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The choroid and lamina cribrosa is affected in patients with Parkinson's disease: enhanced depth imaging optical coherence tomography study

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ABSTRACT.

Purpose: **To compare lamina cribrosa (LC) and choroidal thicknesses using enhanced depth imaging optical coherence tomography (EDI-OCT) in patients with Parkinson's disease (PD) and healthy controls.**

Methods: **A total number of 44 eyes of 22 patients with PD and 50 eyes of 25 healthy subjects were utilized in this institutional cross-sectional study. After a complete ophthalmic examination, all eyes were imaged with OCT (RTVue-100 version 5.1 Fourier-domain optical coherence tomography; Optovue Inc., Fremont, CA, USA); LC and choroidal thickness were assessed.**

Results: **The mean LC thicknesses were 209.4 ± 40.2 μm in patients with PD and 292.5 ± 33.7 μm in control subjects. There was a significant difference in the mean LC thickness between the groups ($p < 0.0001$). The choroidal thickness measurements of the PD group at the subfoveal region and 1.5 mm temporal and 1.5 mm nasal to the fovea were 228.1 ± 44.3, 193.2 ± 41.4 and 188.4 ± 49.0 μm, respectively, whereas measurements for the controls were, respectively, 246.5 ± 38.2, 227.3 ± 34.7 and 216.7 ± 51.4 μm. The choroid was significantly thinner in eyes of the PD group compared to that of the controls ($p = 0.001$, $p < 0.001$, and $p = 0.006$). There was no significant correlation between the disease severity and OCT parameters. The duration of the disease showed a statistically significant negative correlation with LC ($rs[94] = -0.700$, $p < 0.001$), and average subfoveal and temporal and nasal choroid thicknesses ($rs[94] = -0.282$, $p = 0.006$; $rs[94] = -0.324$, $p = 0.001$, $rs[94] = -0.240$, and $p = 0.020$, respectively).**

Conclusions: **Regardless of the disease severity, PD may cause atrophy and volume loss in the lamina cribrosa, and choroid. An enhanced depth imaging technique may be used as an additional modality in the diagnosis and follow-up of patients with PD.**

Key words: choroidal thickness – enhanced depth imaging – enhanced depth imaging – lamina cribrosa – optical coherence tomography – Parkinson's disease – retinal nerve fibre layer – RNFL

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Introduction

Parkinson's disease (PD), with a prevalence of 0.3%, is the second most common neurodegenerative disorder of the central nervous system (CNS) and is characterized by pathologic dopaminergic deficiency in the basal ganglia, resulting in movement disorders and non-motor impairment (Lev et al. 2003; Copeland et al. 2005). Human and animal experimentation studies have shown that the level of dopamine is decreased in dopamine-containing amacrine and interplexiform cell layers of the retina, causing it to become thinner in patients with PD (Harnois & Di Paolo 1990; Denis et al. 1993; Witkovsky 2004). Some ocular abnormalities, such as a loss in the sensitivity to contrast and colour vision, altered visual evoked potential and electroretinographic measurements, have been observed, indicating foveal retinal ganglion cell damage in patients with PD (Bodis-Wollner 2009). Therefore, it is hypothesized that the evaluation of ocular structures like retina and choroid may provide important information on the severity and the duration of neurodegenerative disease (Blanks et al. 1996; Albrecht et al. 2007; Paquet et al. 2007; Brandt et al. 2011).

It has been suggested that abnormal choroidal blood supply plays an important role in the pathogenesis of many vision-threatening ocular diseases, such as choroidal neovascular membrane, uveal effusion syndrome, central serous

chorioretinopathy, Vogt–Koyanagi–Harada disease, angioid streaks and polypoidal choroidal vasculopathy (Cristini et al. 1991; Esmaeelpour et al. 2011; Harada et al. 2011; Kim et al. 2011; Koizumi et al. 2011; Manjunath et al. 2011; Maruko et al. 2011a,b; Nakai et al. 2012).

As the choroid is a highly vascular structure, the thickness varies with the intraocular pressure and perfusion pressure (Kiel & van Heuven 1995). It has also been proposed that choroidal thickness is affected by age, refractive abnormalities, axial length, gender, central corneal thickness, smoking and/or ethnicity (Ramrattan et al. 1994; Inzelberg et al. 2004; Altintas et al. 2008; Fujiwara et al. 2009; Sizmaz et al. 2013; Lee et al. 2014).

The lamina cribrosa (LC) is the region where optic nerve fibres run through and connect to upper centres. There is growing evidence that the laminar region of the optic nerve head is the first part to be damaged in axonal loss, as is seen in glaucomatous optic neuropathy; moreover, *in vitro* studies have shown that the LC becomes thinner following glaucomatous nerve fibre damage (Hernandez & Ye 1993; Bellezza et al. 2003), One of the aims of this study was to investigate the LC thickness through the proposed ganglion cell loss in other reports.

It is difficult to image the choroid and the LC due to the impedance of the pigment in the retinal pigment epithelium and choroid to visualization in conventional eye examination methods. Based on histologic results, choroidal thickness has been reported to range from 170 to 220 μm, which is much thinner than that reported in recent *in vivo* measurements by spectral-domain optical coherence tomography (SD-OCT) (Saracco et al. 1984; Spaide et al. 2008; Margolis & Spaide 2009; Ikuno et al. 2010).

Due to the shrinkage observed following the tissue fixation, histologic 'on slide' results might theoretically underestimate the true thickness of the choroid. As an advancement of standard OCT, Spaide et al. (Spaide et al. 2008; Margolis & Spaide 2009; Ikuno et al. 2010) recently used the device to obtain cross-sectional imaging of the choroid and lamina cribrosa and measured their thicknesses *in vivo* by the application of an enhanced depth imaging (EDI) technique. It was possible to capture the images of the full thickness of the choroid *in vivo* via this technique (Gawlikowski et al. 2007; Fujiwara et al. 2009; Margolis & Spaide 2009).

To the best of our knowledge, there is no other study described in the literature that evaluates choroid and LC of patients with PD, *in vivo*, through the use of EDI-OCT.

Materials and Methods

This cross-sectional study, which included 22 patients with PD and 25 healthy controls, was conducted at the Marmara University School of Medicine Ophthalmology Clinic between January 2013 and March 2014 and in accordance with the amended Declaration of Helsinki. The ethical clearance was obtained from the Human Research Ethics Committee of the University of Marmara.

Inclusion criteria

Subjects with a corrected distance visual acuity (CDVA) of 6/10 or above, −4 to +3 dioptres of spherical refractive error, or ±3≤ dioptres of cylindrical refractive error and with an intraocular pressure (IOP) of 20 mmHg or less were included. The control group was composed of subjects without any ophthalmic pathology except for refractive errors in the above-described limits and who did not have neurological disorders (Margolis & Spaide 2009).

In the PD group, inclusion criteria covered patients who did not have any neurological diseases other than PD. Corrected IOP values through the central corneal thickness (CCT) were calculated as described previously (corrected IOP = measured IOP – (CCT – 545)/50 × 2.5 mmHg) (Shih et al. 2004).

The patients with PD were diagnosed by the Neurology Department according to the criteria of the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB). Patients with PD were examined by a neurologist and severity of the disease was evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS). The scale itself has four components (Part I, Mentation, Behavior and Mood; Part II, Activities of Daily Living; Part III, Motor; Part IV, Complications) which are composed of 42 questions in total and a neurologist scores each question according to the patient's performance from 0 (normal) to 4 (severe). Therefore, higher total scores describe an increased severity and greater disability from PD (total score 0–154) (Movement Disorder Society Task Force on Rating Scales for Parkinson's D 2003). All patients with PD were receiving levodopa therapy and dopamine agonists for treatment of PD.

Exclusion criteria

Subjects with diagnosed uveitic, retinal or optic nerve diseases (including glaucoma); ocular media opacities; severe carotid artery stenosis; uncontrolled hypertension; diabetes mellitus; history of repeated head trauma or protracted loss of consciousness following head trauma within the last 5 years; severe central nervous system infections within the last 5 years; or a history of cerebrovascular disease (stroke, transient ischaemic attacks, cerebral haemorrhage) were excluded (Gharbiya et al. 2014).

Ophthalmologic examination

All patients underwent Snellen CDVA testing, a slit-lamp examination of the anterior segment, Goldmann applanation tonometry, axial length measurement (Lenstar LS 900, Haag-Streit USA, Mason, OH, USA), CCT measurements (Tomey, Ultrasonic Pachymetry, SP-3000, Germany), gonioscopy, OCT scanning including LC and choroidal thickness and optic nerve head (ONH) parameters including ONH disc area (mm^2), ONH cup area (mm^2), ONH rim area (mm^2), ONH volume (mm^3), ONH cup volume (mm^3), ONH cup/disc area ratio, ONH cup/disc horizontal ratio, ONH cup/disc vertical ratio measurement (RTVue-100 version 5.1 Fourier-domain OCT; Optovue Inc.) and fundus examination. All examinations were performed between 9 a.m. and 10 a.m. During scanning, full priority was given to maintain high signal strength index values (>50). Low-quality OCT scans were excluded.

LC and choroid thickness

High-resolution images of the LC and choroid were obtained using the vitreoretinal and chorioretinal settings (EDI-OCT) of the RTVue-100 version

5.1. Within the imaging protocol, 1024 A-scans were performed within 1.25 s, and 32 B-scans were averaged.

Measuring the LC thickness

In this protocol, we used the chorioretinal option on the imaging device and obtained 1024 A-scans on a 6 mm horizontal line within 1.25 s. The scans passing through the centre of the central retinal blood vessels were centred at the optic disc with nasal fixation. In the horizontal B-scan images, the region between the outer and inner boundaries of the hyper-reflective area within the vertical centre of the optic disc (OD) was regarded as the LC. Adjusting contrast settings helped us to identify the image providing the clearest visualization of the LC. The LC thickness was measured manually on vertical lines lying between the inner and outer boundaries of the hyper-reflective area temporal to the central retinal vessels. In cases where the hyporeflective image created by the nerve fibres passing through the laminar pores was too close to the temporal of the central retinal vessels in patients with thinner LCs, the measurement was performed at the points at which the inner and outer boundaries of the LC could be most clearly seen (Park et al. 2012). During the measurement, we gave full weight to use the centre of the LC plate in the measurement of thickness. All measurements were performed three times and averaged.

Measuring the choroid thickness

Chorioretinal option provided a high-resolution image of the choroid. With central fixation, we obtained approximately 1024 A-scans on a 6 mm horizontal line passing through the centre of the fovea. By adjusting the contrast settings, we identified the image on which the choroid could be most clearly examined. Choroidal thickness was measured with horizontal B-scans on vertical lines running towards the chorioscleral junction, at the subfoveal region and 1.5 temporal and 1.5 mm nasal to the fovea (Figs 1 and 2). When the hyper-reflective chorioscleral junction could not be distinguished because of the shadowing caused by choroidal vessels, especially in the subfoveal region, the outer boundaries of the visible choroidal vessels were accepted as the chorioscleral junction. Each measurement was repeated three times, and the mean thickness level was calculated.

Statistics

SPSS (Statistical Package for Social Sciences) Windows version 17.0 (SPSS for Windows Inc., Chicago, IL, USA) was used for data analysis. The mean ± standard deviation and ratio values were used for the descriptive statistics. Normality was tested using the Kolmogorov–Smirnov test. Pearson's correlation was used for analysing the normally distributed data, and Spearman's correlation was used for analysing non-normally distributed data. The ANOVA (Tukey) and Kruskal–Wallis (Mann–Whitney *U*-test) tests were used to analyse the differences between the groups. A chi-square test was used to compare categorical data between two groups. p values of <0.05 were considered statistically significant. Multivariate linear regression analysis was performed to determine the significant predictors of having PD. The predictive ability of OCT values was evaluated with receiver operating characteristic (ROC) curve analysis. Our a priori sample size calculation required 46 patients with effect size of one, $\alpha = 0.05$, for a power of 95%, which would be able to differentiate 15% difference in LC or choroidal thickness. The a priori and post hoc power tests were calculated with G*Power (Version 3.1.7) (Faul et al. 2009).

Results

The study revealed no statistically significant differences in the mean age and distribution by gender between the groups (Table 1). The average duration

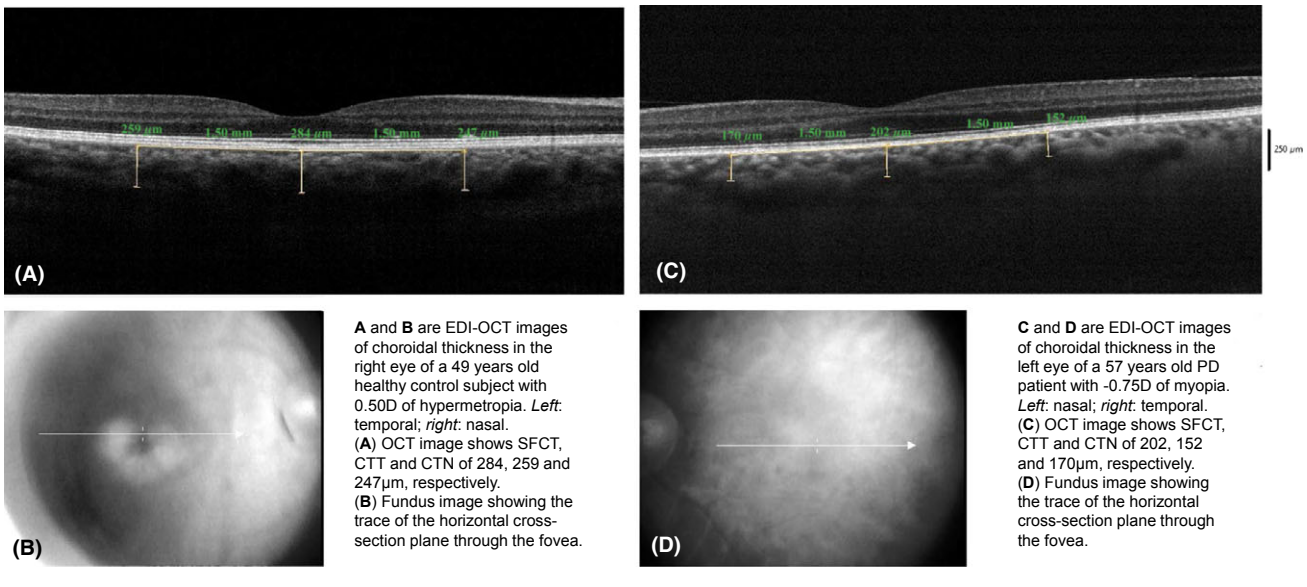
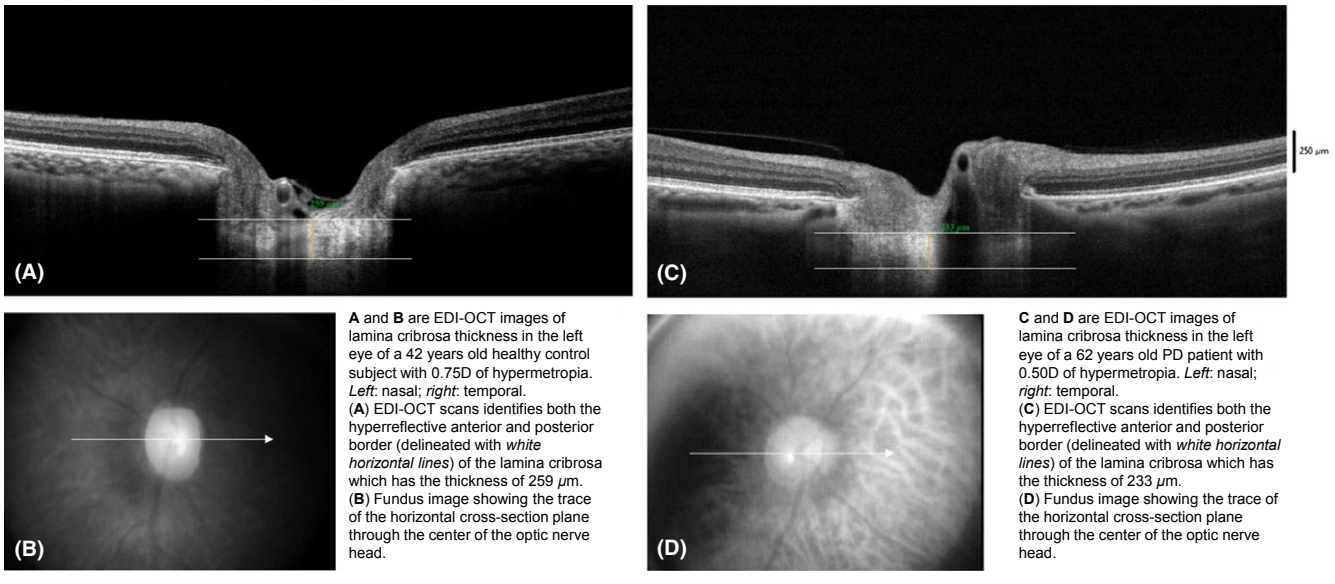


Fig. 1. Enhanced depth imaging optical coherence tomography (EDI-OCT) scans showing lamina cribrosa thickness in a healthy control subject and a patient with PD. Both the anterior and posterior border (delineated with *white horizontal lines*) of the lamina cribrosa are identified in EDI-OCT scans. The anterior border (delineated with superior *white horizontal line)* of the lamina cribrosa is clearly seen, which has a highly reflective plate structure with posterior bowing underlying the optic disc cup. The lamina cribrosa is obscured beneath the rim and intrapapillary central retinal vessels, but the central part of the lamina cribrosa is well observed and deeper layers are visible at the centre. Lamina cribrosa thickness was measured at the centre of the optic nerve head, along a vertical orange line which ran between the horizontal white lines.



A and **B** are EDI-OCT images of lamina cribrosa thickness in the left eye of a 42 years old healthy control subject with 0.75D of hypermetropia. *Left*: nasal; *right*: temporal.
(**A**) EDI-OCT scans identifies both the hyperreflective anterior and posterior border (delineated with *white horizontal lines*) of the lamina cribrosa which has the thickness of 259 µm.
(**B**) Fundus image showing the trace of the horizontal cross-section plane through the center of the optic nerve head.

C and **D** are EDI-OCT images of lamina cribrosa thickness in the left eye of a 62 years old PD patient with 0.50D of hypermetropia. *Left*: nasal; *right*: temporal.
(**C**) EDI-OCT scans identifies both the hyperreflective anterior and posterior border (delineated with *white horizontal lines*) of the lamina cribrosa which has the thickness of 233 µm.
(**D**) Fundus image showing the trace of the horizontal cross-section plane through the center of the optic nerve head.

Fig. 2. Representative images of choroidal thickness in a healthy control subject and a patient with PD. Measurement of choroidal thickness with horizontal B-scans on vertical lines running towards the chorioscleral junction, at the subfoveal region (SFCT), 1.5 temporal (CTT), and 1.5 mm nasal (CTN) to the fovea, is displayed.

Table 1. The demographic features of PD and control subjects.

	Patients with PD (n = 44)	Control (n = 52)	p-value
Age (years) (min–max)	60.45 ± 9.1 (42–80)	60.56 ± 9.9 (42–79)	0.976
Gender	M/F	M/F	0.130
	24 (48.2%)/26 (63.6%)	28 (40.8%)/16 (36.4%)	
Spherical (D)	−0.12 ± 1.12	0.24 ± 1.17	0.361
Cylinder (D)	0.21 ± 0.80	0.45 ± 0.55	0.131
Spherical equivalent (D)	−0.01 ± 1.24	0.46 ± 1.31	0.144
CDVA (logMAR)	0.02 ± 0.05	0.01 ± 0.03	1.000
IOP (mmHg)	13.30 ± 1.94	13.22 ± 1.66	0.597
Axial length (mm)	23.45 ± 0.70	23.37 ± 0.62	0.642
CCT (µm)	553.10 ± 25.70	552.24 ± 10.34	0.402
UPDRS score range (min–max)	34.25 ± 15.5 (11.00–59.00)	–	–
Duration (month)	71.41 ± 53.6	–	–

Values are mean ± standard deviation unless otherwise indicated. Chi-square test/ANOVA (Tukey test)/Kruskal–Wallis (Mann–Whitney *U*-test): PD versus control ($p < 0.01$). All p values were derived from a Kruskal–Wallis test.
PD = Parkinson's disease, CDVA = best corrected visual acuity, logMAR, D = dioptres, IOP = intraocular pressure, CCT = central corneal thickness, UPDRS = unified Parkinson's disease rating scale.

of the disease and the treatment was 71.41 ± 53.6 months (12–240) in the patients with PD. The difference between refractive error outcomes (spherical and astigmatic refractive error), CDVA, IOP and CCT measurements of the groups were not statistically significant ($p > 0.05$) (Table 1). There was no statistically significant difference between groups regarding any of the ONH parameters ($p > 0.05$) (Table 2).

The average LC thickness was measured at 209.4 ± 40.2 µm in the patients with PD and at 292.5 ± 33.7 µm in the control subjects. In the PD group, the LC thickness was found to be significantly thinner than that of the control group ($p < 0.001$) (Table 3) (Fig. 1).

The comparison between the two groups regarding the mean choroidal thickness showed that the patients with PD had significantly thinner values in the subfoveal, temporal and nasal regions compared to the control group ($p < 0.05$) (Fig. 2) (Table 3). The choroidal thickness measurements of the patients with PD at the subfoveal region and 1.5 mm temporal and 1.5 mm nasal to the fovea were 228.1 ± 44.3, 193.2 ± 41.4 and 188.4 ± 49.0 µm, respectively, whereas measurements for the controls were 246.5 ± 38.2, 227.3 ± 34.7 and 216.7 ± 51.4 µm, respectively.

There was no significant difference or relation between refraction and LC or subfoveal, 1.5 mm temporal, 1.5 mm nasal choroidal thickness in PD and control group ($p > 0.05$) (Fig. 3).

Spearman's rho revealed a statistically significant relationship between disease duration and LCC and choroidal thicknesses. There was a strong negative correlation with average LCC thickness ($rs[94] = -0.700$, $p < 0.001$), a moderate negative correlation with average subfoveal and temporal choroid thicknesses ($rs[94] = -0.282$, $p = 0.006$ and $rs[94] = -0.324$, $p = 0.001$, respectively) and a weak negative correlation with nasal choroidal thickness ($rs[94] = -0.240$, $p = 0.020$). However, there was no correlation between UPDRS scores and OCT parameters within the PD group ($p > 0.05$).

Our multivariate linear regression analysis revealed that the LC thickness was the most predictive and choroidal thickness 1.5 mm temporal to the fovea was the second most predictive EDI-OCT parameter for the determination of the presence of PD ($r^2 = 0.62$ CI:−0.015–−0.010 for LC thickness and −0.009–−0.003 for choroidal

Table 2. Optic nerve head parameters of patients with PD and healthy control subjects.

	Patients with PD (n = 44)	Control (n = 52)	p-value
ONH disc area (mm^2)	1.92 ± 0.72	1.67 ± 0.54	0.253
ONH cup area (mm^2)	0.68 ± 0.61	0.42 ± 0.41	0.125
ONH rim area (mm^2)	1.26 ± 0.62	1.33 ± 0.50	0.241
ONH volume (mm^3)	0.31 ± 0.22	0.38 ± 0.22	0.069
ONH cup volume (mm^3)	0.16 ± 0.18	0.06 ± 0.08	0.092
ONH cup/disc area ratio	0.29 ± 0.25	0.24 ± 0.21	0.508
ONH cup/disc horizontal ratio	0.58 ± 0.35	0.47 ± 0.33	0.333
ONH cup/disc vertical ratio	0.49 ± 0.29	0.43 ± 0.32	0.615

Values are mean ± standard deviation unless otherwise indicated. Chi-square test/ANOVA (Tukey test)/Kruskal–Wallis (Mann–Whitney U-test): PD versus control ($p < 0.01$). All p values were derived from a Kruskal–Wallis test.
PD = Parkinson's disease, ONH = optic nerve head.

Table 3. The lamina cribrosa and choroid thickness measurements in the groups.

			Parkinson Disease (n = 44)	Control (n = 52)	p-value
LC thickness (μm)		Mean ± SD (min–max)	209.4 ± 40.2 (144–317)	292.5 ± 33.7 (220–354)	**< 0.001**
Choroid thickness (μm)	Subfoveal	Mean ± SD (min–max)	228.1 ± 44.3 (166–380)	246.5 ± 38.3 (142–313)	**0.001**
	Temporal	Mean ± SD (min–max)	193.2 ± 41.3 (110–282)	227.3 ± 34.7 (153–323)	**< 0.001***
	Nasal	Mean ± SD (min–max)	188.4 ± 49.0 (108–296)	216.7 ± 51.4 (107–362)	**0.006**

Values are mean ± standard deviation unless otherwise indicated. All p values were derived from a ANOVA/(Tukey test)/Kruskal–Wallis (Mann–Whitney U-test) statistical test. p values with * are normally distributed data and derived from ANOVA (Tukey) test. p values with bold characters are < 0.05.

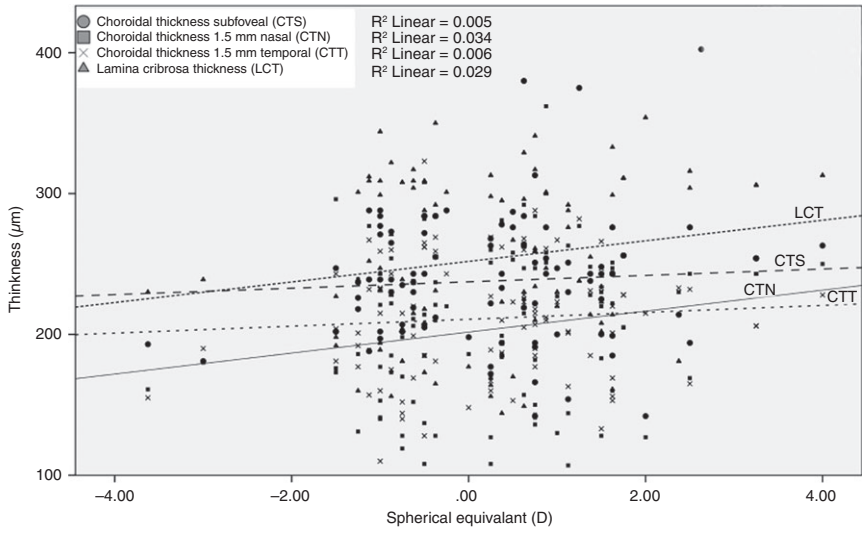


Fig. 3. The correlation (Pearson's) of spherical equivalent refractive error with LC or choroidal thickness in patients with PD and healthy control subjects.

thickness temporal; $p < 0.001$ for both). ROC curve analysis revealed that LC thickness could predict the presence of PD with a 88.6% sensitivity and 86% specificity (Youden index = 0.747; area under ROC curve = 0.923; 95% CI: 0.85–0.97; $p < 0.001$) and the threshold value was 247 μm (Fig. 4). The post hoc power analysis for LC and choroidal thickness revealed to be 97% and 95%, respectively.

Discussion

Studies of the prospective biomarkers of neurodegenerative disease in the eye have been conducted in recent years and promise hope.

In this study, we compared the LC and choroidal changes in PD patients with age-matched, neurologically healthy controls. The patients with PD showed a significant reduction in both LC and choroidal thicknesses. Use of the LC thickness as an option in the diagnosis and follow-up of neurodegenerative diseases such as glaucoma has been discussed. Studies conducted until recently have shown that changes in LC thickness are based on age and on the presence of glaucoma (Kotecha et al. 2006; Park et al. 2012).

According to post-mortem histopathological studies, LC thickness in normal people ranges between 345.4 μm and 555.9 μm; the average is 451.3 μm (Kotecha et al. 2006). In histologic sections, as tissue dyeing and fixation methods lead to swelling in the cells, LC thickness may be found to be greater compared to the thicknesses measured using *in vivo* methods (Kotecha et al. 2006).

It is interesting to note that the mean LC thickness measured in the patients with PD was significantly less than the control patients in our study ($p < 0.001$). It is also known that the inner limiting membrane of Elschnig is thick in optic discs with small cup, while it is thinner in large cups and this structural difference may lead to varying results during LC thickness measurements (Anderson 1970; Hayreh 1974). The ONH parameters and cup sizes did not showed significant difference between the recruited patients with PD and control subjects.

The evidence for the role of apoptosis in pathogenesis of PD has arisen (Copeland et al. 2005). This apoptotic process may give rise to cell death of the dopaminergic neurons of nigrostriatal pathway and ocular structures like retina, which is regarded as an extension of brain. Studies have demonstrated that the accumulation of proteinaceous inclusion bodies caused by misfolded and intracellular aggregation of proteins is a common feature in glaucoma and neurodegenerative diseases (McKinnon et al. 2002; Koronyo-Hamaoui et al. 2011). The apoptosis and dopaminergic neurodegeneration in Parkinson's

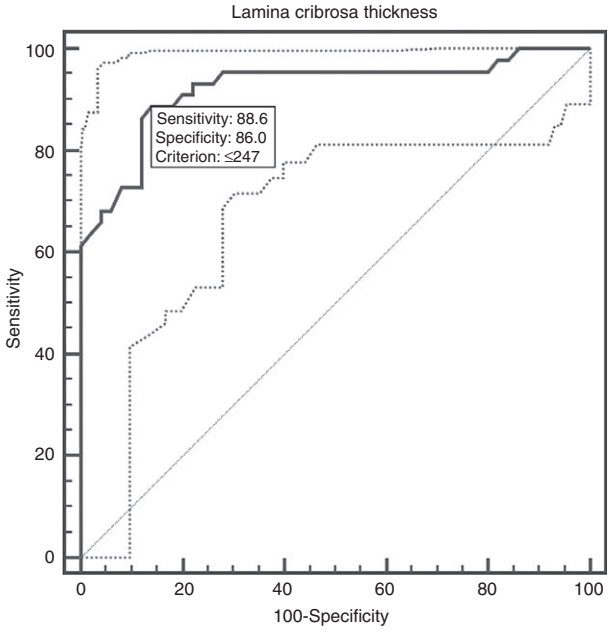


Fig. 4. The receiver operating characteristic (ROC) curve analysis of LC thickness for prediction of the presence of PD.

disease is shown to be associated with the accumulation of α-syn in both dopaminergic and non-dopaminergic areas of central nervous system. This evidence suggests an interesting link between dopaminergic neurodegeneration and Lewy body formation (Giraldez-Perez et al. 2014). As recently shown, a similar protein, called gamma-synuclein, accumulates in the myelination transition zone of astrocytes within the postlaminar region of glaucomatous eyes leading cell loss and LC thinning (Nguyen et al. 2011). The lamina cribrosa has an important role in maintaining the structural integrity of nerve fibres and in transmitting the neurotrophic factors sent from the lateral geniculate nucleus (LGN) to retinal ganglion cells (RGC). The presence of such deposits and damaged astrocyte functions in the PD may lead to structural changes in the LC similar to the changes in glaucoma. We hypothesized that the destruction of the LC during the disease course diminishes the transmission of neurotrophic factors from LGN to RGC leading a negative effect to the functions of RGCs. Thus, the damage to the LC may result in RNFL thinning which is previously shown in patients with PD (Harnois & Di Paolo 1990; Denis et al. 1993; Witkovsky 2004). To the best of our knowledge, until recently, LC has never been histologically or biochemically analysed in with Parkinson's disease. We believe that conducting *in vitro*/post-mortem analyses on the LC may give additional information about the presence of such abnormal protein deposits and about whether such deposits may inhibit the neurotrophic support in the LC in patients with PD.

In the present study, choroid thickness measured in the patients with PD at all regions showed statistically significant differences when compared with the control group ($p < 0.001$). Coscas et al. (2012) analysed emmetropic normal eyes in patients with a mean age of 58 ± 18.1 (ranging between 24 and 87 years) using the same OCT device used in this study (RTVue) and obtained similar choroid thicknesses at the same regions (261.3 ± 84.8 μm, 224.4 ± 90.8 μm and 243.5 ± 74.2 μm).

The role of the choroid in ocular and systemic disease is still under investigation. The findings regarding choroidal thickness show variabilities between reports. Several studies found that age and axial length are negatively correlated with both macular and peripapillary choroidal thickness (Fujiwara et al. 2009, 2012; Margolis & Spaide 2009; Ikuno et al. 2010; McCourt et al. 2010; Mwanza et al. 2011).

The diurnal variation of the choroid thickness has been reported in previous studies (Brown et al. 2009; Tan et al. 2012). Tan et al. (2012) reported a diurnal variation in choroidal thickness with a mean amplitude of 33.7 ± 21.5 μm in 12 healthy volunteers with a mean age of 30.0 ± 4.6. The highest mean choroid thickness was observed to be 372.2 μm at 9 a.m. The mean choroid thickness was found to decrease progressively at the subsequent time-points. In our study, the LC and choroidal thicknesses of all patients were measured between 9 a.m. and 10 a.m.

The alterations of choroidal thickness in neurodegenerative disease have also become a crucial topic in recent days. In their recent study, Gharbiya et al. (2014) compared the 42 eyes of 21 patients (mean age, 73.1 ± 6.9 years) with a diagnosis of Alzheimer's disease (AD) and 42 eyes of 21 age-matched control subjects (mean age, 70.3 ± 7.3 years) in a prospective, cross-sectional study. They found a significant reduction in choroidal thickness in patients with AD and concluded that choroidal thinning may represent an adjunctive biomarker for the diagnosis and follow-up of AD. Using spectral-domain optical coherence tomography (SD-OCT), Bayhan et al. (2015) also assessed chorioretinal thickness changes and evaluated the association between these structural changes and cognitive impairment in patients with AD. Compared with control subjects, the choroidal thickness measurements were significantly less than those in patients with AD, with the exception of the measurements at 3.0 mm temporal to the fovea.

Systemic hypertension and hypotension has also been described as affecting ocular perfusion pressure and choroidal thickness (Kim et al. 2012). PD is known to cause symptomatic orthostatic hypotension (20–58%) by affecting the peripheral nervous system and leading to disorders in the autonomic nervous system (Senard et al. 1997, 2001). In addition, the dopamine agonists used in the treatment of PD have been reported to cause hypotension (Senard et al. 1997). In our study, the inclusion criteria included regulated blood pressure, and although the patients with documented hypertension or hypotension were excluded from the study, blood pressure measurements were not performed at the time of OCT measurements.

Choroidal thinning in PD may be associated with hypoperfusion due to the irregularities in choroidal blood

flow and/or atrophic changes in the choroid. On the other hand, choroidal thinning may be the result of the decreased metabolic activity associated with atrophying RGCs; it may also be related to vascular changes resulting from levodopa therapy. Furthermore, irregularities in the choroidal blood flow may cause ischaemia in the ONH and RGCs blood circulation and may explain the damage in these structures in the patients with PD. However, further studies are needed to analyse changes in ocular and choroidal blood flow in patients with PD and to indicate the presence of a correlation between such changes and choroid thickness.

We did not find significant difference or relation between refraction and LC or choroidal thickness in PD and control group. In the study of Lee et al., they investigated topographical variation of macular choroidal thickness with myopia (Lee et al. 2015). The inclusion criteria covered patients with −6 to +6 dioptres of spherical equivalent and the mean age was 53.9 ± 12.9 years. They found that both axial length and refractive error did not correlate with choroidal thickness at all locations. Only the ratio between choroidal thickness temporal and choroidal thickness subfoveal (CTT/CTF) was negatively correlated with refractive error ($p = 0.012$) and positively correlated with axial length ($p = 0.031$) which only shows a relation between a thickened choroid, temporal to the foveal centre, with the severity of myopic components in normal eyes. Gupta et al. (2015) investigated the choroidal thickness and high myopia in young Chinese men. The inclusion criteria covered emmetropic (spherical equivalent between ± 0.50) patients and three groups of patients with spherical refractive error (between −6 and −8, −8 and −10 and <−10) (Gupta et al. 2015). They found that highly myopic eyes have significant thinner choroid and showed different distribution pattern, compared to emmetropes. These findings led us think that choroidal thinning pattern and refractive error correlation may not be significant in non-highly myopic (spherical equivalent between ± 6 dioptres) eyes. The refractive error and mean age of the recruited patients may influence this correlation. Also, the small number of subjects in the study may be the reason not to be able to reach the statistical significance for that correlation.

Variations in the devices used in different studies, as well as in the level of the signal strength of these devices, need to be taken into consideration with respect to interpretation of RNFL and choroidal thickness measurements. Cheung et al. (Cheung et al. 2015) mentioned that underestimation of RNFL or choroidal thickness due to reduced signal strength can amplify the margin of error in RNFL measurements. Therefore, in this study, maintaining full signal strength index values (>50) during scanning was a priority. Patients and controls with low-quality OCT scans were excluded.

One of the major limitations of this study is the small sample size. The study started with a pool of 65 potential participants; however, the pool shrunk to 47 after the exclusion criteria were met and un-co-operated patients to OCT measurements were eliminated. The other limitations included not revealing orthostatic hypotension and smoking habits.

In conclusion, our study reveals that despite normal IOP rates, there were structural changes (thinning) in the LC and choroid of the patients with PD. To our knowledge, this is the first study comparing *in vivo* anatomical changes of the choroid and the LC via an OCT device and analysing *in vivo* neuronal damage in patients with PD. The *in vivo*, non-invasive assessment of the choroid and the LC with EDI-OCT may provide useful information for the diagnosis and follow-up of patients with PD, correlated with disease duration but not with the disease severity. Further *in vitro* and post-mortem studies are needed to confirm these structural changes in patients with PD.

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ME, AT and SYB design the study; ME and SYB conducted the study; ME, SYB, HC, DS and ENTE performed collection of the data; ME performed the management; ME and SYB performed analysis and interpretation of the data; ME, SYB and OS prepared and ME, EC, AT, OS and ENTE reviewed the study.