Original Article

Connecting the Dots: Exploring the Relationship between Optical Coherence Tomography and ^{99m}Tc-TRODAT-1 SPECT Parameters in Parkinson's Disease

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Abstract

Background and Objective: While optical coherence tomography (OCT) is explored as a potential biomarker in Parkinson's disease (PD), technetium-99m-labeled tropane derivative (^{99m}Tc-TRODAT-1) single-photon emission computed tomography (SPECT) imaging has a proven role in diagnosing PD. Our objective was to compare the OCT parameters in PD patients and healthy controls (HCs) and correlate them with ^{99m}Tc-TRODAT-1 parameters in PD patients. **Materials and Methods:** This cross-sectional study included 30 PD patients and 30 age- and gender-matched HCs. Demographic data, PD details including Movement Disorders Society Unified Parkinson's Disease Rating Scale-III (MDS-UPDRS-III) and Hoehn–Yahr (HY) staging, and OCT parameters including macular and peripapillary retinal nerve fiber layer (RNFL) thickness in bilateral eyes were recorded. PD patients underwent ^{99m}Tc-TRODAT-1 SPECT imaging. The terms "ipsilateral" and "contralateral" were used with reference to more severely affected body side in PD patients and compared with corresponding sides in HCs. **Results:** PD patients showed significant ipsilateral superior parafoveal quadrant (mean ± standard deviation [SD] = 311.10 ± 15.90 vs. 297.57 ± 26.55, $P = 0.02$) and contralateral average perifoveal (mean ± SD = 278.75 ± 18.97 vs. 269.08 ± 16.91, $P = 0.04$) thinning compared to HCs. Peripapillary RNFL parameters were comparable between PD patients and HCs. MDS-UPDRS-III score and HY stage were inversely correlated to both ipsilateral (Spearman rho = –0.52, $P = 0.003$; Spearman rho = –0.47, $P = 0.008$) and contralateral (Spearman rho = –0.53, $P = 0.002$; Spearman rho = –0.58, $P < 0.001$) macular volumes, respectively. PD duration was inversely correlated with ipsilateral temporal parafoveal thickness ($\rho = -0.41$, $P = 0.02$). No correlation was observed between OCT and ^{99m}Tc-TRODAT-1 SPECT parameters in PD patients. **Conclusion:** Compared to HCs, a significant thinning was observed in the ipsilateral superior parafoveal quadrant and the contralateral average perifoveal region in PD patients. Macular volume and ipsilateral temporal parafoveal thickness were inversely correlated with disease severity and duration, respectively. OCT and ^{99m}Tc-TRODAT-1 SPECT parameters failed to correlate in PD patients.

Keywords: ^{99m}Tc-TRODAT-1 SPECT, optical coherence tomography, Parkinson's disease, retinal nerve fiber layer, striatum

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1% of the population aged above 60 years. In the absence of any biomarker, diagnosis of PD remains clinical and primarily based on presence of motor features including rigidity, bradykinesia, rest tremor, and postural instability.[1] However, a recent meta-analysis of 11 clinicopathologic studies reported a pooled diagnostic accuracy of only 80.6%, with a lower accuracy for general neurologists. Expectedly, the diagnostic accuracy improves on follow-up.[2]

While structural imaging including magnetic resonance imaging brain fails to show any significant abnormality early in the disease course, reduced presynaptic dopamine transporter technetium-99m-labeled tropane derivative (^{99m}Tc-TRODAT-1) single-photon emission computed tomography (SPECT) binding can accurately identify early PD cases. ^{99m}Tc-TRODAT-1 attaches to the protein dopamine transporter (DAT) on the presynaptic dopaminergic nerve terminal. Since PD patients have reduced DAT expression, they have a low specific uptake ratio (SUR) of the striatum on ^{99m}Tc-TRODAT-1 SPECT imaging. SPECT binding abnormalities correlate with PD severity.[3]

Retinal imaging using optical coherence tomography (OCT) is a noninvasive, widely available, and affordable investigation and has been explored as a potential biomarker in PD and Parkinson-plus syndromes.[4–8] Following the initial report of

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peripapillary retinal nerve fiber layer (RNFL) thinning in PD,[9] studies have provided inconsistent and often conflicting results of RNFL thinning in PD.[4,10–17]

There is a paucity of studies on the correlation of OCT parameters and semiquantitative ^{99m}Tc-TRODAT uptake of basal ganglia in PD patients. We hypothesized that the nigrostriatal degeneration in PD patients would correlate with the progression in retinal thinning resulting from loss of dopamine in retinal neurons. Since ^{99m}Tc-TRODAT-1 SPECT imaging is invasive with poor accessibility and affordability, especially in developing countries like India, it became prudent to assess the correlation between SPECT imaging and noninvasive OCT. Should such correlation exist, the latter can be used as a proxy marker for the nigrostriatal degeneration. In addition, we also assessed correlation of peripapillary RNFL and central retinal (macular) parameters with disease severity and duration.

Materials and Methods

This cross-sectional study was conducted at a North Indian tertiary care University Hospital, with participants recruited from neurology service from January 2020 to June 2021 after obtaining approval from the Institutional Ethics Committee (AIIMS/IEC/19/398).

Inclusion and exclusion criteria

Consecutive patients aged ≥18 years, fulfilling the Movement Disorder Society Clinical Diagnostic Criteria for PD[18] and on stable dopaminergic therapy for the past 4 weeks were included. Participants were excluded if they were pregnant. Following a detailed ophthalmologic assessment, participants with visual acuity below 20/200 in Snellen (worse than 0.1 in decimal notation), refractive error greater than 5 D of spherical equivalent or 3 D astigmatism, glaucoma, retinal disorders, diabetes, and prior intraocular surgery (except uncomplicated cataract surgery >1 year back) or laser treatment were excluded from the study. Written informed consent was obtained from all participants before including them in the study. Age- and gender-matched caregivers (not genetically related) accompanying patients, or unrelated bystanders, who did not have any neurologic, psychiatric, or other chronic medical disorders including diabetes and hypertension were recruited as healthy controls (HCs). Each patient underwent a detailed general, ophthalmologic, and neurologic examination.

Assessment of PD

Information collected regarding details of PD included age of PD onset, disease duration, laterality at the onset of disease, Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III (motor) score in "off" state, and Hoehn and Yahr (HY) stage for disease severity.[19] The terms "ipsilateral" and "contralateral" were used with reference to the more severely involved body side. For convenience of PD patients, both OCT and ^{99m}Tc-TRODAT-1 SPECT imaging were done during a single visit.

Ophthalmologic evaluation

Both eyes of each participant were examined by an experienced ophthalmologist for best corrected visual acuity (distant and near vision), ocular movements and pupillary reflexes, slit-lamp biomicroscopic examination, dilated fundoscopy with 90 D (following dilation with 1% tropicamide), and intraocular pressure (IOP) assessment using applanation tonometry. In case of high clinical suspicion of glaucoma, automated perimetry was performed even when IOP was normal.

Both peripapillary and central retinal (macular) parameters were assessed. For measurement of peripapillary RNFL thickness, macular thickness, and macular volume, all participants underwent RNFL and macular imaging using spectral domain-optical coherence tomography with CIRRUS HD-OCT 500 (Carl Zeiss Meditec Inc, Dublin, CA, USA) following pupillary dilation. The OCT images were taken ensuring good centration and signal strength of ≥6.

The optic disc 200 × 200 scan was used for RNFL thickness measurement. Each optic disc scan generated a cube of data through a 6-mm square grid consisting of 200 horizontal scan lines, each composed of 200 A-scans. The average RNFL thickness and that in each quadrant (superior, nasal, inferior, and temporal) were calculated in each eye on a measurement circle of 3.6 mm diameter [Figure 1].

The data on thickness of central retina (macula) were measured in nine sectors as per the Early Treatment of Diabetic Retinopathy Study guidelines, using concentric circles of diameter 1, 3, and 6 mm. Central retinal thickness was described in this study with reference to "fovea"(central 1 mm diameter), "parafovea" (area between 1 and 3 mm diameter circles), and "perifovea" (area between 3 and 6 mm diameter circles). The average thickness as well as thickness in each quadrant (superior, inferior, nasal, and temporal) were calculated for both parafoveal and perifoveal areas [Figure 1].

^{9m}Tc-TRODAT imaging

All PD patients underwent ^{99m}Tc-TRODAT-1 SPECT imaging after intravenous injection of 666–740 MBq of ^{99m}Tc-TRODAT-1, following radiolabeling and routine quality control checks. Four hours following injection, SPECT-computed tomography (SPECT–CT) brain images were acquired using a dual-head camera GE-NMCT 670 SPECT–CT (GE Healthcare).

The acquired images were processed in a dedicated Xeleris workstation and interpreted by an experienced nuclear medicine physician (MLN). The SPECT–CT images were reconstructed in axial, coronal, and sagittal planes, and the reconstructed images were co-registered with corresponding CT image of each patient along the canthomeatal line. Reconstructed and co-registered SPECT-CT images were subjected to both qualitative and semiquantitative analyses. ^{99m}Tc-TRODAT-1 uptake in bilateral striatum was visually analyzed and any asymmetry was noted. On qualitative analysis, tracer uptake was categorized as mildly, moderately, or severely reduced

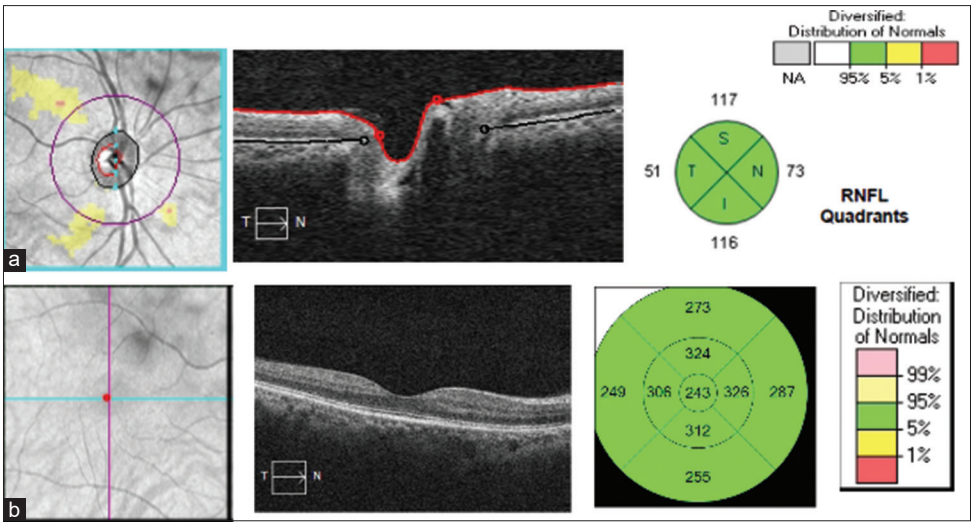

Figure 1: A schematic representation of the macula and optic nerve head in the right eye of a Parkinson's disease patient utilizing OCT scanning techniques. (a) Shows the report on the optic disc, displaying the optic nerve head. Left panel in (a) shows retinal nerve fiber layer thickness measured by scanning the region centered on the optic nerve head and the peripapillary examined area. Central panel in (a) shows the cross-sectional retinal image around the optic nerve head and is represented by the OCT B-scan. Right panel in (a) shows a schematic representation of the measures of peripapillary retinal nerve fiber layer thickness, with values in micrometers, separated into 4-h sectors. (b) Displays the macular area. Left panel in (b) shows fovea as the center of the scan. Central panel in (b) sows the cross-sectional retinal image taken by a horizontal OCT B-scan. Right panel in (b) shows the macular area measuring map. The region in the center is the central area. At different distances from the fovea, the inner (1–3 mm diameter), outer (3–6 mm diameter), and full (6 mm diameter) regions were estimated independently. The total macular thickness measurements are represented in micrometers on a map that is divided into nine sectors. I = inferior, N = nasal, OCT = optical coherence tomography, RNFL = retinal nerve fiber layer; S = superior, T = temporal

by comparing it to background occipital uptake. The images were meticulously reviewed for head motion, attenuation artifacts, and technical issues due to gamma camera during interpretation.

For semiquantitative analysis, we selected transverse slices and delineated regions of interest (ROIs). ROIs were drawn for the striatum of each side on the composite images of five consecutive transverse slices, which showed the highest basal ganglia activity. We also outlined an ROI in the occipital cortex to serve as background tracer activity and calculated the average counts per pixel (ACP) for each striatum and occipital ROI. The following formula was used to calculate the specific uptake ratio (SUR) of either striatum[20]: SUR = difference between striatal and occipital ROI ACP/occipital ROI ACP.

Statistical analysis

In view of lack of any previous studies on the correlation of OCT parameters and semiquantitative ^{99m}Tc-TRODAT uptake of basal ganglia in PD patients, we estimated *a priori* sample size of 30 patients for the study. This was based on a previous study correlating N-(3-[^{18}F] fluoropropyl)-2-carbomethoxy-3-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) with OCT, demonstrating a correlation coefficient between 0.44 and 0.61.[21] Based on this finding, we expected a correlation coefficient of 0.5 between OCT and ^{99m}Tc-TRODAT-1 SPECT imaging parameters for our study. With 80% power and a two-tailed significance of 0.05, we calculated that a total of 29 patients would be required for the study.[22] Data were analyzed using Statistical Package for the Social Sciences version 29.0 for Mac. Descriptive statistics were expressed as mean ± standard deviation or median (interquartile range [IQR]) for numerical variables. Categorical variables were expressed as proportions and percentages. While parametric data were compared using independent *t*-test, nonparametric data were compared using Mann–Whitney *U* test. Categorical variables were compared using Chi-square test. Correlation was assessed using either Pearson correlation coefficient or Spearman's correlation coefficient for normally distributed continuous variables and skewed but continuous or ordinal scales, respectively. A P value of < 0.05 was considered statistically significant.

Results

Demographic profile

A total of 70 participants, 40 with PD and 30 age- and gender-matched HCs, were screened [Supplementary Figure 1]. Thirty eligible PD patients underwent detailed neurologic and ophthalmologic assessment including OCT and ^{99m}Tc-TRODAT-1 brain SPECT scans. Thirty HCs (60 eyes) also underwent OCT analysis. The mean (±standard deviation [SD]) age of onset of PD patients was 51.77 (±12.06) years, and the median (IQR) disease duration was 4 (3–6.25) years [Supplementary Table 1]. Three (10%) PD patients were in HY stage-I, 20 (66.7%) in HY-II stage, six (20%) in HY stage-III, and one (3.3%) patient was in HY stage-IV. While 28 (93.3%) of the PD patients were on antiparkinsonian therapy

Table 1: Optical coherence tomography parameters of the central retina[a] in PD patients and healthy controls

Characteristics	Healthy controls[b] (*n*=30) (A)	PD (*n*=30) (B)	*P* (A vs. B)
I/L foveal thickness (µm)[c], median (IQR)	236 (218.25–245.5)	237.5 (224.75–257.25)	0.45
C/L foveal thickness (µm), mean±SD	241.57±29.85	240.57±39.44	0.91
I/L superior parafoveal thickness (µm), mean±SD	311.10±15.90	297.57±26.55	0.02
I/L inferior parafoveal thickness (µm)[c], median (IQR)	311.5 (300.25–324)	300.5 (288.75–329)	0.26
I/L nasal parafoveal thickness (µm)[c], median (IQR)	309 (291.75–320.25)	294.5 (275–318.25)	0.13
I/L temporal parafoveal thickness (µm), mean±SD	305.50±17.94	296.63±26.06	0.13
I/L average parafoveal thickness (µm), mean±SD	308.23±16.39	302.52±27.11	0.33
C/L superior parafoveal thickness (µm), mean±SD	310.90±20.97	298.77±33.04	0.09
C/L inferior parafoveal thickness (µm)[c], median (IQR)	310 (302.50–326.25)	302.5 (286.5–318.75)	0.10
C/L nasal parafoveal thickness (µm), mean±SD	306.10±24.58	295.43±33.03	0.16
C/L temporal parafoveal thickness (µm)[c], median (IQR)	305 (294–315)	287 (274.75–312)	0.07
C/L average parafoveal thickness (µm), mean±SD	309.50±18.20	301.16±33.48	0.24
I/L superior perifoveal thickness (µm)[c], median (IQR)	271.5 (264.75–284)	269 (259.75–284.75)	0.23
I/L inferior perifoveal thickness (µm)[c], median (IQR)	263.5 (254.5–269.25)	261.5 (255–275)	0.74
I/L nasal perifoveal thickness (µm), mean±SD	274.17±22.28	268.57±23.09	0.34
I/L temporal perifoveal thickness (µm), mean±SD	273.70±20.18	271.93±21.89	0.75
I/L average perifoveal thickness (µm), mean±SD	273.43±15.84	270.25±15.18	0.43
C/L superior perifoveal thickness (µm)[c], median (IQR)	276.5 (265.75–291.25)	269 (262.75–278)	0.08
C/L inferior perifoveal thickness (µm)[c], median (IQR)	268 (252.5–296.25)	256 (247.75–278)	0.09
C/L nasal perifoveal thickness (µm), mean±SD	277.57±23.09	271.07±25.78	0.31
C/L temporal perifoveal thickness (µm), mean±SD	277.27±19.65	269.40±21.78	0.15
C/L average perifoveal thickness (µm), mean±SD	278.75±18.97	269.08±16.91	0.04
I/L macular volume (mm^3)[c], median (IQR)	9.8 (9.5–10.2)	9.85 (9.47–10.32)	0.84
C/L macular volume (mm^3), mean±SD	9.86±0.39	9.74±0.76	0.46

[a]"Fovea" is the center, measuring 1 mm in diameter. "Parafovea" is the area with diameter measuring between 1 and 3 mm, and "perifovea" is the macular region measuring in diameter between 3 and 6 mm. [b]For healthy controls, I/L means the side same as that chosen for the corresponding PD patient. [c]Nonparametric distribution. C/L=Contralateral, I/L=Ipsilateral, IQR=Interquartile range, PD=Parkinson's disease, RNFL=Retinal nerve fiber layer, SD=standard deviation

including dopaminergic agents, levodopa was being used by 27 (90%) patients. The mean (±SD) levodopa equivalent daily dose was 557.70 (±231.63) mg.

OCT parameters in PD versus HCs

Table 1 compares central retinal OCT parameters in PD patients and HCs. Compared to HCs, significant central retinal thinning in the ipsilateral superior parafoveal quadrant (mean ± SD = 311.10 ± 15.90 vs. 297.57 ± 26.55, $P = 0.02$] and the contralateral average perifoveal region (mean ± SD = 278.75 ± 18.97 vs. 269.08 ± 16.91, $P = 0.04$) was observed in PD patients. Although not statistically significant, thinning was observed in contralateral superior (mean ± SD = 310.90 ± 20.97 vs. 298.77 ± 33.04, $P = 0.09$) and temporal (median [IQR] = 305 [294–315] vs. 287 [274.75–312], $P = 0.07$) parafoveal, and contralateral superior (median [IQR] =276.5 [265.75–291.25] vs. 269 [262.75–278], $P = 0.08$), and inferior (median [IQR] =268 [252.5–296.25] vs. 256 [247.75–278], $P = 0.08$) perifoveal quadrants. However, the peripapillary retinal OCT parameters between PD and HCs were comparable [Table 2].

Correlation of OCT parameters with demographic and clinical parameters in PD

A significant negative correlation was noted between MDS-UPDRS-III motor score and both ipsilateral (Spearman rho = −0.52, $P = 0.003$) and contralateral (Spearman rho = −0.53, $P = 0.002$) macular volumes. In addition, a significant negative correlation was observed between HY stage and both ipsilateral (Spearman rho = −0.47, $P = 0.008$) and contralateral (Spearman rho = −0.58, $P < 0.001$) macular volumes. However, neither MDS-UPDRS-III motor scores nor HY stage correlated with macular or peripapillary RNFL thickness. PD duration showed significant negative correlation with ipsilateral temporal parafoveal thickness (Spearman rho = −0.41, $P = 0.02$) [Table 3].

^{99m}Tc-TRODAT brain SPECT parameters and correlation with demographic, clinical, and OCT parameters in PD

The mean ± SD values of ipsilateral, contralateral, and total (right + left) ^{99m}Tc-TRODAT-1 SUR values in the PD group were 0.28 ± 0.18, 0.27 ± 0.15, and 0.56 ± 0.29, respectively. The ^{99m}Tc-TRODAT-1 SUR values on both sides in PD patients were comparable ($P = 0.80$). No significant correlation was observed between ^{99m}Tc-TRODAT-1 SUR and assessed disease parameters [Table 3].

We did not observe any correlation between the macular or peripapillary retinal OCT parameters and ^{99m}Tc-TRODAT-1 brain SPECT parameters in PD patients [Supplementary Table 2].

Discussion

Peripapillary RNFL thickness parameters were comparable between PD patients and HCs. Compared to HCs, significant

Table 2: Optical coherence tomography parameters of peripapillary retina in PD patients and healthy controls

Characteristics	Healthy controls[a] (*n*=30) (A)	PD patients (*n*=30) (B)	*P* (A vs. B)
I/L superior RNFL (μm)[b], median (IQR)	118 (107–123.25)	119.5 (105.75–136.5)	0.44
I/L inferior RNFL (μm), mean±SD	115.73±14.27	118.93±19.81	0.48
I/L nasal RNFL (μm)[b], median (IQR)	72 (63.75–80)	72 (62.75–81.25)	0.90
I/L temporal RNFL (μm), mean±SD	63.37±9.49	61.33±9.67	0.42
I/L total average RNFL (μm)[b], median (IQR)	91.37 (87.31–95.63)	95.63 (85.81–102.81)	0.32
C/L superior RNFL (μm), mean±SD	114.03±8.55	117.93±19.97	0.33
C/L inferior RNFL (μm), mean±SD	118.26±11.93	120.10±19.48	0.66
C/L nasal RNFL (μm), mean±SD	72.50±8.92	76.37±19.08	0.32
C/L temporal RNFL (μm), mean±SD	63.80±6.39	61.37±10.87	0.29
C/L total average RNFL (μm), mean±SD	92.15±6.00	93.94±12.11	0.47

[a]For healthy controls, I/L means the side same as that chosen for the corresponding PD patient. [b]Nonparametric distribution. C/L=Contralateral, I/L=Ipsilateral, IQR=Interquartile range, PD=Parkinson's disease, RNFL=Retinal nerve fiber layer, SD=Standard deviation

central retinal thinning was observed in ipsilateral superior parafoveal and contralateral average perifoveal regions. While both ipsilateral and contralateral macular volumes reduced with increasing disease severity (assessed by MDS-UPDRS-III score and HY stage), a reduction in ipsilateral temporal parafoveal quadrant was associated with increased PD duration. No correlation was observed between the retinal OCT parameters and ^{99m}Tc-TRODAT-1 parameters in PD patients.

Several studies have reported a reduction in peripapillary RNFL thickness in PD patients compared to HCs, with few studies reporting thinning in all four quadrants as well as average RNFL.[23–25] On the contrary, many studies failed to observe any significant RNFL thinning in PD patients compared to HCs.[13,15–17] Despite conflicting results reported in several studies, a recent meta-analysis including 27 studies with 1470 PD patients (2288 eyes) and 1552 HCs (2524 eyes) reported a global central retinal thinning, predominantly involving parafoveal and perifoveal regions.[5] In the present study, we failed to observe any significant difference in peripapillary RNFL thickness between PD patients and HCs. However, we noted significant thinning in the contralateral average perifoveal region in PD patients compared to HCs. This suggests a possible link with contralateral nigrostriatal pathway affection in PD, which shows early involvement on ^{99m}Tc-TRODAT-1 brain SPECT imaging.[3] Similar observations were made in two previous studies. While the first study involving 43 PD patients and 86 HCs reported asymmetrical contralateral peripapillary RNFL thinning in PD,[11] the second study from UK involving 25 PD patients and 25 HCs reported thinning of the contralateral hemi-retinae including macular parameters in PD patients.[25] Besides small sample size being a major reason for inconsistent results reported by these studies,[4] other contributory factors are differences in patient-related parameters including age of onset and assessment, and disease-related parameters including disease duration and disease severity of PD patients included in these studies.[4,6] Moreover, the results may also have been affected by the differences in the type of OCT and assessment protocol used.[4,6] In addition to the reasons discussed above for inconsistent findings in previous studies, proportion of patients on levodopa might also have influenced RNFL thickness in the present study. Twenty-seven (90%) of our patients were on levodopa. Trophic role of levodopa in preserving RNFL thickness has been reported previously.[26,27] Although the present study involved PD patients only, previous studies have also reported RNFL thinning in Parkinson-plus syndromes. Compared to PD patients and controls, progressive supranuclear palsy patients show a significant reduction in superior quadrant peripapillary RNFL thickness.[7] Compared to controls, multiple system atrophy patients report a significantly reduced global as well as inferior quadrant peripapillary RNFL thickness.[8]

Previous studies have shown inconsistent results for macular volume.[10,13,15,16,23] The total macular volumes in PD patients and HCs were comparable in the present study. Interestingly, both ipsilateral and contralateral macular volumes in our PD patients had a negative moderate correlation with clinical markers of PD severity, that is, both MDS-UPDRS-III score and HY stage. PD severity has been shown to be inversely related to peripapillary and/or central retinal parameters.[10,12,28,29] A negative correlation has been reported between foveal thickness and UPDRS score,[10] RNFL thinning and UPDRS score,[14,29] RNFL thinning and HY stage,[28,29] para- and perifoveal thicknesses and HY stage,[28] and macular volume and HY stage as well as UPDRS score.[29] Although we observed a weak negative correlation between contralateral average perifoveal thickness and MDS-UPDRS-III score (Spearman rho = −0.32), it was not statistically significant ($P = 0.08$). With an increase in PD severity, there was progressive reduction in dopaminergic input to the retinal neurons as well as its trophic effect, thereby resulting in retinal structural changes. Considering the trophic effect of levodopa on the retinal structure,[26,27] and that majority of our PD patients were on levodopa, it was not surprising that we failed to find a significant inverse correlation between majority of central retinal parameters and PD severity.

In their study involving 54 PD patients and equal number of HCs, Sari *et al*.[30] reported a negative correlation between macular ganglion cell–inner plexiform layer thickness and PD duration. Since ganglion cells appear to be the primary retinal neurons involved in PD, with nearly half of them

Table 3: Correlations of OCT and ^{99m}Tc-TRODAT brain SPECT parameters with demographic and clinical parameters in PD patients

Parameters	Age of onset (years) ρ (*P*)	Age at assessment (years) ρ (*P*)	Disease duration (years) ρ (*P*)	MDS-UPDRS-III motor score ρ (*P*)	Hoehn and Yahr stage ρ (*P*)
Central retinal OCT parameters					
I/L foveal thickness[a]	-0.14 (0.48)	-0.11 (0.58)	-0.04 (0.84)	-0.06 (0.76)	-0.02 (0.92)
C/L foveal thickness	-0.18 (0.36)	-0.25 (0.18)	-0.28 (0.13)	-0.08 (0.66)	-0.09 (0.64)
I/L superior parafoveal thickness	0.19 (0.33)	0.17 (0.38)	0.14 (0.48)	< 0.001 (0.99)	-0.03 (0.89)
I/L inferior parafoveal thickness	0.08 (0.66)	0.02 (0.90)	-0.24 (0.21)	-0.21 (0.27)	-0.14 (0.46)
I/L nasal parafoveal thickness	-0.07 (0.71)	-0.07 (0.73)	0.002 (0.99)	-0.03 (0.87)	-0.09 (0.63)
I/L temporal parafoveal thickness	0.24 (0.19)	0.17 (0.38)	-0.23 (0.22)	-0.11 (0.55)	-0.11 (0.57)
I/L average parafoveal thickness	-0.04 (0.82)	-0.07 (0.70)	-0.11 (0.58)	-0.05 (0.77)	-0.15 (0.42)
C/L superior parafoveal thickness	-0.02 (0.91)	-0.04 (0.82)	-0.14 (0.46)	-0.13 (0.48)	-0.20 (0.29)
C/L inferior parafoveal thickness	-0.02 (0.94)	-0.08 (0.69)	-0.28 (0.14)	-0.22 (0.24)	-0.29 (0.11)
C/L nasal parafoveal thickness	0.08 (0.69)	0.07 (0.70)	-0.01 (0.98)	-0.12 (0.52)	-0.01 (0.73)
C/L temporal parafoveal thickness	-0.13 (0.49)	-0.12 (0.53)	0.04 (0.84)	0.01 (0.97)	0.01 (0.97)
C/L average parafoveal thickness	-0.12 (0.52)	-0.13 (0.50)	-0.08 (0.67)	-0.20 (0.29)	-0.23 (0.22)
I/L superior perifoveal thickness	0.19 (0.32)	0.14 (0.45)	-0.03 (0.88)	-0.07 (0.70)	-0.09 (0.61)
I/L inferior perifoveal thickness	0.22 (0.24)	0.13 (0.48)	-0.25 (0.29)	-0.17 (0.38)	-0.09 (0.61)
I/L nasal perifoveal thickness	0.15 (0.42)	0.11 (0.57)	-0.09 (0.63)	0.06 (0.77)	0.15 (0.42)
I/L temporal perifoveal thickness	0.26 (0.17)	0.10 (0.60)	-0.41 (0.02)	-0.16 (0.38)	-0.17 (0.37)
I/L average perifoveal thickness	0.17 (0.36)	0.08 (0.66)	-0.29 (0.13)	-0.10 (0.59)	-0.10 (0.59)
C/L superior perifoveal thickness	0.08 (0.65)	0.02 (0.89)	-0.24 (0.21)	-0.14 (0.46)	-0.24 (0.19)
C/L inferior perifoveal thickness	0.18 (0.35)	0.09 (0.61)	-0.26 (0.16)	-0.23 (0.22)	-0.11 (0.57)
C/L nasal perifoveal thickness	0.24 (0.20)	0.22 (0.25)	-0.01 (0.98)	-0.01 (0.61)	-0.01 (0.94)
C/L temporal perifoveal thickness	0.06 (0.77)	-0.04 (0.83)	-0.26 (0.17)	-0.30 (0.11)	-0.23 (0.23)
C/L average perifoveal thickness	0.18 (0.34)	0.09 (0.61)	-0.27 (0.15)	-0.32 (0.08)	-0.22 (0.24)
I/L macular volume (mm^3)	-0.25 (0.18)	-0.27 (0.15)	-0.04 (0.83)	-0.52 (0.003)	-0.47 (0.008)
C/L macular volume (mm^3)	-0.24 (0.20)	-0.34 (0.07)	-0.10 (0.59)	-0.53 (0.002)	-0.58 (<0.001)
Peripapillary retinal OCT parameters					
I/L superior RNFL	-0.06 (0.74)	-0.08 (0.67)	0.12 (0.52)	-0.30 (0.11)	-0.17 (0.36)
I/L inferior RNFL	-0.04 (0.86)	-0.16 (0.41)	-0.15 (0.43)	0.02 (0.92)	-0.23 (0.22)
I/L nasal RNFL	-0.09 (0.60)	-0.24 (0.21)	-0.14 (0.47)	0.02 (0.89)	-0.16 (0.39)
I/L temporal RNFL	-0.23 (0.22)	-0.13 (0.51)	0.30 (0.11)	0.16 (0.39)	0.12 (0.54)
I/L average RNFL	-0.14 (0.47)	-0.22 (0.25)	-0.01 (0.98)	-0.03 (0.89)	-0.18 (0.34)
C/L superior RNFL	-0.18 (0.35)	-0.25 (0.18)	-0.23 (0.22)	-0.15 (0.43)	-0.21 (0.25)
C/L inferior RNFL	-0.13 (0.49)	-0.19 (0.33)	-0.15 (0.44)	-0.05 (0.79)	-0.19 (0.29)
C/L nasal RNFL	-0.14 (0.47)	-0.19 (0.32)	-0.05 (0.80)	0.15 (0.42)	-0.06 (0.76)
C/L temporal RNFL	-0.18 (0.33)	-0.11 (0.57)	0.16 (0.39)	-0.09 (0.65)	0.05 (0.78)
C/L average RNFL	-0.16 (0.39)	-0.26 (0.17)	-0.23 (0.23)	-0.09 (0.68)	-0.20 (0.28)
^{99m}Tc-TRODAT brain SPECT parameters					
I/L SUR	-0.32 (0.09)	-0.27 (0.15)	0.003 (0.99)	-0.19 (0.30)	-0.23 (0.22)
C/L SUR	-0.18 (0.35)	-0.12 (0.52)	-0.03 (0.86)	-0.17 (0.36)	-0.17 (0.36)
SUR-total (right + left)	-0.31 (0.09)	-0.24 (0.21)	0.01 (0.98)	-0.20 (0.28)	-0.23 (0.23)

[a]"Fovea" is the center, measuring 1 mm in diameter. "Parafovea" is the area with a diameter between 1 and 3 mm, and "perifovea" is the macular region measuring in diameter between 3 and 6 mm. ^{99m}Tc-TRODAT=Technetium-99m-labeled tropane derivative, C/L=Contralateral, I/L=ipsilateral, MDS-UPDRS=Movement Disorders Society-Unified Parkinson's Disease Rating Scale, OCT=Optical coherence tomography, PD=Parkinson's disease, RNFL=Retinal nerve fiber layer, SPECT=Single-photon emission computed tomography, SUR=specific uptake ratio

being populated within 4.5 mm of fovea centralis, thicknesses of foveal and parafoveal macular regions are likely to show an inverse correlation with PD duration.[30,31] In the present study, we observed a significant inverse correlation between ipsilateral temporal parafoveal thickness and PD duration. Although worsening of dopaminergic deficit with increasing disease duration is expected to result in progressive RNFL thinning, the peripapillary RNFL parameters in our PD patients did not show a significant negative correlation with PD duration. While several studies reported lack of any correlation between RNFL thickness and disease duration in PD,[9–11] few others reported significant association of disease duration and RNFL thinning.[14,29] Jiménez *et al*.[14] reported an inverse relation between disease duration and inferior and nasal quadrants' RNFL values, as well as between disease duration and the average RNFL values, and proposed

average peripapillary RNFL thickness as a biomarker for PD progression.

Functional imaging with ^{99m}Tc-TRODAT-1 classically reveals reduced tracer uptake in the striatum, with more severe and earlier involvement of the putamen.[3] Degeneration of the dopaminergic system progresses bilaterally, with asymmetrical ^{99m}Tc-TRODAT-1 SUR reported in early PD.[3] We did not observe significant asymmetry in ^{99m}Tc-TRODAT-1 SUR values, probably because 90% of our patients were in stage II, III, or IV and had bilateral clinical involvement. Although previously reported,[3] we did not observe an inverse correlation between SUR values and PD severity. This might have resulted from the low sample size and the fact that nearly 86.7% of our patients were in either HY stage II or III.

The present study could not find a significant correlation between the central or peripapillary retinal OCT parameters and ^{99m}Tc-TRODAT-1 brain SPECT parameters in PD patients. Using (^{18}F-FP-CIT) PET imaging, a recent study showed positive correlation between RNFL thinning and loss of dopaminergic neurons in the substantia nigra.[21] However, it failed to find any association between RNFL thinning and DAT loss in the striatum.[21] Striatal DAT level shows the extent of dopamine loss in the striatum, that is, functional status of the nigrostriatal neurons, but not the surviving nigral dopaminergic neuron counts, as reported by a study from Finland.[32] The study involving 18 patients, including 11 with neuropathologically confirmed PD, concluded that striatal DAT binding is likely associated with axonal involvement, but not the available quantity of nigral neurons.[32] Studies on animal models have also suggested DAT binding to be associated with the amount of striatal dopamine, but not with the quantity of neurons in the substantia nigra.[33] Another animal study reported that striatal radiotracer uptake correlated with striatal dopamine levels over the entire range of dopamine depletion, but failed to correlate with nigral neuron counts if neuronal loss in the substantia nigra exceeded 50%.[34] Majority of nigral neurons are lost in PD by 4–5 years following its diagnosis.[35] Considering the median duration of PD postdiagnosis being 4 years in our cohort, DAT binding is unlikely to correlate with the nigral neuronal degeneration in the present study. Therefore, the lack of correlation between OCT and ^{99m}Tc-TRODAT-1 brain SPECT parameters in the present study only suggests that structural retinal degeneration failed to correlate with striatal dopamine levels. Hence, our results do not rule out the likelihood of correlation between dopaminergic neuronal degeneration affecting both nigrostriatal system and retina.

This study is limited by being a single-center, cross-sectional study with a small sample size. Our sample size calculation was based on a previous study demonstrating a correlation coefficient of 0.5 between OCT and ^{99m}Tc-TRODAT-1 brain SPECT. However, the same could not be recapitulated in the present study. We found nonsignificant correlation between OCT and ^{99m}Tc-TRODAT-1 brain SPECT parameters. Hence, the present study appears to be underpowered with high likelihood of type II error, limiting its generalizability, justifying that further studies with larger sample size should be conducted to confirm our findings. The median duration of illness in our PD patients was 4 years, and nearly all (96.7%) our patients were in either HY stage I, II, or III. Hence, we could not capture the entire spectrum of PD with respect to duration and severity. However, advanced PD patients may find significant difficulty in cooperating for OCT. Thus, a multicentric, longitudinal study including larger sample size from varied geographic distribution may help understand the specific patterns of peripapillary RNFL and macular thinning in PD patients and its relation with nigrostriatal dopamine depletion.

Conclusion

A significant thinning was observed in the ipsilateral superior parafoveal quadrant and contralateral average perifoveal region in PD patients compared to HCs. While both ipsilateral and contralateral macular volumes inversely correlated with PD severity, ipsilateral temporal parafoveal thickness showed a significant negative correlation with PD duration. Absence of correlation between OCT and ^{99m}Tc-TRODAT-1 SPECT parameters in PD indicates lack of association between structural retinal degeneration and striatal dopamine levels, but does not rule out a correlation between dopaminergic degeneration involving the nigrostriatal system and retina in PD.

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Conflicts of interest

There are no conflicts of interest.

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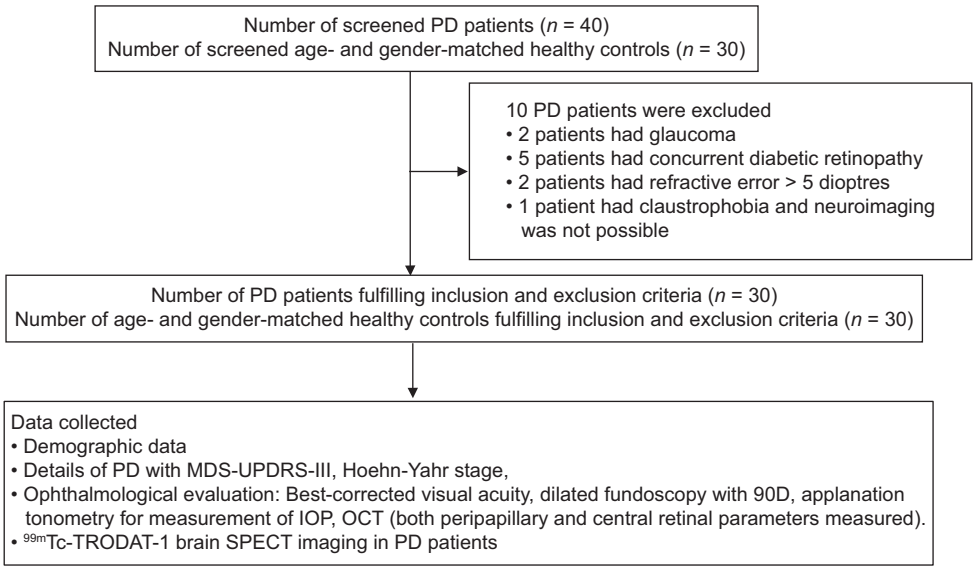

Supplementary Figure 1: Flowchart for screening, inclusion, and exclusion of cases and healthy controls

Supplementary Table 1: Demographic and clinical characteristics of PD patients and healthy controls

Demographic and clinical characteristics	Healthy controls (*n*=30) (A)	PD patients (*n*=30) (B)	*P* (A vs. B)
Age at assessment (years), mean±SD	57.37±7.64	57.07±12.78	0.91
Age at PD onset (years), mean±SD	-	51.77±12.06	-
Gender (male), *n* (%)	18 (60)	21 (70)	0.41
Duration of disease (years)[a], median (IQR)	-	4 (3–6.25)	-
Hoehn and Yahr stage, median (IQR)[a]	-	2 (2–2.25)	-
MDS-UPDRS-III score (“off” state), mean±SD	-	33.03±13.68	-
LEDD (mg), mean±SD	-	557.70±231.63	-

[a]Nonparametric distribution. IQR=Interquartile range, LEDD=Levodopa equivalent daily dose, MDS-UPDRS=Movement Disorders Society-Unified Parkinson’s Disease Rating Scale, PD=Parkinson’s disease, RNFL=retinal nerve fiber layer, SD=standard deviation

Supplementary Table 2: Correlation of optical coherence tomography and ^{99m}Tc-TRODAT brain SPECT imaging parameters in PD (ipsilateral and contralateral to the more severely involved body side)

OCT parameters	^{99m}Tc-TRODAT brain SPECT parameters Spearman's correlation ρ (*P*)		
	I/L SUR	C/L SUR	SUR-total
Central retinal parameters			
I/L foveal thickness[a]	0.24 (0.07)	0.28 (0.14)	0.24 (0.19)
C/L foveal thickness	0.08 (0.67)	0.05 (0.77)	0.01 (0.98)
I/L superior parafoveal thickness	-0.08 (0.66)	-0.15 (0.43)	-0.17 (0.36)
I/L inferior parafoveal thickness	-0.07 (0.73)	-0.01 (0.97)	-0.20 (0.28)
I/L nasal parafoveal thickness	-0.04 (0.81)	-0.11 (0.56)	-0.13 (0.51)
I/L temporal parafoveal thickness	-0.20 (0.29)	-0.16 (0.39)	-0.14 (0.45)
I/L average parafoveal thickness	-0.02 (0.94)	0.05 (0.78)	-0.11 (0.57)
C/L superior parafoveal thickness	-0.21 (0.27)	-0.21 (0.26)	-0.19 (0.30)
C/L inferior parafoveal thickness	0.20 (0.29)	0.23 (0.22)	0.17 (0.38)
C/L nasal parafoveal thickness	0.02 (0.93)	0.01 (0.96)	0.004 (0.98)
C/L temporal parafoveal thickness	0.09 (0.61)	-0.02 (0.93)	-0.04 (0.82)
C/L average parafoveal thickness	0.19 (0.33)	0.07 (0.69)	0.09 (0.65)
I/L superior perifoveal thickness	0.03 (0.89)	-0.18 (0.35)	-0.12 (0.52)
I/L inferior perifoveal thickness	0.01 (0.95)	0.12 (0.52)	-0.01 (0.97)
I/L nasal perifoveal thickness	-0.30 (0.10)	-0.34 (0.07)	-0.34 (0.06)
I/L temporal perifoveal thickness	0.12 (0.54)	0.08 (0.68)	-0.04 (0.81)
I/L average perifoveal thickness	0.03 (0.87)	-0.05 (0.80)	-0.07 (0.71)
C/L superior perifoveal thickness	-0.19 (0.33)	-0.24 (0.21)	-0.35 (0.05)
C/L inferior perifoveal thickness	0.04 (0.87)	-0.04 (0.84)	-0.16 (0.41)
C/L nasal perifoveal thickness	-0.19 (0.32)	-0.24 (0.21)	-0.19 (0.33)
C/L temporal perifoveal thickness	0.16 (0.40)	0.05 (0.78)	-0.07 (0.73)
C/L average perifoveal thickness	-0.10 (0.58)	-0.19 (0.31)	-0.36 (0.07)
I/L macular volume	0.15 (0.44)	0.02 (0.92)	-0.03 (0.88)
C/L macular volume	0.19 (0.31)	-0.01 (0.94)	0.004 (0.99)
Peripapillary retinal parameters			
I/L superior RNFL	0.12 (0.52)	0.15 (0.42)	0.16 (0.39)
I/L inferior RNFL	0.01 (0.97)	0.05 (0.78)	0.08 (0.69)
I/L nasal RNFL	-0.11 (0.56)	-0.01 (0.96)	-0.01 (0.98)
I/L temporal RNFL	-0.06 (0.75)	0.15 (0.42)	0.04 (0.83)
I/L average RNFL	0.01 (0.98)	0.12 (0.52)	0.10 (0.59)
C/L superior RNFL	-0.03 (0.86)	0.19 (0.29)	0.01 (0.95)
C/L inferior RNFL	0.04 (0.84)	0.28 (0.13)	0.09 (0.64)
C/L nasal RNFL	0.15 (0.42)	0.25 (0.18)	0.09 (0.61)
C/L temporal RNFL	-0.08 (0.67)	0.02 (0.90)	-0.04 (0.85)
C/L average RNFL	-0.02 (0.91)	0.27 (0.15)	0.02 (0.93)

[a]"Fovea" is the center, measuring 1 mm in diameter. While the area measuring in diameter between 1 and 3 mm is the "parafovea," that measuring in diameter between 3 and 6 mm is the "perifovea". ^{99m}Tc-TRODAT=Technetium-99m-labeled tropane derivative, C/L=Contralateral, I/L=Ipsilateral, OCT=Optical coherence tomography, PD=Parkinson's disease, RNFL=Retinal nerve fiber layer, SPECT=Single-photon emission computed tomography, SUR=Specific uptake ratio, UPDRS=Unified Parkinson's Disease Rating Scale