ORIGINAL ARTICLE

# Assessment of retinal blood flow changes in early Parkinson's disease: An optical coherence tomography angiography study

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**Background:** To evaluate retinal microvasculature and choroidal thickness in patients with Parkinson's disease (PD) with optical coherence tomography angiography (OCTA). **Materials and Methods:** Forty-one eyes from 41 patients diagnosed with PD and 41 eyes of 41 healthy subjects underwent retinal and choroidal assessment using swept source DRI Triton OCT (Topcon, Tokyo, Japan). Macular perfusion parameters, including superficial and deep foveal avascular zones (FAZs and FAZd, respectively), superficial capillary plexus (vascular density [VDs]), deep capillary plexus (VDd), and choriocapillaris (VDc), were compared with healthy controls. **Results:** The central sectors of the VDs, VDd, and VDc measurements ($P = 0.001$; $P = 0.001$; $P = 0.001$, respectively) and the superior sectors of VDs and VDc ($P = 0.001$; $P = 0.001$, respectively) were found to be significantly higher in the study group compared to the control group. FAZs and FAZd values were found to be decreased significantly in PD patients ($P = 0.001$ and $P = 0.001$, respectively). Choroidal thickness was significantly reduced ($P = 0.007$). Central macular thickness measurement did not differ between the groups ($P > 0.05$). In the multivariate regression model, VDs superior, FAZs, and choroidal thickness variables were determined to have a significant and independent effect in differentiating patients with PD from the individuals in the control group. **Conclusion:** PD seems to affect macular and choroidal microcirculation. The reduced choroidal thickness and increased central sectors of the VDs, VDd, and VDc measurements may provide disease activity information. However, more comprehensive studies on OCTA demonstrating clinical utility in PD are needed to support our findings.

**Key words:** Choroid, optical coherence tomography, Parkinson disease, retinal vessels

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## INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder, characterized by the loss of dopaminergic neurons, especially in the basal ganglia of the brain.[1] PD includes well-known motor symptoms such as rest tremor, rigidity, bradykinesia, and postural instability. In addition, cognitive impairment, psychosis, depression, autonomic dysfunction, and visual disturbances are the leading nonmotor disturbances during the course of illness.[2] Ocular complaints, including ocular surface irritation, decreased visual acuity, diplopia, changes in contrast vision, visual hallucinations, and visuospatial orientation, have been reported by PD patients.[2-5]

Dopamine (DA) is a neuromodulator for visual processing in the retina.[6] Amacrine cells and ganglion cells contain dopaminergic activity in the retina as a part of the central nervous system.[7] The change in dopaminergic activity in the retina in PD has brought up potential retinal biomarkers research for early diagnosis, prognosis, and progression of the disease.[8] Numerous studies have used optical coherence tomography (OCT), a noninvasive retinal imaging technique which enables *in vivo* imaging of the retinal layers, to investigate the

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differences of the retinal and choroidal morphology of PD.[9-17]

Microvascular components of neurodegenerative and psychiatric disorders can be assessed directly from the retina, as an extension of the brain, by OCT angiography (OCTA).[18-20] A comprehensive meta-analysis evaluating studies on retinal and microvascular changes in Parkinson's disease patients reported a statistically significant decrease in superficial vascular complex (SVC) vessel density, while no significant difference was found in deep vascular complex (DVC) vessel density.[21] While other OCTA studies have also shown that SVC is lower in PD patients,[22,23] Rascunà *et al*.[24] found that SVC was slightly higher in the PD group, although the difference was not statistically significant. The differences in findings across studies and the variety of devices used highlight the need for further studies on retinal and microvascular changes in PD.[25] Swept-source OCTA can provide detailed imaging of the retinal vascular network by sequential optical coherence scans of a particular retinal region, based on the motion contrast of erythrocytes in vascular structures.[26] It evaluates the macular microvasculature noninvasively, without the necessity for intravenous contrast material which can cause adverse reactions. In the present study, we aimed to determine the superficial, deep, and choriocapillar retinal flow alterations in eyes of individuals with newly diagnosed early stages of idiopathic PD using Swept-Source DRI OCT Triton (Topcon Corp, Tokyo, Japan). After, we compared the measurements with eyes of age- and sex-matched healthy control individuals.

## MATERIALS AND METHODS

### Study population and design

This observational and cross-sectional study was conducted in a tertiary hospital's Department of Ophthalmology and Neurology in accordance with the provisions of the Helsinki Declaration after the approval of Selcuk University Ethics Committee was obtained through the committee decision number 2019/282. Written informed consent was received from all the eligible participants before registration.

The study included 41 cognitively healthy age- and sex-matched control subjects as control group and 41 patients with PD as case group. The patients had been diagnosed with definite PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria, which included in the first stage, bradykinesia, and one additional symptom, i.e., postural instability, rigidity or 4–6 Hz resting tremor.[27,28] The diagnosis was confirmed by an experienced neurologist (H. G.). The patients were staged according to the Hoehn and Yahr scale (H-Y scale) and their motor symptoms were assessed before starting medication using the motor examination score of the Unified Parkinson's Disease Rating Scale part III.[29] Only the patients newly diagnosed with idiopathic PD at an early stage were enrolled in the current study, defined as H-Y scale <3.[28] Patients in PD group included in this study we had been referred for a routine eye screening to the Department of Ophthalmology by the Neurology clinic. Retinal measurements of the patients were obtained before they started using anti-Parkinson medication (L-DOPA, Selegiline, Rasagiline, Pramipexole, and Ropinirole). The ophthalmologically healthy control group, who was admitted to the outpatient clinic with the symptoms of presbyopia, had no past or present history of neurological or psychiatric disorder or cognitive complaints.

All patients and participants underwent a comprehensive ophthalmological evaluation, including their best-corrected visual acuity values were measured according to the standard Snellen chart, and their intraocular pressures were measured via Goldmann applanation tonometry. The subjects' anterior eye segments were examined with a slit lamp and fundus evaluations were carried out with a +90D lens after pharmacological dilatation with 1% Tropicamide. OCTA imaging was obtained after full pharmacological dilatation. Only the right eye of all subjects was included in OCT image acquisition if they fulfilled the inclusion and exclusion criteria.

Participants were excluded from the study if they required high refractive vision correction (spherical equivalent higher than +3 or −3 diopter), if they had dense cataract causing severe media opacities (Grade 3 or higher on the LOCS III classification), any ocular surgery, ocular trauma, retinal vascular disease, glaucoma, ocular inflammation, optic disc anomaly, optic neuropathy, or if their examinations returned poor image quality due to unstable fixation in OCTA measurements. Neurological exclusion criteria were the presence of other neurological or systemic conditions, including a history of stroke, hypertension, diabetes mellitus, Alzheimer's disease, muscular dystrophy, or multiple system atrophy.

### Optical coherence tomography angiography technique

We obtained OCTA images with the Swept-Source DRI OCT Triton (Topcon Corp, Tokyo, Japan) device after all the individuals took a sitting down and rested for 10 min. All the parameters were measured by one experienced operator who was blind to the outcomes of the neurological and ophthalmologic evaluations using Swept-Source OCT which operates a 1.050 nm wavelength light source and 100,000 A Scan/s.[30] We used OCTA function to obtain 6 mm × 6 mm cubes centered on the fovea [Figure 1]. OCTA Software (IMAGEnet 6 V.1.14.8538) system did the macular segmentation which consists of four "en face" OCT

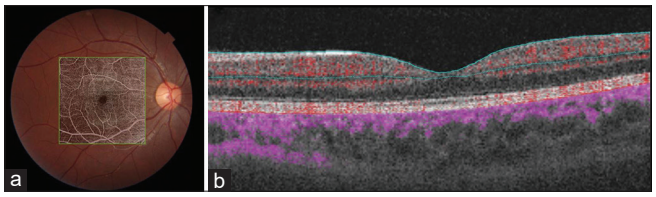


**Figure 1:** Illustrative optical coherence tomography angiography analysis of a 6 mm × 6 mm area on the fovea (a). The image at the side shows a B scan with the blue lines limiting the analyzed zone to measure (b)

slabs: (1) SVC is defined as from 2.6 μm below the internal limiting membrane to the 15.6 μm below the inner plexiform layer (IPL), (2) DVC is defined as from IPL offset of 15.6 μm to the IPL offset of 70.2 μm and (3) choriocapillar vascular complex (CC) is identified as from BM to 10.4 μm under the BM [Figure 2].[31]

GNU Image Manipulation Program (GIMP) 2.8.14 analyzed quantitatively the vascular density (VD) as the SVC (VDs), VD of the DVC (VDd), VD of the choriocapillar vascular complex (VDc), superficial foveal avascular zone (FAZs) and deep foveal avascular zone (FAZd). VD was calculated as the percentage of the vascularized tissue in the grid centered in the macula. VD was calculated as the total length of perfused vasculature, measured in $mm^2$, in the region of measurement in which erythrocyte movement is detected. This software provides the VD of blood vessels in the scanning area (6 mm × 6 mm) as the percentage of that area that is occupied by the lumens of the vessels. In brief, a binary vessel image was subtracted from the OCTA en face image, and the VD was calculated according to the percentage of white pixels in the vessels based on the sectors identified in the binary image. The software produces an Early Treatment Diabetic Retinopathy Study (ETDRS) circular grid (3 mm diameter) which delivers a VD percentage in each of the sections that compose this grid. The grid centered on the fovea divides the macular region into the central foveal area and a perifoveal ring divided into the superior, inferior, nasal, and temporal sectors. The subfoveal choroidal thickness and central macular thickness (SFCT and CMT, respectively) analysis was performed for all subjects of the eyes in the nine regions of the macula. Macula sections were identified objectively with radii of 0.5 mm (center 1 mm), 0.5–1.5 mm (inner ring), and 1.5–3.0 mm (outer ring). CMT and SFCT values were obtained using an ETDRS grid overlay comprising the two inner rings. VD measurements were achieved separately in four parafoveal subfields (superior, inferior, nasal, and temporal) using an ETDRS grid. All the measurements were performed at the same time interval of the day (i.e., 9–10 a.m.) to minimize any influence of the normal diurnal variations of blood pressure. Two experienced observers examined two consecutive scans of a subject to detect interobserver reproducibility in different time zones. To evaluate the interobserver reproducibility, we used two methods: (1) Average: Comparing the mean of three consecutive measurements from each observer, and (2) Single: Comparing the first measurements from each observer. The mean value of two independent parameters was used for each OCTA parameter. Any pathologic condition detected in structural OCT scans was ruled out. OCTA images with poor scan quality (if Image Quality Index were under 70), motion artifact, segmentation artifact, or focal signal loss were excluded due to compliance problems during measurement acquisition or typical tremor in Parkinson's. Considering that these might affect the imaging, 41 patients out of 55 with suitable images were included in the study.

### Statistical analysis

Data on demographic features, VDs of three vascular plexus, FAZs, FAZd, CMT, and SFCT were collected as mean ± standard deviation (SD). The distribution of variables was checked with the Kolmogorov–Smirnov test. The categorical data were compared between the groups using Pearson's Chi-square test and the Mann–Whitney *U*-test was used for all OCTA variables showing abnormal distribution for the comparison of means between groups by the Statistical Package for the Social Sciences software (version 26.0; SPSS Inc., Chicago, IL, USA). To assess the possible association between PD and OCTA parameters, logistic regression analysis was used by considering the presence of PD as the outcome variable. The odds ratios (OR) with 95% confidence intervals and *P* value were examined. $P < 0.05$ was noted as statistically significant.

## RESULTS

We examined 82 eyes of 41 participants with PD (17 women [41.5%] and 24 men [58.5%]; average [SD] age, 62.17 [10.18] years) and 82 eyes of 41 healthy controls (14 women [34.1%] and 27 men [65.9%]; average [SD] age, 64.68 [8.29] years). The age and gender distribution of the participants in both groups did not show significant difference ($P > 0.05$). Demographic data and OCTA parameters of enrolled subjects are demonstrated in Table 1.

FAZs and FAZd values were decreased significantly in PD patients than controls ($P = 0.001$; $P = 0.001$, respectively). VDs central and VDs superior values were found to be increased in PD cases compared to control group, significantly ($P = 0.001$; $P = 0.001$, respectively). In the case group, the VDd central value was significantly higher than the control group ($P = 0.001$). In VDc analysis, VDc central and VDc superior values were increased significantly in PD patients than controls ($P = 0.001$; $P = 0.001$, respectively). CMT measurement did not differ between the groups ($P > 0.05$). A significant decrease in choroidal thickness was detected in the patients with PD ($P = 0.007$).

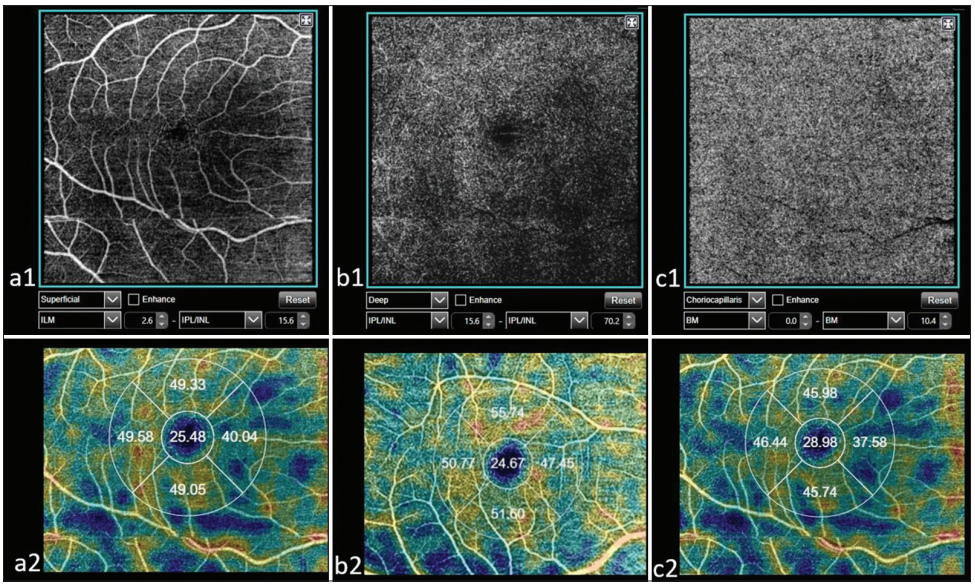


**Figure 2:** A 6 mm × 6 mm area optical coherence tomography angiography (OCTA) image (a1) and vessel density (a2) in the superficial capillary plexus from 2.6 μm below the internal limiting membrane to the 15.6 μm below the inner plexiform layer; a 6 mm × 6 mm area OCTA image (b1) and vessel density (b2) in the deep capillary plexus from inner plexiform layer offset of 15.6 μm to 70.2 μm; and a 6 mm × 6 mm area OCTA image the choriocapillaris' image (c1) and vessel density (c2) from Bruch's membrane to 10.4 μm beneath Bruch's membrane

**Table 1: Comparison of the macular perfusion parameters between Parkinson's disease case group and healthy control group**

| | Control group | | Parkinson disease group | | *P* |
|---|---|---|---|---|---|
| | Mean±SD | Median | Mean±SD | Median | |
| Age | 62.17±10.18 | 58.00 | 64.68±8.29 | 65.00 | 0.100 (Mann–Whitney *U*-test) |
| Sex | | | | | |
| Female | 17 (41.5) | | 14 (34.1) | | 0.494 ($\chi^2$) |
| Male | 24 (58.5) | | 27 (65.9) | | |
| VDs central | 22.34±8.09 | 20.16 | 24.72±3.69 | 24.67 | ***0.001*** (Mann–Whitney *U*-test) |
| VDs superior | 47.93±3.84 | 48.15 | 50.90±3.41 | 51.19 | ***0.001*** (Mann–Whitney *U*-test) |
| VDs temporal | 46.59±3.46 | 46.60 | 47.44±3.77 | 46.73 | 0.361 (Mann–Whitney *U*-test) |
| VDs inferior | 48.11±4.42 | 47.76 | 48.22±4.40 | 47.96 | 0.575 (Mann–Whitney *U*-test) |
| VDs nasal | 44.56±4.30 | 45.17 | 44.12±4.95 | 44.93 | 0.544 (Mann–Whitney *U*-test) |
| VDd central | 21.44±8.36 | 19.23 | 24.56±5.22 | 24.23 | ***0.001*** (Mann–Whitney *U*-test) |
| VDd superior | 50.23±4.82 | 50.84 | 52.15±3.75 | 52.11 | 0.060 (Mann–Whitney *U*-test) |
| VDd temporal | 48.45±3.59 | 48.50 | 48.15±4.21 | 47.52 | 0.412 (Mann–Whitney *U*-test) |
| VDd inferior | 49.78±4.52 | 48.97 | 48.57±4.36 | 49.04 | 0.361 (Mann–Whitney *U*-test) |
| VDd nasal | 46.50±4.76 | 47.87 | 45.60±5.40 | 46.90 | 0.393 (Mann–Whitney *U*-test) |
| VDc central | 22.00±8.06 | 20.18 | 24.35±3.65 | 24.48 | ***0.001*** (Mann–Whitney *U*-test) |
| VDc superior | 47.85±3.99 | 48.26 | 50.87±3.48 | 51.23 | ***0.001*** (Mann–Whitney *U*-test) |
| VDc temporal | 46.44±3.47 | 46.28 | 47.61±3.71 | 46.64 | 0.212 (Mann–Whitney *U*-test) |
| VDc inferior | 48.12±4.39 | 47.42 | 48.40±4.36 | 48.11 | 0.461 (Mann–Whitney *U*-test) |
| VDc nasal | 44.51±4.32 | 45.02 | 44.07±4.90 | 44.82 | 0.603 (Mann–Whitney *U*-test) |
| FAZs | 183.74±127.56 | 127.97 | 107.29±25.55 | 104.06 | ***0.001*** (Mann–Whitney *U*-test) |
| FAZd | 268.34±173.06 | 213.40 | 176.37±43.89 | 170.16 | ***0.001*** (Mann–Whitney *U*-test) |
| CMT | 192.59±27.81 | 185.00 | 188.29±18.65 | 188.00 | 0.756 (Mann–Whitney *U*-test) |
| SFCT | 231.83±66.96 | 234.00 | 190.00±60.14 | 203.00 | ***0.007*** (Mann–Whitney *U*-test) |

Italicized bold values represent *P*<0.05. FAZs=Superficial foveal avascular zone; FAZd=Deep foveal avascular zone; VDs=Superficial vascular density; VDd=Deep vascular density; VDc=Choriocapillaris vascular density; CMT=Central macular thickness; SFCT=Subfoveal choroidal thickness; SD=Standard deviation

In the univariate logistic regression model, significant effect of VDs central, VDs superior, VDc superior, FAZs, FAZd, and SFCT values was observed to distinguish patients with PD ($P < 0.05$). In the multivariate constructed model,

**Table 2: Univariate and multivariate logistic regression analysis to show the effect level of optical coherence tomography angiography parameters for Parkinson's disease cases**

| | Univariate model | | | Multivariate model | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | OR | 95% CI | *P* |
| VDs central | 1.067 | 0.987–1.154 | *0.102* | | | |
| VDs superior | 1.265 | 1.095–1.462 | ***0.001*** | 1.340 | 1.115–1.611 | ***0.002*** |
| VDd central | 1.072 | 0.998–1.151 | *0.056* | | | |
| VDc central | 1.067 | 0.987–1.155 | *0.104* | | | |
| VDc superior | 1.249 | 1.088–1.434 | ***0.002*** | | | |
| FAZs | 0.975 | 0.959–0.991 | ***0.002*** | 0.971 | 0.951–0.990 | ***0.004*** |
| FAZd | 0.987 | 0.978–0.996 | ***0.004*** | | | |
| SFCT | 0.990 | 0.982–0.997 | ***0.006*** | 0.986 | 0.976–0.995 | ***0.003*** |

Italicized bold values represent $P<0.05$. Logistic regression (forward LR). FAZs=Superficial foveal avascular zone; FAZd=deep foveal avascular zone; VDs=Superficial vascular density; VDd=Deep vascular density; VDc=Choriocapillaris vascular density; SFCT=Subfoveal choroidal thickness; OR=Odds ratio; CI=Confidence interval

prominent effects of VDs superior, FAZs, and SFCT values were detected to discriminate between the controls and patients with PD ($P < 0.05$) [Table 2].

## DISCUSSION

Cerebral hypoperfusion and blood–brain barrier dysfunction have been observed in a variety of neurodegenerative and psychiatric disorders.[32] Alterations in cerebral perfusion in PD have been evaluated in several studies using nuclear imaging techniques and magnetic resonance imaging.[33-35] The formation of endothelial clusters, damaged capillary network and the loss of capillary interconnections induce degenerative vascular morphology which is the cause of widespread cortical hypoperfusion in PD.[36] Recently, retinal microvascular parameters, which can be quantitatively detected *in vivo* by OCTA, have been investigated due to vascular changes of PD. In the existing literature, several reports have been published regarding retinal microvascular impairment in PD.[21-24,37-42] The present study was designed because different results regarding PD were reported in the meta-analysis and we aimed to discuss our results by comparing them with the literature.[21] In addition, the advantage of the current study is that it was designed on early-stage patients with PD who had not yet started medication. Several studies have shown that anti-Parkinson's drugs such as L-DOPA, Selegiline, and Rasagiline have effects on the retina.[43-45] In order to avoid the possible changes in the retinal layers or alteration of vascularity because of anti-Parkinson's drugs, we included early-stage patients who had not yet started taking medication in our study.

The structure of the retina and choroid can be easily and noninvasively assessed with OCT. The changes of the inner retinal layers and choroidal thickness have been already published in PD.[8,24,46] Decreased thickness of inner retinal layers in the macular region was reported in PD patients compared to controls. Although α-synuclein is present in the retina of individuals with PD, it is not known to what extent the retinal ganglion cells are affected as a result of the neurodegenerative process. Garcia-Martin *et al*.[46] reported significant thinning of the retinal nerve fiber layer, ganglion cell layer, and IPL in patients with PD. In another study designed with swept-source OCT, significant retinal thinning and increased choroidal thickness were demonstrated.[42] The importance of performing Swept-Source OCT is that researchers can objectively evaluate the choroidal thickness and get more accurate manual and automated images of the retina and choroid. In our study conducted with the Swept-Source OCT device, we showed a decrease in the average choroidal thickness. Similar to our study result, Eraslan *et al.* reported atrophy and volume loss in the lamina cribrosa and choroid with enhanced depth imaging (EDI) spectral-domain OCT methodology.[17] In EDI OCT technology, the inner and outer borders of the choroid are measured manually by the observer and is uncertain in terms of providing definitive results. Satue *et al*.[42] stated that they might find the choroidal thickness high because the Swept-Source OCT device operates depth analysis of the choroid compared to spectral-domain OCT devices. The different results obtained with Swept-source OCT device reveal the necessity of conducting research on this subject. We hypothesize that decreased choroidal thickness may be due to hypoperfusion and perivascular connective tissue density in these patients mentioned previously.[17] However, studies with larger sample size and histological analysis are needed to corroborate our findings. The choroidal thickness may be used in the future when it is strengthened with studies as a biomarker for diagnosis and follow-up. In addition to PD, a significant reduction in choroidal thickness in patients with Alzheimer's disease has been reported and indicated as a biomarker for the diagnosis and follow-up.[47]

PD is associated with the progressive loss of dopaminergic neurons in the substantia nigra.[27] DA is one of the major catecholamines and is involved in chemical and electrical synaptic transmission by opening voltage-gated ion channels through five $D_1$-like and $D_2$-like G-protein coupled receptors.[48] Dopaminergic neurons (inner plexiform cells and amacrine cells) are known to be located in the human retina.[7] It has been reported that there is a decrease in both dopaminergic cells and DA levels in the retina of PD cases.[49] Bhattacharya *et al*.[50] stated that DA is a potent downregulator of the important signaling cascades controlling vascular permeability factor/vascular endothelial growth factor-mediated vascular permeability and angiogenesis.[50] Therefore, a gradual decrease in retinal vasculature can be expected as DA runs out in PD patients. However, it would not be correct to attribute all retinal

vascular autoregulation only to DA. In the current study, we think that we did not find diminished retinal density parameters to be low because we included only early-stage patients. In addition, a significant decrease in DA levels may not have occurred in the early stages of the disease. Nevertheless, reduced choroidal thickness may indicate a decrease in retinal blood flow over time.

Robbins *et al*.[22] stated that VDs was lower in the eyes of individuals with PD. Although they reported an increase in total choroidal area, choroidal vascularity index was reported as reduced in PD. In addition, they found no significant difference in FAZ area comparison with healthy controls. In our study, a significant increase was seen in VDs, VDd and VDc central sector values while a significant decrease was observed in choroidal thickness and FAZ area evaluations. We believe that Robbins *et al*.[22] did not reach generalizable results regarding the disease because they did not use medication status or staging in patient selection contrary to our study protocols. In a comprehensive meta-analysis report evaluating OCTA studies in Parkinson's patients, no statistically significant difference on FAZ areas was reported between PD patients and the control group.[25] The high variability in the FAZ values of the control group in statistical analyses may have inadvertently caused a difference between the patient group in our study. We thought that we found results that were different from the literature due to the high variability. These results need to be examined with comprehensive studies including patient groups at different stages. In the multivariate regression model, VDs superior, FAZs and SFCT values were determined to have a significant and independent effect in differentiating patients with PD. However, since the OR of FAZs and SFCT values were close to 1, it was concluded that this effect is not very strong. As a result of these analyses, the strongest differentiating parameter was thought to be VDs superior. On the other hand, Rascunà *et al*.[24] stated no significant difference neither in the VDs nor in the VDd. Besides, they found thinning of peripapillary retinal nerve fiber layer and inner retinal layers in PD patients as compared to healthy controls. Interestingly, positive correlation between microvascular density and inner retinal layers was reported in their study. Although there was a decrease in the mean CMT in the patients compared to the control group, no statistically significant difference was detected in our study. In the OCT study by Rascunà *et al*.,[24] 21 PD patients with a mean disease duration of 27.4 ± 14.3 months, 11 of whom were using anti parkinsonism drugs, were included. Due to the different patient characteristics of the study group, a common conclusion could not be reached in this study. Our study group consisted of newly diagnosed early-stage patients not started anti-parkinsonism drugs. We think that the duration of the disease and the drugs that affect DA pathways may affect the retinal measurements. The data suggest that vascular degeneration may be an important additional contributing factor to the progress of PD and may even be a contributor to the initial pathology that leads to neuronal degeneration and retinal layers changes.[27]

In a study designed by Xing *et al*.,[51] they discovered that autoregulation is affected with supine or orthostatic position in patients with PD. In patients with impaired cerebral autoregulation, unstable flow through the distal capillary may injure the cerebral microcirculation. Contrary to the literature data, we attributed the increase in retinal microcirculation that we especially found in central sectors of VDs, VDd, and VDc, to impaired autoregulation. Based on this hypothesis, we thought that retinal perfusion parameters might also change during the disease course, because we know the alterations in the autonomic nervous system and blood pressure in PD patients.[52] Moreover, hypoperfusion and hypotension can also be encountered in PD due to the secondary effect of levodopa treatment and/or autonomous dysfunction.[53] In a study designed by Ahn *et al*.,[54] the alterations in systolic and diastolic blood pressure during the head-up tilt test in PD subjects showed a negative correlation with VDd central region. Although blood pressure or autonomic system changes was not evaluated within the scope of our study, we speculate that OCTA markers may vary in PD course. Therefore, we think that it is not suitable to use OCTA perfusion parameters as novel biomarkers in the follow-up of PD.

Several limitations of the current study should be noticed. One of the major limitations of this study is a single-center case–control study and the small sample size. Since it was not planned in advance, power calculations could not be made to justify the sample size. Another is that we only included early-stage patients. We did not measure OCTA parameters with positional effects revealing orthostatic hypotension or controlling blood pressure. Another limitation is that medication use due to additional comorbidities of the patients may affect retinal measurements. Since analysis of retinal layers has been reported already in the literature, we did not investigate retinal layers in this study. However, comprehensive future studies can be conducted with different stages of PD to evaluate retinal neurodegeneration and correlate with cognitive impairment status.

In this study, we showed that retinal blood flow is affected in PD. OCTA devices, which have recently become increasingly used in daily practice, can show the changes in retinal blood flow in patients with PD. The findings of this study highlight the need for further research into retinal

imaging with different devices because of the variability in OCTA measurements. Disturbances in the autonomic nervous system of PD and stages of the disease may change the retinal microvasculature during the disease course.

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**Conflicts of interest**
There are no conflicts of interest.

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