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Dynamics of retinal changes in early-stage Parkinson's disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by motor symptoms, with emerging evidence suggesting retinal pathology, particularly in the ganglion cell-inner plexiform layer (GCIPL), detectable via optical coherence tomography (OCT). This study aimed to characterize early retinal dynamics in PD using OCT. We conducted a prospective one-year longitudinal multicenter study involving 53 early-stage PD patients with a disease duration of 5 years or less and 52 controls. The participants underwent retinal spectral-domain OCT, primary visual function and cognitive examinations. We examined baseline retinal measures and short-term longitudinal differences between groups via linear mixed effects models. In PD patients, the baseline GCIPL thickness in central regions was increased by up to 4 µm, and the rate of thinning in the parafoveal GCIPL was −0.61 [0.29] µm/year faster over a one-year follow-up period than in controls in the 2- to 3-mm ring ($p=0.039$). In PD patients, greater central GCIPL thickness was associated with poorer contrast sensitivity and reduced performance on the Farnsworth D15 color vision test. It also predicted subsequent thinning in both the GCIPL (2- to 3-mm ring) and the inner nuclear layer (2- to 5-mm rings). However, this increased thickness was not linked to prevalent or progressive motor or cognitive manifestations. In conclusion, this study provides the first detailed topographical description of early retinal dynamics in PD patients, revealing increased central GCIPL thickness and accelerated parafoveal GCIPL thinning in PD. However, the macular region shows complex and variable dynamics among PD patients, but these changes precede detectable progression in clinical scales.

Keywords Parkinson's disease, Retina, Optical coherence tomography, Ganglion cell-inner plexiform layer, Fovea

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Introduction

Parkinson's disease (PD) is characterized primarily by motor symptoms due to dopaminergic neurodegeneration in the brain. However, emerging evidence indicates that early pathological changes may also occur in the retina, reflecting neurodegenerative processes [1, 2]. Optical coherence tomography (OCT) has been instrumental in revealing these retinal alterations, providing valuable insights into its potential usefulness as a biomarker for PD [2, 3].

Our previous research demonstrated that ganglion cell–inner plexiform layer (GCIPL) thickness in the parafoveal region was reduced in PD patients with visual dysfunction [1] and that this reduction predicted cognitive decline over a three-year period [2]. Furthermore, we observed that accelerated thinning of the GCIPL occurs before significant cognitive decline, indicating that more rapid GCIPL thinning is an early predictor of subsequent accelerated cognitive deterioration [3]. Although visual function is often regarded as a more effective predictor of cognitive performance than OCT measurements are [4], PD-related visual impairments tend to be mild and may not present as overt symptoms [5]. Additionally, assessing visual function requires multiple modalities and formal clinical tests, which are not always routinely performed, and the cutoff values for these tests to serve as reliable biomarkers for PD are not well established.

Effective biomarkers should be practical, rapidly acquired, and applicable to the general population. In this context, OCT measurements provide a noninvasive and accessible method for assessing retinal structural changes. Understanding the dynamics of these retinal changes in the early stages of PD is essential for identifying prognostic biomarkers that can predict disease progression and stratify patients on the basis of their risk of poor outcomes. While existing studies have investigated retinal thickness in prodromal [6], de novo [7, 8], and early-stage [9–12] PD patients, most of these studies are cross-sectional and rely on whole macular thickness or volume measurements. This approach may obscure subtle changes in specific retinal areas, which could be discernible only through detailed partitioned analysis. Consequently, our understanding of the sequential and localized nature of retinal changes over time in the early stages of the disease remains limited. To effectively utilize OCT as a biomarker and to enhance our understanding of how retinal changes are related to disease progression and clinical outcomes, it is essential to conduct a detailed topographical analysis of the macula and establish correlations between OCT findings and clinical variables. However, comprehensive longitudinal studies focusing on detailed retinal changes in early-stage PD and their relationship with disease progression are still largely lacking.

Therefore, in this study, we aimed to analyze the dynamics of retinal changes in the early stages of PD and their correlation with visual alterations and disease progression over a short-term period. This objective will be pursued through a detailed topographical analysis of the macula and the optic nerve head. By filling the existing research gaps, we seek to establish a robust foundation for leveraging OCT as a reliable tool for the early diagnosis and ongoing monitoring of PD, ultimately enhancing our ability to predict disease progression and tailor interventions effectively.

Materials and methods

Study design and participants

We conducted a one-year longitudinal multicenter study involving 53 patients with PD and 52 controls who were prospectively recruited from five tertiary hospitals in The Basque Country, Spain (Hospital Universitario Cruces, Hospital Universitario Araba, Hospital Urduliz Alfredo Espinosa, Hospital Universitario Galdakao-Usansolo, and Hospital Universitario Donostia), within their respective neurology departments between October 2020 and July 2023 (Fig. 1). PD patients were diagnosed according to the Parkinson's UK Brain Bank criteria and were specifically selected if they were in the early stages of the disease, with a duration of less than 5 years. PD patients with known genetic mutations identified during routine clinical testing [3] were excluded. Control participants were healthy volunteers recruited from Hospital Universitario Cruces (spouses or relatives of PD patients) and the retirees association of Barakaldo (Bizkaia, Spain). Controls were excluded if they had more than one first-degree relative with PD or symptoms suggestive of the disease.

At baseline, all participants underwent a comprehensive screening to exclude potential confounding factors that might affect clinical outcomes or retinal OCT measurements, as detailed previously [2, 3]. This screening included a thorough questionnaire on comorbidities, an ophthalmological examination, and adherence to the OSCAR-IB criteria [13] (Supplementary Methods).

The study was approved by Comité Ético de Investigación Clínica – Euskadi (study code: PI2020025), and all participants provided written informed consent.

Demographics and PD-related variables

We recorded the age, sex, and years of education of all the participants. For PD patients, we also documented disease duration at baseline, the Hoehn & Yahr (H&Y) stage, the Unified Parkinson's Disease Rating Scale (UPDRS) score, and the L-DOPA equivalent daily dose (LEDD) at each visit.

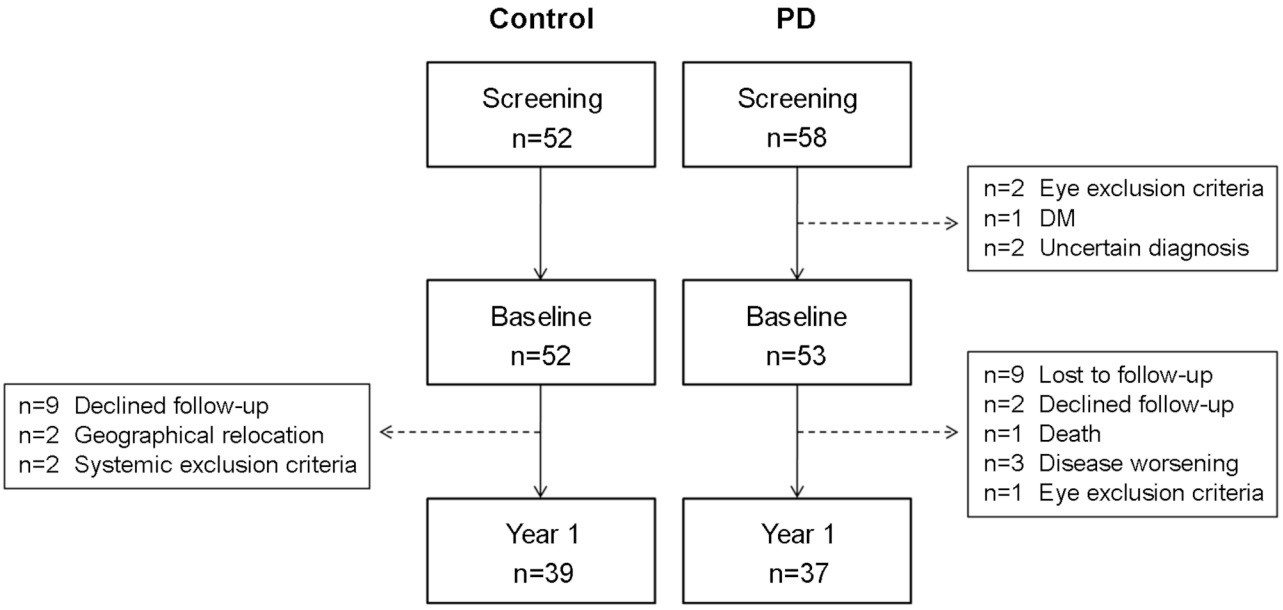

Fig. 1 Study flowchart. Description of the follow-up design of the study participants. Lost to follow-up with reasons in each stage is represented with dashed arrows. *Abbreviations*: DM, diabetes mellitus; PD, Parkinson's disease

Primary visual function and visual cognition

Primary visual function was assessed binocularly via Precision Vision Visual Acuity Test (PVVAT) digital software (Precision Vision, Woodstock, IL) and best-corrected refraction. High-contrast and low-contrast visual acuity were recorded as the total number of letters correctly identified at 4 m. Contrast sensitivity was measured by the number of correctly identified letters and the lowest contrast percentage that could be discerned. Color vision was evaluated via the Farnsworth D-15 test, and the total color difference score (TCDS) was calculated for each participant. Note that a higher contrast sensitivity percentages and higher TCDS scores indicate poorer visual function (Supplementary Methods).

General cognition was assessed via the Montreal Cognitive Assessment (MoCA). Additionally, three visual cognition domains were evaluated through a combination of neuropsychological tests. Visual perception was measured with the Benton Line Orientation Judgment (BLOJ) test and the Visual Object and Space Perception (VOSP) tests, including number location and cube analysis. Visual attention was assessed via the Salthouse Perceptual Comparison Test (SPCT), the Symbol Digit Modality Test (SDMT), and the Trail Making Test, Part A (TMT-A). Visual executive functions were evaluated with the Trail Making Test, Part B (TMT-B), the Modified Wisconsin Card Sorting Test, and the Stroop Word-Color Test. The mean and standard deviation (SD) of each test at baseline were used to calculate z scores at different time points. Composite scores for each visual cognitive domain were derived as the average of the z scores for the corresponding tests within each domain. A total of 38 PD patients and 45 controls were assessed with these neuropsychological tests.

Optical coherence tomography

OCT examinations were performed via spectral-domain OCT (Spectralis, Heidelberg Engineering, Germany), adhering to a standardized acquisition protocol previously detailed [1–3]. Briefly, macular volumetric measurements were obtained with 25 horizontal B-scans, each consisting of 512 A-scans covering a 20° region and 49 slices per B-scan. Peripapillary nerve fiber layer (pRNFL) OCT scans were conducted via a 3.5 mm circular scan manually centered on the optic nerve, with 100 images per scan. Follow-up images of the same eye were acquired via the Spectralis follow-up function.

All OCT scans included in the study met the OSCAR-IB criteria [13]. Retinal layer thicknesses were calculated using a feature extraction pipeline via the RETIMAT toolbox [14, 15]. Thickness measurements were averaged point-by-point across the central circular foveal area with a 1-mm diameter and five concentric rings centered on the fovea, with each successive ring having a diameter 1 mm greater than the previous one (Fig. 2A). Measurements from both eyes were averaged, and the results are reported following the APOSTEL 2.0 guidelines [16].

Statistical analysis

Statistical analyses were performed via RStudio (version 2022.07.0) from May 2024 to July 2024. Baseline characteristics were described using absolute and relative frequencies for categorical variables and means and standard deviations for quantitative variables. Comparisons

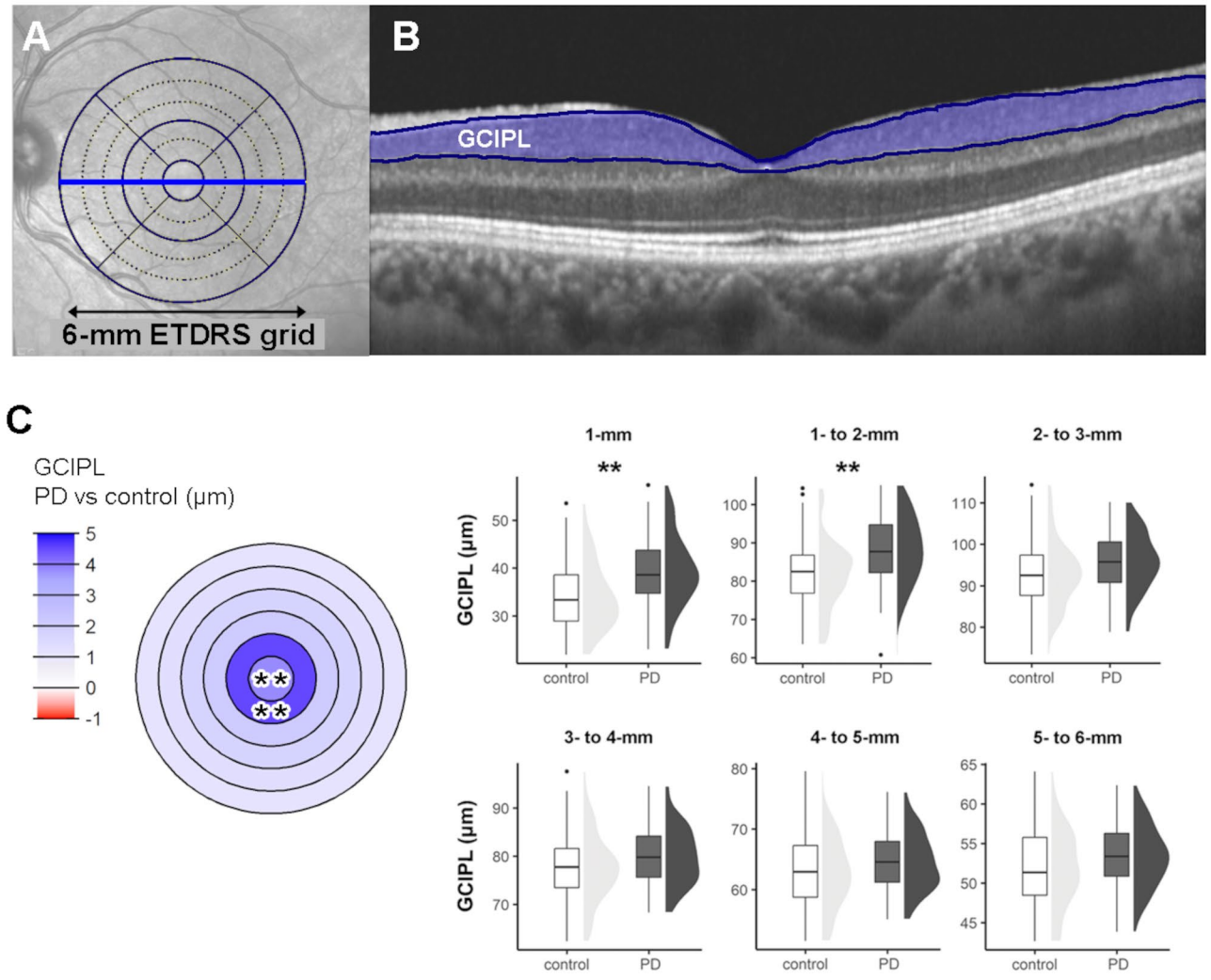

Fig. 2 Baseline retinal differences between PD patients and controls. (**A**) A funduscopic SLO image with superimposed macular parcellation into concentric rings centered on the fovea. Continuous lines represent the ETDRS grid annuli (with diameters of 1-mm, 3-mm, and 6-mm), while dashed lines indicate the additional macular subdivisions introduced in this study, dividing the macula into concentric circular zones spaced 1-mm apart. The blue line represents the region where the B-scan shown in **B** was acquired. (**B**) A horizontal OCT B-scan passing through the fovea. The GCIPL layer is highlighted in blue. (**C**) The circular plot on the left illustrates estimated differences in GCIPL thickness between PD patients and controls at baseline. The combined boxplots and half violin plots on the right depict the distribution of the mean GCIPL thickness across different macular regions for each group. Statistically significant differences are indicated with asterisks (**$p < 0.01$)

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; GCIPL: ganglion cell–inner plexiform layer complex; OCT, Optical Coherence Tomography; SLO, Scanning Laser Ophthalmoscopy

between groups were conducted via the chi-square test or Fisher's exact test for categorical variables and the t test or Wilcoxon test for quantitative variables, depending on the data distribution. Normality was assessed with the Shapiro–Wilk test. The associations between baseline continuous variables were assessed with linear regression models. Longitudinal data were analyzed with linear mixed models (LMMs) using the *lme4* and *lmerTest* packages, which can handle missing data. LMMs included fixed effects for time to follow-up, group, and the interaction term between time and group. We adjusted for the effects of age at baseline, sex, and well-controlled hypertension status (yes/no) in all regression analyses. Models with cognitive outcomes included an additional adjustment for years of education. Separate LMMs were then fitted for the PD and control groups to estimate annualized changes in the outcome variables. LMMs adjusted for the PD group also included LEDD as fixed effect. PD patients were subsequently categorized into retinal thickness tertiles. The tertile cutoffs were selected on the basis of the baseline GCIPL thickness in the central 2-mm diameter area. PD patients above the 66th percentile were assigned to the highest thickness tertiles (> 79.8 μm), and patients below the 33rd percentile were

allocated to the lowest tertile (< 72.9 μm). Owing to the exploratory nature of the study and the multiple aims being investigated, no sample size calculation was predetermined. The significance level was set at $\alpha = 0.05$.

Results

Subjects and clinical characteristics

The baseline characteristics of the study participants are summarized in Table 1. The mean [SD] age of the individuals in the control group was 64.1 [7.8] years, which was comparable to the 64.3 [7.6] years in the PD group ($p = 0.889$). There was a significantly greater proportion of females in the control group than in the PD group (64.7% vs. 35.3%, $p = 0.005$). Both groups had similar levels of education. The PD group presented a mean [SD] disease duration of 2.5 [1.4] years at baseline and an UPDRS III score of 21.5 [11.3]. Approximately 35% had unilateral motor affection, and 10% presented postural instability, according to the H&Y scale. At recruitment, 19 out of 53 PD patients (35.8%) were not on levodopa therapy, of whom 5 were not receiving dopamine agonist therapy and 3 were completely untreated.

PD patients and controls were comparable in terms of refractive error (mean spherical equivalent: PD, 0.9 ± 1.3 D; controls, 0.7 ± 1.4 D, $p = 0.469$) and visual acuity as measured with logMAR (PD, -0.11 ± 0.09; controls, -0.10 ± 0.08, $p = 0.668$; Supplementary Table S1). However, PD patients demonstrated significantly reduced performance in low-contrast visual acuity test and contrast sensitivity assessment. In terms of visual cognition, while the PD group did not exhibit significant impairment in global cognition at baseline compared with the control group, they displayed deficits in visual attention and visual executive function but not in visual perception (Table 1).

Table 1 Descriptive statistics of baseline outcomes

		Control		PD		*p*
		n	**Mean (SD)**	***n***	**Mean (SD)**	
Demographics						
Age (years old)		52	64.1 (7.8)	53	64.3 (7.6)	0.889
Sex, *n* (% females)		52	33 (64.7)	53	18 (35.3)	0.005 **
Education years		52	11.6 (3.0)	53	11.1 (3.5)	0.900
Hypertension (*n*, %)		52	24 (26.3%)	53	27 (30%)	0.706
Disease-related variables						
Disease duration (years)			NA	53	2.5 (1.4)	NA
UPDRS I			NA	49	1.8 (1.6)	NA
UPDRS II			NA	49	7.5 (1.6)	NA
UPDRS III			NA	51	21.5 (11.3)	NA
UPDRS IV			NA	50	2.3 (2.8)	NA
LEDD (mg)			NA	53	395.3 (260.2)	NA
H&Y stage (*n*, %)	1				16 (30.2%)	
	1.5				2 (3.8%)	
	2				25 (47.2%)	
	2.5				2 (3.8%)	
	3				4 (7.5%)	
Primary visual outcomes						
High Contrast VA (no. of letters)		50	44.6 (3.6)	52	43.4 (4.8)	0.136
Low Contrast VA (no. of letters)		50	29.8 (6.0)	52	25.0 (9.6)	0.003 **
CS (no. of letters)		50	72.5 (10.6)	52	66.9 (17.7)	0.008 **
CS, contrast % [§]		50	1.04 (0.28)	52	1.56 (1.18)	0.006 **
Farnsworth D-15 [§]		48	127.0 (17.6)	50	142.9 (35.7)	0.008 *
Cognitive outcomes						
MoCA		49	24.4 (3.0)	51	23.2 (3.7)	0.088
Visual Attention ǂ		45	0.16 (0.81)	38	-0.19 (0.89)	0.041*
Visual Perception ǂ		45	0.08 (0.81)	37	-0.07 (0.70)	0.077
Visual Executive functions ǂ		45	0.18 (0.69)	38	-0.18 (0.84)	0.010 *

Data are represented as mean (SD) unless otherwise specified. The number of correctly identified letters was recorded for visual acuity and contrast sensitivity testing. *p*-values for primary visual and cognitive outcomes were extracted from group effects in LMMs. These models were adjusted for age at baseline, sex and the hypertension status for primary visual outcomes, and for age at baseline, sex, hypertension status, and years of education for cognitive scores. [§] Higher values indicate worse outcome. ǂ Composite scores of visual cognitive functions in z-score

Statistical significance: *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. *Abbreviations*: CS, contrast sensitivity; LEDD, levodopa-equivalent daily dose; H&Y, Hoenh&Yahr scale; MoCA, Montreal Cognitive Assessment; NA, not applicable; VA, visual acuity

Longitudinal clinical changes

The 1-year follow-up visit was completed by 37 PD patients and 39 controls (70.5% of participants), with mean (SD) follow-up times of 1.02 (0.07) and 1.02 (0.05) years, respectively (Supplementary Table S2). The time × group interaction in the LMM did not significantly affect global cognitive decline over the 1-year period between PD patients and controls. No significant differences were observed in the rate of change in primary visual function or visual cognitive domains, except for high-contrast visual acuity, which worsened at a faster rate in PD patients than in controls (β [SE] = -1.7 [0.7] letters/year, $p = 0.023$) (Supplementary Table S3). The UPDRS III score did not significantly increase over the 1-year period, likely due to the significant increase in LEDD (β [SE] = 89.8 [20.9] mg/year, $p < 0.0001$).

Early retinal changes in PD

The results from the fitted LMMs revealed significant group differences in GCIPL thickness at baseline. Specifically, significant differences were observed in the central macular region, with PD patients exhibiting a thicker GCIPL layer than controls did in the central 1-mm disc region (β [SE] = 3.8 [1.4] µm, $p = 0.007$) and the adjacent 1- to 2-mm parafoveal ring (β [SE] = 4.5 [1.7] µm, $p = 0.010$). These findings indicate that, after controlling for age at baseline, sex and hypertension status, the central GCIPL thickness is about 4 µm greater in early PD patients than in controls (Fig. 2C). No other significant differences were found at baseline between the groups in the regional macular layer analysis (Supplementary Table S4).

Longitudinal analysis in PD patients consistently revealed a significant decrease in GCIPL thickness in concentric rings from 2- mm to 6- mm (1-mm apart), with decreases ranging from – 0.88 µm/year to -1.10 µm/year. In contrast, the controls revealed a nonsignificant decrease in the GCIPL layer, ranging from – 0.18 µm/year to -0.30 µm/year, depending on the region. The LMM time × group interaction term was significant for the 2- to 3-mm ring (β [SE] = -0.61 [0.29] µm/year, $p = 0.039$) and nearly significant for the adjacent 3- to 4-mm ring (β [SE] = -0.60 [0.30] µm/year, $p = 0.052$) (Table 2).

Despite the absence of significant baseline differences in pRNFL thickness (β [SE] = 2.5 [1.8] µm, $p = 0.183$), the rate of pRNFL thinning was greater, although not significantly, in PD patients than in controls (time × group, β [SE] = -0.83 [0.42] µm/year, $p = 0.053$).

Association of baseline foveal GCIPL thickness with clinical measures

Given that we observed specific foveal and near parafoveal GCIPL thickening in PD patients, we assessed the associations between these measurements and baseline visual, cognitive, and motor scores. In linear regression models adjusted for age at baseline, sex, hypertension status and LEDD, statistically significant associations were found between color vision and both foveal (β [SE] = 1.6 [0.7], $p = 0.016$) and near parafoveal (β [SE] = 1.6 [0.6], $p = 0.013$) GCIPL thicknesses. No significant associations were found between foveal or near parafoveal GCIPL thickness at baseline with UPDRS or H&Y scores. Further adjusting for years of educations, revealed that a lower parafoveal (1- to 3-mm ring) GCIPL thickness was significantly associated with a lower MoCA score (β [SE] = 0.26 [0.10], $p = 0.011$), as previously reported.

Central GCIPL capturing longitudinal dynamics in PD patients

To explore the predictive value of central GCIPL thickening at baseline, we computed the weighted average thickness of the GCIPL in the foveal and adjacent parafoveal regions. Our analysis revealed that PD patients in the upper tertile of central GCIPL thickness at baseline did not have short-term yearly changes in the UPDRS score or cognitive decline, as determined by the LMM, but displayed decreased baseline contrast sensitivity (no. of correct letters, β [SE] = -12.7 [4.7] µm/year, $p = 0.009$). Also, a significant association was found between greater baseline central GCIPL thickness and greater subsequent GCIPL thinning in the parafovea compared to PD patients in the lowest tertile (Fig. 3). Specifically, PD

Table 2 Linear mixed-model effects estimate of the effect of time on the thickness of ganglion cell-inner plexiform complex (GCIPL)

	PD			Control			Time x group interaction		
	β^a	SE	*p*	β^a	SE	p^1	β^b	SE	*p*
GCIPL 1-mm disc	0.38	0.33	0.258	-0.22	0.23	0.334	0.38	0.34	0.274
GCIPL 1- to 2-mm	-0.21	0.33	0.536	-0.19	0.24	0.447	0.02	0.36	0.956
GCIPL 2- to 3-mm	-1.10	0.24	< 0.001 ***	-0.18	0.20	0.384	-0.61	0.29	0.039 *
GCIPL 3- to 4-mm	-1.00	0.26	< 0.001 ***	-0.23	0.21	0.293	-0.60	0.30	0.052
GCIPL 4- to 5-mm	-0.88	0.24	0.001 **	-0.27	0.17	0.116	-0.45	0.26	0.094
GCIPL 5- to 6-mm	-0.90	0.20	< 0.001 ***	-0.30	0.19	0.130	-0.35	0.27	0.204

β^a represents the within-group estimated annualized change in thickness within each group per GCIPL region, whereas β^b represents the estimated increase or decrease in the annualized change in thickness in PD patients compared to controls. All models were adjusted for age at baseline, sex and hypertension status. Analyses within the PD group were further adjusted for LEDD. Time indicates the time since baseline visit. Significant *p*-values are represented with an asterisk (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). *Abbreviations*: GCIPL, ganglion cell-inner plexiform complex; PD, Parkinson's disease; SE, standard error

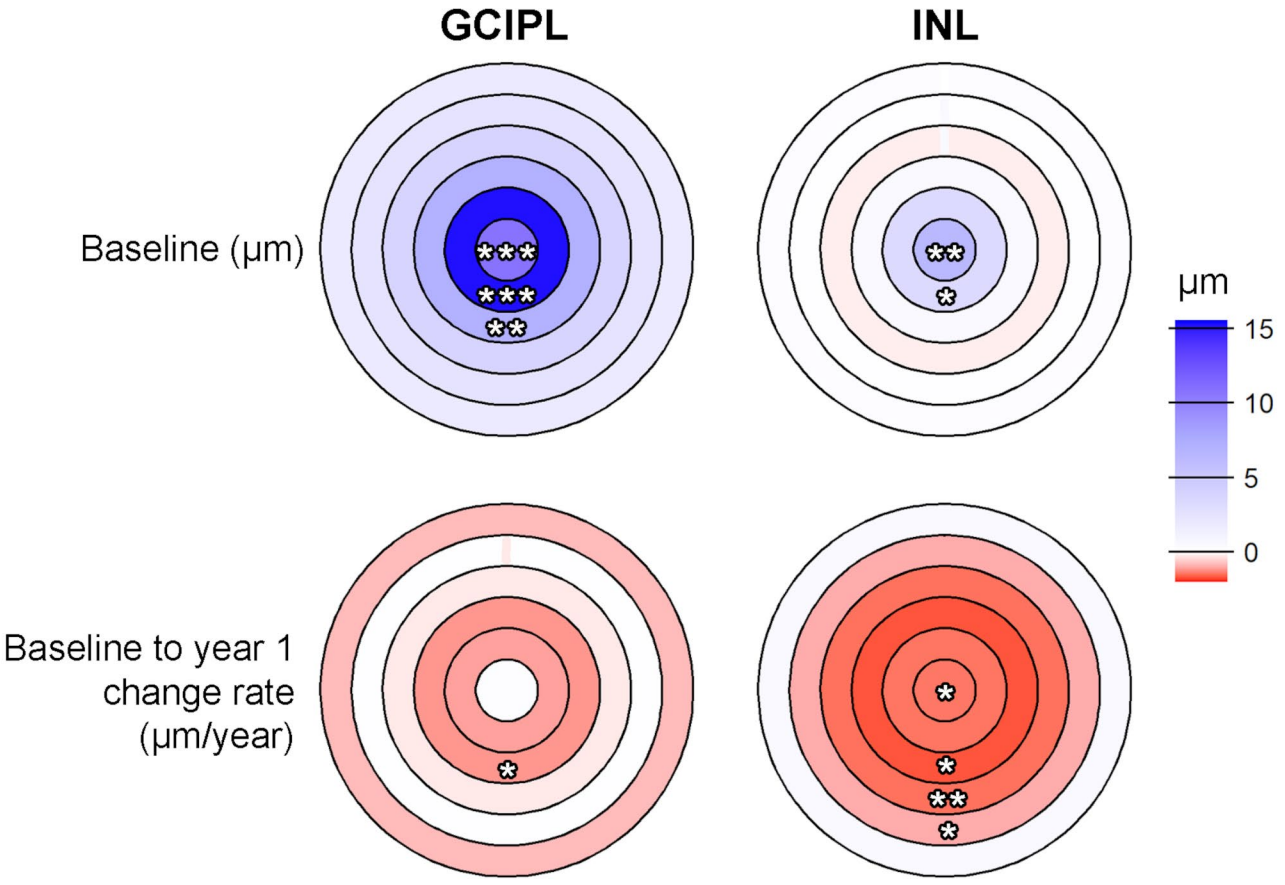

Fig. 3 Linear mixed-effects model estimates of baseline and longitudinal retinal thickness. PD patients were divided into tertiles according to their baseline central GCIPL thickness, and PD patients in the upper and lower tertiles were compared. The parameter estimates from linear mixed-effects models show the difference in thickness between the upper and lower tertiles at baseline (upper panels) and the rate of change over the 1-year follow-up period (lower panels). Significant *p*-values are indicated by asterisks (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$)
Abbreviations: GCIPL: ganglion cell–inner plexiform layer complex; INL, inner nuclear layer; PD, Parkinson's disease

patients in the highest central GCIPL thickness tertile experienced a significant annualized decrease in GCIPL thickness in rings beyond the 2-mm ring, whereas those in the lowest tertile exhibited nonsignificant yearly changes in these regions. The interaction term was significant for the 2- to 3-mm parafoveal (β [SE] = -1.17 [0.48] μm/year, $p = 0.022$) ring (Fig. 3 and Supplementary Table S5).

Additionally, we observed significantly greater thinning of the inner nuclear layer (INL) in PD patients in the upper central GCIPL tertile than in those in the lower tertile (Fig. 3 and Supplementary Table S5). No differences were observed in pRNFL changes over time based on initial central GCIPL thickness.

Discussion

In the present work, for the first time, we report the existence of foveal thickening of the GCIPL in early-stage Parkinson's disease. Notably, this retinal abnormality was not only associated with poorer contrast sensitivity and color vision but also predicted the progression of parafoveal thinning of the inner retinal layers after 1 year of follow-up. Intriguingly, initial foveal GCIPL thickening was not associated with prevalent or progressive pRNFL thinning or motor or cognitive manifestations in the short term. These results support the hypothesis that structural alterations of the macula in PD occur early and before clinical progression of the disease is evident. While the dynamics of macular changes in PD patients are spatially and temporally complex and variable across patients, pRNFL thinning seems to progress more uniformly in this disease.

Previous studies that evaluated retinal neurodegeneration in PD patients with OCT have suggested that retinal changes are primarily restricted to the inner layers of the retina. A recent meta-analysis investigating macular changes in PD patients confirmed thinning of the GCIPL compared with controls in the parafoveal and perifoveal regions of the macula [17]. However, this study did not specifically investigate the central foveal GCIPL

thickness. This omission may be due to limitations in the OCT technology used, as some devices do not provide this specific measurement, or because certain studies focused solely on whole retinal thicknesses without segmenting the central retina. Despite these gaps, a thorough review of the limited literature that does report inner retinal layer thickness in the central fovea suggests that GCIPL thickness may actually be increased in PD patients compared to controls [1, 18, 19]. Notably, studies that have reported changes in the central fovea often found heightened thickness in PD patients, though this was not universally observed. In some cases, particularly among studies involving drug-naïve patients [20, 21], no significant differences were noted, indicating that PD-related medications might contribute to retinal changes.

Retinal OCT studies in prodromal, *de novo*, or early-stage PD remain scarce, with most focusing primarily on overall macular thickness rather than detailed topographical analyses [6–12]. Recently, a large-scale study reported reduced thicknesses of the GCIPL and INL in the parafoveal region of PD patients, with thinner layers being associated with an increased risk of incident PD [22]. Indeed, GCIPL thickness in the parafoveal region has been identified as a potential biomarker of PD progression, as its reduction is linked to poorer visual outcome [1] and an increased risk of cognitive decline [2]. The progression pattern may start in the inferior sector of the parafoveal GCIPL, gradually extending to other parafoveal sectors, and eventually reaching the perifoveal regions of the GCIPL [23]. However, these studies have not specifically examined the GCIPL thickness in the central retina in early stages and its association with subsequent retinal changes, limiting their ability to capture longitudinal dynamics. As a result, they may have missed early increases in central retinal thickness, which could precede the later reductions in GCIPL thickness typically observed. In our study, we confirmed an increased rate of parafoveal GCIPL thinning in PD patients in the short term, a phenomenon also observed in cohorts with longer follow-up periods [2, 3]. Importantly, retinal changes may not be uniform across all PD patients and are likely influenced by disease phenotype. We previously showed that GCIPL thinning is more pronounced in subsets of PD patients with more aggressive phenotypes or worse cognitive prognoses [2, 3]. In the current study, we found that greater increases in central GCIPL thickness were associated with more pronounced parafoveal GCIPL atrophy over the follow-up period, further emphasizing the importance of examining central retinal changes as early indicators of PD progression.

The underlying mechanisms driving the observed increase in central GCIPL thickness remain complex and not fully understood. Interestingly, the areas of increased GCIPL thickness and subsequent GCIPL and INL thinning are adjacent but do not overlap, adding complexity to our understanding. Several hypotheses could account for this phenomenon. One possibility is neuroinflammation; animal studies have indicated that retinal thickness can increase due to neuroinflammation before neural degeneration occurs [24]. Furthermore, neuroinflammation plays a critical role in the progression of neurodegeneration in PD, with evidence suggesting that inflammatory processes and immune system interactions contribute significantly to disease onset and progression [25, 26]. While the types of cells and fibers within the GCIPL do not differ between the fovea and parafovea, these regions exhibit key differences that may contribute to their differential response under pathological conditions. For instance, the fovea's high metabolic demand and its dependence on surrounding capillaries make it particularly vulnerable to metabolic stress, oxidative damage, and neuroinflammation. These factors could make the fovea particularly susceptible to pathological stressors, including early inflammation. This interpretation remains speculative but underscores the need for further investigation into the central retinal changes in PD. In addition to neuroinflammation, vascular changes may also play a significant role. We previously reported a reduced foveal avascular zone (FAZ) in PD patients without cognitive impairment, with a smaller FAZ correlated with increased GCIPL thickness [14]. This suggests that early vascular changes, such as an increased superficial vascular complex, might contribute to the observed increase in central GCIPL thickness. Indeed, neuroinflammation is known to promote vascularization [27], and it is likely that these two processes interact in complex ways, contributing to the observed remodeling of the foveal structure. Furthermore, subclinical inflammation in the central retina could lead to early GCIPL thinning in parafoveal regions, where dopaminergic cells are particularly vulnerable to damage [28]. In PD, dopamine depletion around the fovea is well documented, with postmortem studies revealing reduced dopamine concentrations in the retina [29–31]. These vascular and inflammatory processes may work in tandem to explain the observed changes in GCIPL thickness in both the central and parafoveal retina. However, these hypotheses require further investigation through both basic and clinical research to better understand the precise mechanisms involved.

The global cognition in our early PD cohort was comparable to that in controls at baseline and did not show differential progression at the one-year follow-up, indicating that there was no cognitive decline in this cohort over the examined time frame. However, visual dysfunction was evident, particularly in primary functions such as low contrast visual acuity, contrast sensitivity and color vision, but not in high-contrast visual acuity.

While high-contrast visual acuity may be impaired in PD patients at later stages, early-stage symptoms commonly include contrast sensitivity alterations [32, 33]. These findings are consistent with the work of Oxtoby et al. [34], who used a novel event-based model to estimate the sequence of clinical and neurodegenerative events in PD. These authors concluded that patients at risk for dementia exhibited early deficits in contrast sensitivity, color vision, and visual cognition. However, they observed retinal thinning at later stages, but their study, which utilized global measurements of GCL and IPL thickness and volumes, might have missed subtler early changes owing to the lack of specific topographical analysis of the macula. In our study, we observed that early retinal alterations, such as increased central GCIPL thickness, were associated with primary visual deficits, including contrast sensitivity and color vision, but not with visual cognition. This finding suggests the presence of additional visual pathway alterations beyond the retina. Alternatively, there may be subtle retinal changes contributing to these deficits, such as synapse loss or microstructural alterations below the cellular level [35], changes that might be too subtle to be detected with the current OCT resolution. While retinal OCT may capture early events, its current resolution limits its effectiveness—a limitation that future technological advancements could address.

This study has several limitations. First, the follow-up period may be insufficient to capture the full progression of retinal changes and their relationship with clinically relevant parameters in PD patients. Second, the sample size could be increased to increase the robustness of the findings. Third, owing to the exploratory nature of the analyses, no correction for multiple comparisons was applied. Despite these limitations, our study provides the first description of early retinal dynamics in PD patients, laying the groundwork for further investigation into the use of retinal OCT as a diagnostic biomarker for PD and its relationship with disease progression.

Conclusion

Our results indicate that early retinal alterations in PD patients, particularly in the macular region, exhibit complex and variable dynamics. Interestingly, we observed an increase in central GCIPL thickness, which may represent an early retinal alteration PD. The complex interplay between increased central GCIPL thickness and subsequent thinning of inner retinal layers in the parafoveal and perifoveal regions shows differential progression patterns within PD subjects, whereas pRNFL thinning follows a more consistent trajectory across the cohort. Future studies with longer follow-up periods and the inclusion of OCT-A are needed to validate these findings and to further investigate the clinical implications of retinal changes.

Abbreviations

BLOJ	Benton Line Orientation Judgmenet
FAZ	Foveal Avascular Zone
GCIPL	Ganglion cell-inner plexiform layer
H&Y	Hoehn & Yahr scale
INL	Inner nuclear layer
LEDD	Levodopa equivalent daily dose
LMM	Linear mixed-effect model
MoCA	Montreal Cognitive Assessment
OCT	Optical Coherence Tomography
PD	Parkinson's disease
pRNFL	Peripapillary Nerve Fiber Layer
PVVAT	Precision Vision Visual Acuity Test
SMDT	Symbol Digit Modality Test
SPCT	Salthouse Perceptual Comparison Test
TCDS	Total color difference score
TMT-A	Trail Making Test, Part A
TMT-B	Trail Making Test, Part B
UPDRS	Unified Parkinson's disease Rating Scale
VOSP	Visual Object and Space Perception test

Supplementary Information

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Supplementary Material 1

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Author contributions
AMG and IG contributed to the conception and design of the study. IG, JAU, and JRM obtained funding. STP, EBM, RVP, BRB, JB, JSM, PAD, IC, RDP, MA, BTM, OSA, JAU, and JRM contributed to the data collection. The data were processed by DRB. Data analysis was performed by AMG, and AMG, IRA, JCGE, JAU, JRM and IG contributed to the interpretation of the data. AMG and IG prepared the figures. The first draft of the manuscript was written by AMG, and all coauthors provided critical revision of the manuscript for important intellectual content. All the authors read and approved the final manuscript.

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Data availability
The datasets generated and/or analysed during the current study are not publicly available due ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by Comité Ético de Investigación Clínica – Euskadi (study code: PI2020025), and all participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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