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Correlation of ganglion cell complex thinning with baseline deep and superficial macular vessel density in glaucoma

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Synopsis/Précis

Lower baseline superficial parafoveal vessel density (VD), but not deep VD, correlated with faster parafoveal ganglion cell complex (GCC) thinning in glaucoma. Superficial macular VD may help predict central macular GCC thinning and glaucoma progression.

ABSTRACT

Background/Aims: To investigate the relationship between ganglion cell complex (GCC) thinning and baseline deep and superficial macular vessel density (VD) in glaucoma.

Methods: 97 eyes of 69 primary open-angle glaucoma (POAG) and glaucoma suspect patients from the Diagnostics Innovations in Glaucoma Study with a minimum of 4 visits and 2 years of follow-up after baseline optical coherence tomography angiography (OCTA) examination were included. OCTA 3x3 mm^2 macular scans were acquired at each visit and used to calculate superficial and deep parafoveal VD (pfVD) and OCT-based parafoveal GCC (pfGCC) thickness. Association of baseline superficial and deep pfVD with pfGCC thinning rate was evaluated using linear mixed model.

Results: The included subjects had a baseline mean visual field mean deviation (95%CI) of -2.9 (-3.7, -2.1) dB and a mean follow-up period of 3.6 years. In the univariable model, lower baseline superficial pfVD and higher mean intraocular pressure (IOP) during follow-up were significantly associated with a faster pfGCC thinning rate ($P<0.05$ for all), while deep pfVD was not ($P=0.177$). In the multivariable model, faster pfGCC thinning was correlated with higher mean IOP during follow-up ($\beta=-0.05$, $P=0.002$) and lower baseline superficial pfVD ($\beta=-0.04$, $P=0.011$). Eyes with a baseline superficial pfVD in the lowest tertile (≤ 46%) had significantly faster pfGCC loss compared to eyes with baseline superficial pfVD greater than 46% ($P=0.015$).

Conclusion: Lower baseline superficial pfVD, but not deep pfVD, was associated with faster pfGCC thinning in glaucoma. Moreover, superficial macular VD may help predict central macula thinning in patients with POAG.

INTRODUCTION

Glaucoma is a leading cause of vision loss characterized by progressive retinal ganglion cell (RGC) degeneration,[1] and early detection of progression enables appropriate intensification of treatment. Both optical coherence tomography (OCT) and OCT-angiography (OCTA) have been utilized to evaluate retinal nerve thickness and vessel density (VD) change, respectively, and both have been investigated to assess glaucoma progression.

The ganglion cell complex (GCC), measured with OCT, is known to be preferentially affected in glaucoma, and GCC thinning was shown well correlated with visual field (VF) change.[2-5] Both baseline and longitudinal estimates of GCC or retinal ganglion cell (RGC)-related measurements have demonstrated predictive value for glaucomatous progression.[5-7] In some studies, a lower baseline macular VD was associated with faster retinal nerve fibre layer (RNFL) thinning, subsequent VD loss, and VF progression, suggesting its usefulness in predicting OAG progression.[8 9]

The macular vasculature can be further segmented into a superficial capillary plexus (SCP) and a deep capillary plexus (DCP) by OCTA.[10] Since RGCs and their axons are located in the inner retina,[11 12] it has been presumed that the SCP might be more related to glaucomatous change than the DCP. Several prior studies have shown good correlation between superficial macular VD loss and VF deterioration.[13-15] Moghimi et al. found lower superficial parafoveal VD (pfVD), rather than deep pfVD, was associated with past VF progression,[15] supporting the idea that the SCP is more

affected in OAG. Fard et al. also suggested that superficial macular VD is useful when evaluating OAG progression.[12]

The role of DCP in glaucomatous damage has been less studied than the SCP, and published studies are inconsistent. Although most studies suggest that DCP is not affected in glaucoma,[13 15-17] a few have concluded that it may have a role.[9 18 19] In studies by Jeon et al., deep macular VD was found to be an independent risk factor for central VF loss in addition to retinal nerve thinning,[18] and there was a significant correlation between VF progression and initial deep macular VD.[9] A cross-sectional study also supported a possible indirect influence of the DCP on glaucoma progression, as some risk factors for glaucoma were found related to wider deep vessel defect at the location of focal RNFL defects.[19] These results suggested that DCP may also be affected in glaucoma, and deep macular VD may be helpful in predicting glaucoma progression.

Studies on the relationship between macular VD in different layers and glaucoma progression are sparse. Early detection of macular structural damage is important to patients with glaucoma, as the loss of central vision can dramatically impact patients' quality of life.[20] In the current study, the association between macular GCC thinning and both baseline superficial and deep macular VD measured by OCTA in glaucoma patients was investigated.

MATERIALS AND METHOD

The study protocol was approved by the Institutional Review Board at the University of California San Diego (NCT00221897) and was in accordance with the

tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all participants.

Glaucoma suspects and primary open angle glaucoma (POAG) participants from the Diagnostic Innovations in Glaucoma Study (DIGS) were included in this longitudinal study. Details of the DIGS were described previously.[21] Briefly, all participants completed comprehensive ophthalmic examination with best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, gonioscopy, dilated fundus examination, stereoscopic optic disc photography, and standard automated perimetry (SAP) in both eyes. The inclusion criteria were: older than 18 years of age, open angles on gonioscopy, BCVA of 20/40 or better, and at least 2 years of follow-up with a minimum of 4 follow-up OCTA examinations. Participants were excluded if there was a history of intraocular surgery (except uncomplicated glaucoma and cataract surgery), coexisting retinal pathologies, non-glaucomatous optic neuropathy, uveitis, or ocular trauma, and eyes were excluded if the axial length was more than 26 mm. Participants with the diagnosis of Parkinson's disease, Alzheimer's disease, dementia, or a history of stroke were also ineligible. Other information, including race, age, systemic medical history, blood pressure, medication use, and central corneal thickness (CCT) was also collected.

Glaucoma suspects were defined as having elevated IOP (≥22mmHg) or suspicious-appearing optic discs without a repeatable glaucomatous VF damage. A suspicious-appearing optic disc was defined as a disc with observable neuroretinal rim narrowing or notching, excavation, or a localized or diffuse RNFL defect suggestive of

glaucoma based on standard review of stereophotographs. POAG was defined as the presence of repeatable and reliable (fixation losses and false negatives ≤ 33% and false positives ≤ 33%) abnormal SAP tests using the 24-2 Swedish Interactive Thresholding Algorithm with either a pattern standard deviation outside the 95% normal limits or a glaucoma hemifield test result outside the 99% normal limit. Central VF defect was defined based on 10-2 Swedish Interactive Thresholding Algorithm results using the criteria proposed in a prior study.[22] The severity of glaucoma was defined based on the VF test result at the initial visit: participants with mean deviation (MD) > −6.0 decibels (dB) were classified as mild; and with MD ≤ -6 dB, moderate to advanced.

optical coherence tomography angiography and spectral-domain optical coherence tomography

All participants underwent OCTA and spectral domain-OCT imaging using the Avanti Angiovue system (Optovue, Inc. Fremont, CA), which provides non-invasive visualization of the retinal vascular network by an optimized motion contrast technique for the split-spectrum amplitude-decorrelation angiography algorithm while also providing thickness measurements. The OCT and OCTA images were acquired simultaneously, and the Angiovue software (version 5.6.3.0) performed automatic segmentation with exact registration of the analysed regions. The OCT-based thickness analyses and OCTA-based vascular analyses were then calculated from the same scan slab.

The VD was calculated as the percentage of measured area occupied by flowing blood vessels. In the current study, we analyzed VD from the 3mm x 3mm macula

scans centered on the fovea. The macula OCTA scanning protocol consists of merged Fast-X volume of 304 horizontal B-scans of 304 A-scans per B-scan and Fast-Y volume of 304 vertical B-scans of 304 A-scans per B-scan. The scans were automatically segmented using standard Angiovue software to visualize the SCP, measured from the internal limiting membrane (ILM) to 10 μm above the inner plexiform layer (IPL), and the DCP, measured from 10 μm above the IPL to 10 μm below the outer plexiform layer. Automated projection artifacts removal was performed for calculation of VD in the deep layer. The parafoveal VD (pfVD) was calculated from the instrument-defined annular region with an inner diameter of 1 mm and an outer diameter of 3 mm centered on the fovea.

GCC thickness, which consists of the ganglion cell layer, IPL and RNFL, was calculated using Angiovue software from the macular cube image acquired from the OCTA scan. Each B scan comprises 933 A-scans. The parafoveal GCC (pfGCC) thickness was calculated from the same fovea-centered annular region locating between the 1-3 mm diameter as described above.

Image quality review was performed by trained observers following a standard protocol established by the University of California, San Diego Imaging Data Evaluation and Analysis (IDEA) Reading Center. Only good quality images were included. Poor quality scans were defined by the following criteria: (1) a SQ score is < 4, except for advanced disease; (2) poor clarity; (3) residual motion artifacts visible as irregular vessel pattern on the en-face angiogram; (4) image cropping or local weak signal; (5) off-centered fovea; or (6) segmentation errors that could not be corrected.

statistical analysis

Descriptive statistics were calculated as the mean and 95% confidence interval (CI) unless otherwise specified. Eye characteristics were compared using linear mixed-effects models to account for within-participant variability. Measurements of bilateral eyes were nested within subject to account for the fact that eyes from the same individual were more likely to have similar measurements. Putative factors affecting pfGCC thinning were examined using a univariable and multivariable linear mixed model. The evaluation of baseline pfVD parameters on rates of pfGCC thinning was performed using a linear mixed model with random intercepts and random slopes. In this model, the average value of the outcome variables was explored using a linear function of time, and random intercepts and random slopes were introduced with patient- and eye-specific deviations from this average value. The model can account for the fact that different eyes may have different rates of pfGCC thinning over time, while accommodating correlations between both eyes of the same individual. Multivariable models were constructed including the following potential confounding factors: age, mean IOP during follow-up, SSI, and any other variables with a P value < 0.1 in univariable analysis. The SSI was included to adjust for potential VD measurement variability resulting from change in the OCTA signal.[23 24] Factors showing collinearity with pfGCC thinning rate and other covariates were excluded from the multivariable model. Baseline pfGCC thickness was also not included to avoid an inflated correlation caused by a spurious statistical association.[8 25] Best linear unbiased prediction was used to illustrate the association between pfGCC thinning rate and baseline superficial and deep pfVD. Statistical analyses were performed using Stata software version 16.0

(StataCorp LLC, College Station, TX). A P values < 0.05 were considered statistically significant for all analyses.

RESULTS

Table 1. Demographics and Baseline Clinical Characteristics of the Subjects	
Characteristic	n=97 eyes of 69 patients
Age (years)	66.7 (64.4, 69.1)
Gender (Female/ Male)	35/34
Race (African American/ Non-African American)	19/50
Diagnosis and Disease Severity	
Glaucoma suspect, Eye No. (%)	34 (35.1%)
Early glaucoma, Eye No. (%)	47 (48.5%)
Moderate and advanced glaucoma, Eye No. (%)	16 (16.5%)
Self-reported Diabetes	11 (15.9%)
Self-reported Hypertension	40 (58.0%)
Baseline IOP (mmHg)	15.4 (14.5, 16.2)
Baseline VF MD (dB)	-2.9 (-3.8, -2.1)
Baseline VF PSD (dB)	4.1 (3.4, 4.8)
Baseline central VF defect, Eye No. (%)	66 (68.0%)
Baseline pfGCC thickness (μm)	95.4 (92.9, 97.8)
Baseline superficial pfVD (%)	47.6 (46.8, 48.5)
Baseline deep pfVD (%)	51.7 (51.0, 52.4)
Follow-up (years)	3.6 (3.5, 3.7)
Visits of OCT/OCTA examination	5.2 (5.0, 5.4)
*Values are shown in mean (95% confidence interval), unless otherwise indicated. Abbreviation: IOP = intraocular pressure; MD = mean deviation; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; pfGCC = parafoveal ganglion cell complex; pfVD = parafoveal vessel density; PSD = pattern standard deviation; VD = vessel density; VF = visual field.	

Demographic and baseline clinical characteristics of the recruited subjects are summarized in Table 1. A total of 97 eyes (63 POAG and 34 glaucoma suspect) of 84 subjects were enrolled. Their mean age (95% CI) was 66.7 (64.4, 69.1) years, mean baseline IOP (95% CI) was 15.4 (14.5, 16.2) mmHg, and mean baseline VF MD (95% CI) was -2.9 (-3.8, -2.1) dB. Based on the results of the 10-2 test, 66 (68.0%) eyes showed a central VF defect at baseline. An average of 5.2 (95% CI: 5.0, 5.4) visits of OCT/OCTA examinations were obtained over a mean follow-up period of 3.6 (95% CI: 3.5, 3.7) years. The mean baseline superficial pfVD (95% CI) was 47.6% (46.8, 48.5)%, deep pfVD (95% CI) was 51.7% (51.0, 52.4)%, and baseline global pfGCC thickness (95% CI) was 95.4 (92.9, 97.8) μm. Figure 1 shows the superficial and deep macular OCTA scans and the macular GCC thickness map of a representative case.

Scatter plots with best fitted lines demonstrating the pfGCC thinning rates and baseline superficial and deep pfVD of all included subjects were presented in Figure 2. Factors contributing to the rate of pfGCC thinning over time are presented in Table 2. Higher mean IOP during follow-up (β=-0.05, P=0.002), thinner baseline pfGCC (β=-0.01, P=0.044), and lower baseline superficial pfVD (β=-0.03, P=0.026) were all significantly associated with a faster rate of pfGCC loss in the univariable mixed model, while deep pfVD was not (P=0.177). In the multivariable model, a faster pfGCC thinning was significantly associated with a higher mean IOP during follow-up (β=-0.05, P=0.002) and a lower baseline superficial pfVD (β=-0.04, P=0.011). In addition, compared with eyes with a baseline superficial pfVD greater than 46% (mean pfGCC thinning rate: -0.95 μm/year), eyes with a baseline superficial pfVD ≤ 46% (lowest tertile of the current dataset) had significantly faster pfGCC thinning (mean pfGCC thinning

rate: -1.19 μm/year) in both univariable (P=0.047) and multivariable (P=0.015) mixed model analyses. In the supplementary analysis with glaucoma severity as a covariate for pfGCC thinning rate, no significant difference was found between the early and moderate-severe groups (β=-0.28, P=0.071) in the multivariable model,

Table 2. Factors Contributing to the Rate of Global Ganglion Cell Complex Changes Over Time by Univariable and Multivariable Mixed Model Analysis

Variables	Univariable Model		Multivariable Model	
	β (95 % CI)	P value	β (95 % CI)	P value
Age, per 10 years older	0.00 (-0.10, 0.10)	0.981	0.00 (-0.01, 0.01)	0.486
Gender: Female	0.05 (-0.19, 0.29)	0.698		
Race: African American	0.10 (-0.17, 0.37)	0.478		
Self-reported diabetes	0.14 (-0.21, 0.48)	0.434		
Self-reported hypertension	-0.08 (-0.32, 0.16)	0.538		
Axial length, per 1 mm shorter	-0.10 (-0.28, 0.00)	0.095	-0.09 (-0.21, 0.02)	0.114
CCT, per 100 um thinner	-0.23 (-0.55, 0.09)	0.166		
Baseline IOP, per 1 mmHg higher	-0.02 (-0.05, 0.01)	0.148		
Mean IOP during follow-up, per 1 mmHg higher	-0.05 (-0.09, -0.02)	**0.002**	-0.05 (-0.08, -0.02)	**0.002**
Baseline VF MD, per 1 dB worse	-0.02 (-0.05, 0.01)	0.147		
Average SSI, per 1 score higher	-0.00 (-0.02, 0.01)	0.653	-0.00 (-0.02, 0.01)	0.560
Baseline pfGCC thickness, per 1 um thinner	-0.01 (-0.02, -0.00)	**0.044**		
Baseline superficial pfVD, per 1 % lower	-0.03 (-0.06, -0.01)	**0.026**	-0.04 (-0.06, -0.01)	**0.011**
Baseline deep pfVD, per 1 % lower	0.02(-0.01, 0.06)	0.177		
Follow-up period, per 1 year longer	-0.07 (-0.30, 0.17)	0.592		

*Values are shown in β coefficient (95% CI). Negative β coefficient shows association with faster pfGCC thinning. Statistically significant P values are shown in bold.
Abbreviation: CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; OCTA = optical coherence tomography angiography; SSI = signal strength index; pfGCC = parafoveal ganglion cell complex; pfVD = parafoveal vessel density; VF = visual field.

DISCUSSION

In the current study, the relationship between macular GCC thinning and baseline superficial and deep macular VD in glaucoma was examined. There was a significant correlation between a lower baseline superficial pfVD, but not deep pfVD, and a faster rate of pfGCC thinning. Furthermore, eyes with a baseline superficial pfVD ≤ 46% (the lowest tertile) had a significantly faster pfGCC loss compared to eyes with a baseline superficial pfVD greater than 46%. Our results support that SCP, as compared to DCP, is preferentially affected in POAG, and baseline superficial macular VD may be helpful to predict central macular GCC thinning. As central macula loss is directly related to central VF defects and can negatively affect the patients' quality of life,[20] information about superficial macular VD can help clinicians to identify high-risk patients who need more intensive observation and treatment.

Several earlier studies have explored the differential influence of superficial and deep vasculature on glaucoma, and most showed a meaningful role only for the SCP.[13 14 17 26] Takusagawa et al. reported that, in contrast to the SCP densities, densities of DCP did not differ between healthy and glaucoma subjects nor did they correlate with VF sensitivity.[16] Some studies used macular VD in different layers to differentiate OAG patients from healthy subjects,[17 27] and revealed a superior

diagnostic accuracy and correlation with central VF of superficial macular VD.[13 17] In the study by Moghimi et al., a lower superficial pfVD was observed to correlate positively with past VF progression in OAG, while no correlation was found for deep pfVD.[15] Kim et al. also examined the association between sectoral macular superficial VD and ganglion cell inner plexiform layer (GCIPL) and circumpapillary RNFL in early glaucoma, revealing a significant topographic correlation between nerve thinning and SCP change.[28] These studies collectively support a preferential involvement of SCP in glaucoma progression, as well as a less important role of DCP.

In contrast to earlier studies, we evaluated the roles of SCP and DCP in glaucoma using structural change in GCC. GCC loss was suggested a highly sensitive tool for detecting early glaucoma and a strong predictor for glaucomatous VF progression.[5 29 30] In our study, there was a significant correlation between a lower baseline superficial pfVD and a faster rate of pfGCC thinning, supporting the involvement of the SCP in glaucoma. One earlier study has also shown a similar association between baseline macular VD and RNFL thinning rate, indicating the potential predictive value of this parameter in OAG.[8] In addition, eyes with a baseline superficial pfVD ≤ 46% had a high risk of structural progression in the present study. Although the cut-off value may vary in different populations, our results again suggest the possible usefulness of baseline superficial macular VD in identifying patients at risk of subsequent central macula thinning, which may be helpful for predicting a slightly faster rate of GCC thinning.

Interestingly, in the two studies by Jeon et al., deep macular VD, but not superficial macular VD, was predictive of VF progression and associated with central VF loss.[9 18] Although DCP seemed more affected than SCP based on these results, several points should be considered. In one study, they included only normal tension glaucoma (NTG) patients, and deep VD did not show meaningful relationship with any structural parameters.[18] Thus, the correlation observed might have resulted from the independent effects of deep retinal perfusion on central vision, as pre-existing vascular incompetence and hypoperfusion-induced DCP vasoconstriction are more common in NTG.[31-33] In their other study,[9] OCTA was not performed at baseline. In contrast, the current study recruited patients with OAG and acquired the VD measurements at baseline. Furthermore, the differences in the ethnicity of the study subjects might be another reason for the discrepancy.

Our study has several limitations. First, approximately one third of the images acquired for the current study were deemed poor-quality and excluded for analysis. Such a proportion of poor-quality images would affect the reliability of the testing in clinical practice if they were not excluded there, as well.[34 35] Second, while acquired measurements of superficial VD measured by OCTA are reliable,[36] analysis of deep VD is more prone to projection artifacts; these cannot be completely removed by the projection artifacts removal algorithm.[17] Thus, although minimal, the measured deep pfVD might still possess greater variability than the superficial pfVD. Third, since there were few advanced glaucoma eyes included, the generalizability of these results to moderate-severe glaucoma is unclear. However, we also examined glaucoma severity as a covariate and performed severity-stratified analysis, and the insignificant difference

suggests our findings may be applicable to advanced glaucoma. Last, past studies have discussed the effect of age-related change on VD and nerve thickness when evaluating glaucoma progression.[37-39] Although age was adjusted in the analysis, its impact might not have been fully addressed as it is challenging to differentiate between age-related and glaucoma-related pfGCC thinning.

Although lower baseline superficial macular VD, but not deep VD, was associated with a faster GCC thinning in glaucoma patients, this association was not strong. Moreover, baseline superficial macular VD predicted subsequent central macula GCC thinning and progression of glaucoma. Future studies will determine the relative importance of baseline OCTA-measured superficial macular VD compared to OCT-measured parameters for predicting the rate of central macular GCC thinning.

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d. **Author contribution:** Concept and design: JHW, SM, RNW; Acquisition and reviewing of data: JHW, SM, TN, JAP, AK, LMZ; Analysis or interpretation of data: JHW, SM, TN, JAP, AK, LMZ, RNW; Drafting of the manuscript: JHW, SM, TN; Critical revision of the manuscript: All authors; Obtained funding: SM, LMZ, RNW; Supervision: SM, RNW

e. **Data availability:** The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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FIGURES LEGENDS

Figure 1. Images of a representative case, including macular optical coherence tomography angiography images showing the baseline superficial (a) and deep (b) parafoveal vessel densities and the ganglion cell complex thickness map (c).

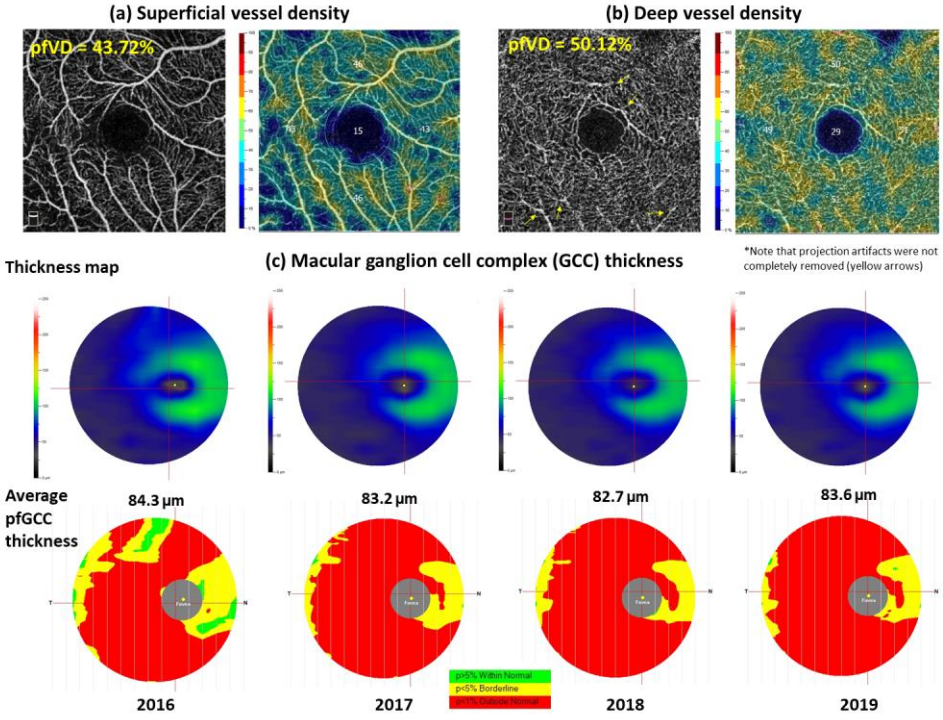

Figure 2. Scatter plots with best fitted lines illustrating the association between parafoveal ganglion cell complex thinning rates and baseline superficial (a) and deep (b) parafoveal vessel densities. Abbreviation: pfGCC = parafoveal ganglion cell complex, pfVD = parafoveal vessel density.