• Clinical Research •

Retinal capillary plexus in Parkinson's disease using optical coherence tomography angiography

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Abstract

● **AIM:** To evaluate the alterations of the retinal microvasculature and foveal avascular zone in patients with Parkinson's disease (PD) using optical coherence tomography angiography (OCT-A).

● **METHODS:** A retrospective study of PD patients examined in the Ophthalmology Department of the General Hospital of Athens, "Georgios Gennimatas" from March 2021 to March 2022 was conducted. Totally 44 patients with PD were included and 18 healthy controls were examined, hence a total of 124 eyes were enrolled in the study. The foveal and parafoveal superficial and deep capillary plexus vascular density (fSCP-VD, fDCP-VD, pSCP-VD, pDCP-CD) and foveal avascular zone (FAZ) were quantified with OCTA. Optical coherence tomography (OCT) was used to measure macular thickness. Our statistical analysis was conducted by using a mixed effect linear regression model.

● **RESULTS:** After adjustment for age and gender, the mean parafoveal superficial capillary plexus vascular density (pSCP-VD) and mean parafoveal deep capillary plexus vascular density (pDCP-VD) were significantly decreased in individuals with PD (P<0.001 in both) by -2.35 (95%CI -3.3, -1.45) and -7.5 (95%CI -10.4, -4.6) respectively. fSCP-VD and fDCP-VD didn't approach statistical significance. The FAZ area and perimeter were significantly decreased (P<0.001 in both) by -0.1 mm^2 (95%CI -0.13, -0.07) and -0.49 mm^2 (95%CI -0.66, -0.32) respectively. Circularity didn't approach statistical significance. Central retinal thickness (CRT) was significantly decreased in individuals with PD (P<0.001) by -23.1 μm (95%CI -30.2, -16) and temporal retinal thickness (TRT) was decreased (P=0.025) by -11 μm (95%CI -22, -1.5) while nasal retinal thickness (NRT) only approached statistical significance (P=0.066).

● **CONCLUSION:** The mean pSCP-VD, pDCP-VD, CRT and TRT are significantly decreased and FAZ is altered in individuals with PD. These findings can be potentially used as biomarkers for the diagnosis and evaluation of early PD.

● **KEYWORDS:** Parkinson's disease; optical coherence tomography angiography; retinal vascular density; foveal avascular zone

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, after Alzheimer's, mainly affecting the motor system of the elderly[1]. It progresses slowly, starting with resting tremor and bradykinesia and ending to behavioral symptoms such as depression and dementia. Ocular manifestations of PDs are very common, ranging from dry eye and ocular surface disease to blepharospasm and convergence insufficiency[2].

Optical coherence tomography (OCT) has been proven as a valuable tool for examining and monitoring patients with PD. It has consistently displayed a thinning of intraretinal layers in these patients, especially in the retinal nerve fiber layer (RNFL), the ganglionic cell layer (GCL) and the inner plexiform layer (IPL)[3].

The use of optical coherence tomography angiography (OCT-A) for microvascular remodeling in patients with neurodegenerative diseases such as Alzheimer's, multiple

sclerosis and dementia disease is a topic of significant interest in literature[4].

There have been a number of studies that have already demonstrated the potential of OCT-A to detect microvascular alterations in PD patients even in early stages[5-11].

At the same time, there have been studies that failed to detect any significant change in the microvascular retinal plexus[12]. Since PD is mainly diagnosed and staged clinically by the treating physician there is the need of objective and reliable biomarkers. The purpose of this study was to evaluate the microvascular retinal plexus, foveal avascular zone (FAZ) and retinal thickness in patients with PD.

SUBJECTS AND METHODS

Ethical Approval Ethical Approval for this study was received by the review board and the ethics commitee of the General Hospital of Athens, "Georgios Gennimatas" (No.29355/15-11-2022), which adheres to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patients.

This is a retrospective study conducted in the Ophthalmology Department of the General Hospital of Athens, "Georgios Gennimatas". The medical files of subjects aged ≥18 years old and diagnosed with PD from the Neurology Department of the hospital were examined. PD patients were evaluated by an experienced specialist in movement disorders diseases (Tagaris G) and had a PD diagnosis that met the Movement Disorder Society clinical criteria[13]. The patients were also staged according to the Hoehn and Yahr clinical scale on the basis of medical record review[14].

Control subject group consists of community volunteers ≥18y, without a history of tremor, cognitive dysfunction, or other motor dysfunction consistent with a parkinsonian phenotype. The scans from OCT and OCT-A (DRI OCT Triton, Topcon, Japan) in the macular and optic disc area were evaluated. Superficial and deep capillary plexus vascular density was assessed within the 3×3-mm circle.

Exclusion criteria included patients with PD stages 4 or 5, treatment with amantadine, significant cataract or cataract surgery in the last 3mo, high intraocular pressure IOP measurements, corrected Early Treatment Diabetic Retinopathy Study best corrected visual acuity worse than 20/40, abnormally high (26.5 mm) or low axial length (22.6 mm), optic disc abnormalities, systemic health issues affecting the microcirculation (diabetes mellitus, systemic hypertension *etc*.), preexisting macular disorders or dystrophies, history of vitreoretinal surgery and smoking.

Primary outcomes were the mean parafoveal superficial capillary plexus vascular density (mean pSCP-VD) and mean parafoveal deep capillary plexus vascular density (mean pDCP-VD) and foveal superficial capillary plexus vascular density (fSCP-VD) and foveal deep capillary plexus vascular density (fDCP-VD), while secondary outcomes were the characteristics of FAZ, central retinal thickness (CRT) and retinal thickness 500 μm nasally and temporally to the fovea (NRT and TRT). Macular vascular measurements were acquired by an OCT-A scan. Parafoveal vascular density in the SCP and DCP was calculated using the parafoveal measurements of the OCT in the four quadrants (superior, inferior, temporal, nasal) while a foveal vascular density was evaluated using the central OCT-A measurement.

FAZ and vascular density were calculated by the system software, while retinal thickness was manually calculated by the same investigator (Doumazos S).

The CRT was manually measured using the OCT scan and the ruler tool and was defined as the distance between the vitreoretinal interface and the anterior surface of the retinal pigment epithelial-choriocapillaris region. Additionally, the retinal thickness was measured 500 μm temporally and 500 μm nasally from the center of the fovea.

Plots (histogram and probability graphs) and corresponding statistical tests (Kolmogorov-Smirnov/Shapiro-Wilk test) were performed to test for normality of our demographic and clinical data. Normally distributed continuous values were summarized by mean and standard deviation (SD) and discrete data by number and percentage. We also applied univariate and multivariate linear regression analysis to investigate the relation between Parkinson and all studied variables for each eye separately and both eyes simultaneously.

To assess the sensitivity of our findings for the latter analysis, we further applied mixed effects linear regression to account for correlation between the eyes from the same subject. All multivariate models were adjusted for age and gender. Statistical significance was set at $P<0.05$. Analysis was conducted in the Stata statistical software package version 13 (STATA Corp., College Station, TX, USA).

To account for the dependence that both eyes correspond to the same individual we used mixed effect linear regression models adjusted for age and gender. In this analysis the mixed effects linear regression model was the optimal fit that better accounted the structure of the observation, since likelihood ratio (LR) test versus linear regression showed statistically significant difference ($P<0.001$) in every comparison. In each model we concluded, that no statistically significant difference in Parkinson's stages was present. As a result, we conducted a new analysis considering Parkinson as a single stage disease.

RESULTS

Totally 44 patients with Parkinson and 18 healthy controls were included in the study. Totally 14 patients were excluded on the basis of poor OCT-A image quality. Hence a total of 124 eyes were enrolled in the study. Overall, 40 (64.52%) of

Table 1 Demographics of the study group

Items	Data
Age (y, mean±SD)	66.53±10.71
Gender, *n* (%)	
Males	40 (64.52)
Females	22 (35.48)
Parkinson, *n* (%)	
Stage 1	5 (8.06)
Stage 2	22 (35.48)
Stage 3	17 (27.42)

Table 2 Mean scores of examined variables per Parkinson's stage

Parameters	Controls	Stage 1	Stage 2	Stage 3
pSCP-VD	46.7±2.6	43.46±2.4	44.3±2.5	44.6±1.8
pDCP-VD	49.41±10.1	41.9±3.6	40.43±6.2	40.4±6.8
fSCP-VD	24.2±4	23,3±2.6	23.5±5.1	24.9±6.97
fDCP-VD	21.8±6.5	18±6.6	19.8±7.2	21.6±4.5
FAZ area	0.33±0.08	0.24±0.1	0.22±0.07	0.24±0.07
Perimeter	2.57±0.27	2±0.8	2.16±0.33	2.11±0.5
Circularity	0.59±0.08	0.6±0.07	0.6±0.09	0.6±0.07
CRT	222.75±13.4	197.9±18.8	194.6±24.2	195.5±16.2
TRT	282.25±188.6	264.9±15.3	264.8±36	263.3±34.9
NRT	268.9±15.8	256.3±19.3	252.7±28.9	254.7±33.9

pSCP-VD: Mean parafoveal superficial capillary plexus vascular density; pDCP-VD: Mean parafoveal deep capillary plexus vascular density; fSCP-VD: Foveal superficial capillary plexus vascular density; fDCP-VD: Foveal deep capillary plexus vascular; FAZ: Foveal avascular zone; CRT: Central retinal thickness; TRT: Temporal retinal thickness (500 μm temporally to the fovea); NRT: Nasal retinal thickness (500 μm nasal to the fovea).

the subjects were males and 22 (35.48%) were females. The mean age of the participants was 66.53±10.71y (range 42-88y). Participants' demographic characteristics are presented in Table 1.

Mean values of examined scores per stage of Parkinson disease are presented in Table 2. All patients were of Caucasian descent. Mean PD stage of the patients was 2.2.

The results of OCT-A measurements analysis are detailed in Table 3. After adjustment for age and gender, we concluded that mean pSCP-VD and mean pDCP-VD were significantly decreased in individuals with PD (P<0.001 in both) and fSCP-VD and fDCP-VD didn't approach statistical significance. More specifically, PD is associated with a decrease in mean pSCP-VD by -2.35 (95%CI -3.3, -1.45) and in pDCP-VD by -7.5 (95%CI -10.4, -4.6) compared to controls (Figures 1 and 2).

The results of FAZ measurements of OCT-A analysis are detailed in Table 4. After adjustment for age and gender as covariates, we concluded that FAZ area and perimeter were significantly decreased in individuals with PD (P<0.001 in both) and circularity didn't approach statistical significance.

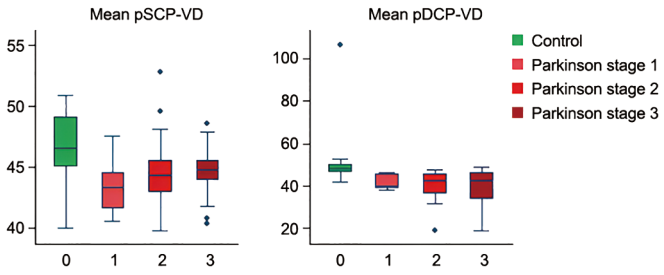

Figure 1 Results from the mixed effects linear regression model of mean parafoveal superficial capillary plexus vascular density (mean pSCP-VD) and mean parafoveal deep capillary plexus vascular density (mean pDCP-VD).

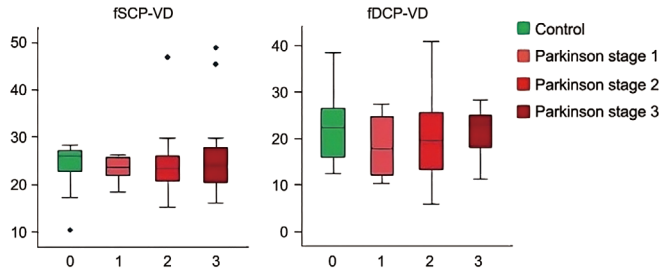

Figure 2 Results from the mixed effects linear regression model of foveal superficial capillary plexus vascular density (fSCP-VD) and foveal deep capillary plexus vascular density (fDCP-VD).

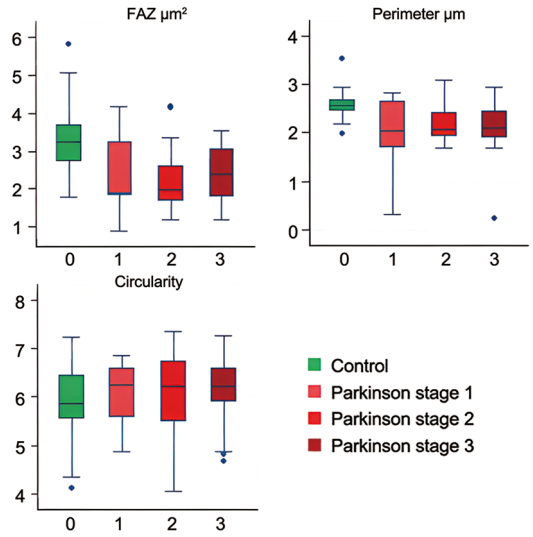

Figure 3 Results from the mixed effects linear regression model of foveal avascular zone (FAZ).

More specifically, PD is associated with a decrease in FAZ by -0.1 mm^2 (95%CI -0.13, -0.07) and in perimeter by -0.49 (95%CI -0.66, -0.32) compared to controls (Figure 3).

The results of the OCT analysis are detailed in Table 5. After adjustment for age and gender as covariates, we concluded that CRT and TRT were significantly decreased in individuals with PD (P<0.001 and P=0.025, respectively), while NRT only approached statistical significance (P=0.066). More specifically, PD is associated with a decrease in CRT by -23.1 μm (95%CI -30.2, -16) and TRT by -11 μm (95%CI -22,

Table 3 Mixed effects linear regression model of OCTA measurements adjusted for age, gender and Parkinson's stages

Items	Mean pSCP-VD			Mean pDCP-VD			fSCP-VD			fDCP-VD		
	Coef.	*P*	95%CI	Coef.	*P*	95%CI	Coef.	*P*	95%CI	Coef.	*P*	95%CI
Age	-0.05	0.007	-0.09, -0.02	-0.23	<0.001	-0.36, -0.11	0.05	0.258	-0.04, 0.14	-0.11	0.043	-0.22, -0.003
Female	-0.84	0.063	-1.7, 0.05	0.75	0.606	-2.1, 3.6	-0.32	0.763	-2.42, 1.77	-0.43	0.732	-2.88, 2.03
Stage 1	-3.05	<0.001	-4.6, -1.5	-7.86	0.002	-12.9, -2.8	-0.76	0.686	-4.44, 2.92	-3.8	0.085	-8.12, 0.52
Stage 2	-2.34	<0.001	-3.3, -1.3	-7.92	<0.001	-11.13, -4.71	-0.99	0.407	-3.34, 1.35	-1.7	0.214	-4.5, 1
Stage 3	-1.95	0.001	-3.1, -0.8	-6.5	0.001	-10.2, -2.78	0.09	0.948	-2.63, 2.81	0.63	0.701	-2.57, 3.82

Coef.: Coefficient; pSCP-VD: Mean parafoveal superficial capillary plexus vascular density; pDCP-VD: Mean parafoveal deep capillary plexus vascular density; fSCP-VD: Foveal superficial capillary plexus vascular density; fDCP-VD: Foveal deep capillary plexus vascular.

Table 4 Mixed effects linear regression model of FAZ measurements of OCTA adjusted for age, gender and Parkinson's stages

Items	FAZ area			Perimeter			Circularity		
	Coef.	*P*	95%CI	Coef.	*P*	95%CI	Coef.	*P*	95%CI
Age	0.0005	0.486	-0.001, 0.002	0.006	0.15	-0.002, 0.01	-0.0001	0.923	-0.001, 0.001
Female	0.03	0.026	0.004, 0.06	0.02	0.845	-0.15, 0.18	0.01	0.427	-0.02, 0.04
Stage 1	-0.11	<0.001	-0.16, -0.05	-0.6	<0.001	-0.89, -0.29	0.02	0.412	-0.03, 0.07
Stage 2	-0.11	<0.001	-0.14, -0.07	-0.4	<0.001	-0.63, -0.25	0.02	0.252	-0.01, 0.05
Stage 3	-0.08	<0.001	-0.12, -0.04	-0.51	<0.001	-0.74, -0.28	0.03	0.108	-0.007, 0.07

FAZ: Foveal avascular zone; Coef.: Coefficient.

Table 5 Mixed effects linear regression model of OCT measurements adjusted for age, gender and Parkinson's stages

Items	CRT			TRT			NRT		
	Coef.	*P*	95%CI	Coef.	*P*	95%CI	Coef.	*P*	95%CI
Age	-0.67	<0.001	-0.97, -0.36	-1.5	<0.001	-1.98, -1.09	-1.2	<0.001	-1.62, -0.80
Female	6.99	0.05	0.01, 13.98	-7.38	0.154	-17.55, 2.78	-0.21	0.965	-9.64, 9.22
Stage 1	-27.3	<0.001	-39.6, -15.03	-16	0.08	-33.87, 1.89	-13.2	0.118	-29.82, 3.37
Stage 2	-24.25	<0.001	-32.1, -16.4	-12.7	0.029	-24.1, -1.29	-11.5	0.033	-22.04, -0.90
Stage 3	-18.28	<0.001	-27.4, -9.16	-7.33	0.279	-20.6, 5.9	-2.99	0.634	-15.3, 9.32

CRT: Central retinal thickness; TRT: Temporal retinal thickness; NRT: Nasal retinal thickness; Coef.: Coefficient.

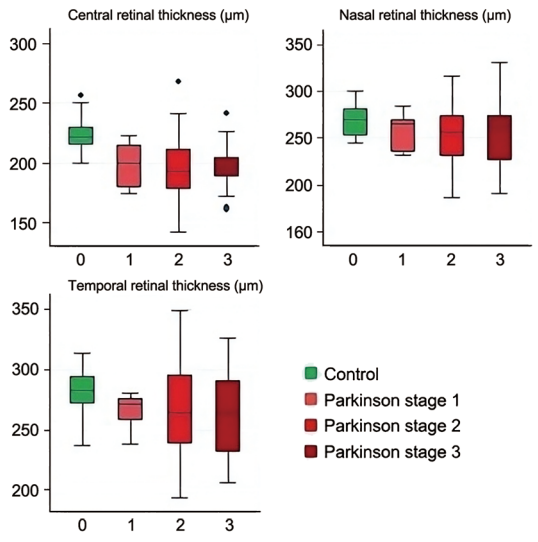

Figure 4 Results from the mixed effects linear regression model of central retinal thickness (CRT), temporal retinal thickness (TRT), nasal retinal thickness (NRT).

-1.5) compared to controls (Figure 4).

We further applied mixed effects linear regression model to account for the correlation among central foveal thickness and different parameters that was statistically significant correlated in a stepwise multivariate linear regression model. Results are demonstrated in Table 6. From this analysis we concluded that every 1y of increase in age is associated with a decrease in CRT by -0.65 μm (95%CI -0.92, -0.37; *P*<0.001). In addition, every 1 unit of increase in fSCP-VD and of increase in fDCP-VD is associated with an increase in CRT by 0.85 μm (95%CI 0.21, 1.50; *P*=0.009) and 0.95 μm (95%CI 0.43, 1.47; *P*<0.001) respectively. Moreover, every 1 unit of increase in mSCP-VD is associated with a decrease in CRT by -1.80 μm (95%CI -3.09, -0.50; *P*=0.007).

Table 6 Mixed effect linear regression model among central foveal thickness and different parameters

Parameters	Coef.	*P*	95%CI
Parkinson	-25.26	<0.001	-32.14, -18.38
Age	-0.65	<0.001	-0.92, -0.37
Gender	4.71	0.118	-1.20, 10.62
fSCP-VD	0.85	0.009	0.21, 1.50
fDCP-VD	0.95	<0.001	0.43, 1.47
pSCP-VD	-1.80	0.007	-3.09, -0.50

pSCP-VD: Mean parafoveal superficial capillary plexus vascular density; fSCP-VD: Foveal superficial capillary plexus vascular density; fDCP-VD: Foveal deep capillary plexus vascular; Coef.: Coefficient.

DISCUSSION

Retinal neurodegeneration in PD is a well-researched subject in literature. Most studies have consistently demonstrated RNFL thinning, total retinal thinning and ganglion cell loss[15-17]. Additionally, PD patients tend to display a broader and thinner foveal pit[18]. There have been reports that the disease's duration and severity can be predictive of disease patients[19]. OCT-A has emerged as a revolutionary tool to evaluate and quantify the retinal microvasculature and potentially provide biomarkers for the evaluation, staging and monitoring of neurodegenerative diseases. The retinal microvasculature comprises an extension of the brain microvasculature it can potentially provide a window to the overall state of the brain vessels[20]. Since the distortion of brain vasculature in PD has already been demonstrated in literature[21-22], it stands to reason that imaging of the retinal vessels can be used to assess PD. In the existing literature some studies have already demonstrated a negative correlation between retinal vessel density and PD. Kawpong *et al*[4] found a reduction in the microvascular density of the totally annular zone TAZ region in superficial retinal capillary plexus but no difference in the deep retinal capillary plexus.

Similarly Zou *et al*[6] demonstrated changes in the macular micro vascularity as the vessel length density and vessel perfusion density of eyes in PD patients was significantly decreased. Xu *et al*[10] also showed that the macular vessel density parameters declined in all participants. In our study pSPC-VD and fDCP-VD were statistical significantly reduced in PD patients. fSPC-VD and fDCP-VD had no difference between PD patients and controls. Like Kwapong *et al*[4] we did not observed correlation between the vascular density (VD) and PD's severity and duration. As Kwapong *et al*[4] mentioned, there are also studies that did not find correlation with severity and duration[23-25]. In contrast Shi *et al*[5] found a correlation with retinal capillary complexity and duration but not with severity while Xu *et al*[10] found that the Hoehn-Yahr (H-Y) III stage group and the duration of PD had a positive correlation with decrease of vascular density in the fovea and some areas of the parafovea. PD has been correlated with smaller FAZ in comparison with healthy controls[26]. In our study FAZ area and perimeter were significantly lower in PD patients compared with controls while the circularity of FAZ showed no difference. On the contrary Zou *et al*[6] found no differences in the FAZ area and perimeter while finding a lower FAZ circularity index in PD patients. Xu *et al*[10] also showed that the FAZ area decreased in the SCP of the PD patients and that FAZ area declined early in PD.

In our study CRT and TRT were significantly reduced in comparison with controls while NRT was not. The uneven reduction of the central retina is something that has been observed in other studies as well. Yu *et al*[26] as well as Visser *et al*[27] have hypothesized that since the papillomacular fibers are located in the temporal retinal quadrant, they may be more affected by the neurodegenerative process in PD. Furthermore, recent studies have suggested that changes in peripapillary RNFL (pRNFL) and peripapillary vessel density (pVD) detected by OCT-A are significant in PD patients[28-29]. As shown by Yang *et al*[29] the thickness of pRNFL is significantly decreased in PD patients and is correlated with disease severity, while they also show significant alteration in pVD according to disease severity. In our study we did not look into the vascular density of the peripapillary area but instead focused on the macular vascular density, so that we can provide a better understanding of the retinal microcirculation in patients with PD. Moreover, we feel that our statistical method can provide reliable results in such a complex topic.

To our knowledge this is the first study to evaluate both foveal and parafoveal superficial and deep capillary plexus density in PD patients as well as being the first study to use a mixed effect linear regression model for the evaluation of these parameters. We believe that this study will help to further understand the microvascular changes in PD and potentially contribute to the establishment of biomarkers for the diagnosis and evaluation of the disease.

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