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The Association Between Macula and ONH Optical Coherence Tomography Angiography (OCT-A) Vessel Densities in Glaucoma, Glaucoma Suspect and Healthy Eyes

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Abstract

Purpose—To evaluate strength of associations between Optical Coherence Tomography-Angiography (OCT-A) vessel density (VD) measurements in the macula and peripapillary region of the optic nerve head (ONH) with standard structural OCT thickness measures.

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Methods—This cross-sectional study included 333 eyes of 219 primary open angle glaucoma patients, 41 glaucoma suspects, and 73 healthy participants from the Diagnostics Innovations in Glaucoma Study (DIGS) with good quality OCT-A images. The strength of associations between microvasculature measures in the ONH retinal nerve fiber layer (RNFL) and superficial macula layer was assessed using linear regression models. Associations between ONH and macula VD, and circumpapillary (cp) RNFL thickness and macula ganglion cell complex (mGCC) measures were also evaluated.

Results—The strength (r^2) of associations among VD and thickness measures of ONH and macula ranged from 14.1% to 69.4%; all were statistically significant ($p < 0.001$). The association between ONH and macula whole image VD ($r^2 = 41.0\%$) was significantly weaker than the relationship between mGCC and cpRNFL thickness ($r^2 = 69.4\%$) ($p < 0.001$). Although both cpRNFL and mGCC thicknesses tended to be more strongly associated with ONH VD ($r^2 = 39.2\%$ and 26.7%, respectively) than macula VD ($r^2 = 27.5\%$ and 17.7%, respectively), differences did not reach statistical significance ($p=0.050$ and $p=0.113$, respectively).

Conclusions—The strength of the association of VD with cpRNFL and mGCC thicknesses varies by retinal layer. The weaker association of macula VD compared to ONH VD with tissue thickness may be due to differences in micorovasculature between the macula and ONH.

Keywords

OCT Angiography; vessel density; correlation; strength of association

INTRODUCTION

Optical Coherence Tomography (OCT) Angiography (-A) is a new technology that allows non-invasive visualization of the retinal and choroidal vasculature using contrast imaging,[1] and quantitative assessment of the retinal microvasculature [2] which includes the optic nerve head (ONH), [3,4] the peripapillary region, [5] as well as the retina and choroid. [6]

OCT-A ONH vessel density measurements has similar diagnostic accuracy as retinal nerve fiber layer (RNFL) thickness [7] and lower vessel density is significantly associated with worse visual field damage in glaucoma patients. [8,9] Microvasculature dropout has also been demonstrated in eyes with focal lamina cribrosa defects [10] and in those with larger beta parapapillary atrophy. [9] A previous study also has demonstrated that lower ONH perfusion is related to a thinner macular ganglion cell complex (mGCC) ($r^2 = 0.404$, $p=0.001$). [4]

There is limited information regarding the relationship between microvasculature of the superficial macula and the peripapillary region of the ONH in glaucoma patients. The objective of the current study is to evaluate the strength of associations between macula and ONH OCT-A vessel density measurements with each other as well as with standard OCT thickness measurements.

MATERIALS AND METHODS

Participants

All subjects in this cross-sectional study were recruited from the longitudinal Diagnostic Innovation in Glaucoma Study (DIGS). [11–13] The protocol was approved by the University of California San Diego Institutional Review Board, and adheres to the tenets of the Declaration of Helsinki.

Subjects were at least 18 years old, had open anterior chamber angles upon gonioscopy, and had clear media. They were identified as healthy if they had no clinical signs of retinal or glaucomatous pathologies based on dilated eye examination, and had reliable and repeatable visual field (VF) tests without any evidence of VF damage. Primary open angle glaucoma (POAG) eyes were identified as those with at least three consecutive, reliable (≤33% fixation losses and false negatives, as well as ≤15% false positives), and repeatable abnormal VF tests with the Humphrey Field Analyzer 24-2 (Carl Zeiss, Meditec; Dublin, California, USA) Swedish Interactive Thresholding Algorithm with Pattern Standard Deviation (PSD) or Glaucoma Hemifield Test (GHT) results outside of normal limits, as well as glaucomatous optic nerves on dilated examination. Glaucoma suspect eyes were defined as those that have suspicious-looking optic nerves on dilated exam with or without high intraocular pressures (> 21 mmHg), without repeatable visual field damage. One eye with the worse VF mean deviation (MD) from each subject was included in the study.

OCT Image Acquisition

The Avanti AngioVue (Optovue Inc.; Fremont, California, USA, software version 2016.1.0.26) was used to acquire all Spectral Domain (SD-) OCT images, including circumpapillary (cp) RNFL thickness analysis, mGCC thickness analysis, and OCT-A images, which made use of an A-scan rate of 70,000 scans per second, a bandwidth of 50nm, and an 840nm diode laser source.

As described previously, [4,7–10,14–17] circumpapillary vessel density (cpVD) and ONH whole image vessel density (wiVD) was calculated from an ONH scan with a 4.5mm x 4.5mm field of view and limited to the RNFL (radial peripapillary capillaries, RPC). The macula wiVD was calculated from a scan size of 3mm × 3mm and limited to the superficial layer, while the parafoveal vessel density (pfVD) was measured in a 3mm annular region centered on the fovea with an inner diameter of 1mm (Figure 1).[14–17] Each OCT-A ONH and macula scan volume has 304 × 304 A-scans consisting of 2 orthogonal volumes to minimize motion artifacts. Split Spectrum Amplitude Decorrelation Angiography (SSADA) uses the dynamic motion of red blood cells to give high-resolution 3D images of perfused retinal vasculature. [2] Only good quality images based on a standard protocol established by the University of California, San Diego Image Data Evaluation and Analysis (IDEA) Reading Center were included. Images that had signal strength indices (SSI) of less than 48, poor clarity, residual motion artifacts (which gave images with irregular vessel patterns and disc boundaries), local weak signals caused by media opacities (such as floaters and hemorrhages), and segmentation errors were excluded.

Avanti AngioVue SD-OCT (Optovue Inc.; Fremont, CA, USA, software version 2016.1.0.26) was used to acquire mGCC and cpRNFL thickness scans. It uses an 840nm central wavelength, a 22-mm focal spot diameter and a 70-kHz axial line scan rate that yields an axial resolution of 5 mm in tissue. mGCC thickness was measured by covering a 7mm × 7mm square grid on the central macula, and is measured from the inner limiting membrane (ILM) to the inner plexiform membrane (IPL). cpRNFL average thickness was measured using a 10-pixel-wide band along a 3.45mm diameter circle that was centered on the ONH. Only images with good quality (SSI of more than 36 and good segmentation) were included.

Statistical Analysis

Linear and quadratic regression analyses, as well as multivariable analysis using JMP (SAS Institute Inc., Cary, NC,) [18] were used to characterize the associations among vessel density in the superficial macula and peripapillary region of the ONH and cpRNFL and mGCC thickness, and the significance in differences were evaluated using Fisher (r to) z transformation.

RESULTS

Three hundred and thirty-three eyes of 333 subjects (219 POAG, 41 glaucoma suspects, and 73 normal participants) were included. The demographic characteristics of the participants are presented in Table 1. Glaucoma patients and glaucoma suspects were significantly older than normal subjects (ANOVA $p<0.001$) Glaucoma patients represented a wide range of disease severity (VF MD ranging from −30.1dB to 0.10 dB, mean = −8.6 dB). Glaucoma eyes tended to have sparser vessel densities and thinner mGCC and cpRNFL compared to suspect and normal eyes (Table 2).

The strength (R^2) of the associations among vessel density and thickness measures in the ONH and macula region ranged from 14.1% to 69.4%; all were statistically significant ($p <0.001$) (Figure 2). Specifically, the association between ONH peripapillary whole image and macula whole image vessel densities ($R^2 = 41.0\%$) was significantly weaker than the relationship between mGCC and cpRNFL thickness ($R^2 = 69.4\%$) ($p < 0.001$). The associations between ONH vessel density (ONH wiVD and cpVD) and standard structural measures (cpRNFL and mGCC thickness) were stronger than the associations between macula wiVD and structural measures (both cpRNFL and mGCC thickness) (Figure 2), but the differences did not reach statistical significance. Specifically, the associations between ONH wiVD and cpRNFL ($r^2 = 39.2\%$) and mGCC thicknesses (26.7%), were stronger than the associations between macula wiVD and cpRNFL thickness ($r^2 = 27.5\%$, $p = 0.050$) and mGCC thickness (17.7%, $p = 0.113$).

The strength of the associations between macula wiVD and cpVD ($r^2 = 39.7\%$), between ONH wiVD and cpVD (41.0%) and between macula pfVD and ONH wiVD ($r^2 = 38.4\%$) were similar (Figure 2). Significantly stronger correlations with standard OCT thickness parameters were found with ONH cpVD ($r^2 = 40.4\%$ and 29.3% for cpRNFL and mGCC thicknesses, respectively) ($r^2 = 40.4\%$ vs. $r^2 = 29.3\%$, $n = 333$, $p = 0.004$) than with macula pfVD ($r^2 = 23.7\%$ and 14.1%, respectively) ($r^2 = 23.7\%$ vs. $r^2 = 14.1\%$, $n = 333$, $p = 0.007$).

Quadratic regression analyses of these associations were also performed, but the relationships were similar to linear regression models; there were only slight improvements in the amount of variation explained by the modes (differences in R^2 <3.0%).

Multivariable analysis was completed to estimate the effect of covariates including age, gender, diagnosis, and SSI, on macula wiVD (Table 3) and ONH wiVD (Table 4) as dependent variables. Increasing age, lower SSI's for OCT-A scans, thinner RNFL measurements were significantly associated with lower macula and ONH wiVD measurements.

DISCUSSION

Our findings suggest that compared to peripapillary vessel density measures in the ONH, macula vessel density measurements have a weaker correlation with cpRNFL and macular thickness. There are several possible reasons why vessel density in the peripapillary region of the ONH was more strongly associated with both cpRNFL and macular thickness compared to the association of macula vessel density with these measures. The weaker correlation may be due in part to the complexity of the vascular supply to the macula.

Macula vessel density can be measured using 2 layers, the superficial and deep capillary plexuses (SCP and DCP) [19] but our study measured vessel density only in the SCP to avoid projection artifacts seen with deep vessel density measurements of the DCP. These projection artifacts are produced when superficial vessels produce duplicates of their vascular patterns on the deeper layers, making it difficult to obtain good quality images of the DCP. [2,19] Avanti mGCC thickness measurements are acquired from the ILM to the IPL (which includes the RNFL, ganglion cell layer, and IPL). It should be noted that SCP supplies only until the IPL, while the DCP supplies the IPL and inner nuclear layer (INL) of the retina. Another possible reason that the association is stronger with the ONH compared to macula measurements is that scan sizes for mGCC thickness and macula vessel density differ, with the former having a 7mm × 7mm scan size and the latter having a 3mm × 3mm scan size in this study.

Our results are consistent with a study of healthy subjects that measured pfVD in the foveal avascular zone (FAZ), parafoveal, and peripapillary areas, and compared it with cpRNFL thickness with the Avanti SD-OCT and ganglion cell complex thickness with the Spectralis SD-OCT which measured from the ILM to the INL.[16] They also found that pfVD had a weaker correlation with ganglion cell complex thickness (r^2 = 22.3%, p = 0.014) than with cpRNFL thickness (r^2 = 41.0%, p < 0.001). The current results are also consistent with studies showing that the RPC plexus also is thinner as the NFL decreases. [19] This may explain why there is higher correlation between ONH vessel density and cpRNFL thickness compared to macula vessel density and mGCC thickness. Our study is consistent with a report that macula vessel density had lower diagnostic ability for glaucoma compared to other OCT-A parameters such as cpVD. [14]

Based on previous work demonstrating that age [20] and SSI are significantly associated with quantitative OCT measurements, [21] we included these variables in the multivariable models

of ONH and macula vessel density. We also included history of diabetes and systemic hypertension in the multivariable models in order to account for possible hemodynamic influences. However, multivariable analyses showed that the presence of hypertension and diabetes were not significantly associated with macula and ONH wiVD measurements. It should be noted that cross-sectional studies cannot determine whether vascular diseases alter retinal circulation; longitudinal studies are required to adequately evaluate the influence of vascular disease on retinal microvasculature.

This study is unique as it systematically examines the relationship between both macula and ONH vessel density and standard macular and ONH OCT thickness measurements. Most papers examining the microvasculature in glaucoma have compared vessel density and thickness measurements to VF, or macula vessel density to VF or GCC measurements.[7–10,16,22,23] There is limited information regarding which OCT-A parameter is most useful in assessing and monitoring glaucoma, and how well each parameter relates to standard OCT thickness measurements. This study provides important information on these relationships and thus informs on how OCT-A can be interpreted for monitoring of glaucoma.

There are several limitations to our study. First, healthy participants were significantly younger than both glaucoma suspects and POAG patients and SSI had significant effects on macula and ONH vessel density measurements. For these reasons, we included age and SSI in our multivariable analyses. Second, in this cross-sectional study, macula vessel density measurements were limited to the SCP in part to limit the influence of projection artifacts on the vessel density measurements in the deeper layers.[19] Imaging of deep layer microvasculature is problematic as it is compromised by superficial retinal vessels causing a projection (shadow) artifact.[25] Last, this study utilized OCT-A 3mm × 3mm macula scan size. Stronger correlations between ONH and macula vessel density may be found with a larger scan size.

Our study demonstrates that ONH vessel density measurements are more strongly correlated with cpRNFL and mGCC thicknesses than with macula vessel density. This stronger correlation may be in part due to differences of the microvasculature of the macula and the optic disc. OCT-A shows promise for improving our understanding the role of ONH and macula retinal microvasculature in the pathophysiology of glaucoma.

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Abbreviations and Acronyms

OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography

ONH	optic nerve head
RNFL	retinal nerve fiber layer
mGCC	macular ganglion cell complex
DIGS	Diagnostic Innovations in Glaucoma Study
VF	visual field
POAG	primary open angle glaucoma
PSD	pattern standard deviation
GHT	glaucoma hemifield test
MD	mean deviation
SD-OCT	spectral domain optical coherence tomography
cp	circumpapillary
VD	vessel density
cpVD	circumpapillary vessel density
wiVD	whole image vessel density
RPC	radial peripapillary capillaries
pfVD	parafoveal vessel density
SSADA	Split Spectrum Amplitude Decorrelation Angiography
IDEA	Image Data Evaluation and Analysis
SSI	signal strength indices
ILM	inner limiting membrane
IPL	inner plexiform layer
ANOVA	analysis of variance
SCP	superficial capillary plexus
DCP	deep capillary plexus
INL	inner nuclear layer
FAZ	foveal avascular zone

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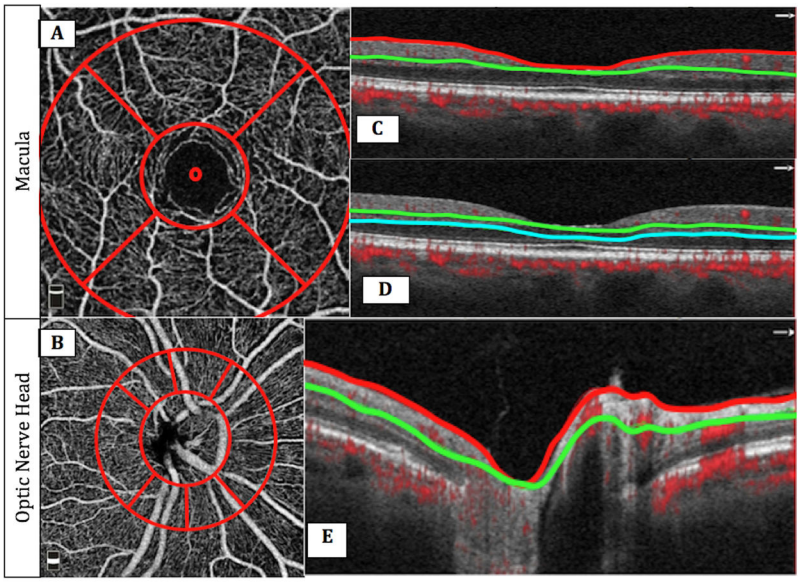

Figure 1.

A) 3mm × 3mm macula vessel density scan with the parafoveal measurement circle. B) 4.5mm x 4.5mm ONH vessel density scan with the circumpapillary measurement circle. C) B-scan image of the macula of the superficial capillary plexus segmentation starting from the inner limiting membrane (red line) to the inner plexiform layer (green line). D) B-scan image of the macula with a manually superimposed deep capillary plexus segmentation starting from the inner nuclear layer (green line) to the outer plexiform layer (light blue line). E) B-scan image of the segmentation of the optic nerve head radial peripapillary capillary plexus.

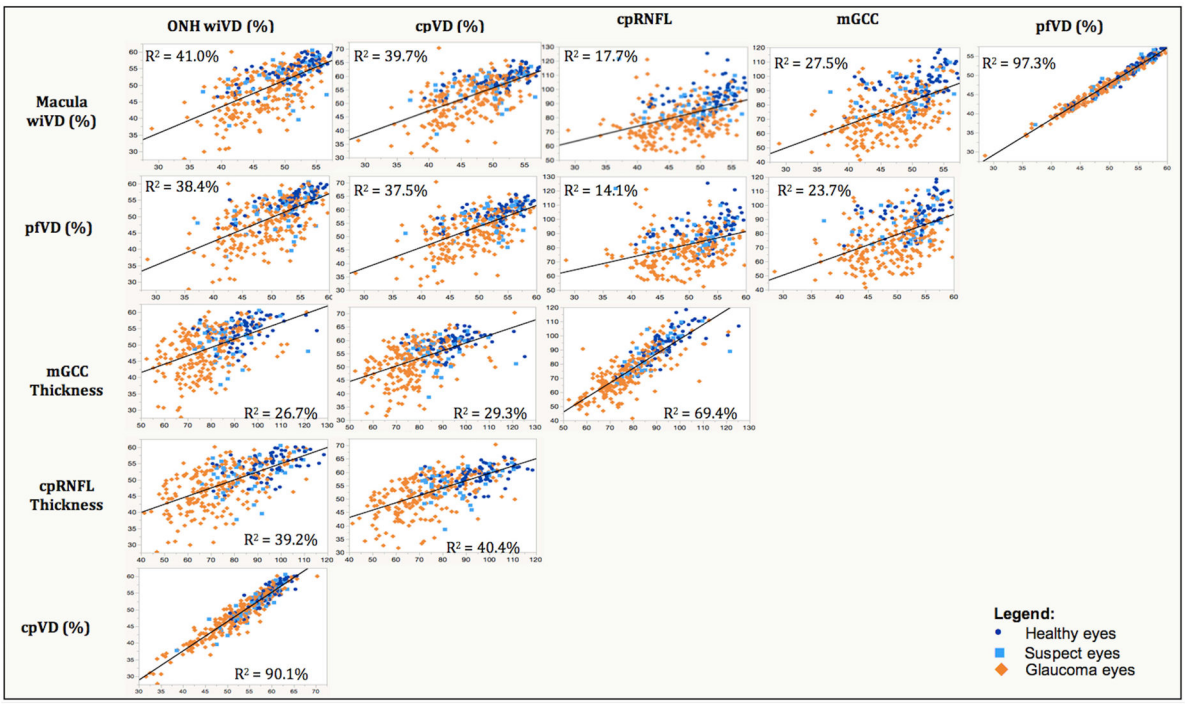

Figure 2.

Adjusted linear regression models showing the relationship between optic nerve head and macula vessel densities, and circumpapillary retinal nerve fiber layer and macula ganglion cell complex thicknesses. Orange diamonds represent glaucoma eyes, light blue squares represent suspect eyes, and dark blue circles represent healthy eyes. Associations between all variables were significant ($p<0.001$) and positively correlated to each other. ONH = optic nerve head; wiVD = whole image vessel density; cpVD = circumpapillary vessel density; cpRNFL = circumpapillary retinal nerve fiber layer; mGCC = macular ganglion cell complex; pfVD = parafoveal vessel density.

Table 1

Demographics Mean (95% CI)				
	Normal eyes (n=73)	**Suspect eyes (n=40)**	**Glaucoma eyes (n=220)**	**p-value**
Mean age (years)	62.3 (59.37 – 65.40)	72.6 (68.77 – 75.35)	72.6 (71.31 – 74.23)	**<0.001**
Gender (% Male)	35.6%	36.5%	50.2%	**0.044**
Race				
European Descent	71.2%	56.0%	65.2%	**0.034**
African Descent	21.9%	34.1%	21.4%	
Other	6.7%	9.6%	13.1%	
Mean VF MD (dB)	−0.15 (−0.42 – 0.12)	−1.59 (−2.20 – −0.77)	−8.59 (−9.62 – −7.67)	**<0.001**

VF MD = Visual field mean deviation

Table 2

Mean distributions of Vessel Density, cpRNFL and mGCC Thicknesses in Diagnostic Groups (95% Confidence Interval)

	Normal eyes	Suspect Eyes	Glaucoma Eyes	p-value ANOVA with post-hoc testing
ONH wiVD (%)	54.61 (53.26 – 55.95)	51.49 (49.70 – 53.28)	47.81 (47.03 – 48.58)	<0.001●◆+
cpVD (%)	58.99 (57.55 – 60.44)	56.01 (54.07 – 57.94)	51.69 (50.85 – 52.53)	<0.001●◆+
Macula wiVD (%)	51.00 (49.89 – 52.12)	49.23 (47.74 – 50.73)	46.58 (45.94 – 47.23)	<0.001◆+
pfVD (%)	53.29 (52.10 – 54.48)	51.52 (49.93 – 53.11)	48.81 (48.12 – 49.50)	<0.001◆+
cpRNFL Thickness (μm)	94.49 (91.41 – 97.56)	86.46 (82.35 – 90.56)	72.78 (71.01 – 74.56)	<0.001●◆+
mGCC Thickness (μm)	94.09 (91.55 – 96.64)	88.02 (84.63 – 91.41)	77.30 (75.84 – 78.77)	<0.001●◆+

ONH = Optic nerve head; wiVD = Whole image vessel density; cpVD = Circumpapillary vessel density; pfVD = Parafoveal vessel density; cpRNFL = Circumpapillary retinal nerve fiber layer; mGCC = Macular ganglion cell complex

● indicates a significant relationship between normal and suspect eyes.

◆ indicates a significant relationship between normal and glaucoma eyes.

+ indicates a significant relationship between suspect and glaucoma eyes.

Table 3

Multivariable Analysis for Associations with Macula wiVD

Variable	Coefficient (95% Confidence Interval)	p Value	R^2
Age (per year)	−0.058 (−0.096 – −0.020)	**0.002**	
Gender (Female)	0.249 (−0.125 – 0.624)	0.191	
Diagnosis (Suspect eyes vs. normal eyes)	0.397 (−0.354 – 1.147)	0.299	
Diagnosis (Glaucoma eyes vs. normal eyes)	−0.154 (−0.765 – 0.456)	0.618	60.1%
Diabetes	−0.238 (−1.325 – 0.848)	0.665	
Hypertension	−0.054 (−0.848 – 0.740)	0.893	
Macula SSI	0.230 (0.182 – 0.277)	**<0.001**	
ONH wiVD (per %)	0.160 (0.078 – 0.242)	**<0.001**	
mGCC thickness (per μm)	0.018 (−0.031 – −0.068)	0.477	
cpRNFL thickness (per μm)	0.056 (0.011 – 0.101)	**0.014**	

wiVD = Whole image vessel density; SSI = Signal strength index; ONH = Optic nerve head; mGCC = Macular ganglion cell complex; cpRNFL = Circumpapillary retinal nerve fiber layer.

Table 4

Multivariable Analysis for Associations with ONH wiVD

Variable	Coefficient (95% Confidence Interval)	p Value	R^2
Age (per year)	0.017 (−0.021 – 0.056)	0.368	
Gender (Female)	0.052 (−0.326 – 0.431)	0.784	
Diagnosis (Suspect eyes vs. normal eyes)	0.325 (−0.432 – 1.082)	0.398	
Diagnosis (Glaucoma eyes vs. normal eyes)	−0.232 (−0.844 – 0.380)	0.456	74.0%
Diabetes	0.451 (−0.636 – 1.539)	0.414	
Hypertension	−0.303 (−1.103 – 0.495)	0.455	
ONH SSI	0.320 (0.281 – 0.359)	**<0.001**	
Macula wiVD (per %)	0.212 (0.118 – 0.307)	**<0.001**	
mGCC thickness (per μm)	0.032 (−0.017 – 0.082)	0.205	
cpRNFL thickness (per μm)	0.137 (0.092 – 0.181)	**<0.001**	

wiVD = Whole image vessel density; ONH = Optic nerve head; SSI = Signal strength index; mGCC = Macular ganglion cell complex; cpRNFL = Circumpapillary retinal nerve fiber layer