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Inter-eye Asymmetry of Optical Coherence Tomography Angiography Vessel Density in Bilateral Glaucoma, Glaucoma Suspect, and Healthy Eyes

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Abstract

Purpose—To investigate inter-eye retinal vessel density asymmetry in healthy, glaucoma suspect, and mild to moderate glaucoma subjects, and its potential utility for early detection of glaucomatous damage.

Design—Cross-sectional study.

Methods—153 subjects including 55 healthy, 32 glaucoma suspect, and 66 glaucoma subjects enrolled in the Diagnostic Innovations in Glaucoma Study(DIGS). Vessel density was obtained from optical coherence tomography angiography (OCT-A) macular and optic nerve head scans. Thickness of peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell complex (mGCC) was measured with spectral-domain optical coherence tomography (SD-OCT) scans. Inter-eye asymmetry was calculated by taking the absolute value of difference in vessel density and thickness between the right and left eyes.

Results—Inter-eye retinal vessel density asymmetry parameters were significantly different among the three groups. Glaucoma suspects had significantly higher peripapillary and macular inter-eye vessel density asymmetries compared to healthy groups in univariate (1.1% vs. 2.0%, P=0.014 and 1.2% vs. 2.5%, P=0.027, respectively) and multivariate analyses (P=0.007 and 0.038,

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respectively). No significant differences in asymmetry of thickness parameters were found between glaucoma suspect and healthy groups (all $P > 0.718$). However significant differences in asymmetry of thickness parameters between glaucoma suspects and glaucoma patients ($P < 0.01$) were found for all parameters.

Conclusion—Inter-eye vessel density asymmetry can be quantified by OCT-A measurement. Glaucoma suspects have significantly greater vessel density asymmetry than healthy eyes. Longitudinal studies are needed to better characterize the relationship of vessel density asymmetry with the development and progression of glaucoma.

Keywords

Primary open angle glaucoma; optical coherence tomography angiography; vessel density; SD-optical coherence tomography

INTRODUCTION

Primary open angle glaucoma (POAG) is a leading cause of irreversible vision loss.[1] If detected early, disease progression can frequently be arrested or slowed with medical and surgical treatment.[2] However, it may be asymptomatic until relatively late in the course of the disease. Moreover, standard visual field loss may not be detected until a large complement of the retinal ganglion cells have been lost.[3] Understanding early events in the disease cascade is crucial to facilitate early diagnosis or detection of glaucomatous damage.

POAG is generally bilateral, but often asymmetrical in its earlier stages.[2] Asymmetry has been described as an early sign of glaucomatous damage.[4] Therefore, many studies have addressed the degree of inter-eye asymmetry and its implication in glaucoma management. Measurements of visual field, intraocular pressure (IOP) and cup-disc ratio of optic nerve head (ONH) asymmetry are often used in the differential diagnosis of glaucoma,[4,5] and asymmetry of optic disc cupping is characteristic of glaucomatous damage.[2] Recently, two studies using spectral-domain optical coherence tomography (SD-OCT) found that inter-eye retinal and retinal nerve fiber layer (RNFL) thickness asymmetry was a useful measurement for assessing early glaucomatous damage.[6,7]

Optical coherence tomography angiography (OCT-A) provides a reproducible quantitative assessment of the retina vasculature.[8,9] Studies using OCT-A have found that decreased vessel density was significantly associated with increasing severity of visual field damage,[10] and that vessel density had similar diagnostic accuracy to RNFL thickness measurements for differentiating between healthy and glaucoma eyes.[8] Further, retinal vessel density showed a stepwise decrease from healthy eyes to glaucoma suspect eyes to mild POAG eyes.[11] This suggested that retinal vascular dropout may occur early in the glaucomatous process.[11] However, inter-eye asymmetry of retinal vessel density has not been characterized previously.

The purpose of this study was to investigate the inter-eye retinal vessel density asymmetry in healthy, glaucoma suspect, and glaucoma subjects with mild to moderate disease, and its potential utility for early detection of glaucomatous damage.

METHODS

This was a cross-sectional study. Glaucoma patients, glaucoma suspect, and healthy subjects were recruited from the Diagnostic Innovations in Glaucoma Study (DIGS)[12]. The Institutional Review Boards of the University of California San Diego approved the protocol, and the methodology adheres to the tenets of the Declaration of Helsinki for research involving human subjects and to the Health Insurance Portability and Accountability Act. This study was registered at http://clinicaltrials.gov (no. NCT00221923) on September 14, 2005. Informed consent was obtained from all participants.

Participants

Participants underwent extensive clinical examinations. Inclusion criteria for these studies[12] were open angles upon gonioscopy, a best-corrected visual acuity of 20/40 or better, and a refraction less 5.0 diopters sphere and 3.0 diopters cylinder. Participants with a history of intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), retinal pathologies including diabetic retinopathy and hypertensive retinopathy, non-glaucomatous optic neuropathy, uveitis, ocular trauma, Parkinson's disease, Alzheimer's disease, or stroke were excluded. Other information including race, age, non-ocular disease history, blood pressure, and central corneal thickness (CCT) was also collected. Mean arterial pressure was calculated as one-third systolic BP + two-thirds diastolic BP. Mean ocular perfusion pressure (MOPP) was defined as the difference between two-thirds of mean arterial pressure and IOP.

Healthy subjects had bilateral (1) IOP < 21 mm Hg with no history of elevated IOP; (2) normal appearing optic disc, intact neuroretinal rim and RNFL; and (3) a minimum of two reliable normal visual fields, defined as a pattern standard deviation (PSD) within 95% confidence limits and a glaucoma hemifield test (GHT) result within normal limits.[8] Bilateral mild to moderate glaucoma patients were defined as individuals who had reliable (≤33% fixation losses and false negative results and ≤15% false positive results) and repeatable abnormal Standard Automated Perimetry tests with the Humphrey 24-2 Swedish Interactive Threshold Algorithm with PSD outside the 95% normal limits and a GHT results outside normal limits[8], and mean deviation (MD) >−12 dB in both eyes.[13] This group was named glaucoma group. Bilateral glaucoma suspect was defined as both eyes having optic discs appearance suspicious of glaucoma and/or ocular hypertension (IOP >21 mmHg) but without evidence of repeatable glaucomatous visual field damage.[14,15] A suspicious appearing optic disc was defined as a disc with observable excavation, neuroretinal rim thinning or notching, localized or diffuse retinal nerve fiber layer defect suggestive of glaucoma on optic disc stereophotographs.[12] Each photograph was reviewed by 2 independent certified reviewers according to a standard protocol. Each reviewer was masked to the participant's identity, diagnostic status, study, race, and other results. In cases of disagreement, a third senior reviewer adjudicated.[12,15] Individuals that did not have both eyes classified in the same diagnostic category were excluded. Cut-off values of age were defined for selecting healthy subjects to match the age range of glaucoma suspect and glaucoma patients. The mean ages of the three groups were then compared to confirm that there was not any significant difference among them.

Optical Coherence Tomography Angiography

The OCT AngioVue system (Optovue, Inc., Fremont, CA, USA) was used for characterizing the vascular structures of the retina at the capillary level. This system has been described previously.[8] The split- spectrum amplitude-decorrelation angiography method was used to capture the dynamic motion of the red blood cells and provide a high-resolution 3D visualization of perfused retinal vasculature. The OCT-A characterizes vascular information at each retinal layer as an en face angiogram, a vessel density map, and quantitatively as vessel density (percentage), calculated as the percentage area occupied by flowing blood vessels in the selected region using the commercial Optovue Angiovue system software (Optovue, Inc. version 2015.1.1.98).[10,16] Vessel density within the RNFL was measured from internal limiting membrane (ILM) to RNFL posterior boundary. Whole enface image vessel density in ONH (wiVD-ONH) was measured in the entire 4.5×4.5 mm^2 image, and circumpapillary vessel density (cpVD) was calculated in the region defined as a 750μm-wide elliptical annulus extending from the optic disc boundary. Macular superficial vessel density measurements were calculated in a slab from the ILM to the posterior border of the inner plexiform layer (IPL). Macular whole enface image vessel density (wiVD-M) measurements were calculated from 3×3 mm^2 scans centered on the fovea. Perifoveal vessel density (pfVD) was measured in an annular region with an inner diameter of 1 mm and outer diameter of 2.5 mm. Image quality review was completed according to the Imaging Data Evaluation and Analysis (IDEA) Reading Center standard protocol on all scans processed with standard AngioVue software (version 2015.1.1.98). Poor quality images, defined as images with (1) a signal strength index (SSI) of less than 48, (2) poor clarity, (3) residual motion artifacts visible as irregular vessel pattern or disc boundary on the enface angiogram, (4) local weak signal (due to vitreous opacity, floater, etc.), or (5) segmentation errors, were excluded.

Spectral-Domain Optical Coherence Tomography

The Spectralis SD-OCT (Spectralis HRA+OCT; Heidelberg Engineering Inc., Heidelberg, Germany, software version 5.4.7.0) was used to calculate the peripapillary RNFL measurements from a high resolution RNFL circle scan in a 10-pixel-wide band along a circle of 12 degrees centered on the ONH. The acquisition rate is 40,000 A-scans per second at an axial resolution of 3.9 mm and a lateral resolution of 6mm. All images were processed and reviewed by the IDEA Center graders. Images with noncentered scans, inaccurate segmentation of the RNFL that could not be manually corrected, or quality scores of ~15 dB or less were excluded from the analysis.

The Avanti (Optovue Inc.) macula cube scanning protocol, which consists of a 7×7 mm^2 raster scan, was used to measure the macular ganglion cell complex (mGCC) thickness. Macular GCC thickness measurements consist of the ganglion cell layer, IPL, and RNFL. Good-quality images defined as scans with a signal strength index ≥ ~37 and without segmentation failures or artifacts.

Statistical Analysis

Descriptive statistics, including mean, standard deviation (SD), and 95% confident interval (CI) for normally distributed variables, and median and interquartile range for non-normally

distributed variables, were computed. Inter-eye asymmetry values were calculated as the absolute value of the difference between the values of the right eye and left eye |OD-OS|. For normally distributed data, analysis of variance (ANOVA) and the post-hoc Tukey Honestly Significant Difference test were used to evaluate differences among groups and differences between each pair of groups. Otherwise, nonparametric analyses, Kruskal-Wallis test and Steel-Dwass tests, were used in univariate analysis. In multivariate analysis, non-normally distributed data were transformed into logarithmic scale, then analysis of covariance (ANCOVA) test was used. Turkey's least significance test was used as a post hoc pairwise test to determine which diagnostic groups were driving the statistical significance in the ANCOVA analysis. Age, gender, race, inter-eye difference of SSI and any other demographics or ophthalmic characteristics with P value <0.1 in univariate analysis were included in multivariable analysis. Area under the receiver operating characteristic (ROC) curves were used to describe the diagnostic utility.

Statistical analyses were performed using statistical software JMP pro 12 (SAS Institute Inc, Cary, NC) and Stata 14.2 (StataCorp LLC, College Station, TX). P values less than 0.05 were considered statistically significant.

RESULTS

A total of 153 subjects (306 eyes), including 55 healthy subjects, 32 glaucoma suspect subjects, and 66 mild to moderate glaucoma patients were included in the analysis. The demographic and ophthalmic characteristics of the three groups are summarized in Table 1. There was no statistically significant difference among the three groups in term of age, gender, race, self-reported history of diabetes, and inter-eye asymmetries of axial length and CCT. The groups differed by self-reported history of hypertension, and inter-eye asymmetries of MOPP, IOP, MD, and PSD. The glaucoma group had the greatest inter-eye asymmetries of MOPP, IOP, MD and PSD. The suspect group had the highest proportion of self-reported history of hypertension. Patients included in the glaucoma group had both eyes with mild to moderate glaucoma. The MD (mean ± SD) of eyes in the glaucoma group was −4.2 ± 2.9 dB (right eye −3.7±2.8 dB; left eye −3.7±2.8 dB), which was significantly worse than healthy and glaucoma suspect eyes.

The average wiVD-ONH, cpVD, wiVD-M, and pfVD of healthy eyes were 54.8±3.2%, 62.1±3.5%, 51.5±3.7%, and 53.9±3.8%, respectively. There were no significant differences in OCT-A measurements asymmetry of healthy subjects by race (African American vs. Caucasian, all P>0.10) or gender (female vs. male, all P>0.10).

There was no significant difference in inter-eye SSI difference among the groups for all measurements (OCT-A and SD-OCT) (P > 0.10 for all). In univariate analysis, statistically significant differences were found among the three groups for all macular and peripapillary vessel density asymmetry parameters (Table 2). Glaucoma patients showed the largest asymmetry in all parameters except for wiVD-M asymmetry, followed by glaucoma suspects and healthy subjects. The post-hoc pairwise comparison showed that peripapillary and macular wiVD inter-eye asymmetries were statistically lower in healthy group compared to glaucoma suspect group. However, there was no difference in vessel density asymmetry in

the macula and ONH between glaucoma suspect and glaucoma eyes. Inter-eye asymmetries in average global peripapillary RNFL (G-RNFL) thickness and mGCC thickness were also significantly different among the three groups, with the glaucoma group having the largest asymmetry. In contrast to vessel density asymmetry analysis, significant differences were found between glaucoma suspects and glaucoma patients but not between healthy subjects and glaucoma patients. The multivariate model included potential confounders such as age, gender, race, self-reported history of hypertension and diabetes, and inter-eye difference of SSI. All the significant associations found in univariate analysis remained significant after adjustment for confounders (Figure 1). Figure 2 shows the measurements of a representative glaucoma suspect showing larger asymmetry in vessel density compared to structure.

Table 3 summarizes the diagnostic accuracy of vessel density and structure thickness asymmetries for differentiating between 1) healthy and glaucoma suspect eyes and between 2) glaucoma suspect and glaucoma eyes. The AUC for discriminating between healthy and glaucoma suspect was highest for inter-eye asymmetry of wiVD-ONH, followed by wiVD-M, cpVD and pfVD inter-eye asymmetries. Among disc asymmetry parameters, the AUC for differentiating between healthy subjects and glaucoma suspects of wiVD-ONH inter-eye asymmetry was significantly higher than that of G-RNFL inter-eye asymmetry (P= 0.038). However, the differences in AUC between wiVD-M and mGCC inter-eye asymmetries for differentiating between healthy and glaucoma suspects did not reach statistical significance (P= 0.217). Although AUCs of thickness asymmetry were higher for differentiating glaucoma patients from healthy than the vessel density inter-eye asymmetry, the differences between AUCs of vessel density and thickness inter-eye asymmetry did not reach statistical significance.

DISCUSSION

In the present study, we evaluated inter-eye retinal vessel density asymmetry in healthy individuals, glaucoma suspects, and glaucoma patients with early to moderate disease. Inter-eye asymmetry of vessel density was significantly larger in the glaucoma suspects compared to healthy eyes. These findings suggest that glaucoma suspects develop significant vessel density asymmetry.

Wide variability in the appearance and values of the ONH and structure measurements in the healthy population makes identification of early glaucoma damage challenging.[1] Asymmetry between eyes is potentially advantageous for identifying pathological conditions compared to raw measurements. The comparison is not to another individual with different genetic or environment background, but between two eyes of the same individual. Asymmetry analyses are based on following assumptions. First, inter-eye anatomic symmetries are preserved in healthy eyes.[17] Second, although glaucoma is generally a bilateral disease, it often shows asymmetric features, particularly in the early stages of the disease.[2,17] Therefore, asymmetry greater than expected in comparison to healthy eyes may indicate glaucomatous damage.

There have been several investigations of inter-eye asymmetries in healthy subjects and glaucoma patients. In these studies, inter-eye asymmetry was calculated, for the most part, as the absolute value of the measurement; this is similar to what was done in the current study.

[6,7,18] In the current healthy group, the median inter-eye G-RNFL thickness asymmetry was 4 μm, which is similar to that found by Field and colleagues (3.58 μm).[7] The average retinal vessel density of this group was also similar to previous reports[8,19]; vessel density asymmetry ranged between 2–5%.

Studies using OCT-A have shown vasculature dropout in glaucoma suspect eyes.[8,9] Moreover, a recent longitudinal study observed a reduction in macular vessel density in eyes without detectable mGCC changes.[14] Recently, vasculature dropout was suggested as an early event in glaucomatous damage before detectable visual field damage.[11,20] If the decrease of vessel density happens in the early stage of glaucoma, then asymmetry develops earlier. By comparing inter-eye vessel density asymmetry and thickness asymmetry parameters among healthy, glaucoma suspect and mild to moderate glaucoma eyes, we found that the glaucoma suspect had significantly greater inter-eye asymmetry of both ONH and macular wiVD. In contrast, the mGCC and RNFL thickness asymmetry was not larger in glaucoma suspect compared to healthy eyes. This suggests that inter-eye retinal vessel density asymmetry could be detected in glaucoma suspect without significant thickness asymmetry.

Structure related parameters are increasingly being used as tools in the detection of early glaucoma.[21–23] Several studies have shown that structural asymmetry indices were comparable to raw measurements in identifying early glaucoma from healthy, and could be a potential ancillary tool evaluating glaucomatous damage.[24,25] Yarmohammadi et al[8] compared the diagnostic ability of vessel density and RNFL thickness for differentiating between glaucoma suspect eyes and healthy eyes, wiVD-ONH showed the highest AUC. The current study showed that for discriminating between healthy subjects and glaucoma suspect, wiVD-ONH asymmetry had the highest AUC; this was significantly higher than G-RNFL asymmetry. However, all AUC results suggest that the diagnostic accuracy differentiating between healthy and glaucoma eyes was modest for this study. Along with other measurements, these results suggested vessel density asymmetry could be helpful in screening pre-perimetric glaucoma eyes.

To exclude the possibility that the image quality was responsible for the difference between eyes, the inter-eye difference in SSI of all measurements among the three groups was compared and included in the multivariable model. The SSI inter-eye differences of OCT-A and SD-OCT measurements were similar among the three groups (all P values > 0.192). However, considering SSI showed a significant association with the vessel densities,[14,26] and SSI of both OCT-A and OCT were significantly greater in the healthy subjects compared to the glaucoma patients,[27] the inter-eye difference in SSI was included in the multivariate models. The inter-eye difference in SSI was not associated with either ONH vessel density asymmetries or G-RNFL and mGCC thickness asymmetries, but significantly correlated with vessel density asymmetries in the macula (wiVD-M asymmetry, P=0.001; pfVD asymmetry, P=0.016). There is no clear explanation for why macular vessel density asymmetries are more strongly associated with inter-eye SSI difference. Further study is warranted to clarify the role of scan quality in interpreting vessel density maps. In addition, although SSI represents general overall signal strength of the entire cube of OCT data, vasculature visibility depends on many other aspects that cannot be covered by SSI.

Therefore, a thorough review and control of the image quality, considering not only SSI but also clarity, motion artifacts, local weak signal due to vitreous opacities, etc. is necessary. However, one cannot completely rule out the influence of a local weak signal or other differences in quality between eyes as contributing to the measured asymmetries.

A limitation of this study is that, most of the glaucoma suspects had visible glaucomatous ONH abnormality. This was according to our entry criteria and introduces a potential source of bias for the comparisons of disc and macular parameters. Nevertheless, the change in optic nerve head and macular parameters were parallel in this study, and the density parameters showed a significant difference between healthy eyes and glaucoma suspects both for macula and optic nerve. Also, subjects in the current study only were included if both eyes were classified in the same diagnostic category (suspect or mild to moderate glaucoma). This design may underscore the discrimination power of inter-eyes symmetry parameters in detection of early glaucoma, and this study cannot extrapolate directly the asymmetries of the current bilateral suspects/mild-moderate glaucoma to other permutations of glaucomatous severity. In addition, it has reported that, after subtraction of large vessels by using a custom MATLAB program, perfused capillary density was less than the corresponding value derived from the intrinsic OCT-A software. This process increased the capability of vessel density to distinguish mild glaucoma from healthy eyes.[28] The OCT-A software utilized in this analysis didn't remove major retinal vessels, so the calculated vessel density includes both microvasculature and large vessels. A more recent Angiovue software version (version 2017.1.0.144) which includes vessel density measurements with large vessels removed was applied on a subset of eyes, and the results were similar. Future studies are needed to investigate the quality and reproducibility strategies for large vessel masking.

The present asymmetry analysis showed significant differences among bilateral healthy, glaucoma suspect, and glaucoma subjects. Glaucoma suspects developed significantly greater vessel density asymmetry compared to healthy eyes. This suggests that the evaluation of inter-eye vessel density asymmetry could be helpful for screening of glaucoma suspects. Longitudinal studies are needed to better characterize the relationship of vessel density asymmetry with the development and progression of glaucoma.

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References

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014; 311(18):1901–11. [PubMed: 24825645]
2. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet. 2004; 363(9422):1711–20. [PubMed: 15158634]

3. Harwerth RS, Wheat JL, Fredette MJ, Anderson DR. Linking structure and function in glaucoma. Prog Retin Eye Res. 2010; 29(4):249–71. [PubMed: 20226873]

4. Poinoosawmy D, Fontana L, Wu JX, Bunce CV, Hitchings RA. Frequency of asymmetric visual field defects in normal-tension and high-tension glaucoma. Ophthalmology. 1998; 105(6):988–91. [PubMed: 9627646]

5. Ong LS, Mitchell P, Healey PR, Cumming RG. Asymmetry in optic disc parameters: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci. 1999; 40(5):849–57. [PubMed: 10102281]

6. Jacobsen AG, Bendtsen MD, Vorum H, Bogsted M, Hargitai J. Normal Value Ranges for Central Retinal Thickness Asymmetry in Healthy Caucasian Adults Measured by SPECTRALIS SD-OCT Posterior Pole Asymmetry Analysis. Invest Ophthalmol Vis Sci. 2015; 56(6):3875–82. [PubMed: 26070059]

7. Field MG, Alasil T, Baniasadi N, et al. Facilitating Glaucoma Diagnosis With Intereye Retinal Nerve Fiber Layer Asymmetry Using Spectral-Domain Optical Coherence Tomography. J Glaucoma. 2016; 25(2):167–76. [PubMed: 24921896]

8. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Optical Coherence Tomography Angiography Vessel Density in Healthy, Glaucoma Suspect, and Glaucoma Eyes. Invest Ophthalmol Vis Sci. 2016; 57(9):OCT451–9. [PubMed: 27409505]

9. Jia Y, Wei E, Wang X, et al. Optical coherence tomography angiography of optic disc perfusion in glaucoma. Ophthalmology. 2014; 121(7):1322–32. [PubMed: 24629312]

10. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Relationship between Optical Coherence Tomography Angiography Vessel Density and Severity of Visual Field Loss in Glaucoma. Ophthalmology. 2016; 123(12):2498–508. [PubMed: 27726964]

11. Akil H, Huang AS, Francis BA, Sadda SR, Chopra V. Retinal vessel density from optical coherence tomography angiography to differentiate early glaucoma, pre-perimetric glaucoma and normal eyes. PLoS One. 2017; 12(2):e0170476. [PubMed: 28152070]

12. Sample PA, Girkin CA, Zangwill LM, et al. The African Descent and Glaucoma Evaluation Study (ADAGES): design and baseline data. Arch Ophthalmol. 2009; 127(9):1136–45. [PubMed: 19752422]

13. Hodapp, E., Parish, IIRK., Anderson, DR. Clinical Decisions in Glaucoma. St Louis, MO; Mosby: 1993. p. 52-61.

14. Shoji T, Zangwill LM, Akagi T, et al. Progressive Macula Vessel Density Loss in Primary Open-Angle Glaucoma: A Longitudinal Study. Am J Ophthalmol. 2017; 182:107–17. [PubMed: 28734815]

15. Khachatryan N, Medeiros FA, Sharpsten L, et al. The African Descent and Glaucoma Evaluation Study (ADAGES): predictors of visual field damage in glaucoma suspects. Am J Ophthalmol. 2015; 159(4):777–87. [PubMed: 25597839]

16. Chen HS, Liu CH, Wu WC, Tseng HJ, Lee YS. Optical Coherence Tomography Angiography of the Superficial Microvasculature in the Macular and Peripapillary Areas in Glaucomatous and Healthy Eyes. Invest Ophthalmol Vis Sci. 2017; 58(9):3637–45. [PubMed: 28728171]

17. Lee SY, Lee EK, Park KH, Kim DM, Jeoung JW. Asymmetry Analysis of Macular Inner Retinal Layers for Glaucoma Diagnosis: Swept-Source Optical Coherence Tomography Study. PLoS One. 2016; 11(10):e0164866. [PubMed: 27764166]

18. Sharifipour F, Morales E, Lee JW, et al. Vertical Macular Asymmetry Measures Derived From SD-OCT for Detection of Early Glaucoma. Invest Ophthalmol Vis Sci. 2017; 58(10):4030–7.

19. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Peripapillary and Macular Vessel Density in Patients with Glaucoma and Single-Hemifield Visual Field Defect. Ophthalmology. 2017; 124(5): 709–19. [PubMed: 28196732]

20. Cennamo G, Montorio D, Velotti N, Sparnelli F, Reibaldi M, Cennamo G. Optical coherence tomography angiography in pre-perimetric open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 2017.06.19.

21. Cennamo G, Montorio D, Romano MR, et al. Structure-Functional Parameters in Differentiating Between Patients With Different Degrees of Glaucoma. J Glaucoma. 2016; 25(10):e884–e8. [PubMed: 27483418]

22. Abe RY, Diniz-Filho A, Zangwill LM, et al. The Relative Odds of Progressing by Structural and Functional Tests in Glaucoma. Invest Ophthalmol Vis Sci. 2016; 57(9):OCT421–8. [PubMed: 27409501]

23. Oli A, Joshi D. Can ganglion cell complex assessment on cirrus HD OCT aid in detection of early glaucoma? Saudi J Ophthalmol. 2015; 29(3):201–4. [PubMed: 26155079]

24. Sullivan-Mee M, Ruegg CC, Pensyl D, Halverson K, Qualls C. Diagnostic precision of retinal nerve fiber layer and macular thickness asymmetry parameters for identifying early primary open-angle glaucoma. Am J Ophthalmol. 2013; 156(3):567–77. e1. [PubMed: 23810475]

25. Yamada H, Hangai M, Nakano N, et al. Asymmetry analysis of macular inner retinal layers for glaucoma diagnosis. Am J Ophthalmol. 2014; 158(6):1318–29. e3. [PubMed: 25194230]

26. Rao HL, Pradhan ZS, Weinreb RN, et al. Determinants of Peripapillary and Macular Vessel Densities Measured by Optical Coherence Tomography Angiography in Normal Eyes. J Glaucoma. 2017; 26(5):491–7. [PubMed: 28263261]

27. Rao HL, Pradhan ZS, Weinreb RN, et al. A comparison of the diagnostic ability of vessel density and structural measurements of optical coherence tomography in primary open angle glaucoma. PLoS One. 2017; 12(3):e0173930. [PubMed: 28288185]

28. Geyman LS, Garg RA, Suwan Y, et al. Peripapillary perfused capillary density in primary open-angle glaucoma across disease stage: an optical coherence tomography angiography study. Br J Ophthalmol. 2017; 101(9):1261–8. [PubMed: 28148529]

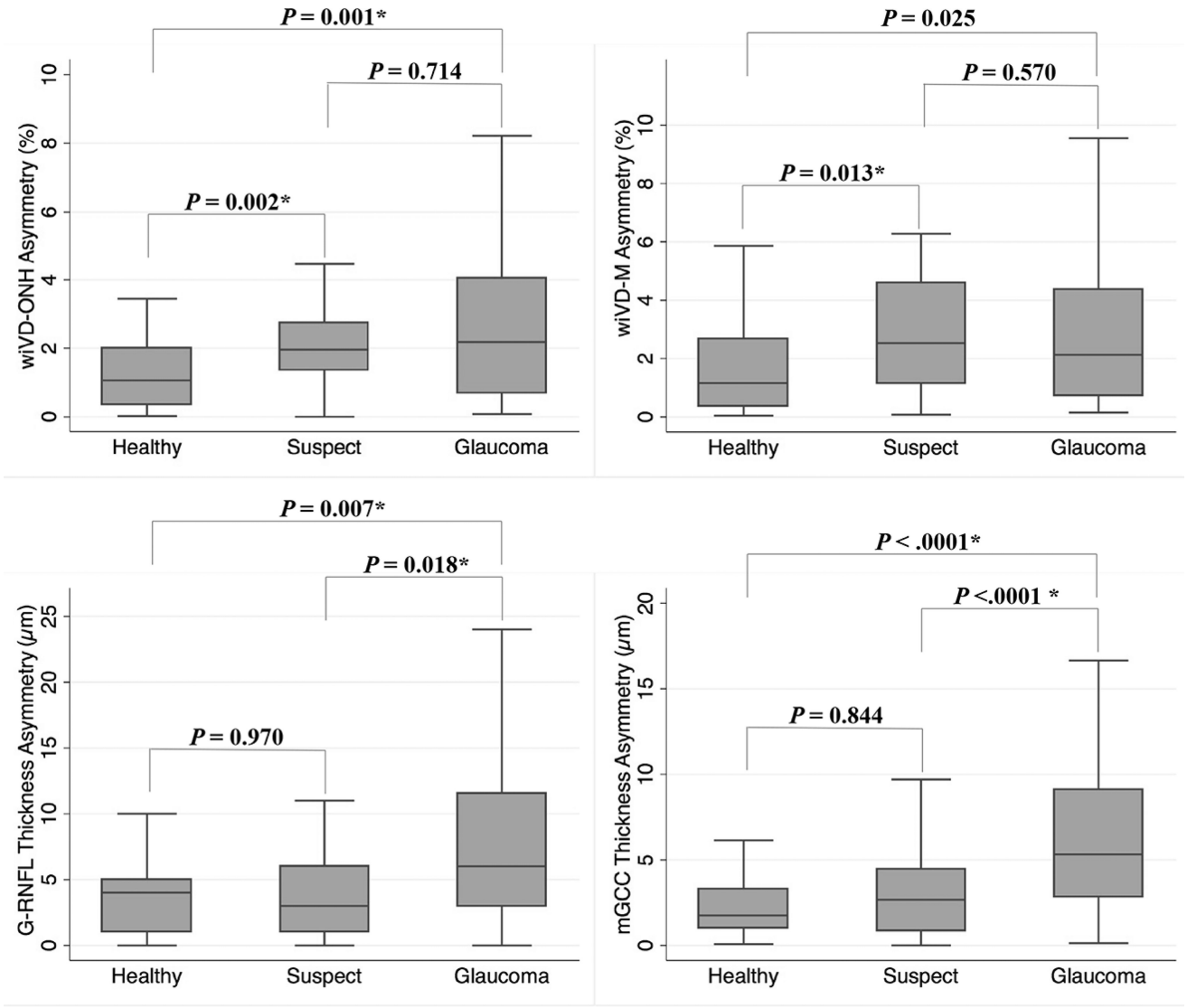

Figure 1.

Boxplots illustrating the distribution of inter-eye vessel density and thickness asymmetry parameters in healthy, glaucoma suspect, and glaucoma subjects, with *P* values from the multivariate analysis. The medians are represented by horizontal lines in the boxes. Boxes represent the interquartile range between the first and third quartiles. *P* values derived from the multivariate analysis show a significant difference in whole enface image vessel density of optic nerve head (wiVD-ONH) asymmetry (top left) and a borderline significant difference in whole enface image vessel density of macula (wiVD-M) asymmetry (top right) between healthy and glaucoma suspect group, which was not found in average global peripapillary retinal nerve fiber layer (G-RNF) thickness asymmetry (bottom left) and macular ganglion cell complex thickness (mGCC) asymmetry (bottom right) analysis. *, significant difference, $P < 0.05$.

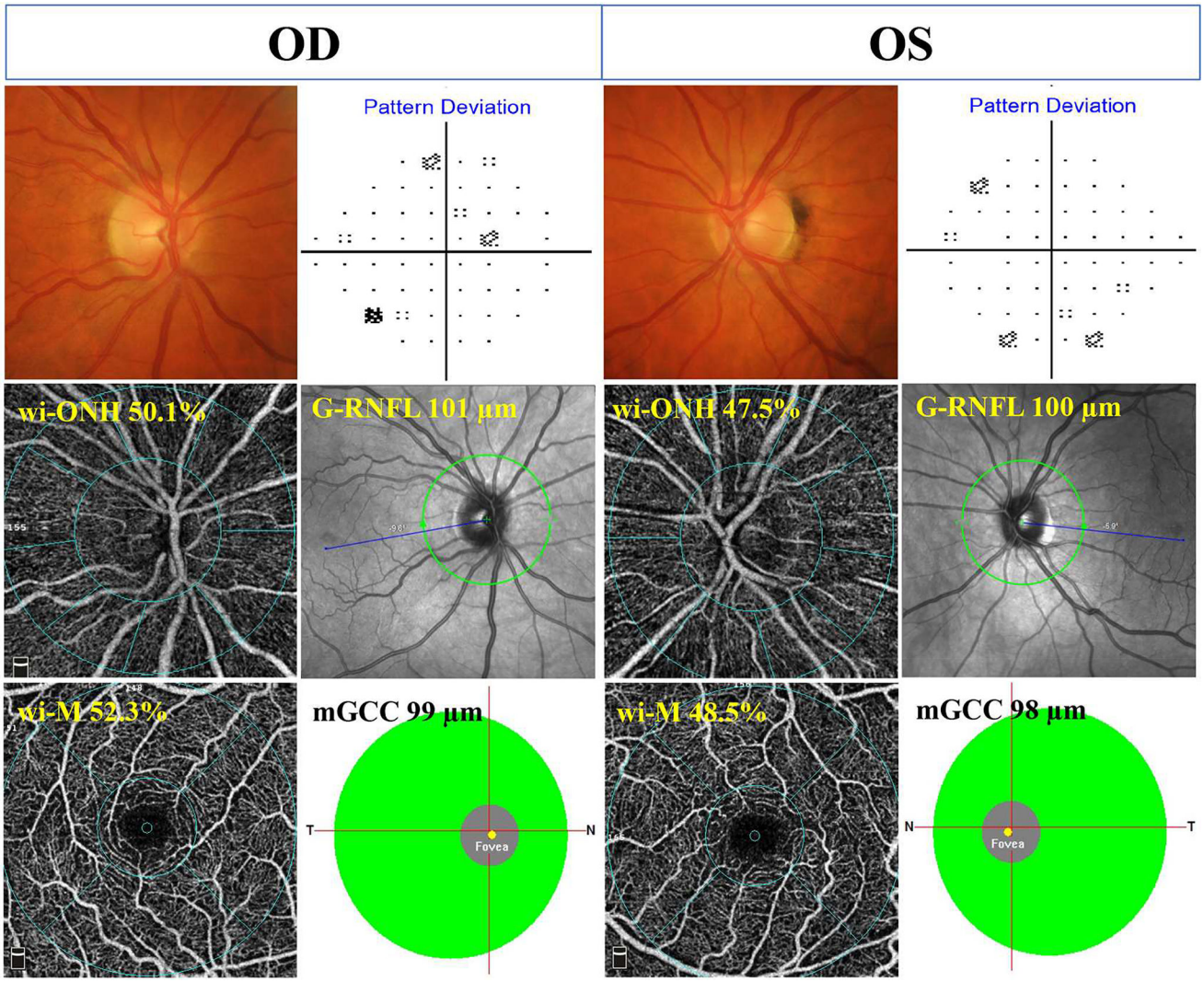

Figure 2.

Case example of a sixty-two-year old male glaucoma suspect. Top row: Optic disc photographs classified as suspicious of glaucoma (first and third from left) and visual field tests results within normal limits (second and fourth from left). Optical coherence tomography angiography measurements of whole enface image vessel density of optic nerve head (second row, first from left, right eye 50.1% (SSI 65); third from left, left eye 47.5% (SSI 67)) and whole enface image vessel density of macula (third row, first from left, right eye 52.3% (SSI 75); third from left, left eye 48.5% (SSI 75)) with inter-eye vessel density asymmetries of 2.6% and 3.8%, respectively. The optical coherence tomography measurements of average global peripapillary retinal nerve fiber layer thickness (second row, second from left, right eye 101 µm; fourth from left, left eye 100 µm) and macular ganglion cell complex thickness (third row, second from left, right eye 99 µm; fourth from left, left eye 98 µm) with inter-eye thickness asymmetries of 1 µm for both parameters.

Table 1

Summary of Demographics and Ophthalmic Characteristics of Healthy Subjects, Glaucoma Suspects and Glaucoma Patients

	Healthy (n=55)	Suspect (n=32)	Glaucoma (n=66)	*P* value
Age (yrs)	64.4±12.5	67.1±12.1	67.1±8.2	0.339
Gender (F/M)	42/13	24/8	38/28	0.056
Race, no. (%)				0.132
Caucasian	41 (74.6%)	20 (62.5%)	35 (53.0%)	
African American	10 (18.2%)	7 (21.9%)	23 (34.9%)	
Other	4 (7.3%)	5 (15.6%)	8 (12.1%)	
Diabetes, no. (%)	4 (7.3%)	5 (15.6%)	15 (22.7%)	0.056
Hypertension, no. (%)	18 (32.7%)	22 (68.8%)	30 (45.8%)	0.005 *
Diastolic BP (mmHg)	81.6±11.2	86.2±10.6	80.8±13.8	0.120
Systolic BP (mmHg)	130.1±18.0	131.6±18.4	126.7±23.1	0.483
Mean arterial pressure (mmHg)	97.8±12.1	101.3±12.3	96.1±16.1	0.235
MOPP (mmHg)	OD: 49.6±7.6	OD: 48.8±9.9	OD: 49.9±11.6	
	OS: 49.7±7.7	OS: 49.3±9.7	OS: 49.2±11.3	
Axial Length (mm)	OD: 23.7±1.1	OD: 24.2±1.0	OD: 24.5±1.3	
	OS: 23.6±1.1	OS: 24.2±1.0	OS: 24.5±1.3	
CCT (μm)	OD: 558.0±36.3	OD: 560.4±49.8	OD: 538.7±35.6	
	OS: 560.0±35.2	OS: 563.2±51.1	OS: 540.7±35.8	
IOP (mmHg)	OD: 15.6±3.2	OD: 18.7±4.9	OD: 14.2±4.1	
	OS: 15.5±3.0	OS: 18.2±4.6	OS: 14.7±3.9	
MD (dB)	OD: 0.4±1.1	OD: −0.03±1.2	OD: −3.7±2.8	
	OS: 0.2±1.3	OS: −0.6±1.7	OS: −4.7±3.0	
PSD (dB)	OD: 1.6±0.4	OD: 1.7±0.5	OD: 5.0±3.2	
	OS: 1.6±0.4	OS: 2.0±0.9	OS: 5.9±3.3	

For normally distributed variables, results are shown in mean ± standard deviation.

MOPP=mean ocular perfusion pressure; CCT=central corneal thickness; IOP=intraocular pressure; MD=mean deviation; PSD=pattern standard deviation; BP=blood pressure; M=male; F=female; yrs=years.

*, statistically significant.

Table 2

Inter-eye Asymmetry of Healthy, Glaucoma Suspect, and Glaucoma Subjects: Univariate Analysis

	Median (25% quartile, 75% quartile)			*P* value	Post Hoc		
	Heathy	Suspect	Glaucoma		$P_{H\text{-}G}$	$P_{H\text{-}S}$	$P_{S\text{-}G}$
Inter-eye Asymmetry of Vessel Density in Optic Nerve Head (%)							
Whole image	1.1 (0.3, 2.0)	2.0 (1.3, 2.8)	2.2 (0.7, 4.0)	<.001*	0.001*	0.014*	0.803
Circumpapillary	1.7 (0.8, 2.6)	2.0 (1.3, 4.1)	2.2 (1.3, 4.3)	0.026*	0.027*	0.151	0.937
Inter-eye Asymmetry of Vessel Density in Macula (%)							
Whole image	1.2 (0.4, 2.7)	2.5 (1.2, 4.6)	2.1 (0.7, 4.4)	0.015*	0.046*	0.027*	0.944
Perifoveal	1.4 (0.7, 3.3)	2.4 (1.2, 4.7)	2.7 (1.4, 4.6)	0.012*	0.009*	0.174	0.819
Inter-eye Asymmetry of Structure Thickness (μm)							
Peripapillary retinal nerve	4 (1, 5)	3 (1,6)	6 (3,12)	<.001*	<.001*	0.943	0.003*
Macular ganglion cell	1.8 (1, 3.3)	2.7 (0.7, 4.8)	5.3 (2.8, 9.1)	<.001*	<.001*	0.718	0.006*
Inter-eye Asymmetry of Other Ocular measures							
MOPP (mmHg)	1 (0, 2)	1 (0, 2)	2 (1, 3)	0.021*			
Axial Length (mm)	0.1(0.04, 0.2)	0.1 (0.03, 0.2)	0.1 (0.05, 0.2)	0.500			
CCT (μm)	8.0 (2.5, 13.7)	3.84(2.3, 10.6)	8.0 (3.7, 14.3)	0.106			
IOP (mmHg)	1.0 (0, 2.0)	1.0 (0, 2.0)	2.0 (1.0, 3.3)	0.011*			
MD (dB)	0.5 (0.3, 0.9)	1.0 (0.4, 1.6)	1.8 (0.9, 3.5)	<.0001*			
PSD (dB)	0.2 (0.1, 0.4)	0.3 (0.1, 0.6)	2.2 (0.6, 4.0)	<.0001*			

MOPP=mean ocular perfusion pressure; CCT=central corneal thickness; IOP=intraocular pressure; MD=mean deviation; PSD=pattern standard deviation; BP=blood pressure; M=male; F=female; yrs=years.

*, statistically significant.

Table 3

Diagnostic Performance of Inter-eye Asymmetry of OCT-A and Structure Measurements in Healthy, Glaucoma Suspects, and Glaucoma Patients

	Healthy vs Suspects Discrimination AUC		Healthy vs Glaucoma Discrimination AUC	
	Mean	**95% CI**	**Mean**	**95% CI**
Inter-eye Asymmetry of Vessel Density in Optic Nerve Head				
Whole image	0.69	0.57, 0.82	0.70	0.58, 0.80
Circumpapillary	0.63	0.50, 0.76	0.63	0.51, 0.74
Inter-eye Asymmetry of Vessel Density in Macula				
Whole image	0.67	0.55, 0.79	0.64	0.52, 0.75
Perifoveal	0.62	0.48, 0.75	0.67	0.56, 0.78
Inter-eye Asymmetry of Structure Thickness				
Peripapillary retinal nerve fiber	0.52	0.39, 0.65	0.74	0.64, 0.84
Macular ganglion cell complex	0.55	0.41, 0.69	0.73	0.62, 0.84

AUC= area under receiver operating characteristic curve; CI= confidence interval.