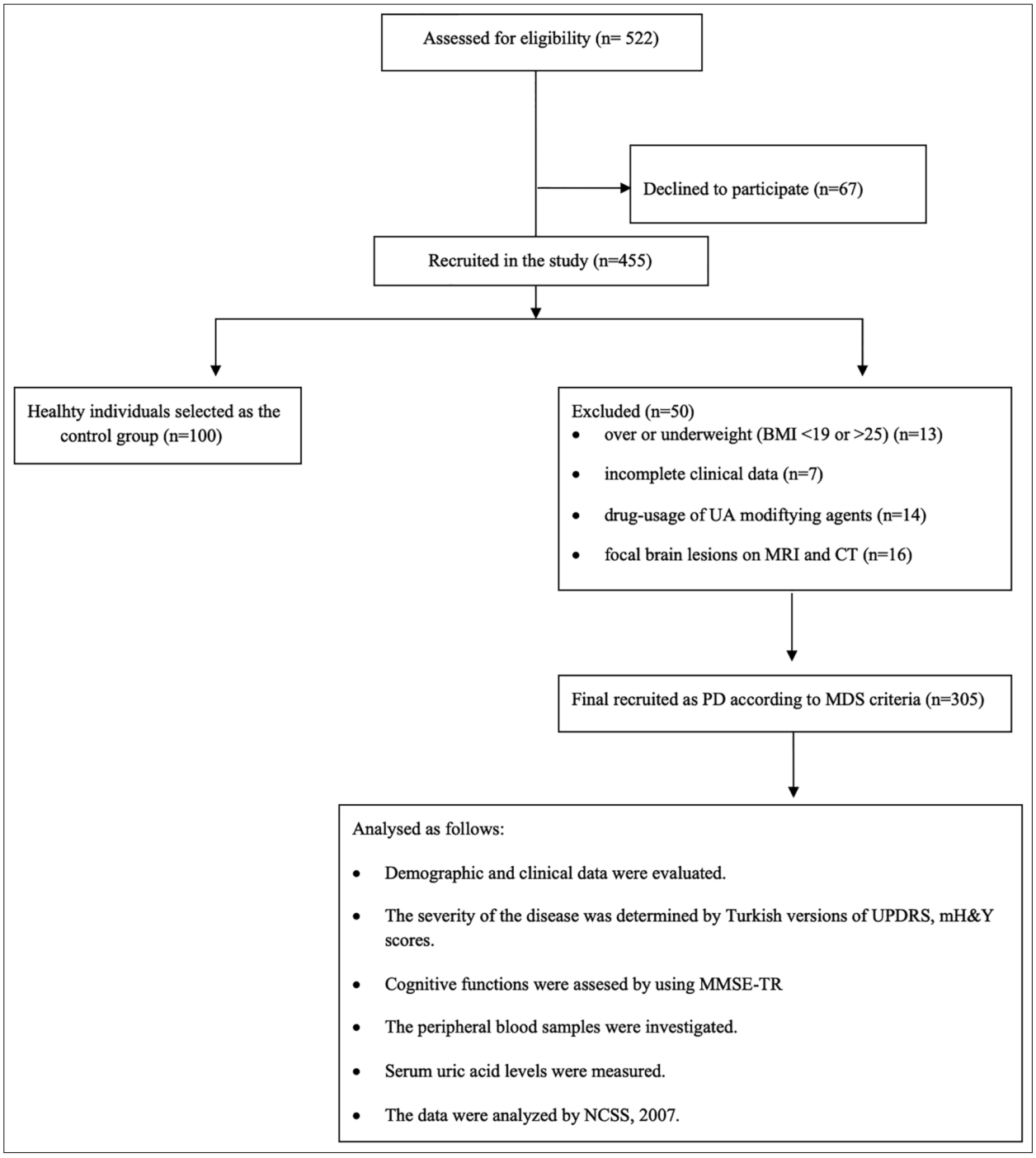

Figure 1. *STROBE diagram for the evaluation of the individuals*

(BCA and EKT), and among them, we identified 305 patients as PD according to the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's Disease (MDS–PD)[9] and selected 100 individuals as healthy controls abiding by the exclusion criteria selected by a simple random sampling method (**Figure 1**). We collected the clinical and demographic data by patients' recorded files. In eligibility criteria, we required individuals to have fulfilled the diagnostic criteria of MDS–PD, to have the diagnosis of PD for at least one year at the time we included into the study, not to take any medication or have any rheumatological, metabolic, urinary, or any infectious disease that may affect serum uric acid concentrations. Patients with Body Mass Index (BMI) (kg/m^2) between 19 and 25 were

Table 1. *Demographic and clinical features of the groups*

		Total (n=405)	Patients (n=305)	Controls (n=100)	p
Age (year)	Min-max (median)	29-93 (70)	29-93 (70)	44-92 (71)	0.132[d]
	Avg±Sd	68.65±11.35	68.17±11.48	70.14±10.88	
	≤70 age	208 (51.4)	158 (51.8)	50 (50)	
	>70 age	197 (48.6)	147 (48.2)	50 (50)	
Sex; (%) n	Female	169 (41.7)	118 (38.7)	51 (51)	0.030[b]*
	Male	236 (58.3)	187 (61.3)	49 (49)	
Uric acid (mg/dL) (n=395)	Min-max (median)	2-9.9 (5.1)	2-9.9 (4.9)	2.5-9.2 (5.2)	0.022[e]*
	Avg±Sd	5.16±1.37	5.06±1.33	5.46±1.44	
MMSE-TR (n=351)	Min-max (median)	12-30 (26)	12-30 (26)	24-30 (27)	0.001[d]**
	Avg±Sd	25.48±3.98	24.83±4.35	27.09±2.13	
	<24	94 (26.8)	94 (37.5)	0 (0)	
	≥24	257 (73.2)	157 (62.5)	100 (100)	

[b]Pearson Chi-Square Test, [d]Student t Test, [e]Mann Whitney U Test, *p<0,05, **p<0,01
n: number, min: minimum, max: maximum, avg: average, sd: standard deviation

accepted. We divided the patients into three motor subgroups: tremor-dominancy, postural-instability-and-gait difficulty (PIGD), and the mixed-type[10]. We assessed the disease severity with the Unified Parkinson's Disease Rating Scale (UPDRS)[11] and the modified Hoehn&Yahr Staging Scale (mH&Y)[12]. The patients were separated into two subgroups consistent with their mH&Y scores as "early" (≤2.5) and "moderate-advanced" stage (>2.5)[13]. Patients were also divided into two subgroups as "under" and "over" 70 years-old since hormonal fluctuations continue until that age[14]. Patients with focal brain lesions on basal ganglia in the cranial magnetic resonance imaging (MRI) were excluded from the study. We evaluated the cognitive functions with the Turkish version of the standardized Mini-Mental State Examination test (MMSE-TR)[15], and those that scored less than 24 and those diagnosed with dementia were also excluded. Finally, to screen the depression, we preferred the Beck Depression Inventory (BDI)[16], and individuals scored under ten were excluded since depression might negatively influence cognitive functions. We obtained the peripheral blood samples from the medial cubital vein after 8-hours of the feast and protected them in ethylenediaminetetraacetic acid (EDTA) coated tubes at 4°C until used. Laboratory data were tested by ADVIA 1800 (Siemens Healthcare Diagnostics, Tokyo, Japan). The values of serum UA levels were stated in milligrams per decilitre (mg/dL). Institutional Review Board approved the study.

For data processing and statistical evaluation, Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) software was initiated. Average, standard deviation, median, mean, frequency, rate, minimum, and maximum ratios were used as descriptive statistics. We conducted for analyzing the normality of the quantitative variables with the Shapiro–Wilk test. Mann–Whitney U test evaluated the non-normal distributed data. For comparing more than two groups, we preferred one-way analysis of variance (ANOVA) for normally-distributed data, and Kruskal–Wallis test for non-normally distributed data. The Bonferroni and Bonferroni–Dunn tests were chosen for the post hoc examinations of subgroups. The Pearson chi-square test analyzed categorical data. We tested the correlation between UA, UPDRS and MMASE-TR scores with Spearman's Correlation Analysis. Diagnostic screening tests [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)] and Receiver Operating Characteristic (ROC) curve analysis were applied to determine the predictive value for uric acid. We operated enter linear regression analyses to predict the variables that affect serum UA levels. The results are significant at the p=0.05 value.

Results

The study included 305 Parkinson's disease patients with a mean age of 68.17±11.48 and 100 healthy controls with 70.14±10.88 years. There was not any significant difference according to the age between the groups (p=0.132). Sixty-one percent of patients (n=187) and forty-nine percent of healthy subjects (n=49) were of the male gender, and there was a statistically significant difference between the groups (p=0.030). The mean serum UA concentrations were 5.06±1.33 in the patient group and

Table 2. *Demographic and clinical features of the subtypes and the control group*

		Total (n=405)	Tremor dominancy (n=119)	PIGD dominancy (n=130)	Mixed type (n=56)	Controls (n=100)	p-value
Age (year)	Min-max (median)	29-93 (70)	33-93 (70)	29-91 (69.5)	37-88 (70)	44-92 (71)	*0.355*[a]
	Avg±Sd	68.65±11.35	68.73±10.12	67.32±12.74	68.95±11.17	70.14±10.88	
	≤70 age	208 (51.4)	60 (50.4)	69 (53.1)	29 (51.8)	50 (50)	
	>70 age	197 (48.6)	59 (49.6)	61 (46.9)	27 (48.2)	50 (50)	
Sex; (%) n	Female	169 (41.7)	49 (41.2)	49 (37.7)	20 (35.7)	51 (51)	*0.152*[b]
	Male	236 (58.3)	70 (58.8)	81 (62.3)	36 (64.3)	49 (49)	
Uric acid (mg/dL)	Min-max (median)	2-9.9 (5.1)	2-9.9 (4.8)	2.4-8 (5.1)	2-9.8 (5)	2.5-9.2 (5.2)	*0.045*[c]*
(n=395)	Avg±Sd	5.16±1.37	5.01±1.42	5.04±1.17	5.19±1.48	5.46±1.44	
MMSE-TR (n=351)	Min-max (median)	12-30 (26)	12-30 (26)	14-30 (25)	16-30 (26)	24-30 (27)	*0.001*[a]**
	Avg±Sd	25.48±3.98	24.99±4.42	24.59±4.51	25.06±3.94	27.09±213	
	<24	94 (26.8)	34 (37)	41 (38.3)	19 (36.5)	0 (0)	
	≥24	257 (73.2)	58 (63)	66 (61.7)	33 (63.5)	100 (100)	
UPDRS (n=305)	Min-max (median)	10-152 (60)	10-152 (60)	18-122 (56)	17-96 (63.5)	-	*0.901*[a]
	Avg±Sd	59.74±22.33	59.91±23.95	59.15±22.48	60.75±18.38	-	
mH&Y (n=305)	Min-max (median)	1-5 (2)	1-5 (2)	1-5 (2)	1-4 (2,5)	-	*0.078*[c]
	Avg±Sd	2.29±0.91	2.17±0.92	2.34±0.93	2.44±080	-	
	≤2,5	195 (63.9)	83 (69.7)	80 (61.5)	32 (57.1)	-	
	>2,5	110 (36.1)	36 (30.3)	50 (38.5)	24 (42.9)	-	
Disease duration	Min-max (median)	1-25 (5.5)	1-18 (6)	1-25 (5)	1-20 (6)	-	*0.825*[c]
(year)	Avg±Sd	6.31±4.16	6.27±3.93	6.31±4.51	6.38±3.86	-	
(n=305)	*≤5 years*	123 (40.3)	49 (41.2)	54 (41.5)	20 (35.7)	-	
	>5 years	182 (59.7)	70 (58.8)	76 (58.5)	36 (64.3)	-	

[a]Oneway ANOVA Test, [b]Pearson Chi-Square Test, [c]Kruskal Wallis Test
*p<0.05, **p<0.01

5.46±1.44 in the control group. We detected a statistical significance consistent with their UA concentrations (p=0.022). The mean MMSE-TR scores were 24.83±4.35 in the patient group and 27.09±2.13 in the control group. 37.5% of the patients scored under 24, and there was a statistically significant decrease according to the MMSE-TR scores in the patient group compared to controls (p=0.001). **Table 1** presents an overview of baseline characteristics.

In the patient group, the mean duration of the disease was 6.31±4.16 years. When detailed, 40.3% (n=123) of the patients have had a diagnosis for less than five years, and 59.7% (n=182) of them had more than 5 years. The mean UPDRS scores were 59.74±22.33, and mH&Y scores were 2.29±0.91. When detailed, 63.9% (n=195) of the patients were "early" staged (≤2.5), and 36.1% (n=110) were "moderate-advanced" staged (>2.5), according to the mH&Y scores. On clinical manifestation according to motor subtypes, 39% (n=119) were tremor-dominant, 42.6% (n=130) were PIGD typed, and 18.4% (n=56) were mixed-typed **(Table 1)**. We detected no statistical significance regarding the age, sex, duration of disease, mH&Y, and UPDRS scores between the motor subtypes (p>0.05). Detailed demographic and clinical findings of the patient group are shown in **Table 2**. The post hoc analysis revealed that patients with tremor-dominant motor subtype had lower UA levels than controls (p=0.014). We detected a significant difference in MMSE-TR scores between tremor-dominancy, PIGD and the mixed-type than controls (p=0.001, p=0.00, and p=0.005; respectively). The whole binary comparisons were presented in **Table 3**.

The second part of the study was to evaluate the serum UA concentrations among the patients. We separated the patients into two subgroups regarded as their age, and the UA levels of the patients who

Table 3. *Post-Hoc tests in analysis of variance of the subgroups*

	Uric acid (n=395) p	MMSE-TR (n=351) p
Tremor – PIGD	0.480	0.964
Tremor – Mixed	0.296	1.000
Tremor – Controls	0.014*	0.001**
PIGD – Mixed	0.606	0.951
PIGD – Controls	0.069	0.001**
Mixed – Controls	0.366	0.005**

*p<0.05, **p<0.01

are under 70-year-old were significantly lower than the patients over 70 (p=0.008). Even though we did not find any statistically significant difference between uric acid levels and gender (p=0.078), it is noteworthy that the UA values in female patients were lower than males. The detailed analysis revealed a decrease in UA levels in patients under 70 years-old in both genders (p=0.048, p=0.079). The comparisons between the MMSE-TR scores, mH&Y stages, motor subtypes, the duration of the disease, and UA concentrations did not reveal a significance (p>0.05). The correlation analysis revealed a positive correlation between the UPDRS scores and uric acid significantly. We observed an increase in UA concentrations in parallel with the increase in the UPDRS scores (r: 0.119; p=0.042). However, there was no correlation detected between UA and MMSE-TR scores (r: 0.013; p=0.812). The results of the analyzes are summarized in **Table 4**.

The ROC curve analysis revealed the cut-off value of uric acid to predict the disease. The cut-off value was ≤9.15, the specificity was 99.3, the sensitivity was 10.0, and the area under the curve was calculated as 0.576 (p<0.005), as shown in **Figure 2**. The complete results of the analysis are presented in **Table 5**.

Enter linear regression analysis revealed that age affects the increasing of the UA levels apart from the other indicators. Being over 70 years-old increases the UA levels by 0.352 units. There were no significant impact of sex and UPDRS scores on the alterations in UA values. The results of the regression analysis are set out in **Table 6**.

Discussion

This cross-sectional study is set out with the aim of assessing the importance of uric acid values and predicting its contribution to the clinical decision-making process in a short time and at a low-cost price in Parkinson's disease. The study's results

Table 4. *The comparions between uric acid levels and the data of the patients*

		n	Uric acid (mg/dL) Min-max (med)	Avg±Sd	p
Age (year)	≤70 years	153	2-9.8 (4.7)	4.86±1.30	*0.008[d]***
	>70 years	142	2-9.9 (5.2)	5.27±1.34	
Sex	Female	115	2-8.4 (4.7)	4.89±1.40	*0.078[d]*
	Male	180	2.7-9.9 (5.1)	5.16±1.27	
Female	≤70 years	62	2-8.4 (4.5)	4.67±1.39	*0.048[d]**
	>70 years	53	2-8.1 (5.1)	5.14±1.38	
Male	≤70 years	91	2.7-9.8 (4.9)	4.99±1.21	*0.079[d]*
	>70 years	89	3-9.9 (5.3)	5.34±1.31	
MMSE-TR (n=241)	<24	89	2-8.1 (4.9)	5.05±1.32	*0.905[d]*
	≥24	152	2-9.8 (5)	5.02±1.29	
mH&Y	≤2.5	186	2-9.9 (5)	5.08±1.34	*0.803[d]*
	>2.5	109	2.4-8.8 (4.9)	5.02±1.31	
Motor subtypes	Tremor-dominancy	118	2-9.9 (4.8)	5.01±1.42	*0.529[c]*
	PIGD	127	2.4-8 (5.1)	5.04±1.17	
	Mixed-type	50	2-9.8 (5)	5.19±1.48	
Disease duration	≤5 years	116	2-8.4 (4.9)	4.97±1.28	*0.434[d]*
(year)	>5 years	179	2-9.9 (4.9)	5.11±1.36	
UPDRS	r	305	0.119		
	p		*0.042**		
MMSE-TR	r	305	0.013		
	p		*0.812*		

[c]Kruskal Wallis Test, [d]Mann Whitney U Test, r: Spearman's correlation coefficient, *p<0.05, **p<0.01

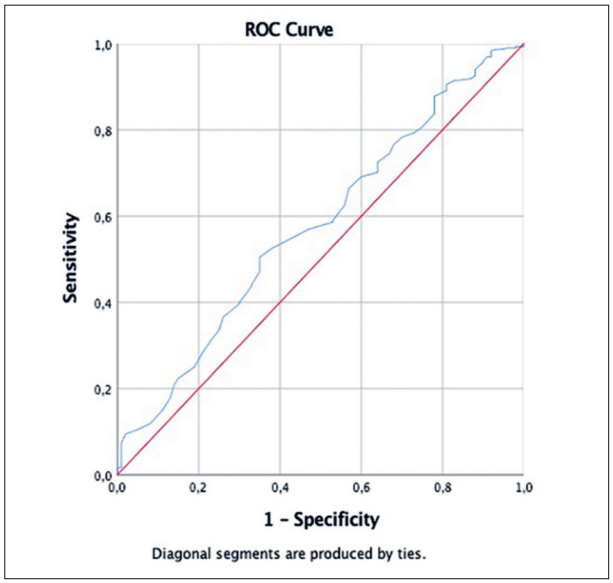

Figure 2. *ROC curve of uric acid*

indicate that patients with PD have lower serum UA values than healthy individuals, and among all the motor subgroups, patients with tremor-dominant type were found to have the lowest concentrations. We found a decrease in MMSE-TR scores in the patients, and this was significant in all motor subtypes. The gender did not have an impact on UA levels in patients. Except, we found a reduction in UA levels in patients who are under 70-year-old. One unanticipated finding was that we found an increase in UA concentrations as the UPDRS scores raised. It is somewhat surprising that being over 70 years was noted as an independent variable to increase UA levels in this condition. Unfortunately, the ROC analysis led us to conclude a weak correlation in uric acid values on predicting the diagnosis. Therefore, we cannot determine that uric acid could function as an efficient biomarker to predict PD at the early-period.

This study confirms that lower serum uric acid levels are associated with patients with Parkinson's disease. Patients with tremor-dominant type were found to have the lowest levels in our study group. Several studies have investigated the relationship between the motor subtypes and UA, and found that UA levels were higher on the tremor-dominant subtype[17]. It is observed that patients with tremor-dominant subtype have milder cell loss in the ventrolateral part of the substantia nigra pars compacta and the locus coeruleus, as well as lower cortical Lewy body deposition than patients with other subtypes. A study using functional neuroimaging showed a prominent reduction of striatal dopamine and glucose metabolism in the ventral striatum, mainly in the caudate and anterior putamen in other motor subtyped patients as disease progressed. Furthermore, tremor-dominant patients had relatively stable course of the disease[17, 18]. These studies are consistent with the hypothesis that neurodegeneration develops tremor rather than bradykinesia and rigidity[19]. Moreover, some researchers believe that tremor is a compensatory mechanism in response to akinesia in PD and may reflect evidence of neuroprotective substances[18]. However, this study has been unable to demonstrate previous researchers' findings.

Although these results differ from some published studies, they may be consistent with those implicating that genetic variabilities impact serum UA levels. Several genetic alleles have been related

Table 5. *ROC Curve Analysis Results*

	Cut off	Diagnostic Scan Sensitivity	Specificity	Positive Predictive value	Negative Predictive value	ROC Curve Area	95% Confidence interval	p
Uric acid	≤*9.15*	10.00	99.30	97.75	26.56	0.576	0.512-0.641	*0.220*

p<0.05

Table 6. *Linear regression analysis results in determining the factors affecting uric acid concentrations*

	Non-standardized Ratio B	Std. error	t value	p	95% CI Lower	Upper
Age *(year)*	0.352	0.160	2.201	*0.028**	0.037	0.666
Sex	0.257	0.157	1.638	*0.103*	-0.052	0.566
UPDRS	0.003	0.004	0.908	*0.365*	-0.004	0.010
Coefficient	3.929	0.366	10.739	*0.001***	3.209	4.649

CI: confidence interval, *p<0.05, **p<0.01

to affect plasma UA levels[20]. *Gonzalez-Aramburu* et al. revealed that patients with some genetic alleles are related to lower UA concentrations, and they have more probability for PD risk[21]. Moreover, according to this research, genetic alterations might have been contributed to the differentiation of motor subtypes besides UA. However, we did not set this study to investigate genetic variances. Consequently, our results did not suggest a protective effect of UA on motor subtypes of PD and we could not agree on a common consensus with previous studies.

We wanted to determine if there is an association between UA levels and cognitive functions, and concluded that MMSE-TR scores were decreased in PD patients. *Moccia* et al. stated that higher plasma UA concentrations were related to the modulated cognitive functions[8]. A four-year follow-up study revealed a diverse association between uric acid and the early occurrence of cognitive impairment. The pathophysiology of cognition in PD is complex and important gaps remain. However, it is hypothesized that higher amount of UA levels may exert the antioxidant effect on degeneration, decelerate the neuronal damage and protect the circuits' disruption that involves the caudate and subcortical nuclei, prefrontal cortex, and prevent cognitive impairment consequently[3, 4, 22]. While many unknown factors may have a role in cognitive decline, UA's role in PD still remains unclear[8]. Even though we revealed a relationship between decreased UA levels and cognitive deterioration, we did not detect any correlation between UA concentrations and MMSE-TR scores. Nonetheless, our results are partially consistent with the findings of other studies.

In a meta-analysis by Wen et al., patients were divided into "early" and "middle-late" stage PD according to their H&Y scores. They revealed that serum UA concentrations were lower in "middle-late" staged patients. However, this result is contentious due to that the H&Y staging criteria was inconsistent. Some studies included in this meta-analysis preferred H&Y, and some the modified H&Y scale.[7] Considering mH&Y scale is more up-to-date, we evaluated the severity by mH&Y, but did not find any relationship according to the UA concentrations. However, when assessed with the UPDRS scale, we found a positive correlation in UA, just the opposite. This unpredicted significant outcome may be explained by that the amount of patients with higher UPDRS scores was outnumbered in our study; hence, this condition might have affected the statistical analysis. Consequently, our results are not consistent with the preceding reports.

Several studies implicated that serum UA levels were higher in males. A central factor behind this difference is thought to be the female hormonal influence, and may be clarified by the neuroprotective effect of estrogen and its inducing effect upon UA[14, 19]. Estrogen acts as a neuroprotector and reduces the oxidative stress. Several studies observed an increase in UA concentrations up to 70-years or over due to the alterations in estrogen levels[14]. Likewise, in our study, we revealed that UA concentrations in females were higher until age 70-and-backwards, and then decreased after 70-years-of-age. Therefore, we concluded that these results were consistent with prior studies'. Previous reports revealed an age-related rise in serum UA levels, but it is uncertain if it occurs independently. Age-related differences in serum UA levels may be predicted by additional changes in renal functions, hormonal alterations, medications, and metabolic diseases[6, 14]. To explore the effect of gender on the uric acid levels in patients with PD, we then performed a sex subgroup analysis but did not find any association. Even though we did not detect an association, we observed that being over 70-year-old affects increasingly the UA levels independently. Consequently, our results are consistent with the preceding reports.

This study's key strengths are to investigate the effect of uric acid in a large proportion of individuals with PD because of the strong *a priori* evidence that individuals with high serum uric acid levels have a markedly reduced risk of developing PD, and to predict its ability as an inexpensive biomarker. However, the convergence between previous epidemiological studies and the present investigation is striking. The lack of association between serum UA levels, cognitive decline, and motor subtypes might be related to being attributed to the hormonal, genetic, environmental or gender-based differential effects of urate mechanisms in PD, as already suggested.

Finally, a number of important limitations need to be considered. Firstly, this was a cross-sectional, prospective, one-point-in-time study. We were unable to relate the uric acid and UPDRS scores during follow-up; therefore, we could not comment about uric acid's effect upon disease progression. The second one was the lack of assigning the Neuropsychological Assessment Battery (NAB) for cognitive functions. MMSE-TR is primarily a screening test and not powerful enough to determine cognitive deficits in a disease where we face subcortical dementia, like in PD. Therefore we would not detect the exact subtypes of cognitive

impairment. However, this is the most extensive nation-wide study in Turkey to investigate the associations and indicates that these results should be considered as positive exploratory findings. Due to some factors as dietary and smoking habits may influence UA's concentrations, further controlled and more extensive prospective studies should be performed with exactly-matched age and sex of the individuals.

In conclusion, the evidence from this study suggests that lower uric acid concentrations are associated with PD; however, it is not a powerful indicator to predict the PD risk. As we reveal more about UA and its effect in further investigations, its significant role will become well-defined.

AUTHOR CONTRIBUTIONS

BCA: Conceptualization, methodology, research, resources, writing - original draft. EKT: Conceptualization, formal analysis, research, resources, writing - review & editing. GOK: Supervision. FMD: Supervision.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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