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Structural and functional associations of macular microcirculation in the ganglion cell-inner plexiform layer in glaucoma using optical coherence tomography angiography

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Abstract

Purpose—To quantify retinal microvasculature within the macular ganglion cell-inner plexiform layer (GCIPL) in primary open angle glaucoma (POAG) and normal eyes, determine association of vessel parameters with structural and functional measures, and report diagnostic accuracy of vessel parameters.

Methods—POAG and normal patients underwent 6mm×6mm macula scans (AngioplexTM optical coherence tomography angiography [OCTA]; CirrusTM HD-OCT 5000); and Humphrey Field Analyzer II-i 24-2 visual field (VF) (Zeiss, Dublin, CA). Prototype software performed semi-automatic segmentation to create GCIPL *en face* images, and quantified vessel area density (VAD), vessel skeleton density (VSD), and vessel complexity index (VCI) for the macula (globally, hemifields, and six focal sectors). Linear regression assessed association of OCTA parameters with VF mean deviation (MD) and GCIPL thickness globally and focally.

Results—34 POAG and 21 normal eyes were studied. VAD, VSD, and VCI were reduced in POAG versus normal (0.463 vs 0.486, $P=0.00029$; 0.230 vs 0.219, $P=0.0014$; 1.15 vs 1.09, $P=0.0044$, respectively), with a trend of worsening with increased POAG severity. Reduced global VF mean deviation (MD) was associated with reduced VAD and VCI, controlling for age and inter-eye correlation ($P_s=0.0060, 0.0080$; $R^2=0.205, 0.211$). Both superior and inferior hemifield MD were associated with corresponding VAD, VSD, and VCI (all $P_s<0.007$; R^2 ranged from 0.12 to 0.29). Global GCIPL thickness was not associated with global OCTA parameters, and only inferior sector GCIPL thickness was associated with corresponding VAD, VSD, and VCI ($P_s<0.05$; R^2 ranged from 0.15–0.16). Area-under-curves for VAD, VSD, and VCI were fair to good (0.83, 0.79, 0.82; respectively; $P_s<0.0001$).

Conclusions—Glaucomatous eyes had reduced GCIPL microcirculation. OCTA parameters had stronger associations with functional rather than structural measures of glaucoma. This observation deserves further study.

Keywords

optical coherence tomography angiography (OCTA); macula; ganglion cell – inner plexiform layer; primary open angle glaucoma; structure; function

Introduction

Primary open angle glaucoma (POAG) is an optic neuropathy characterized by progressive degeneration of retinal ganglion cells and its axons, which results in characteristic excavation of the neuroretinal rim with corresponding visual field (VF) deficits.¹ Several studies have suggested that vascular factors contribute to the development and progression of glaucomatous optic neuropathy and that vascular dysfunction is an important cause of POAG.^{2–8} Recent studies using optical coherence tomography angiography (OCTA) have mainly focused on the microcirculation of the optic disc and peripapillary region, and have demonstrated reduced microcirculation in glaucoma^{9–18}, but less attention has been paid to the macula in OCTA glaucoma studies thus far^{19–21}.

The macula is the retinal region with the highest density of retinal ganglion cells,²² and structural measures of the inner macula have been useful in glaucoma assessment.^{23, 24} Significant work now supports a strong diagnostic accuracy of ganglion cell - inner plexiform layer (GCIPL) thicknesses, as measured by OCT, for glaucoma.^{25, 26} Prior to OCTA technology, our ability to assess the microcirculation supplying the GCIPL layer was limited, but OCTA now allows us to study the macular microcirculation in precise retinal layers.

In this study, we used an optical microangiography (OMAG)-based form of OCTA to precisely segment the GCIPL layer.^{27, 28, 15} From the generated *en face* images, we aimed to quantify the perfused retinal microvasculature within the GCIPL layer in glaucoma and normal patients using three OCTA measures (vessel area density [VAD], vessel skeleton density [VSD], and vessel complexity index [VCI]), determine whether perfusion measures are associated with structural and functional measures of glaucoma, and to report the diagnostic accuracy of these OCTA measures. Characterizing the GCIPL microcirculation and assessing its associations with traditional structural and functional measures of glaucoma may provide insight into glaucoma pathogenesis and the utility of macular OCTA in early detection of glaucoma.

Methods

Study Population and Clinical Assessment

An observational, cross-sectional study was performed on patients with primary open angle glaucoma (POAG) presenting to the glaucoma service and normal participants presenting to the optometry service at USC Roski Eye Institute, Keck School of Medicine of University of Southern California over 12 months (October 1, 2015 to September 30, 2016). The research

protocol was approved by the institutional review board and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject following an explanation of the nature of the study. The diagnosis of POAG was based on diagnosis by a fellowship-trained glaucoma specialist, incorporating clinical exam demonstrating an optic nerve rim defect (notching or localized thinning) characteristic of glaucoma. As is routine in clinical settings, RNFL thickness and deviation maps from OCT (Cirrus HD-OCT 5000; Zeiss, Dublin, CA) were reviewed on all patients, and all glaucoma cases demonstrated focal RNFL thinning consistent with the funduscopy disc findings. For perimetric glaucoma, Humphrey Swedish Interactive Threshold Algorithm (SITA) 24-2 VFs had at least one of the three: a glaucoma hemifield tests outside normal limits, pattern standard deviation (PSD) outside normal limits ($P < 0.05$), or a cluster of 3 or more adjacent points in characteristic glaucomatous locations, all of which were reduced on the pattern deviation plot at a $P < 5\%$ level. Preperimetric glaucoma eyes had the optic nerve rim defect on exam, consistent OCT findings of RNFL thinning, without qualifying VF findings. Staging of disease was based on the International Classification of Disease and Related Health Problems (ICD-9), as validated previously.²⁹ Normal participants in the study had a normal clinical exam including non-glaucomatous optic discs, no family history of glaucoma, and IOP ≤ 21 mm Hg. Inclusion criteria for both glaucoma and normal groups included age ≥ 18 years and best corrected visual acuity of 20/40 or better. Exclusion criteria included known media opacities (significant corneal scar or cataract); refractive error greater than +5.00D or less than -7.00D; macular or other retinal or optic nerve disease; history of ocular trauma or ocular surgeries other than uncomplicated cataract and glaucoma surgery; and unreliable visual field tests ($< 33\%$ fixation losses, false negative, and false-positive results). Only images with signal strength ≥ 6 (out of 10) and that were qualitatively observed to have lack of motion, media opacity (i.e. vitreous opacities), or defocus artifacts were included in the study. All subjects underwent slit lamp biomicroscopy, intraocular pressure measurement using Goldman applanation tonometry, VF testing (Humphrey Field Analyzer™ II-i 24-2; Zeiss), OCT imaging of GCIPL thickness (Cirrus™ HD-OCT 5000; Zeiss), and OCT angiography imaging (Zeiss Angioplex OCT Angiography; center wavelength 840 nm) acquiring 6×6 mm² scans of the macula. Demographic information collected from the clinical chart included age, sex, intraocular pressure, central corneal thickness (CCT), glaucoma medications, presence of diabetes or hypertension, prior ocular surgeries, VF mean deviation (MD), VF pattern standard deviation (PSD), average global GCIPL thickness, GCIPL thickness within each of six sectors (Figure 1) and cup to disc ratio in glaucomatous and normal eyes included in the study.

Visual Field and OCTA image analysis

The total MD from the VF 24-2 was recorded from the HVF output. The superior and inferior hemifield MDs were calculated by obtaining weighted averages of the total deviation values in each hemifield, using weightings provided by the manufacturer and based on the instrument's normative database. This is the same procedure used in the instrument for calculation of total MD. (Zeiss; Dublin, CA).

Prototype OMAG-based semi-automatic segmentation software of the raw OCTA data was used to obtain a GCIPL *en face* image of the macula, as has been previously described.³⁰

Briefly, structural data was used to delineate the anterior border of the ganglion cell layer and the posterior border of the inner plexiform layer on each B scan. These segmentation results were applied to the OMAG flow data. From this, vascular *en face* images of the GCIPL were created. (Figure 2) Of note, because the RNFL layer is superficial to the GCIPL, there is a theoretical risk of flow projection artifact from the RNFL layer. However, we evaluated for this by creating composite correlation coefficient images and found nearly no flow projection artifact from the RNFL layer.

Following this, custom quantification software with an interactive interface was used to quantify retinal vascular density and morphology from three parameters for the entire macula as well as for 6 focal sectors and hemispheres of the macula (MATLAB R2016a; MathWorks Inc, Natick, MA, USA). For the 6 sectors, the areas of quantification were demarcated to match the six sectors from the 6×6 Cirrus OCT macular ganglion cell analysis (Figure 1). That is, the area consisting of the six sectors were demarcated by two ellipsoids, with the outer ellipsoid having a vertical diameter of 4mm and horizontal diameter of 4.8mm, while the inner blacked-out ellipsoid was 1mm vertically and 1.2mm horizontally. The global OCTA parameter values were based on the entire 6mm×6mm scan. The original grayscale *en face* OCTA image of the macular GCIPL layer was converted to a binarized, black and white image using a three-way combined method consisting of global thresholding, Hessian filter, and adaptive threshold. The area within the foveal avascular zone was selected to establish the baseline signal-to-noise ratio for global thresholding. A vessel perimeter map was created by outlining vessels in the binarized image. A vessel skeleton map was created by linearizing vessel signals into 1-pixel width.

Three vessel parameters provided distinct and biologically relevant information about microvasculature perfusion. Vessel area density (VAD) provided information about both larger vessels and capillaries; vessel skeleton density (VSD) placed weight on the capillary-level vasculature and thus was considered a marker for capillary density; and vessel complexity index (VCI) was used to detect presence of degree of vessel branching or morphologic abnormalities. (Figure 3–4) From the binarized image, VAD was the unitless proportion of total sum area of pixels with detected OCTA signal ($A_{(i,j)}$; colored pixels in binarized image) divided by the total sum area of pixels

$$VAD = \frac{\sum_{i=1, j=1}^n A_{(i,j)}}{\sum_{i=1, j=1}^n X_{(i,j)}}$$

in the binarized image ($X_{(i,j)}$). The pixel coordinates were represented by (i,j) within the $(N \times N)$ pixel array of the binarized image:

VSD was the sum of $S_{(i,j)}$ (white pixels in the skeletonized image from linearized OCTA signal divided by the sum of $X_{(i,j)}$ (all pixels in skeletonized image):

$$VSD = \frac{\sum_{i=1, j=1}^n S_{(i,j)}}{\sum_{i=1, j=1}^n X_{(i,j)}}$$

Finally, for VCI, $P_{(i,j)}$ represented pixels occupied by the perimeter image, and $A_{(i,j)}$ represented colored pixels in the binarized image. From this, a vessel complexity map was created. VCI was the square of the sum of all P pixels divided by 4π times the sum of all A pixels:

$$VCI = \frac{\left(\sum_{i=1, j=1}^n P_{(i,j)} \right)^2}{4\pi \sum_{i=1, j=1}^n A_{(i,j)}}$$

Statistical analysis

SAS 9.4 Software (Cary, NC) and STATA 14.1 (College Station, TX) were used for all data analyses. Fisher's exact and Wilcoxon rank sum tests were used to compare differences in person-specific demographics between the glaucoma and normal groups. Clustered Wilcoxon rank sum test was used to compare differences in eye-specific demographics between the two groups and to report differences between normal, mild-moderate glaucoma, and severe glaucoma (controlling for age and inter-eye correlation). Fisher's exact or chi square tests were used to test differences in categorical variables between disease groups. Area-under-receiver-operating-curve statistics were calculated to assess diagnostic accuracy and controlled for age and inter-eye correlation. Because our data met all assumptions necessary for linear regression, linear regression using the generalized estimating equation (GEE) were performed to assess the association of functional and structural measures of glaucoma with each OCTA parameter, controlling for age and inter-eye correlation, among glaucoma patients. This was done globally, for hemispheres (VF MD, GCIPL thickness), and for six sectors (GCIPL thickness). Because GEE was utilized, pseudo R^2 values were calculated for the linear regressions in order to report the amount of variation in the dependent variable that can be explained by the model. Pearson's correlation coefficients were calculated to test the agreement of quantification results between repeated testing by the same operator (test-retest reliability) and again between two operators (intergrader reliability), based on a subset of 8 normal and 8 glaucoma eyes.

Results

Of 42 eyes from 28 POAG patients who underwent SD-OCTA macula imaging and met our inclusion and exclusion criteria, 34 eyes from 23 POAG patients were studied. Of the 27 healthy eyes from 19 control subjects imaged, 21 eyes from 16 controls were included. The other 14 eyes were excluded due to poor image quality from motion artifact or media

opacities such as vitreous floaters. 18 eyes had mild to moderate POAG (5 of which were preperimetric), and 16 had severe POAG. Of the POAG eyes, 10 eyes had both superior and inferior VF defects, 10 had superior defects, 9 had inferior defects, and 5 had neither. The average age was 62 years in the glaucoma group (61 years in mild to moderate group and 63 years in severe group) and 55 years in the normal group ($P=0.11$). Nonetheless, both age and inter-eye correlation were controlled for in our analyses. There was no difference in gender, hypertension, diabetes, central corneal thickness, or intraocular pressure between the POAG and normal groups. Additionally, it was evaluated whether hypertension was associated with any OCTA parameters, controlling for age, inter-eye correlation, and disease severity, but this was not found to be the case ($P=0.29$). In terms of glaucoma treatment, the mild-moderate POAG versus severe POAG group were on similar medications, except the severe POAG group had more eyes on brimonidine; additionally, more of the severe POAG eyes had had glaucoma surgery. (Table 1) We also evaluated whether each of the medication classes was associated with any OCTA parameters, controlling for age and disease severity; however, none were found to have an association. As expected, there was a significant difference in VF MD and PSD, GCIPL thickness, and cup-disc ratio between the glaucoma and normal eyes, controlling for age and inter-eye correlation. In addition, there was significantly reduced global vessel area density (VAD), global vessel skeleton density (VSD), and global vessel complexity index (VCI) in the GCIPL microcirculation in the POAG compared to normal groups, controlling for age and inter-eye correlation. (Table 1) The test-retest reliability was >0.9999 for each parameter, and the inter-user reliability was 0.995 for VAD, 0.996 for VSD, and 0.998 for VCI.

On qualitative review of the macular GCIPL microcirculation *en face* images, the microcirculation in POAG showed attenuation globally and focally that appeared to increase with worsening disease severity (Figure 3–4). This trend can be noted quantitatively with decreasing mean VAD, VSD, and VCI from normal to mild-moderate POAG to severe POAG. There was a significant difference in VAD, VSD, and VCI between normal and mild-moderate POAG, controlling for age and inter-eye correlation ($P_s=0.011$, 0.027, 0.035 respectively). Though the trend of decreased perfusion parameters with increased disease severity was present, there was no significant difference between mild-moderate and severe POAG groups for VAD, VSD, VCI, controlling for age and inter-eye correlation ($P_s=0.12$, 0.39, 0.14; respectively). Significant differences in OCTA parameters were present between normal and severe POAG for all three OCTA parameters ($P_s = 0.00025$, 0.0045, 0.00042, respectively). GCIPL thickness was significantly different between normal and mild-moderate POAG, mild-moderate and severe POAG, and normal vs severe POAG ($P_s = 0.0031$, 0.043, 0.0010, respectively). (Table 2)

In terms of sectoral values of the vessel parameters, there was no difference for each of the six sectors between normal versus mild-moderate POAG or between mild-moderate versus severe POAG, but some sectors did have significantly different OCTA parameter values for normal versus severe POAG. For VAD, the superonasal, inferonasal, inferior, and inferotemporal sectors were significantly reduced in severe POAG compared to normal ($P_s = 0.0089$, 0.0055, 0.0027, and 0.013, respectively). For VSD, which was a marker of capillary density, the superonasal, inferonasal, and inferior sectors were significantly reduced in the same comparison groups ($P_s= 0.041$, 0.016, 0.0028, respectively). For VCI, the

superotemporal, superonasal, inferonasal, inferior, and inferotemporal sectors had significant reductions (P s= 0.0056, 0.0044, 0.0015, 0.00089, 0.032 respectively). In contrast to the OCTA parameters, there was a significant difference in GCIPL thickness between normal and mild-moderate POAG (P s ranging from 0.0014 to 0.010) and between normal and severe POAG (P s ranging from 0.00067 to 0.0015) for each of the six sectors, and between mild-moderate POAG and severe POAG for the superotemporal, inferior, and inferotemporal sectors (P s 0.014, 0.0024, 0.0013, respectively). These analyses controlled for age and inter-eye correlation. (Table 2)

Table 3 reports the association of VF MD (global and hemispheric) with OCTA parameters in the corresponding regions, based on linear regressions controlling for age and inter-eye correlation. Globally, there were significant positive associations of global VF MD with global VAD and VCI (β s= 112.1, 4.36; P s=0.0060 and 0.0080), but this was not quite significant for VSD (β =134.7; P =0.081). For example, for a 0.01 change in VAD, a 1.12 dB change in global VF MD is predicted. The superior VF MD was significantly associated with corresponding VAD, VSD, and VCI (β s= 100.4, 152.4, 2.35; P s 0.0005, 0.0026, <0.0001, respectively), as was the inferior VF MD significantly associated with corresponding VAD, VSD, and VCI (β s= 122.2, 262.5, 2.97; P s = 0.0067, 0.0022, 0.0020). The pseudo R^2 values, which can be interpreted as the amount of variation in the VF MD that can be explained by the variation in the linear regression model, ranged from 0.12 to 0.29. Table 4 reports the association globally, hemispherically, and sectorally of GCIPL thickness with corresponding values for VAD, VSD, and VCI, controlling for age and inter-eye correlation. Globally and hemispherically, there were no significant associations. There were significant associations for the inferior sector only between GCIPL structural thickness and corresponding VAD, VSD, and VCI (β s= 56.0, 87.2, 5.68; P s = 0.018, 0.047, 0.024, respectively). All other sectors did not have significant associations between OCTA parameters and the structural thickness. The pseudo R^2 values for structural correlations ranged from 0.005 to 0.19.

Table 5 demonstrates the diagnostic accuracy of each of the global OCTA parameters, controlling for age and inter-eye correlation. Diagnostic accuracy was 0.83 for VAD (P <0.0001), 0.79 for VSD (P <0.0001), 0.82 for VCI (P <0.0001). There were no significant differences between each of the three parameters. This is in comparison to the diagnostic accuracy of global GCIPL thickness, which had diagnostic accuracy of 0.97 (P <0.0001).³¹

Discussion

Our study used a prototype semi-automatic segmentation algorithm for OMAG-based OCTA to identify the microvasculature within the GCIPL layer of the macula. We found significantly lower VAD, VSD, and VCI measurements in glaucoma compared to normal. While VAD provided total vessel area density, VSD was a marker for capillary density, and VCI was a marker for degree of vessel branching. Based on some interpretations of AUC, the diagnostic accuracy for all three global OCTA parameters could be considered fair to good.³¹ Rao et al., who also studied the diagnostic accuracy of the macular microcirculation, reported a diagnostic accuracy of 0.69 for vessel density of the global macula; in contrast, we reported diagnostic accuracy of 0.83 for vessel density (VAD) for the global macula.

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Their study differed in the size of their macula scan ($3 \times 3 \text{ mm}^2$ as opposed to $6 \times 6 \text{ mm}^2$ in our study), so their smaller scan size may have missed relevant ganglion cell pathology.¹⁹ In addition, their segmentation was automatic and extended from the inner limiting membrane to the IPL, which included the retinal nerve fiber layer (RNFL).¹⁹ Takusagawa et al. reported a diagnostic accuracy of 0.961 for macular vessel density also in the same segmentation zone including the RNFL. They used a $6 \times 6 \text{ mm}^2$ scan size like our study but unlike both Rao et al. and our study, they utilized reflectance-adjusted quantification algorithms aimed to remove media artifacts, and they included only perimetric glaucoma cases, which may create more contrast between perfusion values and thus inflate diagnostic accuracy compared to a study like ours that included more mild cases. Though Campbell et al have reported a distinct superficial vascular plexus extending from the ILM to IPL based on small histology and OCTA studies,³² our study suggests the possibility that excluding the RNFL from macular microcirculation assessments for glaucoma may offer equivalent diagnostic ability. Larger studies with direct comparisons of various segmentation patterns and using populations of similar glaucoma severity are needed to verify this.

In terms of functional associations of OCTA vessel parameters, there were significant positive associations globally for VAD and VCI with global VF MD. For both the superior and inferior hemifield MDs, there were significant associations with all three OCTA parameters (VAD, VSD, VCI). Based on the linear regression models, a change in VF MD of about 1.00 to 1.22 dB is expected to occur with a change in VAD of 0.01, depending on the region. A change in VF MD of 1.52 dB for the superior VF and 2.62 dB for the inferior VF is expected to occur for a 0.01 change in corresponding VSD. Interestingly, microcirculation perfusion measurements did not have significant positive associations with our structural measure, GCIPL thickness, globally nor hemispherically. Only the central inferior sector of the macula showed significant association between GCIPL thickness and the three OCTA parameters.

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It is interesting that OCTA measures of perfusion were significantly associated with functional measures of glaucoma both globally and in hemifields, but there was no significant association with structural measures of glaucoma in nearly all anatomic regions in our study. While Takusagawa et al. reported similar functional correlations to our study ($R = 0.444$ between visual field sensitivity and SVC vessel density versus $R = 0.452$ between visual field mean deviation and GCIPL VAD in our study), Takusagawa et al. reported a higher correlation for structural correlation with perfusion ($R = 0.804$ for GCC thickness and SVC vessel density versus $R = 0.42$ for GCIPL thickness and VAD in our study). This difference may be related to the fact that Takusagawa et al. included the RNFL in both the structural and perfusion measures, increasing the total anatomic structures and corresponding microvasculature being assessed that are affected by glaucoma. While we know from studies of the peripapillary region that RNFL thickness has good correlation with perfusion in RNFL en face images, we chose to focus on the perfusion more specific to the macular ganglion cell layer and inner plexiform layer. The fact that our degree of functional correlation was like that in Takusagawa et al. indicates that including the RNFL perfusion within the macula may not provide any additional insight into visual function beyond what the GCIPL macular perfusion provides. On the other hand, Yarmohammadi et al., which also studied the RNFL-GC-IPL perfusion, previously demonstrated that OCTA vessel density in

the macula was better associated with functional visual field measures rather than structural ganglion cell complex thickness.²⁰ Further research is needed to explore these relationships.

Based on studies showing improved VF function after surgical glaucoma treatment,^{33, 34} it has been suggested that sick RGCs that are responsible for VF defects can recover after appropriate glaucoma treatment. Studies have also shown improved ocular blood flow after glaucoma treatment.^{35, 36} In the future, studying the relationship of GCIPL microcirculation to visual function in longitudinal studies could provide great insight into this hypothesis and into our ability to identify sick and potentially recoverable RGCs.

It was interesting that there were distinct differences in VAD and VCI between normal and mild-moderate POAG but none of the three OCTA parameters (VAD, VSD, VCI) had significant differences between mild-moderate and severe POAG. It is possible that earlier stages of POAG are characterized by distinct incremental microvascular changes with disease severity as opposed to more severe stages, which may be predominated by apoptotic RGCs with perhaps less incremental microvascular change with worsening severity. Alternatively, the distinct incremental perfusion differences at the milder end of the severity spectrum may reflect a limited dynamic range in OCTA or in our particular thresholding algorithm. For comparison, global GCIPL thickness did have significant differences with each step of increasing disease severity for this patient population, suggesting that this traditional macular OCT measure is still better at distinguishing disease severity overall compared to our global vessel parameters. Prior studies have endorsed GCIPL thickness as good at detecting glaucomatous change both early or late.^{37, 38} Regardless, our preliminary data suggests GCIPL microcirculation may offer distinct information about glaucoma state than does GCIPL thickness.

When evaluating differences of OCTA measurements within focal sectors across disease severity, no OCTA parameter could detect differences between normal and mild-moderate POAG, whereas VSD in the superior, superonasal, and inferonasal sectors had significant differences between the mild-moderate and severe POAG groups. This may suggest that monitoring focal capillary density within the macular GCIPL may be particularly helpful at later disease stages, whereas global VAD and VCI were better at early stages. Larger studies will be needed to verify this observation. Otherwise, the lack of significant difference with increasing increments of disease severity for most OCTA measurements within a focal sector can likely be attributed to the fact that each patient has focal losses of microcirculation in variable regions specific to their own glaucoma damage; thus, for the entire study population, VAD and VCI appeared to perform best when considering their global values across the entire macula. This finding that global macular changes perform better than focal regions for discriminating glaucoma is supported by some prior studies.^{19, 39}

The strengths of our study included: our segmentation algorithm that allowed us to study the GCIPL circulation specifically; our quantification algorithm which allowed us to study vessel density separately from capillary density and vessel complexity; and inclusion of milder, preperimetric glaucoma cases, which provided a more realistic representation of glaucoma patients. Limitations include its small size, cross-sectional design precluding ability to study patients longitudinally, case-control design precluding full application to a

true clinic population, our lack of understanding of the effects of glaucoma treatment on macular microcirculation (though we did not see association between any medication type and perfusion parameters), and some technical limitations of a 6×6 mm² scanning algorithm. Namely, our 6×6 algorithm has lower resolution (17 microns/pixel) than smaller scan areas and while the FastTracTM algorithm was used to reduce motion artifact, some areas of minor motion artifact still represent a limitation in some of our data.

In summary, we demonstrated that GCIPL microcirculation in the macula was significantly reduced in glaucoma patients, that our global macula OCTA parameters had fair to good diagnostic accuracy, and there was more discriminating ability for global parameters than sectoral ones and at earlier rather than later stages of disease. We also demonstrated that GCIPL microcirculation appears to have better associations with functional rather than structural measures of glaucoma. Additional larger, longitudinal studies are needed to verify these ideas, should directly compare structural and functional associations, should compare RNFL-GC-IPL (“ganglion cell complex”) to GC-IPL microcirculation,^{23, 40} and should incorporate improved scanning and quantification algorithms as they become available.

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Figure 1. Sector definitions for right and left eyes, respectively, (ST=superotemporal, S=superior, SN=superonasal, IN=inferonasal, I=inferior, IT=inferotemporal) matches sectors from OCT ganglion cell analysis (ganglion cell-inner plexiform layer).

Figure 2.

Left eye macula of a glaucoma patient. (a) *En face* image of the superficial retinal layer from the Angioplex device. (b) *En face* image after semi-automatic (manually-verified) segmentation of the ganglion cell-inner plexiform layer shows increased contrast between areas of greater and lesser microcirculation.

Figure 3.

Right eye with mild-moderate glaucoma: a) OCTA *en face* with superotemporal microcirculation defects within the ganglion cell-inner plexiform (GCIPL layer); b) vessel skeleton map, c) vessel density map overlaid on binary vessel map, and d) vessel complexity map overlaid on binary vessel map showing reduced vessel density, capillary density, and vessel complexity in similar macular regions; e) GCIPL thinning in similar macular region; and f) visual field showing corresponding inferonasal defect.

Figure 4.

Right eye with severe glaucoma: a) OCTA *en face* with temporal microcirculation defects extending centrally within the ganglion cell-inner plexiform (GCIPL layer); b) vessel skeleton map, c) vessel density map overlaid on binary vessel map, and d) vessel complexity map overlaid on binary vessel map showing reduced vessel density, capillary density, and vessel complexity in similar macular regions; e) GCIPL thinning in similar macular regions; and f) visual field showing corresponding nasal defects extending centrally.

Figure 5.

Scatterplots of structural (GCIPL thickness; top row) and functional (visual field mean deviation; bottom row) correlations with global vessel area density (VAD), vessel complexity index (VCI), and vessel skeleton density (VSD), respectively. There are positive associations for all plots with a possibly stronger association being observed between visual field and OCTA parameters rather than GCIPL thickness and OCTA parameters. It is important to note that these are raw relationships, unadjusted for age or inter-eye correlation. See Tables 3–4 for correlation coefficient values, after adjusting for age and inter-eye correlation. GCIPL = ganglion cell-inner plexiform layer; OCTA = optical coherence tomography angiography.

Table 1

Demographic and Clinical Data of Normal and Glaucoma Groups by Severity

Variable	Normal (21 eyes from 16 patients)	Glaucoma (34 eyes from 23 patients)		P-Value ^o
		Mild/Moderate	Severe	
Age (patients)	55 (11) [^]	61 (12)	63 (13)	0.11
Female Sex (patients)	11 (69%)	8 (62%)	9 (64%)	0.61
Hypertension (patients)	1 (6%)	4 (31%)	6 (43%)	0.064
Diabetes (patients)	2 (13%)	3 (23%)	2 (14%)	0.68
Number of Glaucoma Medications	0	2.11 (1.08)	2.94 (1.34)	0.064
Eyes on Timolol	0	10 (56%)	13 (81%)	0.11
Eyes on Brimonidine	0	5 (28%)	11 (69%)	0.017
Eyes on Prostaglandin Analogs	0	14 (78%)	13 (81%)	0.80
Eyes on Carbonic Anhydrase Inhibitors	0	10 (56%)	11 (69%)	0.43
History of glaucoma surgery	0	1 (5%)	7 (44%)	0.0088
Central Corneal Thickness (microns)	565 (34)	561 (38)	547 (35)	0.415
Intraocular Pressure (mm Hg)	14.2 (3.1)	13.3 (3.6)	12.5 (2.8)	0.283
Ganglion Cell Layer-Inner Plexiform Layer (GCIPL) Thickness (microns)	88.2 (7.5)	68.4 (10.5)	61.6 (5.7)	0.00027
Cup-Disc Ratio	0.36 (0.13)	0.72 (0.21)	0.92 (0.04)	0.0000072
Visual field Mean Deviation (dB)	-0.84 (1.57)	-4.00 (3.94)	-10.97 (6.40)	0.0033
Visual field Pattern Standard Deviation (dB)	1.57 (0.38)	4.37 (3.31)	9.89 (3.10)	0.00043
Global Vessel Area Density	0.486 (0.014)	0.471 (0.019)	0.453 (0.024)	0.00029
Global Vessel Skeleton Density	0.230 (0.008)	0.223 (0.011)	0.215 (0.016)	0.0014
Global Vessel Complexity Index [~]	1.15 (0.04)	1.11 (0.05)	1.06 (0.06)	0.0044

[^] All data listed as mean (standard deviation) or percent (frequency).

^o P-values are for normal vs glaucoma, except for treatment-related parameters, which are between disease severity. P-values for person-specific continuous variables were based on Wilcoxon rank sum test on glaucoma and normal, and those for eye-specific variables were based on clustered Wilcoxon rank sum test, adjusting for age and inter-eye correlation. Fisher's exact test or Chi-square test were used for the categorical variables, including those distinguishing glaucoma treatment between disease severities.

[~] All VCI values are on the order of 10⁹.

Table 2
Mean OCTA and OCT (GCIPL thickness) Parameters for Normal, Mild-Moderate POAG, and Severe POAG Eyes

Parameter	Normal	Mild-Moderate POAG	Severe POAG	P-Values *		
	Mean (SD)	Mean (SD)	Mean (SD)	Normal vs Mild-Mod POAG	Mild-Mod vs Severe POAG	Normal vs Severe POAG
GLOBAL						
Vessel Area Density (VAD)	0.486 (0.014)	0.472 (0.018)	0.450 (0.02)	0.011	0.120	0.00025
Vessel Skeleton Density (VSD)	0.230 (0.008)	0.223 (0.010)	0.215 (0.016)	0.027	0.39	0.0045
Vessel Complexity Index (VCI)~	1.15 (0.38)	1.11 (0.50)	1.06 (0.62)	0.035	0.15	0.00042
GCIPL Thickness (microns)	88.2 (7.5)	69.0 (10.5)	61.6 (5.7)	0.0031	0.043	0.0010
SECTORAL DATA						
VAD - Sectoral Data						
ST	0.495 (0.017)	0.488 (0.029)	0.475 (0.036)	0.98	0.81	0.14
S	0.489 (0.015)	0.488 (0.024)	0.474 (0.023)	0.98	0.28	0.074
SN	0.491 (0.018)	0.486 (0.020)	0.470 (0.024)	0.54	0.13	0.0089
IN	0.492 (0.017)	0.485 (0.030)	0.472 (0.022)	0.42	0.14	0.0055
I	0.487 (0.014)	0.474 (0.035)	0.447 (0.044)	0.40	0.074	0.0027
IT	0.507 (0.017)	0.488 (0.023)	0.458 (0.045)	0.47	0.22	0.013
VSD - Sectoral Data						
ST	0.240 (0.010)	0.236 (0.013)	0.230(0.015)	0.51	0.87	0.18
S	0.235 (0.011)	0.233 (0.015)	0.228 (0.012)	0.96	0.63	0.20
SN	0.241 (0.009)	0.241 (0.013)	0.235 (0.009)	0.56	0.14	0.041
IN	0.240 (0.080)	0.238 (0.014)	0.233 (0.011)	0.86	0.38	0.016
I	0.233 (0.010)	0.225 (0.017)	0.214 (0.028)	0.072	0.24	0.0028
IT	0.235 (0.009)	0.234 (0.010)	0.223 (0.028)	0.92	0.71	0.38
VCI - Sectoral Data						
ST	464.8 (16.8)	449.7 (31.4)	435.8 (32.7)	0.17	0.44	0.0056
S	353.8 (16.0)	348.2 (25.7)	340.1 (21.2)	0.71	0.53	0.054
SN	458.0 (14.3)	454.3 (21.5)	438.6 (19.5)	0.90	0.12	0.0044
IN	451.3 (15.8)	442.7 (29.8)	428.9 (23.4)	0.31	0.31	0.0015

Parameter	Normal Mean (SD)	Mild-Moderate POAG Mean (SD)	Severe POAG Mean (SD)	P-Values*		
				Normal vs Mild-Mod POAG	Mild-Mod vs Severe POAG	Normal vs Severe POAG
I	348.4 (17.0)	335.2 (33.3)	312.5 (35.9)	0.23	0.25	0.00089
IT	448.3 (18.5)	445.8 (21.7)	413.5 (48.0)	0.85	0.33	0.032
<i>GCIPL thickness (microns)-Sectoral Data</i>						
ST	87.0 (7.8)	72.6 (17.2)	57.2 (12.0)	0.010	0.014	0.0015
S	89.6 (8.7)	71.7 (17.5)	61.6 (11.4)	0.010	0.074	0.0018
SN	90.9 (8.3)	72.0 (12.7)	67.9 (14.5)	0.0071	0.74	0.0032
IN	89.1 (8.0)	70.7 (11.3)	65.1 (7.6)	0.0052	0.19	0.00067
I	86.3 (8.0)	67.8 (8.0)	56.6 (4.5)	0.0015	0.0024	0.0015
IT	87.5 (6.1)	68.5 (7.7)	54.4 (6.4)	0.0014	0.0013	0.0019

* P-Values are based on clustered Wilcoxon rank sum test, controlling for age and inter-eye correlation, comparing: normal vs. mild-moderate POAG; mild-moderate vs. severe POAG; normal vs. severe POAG.

~ Global Vessel Complexity Index values should be multiplied by 10^9 .

OCTA= optical coherence tomography angiography; GCIPL= ganglion cell-inner plexiform layer; POAG= primary open angle glaucoma; Mod=moderate; SD= standard deviation; ST=superotemporal sector; S=superior sector; SN=superonasal sector; IN=inferonasal sector; I=inferior sector; IT=inferotemporal sector

Table 3

Linear regression ^{*} of visual field mean deviation (VF MD) on OCTA parameters globally and by hemispheres in glaucoma

	Corresponding Vessel Area Density (VAD)			Corresponding Vessel Skeleton Density (VSD)			Corresponding Vessel Complexity Index (VCI)		
	Beta	P-Value	R (R ² [°])	Beta	P-Value	R (R ²)	Beta [~]	P-Value	R (R ²)
Global VF MD	112.1	0.0060	0.452 (0.205)	134.7	0.081	0.347 (0.120)	4.36	0.0080	0.460 (0.211)
Superior VF MD	100.4	0.0005	0.470 (0.221)	152.4	0.0026	0.445 (0.198)	2.35	<0.0001	0.539 (0.290)
Inferior VF MD	122.2	0.0067	0.363 (0.132)	262.5	0.0022	0.385 (0.120)	2.97	0.0020	0.436 (0.190)

^{*} Controlled for age and inter-eye correlation.

OCTA =optical coherence tomography angiography.

[°] Pseudo R and R² is reported because this is the coefficient of determination that results from regression involving the generalized estimating equation. It can be interpreted as the amount of the VF MD that can be explained by the model.

[~]The beta values for vessel complexity index were scaled per 10⁹ change in VCI.

Table 4

Linear regression ^{*} of GC-IPL thickness on OCTA parameters by hemifield, sector, and globally in glaucoma

	Corresponding Vessel Area Density			Corresponding Vessel Skeleton Density			Corresponding Vessel Complexity Index		
	Beta	P-Value	R (R ²)	Beta	P-Value	R (R ²)	Beta	P-Value	R (R ²)
Global GCIPLt	33.9	0.58	0.42 (0.17)	9.28	0.93	0.42 (0.18)	0.89	0.73	0.42 (0.18)
Superior Hemifield GCIPLt	95.1	0.30	0.16 (0.024)	-32.0	0.88	0.072 (0.0051)	1.28	0.52	0.12 (0.013)
Inferior Hemifield GCIPLt	63.0	0.099	0.39 (0.15)	45.6	0.35	0.34 (0.11)	0.995	0.14	0.37 (0.14)
<i>Sectors</i>									
Superotemporal GCIPLt	97.6	0.094	0.27 (0.071)	128	0.41	0.22 (0.047)	9.65	0.10	0.26 (0.070)
Superior GCIPLt	95.4	0.20	0.17 (0.030)	-50.6	0.82	0.12 (0.010)	4.90	0.63	0.10 (0.014)
Superonasal GCIPLt	60.6	0.72	0.17 (0.028)	-75.3	0.73	0.15 (0.022)	4.89	0.76	0.15 (0.024)
Inferonasal GCIPLt	33.1	0.52	0.44 (0.19)	35.3	0.67	0.43 (0.19)	1.55	0.78	0.43 (0.19)
Inferior GCIPLt	56.0	0.018	0.40 (0.16)	87.2	0.047	0.39 (0.15)	5.68	0.024	0.39 (0.15)
Inferotemporal GCIPLt	40.8	0.21	0.20 (0.038)	22.7	0.73	0.13 (0.017)	4.31	0.16	0.21 (0.043)

^{*} Controlled for age and inter-eye correlation.

GCIPLt = ganglion cell-inner plexiform layer thickness; OCTA =optical coherence tomography angiography.

^o Pseudo R² is reported due to the linear regression involving the generalized estimating equation technique. It can be interpreted as the amount of the VF MD that can be explained by the model.

Table 5

Diagnostic Accuracy of Global OCTA Parameters

	<i>Area-Under-Curve Statistic</i> [*]	P-Values
Vessel Area Density (VAD)	0.83	<0.0001
Vessel Skeleton Density (VSD)	0.79	<0.0001
Vessel Complexity Index (VCI)	0.82	<0.0001
GCIPL Thickness	0.97	<0.0001

^{*} Controlled for age and inter-eye correlation.

P-values for area-under-curve contrasts between VAD-VSD, VAD-VCI, and VSD-VCI were all >0.05.

OCTA=optical coherence tomography angiography