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Central Macular OCTA Parameters in Glaucoma

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Abstract

Background/Aims: To investigate the relationship between the foveal avascular zone (FAZ) parameters assessed by optical coherence tomography angiography (OCTA) and central visual field parameters in glaucoma and healthy subjects.

Methods: One hundred eighty-eight subjects (248 eyes), including 24 healthy (38 eyes), 37 glaucoma suspect (42 eyes), and 127 primary open angle glaucoma (POAG) patients (168 eyes) underwent imaging using OCTA and standard automated perimetry using the 24-2 and 10-2 Swedish Interactive Thresholding Algorithm. OCTA- and OCT-based FAZ parameters (superficial FAZ area, FAZ circumference), foveal vessel density (FD300) and foveal thickness were measured. The correlation between FAZ parameters and visual field parameters were assessed using linear mixed model.

Results: Axial length adjusted-FAZ area was not different among the three groups (mean (95%CI)): in healthy 0.31 (0.27, 0.36) mm^2, glaucoma suspect 0.29 (0.26, 0.31) mm^2, and POAG eyes 0.28 (0.27, 0.30) mm^2 (P=0.578). FD300 was lower in glaucoma suspect 49.1 (47.9, 50.4) % and POAG eyes 48.7 (48.1, 49.4) % than healthy eyes 50.5 (49.3, 51.7) % though the difference was not statistically significant (P=0.071). Lower FD300 was associated with worse 24-2 and 10-2 visual field mean deviation and foveal threshold in multivariable linear mixed models (all P<0.05). In addition, a smaller FAZ area was associated with lower intraocular pressure (P=0.026).

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Involved in design and conduct of study: TN, WHK and SM. Data collection: TN, SM, HH, RCCD, AK, NE and JR. Analysis and interpretation of data: TN, WHK, SM and RNW. Writing: TN, AY and RNW. Critical revision: TN, SM, TS and RNW. Approval of the manuscript: TN, WHK, SM, AY, HH, RCCD, AK, TS, NE, JR, LMZ and RNW

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Conclusions: The FD300, but not the FAZ area was correlated with 10 degree central visual field mean deviation and foveal threshold in healthy, glaucoma suspect and POAG eyes. In contrast, a smaller FAZ area was associated with lower IOP.

Keywords

central visual field; foveal avascular zone; glaucoma; optical coherence tomography angiography

INTRODUCTION

Glaucoma is a progressive multifactorial optic neuropathy that is characterized by progressive retinal ganglion cell (RGC) death and axonal loss[1 2]. Despite the mounting evidence regarding the role of vascular factors in the pathogenesis of glaucoma,[3-6] the nature of its association with glaucomatous optic neuropathy remains elusive. Optical coherence tomography angiography (OCTA) is a non-invasive imaging technique that enables characterization of the retinal vasculature and provides reproducible quantitative assessments of the retinal microvascular networks.[7]

The macula is the area with the highest density of RGCs. Several studies have reported that early glaucomatous damage can affect the macular area.[8 9] Many reports have documented attenuation of vasculature in the macular region using OCTA in eyes with glaucoma compared with healthy eyes.[10-13] Winegarner et al. showed that in central retinal vein occlusion eyes, microvascular ischemic changes in the macular region can lead to foveal avascular zone (FAZ) changes, which might reflect the severity of photoreceptor damage associated with visual function.[14] Several studies have also shown changes in the FAZ associated with glaucomatous damage in glaucoma eyes.[15-18]

Inanc et al. showed that changes in the foveal vessel density (FD300; vessel density in a 300 μm band around the outer border of FAZ) and parafoveal vessel density (pfVD) in the deep capillary plexus precede the enlargement of FAZ.[19] While whole image vessel density (wiVD) and pfVD are affected by the size of FAZ area, FD300 is not affected. From that perspective, FD300 may be a candidate for a clinically relevant parameter that provides information about the perfusion of the region responsible for foveal thresholds.

We hypothesized that FAZ parameters could provide valuable information about macular perfusion in association with glaucomatous damage. The aim of the current study was to evaluate the difference in FAZ parameters in normal, glaucoma suspect, and glaucoma eyes and to further evaluate the association between FAZ parameters and central visual field measurements.

METHODS

Study Population

This was a cross-sectional study of healthy, glaucoma suspect and primary open angle glaucoma (POAG) patients enrolled in Diagnostic Innovations in Glaucoma Study (DIGS) [20] who underwent OCTA (Angiovue; Optovue Inc., Fremont, CA). This prospectively designed study received the institutional review board approval of the University of

California, San Diego (NCT00221897) and the methodology adhered to the tenets of the Declaration of Helsinki for research involving human subjects and to the Health Insurance Portability and Accountability Act. Details of the DIGS protocol and eligibility criteria have been described previously.[20 21] Briefly, all participants underwent an annual comprehensive ophthalmologic examination. In addition, there was a semi-annual examination that included intraocular pressure (IOP), OCT and OCTA imaging, and visual field (VF) testing by standard automated perimetry (Humphrey Field Analyzer; Carl Zeiss Meditec). Axial length measurements were acquired from all patients with the IOLMaster (Carl Zeiss Meditec). Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), Parkinson's disease, Alzheimer's disease, or stroke. Eyes with coexisting retinal pathology, non-glaucomatous optic neuropathy, uveitis, ocular trauma were excluded. Eyes with an axial length of 27 mm or more were also excluded from this study.

Participants were classified into 3 groups: healthy controls, glaucoma suspect, and POAG patients. Healthy subjects were defined as having IOP of 21mmHg or lower, without a history of elevated IOP; normal-appearing optic discs; and normal VF tests using the 24-2 Swedish Interactive Thresholding Algorithm (SITA), defined as pattern standard deviation (PSD) within the 95% confidence limits and glaucoma hemifield test (GHT) result within normal limits in both eyes. Glaucoma suspect were defined as having elevated IOP (≥ 22mmHg) or suspicious-appearing optic discs without the presence of repeatable glaucomatous VF damage. POAG was defined as having both glaucomatous optic neuropathy and repeatable abnormal VF tests with good reliability indices (fixation losses and false negatives ≤ 33% and ≤ 15% false positives) on the SITA 24-2 tests; either a PSD outside the 95% normal limits or a GHT result outside the normal limits. A subject could have one eye in the glaucoma suspect group and one eye in the glaucoma group. POAG eyes were classified into 3 groups based on mean deviation (MD) of the latest 24-2 VF test (Mild: MD>−6dB, Moderate: −6dB≥MD>−12dB, Advanced: MD≤−12dB).[22 23] All study eyes were required to also have reliable 10-2 tests within 6 months of reliable 24-2 VF tests and within 230 days of OCTA scans.

Optical coherence tomography angiography

OCTA imaging was performed using the AngioVue imaging system (Optovue, Inc, Fremont, California, USA; Software version 2017, 1, 0, 151). Macula 3×3-mm2 scans (304 B-scans × 304 A-scans per B-scan) centered on the fovea were acquired with the OCTA AngioVue system. OCTA-based ganglion cell complex (GCC) vessel density and OCT-based GCC thickness measures were calculated from the same macula scan. The retinal layers of each scan were automatically segmented by the AngioVue software in order to visualize the superficial retinal capillary plexuses in a slab from the internal limiting membrane (ILM) to the inner plexiform layer (IPL) - 10 mm. For this study, wiVD was derived from the entire 3 × 3-mm^2 scan and perifoveal vessel density (pfVD) was measured in an annular centered on the fovea with an inner diameter of 1 mm and outer diameter of 3 mm. The software detects capillary-free area and calculates FAZ parameters automatically based on the retinal slab. For the FAZ, images from the superficial retinal layer were evaluated. The FAZ was defined as the region that enclosed by innermost macular arcade. We used the FAZ parameter: FAZ

area, FAZ circumference, and foveal density 300 (FD300). FD300 is defined as the vessel density of the 300 μm width ring surrounding the FAZ (Figure 1).

FAZ area was corrected to consider the magnification effect using Littman formula, which uses axial length as the main correction factor, as this formula has been previously reported to be more accurate than the method using keratometry.[24] Given 23.95 mm as the default for axial length Avanti systems used, the value of 3.46 was used as the magnification factor for the measurements. Corrected FAZ area = FAZ area * 3.46^2 * 0.013062^2 * (Axial length - $1.82)^2$[25-27]

OCTA image quality review was performed by trained investigators following a standard protocol established by the University of California, San Diego Imaging Data Evaluation and Analysis (IDEA) Reading Center.[28] A poor-quality image was defined as an image with a signal strength index <48, poor clarity, residual motion artifacts recognized as an irregular vessel pattern on the enface image, local weak signal or segmentation errors, and off-centered fovea.

Central visual field parameters

Central VF sensitivity was evaluated using the mean sensitivities of the eight (MS8) and four (MS4) innermost central points of 10-2 tests, and foveal threshold (FT) of both 10-2 and 24-2 VF tests (10-2 VF FT and 24-2 VF FT).[10] The mean sensitivities of the eight and four central points (MS8 and MS4) were calculated by averaging the threshold sensitivity values of the eight (4 points located 1 degree in each direction away from the fovea and 4 points located 3 degrees in each direction away from the fovea) and four (4 points located 1 degree) central points of the 10-2 VF, respectively.[10]

Reproducibility of FAZ parameters

Reproducibility of FAZ parameters was assessed in 33 healthy eyes of 20 subjects who had 3 visits in 1 year. Intraclass correlation coefficient (ICC) as a measure of agreement between test and re-test values of each measurement was calculated. The coefficient of variation (CV) was calculated by dividing the standard deviation of measurements by their mean values.

Statistical analysis

Continuous and categorical data are presented as mean (95% confidence interval, CI) and count (%). Statistically significant differences in patient characteristics between the healthy, glaucoma suspect, and POAG groups were determined by linear regression model for continuous variables and Fisher's exact test for categorical variables. Post hoc significance was calculated using Tukey honest significant difference test. R-squared values were obtained using linear mixed model to examine which of the FAZ parameters (corrected FAZ area, FAZ circumference, FD300) correlate well with the VF parameters and IOP. Measurements of bilateral eyes were nested within subject to take account for within-subject variability. Similarly, the correlation between average ILM-IPL thickness within central 1 mm (foveal ILM-IPL thickness) and the VF parameters, as well as correlation between foveal ILM-IPL thickness and the FAZ parameters were analysed. Univariable and multivariable linear mixed analysis were performed to determine the factors

associated with FAZ area and FD300. Multivariable models were fit including age and other ocular characteristics with P value of less than 0.10 in the univariable analysis. Statistical significance was defined at P<0.05. All statistical analyses were conducted using Stata/IC version 15.0 (StataCorp, Texas, USA).

RESULTS

A total of 188 subjects (248 eyes), comprising of 24 healthy (38 eyes), 37 glaucoma suspect (42 eyes), and 127 POAG (168 eyes) patients were included. The POAG group included 121 mild, 28 moderate, and 19 advanced glaucoma patients determined by MD of latest 24-2 VF. Mean age in the healthy group was significantly lower than in both glaucoma and glaucoma suspect groups (P=0.003; Table 1). Statistically significant differences were seen among the groups with respect to all VF indices (24-2 VF MD, PSD and FT; 10-2 VF MD, PSD and FT; MS4 and MS8) (P<0.05 for all), and macular wiVD (P<0.001) and macular pfVD (P<0.001). There were no significant differences in the IOP measurements at the time of image acquisition among healthy 14.6 (13.6, 15.6) mmHg, glaucoma suspect 16.7 (15.2, 18.3) mmHg, and glaucoma 14.5 (13.8, 15.2) mmHg eyes (P=0.067).

Reproducibility of the FAZ parameters measured was best (highest ICC and lowest CV) for the FAZ circumference followed by FAZ area and FD300 ((ICC 95% CI of 0.985 (0.971, 0.992), 0.979 (0.960, 0.989) and 0.773 ((0.565, 0.882)) respectively, P<0.05) and (CV 95% CI: 2.5 (1.7, 3.4) %, 3.1 (2.1, 4.2) % and 0.044 (0.019, 0.070) % respectively.

Univariable linear mixed analysis showed that axial length was associated with FAZ area (coefficient (95% CI): −0.02 (−0.03, −0.01); P=0.002; n=248 eyes). Corrected FAZ area was not different among the three groups: in healthy 0.31 (0.27, 0.36) mm^2, glaucoma suspect 0.29 (0.26, 0.31) mm^2, and POAG eyes 0.28 (0.27, 0.30) mm^2 (P=0.578). FD300 was considerably lower in glaucoma suspect and POAG eyes than healthy eyes though the differences were not statistically significant 49.1 (47.9, 50.4) % in glaucoma suspect eyes, and 48.7 (48.1, 49.4) % in POAG eyes (P=0.071). Patient characteristics are summarized in Table 1.

Table 2 summarizes the r-squared values corresponding to FAZ parameters, VF parameters, and IOP using linear mixed models. Three of the variables were FAZ parameters, and 8 of these were VF parameters (24-2 VF MD, PSD and FT; 10-2 VF MD, PSD and FT; MS4 and MS8). Corrected FAZ area was not correlated well with VF parameters. FD300 was correlated with VF parameters, particularly with the variables reflecting the visual function of the fovea (10-2 VF MD: r-squared=0.079, P<0.001; 10-2 VF FT: r-squared=0.157, P<0.001; MS4: r-squared=0.080, P<0.001; MS8: r-squared=0.120, P<0.001).

Small effect size was found between the corrected superficial FAZ area and FD300 (r-squared=0.115, P<0.001) (Figure 2). Linear mixed model showed a strong association between corrected superficial FAZ area and foveal ILM-IPL thickness (r-squared=0.487, P<0.001) (Figure 3).

Table 3 shows the univariable and multivariable linear mixed analysis of factors correlated with FD300. In univariable analysis, age (coefficient (95% CI): −0.14 (−0.19, 0.09);

P<0.001), gender (1.72 (0.47, 2.97); P=0.007), race (2.47 (1.11, 3.82); P<0.001), self-reported diabetes (−1.64 (−3.41, 0.13); P=0.069), IOP (0.19 (0.06, 0.32); P=0.004), corrected FAZ area (14.57 (9.24, 19.89); P<0.001), FAZ circumference (3.03 (1.67, 4.39); P<0.001), and all the VF parameters were associated with FD300 (P<0.1), and introduced into the multivariable analysis. As both 10-2 and 24-2 parameters were significantly correlated with each other, these VF parameters were included in separate multivariable models to avoid multicollinearity. In model 1, 10-2 VF MD and FT were selected in addition to age, gender, race, self-reported diabetes, IOP, and FAZ area. In model 2, 10-2 VF MD was replaced by 24-2 VF. In model 1, MD and FT were significantly associated with FD300 (coefficient (95% CI) 10-2 VF MD: 0.14 (0.05, 0.23); P=0.003, 10-2 VF FT: 0.31 (0.11, 0.51); P=0.003, respectively).

Table 4 compares the correlation between vessel density parameters and mean VF sensitivity of central points after adjustment for confounders. The strength of association between 10-2 VF FT and vascular parameters was the largest for FD300 (r-squared 0.377), followed by wiVD (0.307) and pfVD (0.287). Similar results were found for MS4. However, the strength of association between MS8 and vascular parameters was highest for wiVD (0.372), followed by FD300 (0.364) and pfVD (0.352) (all P<0.001).

Table 5 shows the univariable and multivariable linear mixed analysis of factors correlated with corrected superficial FAZ area. The value of FAZ area was multiplied by one thousand to enhance the readability of the Table. In the univariable analysis (coefficient (95% CI)), race (57.28 (22.96, 91.59); P=0.001), IOP (2.28 (−0.32, 4.87); P=0.086), foveal ILM-IPL thickness (−-6.26 (−7.21, −5.31); P<0.001), FD300 (6.01 (3.75, 8.27); P<0.001), FAZ circumference (227.34 (215.13, 239.54); P<0.001), 10-2 VF MD (−2.09 (−3.80, −0.38); P=0.017), 24-2 VF MD (−2.08 (−3.72, −0.45); P=0.013), MS4 (−9.64 (−18.15, −1.13); P=0.026), and MS8 (−10.2 (−20.56, 0.17); P=0.054) were associated with corrected FAZ area (P<0.1), and were included into the multivariable analysis. In the multivariable analysis, as in Table 3, the model was constructed excluding variables with high collinearity. In model 1, 10-2 VF MD was selected in addition to gender, race, IOP, foveal ILM-IPL thickness, and in model 2, 24-2 VF MD was selected. IOP was significantly associated with FAZ area (coefficient (95% CI)) (2.46 (0.30, 4.62); P=0.026) in multivariable model 2, and showed a borderline significant trend in multivariable model 1 (2.15 (−0.02, 4.33); P=0.052). Similar results were found even if the sample was limited to POAG patients (Supplemental Tables 1 and 2).

DISCUSSION

The present study shows that MS4, MS8, MD and FT of central 10 degree VF tests were significantly associated with lower FD300 measurements, and lower IOP is associated with a smaller corrected FAZ area. And corrected FAZ area was not significantly associated with glaucoma or its severity.

Previous studies have reported relationships between central VF parameters and OCTA parameters. Penteado et al. reported that a central 10-2 VF defect is associated with loss of macular vessel density,[10] specifically between MS8 and wiVD and between MS4 and

pfVD. In the present study, the strongest association was found between FD300 and 10-2 VF FT followed by FD300 and MS8 and FD300 and MS4. FT has a significant correlation with best-corrected visual acuity and may be an important alternative indicator for measuring central visual function in glaucoma patients.[29 30] While wiVD and pfVD were affected by the size of the FAZ area, FD300 is thought to be not affected by FAZ diameter, as it is measured at a distance of 300 μm from the FAZ region.[19] From this perspective, FD300 may provide information about the perfusion of the region responsible for FT.

Several investigators have suggested the usefulness of FD300 for monitoring retinal diseases. FD300 has been reported to decrease in diabetic retinopathy,[31] retinal arterial occlusion,[32] and retinal vein occlusion.[33] Zeng et al. reported that FD300 was decreased significantly in diabetic patients despite having no retinopathy compared with the healthy subjects.[34] Moreover, it has been reported that macular vessel density loss correlates with glaucoma severity.[10] [35] Our results suggest that FD300 is also decreased in glaucoma, and may reflect the visual function in the foveal area. The results were similar in a sub-analysis including only POAG patients.

Changes in FAZ area may be an good indicator of capillary non-perfusion[14] and have been reported to increase especially in patients with a central VF defect.[15 16] Igarashi et al. reported that FAZ area has a significant negative correlation with 10-2 VF MD in the univariable but not multivariable analysis[17]. The stronger association between 10-2 VF MD with FAZ area compared with 24-2 VF MD is likely due to the known correlation between FAZ area with central VF parameters.[15] It is not well established whether FAZ area differs between healthy and glaucoma subjects. Kwon et al. reported that FAZ area is smaller in healthy compared to glaucomatous eyes,[36] and FAZ area associates with central VF defect.[15] Conversely, Choi et al. reported no significant difference between healthy and glaucoma subjects.[37] The difference may be due to population differences, differences in OCTA instruments used and the large variability in FAZ area measurements. FD300 may reflect the perfusion status of RGCs for foveal functions. This could also explain why there was a borderline difference in FD300 among healthy, glaucoma suspect, and glaucoma eyes while not in the FAZ area. However, caution should be exercised when comparing individual cases since FAZ area has large variability even in healthy eyes.[38 39] In addition, foveal ILM-IPL thickness was negatively correlated with the FAZ area, similar to what has been reported previously.[15 17 40] In this study no significant difference was found between corrected FAZ area and age, consistent with earlier studies.[17 38 41] Future longitudinal studies may need to take into account the effect of age on FAZ area as well as the reproducibility when looking at long-term outcomes.

There are few studies on the relationship between FAZ area and IOP. Ch'ng et al. reported that FAZ area expands after glaucoma surgery and gradually returns to its baseline value after 1 year.[42] However, it is unclear whether the decrease in IOP or inflammation in the early postoperative period are the cause for the transient enlargement in the FAZ area. Our study excluded eyes with the history of intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery) and any possible inflammatory ocular conditions. Furthermore, Shoji et al. showed that FAZ area was significantly decreased after glaucoma surgery in POAG patients.[43] In addition, changes in FAZ area were significantly correlated

with both preoperative FT and changes in IOP. This suggests that decreased IOP improves macular blood flow, and FAZ area may be a marker for glaucoma treatment efficacy though we cannot exclude the possibility of coincidence because of large inter-individual variability in FAZ area measurements. Further longitudinal studies are needed to investigate the association of changes in FD300 and glaucoma progression, and whether changes in FAZ area occur with IOP reduction.

This study has several limitations. First, only the superficial FAZ area was investigated, as deep FAZ area has lower reproducibility compared with superficial FAZ area.[44] It has been reported that superficial FAZ area correlates well with FAZ areas of the entire retinal layer.[45] Second, the healthy group was different from other groups in some characteristics including age and use of ocular hypotensive eye drops, and treatment status. There is some evidence that topical glaucoma medications may influence ocular blood flow.[46 47] Therefore, we cannot exclude the possibility that the use of topical eye drops accounts for the observed vascular differences between the study groups. Similarly, it is unclear whether systemic medications have an effect on macular vascular changes.[46] Although we adjusted our results for confounders, it is possible that some of these differences influenced our results. Finally, the OCTA signal depends on red blood cells density and velocity, which may result in inadequate detection of microcirculation around the FAZ. This issue may improve with equipment and software improvements in the future.

In conclusion, central 10 degree and peripheral MD, MS4, MS8, and FT loss were associated with low FD300. VF parameters within the central 10 degrees showed a stronger correlation with FD300 than FAZ area. Moreover, lower IOP was associated with a smaller FAZ area. Further longitudinal studies are needed to clarify the relationship between OCTA-derived FAZ metrics and VF parameters or IOP in glaucoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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e. Data availability

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

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SYNOPSIS

OCTA-measured foveal vessel density was associated with central 10 degree visual sensitivity and foveal threshold. Central 10 degree visual sensitivity and foveal threshold were both associated with a smaller foveal avascular zone area.

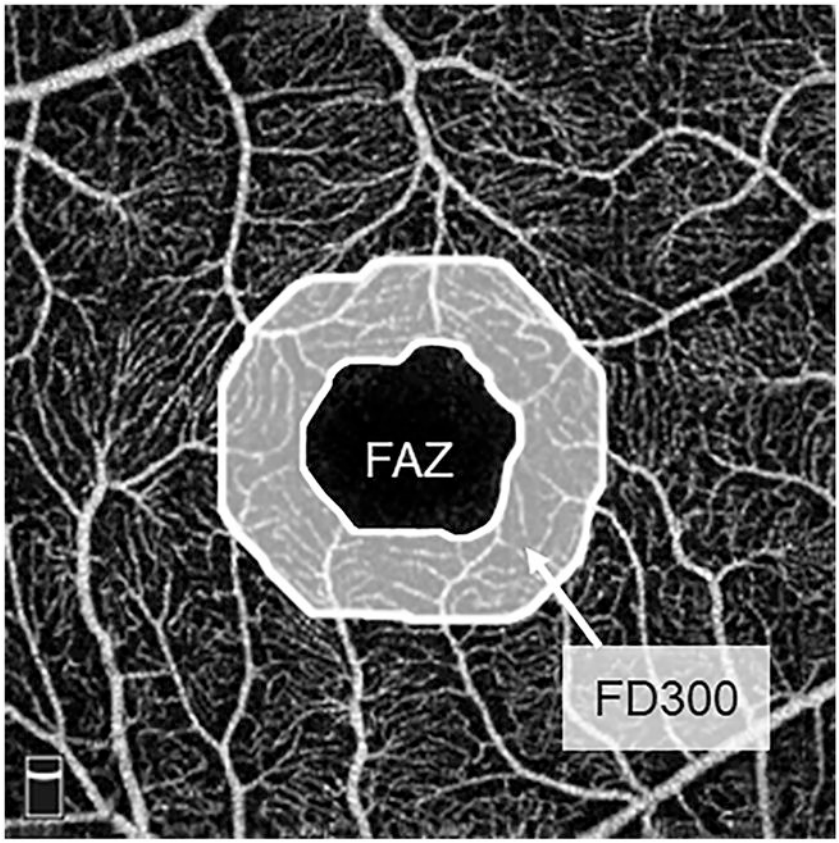

Figure 1.
Foveal avascular zone (FAZ) was defined as the region that enclosed by innermost macular arcade. Foveal vessel density (FD300) is defined as the vessel density of the 300 μm width ring surrounding the FAZ.

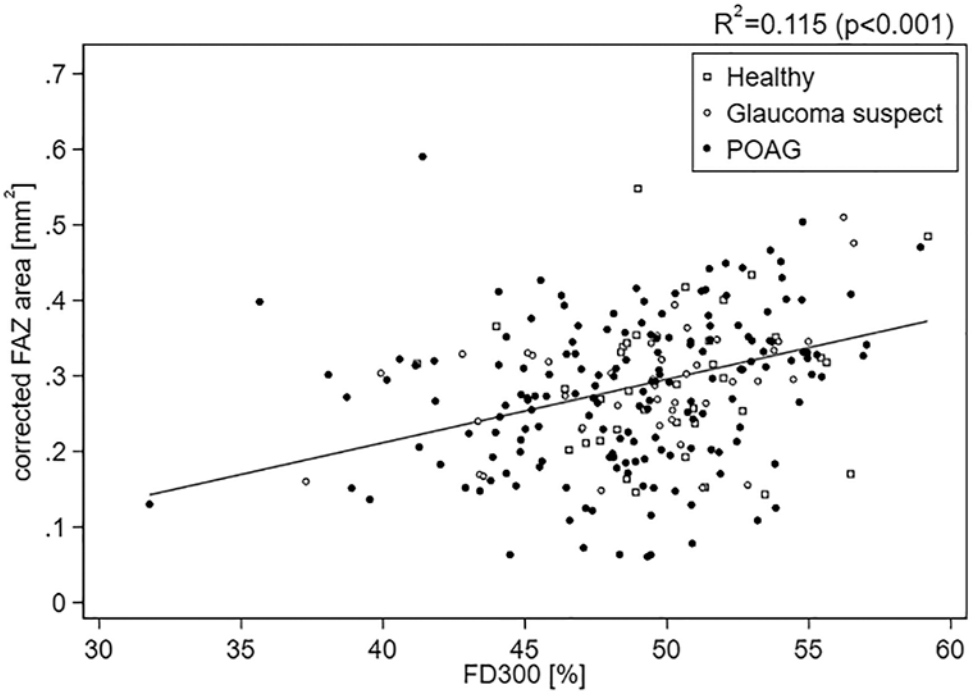

Figure 2.

Scatterplot illustrating the linear association between corrected foveal avascular zone (FAZ) area and foveal vessel density (FD300)

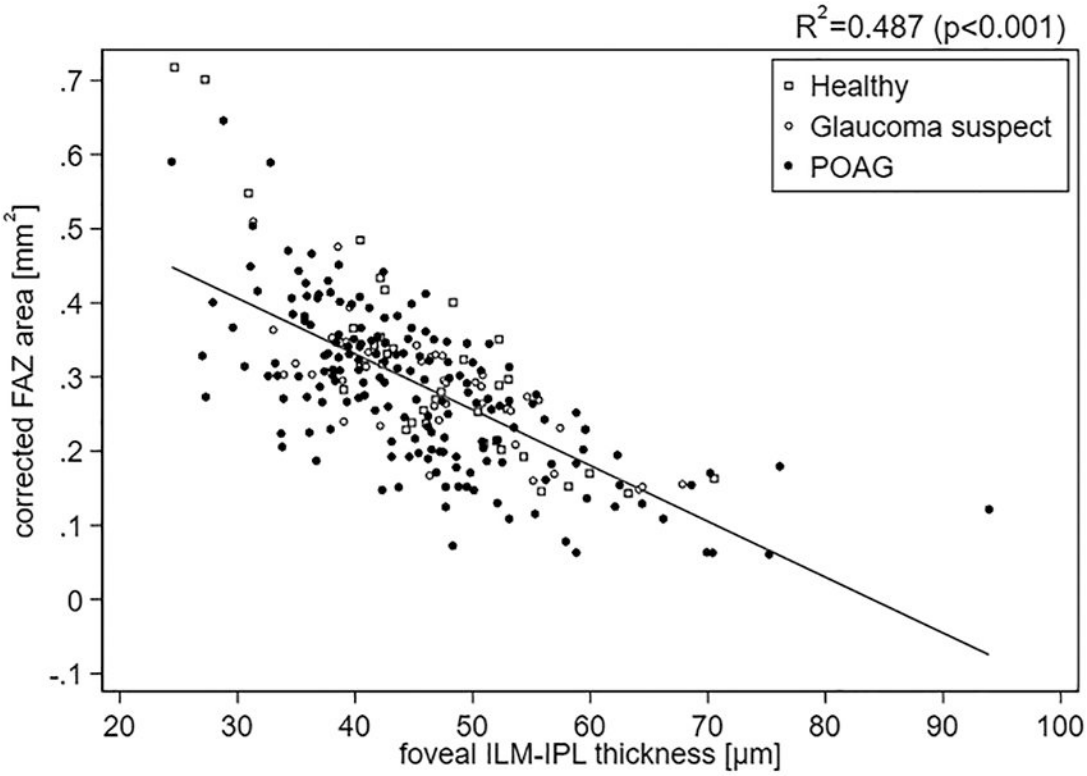

Figure 3.

Scatterplot illustrating the linear association between corrected foveal avascular zone (FAZ) area and foveal internal limiting membrane to the inner plexiform layer (ILM-IPL) thickness

Table 1.

Demographics and Ophthalmic Characteristics of Healthy, Glaucoma suspect and Glaucoma Group

	Healthy	Glaucoma suspect	POAG	P Value
By Subject (No.)	24	37	127	
Age (years)	61 (55.7, 66.3)	69.4 (64.9, 73.8)	70 (68.1, 71.9)	0.003 *†
Gender (male/female)	8/16	17/20	62/65	0.385
Race, no. (%)				
African American	10 (41.7)	8 (21.6)	35 (27.6)	0.245
Others	14 (58.3)	29 (78.4)	92 (72.4)	
Self-reported history of diabetes, no. (%)	2 (8.3)	4 (10.8)	22 (17.3)	0.491
Self-reported history of hypertension, no. (%)	11 (45.8)	18 (48.6)	73 (57.5)	0.439
Diastolic BP (mmHg)	80.3 (75.7, 84.8)	79.6 (76.3, 82.9)	78.5 (76.6, 80.4)	0.703
Systolic BP (mmHg)	126.8 (120, 133.6)	126.2 (120.2, 132.1)	124.7 (121.5, 128)	0.829
Mean arterial pressure (mmHg)	95.8 (90.8, 100.8)	95.1 (91.4, 98.9)	93.9 (91.8, 96.1)	0.721
By Eye (No.)	38	42	168	
Axial length (mm)	24.1 (23.7, 24.4)	24.6 (24.3, 24.9)	24.3 (24.1, 24.4)	0.148
CCT (μm)	549.5 (536.6, 562.4)	529.5 (511.0, 547.9)	538.4 (529.8, 547)	0.256
IOP (mmHg)	14.6 (13.6, 15.6)	16.7 (15.2, 18.3)	14.5 (13.8, 15.2)	0.067
24-2 VF MD (dB)	−0.1 (−0.4, 0.3)	−0.8 (−1.4, −0.3)	−5.3 (−6.2, −4.4)	<.001 †‡
24-2 VF PSD (dB)	1.7 (1.5, 1.8)	1.9 (1.7, 2.1)	5.9 (5.3, 6.5)	<.001 †‡
24-2 VF FT (dB)	36.5 (35.9, 37.1)	36.2 (35.7, 36.8)	35.3 (34.7, 35.9)	0.025 †‡
10-2 VF MD (dB)	−0.2 (−0.5, 0.0)	−0.7 (−1.2, −0.1)	−4.7 (−5.7, −3.8)	<.001 †‡
10-2 VF PSD (dB)	1.3 (1.2, 1.4)	1.4 (1.3, 1.5)	5.2 (4.5, 6.0)	<.001 †‡
10-2 VF FT (dB)	36.9 (36.3, 37.6)	36.0 (35.2, 36.8)	35.2 (34.7, 35.6)	<.001 †
MS4 (dB)	34.1 (33.7, 34.5)	33.0 (32.3, 33.7)	31.8 (31.4, 32.3)	<.001 *†‡
MS8 (dB)	33.8 (33.4, 34.1)	32.8 (32.2, 33.4)	31.5 (31.1, 31.9)	<.001 *†‡
Foveal ILM-IPL thickness (μm)	46.5 (43.5, 49.5)	47.1 (44.4, 49.8)	45.2 (43.7, 46.8)	0.478
Vessel density (%)				
Whole image	46.8 (45.5, 48.1)	44.7 (43.5, 45.9)	42.5 (41.6, 43.3)	<.001 *†‡
Parafoveal	46.4 (45.1, 47.8)	44.6 (43.4, 45.7)	42.5 (41.7, 43.3)	<.001 †‡
Corrected FAZ area (mm^2)	0.31 (0.27, 0.36)	0.29 (0.26, 0.31)	0.28 (0.27, 0.30)	0.578
FAZ circumference (mm)	2.2 (2.1, 2.4)	2.1 (2.0, 2.2)	2.1 (2.0, 2.2)	0.491
FD300 (%)	50.5 (49.3, 51.7)	49.1 (47.9, 50.4)	48.7 (48.1, 49.4)	0.071

BP = blood pressure; CCT = central corneal thickness; CI = confidence interval; FAZ = foveal avascular zone; FT = foveal threshold; ILM = inner limiting membrane; IOP = intraocular pressure; IPL = inner plexiform layer; MD = mean deviation; MS = mean sensitivity; MS4 = visual field MS of the 4 central points (dB); MS8 = visual field MS of the 8 central points (dB): PSD = pattern standard deviation; VF = visual field. Boldface values indicate statistical significance. Categorical variables were compared using Fisher exact test. Continuous variables expressed as mean and 95% CI. Post hoc significance was calculated using Tukey honest significant difference test.

*Healthy vs. Glaucoma suspect significant.

†Healthy vs. POAG significant.

[≠]Glaucoma suspect vs. POAG significant.

Table 2.

R-squared values corresponding to FAZ, visual field parameters, and IOP

	FAZ circumference	FD300	IOP	24-2 VF MD	24-2 VF PSD	24-2 VF FT	10-2 VF MD	10-2 VF PSD	10-2 VF FT	MS4	MS8
Corrected FAZ area	0.871 (P<0.001)	0.115 (P<0.001)	0.001 (P=0.095)	0.013 (P=0.020)	0.003 (P=0.394)	0.007 (P=0.302)	0.013 (P=0.016)	0.004 (P=0.164)	0.000 (P=0.261)	0.010 (P=0.021)	0.011 (P=0.048)
FAZ circumference		0.075 (P<0.001)	0.000 (P=0.171)	0.016 (P=0.007)	0.004 (P=0.229)	0.021 (P=0.167)	0.023 (P=0.001)	0.008 (P=0.023)	0.008 (P=0.042)	0.022 (P=0.004)	0.028 (P=0.006)
FD300			0.037 (P=0.004)	0.061 (P<0.001)	0.027 (P=0.004)	0.050 (P=0.002)	0.079 (P<0.001)	0.047 (P<0.001)	0.157 (P<0.001)	0.080 (P<0.001)	0.120 (P<0.001)
IOP				0.033 (P=0.010)	0.045 (P=0.006)	0.002 (P=0.569)	0.054 (P=0.001)	0.083 (P<0.001)	0.004 (P=0.145)	0.005 (P=0.526)	0.013 (P=0.172)

FAZ = foveal avascular zone; FT = foveal threshold; IOP = intraocular pressure; MD = mean deviation; MS = mean sensitivity; MS4 = visual field MS of the 4 central points (1/Lambert); MS8 = visual field MS of the 8 central points (1/Lambert); PSD = pattern standard deviation: VF = visual field. The grayscale shading of the column indicates the strength of association, with darker indicating stronger associations

Table 3.

Univariable and multivariable linear mixed analysis of factors correlated with FD300

Variables	Univariable Model		Multivariable Model 1		Multivariable Model 2	
	coefficient, 95% CI	P value	coefficient, 95% CI	P value	coefficient, 95% CI	P value
Age (years) per 1 year	**−0.14 (−0.19, −0.09)**	**<0.001**	**−0.08 (−0.13, −0.04)**	**<0.001**	**−0.10 (−0.15, −0.06)**	**<0.001**
Gender: male/female	**1.72 (0.47, 2.97)**	**0.007**	**1.27 (0.26, 2.29)**	**0.014**	**1.38 (0.33, 2.43)**	**0.010**
Race: African American/Others	**2.47 (1.11, 3.82)**	**<0.001**	0.97 (−0.19, 2.13)	0.102	0.95 (−0.25, 2.16)	0.121
Axial length (mm) per 1 mm	0.08 (−0.49, 0.65)	0.793				
CCT (μm) per 1 μm	0.00 (−0.02, 0.01)	0.849				
Self-reported diabetes	**−1.64 (−3.41, 0.13)**	**0.069**	−0.96 (−2.43, 0.50)	0.199	−1.04 (−2.56, 0.47)	0.176
Self-reported hypertension	−0.86 (−2.12, 0.41)	0.184				
IOP (mmHg) per 1 mmHg	**0.19 (0.06, 0.32)**	**0.004**	0.08 (−0.03, 0.19)	0.152	0.09 (−0.02, 0.20)	0.117
Foveal ILM-IPL thickness (μm) per 1 μm	0.08 (−0.50, 0.66)	0.794				
Corrected FAZ area (mm^2) per 1 mm^2	**14.57 (9.24, 19.89)**	**<0.001**	**13.86 (9.28, 18.45)**	**<0.001**	**14.28 (9.54, 19.02)**	**<0.001**
FAZ circumference (mm) per 1 mm	**3.03 (1.67, 4.39)**	**<0.001**				
10-2 VF MD (dB) per 1 dB	0.23 (0.14, 0.32)	**<0.001**	**0.14 (0.05, 0.23)**	**0.003**		
10-2 VF PSD (dB) per 1 dB	**−0.21 (−0.33, −0.10)**	**<0.001**				
10-2 VF FT (dB) per 1 dB	**0.54 (0.36, 0.72)**	**<0.001**	**0.31 (0.11, 0.51)**	**0.003**		
24-2 VF MD (dB) per 1 dB	**0.20 (0.11, 0.29)**	**<0.001**			**0.16 (0.08, 0.25)**	**<0.001**
24-2 VF PSD (dB) per 1 dB	**−0.19 (−0.33, −0.06)**	**0.004**				
24-2 VF FT (dB) per 1 dB	**0.24 (0.09, 0.40)**	**0.002**			0.14 (−0.01, 0.28)	0.066
MS4 (1/Lambert) per 1000 unit	**1.24 (0.78, 1.71)**	**<0.001**				
MS8 (1/Lambert) per 1000 unit	**1.72 (1.18, 2.27)**	**<0.001**				

CCT = central corneal thickness; CI = confidence interval; FAZ = foveal avascular zone; FT = foveal threshold; ILM = inner limiting membrane; IOP = intraocular pressure; IPL = inner plexiform layer; MD = mean deviation; MS = mean sensitivity; MS4 = visual field MS of the 4 central points (1/Lambert); MS8 = visual field MS of the 8 central points (1/Lambert); PSD = pattern standard deviation. Boldface values indicate statistical significance.

Table 4.

Comparison of correlation between vessel density parameters and mean sensitivity of central points

Variables	FD300			wiVD			pfVD		
	R-squared	coefficient, 95% CI	P value	R-squared	coefficient, 95% CI	P value	R-squared	coefficient, 95% CI	P value
10-2 VF FT (dB) per 1 dB	0.377	0.45 (0.27, 0.64)	<0.001	0.307	0.63 (0.39, 0.87)	<0.001	0.287	0.67 (0.42, 0.93)	<0.001
MS4 (1/ Lambert) per 1000 unit	0.350	1.09 (0.65, 1.53)	<0.001	0.330	1.97 (1.41, 2.53)	<0.001	0.313	2.07 (1.48, 2.67)	<0.001
MS8 (1/ Lambert) per 1000 unit	0.364	1.45 (0.92, 1.98)	<0.001	0.372	2.69 (2.02, 3.35)	<0.001	0.352	2.80 (2.09, 3.50)	<0.001

CI = confidence interval; FAZ = foveal avascular zone; IOP = intraocular pressure; MS = mean sensitivity; MS4 = visual field MS of the 4 central points (1/Lambert); MS8 = visual field MS of the 8 central points (1/Lambert); pfVD = parafoveal vessel density; wiVD = whole image vessel density

*Adjusted to age, gender, race, self-reported diabetes, IOP, and corrected FAZ area.

Table 5.

Univariable and multivariable linear mixed analysis of factors associated with corrected FAZ area

Variables	Univariable Model		Multivariable Model 1		Multivariable Model 2	
	coefficient, 95% CI	P value	coefficient, 95% CI	P value	coefficient, 95% CI	P value
Age (years) per 1 year	−0.31 (−1.64, 1.03)	0.654				
Gender: male/female	22.18 (−9.63, 53.99)	0.172				
Race: African American/Others	57.28 (22.96, 91.59)	**0.001**	**32.68 (6.07, 59.29)**	**0.016**	**34.09 (7.23, 60.95)**	**0.013**
Axial length (mm) per 1 mm	4.58 (−9.23, 18.39)	0.516				
CCT (μm) per 1 μm	−0.20 (−0.58, 0.17)	0.290				
Self-reported diabetes	4.49 (−40.28, 49.27)	0.844				
Self-reported hypertension	6.99 (−24.83, 38.81)	0.667				
IOP (mmHg) per 1 mmHg	**2.28 (−0.32, 4.87)**	**0.086**	2.15 (−0.02, 4.33)	0.052	**2.46 (0.30, 4.62)**	**0.026**
Foveal ILM-IPL thickness (μm) per 1 μm	−6.26 (−7.21, −5.31)	**<0.001**	**−6.58 (−7.67, −5.49)**	**<0.001**	**−6.28 (−7.34, −5.22)**	**<0.001**
FD300 (%) per 1 %	**6.01 (3.75, 8.27)**	**<0.001**				
FAZ circumference (mm) per 1 mm	**227.34 (215.13, 239.54)**	**<0.001**				
10-2 VF MD (dB) per 1 dB	**−2.09 (−3.80, −0.38)**	**0.017**	1.30 (−0.39, 2.98)	0.132		
10-2 VF PSD (dB) per 1 dB	1.43 (−0.62, 3.48)	0.172				
10-2 VF FT (dB) per 1 dB	−1.64 (−5.17, 1.90)	0.364				
24-2 VF MD (dB) per 1 dB	**−2.08 (−3.72, −0.45)**	**0.013**			0.21 (−1.32, 1.73)	0.792
24-2 VF PSD (dB) per 1 dB	1.26 (−1.11, 3.63)	0.299				
24-2 VF FT (dB) per 1 dB	−1.17 (−4.25, 1.90)	0.456				
MS4 (1/Lambert) per 1000 unit	**−9.64 (−18.15, −1.13)**	**0.026**				
MS8 (1/Lambert) per 1000 unit	**−10.2 (−20.56, 0.17)**	**0.054**				

CCT = central corneal thickness; CI = confidence interval; FAZ = foveal avascular zone; FT = foveal threshold; ILM = inner limiting membrane; IOP = intraocular pressure; IPL = inner plexiform layer; MD = mean deviation; MS = mean sensitivity; MS4 = visual field MS of the 4 central points (1/Lambert); MS8 = visual field MS of the 8 central points (1/Lambert); PSD = pattern standard deviation. Boldface values indicate statistical significance.

The value of FAZ area was multiplied by one thousand to enhance the readability of the Table.