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Research Article

Spectral Domain and Angiography Optical Coherence Tomography in Parkinson's Disease: Structural And Vascular Changes in the Retina Correlate with Disease Severity and Progression

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Background. Parkinson's disease (PD) is a common neurodegenerative disorder characterized by bradykinesia, resting tremor, and muscle rigidity. Visual disturbances have been also described among non-motor features. *Objective*. We aimed to investigate the structural and vascular changes in the retinal and choroidal vascular networks, and to assess any relationship with motor and non-motor symptoms (NMS) in PD patients. *Methods*. Ganglion cell complex (GCC), retinal nerve fiber layer (RNFL), and subfoveal choroidal thickness (SFCT) were examined using spectral domain-optical coherence tomography (SD-OCT). The vessel density (VD) of retinal and choriocapillary vascular networks in macular area and the foveal avascular zone (FAZ) area were evaluated by OCT angiography (OCTA). All patients underwent clinical evaluation using motor section of the Unified PD Rating Scale (UPDRS-III) and the Hoehn and Yahr (HY) scale. *Results*. A total of 48 eyes from 24 PD patients and 50 eyes from 25 controls were assessed. At SD-OCT, GCC and RNFL were more significantly thin in patients compared to controls. At OCTA exam, PD subjects showed lower values in VD of superficial capillary plexus (SCP) and radial peripapillary capillary plexus in comparison to controls, whereas FAZ area resulted in a significant increase in the patient group. We found a negative correlation between the age at onset and VD of SCP, and between HY score and RNFL thickness and FAZ. UPDRS-III score was negatively correlated with VD of deep capillary plexus. *Discussion*. The impairment of retinal structure and microvasculature seems to correlate with disease severity and progression in PD. Retinal anomalies can be considered as non-motor manifestations that could occur already in the early stage of the disease.

1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative disorder after Alzheimer's disease (AD) [1]. The pathological hallmark is represented by Lewy bodies (LB), eosinophilic cell inclusions consisting mainly of alpha-synuclein [2]. The cardinal motor symptoms are bradykinesia, resting tremor, and muscle rigidity, but non-motor features are also frequent, including cognitive, psychiatric, gastrointestinal, urinary, cardiovascular, and sensory disorders [1, 2]. The non-motor symptoms (NMS) appear to closely correlate with the spread and the progression of LB pathology beyond the dopaminergic nigrostriatal pathway, resulting in involvement of cortical and limbic regions, non-motor midbrain nuclei, and peripheral autonomic nervous system. Among NMS, PD patients also complain

of several visual disturbances, such as decreased visual acuity, impaired color vision, abnormal sensitivity to contrast, eye movement dysfunction, and visual hallucinations [3, 4]. Dopamine is known to play a role in the retinal visual process [5, 6]. Retinal pathologic studies in PD have shown thinning of the retinal inner nuclear layers, as well as intracellular and extracellular alpha-synuclein aggregates in the macular ganglion cell layer and retinal inner layer [7, 8].

As the retina represents an open window on the central nervous system, the measurement of the retinal nerve fiber layer (RNFL) thickness may provide reliable information on the neurodegenerative process underlying PD. Moreover, the retinal and choroidal vascular networks show striking similarities with the brain vascular network and potentially reflect its changes. Therefore, spectral domain-optical coherence tomography (SD-OCT) and OCT angiography (OCTA) have recently emerged as safe and noninvasive imaging tools to analyze in vivo retinal structure and choroidal microvasculature in neurodegenerative diseases. Previous studies have already reported thinning of the outer plexiform layer, inner plexiform layer (IPL), ganglion cell layer, and RNFL in PD [9–14]. In addition, decreased microvascular density in most areas of the whole retina has been also described in PD [15].

In a recent cross-sectional analysis collecting data from both a retrospective and a prospective study, the authors confirmed a reduced thickness of the retinal ganglion cell-inner plexiform layer and inner nuclear layer among patients in comparison with the controls [16]. They also observed that these findings occurred in incident PD several years before clinical presentation, suggesting that retina abnormalities may be considered a very early in vivo biomarker, and retina imaging may be a tool to stratify PD risk [16].

The correlation between ophthalmological findings and severity and progression of disease is still controversial. El-Kattan et al. found that duration, stage, and severity of disease were inversely correlated with macular volume, ganglion cell complex (GCC), and RNFL thicknesses [17]. Conversely, a previous study did not report any correlation between clinical and pharmacological scores and ophthalmological parameters [14].

Furthermore, until now, a potential association between retina morphology and vascularization and other NMS, which may occur in prodromal and early stage of disease, has not been assessed.

Our aim was to detect any structural retinal and choroidal changes in PD, and to look for potential correlations between SD-OCT and OCTA results with PD motor features. For the first time, we will assess the possible correlation between ophthalmological findings and NMS, such as cognitive, affective, sleep, and autonomic disorders.

2. Patients and Methods

The study sample size was calculated by referring to mean RNFL thickness values previously reported in PD patients [18]. Written informed consent was obtained from all participants, according to the Declaration of Helsinki and with the local Ethics Committee approval (protocol number 420/20). We enrolled 24 (18 M, 6 F) unrelated consecutive subjects 40 years or older, diagnosed with PD, according to current criteria, with the stage of disease ranging between 1 and 3, and assessed by the Hoehn and Yahr (HY) scale. All subjects were able to understand the aims and procedures applied in the study and to provide written informed consent. The study was completed in one year and required two visits. All patients were recruited from the Movement Disorders Outpatient Clinic at the Department of Neurosciences and Reproductive and Odontostomatological Sciences at Federico II University Hospital in Naples, where they were regularly visited by neurologists experienced in movement disorders (ADR, GiuDM). Exclusion criteria included pharmacologically uncontrolled hypertension, heart diseases, diabetes, history of ocular surgery, congenital eye disease, myopia greater than 6 diopters, retinal vascular diseases, glaucoma, and significant lens opacities. We also excluded subjects with inability to comply with the study procedures.

After the acquisition of informed consent, the following assessments were performed during the first visit: detailed anamnestic examination, consisting of collection of demographic data and medical history aimed at exploring lifestyle habits (smoking and alcohol abuse), and concomitant diseases, such as endocrine, metabolic, and cerebrovascular disease; neurological examination; scales and questionnaires.

During the second visit, the patients underwent comprehensive ophthalmological assessment, including measurement of intraocular pressure (IOP) by the Goldmann applanation tonometry, and of best-corrected visual acuity (BCVA), according to the Early Treatment of Diabetic Retinopathy Study (ETDRS), slit-lamp biomicroscopy, fundus examination, SD-OCT, and OCTA. The ophthalmological assessment was performed by two examiners (GC and LGDM).

We also recruited 25 healthy controls (17 M and 8 F) from spouses and unrelated caregivers, comparable for gender and age, with no family history of glaucoma or previous retinal vascular or neurological diseases, IOP less than 21 mmHg, and SD-OCT/OCTA parameters within normal limits.

2.1. Spectral Domain-OCT (SD-OCT). The RNFL, ganglion cell complex (GCC), and the subfoveal choroidal thickness (SFCT) were obtained using SD-OCT (software RTVue XR version 2017.1.0.151, Optovue Inc., Fremont, CA, USA). The evaluation of RNFL thickness average was based on the protocol for optic nerve head that consisted of the measurements around a circle 3.45 mm in diameter centered on the optic disc. The GCC thickness average included the measurements from the internal limiting membrane (ILM) to the outer boundary of the IPL and was obtained by centering the scan 1 mm temporal to the fovea and covering a 7×7 mm area over the macular region [19]. Each OCT scan was analyzed in agreement to APOSTEL recommendations [20]. SFCT was measured using the SD-OCT (software RTVue XR version 2017.1.0.151, Optovue Inc., Fremont, CA, USA). It was evaluated in the subfoveal region as a manual linear measurement between the outer border of Bruch's membrane and the most posterior identifiable aspect of the choroidal-scleral interface, which is seen as a hyperreflective layer in the posterior margin of the choroid [21].

2.2. OCTA. OCTA images, obtained by the Optovue Angiovue System (software ReVue XR version 2017.1.0.151, Optovue Inc., Fremont, CA, USA), were used to examine the vessel density (VD), which is defined as the percentage area occupied by vessels in the retinal capillary networks in 6 mm × 6 mm scan over the macular region and classified into superficial capillary plexus (SCP), deep capillary plexus (DCP), and in the choriocapillaris (CC) [22]. Moreover, the software automatically calculated the foveal avascular zone (FAZ) area in the full retinal plexus [23].

The Angio Vue disc mode automatically segmented the radial peripapillary capillary (RPC) VD analyzing the whole papillary region with an area scan of 4.5 × 4.5 mm. The VD was analyzed in the superficial retinal layers and extended from the ILM to the RNFL posterior boundary [24].

The software includes the 3D projection artifact removal algorithm to improve the quality of OCTA images. The images with a signal strength index less than 80 and residual motion artifacts and incorrect segmentation were excluded from the analysis.

2.3. Clinical Evaluation. All patients were assessed using the motor section of the Unified PD Rating Scale (UPDRS-III), Freezing of Gait (FOG) Questionnaire, and section A of UPDRS-IV, whereas the disease stage was evaluated by the HY scale (ADR, GiuDM). All participants were categorized into tremor-dominant (TD-PD), akinetic-rigid (AR), or mixed subtypes according to a previously established classification system [25]. All patients, supported by their caregivers when required, were interviewed about the presence of sleep, cognitive, neuropsychiatric, and autonomic disorders (e.g., cardiovascular, urinary, gastrointestinal, sweating, and sensory symptoms) using the following questionnaires: Mini-Mental State Examination (MMSE), Non-Motor Symptoms Scale (NMSS), Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction (SCOPA-AUT), Hamilton Depression Scale (HAM-D), Hamilton Anxiety Scale (HAM-A), Epworth Sleepiness Scale (ESS), REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), King's Parkinson Disease Pain Scale (KPDPS), and Parkinson's Disease Fatigue Scale-16 (PSF-16). All patients or their caregivers were also asked via semistructured interviews about the presence of smell impairment and psychosis. Clinical scales and questionnaires were administered by four experienced neurologists (GDM, GRP, SP, and AG) trained for the purpose.

2.4. Statistical Analysis. Data distribution was obtained by the Shapiro-Wilk test, and all variables were normally distributed. The differences in OCTA and SD-OCT parameters between PD patients and controls were assessed by two-way repeated measures ANOVA with the right and left eye included as a "within subject" factor. The differences in demographic data between the patients and controls were evaluated by Student's *t*-test analysis for independent samples. Qualitative data were compared by Fisher's exact test. The relationship between variables was examined using the Pearson correlation coefficient. A p value <0.05 was considered statistically significant. The Statistical Package for the Social Sciences software for Windows (version 27.00, SPSS, Chicago, IL, USA) was used for the statistical analyses.

3. Results

The demographic and clinical characteristics of both groups have been reported in Table 1, whereas the ophthalmological data are shown in Table 2. The most common motor phenotype at onset was TD-PD in eleven patients (46%), whereas nine subjects (37%) showed AR and four (17%) mixed clinical subtype. All patients were treated with levodopa, and sixteen of them also received dopamine agonists (DA) (Table 1). Monoamine oxidase-B (MAO-B) inhibitors were administered in nine subjects, and catechol-O-methyl transferase (COMT) inhibitors in one.

IOP was normal (less than 21 mmHg) in both patients and controls.

At SD-OCT exam, we evaluated all the quadrants of the RNFL, and, as no significant differences were found between them, we only considered the average value. We observed a statistically significant decrease in PD patients in comparison to controls in GCC average (97.56 ± 6.3 μm vs 101.56 ± 4.9 μm; $p = 0.002$) and in RNFL average (99.92 ± 11.6 μm vs 106.38 ± 8.5 μm; $p = 0.010$), whereas SFCT was comparable between two groups ($p = 0.988$) (Figure 1).

At OCTA, PD subjects showed a significantly lower VD of SCP (47.91 ± 3.5% vs 50.62 ± 3.6%; $p = 0.002$) and RPC (47.54 ± 2.7% vs 50.53 ± 4.5%; $p = 0.002$), in comparison to controls (Figure 2), and a significant increase in FAZ area (0.329 ± 0.08 vs. 0.287 ± 0.05; <0.001). Finally, the two groups were comparable for VD of DCP and CC (49.77 ± 6.9% vs. 49.03 ± 4.2%; $p = 0.878$; 72.86 ± 3.2% vs. 71.95 ± 4.5%; $p = 0.517$) (Figure 2).

We also found a negative relationship between the age at onset and VD of SCP ($r = -0.539$, $p = 0.007$), and a trend toward statistical significance with VD of DCP ($r = -0.383$; $p = 0.064$) (Table 3). As expected, a negative relationship was also observed between the age at exam and VD of SCP ($r = -0.617$, $p = 0.001$) and VD of DCP ($r = -0.483$; $p = 0.017$). UPDRS-III score was negatively correlated with DCP vessel density ($r = -0.428$, $p = 0.037$), and section A of UPDRS-IV with SFCT ($r = -0.776$, $p = 0.040$). A negative relationship also resulted between HY stage and RNLF thickness ($r = -0.550$, $p = 0.005$), and FAZ ($r = -0.622$, $p = 0.001$). Interestingly, we observed a negative relationship between SCOPA-AUT score and VD of DCP ($r = -0.406$; $p = 0.049$), between HAM-A score and RNFL thickness ($r = -0.597$; $p = 0.007$), and between ESS score and FAZ ($r = -0.407$; $p = 0.048$). PSF-16 score was negatively related to VD of SCP and DCP ($r = -0.451$, $p = 0.027$; $r = -0.700$, $p < 0.001$), and RNFL thickness ($r = -0.416$; $p = 0.043$).

A trend toward statistical significance was found in the negative relationship between RBDSQ and VD of RCP ($r = -0.398$; $p = 0.054$), and FOG questionnaire and VD of DCP ($r = -0.399$; $p = 0.054$) (Supplementary Table (available here). No significant correlations were found between ophthalmological data and the clinically more affected side, TD or AR phenotype, levodopa equivalent daily dose (LEDD), MMSE, NMSS, HAM-D, and KPDPS (Supplementary Table).

Table 1: Demographic and clinical characteristics of PD patients and controls.

	PD patients	Controls	p^*
Gender (men/women)	18/6	17/8	0.753
Eyes (n.)	48	50	—
Age (years)°	62.2 ± 8.8	63.2 ± 7.5	0.906
Age at onset	55.5 ± 9.5	—	—
Disease duration	7.4 ± 3.7	—	—
UPDRS-III	22.7 ± 10.9	—	—
HY$	2	—	—
Levodopa (patients)	24	—	—
DA	16	—	—
MMSE	28.2 ± 2.0	—	—
NMSS	49.5 ± 31.4	—	—
SCOPA-AUT	16.1 ± 7.7	—	—
HAM-D	10.9 ± 7.9	—	—
HAM-A	16.4 ± 9.8	—	—
ESS	6.2 ± 3.6	—	—
RBDSQ	5.2 ± 3.1	—	—
KPDPS	15.2 ± 18.2	—	—
PSF-16	43.5 ± 7.5	—	—

*Unpaired Student's t-test. °Data expressed as mean ± SD. $Median. $p < 0.005$ was considered significant. UPDRS-III: Unified Parkinson's Disease Rating Scale section III; HY: Hoehn and Yahr scale; DA: dopamine agonists; MMSE: Mini-Mental State Examination; NMSS: Non-Motor Symptoms Scale; SCOPA-AUT: Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; HAM-D: Hamilton Depression Scale; HAM-A: Hamilton Anxiety Scale; ESS: Epworth Sleepiness Scale; RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire; KPDPS: King's Parkinson Disease Pain Scale; PSF-16: Parkinson's Disease Fatigue Scale-16.

Finally, we did not observe any significant differences in retinal thickness and other morphological and vascular parameters between patients treated with DA and those not treated (Table 4).

4. Discussion

Dopamine, in addition to being involved in the modulation of movement, memory, mood, and attention, also acts as a neurotransmitter along the optic pathway, particularly in amacrine cells, whose dopaminergic output controls GCC maturation and survival. Progressive dopamine depletion and alpha-synuclein-induced degeneration in PD also seem to occur in the retina during the premotor and early stages of the disease [3]. Furthermore, several retinal visual disturbances are complained of by PD subjects, such as reduced visual acuity, visual field defects, color vision impairment, and reduced contrast sensitivity [3, 4]. Therefore, in recent years, research has focused on the study of structural and vascular alterations in the retina of PD patients, with the aim to find noninvasive and reliable in vivo markers for early diagnosis and progression monitoring.

In addition to morphological and functional brain imaging, retinal imaging techniques, such as SD-OCT and OCTA, have been increasingly applied in neurodegenerative diseases [8] and may contribute to detect PD in prodromal stage of disease [16].

In our study, at SD-OCT, we found a decreased thickness of GCC and RNFL in PD subjects in comparison to the controls, as previously reported by other authors [9, 10, 13, 26, 27], whereas SFCT was comparable between the two groups. At OCTA, we found that VD of the SCP and RPC was decreased and the FAZ area increased in the PD group in comparison to the controls.

Until now, several studies investigating the macula in PD patients in comparison to healthy controls reported significant thinning in one or more layers, especially in RNFL, GCL, and IPL [9–13, 26, 27]. Moschos and Chatziralli performed a cross-sectional study in 31 PD subjects and 25 healthy controls, reporting a significant reduction of the thickness in the GCC and in the superior and temporal areas of RNFL among patients, supporting our findings [18]. In contrast to our results, the choroidal thickness was also significantly decreased in the subfoveal area and in all inner and outer quadrants in the patient cohort in comparison with the controls [18].

On the other hand, Robbins et al., who assessed the structure and microvasculature of the retina and choroid in the eyes of 50 individuals with PD and 50 healthy controls, did not observe any significant differences in the retinal structure, as GCC and RNFL thickness or SFCT, between individuals with PD and healthy controls [27].

These findings would already be evident at an early stage of the disease and independently of dopaminergic treatment [14, 28]. Pathological evidence from postmortem studies of retinas in PD patients confirmed the results of in vivo OCT research, showing thinning of the inner retinal layers, and intracellular and extracellular aggregates of alpha-synuclein corresponding with the anatomic distribution of dopaminergic amacrine cells [7, 8]. Furthermore, the deposition of phosphorylated alpha-synuclein seems to correlate with cortical synucleinopathy, disease severity, and functional motor score [29].

Several previous papers are in agreement with our OCTA findings, reporting a significantly decreased vessel density of SCP in PD patients [27, 30–32], in contrast to Rascunà et al. who did not describe any significant changes in the foveal SCP [14]. On the other hand, Robbins et al. observed increased RCP microvascular density in a cross-sectional study comparing RPC plexus vascular parameters and RNFL thickness between 81 PD participants and 266 controls [33]. Abnormalities of the retinal microvascular density, characterized by the flattening of the foveal pit and affecting the FAZ of the macula, have been already reported [14, 27]. Conversely, a recent meta-analysis including five studies showed no significant differences in the FAZ area between PD and controls [31]. It is likely that the heterogeneity of the findings might be due to different OCTA device model and software applied by the authors.

The pathological examination of the vascular morphology in human brain tissue from PD patients might explain OCTA findings. Guan et al. observed that cerebral vessels appeared to be fewer in number, shorter in length, and more

Table 2: SD-OCT and OCTA parameters in PD patients and controls.

	PD (48 eyes)	Controls (50 eyes)	p^*
BCVA (logMAR)	0.03 ± 0.1^	0.04 ± 0.1	0.484
Ganglion cell complex (μm)	97.56 ± 6.3	101.56 ± 4.9	**0.002**
Retinal nerve fiber layer (μm)	99.92 ± 11.6	106.38 ± 8.5	**0.010**
Subfoveal choroidal thickness (μm)	301.56 ± 64.9	306.44 ± 51.5	0.988
Superficial capillary plexus (%)	47.91 ± 3.5	50.62 ± 3.6	**0.002**
Deep capillary plexus (%)	49.77 ± 6.9	49.03 ± 4.2	0.878
Choriocapillaris (%)	72.86 ± 3.2	71.95 ± 4.5	0.517
Radial peripapillary capillary (%)	47.54 ± 2.7	50.53 ± 4.5	**0.002**
FAZ area (mm^2)	0.329 ± 0.1	0.287 ± 0.1	**<0.001**

*Two-way repeated measures ANOVA. ^Data expressed as mean ± SD. p value <0.05 was considered statistically significant. BCVA: best-corrected visual acuity; logMAR: logarithm of the minimum angle of resolution. FAZ: foveal avascular zone. Significant values are in bold.

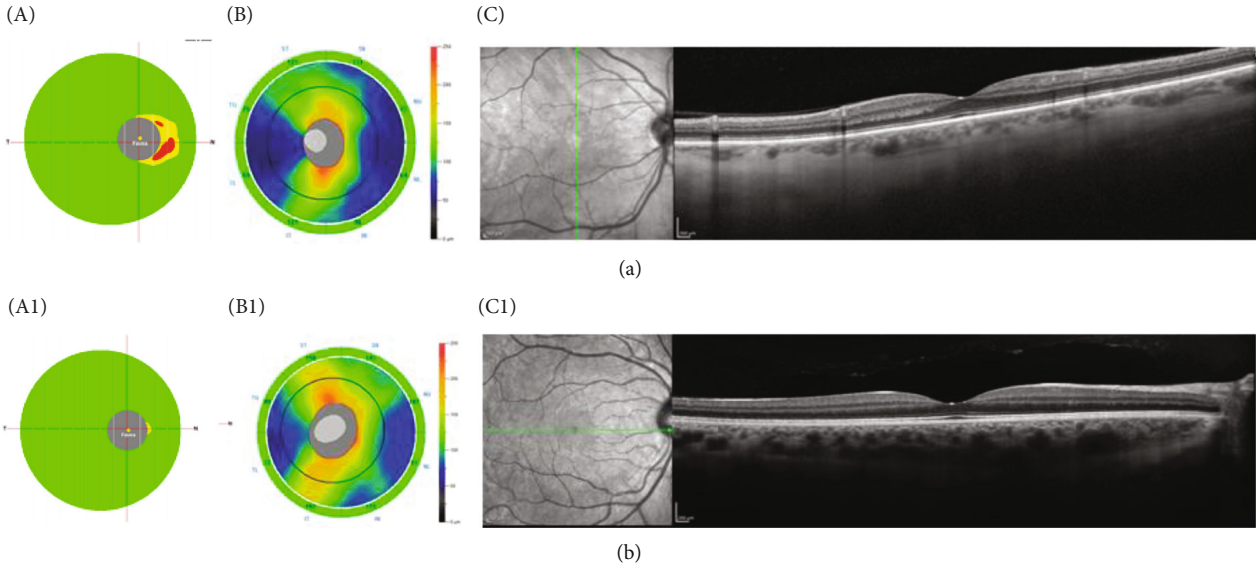

Figure 1: The figure shows the alteration in (a–A) ganglion cell complex, (a–B) retinal nerve fiber layer, and (a–C) normal central choroidal thickness at SD-OCT in the right eye of the PD patient in comparison to a (b(A1–C1)) control subject.

fragmented in PD cases compared to the controls [34]. The authors reported a damage of the capillary network, likely due to vessel fragmentation, and loss of capillary connections in brain areas involved in neurodegeneration, such as the substantia nigra, the middle frontal gyrus, and the brainstem nuclei. Therefore, it is conceivable that the vascular remodeling may be associated with or contribute to the neurodegenerative process in the retina, due to breakdown of the blood-brain barrier and the accumulation of multiple peripheral neurotoxic molecules, including circulating proinflammatory factors [34].

The ophthalmological abnormalities observed in PD might be partially explained by recent exome sequencing reports in this disease [35]. Yemni et al. found missense variants in genes never previously linked to PD, such as *BCOR*, *HRH4*, *SPG7*, *MAGI2*, *HEPHL1*, *EPRS*, and *CLSTN1*, all involved in regulating the production, survival, and function of photoreceptor cells and retinal angiogenesis [35].

In our study, UPDRS-III score was inversely related with DCP vessel density, but we did not identify any association with SD-OCT measures, in agreement with a previous study [36]. Conversely, Powell et al. found that the RNFL thickness negatively correlates with PD severity and duration [37], whereas Garcia-Martin et al. described a negative correlation between GCC thickness and the severity of PD [38]. Moreover, the thinning of RNFL was similarly reported in PD patients with both mild and severe disease [39].

In our study, a more advanced stage of disease, established according to the HY scale, was negatively correlated with higher RNFL thinning and more extensive FAZ, as previously reported [13, 17]. Particularly, El-Kattan et al. observed a statistically significant negative correlation between the HY scores and GCC thickness and the temporal RNFL thickness [17].

As a new finding, we observed an inverse relationship between the age at onset and decreased vessel density of

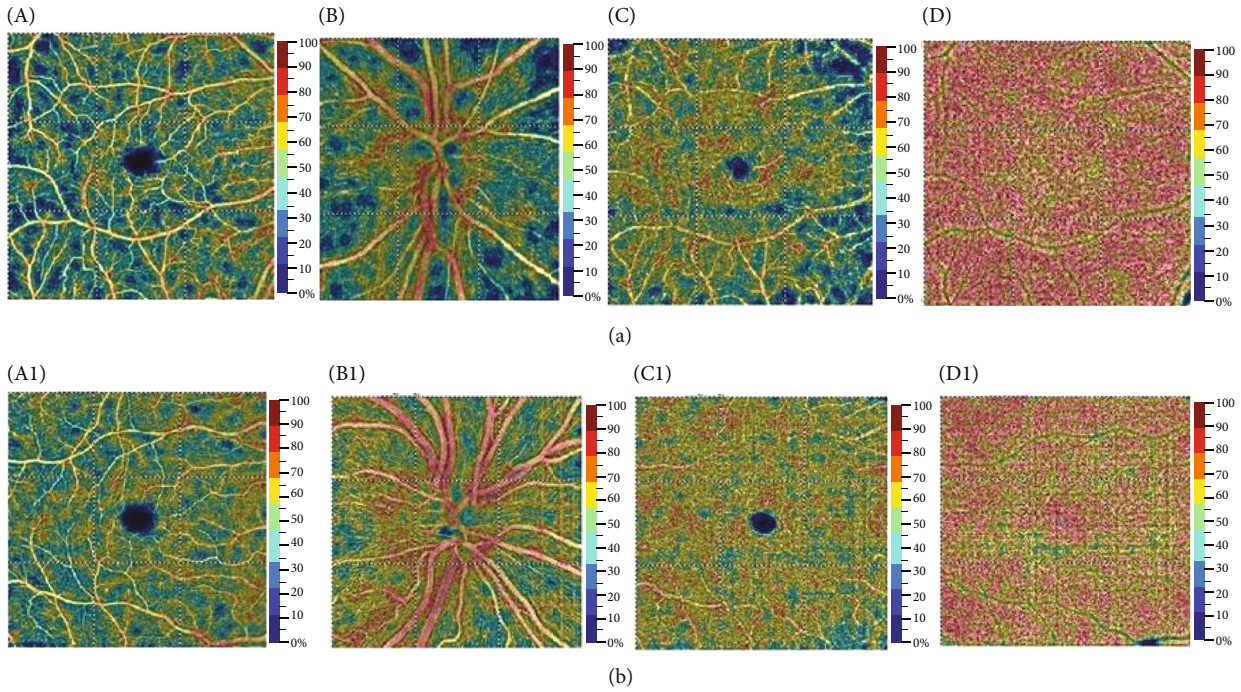

Figure 2: The figure shows the reduction of the vessel density in (a–A) superficial capillary plexus and (a–B) radial peripapillary plexus, with no alteration in (a–C) deep capillary plexus and (a–D) choriocapillaris in the right eye in a PD patient in comparison to a (b(A1–D1)) control subject at OCTA exam.

Table 3: Correlations between motor and non-motor symptoms and ophthalmological data.

	VD-SCP^	VD-DCP^	FAZ^^	CC^	RCP^	GCC§	th-RNFL§	SFCT§
Age*	**-0.617*** **/0.001°**	**-0.483/0.017**	-0.210/0.324	-0.249/0.240	-0.397/0.055	-0-370/0.069	-0.138/0.519	-0.364/0.080
Age at onset	**-0.539/0.007**	-0.383/0.060	-0.149/0.487	-0.195/0.361	-0.254/0.231	-0.254/0.232	-0.060/0.782	-0.309/0.142
UPDRS-III	-0.349/0.095	**-0.428/0.037**	-0.373/0.073	-0.356/0.088	-0.108/0.616	-0.108/0.616	-0.089/0.679	-0.071/0.741
UPDRS-IV	-0.572/0.180	-0.153/0.744	-0.420/0.348	-0.552/0.199	-0.416/0.353	-0.088/0.851	-0.685/0.089	**-0.776/0.040**
HY	-0.352/0.092	-0.152/0.477	**-0.622/0.001**	-0.133/0.534	-0.094/0.662	-0.113/0.597	**-0.550/0.005**	-0.035/0.872
SCOPA-AUT	-0.065/0.762	**-0.406/0.049**	-0.182/0.394	-0.230/0.279	-0.293/0.164	-0.385/0.063	-0.025/0.908	-0.071/0.743
HAM-A	-0.275/0.254	-0.315/0.288	-0.392/0.097	-0.193/0.429	-0.060/0.806	-0.292/0.225	**-0.597/0.007**	-0.023/0.925
ESS	-0.188/0.380	-0.353/0.090	**-0.407/0.048**	-0.193/0.367	0.055/0.798	0.277/0.224	-0.090/0.677	-0.025/0.908
PSF-16	-0.451/0.027	**-0.700/<0.001**	-0.175/0.413	-0.229/0.282	-0.216/0.310	0.149/0.486	**-0.416/0.043**	-0.090/0.675

VD: vascular density; SCP: superficial capillary plexus: DCP: deep capillary plexus; FAZ: foveal avascular zone; CC: choriocapillaris; RCP: radial peripapillary capillary; GCC: ganglion cell complex; th-RNFL: thickness of retinal nerve fiber layer; SFCT: subfoveal choroidal thickness; UPDRS-III: Unified Parkinson's Disease Rating Scale section III; UPDRS-IV: Unified Parkinson's Disease Rating Scale section IV; HY: Hoehn and Yahr scale; SCOPA-AUT: Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; HAM-A: Hamilton Anxiety Scale; ESS: Epworth Sleepiness Scale; PSF-16: Parkinson's Disease Fatigue Scale-16. ^%; ^^mm; §μm; *Pearson's coefficient; °p value. Significant values are in bold.

SCP, suggesting that PD with earlier onset may be characterized by a different pattern and higher impairment of microvascular distribution. There was also a significant association between retinal abnormalities and higher occurrence of motor complications, as freezing of gait and dyskinesias, both usually observed in a more advanced stage of disease. Our results suggest that the impairment of retinal morphology and microvasculature worsens over the course of the disease and is associated with more severe motor symptoms.

We also attempted to evaluate the relationship between SD-OCT and OCTA data and non-motor features. Interestingly, a negative correlation was observed between retinal vascular density and RNFL thickness and some NMS, such as autonomic disturbances, daytime sleepiness, anxiety, and fatigue, suggesting that the retinal degenerative damage, even subclinical, may be considered a non-motor manifestation of disease and should be studied like other NMS in clinical practice.

Although the role played by anti-PD treatment in the pathophysiology of retinal changes is still unclear, research conducted in humans and animal models has suggested the protective role of levodopa on retinal dysfunction. In the present study, levodopa and DA treatment did not appear to affect ophthalmological findings, in agreement with other

Table 4: Comparison of SD-OCT and OCTA parameters between PD patients treated and not treated with dopamine agonists.

	PD-DA (32 eyes)	PD-nDA (16 eyes)	p^*
Gender (M/W)	12/4	6/2	1.000
BCVA (logMAR)	0.02 ± 0.2^	0.03 ± 0.1	0.736
Ganglion cell complex (μm)	97.63 ± 3.9	84.60 ± 33.9	0.457
Retinal nerve fiber layer (μm)	99.50 ± 3.9	88.24 ± 33.9	0.987
Subfoveal choroidal thickness (μm)	301.38 ± 56.8	276.78 ± 122.6	0.935
Superficial capillary plexus (%)	47.55 ± 3.9	41.83 ± 16.8	0.745
Deep capillary plexus (%)	49.34 ± 6.6	42.50 ± 18.0	0.938
Choriocapillaris (%)	72.55 ± 3.1	63.57 ± 25.8	0.880
Radial peripapillary capillary (%)	47.43 ± 1.9	41.66 ± 16.8	0.899
FAZ area (mm^2)	0.320 ± 0.1	0.290 ± 0.1	0.988

PD-DA: patients treated with dopamine agonists; PD-nDA: patients not treated with dopamine agonists; BCVA: best-corrected visual acuity; logMAR: logarithm of the minimum angle of resolution; FAZ: foveal avascular zone. *Two-way repeated measures ANOVA. ^Data are expressed as mean ± SD. p value <0.05 was considered statistically significant.

studies that did not find significant correlations between retinal thickness and levodopa doses [14, 39–41]. A study assessing the effect of levodopa and DA on optic nerve head showed that RNFL was significantly greater among PD patients treated with levodopa in comparison to the group receiving DA monotherapy [27, 42]. Another research showed improvement in visual contrast sensitivity after levodopa treatment in PD subjects [43]. Furthermore, in a recent study, levodopa supplementation improved hyperglycemic stress-induced microvascular dysfunction in the mouse retina, suggesting a protective effect against microvascular leakage and endothelial apoptosis [44]. Finally, Motz et al. observed that a two-week levodopa/carbidopa treatment was able to reverse electroretinography findings in diabetic individuals without clinically detectable retinopathy [45].

Levodopa therapy has several limitations in PD treatment, resulting in little or no effect on NMS such as autonomic dysfunction, pain, sleep, and mood disorders. Finally, the heterogeneity of the sample regarding disease severity, treatment duration, and additional medications, such as anticholinergic drugs and MAO-B and COMT inhibitors, could also affect the results. After all, further analyses would be unreliable in view of the limited sample size.

5. Conclusions

Although the small sample size is a limitation of the study, our data suggest that abnormalities of retinal morphology and microvasculature should be considered as a non-motor marker in PD, in a similar way to abnormalities in olfaction, sleep, and mood. The correlations between SD-OCT and OCTA parameters with age at onset, stage and severity of disease suggest that those changes are related to the progression of the neurodegenerative process. Further and larger longitudinal studies are needed to confirm these findings.

Data Availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Ethical Approval

The study was approved by the ethical committee.

Consent

Written informed consent was obtained by the participants.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Conception and design were conducted by ADR, GC, and LGDM. Data collection was conducted by all authors. Analysis and interpretation of data were conducted by ADR, GC, DM, and GiuDM. Drafting the manuscript was conducted by ADR, GC, LGDM, DM, and GiuDM. Critical revisions and approval of final manuscript were conducted by all authors.

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Supplementary Materials

OCTA findings were inversely related with RBD and freezing of gait with a trend toward the statistical significance, whereas a significant relationship has not been found between ophthalmological data and dopaminergic treatment, global cognitive function, mood depression, pain, and other non-motor symptoms. *(Supplementary Materials)*

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