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Assessment of Bilirubin Levels in Parkinson's Disease

Parkinson Hastalığında Bilirubin Düzeylerinin Değerlendirilmesi

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ABSTRACT

Objectives: Excessive generation of the reactive oxygen species triggers oxidative stress. Bilirubin suppresses oxidation more vigorously than many other antioxidants. Since it has received significant attention on Parkinson's disease (PD) pathophysiology, researchers have started investigating its impact on the disease. The correlation between PD and antioxidant status has not entirely been researched. Therefore, our aim in this study is to assess serum bilirubin levels in association with demographic and clinical features of patients with PD.

Methods: A total of 289 individuals were involved in this study. Their serum total bilirubin (TB), direct bilirubin (DB), and indirect bilirubin (IB) concentrations were compared with demographic and clinical characteristics. We determined the severity of the disease by the modified Hoehn and Yahr Staging Scale (mHYRS), and the clinical features by the Unified Parkinson's Disease Rating Scale (UPDRS). We separated the patients into three motor subgroups according to their clinical features as tremor dominant (TD), postural instability and gait difficult, and the mixed type and based on mHYRS stages as early (≤2) and advanced (>2).

Results: There were 189 patients with PD and 100 healthy controls in the study. IB levels were significantly higher in the patients with PD after adjusting age (p=0.024). Male patients had higher levels of bilirubin levels (DB, IB, and TB) than the females (p<0.05). Bilirubin levels were also similar between the different motor subtypes of PD patients and in the early and advanced stages of PD (p>0.05).

Conclusion: Bilirubin is an essential antioxidant marker indicating a dopaminergic deficiency in PD. Increased bilirubin levels may be an improved response to oxidative stress that occurs during the progression of PD.

Keywords: Antioxidant; bilirubin; disease severity; oxidative stress; Parkinson's disease.

ÖZET

Amaç: Reaktif oksijen radikallerinin aşırı üretimi oksidatif stresi tetikler. Bilirubin oksidasyonu diğer birçok antioksidandan daha güçlü bir şekilde bastırır. Araştırmacılar, Parkinson hastalığı patofizyolojisine büyük önem verdiklerinden, hastalık üzerindeki etkisini incelemişlerdir. Parkinson hastalığı ile antioksidan durum arasındaki ilişki tam olarak araştırılmamıştır. Bu çalışmanın amacı, Parkinson hastalarının serum bilirubin düzeyleri ile demografik ve klinik özellikleri arasındaki ilişkiyi değerlendirmektir.

Yöntem: Çalışmaya toplam 289 kişi dahil edildi. Serum total, direkt ve indirekt bilirubin düzeyleri demografik ve klinik özelliklerle karşılaştırıldı. Hastalığın şiddeti modifiye Hoehn&Yahr Evreleme Ölçeği ile, klinik özellikleri ise Birleşik Parkinson Hastalığı Derecelendirme Ölçeği ile belirlendi. Hastalar, klinik özelliklerine göre tremor dominant tip, postüral instabilite ve yürüme zorluğu tipi, karışık tip olarak üç motor alt gruba ayrıldı. Modifiye Hoehn&Yahr Evreleme Ölçeği evrelerine göre ise erken (≤2) ve ileri (>2) evre olarak ayrıldı.

Bulgular: Çalışma, 189 hasta ve 100 sağlıklı kontrolden oluştu. Yaş ayarlandıktan sonra Parkinson hastalarında indirekt bilirubin düzeyleri anlamlı olarak daha yüksek saptandı (p=0,024). Erkek hastalarda kadın hastalardan daha yüksek bilirubin düzeyleri (direkt, indirekt ve total bilirubin) vardı (p<0,05). Parkinson hastalarının motor alt tipleri arasında ve Parkinson hastalığı evrelerinde bilirubin düzeyleri benzerdi (p>0,05).

Sonuç: Bilirubin, Parkinson hastalığında dopaminerjik eksikliği gösteren önemli bir antioksidan belirteçtir. Artan bilirubin seviyeleri, Parkinson hastalığının ilerlemesi sırasında ortaya çıkan oksidatif strese karşı geliştirilmiş bir yanıt olabilir.

Anahtar sözcükler: Antioksidan; bilirubin; hastalık şiddeti; oksidatif stres; Parkinson hastalığı.

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Parkinson's disease (PD) is a progressive disorder with motor (bradykinesia, rigidity, postural instability, and rest tremor) and non-motor (sleep, psychiatric, and urinary conditions) manifestations. It is the second most-seen neurodegenerative syndrome of older adults.[1] Several studies have revealed the loss of dopaminergic neurons in the substantia nigra, Lewy body accumulation, mitochondrial dysfunction, and neuroinflammation on pathophysiology. Recently, dopaminergic neurons in substantia nigra were noticed to be sensitive to oxidation; therefore, oxidative stress has risen as a prominent cause in disease development. Pathological studies demonstrated the accumulation of reactive oxygen species (ROS) or reduced antioxidant products on basal ganglia. Therefore, researchers have shown increased attention to the importance of antioxidants.[1-3] Protection systems control ROS production by scavenging or decreasing their concentrations, thus preserving suitable cellular stability. Changes in this stability resulting from increased ROS production or reduced concentrations of antioxidants cause a state of oxidative stress; therefore, an enhanced vulnerability of membranes to respond with oxygen radicals.[4] Bilirubin is an adjustable element that eliminates ROS due to its antioxidant effect, and its increased values are related to reducing the risk of developing PD.[2] It is the final product of heme catabolism that transformed from biliverdin. It was used to be known as a toxic metabolite to be excreted.[5] However, bilirubin is a modifiable factor that removes ROS by its antioxidant effect. Various studies have revealed an inverse association among serum bilirubin concentrations, disease' development, and progression.[2,6,7] According to these implications, we set out to define whether higher serum bilirubin concentrations decreased the PD risk by investigating its relationship with the patients' demographic and clinical features and determining whether the previous studies are compatible with the Turks.

Methods

We included 189 patients in this cross-sectional, retrospective study between January 2016 and December 2020 at Siirt training and research hospital and Fatih Sultan Mehmet training and research hospital, departments of neurology in Siirt and Istanbul, Turkey. One hundred healthy individuals were considered as controls. Patients were diagnosed as PD according to the Movement Disorder Society Clinical Diagnostic Criteria for PD.[8] We excluded the patients who had a history of secondary parkinsonism, any metabolic, gastrointestinal, or infectious disease that may affect the serum bilirubin levels. Furthermore, we excluded those who had treatment with statins or chemotherapy, alcoholism, liver disease, biliary surgery, history of biliary colic, and recent hemolytic anemia.

We separated the patients into three motor subgroups according to their clinical features as tremor dominancy (TD), postural instability and gait difficulty (PIGD), and the mixed type (MT).[9] Clinical features of the disease were determined by the Unified PD Rating Scale (UPDRS)[10] and the severity by the modified Hoehn and Yahr Rating Scale (mHYRS).[11] The patients were separated into subgroups consistent with their sex (male and female subgroups), and mHYRS scores, as mild (Stages I and II), moderate (Stage III), and severe (Stages IV and V).[11] Furthermore, we separated the patients based on mHYRS stages as early (≤2) and advanced (>2).

Clinical and demographic data were collected by patient's evaluation charts. Their serum bilirubin levels were measured during their follow-up examinations. Laboratory data were collected from blood samples that performed by automatic blood sample analysis device (MINDREY BC30-2017). The measurements of serum total bilirubin (TB), direct bilirubin (DB), and indirect bilirubin (IB) levels were stated in milligrams per deciliter (mg/dL).

The study had the approval of Siirt University Ethical Committee with the number of 2020/13.01.

Statistical analysis

For statistical analysis, "Jamovi project (2020), Jamovi (Version 1.8.1) (Computer Software) (Retrieved from https://www.jamovi.org), JASP (Version 0.14.1.0) (Retrieved from https://jasp-stats.org), and R-project (version 4.0.5 for Windows) were used. Descriptive statistics were given as mean±standard deviation and median with minimum-maximum values for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. The normal distribution of the numerical variables was analyzed by the Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson-Darling tests. In comparing two independent groups, the Mann–Whitney U-test was applied for variables without normal distribution. The Pearson Chi-square test was used to compare the differences in sex distribution between the groups. The one-way ANOVA test was used to compare more than 2 independent groups where numerical variables had a normal distribution. For variables without normal distribution, the Kruskal–Wallis test was

applied. The Pearson Chi-square in 2×2 tables and Fisher Freeman-Halton tests were used in R×C tables in comparing the differences between categorical variables. Since the assumptions of the two-way analysis of variance were not met, "Two-Way Analysis of Variance for Trimmed Means" was preferred as the more powerful (robust) method. The calculations to analyze whether sex distribution affects the differences between the bilirubin levels between the groups were made using the "2-way" function (A two-way ANOVA for trimmed means, M-estimators, and medians) from the WRS2 package. The effect of age between the groups was evaluated by the non-parametric covariance analysis using the "sm. ANCOVA" package in the R software. Spearman rho correlation coefficient was used to analyze the correlations between the numerical. The significance level (p-value) was set at 0.05 in all statistical analyses.

Table 1. Demographic and clinical characteristics of the patients and the controls

	Groups		p-value
	PD patients (n=189)	Healthy controls (n=100)	
Age (year)†	66.4±11.6	69.7±11.2	0.021
Sex‡			
Female	76 (40.2)	62 (62.0)	0.001
Male	113 (59.8)	38 (38.0)	
UPDRS score†	64.4±21.9	–	–
mHYRS stage‡			
1	37 (19.6)	–	
1.5	1 (0.5)	–	
2	58 (30.7)	–	
2.5	20 (10.6)	–	
3	54 (28.6)	–	
4	17 (9.0)	–	
5	2 (1.1)	–	
mHYRS groups‡			
Early (≤2)	96 (50.8)		
Advanced (>2)	93 (49.2)		
PD disease severity (based on mHYRS stage)‡			
Mild (1–2)	96 (50.8)	–	
Moderate (2.5–3)	74 (39.2)	–	
Severe (4–5)	19 (10.1)	–	
Motor symptom types‡			
Tremor	86 (45.5)	–	–
Akinetic	62 (32.8)	–	
Mixed	41 (21.7)	–	

†: Mean±standard deviation, ‡: n (%). UPDRS: Unified Parkinson's disease rating scale; mHYRS: Hoehn-Yahr; PD: Parkinson's disease.

Results

In the study, there were 189 patients with PD and 100 healthy controls. The mean UPDRS score was 64.4±21.9. The most frequent mHYRS stages were Stage 2 and Stage 3, seen in 58 (30.7%) and 54 patients (28.6%), respectively. Grouping based on mHYRS stages as early (≤2) and advanced (>2) revealed almost similar distribution (50.8% and 49.2%). Mild severity of PD was the most frequently detected type of disease (96 patients, 50.8%). Tremor-dominant (TD) and akinetic-dominant motor symptoms were observed in 45.5% and 32.8% of the patients. The demographic and clinical characteristics of the patients are given in Table 1.

Comparison of the bilirubin levels between the patient group and the healthy control group showed no difference (Table 2). We detected higher DB levels more frequently in healthy controls after adjusting the distribution of sex (p=0.049). After adjusting the age, IB levels were significantly found to be higher in the patients with PD (p=0.024).

Demographic and clinical characteristics of the patients according to the dominancy type of the motor symptoms are summarized in Table 3. We detected no significant difference in age, sex distribution, UPDRS score, mHYRS stages, mHYRS groups, and disease severity. Bilirubin levels were also similar between the different types of motor symptoms

Table 2. Comparison of the bilirubin levels between the groups after adjusting age and sex

	Groups			Covariate: Age	Factor: Sex
	PD patients (n=189)	Healthy controls (n=100)	p-value	p-value	p-value
Direct bilirubin (mg/dL)§	0.2 (0.1–0.9)	0.2 (0.1–0.7)	0.953	0.300	0.049
Indirect bilirubin (mg/dL)§	0.4 (0.0–1.8)	0.4 (0.0–1.4)	0.367	0.024	0.093
Total bilirubin (mg/dL)§	0.6 (0.2–7.3)	0.6 (0.2–2.1)	0.499	0.338	0.066

§: Median (min-max), PD: Parkinson's disease.

Table 3. Demographic and clinical characteristics of the patients according to the type of Parkinson's disease

	Dominant motor symptoms			
	Tremor (n=86)	Akinetic (n=62)	Mixed (n=41)	p-value
Age (year)†	66.4±10.6	66.5±13.0	66.4±11.7	0.996
Sex‡				
Female	34 (39.5)	26 (41.9)	16 (39.0)	0.943
Male	52 (60.5)	36 (58.1)	25 (61.0)	
UPDRS score‡	64.0 (10.0–152.0)	68.0 (15.0–106.0)	70.0 (18.0–115.0)	0.153
mHYRS stage‡				
1	18 (20.9)	7 (11.3)	12 (29.3)	0.425
1.5	1 (1.2)	0 (0.0)	0 (0.0)	
2	28 (32.6)	17 (27.4)	13 (31.7)	
2.5	8 (9.3)	8 (12.9)	4 (9.8)	
3	23 (26.7)	22 (35.5)	9 (22.0)	
4	7 (8.1)	8 (12.9)	2 (4.9)	
5	1 (1.2)	0 (0.0)	1 (2.4)	
mHYRS groups‡				
Early (≤2)	47 (54.7)	24 (38.7)	25 (61.0)	0.054
Advanced (>2)	39 (45.3)	38 (61.3)	16 (39.0)	
PD disease severity (based on mHRYS stage)‡				
Mild (1–2)	47 (54.7)	24 (38.7)	25 (61.0)	0.214
Moderate (2.5–3)	31 (36.0)	30 (48.4)	13 (31.7)	
Severe (4–5)	8 (9.3)	8 (12.9)	3 (7.3)	
Direct bilirubin (mg/dL)§	0.2 (0.1–0.9)	0.2 (0.1–0.6)	0.2 (0.1–0.5)	0.759
Indirect bilirubin (mg/dL)§	0.4 (0.0–1.8)	0.3 (0.1–1.1)	0.4 (0.1–1.4)	0.115
Total bilirubin (mg/dL)§	0.6 (0.2–2.7)	0.6 (0.2–1.4)	0.7 (0.2–7.3)	0.414

†: Mean±standard deviation, ‡: n (%), §: Median (min-max). UPDRS: Unified Parkinson's disease rating scale; mHYRS: Hoehn-Yahr; PD: Parkinson' disease.

of PD patients (p>0.05) (Table 3). There were no significant correlations between bilirubin levels, age, and UPDRS scores of the patients (Table 4).

Table 5 presents the level of bilirubin based on the mHYRS groups and the sex distribution. The bilirubin levels in the early and advanced groups based on mHYRS stages were similar p>0.05); nevertheless, male patients had higher bilirubin levels (DB, IB, and TB) than the female patients (p<0.05) (Table 5).

Table 4. Correlation analysis of the bilirubin levels with age and UPDRS score

		PD patients	
		r	p-value
Direct bilirubin	Age	0.036	0.620
Direct bilirubin	UPDRS score	−0.004	0.954
Indirect bilirubin	Age	−0.042	0.568
Indirect bilirubin	UPDRS score	−0.127	0.082
Total bilirubin	Age	−0.006	0.940
Total bilirubin	UPDRS score	−0.108	0.140

Spearman's rho correlation coefficient. UPDRS: Unified Parkinson's disease rating scale.

Discussion

The main findings of our study were: (1) IB levels were significantly higher in the patients with PD, after adjusting age, (2) bilirubin levels were also similar between the motor types of PD patients and in the early and advanced stages of PD based on mHYRS stages; and (3) male patients had higher bilirubin levels (DB, IB, and TB) than the female patients.

Although oxidative stress is considered a potential mechanism in the pathogenesis of PD, the exact causes of selective dopaminergic cell death underlying the disease is unknown. Heme oxygenase (HO) is an important enzyme that converts heme molecules into carbon monoxide, iron, and bilirubin and regulates oxidative balance.[12] The studies concerning

Table 5. Association of the stages of mHYRS and sex with bilirubin levels

	Direct bilirubin§	p-value	Indirect bilirubin§	p-value	Total bilirubin§	p-value
mHYRS groups						
Early (≤2)	0.21 (0.1–0.9)	0.081	0.39 (0.04–1.8)	0.143	0.6 (0.17–7.3)	0.549
Advanced (>2)	0.24 (0.1–0.64)		0.34 (0.1–1.09)		0.59 (0.19–1.62)	
Sex						
Female	0.19 (0.1–0.44)	<0.001	0.3 (0.08–1)	<0.001	0.51 (0.22–1.36)	<0.001
Male	0.25 (0.1–0.9)		0.41 (0.04–1.8)		0.66 (0.17–7.3)	

§: Median (min-max), mHYRS: Hoehn-Yahr.

the role of bilirubin in PD pathogenesis show conflicting results.[2,6,12,13] The first retrospective study on the relationship between PD and bilirubin reported by Scigliano et al.[13] who showed that the PD patients receiving levodopa treatment had significantly higher bilirubin levels than untreated PD patients and control groups. A recent study performed newly diagnosed and untreated PD patients also possessed higher bilirubin levels. After 2 years of the follow-up, they found a negative correlation between the daily levodopa doses and bilirubin levels.[2] In a current meta-analysis, serum TB and DB were significantly increased in PD patients compared with the control groups. They did not find any difference in serum IB levels, and they explained this result as the small number of the included literature.[14] They suggested that HO upregulation in substantia nigra might be an adaptive response to increased oxidative stress that emerged in PD.[2] It was speculated that increased bilirubin concentration in PD patients might be related to the overexpression of HO.[14] HO has a neuroprotective effect on the central nervous system. The studies confirmed that HO plays an essential role in regulating the oxidative balance of the neurodegenerative disease brain.[15,16] Our results are in line with the previous findings by Macías-García et al.[12] who conducted a study of PD patients at different disease stages and found that PD patients had higher bilirubin levels. Furthermore, higher bilirubin levels were observed in males with PD. Likewise, they established that the TB was negatively related to the severity of PD; however, we could not determine such relationship between disease severity and bilirubin levels. The cross-sectional studies conducted in the Chinese population were in disagreement with our results.[6,17] Qin et al.[6] found decreased serum IB concentration in 425 PD patients and 460 controls. They suggested that IB exerted anti-ROS properties and lower serum IB concentrations influenced PD development by reducing endogenous anti-lipid peroxidation resistance. Li et al.[17] studied the association of serum IB concentrations with motor subtypes of PD and found that IB levels were significantly lower for PIGD than TD. Bilirubin levels on motor subtypes of PD patients did not reveal a significant statistical difference in our study. This difference could be related to the exclusion criteria of each study, beyond genetic and environmental differences between different ethnicity.

In recent years, rare studies have been conducted on the effect of gender differences on bilirubin levels. Bilirubin levels were higher in males compared to females as in our study.[18,19] Macías-García et al.[12] found a relationship between bilirubin levels and sex. Higher bilirubin levels were seen in males with PD. However, the underlying mechanisms of these differences are not well understood. Females' serum bilirubin levels may reflect the effects of estrogens related to increased bilirubin excretion by induction of uridine diphosphate-glucuronyltransferase1A1 in the liver.[20] Our study did not determine the clinical information on menopausal status and hormone replacement therapy of the patients.

Some limitations temper the strength of our conclusions. Since our study was conducted retrospectively, we cannot obtain sufficient results about the predictive value of serum bilirubin levels in PD progression. Serum bilirubin concentrations could be affected by other factors, including body mass index, cholesterol levels, smoking status, alcohol intake, regular exercise, diabetes, hypertension, and so on, which we did not discuss in our study. However, this is the first study investigating the serum bilirubin levels in PD in our country. Consequently, more prospective studies on this topic need to be undertaken in different stages of PD patients and might also include HO polymorphisms and bilirubin levels for a clear understanding.

Evidence from several studies has identified that bilirubin is an essential antioxidant marker indicating a dopaminergic deficiency in PD. Consistent with their results, the data presented in this study so far support the idea that serum

bilirubin levels are associated with PD. Increased bilirubin levels may be an improved response to oxidative stress that occurs during the progression of PD.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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