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Neurovascular Changes in the Retina of Parkinson's Disease Patients: A Comprehensive Study on Disease Severity, Levodopa Dosage, and Stroke Risk

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ABSTRACT

Introduction: This study aims to investigate retinal neuronal and vascular structural alterations in Parkinson's disease (PD) patients concerning disease duration and severity, levodopa dosage, and stroke risk.

Methods: This retrospective study included 40 PD patients and 40 age- and sex-matched controls. Retinal parameters, including central foveal thickness (CFT), macular thickness (MT), retinal nerve fiber layer (RNFL), and retinal vascular density, were measured using optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). Disease severity was assessed using the Hoehn & Yahr (H&Y) scale, and stroke risk was evaluated using the Stroke Risk Assessment (SRA) tool.

Results: PD patients demonstrated significantly reduced MT in the temporal quadrant and reduced vascular density in both the superficial (SCP) and deep (DCP) capillary plexuses compared to controls. Additionally, the superficial and deep foveal avascular zone (FAZ) areas showed notable enlargement. A negative correlation between disease duration and both the temporal and nasal quadrants of the SCP and a positive correlation between disease severity and deep FAZ area was observed, while disease severity exhibited negative correlations with temporal MT, average and superior quadrant RNFL. Levodopa dosage was inversely correlated with inferior and temporal MT and temporal SCP and DCP and positively correlated with the deep FAZ area. No significant correlation was found between the SRA score and retinal vascular changes.

Conclusion: This study is the first to evaluate retinal neuronal and vascular changes in PD regarding stroke risk assessment. Our findings suggest that retinal changes are associated with disease severity and duration in PD patients. Further prospective studies with larger sample sizes are needed to validate these findings and explore the potential role of OCTA in early detection and stroke prevention in PD.

Keywords: Hoehn & Yahr (H&Y) scale, macular vascular density, optical coherence tomography angiography, Parkinson's disease, stroke risk assessment score

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INTRODUCTION

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder in the elderly population, and affects multiple systems, including olfactory, cognitive, and motor functions, and the intestinal system, even before clinical symptoms related to the disease manifest (1). Parkinson's disease leads to motor symptoms such as bradykinesia, resting tremor, and rigidity, as well as non-motor symptoms, including cognitive impairments, depression, autonomic dysregulation, and sleep disturbances, all of which significantly reduce the quality of life of affected individuals (2,3).

Parkinson's disease is characterized by the loss of dopaminergic neurons in the Substantia Nigra, and the underlying causes of the disease have been extensively studied. Dopamine is also a crucial biochemical

Highlights

- **OCT and OCT-A are non-invasive tools to assess retinal changes.**
- **OCT and OCT-A may help understand the pathogenesis of Parkinson's disease.**
- **Retinal changes may be a stroke risk factor in patients with Parkinson's disease.**
- **OCT and OCT-A changes may help predict stroke risk in Parkinson's disease patients.**

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molecule involved in retinal development, refractive development, and the transmission of visual signals. It is predominantly found in amacrine cells and the inner plexiform layer (IPL) of the retina. In PD, dopamine dysregulation leads to changes in ocular tissues and contributes to visual impairments, including reduced visual acuity, decreased contrast sensitivity, and color vision deficits (4). Studies in animal models and in vivo research have demonstrated that the loss of dopaminergic neurons in the retina is associated with the accumulation of α-synuclein (5,6). Furthermore, α-synuclein accumulation around retinal arteries has been shown to induce microvascular damage, which subsequently leads to retinal degeneration (7).

Some studies suggest that, in addition to neurodegenerative changes associated with dopaminergic neuron loss and α-synuclein accumulation, vascular factors may also play a role in the pathogenesis of PD (8,9). It has been reported that up to 75% of PD patients may have vascular comorbidities (10). In a meta-analysis including 13 case-control studies, Yumei et al. found that the likelihood of stroke during the lifetime of PD patients is increased, with the potential link between PD and stroke possibly being related to similar pathogenic mechanisms (11). Additionally, Unal et al. demonstrated that transgenic mice overexpressing α-synuclein were more susceptible to experimental ischemic brain damage, suggesting that PD pathology may promote cerebral ischemia and increase the risk of stroke (12). It is also known that levodopa therapy, used to treat PD, increases serum homocysteine levels, thereby raising the risk of stroke. This is because elevated homocysteine levels promote the formation of free radicals, enhance inflammation, and trigger atherosclerosis (11). Levodopa has been linked to an increased risk of stroke in PD. However, it has also been shown to exert a protective effect on retinal neural structures (13,14).

The retina is the only tissue in the body that allows direct, non-invasive imaging of the microvascular and nervous systems. Due to its anatomical, physiological, and embryological similarities to the brain, the retina has the potential to play a significant role in predicting both neurodegenerative and cerebrovascular diseases (15,16). In a meta-analysis by Wu et al., which included 20,659 patients, 1,178 of whom had experienced a stroke, it was found that retinal vascular changes were significantly associated with cerebral stroke. The study suggested that widespread microvascular alterations in the small vessels could serve as a predictor of stroke (16).

Optical coherence tomography angiography (OCT-A) is a non-invasive imaging technique that allows for high-resolution assessment of the neuronal and microvascular structures in the retina. Several studies have suggested that OCT-A could serve as a potential imaging tool for the early and accurate detection of neurodegenerative diseases, such as Alzheimer's disease and PD (17,18). However, to date, there has been no study in the literature that simultaneously evaluates retinal neuronal and vascular changes in PD alongside stroke risk assessment. This study aims to analyze the changes in retinal neuronal and vascular structures in PD patients in relation to disease severity, duration, levodopa dosage, and stroke risk assessment.

METHODS

This retrospective study was conducted between February and September 2022 in accordance with the principles of the Declaration of Helsinki under the collaboration of the Neurology and Ophthalmology Clinics. Approval for the study was obtained from the Ethics Committee of Dr. Lütfi Kırdar Kartal City Hospital, and since the study was retrospective in design, written informed consent was not required from the patients.

The study included adult patients diagnosed with PD according to the Movement Disorder Society clinical criteria determined by the Neurology Clinic (19). Patient data, including age, sex, disease duration, clinical examination findings related to the disease, levodopa dosage, systolic and diastolic blood pressure, fasting blood glucose, body mass index (calculated as weight/height^2), total cholesterol, the presence of systemic conditions such as diabetes mellitus (DM), hypertension (HT), atrial fibrillation, as well as information on lifestyle factors such as diet and exercise habits, smoking history, and a family and personal medical history of stroke, transient ischemic attacks (TIA), or myocardial infarction, were collected. Additionally, best-corrected visual acuity (BCVA) measured using the Snellen chart, intraocular pressure, detailed anterior and posterior segment examination findings using slit-lamp biomicroscopy, and posterior segment parameters measured with OCT and OCT-A were obtained from the patient records.

In the patients, disease severity was assessed based on motor symptoms using the Hoehn & Yahr (H&Y) clinical scale (Table 1), while stroke risk was calculated using the Stroke Risk Assessment (SRA) tool developed by the American Heart Association/American Stroke Association (Table 2). To establish a healthy control group for comparison with the PD patient cohort, the group was composed of age– and sex-matched individuals who presented with mild ocular manifestations, such as refractive errors or findings from routine ophthalmic assessments, and had no history of PD or other neurological disorders. Additionally, the individuals in this group had healthy anterior and posterior segment examinations. Data from one randomly selected eye from each participant in the PD patient and the control groups were included in the study.

Patients receiving non-levodopa treatments (dopamine agonists, Monoamine Oxidase B (MAO-B) inhibitors, COMT inhibitors (Catechol-O-Methyltransferase inhibitors), anticholinergics, amantadine, glutamate antagonists, and other long-term medications) and those with serious systemic diseases (such as diabetes mellitus, hypertension,

Table 1. The H&Y scale in PD

Stage	Describe
0	No symptom
1	Unilateral limb symptoms
1.5	Unilateral limb combined with trunk symptoms
2	Bilateral limb symptoms, no balance disorder
2.5	Patients can recover from the pull test with mild bilateral limb symptoms.
3	Patients have severe disabilities, but they can still stand and walk without others' help.
4	Patient can only sit in a wheelchair or lie in bed, and their life depends entirely on the help of others.

H&Y: Hoehn & Yahr; PD: Parkinson's disease.

Table 2. Stroke risk assessment (SRA) tool developed by the American Heart Association/American Stroke Association

Risk factor	High risk	Low risk
Is your blood pressure more than 120/80 mm/Hg?	Yes or unknown	No
Have you ever been diagnosed with atrial fibrillation	Yes or unknown	No
Is your blood sugar more than 100 mg/dL?	Yes or unknown	No
Is your body mass index greater than 25 kg/m^2	Yes or unknown	No
Is your diet high in saturated fat, trans fat, sugary drinks, salt, excess calories**?	Yes or unknown	No
Is your total blood cholesterol more than 160 mg/dL?	Yes or unknown	No
Have you ever been diagnosed with diabetes mellitus?	Yes or unknown	No
Do you do less than 150 minutes of moderate to vigorous intensity activity per week?	Yes or unknown	No
Do you have a personal or family history of stroke, TIA or heart attack?	Yes or unknown	No

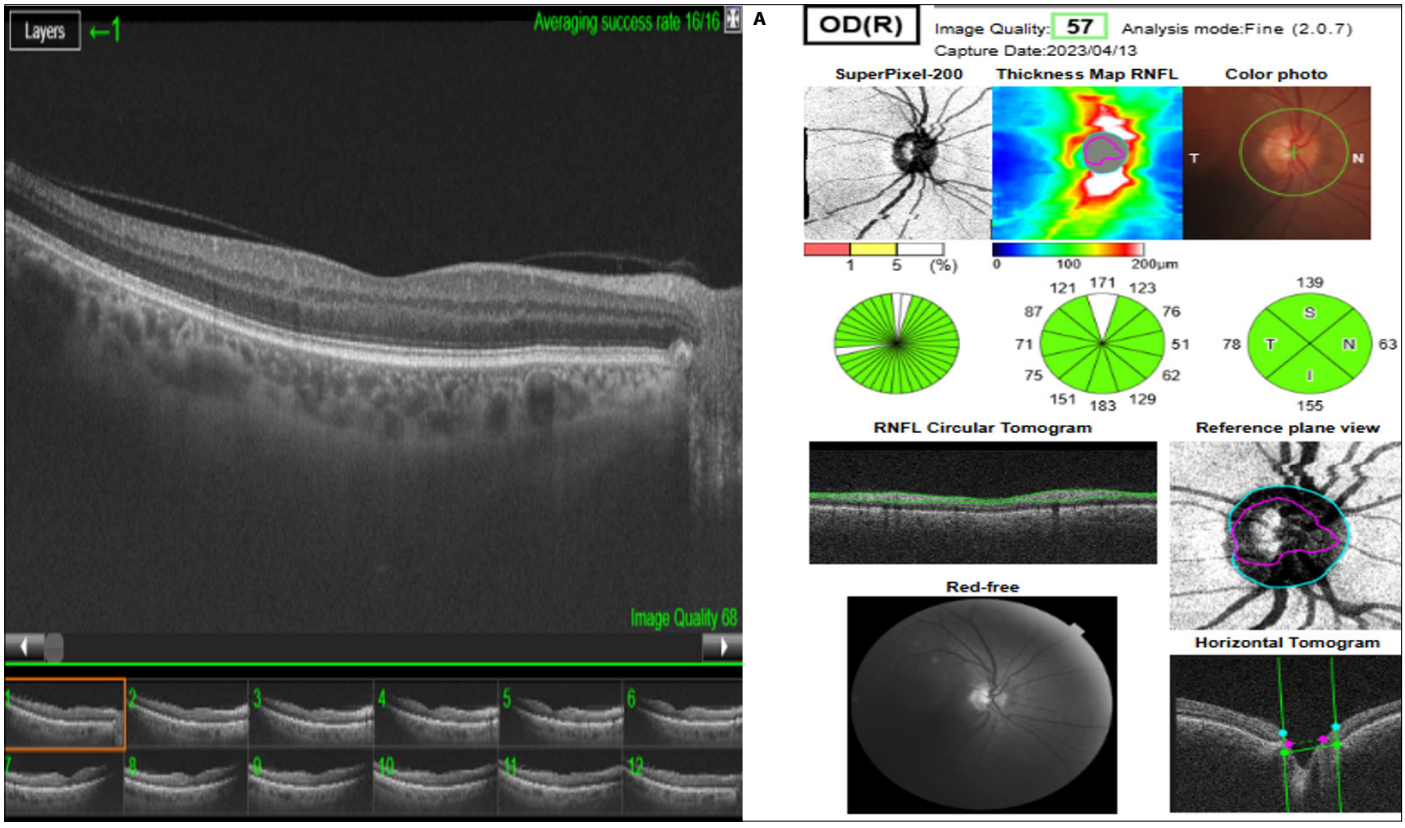

Figure 1. Optical coherence tomography images of the macula **(A)**. Optical coherence tomography images of the optic disc **(B)**.

heart disease, etc.), which could potentially affect retinal neural and vascular structures, were excluded from the study. Additionally, patients with PD stages 4 and 5, those with neurological disorders other than PD, patients with a history of stroke, individuals with refractive errors greater than ±3D, those with BCVA worse than 0.1 logMAR, patients with glaucoma or optic disc anomalies or diseases, individuals with a history of macular disease or dystrophy, those with uveitis, ocular trauma, or conditions that obstructed OCT and OCT-A measurements, as well as patients unable to cooperate with the imaging procedure, were excluded from the study.

Optic Coherence Tomography and Optic Coherence Tomography Angiography

Optical coherence tomography and OCT-A images (DRI OCT Triton, Topcon, Japan) from all participants were evaluated in this study. Using OCT, the fovea was examined as a 1×1 mm circular area, while a 3×3 mm ring surrounding the fovea was analyzed as the parafovea. The central foveal thickness (CFT) and the macular thicknesses (MT) of the four parafoveal quadrants (nasal, superior, temporal, and inferior) were automatically measured by the device. A circle with a 3.45 mm diameter was automatically placed at the center of the optic disc, and a round ring with a 1.0 mm width extending from the optic disc margin was considered the peripapillary region. The total peripapillary retinal nerve fiber layer thickness (RNFL) and the average thickness of the four peripapillary quadrants were determined using automated segmentation. Images with a signal strength index (SSI) of ±7 were excluded from the study (Fig. 1. a, b).

Using OCT-A (DRI OCT Triton Plus, Topcon, Japan), en-face OCT-A images were obtained from the central macular area (6× 6 mm^2). Measurements for the superficial capillary plexus (SCP) and deep capillary plexus (DCP) were made through Topcon's IMAGEnet software, and vessel density was defined as the percentage of area occupied by vessels (Fig. 2. a, b). The foveal avascular zone (FAZ) area was manually outlined by two separate researchers, and the average of these measurements was used (Fig. 3. a, b). To minimize diurnal variation effects, all measurements were performed between 10:00 AM and 12:00 PM. Images with a signal strength index (SSI) <45, segmentation errors, and motion artifacts were excluded from the analysis.

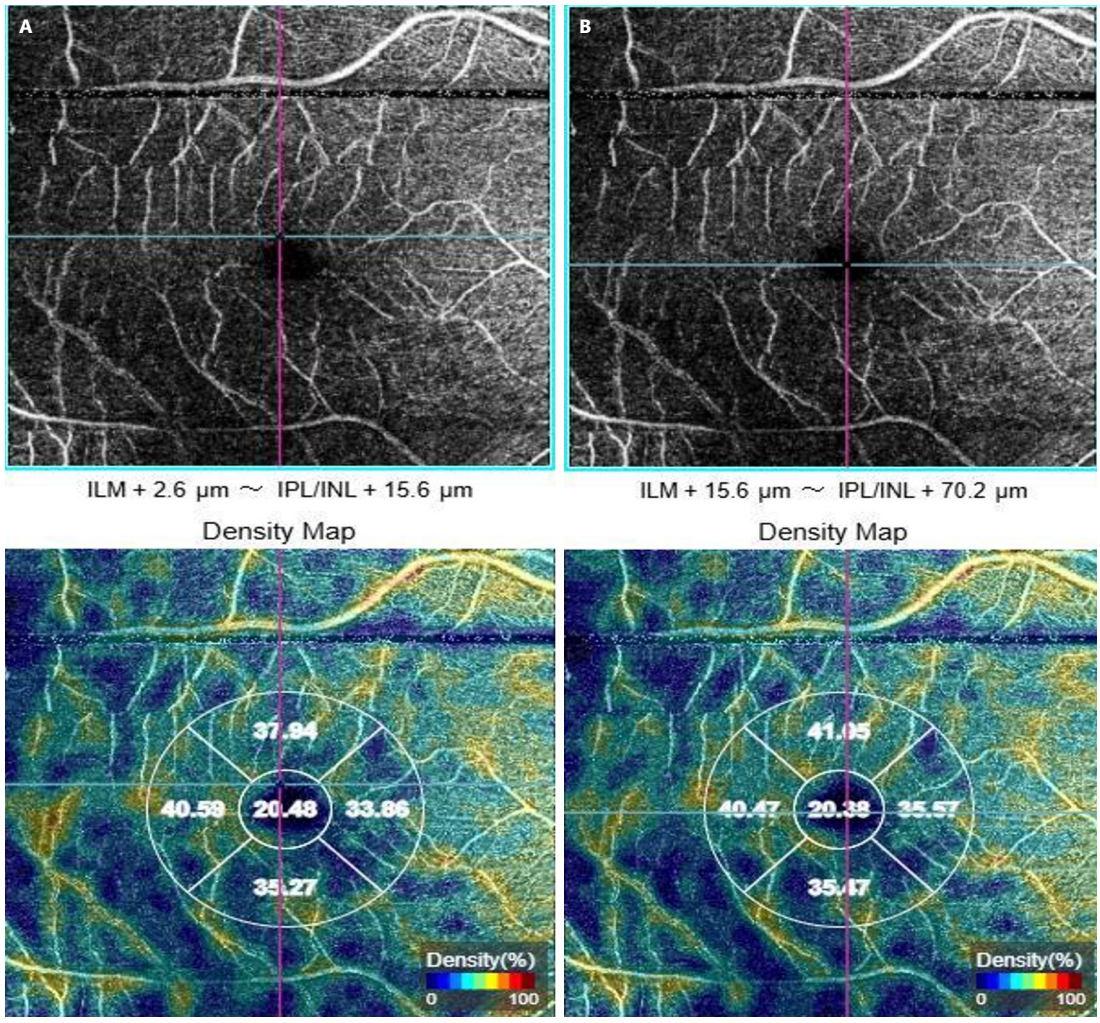

Figure 2. Superficial capillary plexus of the macula **(A)**. Deep capillary plexus of the macula **(B)**.

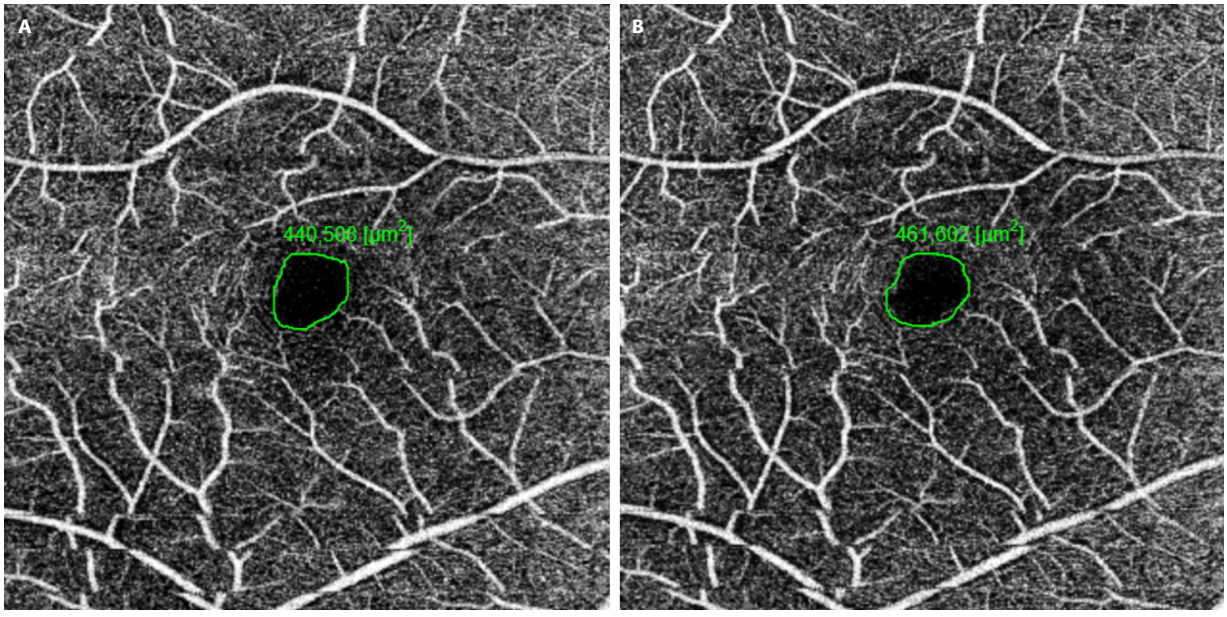

Figure 3. Superficial foveal avascular zone area **(A)**. Deep foveal avascular zone area **(B)**.

Statistics

Statistical Analysis The data were analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 25 software (Armonk, New York: IBM Corp., 2017). Descriptive statistics are presented as the number of units (n), percentage (%), mean ± standard deviation, median (M), minimum (min), and maximum (max) values. For numerical variables, comparisons between Parkinson's disease patients and healthy controls were made using the Student's t-test, assuming parametric conditions

were met, and the Mann-Whitney U test when parametric conditions were not met ($p < 0.05$). The relationship between disease duration and numerical variables was evaluated using the Spearman correlation coefficient. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 40 patients diagnosed with PD and 40 age- and sex-matched controls were enrolled in the study. The mean age of the PD patients was 64.47±9.10 years, compared to 62.32±9.96 years in the control group (p=0.755). The mean H&Y stage in the PD group was 2.6±0.82, while the mean SRA score was 2.72±1.43. The clinical and demographic characteristics of all participants are detailed in Table 3.

Slit-lamp examinations of both the anterior and posterior segments revealed no abnormalities in any of the participants. In the analysis of posterior segment parameters, CFT and MT across all quadrants were significantly reduced in the PD group compared to the control group, with a statistically significant difference noted only in the temporal quadrant (p=0.004). Although RNFL thickness was lower in the PD group across both the average and all quadrants, no statistically significant differences were observed when compared to the control group (p >0.005 for all). Concerning the macular vascular plexus, both the SCP and DCP exhibited significantly reduced vascular densities in all quadrants in the PD group (p <0.005 for all). Additionally, both the superior and deep FAZ areas were significantly larger in the PD group (p <0.001 for all) (Table 4).

Table 3. Demographic and clinic features of all study participants

	Patients with PD (n=40)	Control Group (n=40)	p
Age, (years) (mean ± sd)	64.47±9.10	62.32±9.96	0.755
Gender, Female, n (%)	18 (45%)	30 (75%)	0.125
BCVA (logMAR), (mean ± sd)	0.01±0.20	0.0±0.0	0.715
IOP (mm Hg), (mean ± sd)	14.71±2.96	15.09±3.38	0.760
Disease duration, months, (mean ± sd)	74.0±39.6	-	-
Levodopa dose (mg), (mean ± sd)	741.12±347.32	-	
H&Y score, (mean ± sd)	2.6±0.82	-	-
SRA, (mean ± sd)	2.72±1.43	-	-

PD: Parkinson's disease; BCVA: best corrected visual acuity; IOP: intraocular pressure; H&Y: Hoehn & Yahr; SRA: stroke risk assessment.

Table 4. Comparison of posterior segment parameters between patients with PD and the control group

		Patients with PD	Control Group	p
Central foveal thickness (µm)		243.77±32.85	250.05±36.15	0.258
Superior quadrant MT (µm)		296.35±24.51	303.85±82.24	0.059
Inferior quadrant MT (µm)		297.20±23.18	303.14±20.35	0.211
Nasal quadrant MT (µm)		294.20±37.14	302.58±13.83	0.587
Temporal quadrant MT (µm)		292.35±17.88	303.58±16.75	**0.004**
Average RNFL (µm)		103.95±12.90	106.95±15.95	0.281
Superior quadrant RNFL (µm)		122.75±20.64	133.85±21.47	0.057
Inferior quadrant RNFL (µm)		130.13±22.37	134.01±18.55	0.647
Nasal quadrant RNFL (µm)		80.65±85.77	87.03±12.90	0.015
Temporal quadrant RNFL (µm)		74.15±12.78	75.03±12.89	0.470
SCP (%)	**Foveal**	17.75±4.55	25.57±9.01	**<0.001**
	Superior	35.71±4.85	40.50±5.03	**<0.001**
	Inferior	34.93±5.42	38.65±4.38	**0.001**
	Temporal	33.00±5.62	41.19±6.65	**<0.001**
	Nasal	33.97±4.74	38.93±7.12	**<0.001**
DCP (%)	**Foveal**	17.45±6.82	24.97±7.10	**<0.001**
	Superior	33.48±5.65	44.10±3.51	**<0.001**
	Inferior	33.35±4.76	40.87±5.28	**<0.001**
	Temporal	35.22±6.24	43.39±4.55	**<0.001**
	Nasal	34.07±5.94	42.46±3.78	**<0.001**
FAZ (μm^2)	**Superficial**	619.90±311.24	318.19±102.49	**<0.001**
	Deep	628.13±209.82	344.90±103.16	**<0.001**

Mean ± standard deviation values are shown.
PD: Parkinson's disease; MT, macular thickness; RNFL: retinal nerve fiber layer; SCP: superficial capillary plexus; DCP: deep capillary plexus; FAZ: foveal avascular zone.

Table 5. Correlations between the differences in Disease Duration, H&Y score, SAR, Levodopa dose, and posterior segment parameters of patients with PD

		Disease Duration (months)		H&Y score		SRA score		Levodopa dose (mg)	
		Spearman's rho	p	Spearman's rho	p	Spearman's rho	p	Spearman's rho	p
Central Foveal Thickness (µm)		-0.147	0.366	-0.140	0.388	-0.068	0.618	-0.307	0.054
Superior quadrant MT (µm)		0.072	0.658	-0.095	0.559	-0.497**	**0.005**	0.025	0.877
Inferior quadrant MT (µm)		-0.213	0.187	-0.119	0.463	-0.229	0.224	-0.327	**0.039***
Nasal quadrant MT (µm)		-0.180	0.266	-0.004	0.982	-0.138	0.468	-0.183	0.258
Temporal quadrant MT (µm)		-0.199	0.218	-0.319	**0.045***	0.146	0.442	-0.387	**0.014***
Average RNFL (µm)		-0.250	0.120	-0.388	**0.013***	-0.147	0.437	0.035	0.829
Superior quadrant RNFL (µm)		-0.198	0.221	-0.369	**0.019***	0.052	0.785	0.242	0.133
Inferior quadrant RNFL (µm)		-0.172	0.288	-0.223	0.166	-0.089	0.639	0.018	0.914
Nasal quadrant RNFL (µm)		-0.199	0.218	-0.299	0.061	0–0.108	0.570	-0.010	0.951
Temporal quadrant RNFL (µm)		-0.294	0.066	-0.289	0.066	-0.246	0.190	-0.003	0.984
SCP (%)	Foveal	-0.033	0.841	-0.195	0.227	-0.004	0.981	-0.043	0.792
	Superior	0.029	0.857	-0.049	0.765	-0.297	0.111	-0.033	0.840
	Inferior	-0.149	0.359	0.087	0.594	-0.022	0.873	-0.091	0.578
	Temporal	-0.339	**0.032***	-0228	0.158	-0.216	0.252	-0.401	**0.010***
	Nasal	-0.360	**0.023***	-0.004	0.982	-0.087	0.647	-0.112	0.492
DCP (%)	Foveal	0.024	0.882	-0.183	0.258	-0.112	0.557	-0.108	0.505
	Superior	0.047	0.775	-0.059	0.717	-0.224	0.234	-0.012	0.940
	Inferior	-0.231	0.152	-0.185	0.253	-0.021	0.912	-0.094	0.563
	Temporal	-0.288	0.720	-0.274	0.087	-0.096	0.615	-0.329	**0.038***
	Nasal	-0.271	0.091	-0.088	0.589	-0.130	0.494	-0.188	0.246
FAZ (µm²)	Superficial	0.310	0.052	0.265	0.098	0–0.100	0.597	0.222	0.168
	Deep	0.095	0.559	0.332	**0.036***	0.036	0.851	0.404	**0.010***

*Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
PD: Parkinson's disease, MT, H&Y: Hoehn & Yahr, SAR: stroke risk assessment. MT: macular thickness; RNFL: retinal nerve fiber layer; SCP: superficial capillary plexus; DCP: deep capillary plexus; FAZ: foveal avascular zone.

In patients with PD, the correlations between posterior segment parameters and disease duration, H&Y score, SRA score, and levodopa dosage were evaluated. A significant negative correlation was found between disease duration and the SCP in both the temporal and nasal quadrants (rho=-0.339, p=0.032; rho=-0.360, p=0.023, respectively). Disease severity was negatively correlated with MT in the temporal quadrant, as well as with RNFL thickness in the average and superior quadrants (rho=-0.319, p=0.045; rho=-0.388, p=0.013; rho=-0.369, p=0.019). Conversely, a significant positive correlation was observed between the H&Y score and the deep FAZ area (rho=0.423, p=0.007). A significant negative correlation was also observed between the SRA score and MT in the superior quadrant (rho=-0.497, p=0.005). Regarding levodopa dosage, negative correlations were identified with MT in the inferior and temporal quadrants, SCP in the temporal quadrant, and DCP in the temporal quadrant (rho=-0.327, p=0.039; rho=-0.387, p=0.014; rho=-0.401, p=0.010; rho=-0.329, p=0.038). Additionally, a significant positive correlation was observed between levodopa dosage and the deep FAZ area (rho=0.404, p=0.010) (Table 5).

DISCUSSION

Stroke is the second leading cause of death and disability worldwide, with approximately 80% of cases considered preventable (20). Research has shown that individuals with PD are at a significantly higher risk of stroke compared to healthy controls. Furthermore, post-stroke complications, particularly during the first 30 days, are more prevalent in PD patients. These complications include pneumonia, urinary tract infections, epilepsy, and gastrointestinal bleeding, all of which contribute to a higher mortality risk (21). Several factors contribute to the increased risk of stroke in PD patients. These include advanced age, orthostatic hypotension, fluctuations in blood pressure, increased oxidative stress, and associated atherosclerosis. Additionally, the reduced mobility characteristic of PD, along with movement-related disorders, frequent falls, and repetitive trauma, further exacerbates the risk. Hyperhomocysteinemia is also a contributing factor, often correlating with elevated levodopa levels (21). Assessing and preventing stroke risk in PD patients is crucial for improving their quality of life. In this study, it was observed that MT and RNFL thickness were reduced in PD patients compared to a control group, with a particularly significant decrease noted in the temporal MT. Additionally, both the SCP and DCP vascular density were significantly reduced in PD patients, while the superficial and deep FAZ areas showed notable enlargement. We identified significant negative correlations between disease duration and both the temporal and nasal quadrants of the SCP. Furthermore, the H&Y scale exhibited negative correlations with temporal MT, average, and superior quadrant RNFL. Conversely, a positive correlation was observed between the H&Y scale and the deep FAZ area. Levodopa levels were inversely correlated with inferior and temporal MT and temporal SCP and DCP. A positive association was noted between levodopa levels and deep FAZ area. However, no significant correlation was found between the SRA score and vascular parameters.

In a review by Devi et al., which analyzed 17 studies evaluating RNFL thickness in PD, significant thinning of the RNFL across different quadrants was observed in 12 of the studies, while five studies reported no significant differences compared to control groups. The authors attributed these discrepancies to variations in factors such as age, disease duration, and disease severity across the studies (4). Additionally, some studies have shown that MT is thinner in PD patients (22,23). Unlu et al. reported thinning of the retinal ganglion cells, IPL, inner nuclear layer, outer plexiform layer, outer nuclear layer, photoreceptor layer,

retinal pigment epithelium, and peripapillary RNFL in PD patients. This thinning was found to have a negative correlation with the H&Y scale score, indicating that the degree of retinal thinning was related to disease severity. Furthermore, the study also observed a reduction in multifocal electroretinogram amplitudes and an increase in latency, which were linked to the retinal neurodegenerative changes associated with PD (24). In this study, while the average and all quadrants of RNFL and MT were lower in PD patients, the differences were not statistically significant. However, a significant decrease was observed specifically in temporal MT. Similar to other studies, this condition has been associated with the degeneration of neuronal structures resulting from the loss of dopaminergic neurons in the retina, which is linked to PD pathogenesis, as dopamine is essential for developing retinal tissues and visual functions (4,5). Furthermore, vascular damage caused by the accumulation of α-synuclein, particularly around intra-retinal vascular structures, along with ischemic processes, contributes to further degeneration, as considered in this study. Additionally, statistically significant negative correlations were found between temporal MT, average RNFL, and superior quadrant RNFL with the H&Y scale score, suggesting that retinal thinning may be related to disease severity, and statistically significant negative correlations were observed between levodopa dose and inferior and temporal MT. It is known that levodopa has a protective effect on neuronal tissues. However, its impact on retinal vascular factors has not been studied. We attribute this change to the impact of increased homocysteine on vascular structures, which is dose-dependent on levodopa, similar to the pathogenesis of stroke.

Studies using OCT-A to assess retinal microvascular changes have also reported a reduction in macular vascular density in PD patients (25–27). Kawpong et al. specifically noted thinning in the SCP, although they found no correlation with disease duration or severity (25). Conversely, Zou et al. reported thinning in both the SCP and DCP (26), while Xu et al. observed a positive correlation between vascular thinning in both the SCP and DCP and disease duration and severity (27). This finding suggests that similar to cerebrovascular changes observed in the brain in PD pathogenesis, there are also alterations in the retinal vascular structure, particularly a reduction in vascular density within the SCP, which is linked to the loss of ganglion cells (27). Another study has suggested that these vascular changes may contribute to the development of retinal neurodegeneration (28). In our study, we also observed a statistically significant decrease in vascular density in both the SCP and DCP. In our study, based on the results obtained, we propose that not only neurodegenerative processes but also vascular factors play a role in the pathogenesis of PD. Furthermore, we suggest that this condition may develop as a result of the overexpression of α-synuclein. A statistically significant negative correlation was found between disease duration and the temporal and nasal quadrants of the SCP. However, no statistically significant correlation was observed between the H&Y and both the SCP and DCP. This can be explained by the fact that the H&Y scale, which evaluates the PD solely based on motor function, is used as an indicator of cerebral neurodegeneration leading to changes in motor function, and is not associated with vascular changes (29). In our study, while no correlation was found between the H&Y scale and vascular structures, a negative correlation was observed with certain RNFL and MT parameters. This suggests that the H&Y scale may be associated with retinal neurodegenerative processes. In addition, there was a statistically significant negative correlation between levodopa levels and the temporal SCP and DCP. This condition may be associated with the disease pathogenesis or the mechanism of action of the medication. However, since patients with PH who were not using medication were not included in our study, it is not possible to draw a definitive conclusion.

Results regarding the FAZ area in PD patients are conflicting. Xu et al. demonstrated no change in PD patients compared to controls (27), while others have found a reduction in the FAZ area in PD patients (26,30). These discrepancies have been attributed to the vascular remodeling that occurs in response to the loss of foveal dopaminergic neurons in the early stages of the disease. In our study, we observed a significant expansion of the FAZ area in PD patients compared to healthy controls. We attributed this finding to vascular damage resulting from ongoing α-synuclein accumulation, which, despite the patients in our study being in the early stages of the disease, has led to insufficient vascular remodeling.

A relationship has been found between stroke and retinal vascular changes, such as microaneurysms, hemorrhages, arteriovenous nicking, and focal arteriolar narrowing (31). These changes are thought to be associated with degenerative alterations in small blood vessels, including fibrinoid degeneration, fibrous nodules, fibrohyaloid thickening, and calcification, which contribute to the stroke development process. (32) Liu et al. demonstrated in their study on stroke patients using OCT-A that retinal vascular density was reduced, and this change occurred independently of traditional risk factors (33). Wu et al., in their meta-analysis and literature review, have stated that retinal vascular changes provide a non-invasive means to evaluate the effects of common vascular risk factors on small vessels and offer a better understanding of the pathophysiological processes involved in cerebral small-vessel disease. They also highlighted the established relationship between retinal vascular changes and stroke (34). Various risk assessment tools are used to predict stroke outcomes. In our study, the SRA scale was employed to assess stroke risk in PD patients. The SRA scale is a tool that assesses traditional risk factors such as blood pressure, blood sugar, cholesterol, body mass index, exercise habits, dietary habits, and family history (35). However, it does not provide information on the duration of risk factors, their severity, or potential changes that may develop based on individual sensitivity to these risk factors. In this study, we did not observe a correlation between the SRA scale and retinal vascular changes. We believe that the SRA scale is not sufficient to demonstrate which individuals are affected by these risk factors and after what duration and intensity they may become impactful. In this regard, retinal vascular parameters, which are non-invasive and can be repeatedly measured, may be highly beneficial in risk assessment by revealing the effects of all risk factors on small vessels. Additionally, Liu et al. have similarly suggested that retinal microvascular changes may be associated with stroke independently of traditional risk factors (33).

This study had several limitations. These included its retrospective design, the small sample size, and the absence of patients with advanced PD severity. Additionally, all participants in the study were receiving levodopa therapy, and a group of patients not receiving medication could not be included in the study.

In conclusion, to the best of our knowledge, this is the first study to simultaneously assess disease severity, stroke risk, and posterior segment parameters in PD patients. In cases where stroke risk is elevated due to various pathophysiological processes, as in PD, the use of personalized biomarkers and stroke risk scoring systems beyond traditional risk factors is crucial for preventive treatment strategies. To further investigate this, prospective studies with larger sample sizes and long-term follow-up using OCT-A would be beneficial.

Ethics Committee Approval: Approval was obtained from the Dr. Lütfi Kırdar Kartal City Hospital ethical review committee (Protocol Number: 2022/514/234/11)

Informed Consent: Since the study was retrospective in design, written informed consent was not required from the patients.

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