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Association of foveal avascular zone change and glaucoma progression

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Abstract

Background/aims: To investigate the association between longitudinal changes of foveal avascular zone (FAZ) area and the rate of structural and functional progression in glaucoma.

Methods: A longitudinal cohort included 115 eyes (46 glaucoma suspect and 66 primary open angle glaucoma [POAG]) of 81 patients having 2yr follow-up, and 4 visits with optical coherence tomography angiography (OCTA) and visual field (VF). Eyes in the longitudinal cohort with a slope greater than that found in 95 percentile of separate healthy test-retest series for FAZ area were categorized into FAZ progressors; all other eyes were defined as FAZ non-progressors. A generalized linear mixed-effects model was used to investigate the association of FAZ progressors with demographic and clinical characteristics.

Results: Faster ganglion cell complex (GCC) thinning and faster VF mean deviation (MD) loss were found in eyes with FAZ progressors compared with FAZ non-progressors (mean difference: –0.7 (95%CI, –1.4 to –0.1) μm/y; P=0.026, –0.3(–0.5 to –0.1) dB/y; P=0.017, respectively), while whole image vessel density was not associated with FAZ progressors (P=0.929). Standard deviation of IOP and IOP range were also associated with FAZ progressors in separate multivariable models (OR: 1.54 (1.02 to 2.32) per 1-mmHg higher, P=0.041; OR: 1.20 (1.01 to 1.41) per 1-mmHg higher; P=0.035, respectively).

Conclusions: Significant FAZ increase was weakly associated with moderately faster rates of both GCC thinning and VF MD loss, but not macular vessel density change in glaucoma eyes. Additional studies are needed to elucidate the pathophysiological associations between macula GCC thinning and FAZ area increases in glaucoma.

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Ethics approval: This study involves human participants and was approved by The University of California San Diego Human Subjects Committee approved all protocols (NCT00221897), and the methods described adhered to the tenets of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Disclaimer: The sponsor or funding organizations had no role in the design or conduct of this research.

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Keywords

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

Introduction

Glaucoma is a progressive optic neuropathy and a leading cause of irreversible blindness worldwide. Described by a characteristic pattern of retinal ganglion cells (RGC) loss and visual field (VF) defects,[1 2] the precise pathogenesis for glaucoma has not yet been elucidated. However, intraocular pressure (IOP) and impaired ocular blood flow are thought to be significant contributors to the development of this disease.[3–5]

Contrary to longstanding belief that the fovea and macula are not affected until the late stages of glaucoma, recent studies have shown that papillofoveal and papillomacular bundle defects are frequently affected in early glaucoma.[6] Several studies have demonstrated macular ganglion cell damage in the early stages of glaucoma.[7 8] In view of the potential for early involvement in the disease process, macular assessment in glaucoma has garnered considerable interest. The high density of RGCs in the macular area may also account for its role in glaucoma.[9]

Optical coherence tomography angiography (OCTA) is being used to investigate the microcirculation of the optic nerve head and macular, as its impairment is hypothesized to have a major role in the etiology of at least some patients with glaucoma. OCTA provides a no-ninvasive method to evaluate the retinal vasculature as a surrogate for microvascular integrity.[10 11] Patients with glaucoma have been shown to have a reduction in vessel density within the macula in recent studies.[12 13] Additional potential indicators of vascular viability include measurements of the foveal avascular zone (FAZ), a unique capillary-free region formed by a ring of interconnected capillaries of foveal vascular plexus..[14–16]

An enlargement of the FAZ area was noted in eyes with glaucoma in prior cross-sectional studies[17–19], however there is limited information on the association between specific changes in the FAZ area and glaucoma progression. Therefore, the current study was designed to investigate the longitudinal increase of FAZ area and its association with the rate of structural, microvascular and functional progression of glaucoma.

Methods

Participants

This is a retrospective, longitudinal cohort study of primary open angle glaucoma suspect, glaucoma patients and healthy participants who were enrolled in the Diagnostic Innovations in Glaucoma Study (DIGS).[20 21] The participants were assessed longitudinally according to established protocols consisting of semi-annual follow-up visits with imaging, and functional tests.[20] Written informed consent was obtained from all study participants. The University of California, San Diego Human Subject Committee approved all protocols

(NCT00221897), and the methods described adhered to tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act. Further details are described in Supplemental Method 1. At least 4 visits and 2 years of follow-up for OCTA/OCT (Optovue, Inc. Fremont, CA) and visual field (VF) testing in the corresponding time period without intraocular surgeries were included in this study. All participants from the study who met the inclusion and exclusion criteria were included.

OCTA and OCT imaging

This study included 3 mm × 3 mm macular OCT/OCTA scans (304-A scans in each B-scan and 304-B scans) acquired using the Avanti Angiovue system (software version 2018.1.1.63). The OCT/OCTA images were acquired simultaneously, and OCTA-based whole image vessel density (wiVD) and OCT-based ganglion cell complex (GCC) thickness were calculated from the same scan slab. The software detects capillary-free area and calculates superficial foveal avascular zone (FAZ) parameters automatically. The FAZ was defined using standard commercial instrument software as the region that enclosed by innermost macular arcade. Reproducibility of FAZ area using this device was described in the previous study (ICC = 0.979 (95% CI, 0.960 to 0.989)).[22] FAZ area was corrected to consider the magnification effect using Littman formula, which uses axial length as the main correction factor.[23] Corrected FAZ area = FAZ area * 3.46^2 * 0.013062^2 * (Axial length − $1.82)^2$. [22 24] Quality review of OCT/OCTA images was performed by trained graders according to UCSD Imaging, Data, Evaluation and Assessment standard protocol, and images with any of the following features were considered poor quality and excluded: (1) low scan quality <4; (2) residual motion artifacts visible as irregular vessel pattern on the en-face angiogram; (3) image cropping or local weak signal; (4) off-centered fovea; (5) poor clarity; (6) uncorrectable severe segmentation errors.

IOP measurement

IOP was measured by Goldmann applanation tonometer model AT 900 (Haag-Streit International) at baseline and at all follow-up examinations without dilation of the pupil. An IOP summary measurement was calculated based on each participant‟s longitudinal IOP data. These measures included mean IOP, peak IOP, IOP range, and IOP fluctuation. Mean IOP was calculated by averaging all IOP measurements during follow-up. Peak IOP was the highest single measurement during follow-up. IOP range was calculated by subtracting the lowest value from the highest value during follow-up. IOP fluctuation was defined as the SD of IOP measurements during follow-up.

Simulation dataset

For the longitudinal cohort of glaucoma suspects and patients and test-retest cohort of healthy participants, the same inclusion and exclusion criteria were employed as for the diagnosis. Since no previous studies have reported on the rate of change in FAZ area, the definition of progressors and non-progressors was defined by the simulation analysis based on OCTA measurements in the test-retest cohort. This was done to prevent inconsistent results when determining the specificity with a small number of samples and to obtain more robust results. For the test-retest healthy cohort, the initial 4 visits of OCTA scans were selected, and then 4 visits were assumed to be equally spaced and duplicated for

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all 24 possible permutations of the test order of each eye.[25] The rate of change were calculated using linear regression for all permutations. The 95th percentile of these slopes was recorded, and any eyes having slope greater than that found from the 95th percentile (Crit95%) of the healthy cohort was determined to be the FAZ progressor in the longitudinal cohort, while others were defined as non-progressors. The primary analysis defined the specificity at 95%, and the analysis was also repeated setting specificity at 90% (Crit90%), 85% (Crit85%), and 80% (Crit80%) for the sensitivity analysis.

Statistical analysis

Participant and eye characteristic data are presented as mean (95% CI) for continuous variables and count (%) for categorical variables. Measurements of bilateral eyes were nested within participant to account for the fact that eyes from the same individual are more likely to provide correlated measurements. The rates of change in GCC thickness, wiVD, and VF MD over time for each eye was calculated using best linear unbiased prediction. Best linear unbiased predictions are shrinkage estimates that take into account the results obtained by evaluating the whole sample of eyes, giving less weight to estimates obtained from eyes with fewer measurements or large intraindividual variability.[13 26] The differences between the progressors and non-progressors for FAZ area change were determined using analysis of covariance for the changes in GCC, wiVD, and VF MD using the longitudinal cohort.

As a preparatory step to the model fitting, collinearity between covariates was explored with a hierarchical cluster analysis based on the squared Pearson correlations; values of r-squared 0.36 or less were accepted in order to select the final set of clinical factors used for the modeling.[27] Variables with underlined labels are retained in the final analysis (Supplemental Figure 1) for the multivariable analysis. The following variables were included as potential predictors for fast FAZ progression: MD slope, GCC slope, wiVD slope, IOP fluctuation, IOP range, mean IOP, CCT, follow-up period, number of visits, baseline VF MD, spherical equivalent, axial length, mean arterial pressure (MAP), average SSI, baseline age, baseline FAZ area, sex, self-reported race, diabetes, and hypertension. IOP fluctuation and IOP range were retained and modeled separately since IOP variability was of particular interest in investigating its effect on FAZ changes.[22 28–30]

Generalized Linear Mixed-effects models were used to investigate the association between demographic and clinical characteristics with the fast FAZ change (at 95% specificity). The function dredge in the R-package “MuMIn”[31] was used to select the most parsimonious model based on second-order Akaike Information Criterion (AICc).[32] This function utilizes a method where models are fitted using repeated evaluation until all possible combinations of independent predictors are fit, and model performance is ranked thereafter. Statistical analyses were performed using statistical software R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) with the packages “dplyr” and “glmmTMB”, and Stata (version 16.0; StataCorp). A 2-sided $P < .05$ was considered to be statistically significant.

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Results

The longitudinal cohort included a total of 115 eyes (47 glaucoma suspect and 68 primary open angle glaucoma [POAG]) of 28 glaucoma suspects and 48 glaucoma patients. Of this cohort, mean (95%CI) age was 68.2 years (65.7 to 70.7) and baseline VF MD was −3.1 (−3.9 to −2.2). Participants had a mean (95%CI) of 7.4 (95% CI, 6.9 to 7.9) VF tests, and 5.5 (95% CI, 5.2 to 5.8) OCT/OCTA tests over the 4.0 (95% CI, 3.9 to 4.2) years follow-up period. Mean (95%CI) baseline corrected FAZ area was 0.28 mm^2 (95%CI, 0.24 to 0.33) for the test-retest healthy cohort and 0.28 mm^2 (95%CI, 0.26 to 0.31) for the longitudinal cohort. The test-retest cohort included series of 4 reliable OCTA scans from 32 eyes of 24 healthy participants. Of this cohort, mean age was 60.6 years (95%CI, 52.6 to 68.6) and baseline VF MD was −0.3 dB (95%CI, −0.8 to 0.2). In the longitudinal cohort, mean FAZ change was 0.006 (95% CI, 0.004 to 0.008) (mm^2/y). Demographic and baseline clinical characteristics of the participants are presented in Table 1.

The rates of corrected FAZ area change in longitudinal cohort and test-retest cohort of healthy eyes are presented in Figure 1. Using all 24 permutations of the test order for each of the 32 eyes in the test-retest cohort, 768 series of FAZs were obtained. The FAZ area change cutoff values to define FAZ progression were 0.0102 mm^2/y (Crit 95%), 0.0078 mm^2/y (Crit 90%), 0.0062 mm^2/y (Crit 85%), and 0.0049 mm^2/y (Crit 80%).

At 95% specificity (Crit95%), faster GCC thinning and faster VF MD loss were found with FAZ area progressor group compared with FAZ area non-progressor group (1.5 (95%CI, −2.6 to −0.4) μm/y vs −0.8 (95%CI, −1.0 to −0.5) μm/y; P=0.026, −0.5 (95%CI, −0.9 to 0.0) dB/y vs −0.2 (95%CI, −0.3 to −0.1) dB/y; P=0.017, respectively), while wiVD was not faster in the FAZ area progressor group (−1.3 (95%CI, −1.8 to −0.8) %/y vs −1.3 (95%CI, −1.5 to −1.1) %/y; P=0.993) (Table 2). Similar trends were observed at 90% (Crit90%), 85% (Crit85%), and 80% (Crit80%) specificity. Scatterplots (Figure 2) show the relationship between the rates of corrected FAZ area change (y-axis) and (A) VF MD slope, (B) GCC slope, (C) wiVD slope (x-axis).

Table 3 summarizes the factors associated with fast FAZ change by generalized mixed-effects model. In the multivariable model 1, FAZ progression was associated with IOP fluctuation for model 1 (OR: 1.54 (1.02 to 2.32) per 1-mmHg higher; P=0.041). While, in the multivariable model 2, FAZ progression was associated with IOP range for model 1 (OR: 1.20 (1.01 to 1.41) per 1-mmHg higher; P=0.035).

Discussion

This longitudinal study investigated the factors associated with the FAZ area change in patients suspected of having glaucoma and patients with POAG. The rates of GCC thinning and VF MD loss were more rapid in glaucoma eyes with FAZ area progressors compared to those with FAZ area non-progressors. However, the correlation between the rate of FAZ area change and the rate of GCC thinning and VF MD loss was weak (R^2 range between 0.023 and 0.109) Moreover, the rate of OCTA macula vessel density change was not associated

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with FAZ progression, suggesting a complex relationship between macula GCC thinning, microvasculature and FAZ area in glaucoma eyes.

Although the FAZ area is highly variable among individuals,[33] longitudinal observation of an individual may be useful. Little is known about longitudinal change of FAZ area in eyes of glaucoma patients – which tended to show small increases in most eyes, with some eyes exhibiting no change or small decrease in FAZ area. In our study, IOP fluctuation and IOP range were associated with fast FAZ area change. Shoji et al. reported a shrinkage of FAZ area following glaucoma surgery and proposed that it could be due to amicrovascular enhancement with recovery of macular RGC function by IOP reduction.[28] In our study, 27 eyes (23.5%) had glaucoma surgery at baseline, and longitudinal data and rate of change were calculated without glaucoma surgery in the visits analyzed. In another words, as glaucoma surgery can reduce IOP and also increase IOP fluctuation, the analysis only inclued visits before and after glaucoma surgery to ensure that IOP fluctuation would not be affected.

There are several reports on the association between FAZ area and OCT-measured retinal thickness. A cross-sectional study by Kwon et al. reported an association between larger FAZ area and thinner macular GCIPL.[34] Another longitudinal study by Li et al. showed that larger FAZ area at baseline was asscoated with a higher risk of GCIPL thinning in glaucoma eyes.[35]. Approximately 50% of RGCs reside in the macula, and a maximum RGC density is found approximately within 0.5 mm from the foveal pit.[36] A change in the FAZ area may indicate a lack of capillary perfusion. Choi et al. showed that focal loss of parafoveal capillary arcade may precede FAZ change, [37] therefore, poor perfusion to the macular area could lead to faster RGC death.[13] However, out study did not find significant association between the rate of FAZ area change and rate of macula wiVD loss. This discrepancy might be attributed to the macular sector in which the vasculature is affected earlier in glaucoma. It is unclear from the present results whether the lack of association between the rate FAZ area change and rate of macular wiVD loss (and that there was no difference in the rate of macular wiVD loss in progressing and non-progression FAZ area eyes regardless of specificty cut-off) was because the microvascular changes had already occurred to the entire macula.

Prior studies have also demonstrated an association between FAZ area and VF parameters. Kwon et al. reported an association between larger FAZ area and worse VF mean sensitivity in both global and central regions.[34] The same authors demonstrated in another study in POAG eyes with comparable glaucoma severity that the FAZ area was larger when central VF defects, instead of peripheral VF defects, were present in 24–2 VF testing. The authors opined that microvasculature change in macula is associated with central VF defects, given that the FAZ border is formed by the superficial vessel plexus in the fovea.[38] In our study, faster change in FAZ area was associated with faster VF MD loss. Central visual function is mainly maintained by perifoveal microcirculation; therefore the enlargement of the FAZ area, which may result from vascular dropout in the perifoveal region, could account for the observed central VF defects in glaucoma patients.[34] Our results, however did not find an association between vessel density and FAZ area. A recent longitudinal study by Li et al., however, found no association between a larger FAZ area at baseline and VF progression.

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[35] These differences could be attributed to variations in the OCTA instruments that were used as different instruments have varying reproducibility profiles.[39]

This study has several limitations. First, test-retest cohort is based on healthy eyes of small sample size whereas the longitudinal cohort consisted of glaucoma suspect and glaucoma eyes which likely are more variable. To address the small sample size, we completed simulation analysis to determination the specificity cut-offs. There are also differences with age and the use of glaucoma medications between the longitudinal cohort of glaucoma eyes and test-retest cohort of healthy eyes. There is some evidence suggesting that topical glaucoma medications may influence ocular blood flow.[40 41] It is possible that the use of topical eye drops may have influenced to the FAZ area for the longitudinal cohort, but the purpose of this study was to investigate the longitudinal changes on FAZ in the glaucoma patients, not to compare the two cohorts. Moreover, changes in medication can reduce IOP, leading to larger measures of variability which may have influenced the IOP variability measurement. It should be noted the longitudinal data analyzed included dates either only before or after glaucoma surgery to avoid the influence of surgery on IOP fluctuation. Second, IOP was measured at six-month intervals. Although we were able to study the association between FAZ change and long-term IOP variability, the relationship with short-term IOP variability is not clear. The use of sensors that continually measure IOP may may provide additional information about its relationship with vascular parameters.[42] Last, we used 24–2 VF testing in our study. The 24–2 VF testing is frequently utilized in glaucoma patients in the early to moderate stages of glaucoma, as was the case in our study population. Future studies utilizing longituidinal 10–2 VF testing may provide a additional insight into whether central visual field loss is associated with the FAZ changes.

In conclusion, significant FAZ increase was weakly associated with faster rates of both GCC thinning and VF MD loss in glaucoma eyes, but was not associated with vessel density change. These results suggest the complexity of the pathphysiological relationship between structural and functional change in glaucoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests:

Takashi Nishida: Consultant – Topcon; Sasan Moghimi: Consultant – Topcon; Evan Walker: none; Gopikasree Gunasegaran: none; Jo-Hsuan Wu: none; Alireza Kamalipour: Fight for sight, Linda M. Zangwiill: Consultant - Topcon, Abbvie; Financial support - Carl Zeiss Meditec, Heidelberg Engineering, OptoVue Inc. Patent: AISight Health (co-founder), Robert N. Weinreb: Consultant - Abbvie, Aerie Pharmaceuticals, Allergan, Amydis, Editas, Equinox, Eyenovia, Iantrek, IOPtic, Implandata, iSTAR Medical, Nicox, Santen, Tenpoint and Topcon; Financial support - Heidelberg Engineering, Carl Zeiss Meditec, Optovue, Centervue, Zilia and Topcon.

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Data availability statement:

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

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SYNOPSIS

In this longitudinal cohort study of glaucoma eyes, significant foveal avascular zone area increase was associated with faster visual field mean deviation loss and faster ganglion cell complex thinning, but not macular vessel density change.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous cross-sectional studies have shown that foveal avascular zone (FAZ) enlargement is associated with glaucoma severity, but its longitudinal change in glaucoma is not well understood.

WHAT THIS STUDY ADDS

This longitudinal study found that eyes with FAZ progression (those with a significant increase in FAZ area) had faster rates of ganglion cell complex thinning and visual field mean deviation loss compared to FAZ non-progressors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

The findings suggest that FAZ enlargement may be associated with glaucoma progression.

Further studies are needed to understand the underlying pathophysiological mechanisms.

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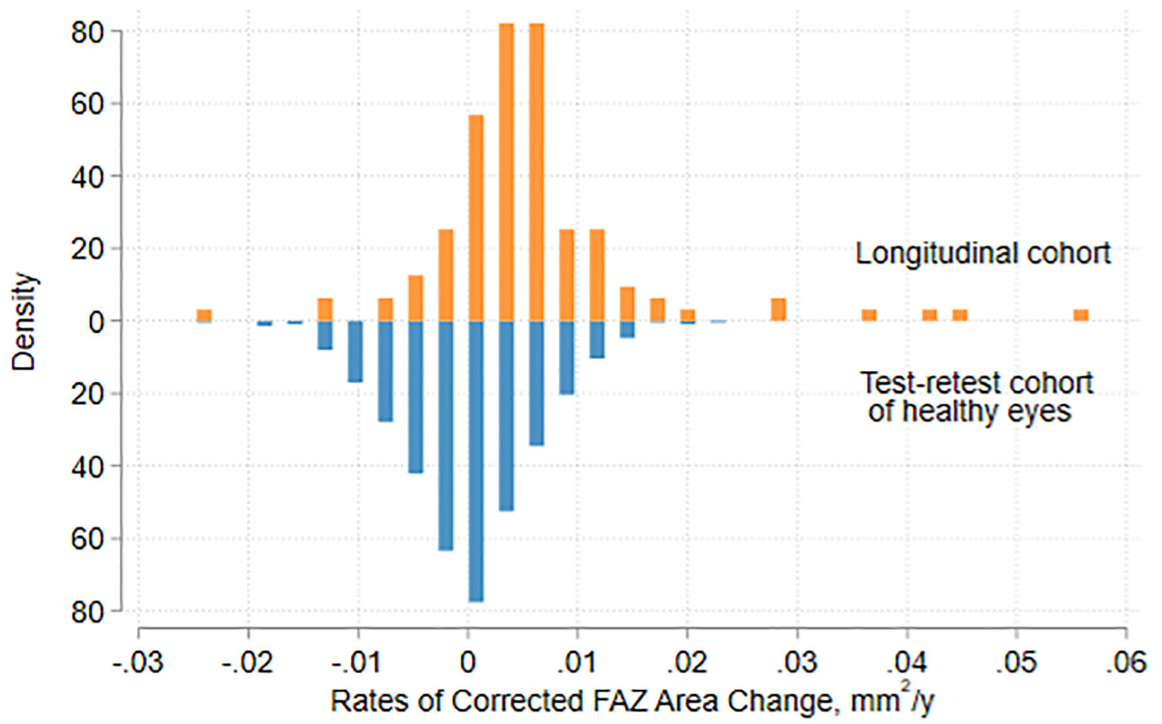

Figure 1.

Rates of corrected foveal avascular zone (FAZ) area change (mm2/y) in eyes with longitudinal cohort of glaucoma and glaucoma suspects eyes, and test–retest cohort of healthy eyes.

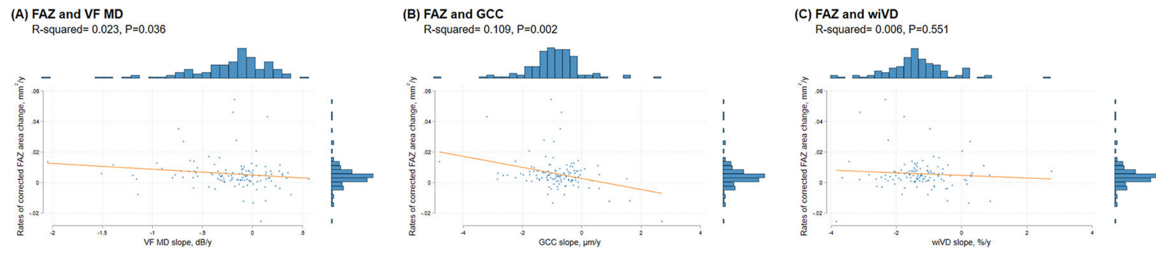

Figure 2.

Scatterplots show the relationship between the rates of corrected foveal avascular zone (FAZ) area change (y-axis) and (A) visual field (VF) mean deviation (MD) slope, (B) ganglion cell complex (GCC) slope, (C) whole image vessel density (wiVD) slope (x-axis). The histogram for the FAZ and VF MD, GCC and wiVD are also shown on the right and top of the scatter plot.

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Table 1.

Demographic and Clinical Characteristics of the Study Population in the Test-retest and Longitudinal Cohort

Variables	Longitudinal cohort (n = 81, 115 Eyes)	Test-retest cohort of healthy eyes (n = 24, 32 Eyes)
Patient Characteristics		
Age (years)	67.7 (65.2 to 70.2)	60.6 (52.6 to 68.6)
Sex (% Female)	44 (54.3%)	16 (66.7%)
Race, n (%)		
African Descent	23 (28.4%)	9 (37.5%)
European Descent	45 (55.6%)	10 (41.7%)
Others	13 (16.0%)	5 (20.8%)
Self-reported hypertension, n (%)	51 (63.0%)	13 (54.2%)
Self-reported diabetes, n (%)	11 (13.6%)	3 (12.5%)
Eye Characteristics		
Diagnosis, n (%)		
Healthy	0 (0.0%)	32 (100.0%)
Glaucoma suspect	47 (40.9%)	0 (0.0%)
Early glaucoma (VF MD>−6)	47 (40.9%)	0 (0.0%)
Moderate and severe Glaucoma (VF MD −6)	21 (18.3%)	0 (0.0%)
Axial length (mm)	24.3 (24.2 to 24.5)	24.1 (23.7 to 24.6)
CCT (μm)	537.9 (530.6 to 545.2)	541.2 (530.4 to 551.9)
Mean IOP during follow-up (mmHg)	15.6 (14.9 to 16.3)	13.8 (13 to 14.6)
Baseline visual field MD (dB)	−3.2 (−4.1 to −2.4)	−0.3 (−0.8 to 0.2)
Baseline GCC thickness (μm)	94.2 (91.8 to 96.6)	106.1 (103 to 109.1)
Baseline wiVD (%)	45.0 (44.2 to 45.8)	47.1 (45.9 to 48.3)
Baseline corrected FAZ area (mm^2)	0.29 (0.26 to 0.31)	0.28 (0.24 to 0.33)

CCT = central corneal thickness; FAZ = foveal avascular zone; GCC = ganglion cell complex; IOP = intraocular pressure; MD = mean deviation; VF = visual field, wiVD = whole image vessel density. Values are shown in mean (95% confidence interval), unless otherwise indicated.

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Table 2.

Changes in Ganglion Cell Complex, Macular Vessel Density, and Visual Field Mean Deviation Classified by Foveal Avascular Zone Change at Fixed Specificity

	Variables	FAZ progressors	FAZ non-progressors	Difference, Mean (95% CI)	P value
95% Specificity		n = 19	n = 96		
	GCC (μm/y)	−1.5 (−2.6 to −0.4)	−0.8 (−1.0 to −0.5)	−0.7 (−1.4 to −0.1)	**0.026**
	wiVD (%/y)	−1.3 (−1.8 to −0.8)	−1.3 (−1.5 to −1.1)	0.0 (−0.5 to 0.5)	0.993
	VF MD (dB/y)	−0.5 (−0.9 to 0.0)	−0.2 (−0.3 to −0.1)	−0.3 (−0.5 to −0.1)	**0.017**
90% Specificity		n = 28	n = 87		
	GCC (μm/y)	−1.2 (−1.9 to −0.5)	−0.8 (−1.0 to −0.5)	−0.4 (−1.0 to 0.1)	0.141
	wiVD (%/y)	−1.3 (−1.6 to −0.9)	−1.3 (−1.5 to −1.1)	0.0 (−0.4 to 0.4)	0.978
	VF MD (dB/y)	−0.4 (−0.7 to −0.1)	−0.2 (−0.3 to −0.1)	−0.3 (−0.5 to 0.0)	**0.019**
85% Specificity		n = 41	n = 74		
	GCC (μm/y)	−1.1 (−1.6 to −0.6)	−0.7 (−1.0 to −0.5)	−0.4 (−0.9 to 0.1)	0.138
	wiVD (%/y)	−1.2 (−1.5 to −0.9)	−1.3 (−1.5 to −1.1)	0.1 (−0.2 to 0.5)	0.437
	VF MD (dB/y)	−0.3 (−0.6 to −0.1)	−0.2 (−0.3 to −0.1)	−0.2 (−0.4 to 0.0)	0.080
80% Specificity		n = 54	n = 61		
	GCC (μm/y)	−1.1 (−1.5 to −0.7)	−0.7 (−1.0 to −0.4)	−0.4 (−0.9 to 0.1)	0.086
	wiVD (%/y)	−1.2 (−1.5 to −0.9)	−1.3 (−1.6 to −1.1)	0.1 (−0.2 to 0.5)	0.403
	VF MD (dB/y)	−0.3 (−0.5 to −0.2)	−0.2 (−0.2 to −0.1)	−0.2 (−0.4 to 0.0)	0.074

CCT = central corneal thickness; FAZ = foveal avascular zone; GCC = ganglion cell complex; IOP = intraocular pressure; MD = mean deviation; VF = visual field, wiVD = whole image vessel density. Values are shown in mean (95% confidence interval), unless otherwise indicated. Bold text indicates a statistically significant difference with $p<0.05$.

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Table 3.

Factors Associated with FAZ Area Progression by Generalized Mixed-effects Model

Variables	Univariable Model		Multivariable Model 1 IOP fluctuation		Multivariable Model 2 IOP range	
	Odds ratio, 95 % CI	P value	Odds ratio, 95 % CI	P value	Odds ratio, 95 % CI P value	P value
MD slope, 0.1 dB/y slower	0.91 (0.83 to 0.99)	**0.029**	0.90 (0.80 to 1.02)	0.101	0.91 (0.81 to 1.02)	0.114
GCC slope,1 μm/y slower	0.66 (0.46 to 0.95)	**0.024**				
IOP fluctuation, 0.5 mmHg higher	1.45 (1.04 to 2.02)	**0.029**	1.54 (1.02 to 2.32)	**0.041**		
IOP range, 1 mmHg higher	1.16 (1.04 to 1.29)	**0.006**			1.20 (1.01 to 1.41)	**0.035**
Follow-up period 1 y longer	0.80 (0.46 to 1.37)	0.416				
Number of visits, 1 visit higher	0.87 (0.62 to 1.23)	0.433	0.82 (0.56 to 1.20)	0.323	0.79 (0.53 to 1.20)	0.271
Baseline GCC thickness, 1 μm thicker	0.97 (0.92 to 1.02)	0.222				
Baseline wiVD, 1% higher	0.84 (0.75 to 0.95)	**0.007**				
Baseline VFI, 1%, higher	1.00 (0.96 to 1.04)	0.889				
Baseline VF MD, 1 dB higher	0.99 (0.89 to 1.10)	0.817				
Baseline PSD, 1 dB higher	0.93 (0.80 to 1.08)	0.349				
wiVD slope, 1%/y faster	1.00 (0.57 to 1.75)	0.993				
Spherical equivalent, 1 diopter higher	1.04 (0.87 to 1.26)	0.654				
Axial length, 1 mm longer	1.35 (0.89 to 2.03)	0.156				
Mean arterial pressure, 1 mmHg higher	0.99 (0.95 to 1.03)	0.645				
Diastolic pressure, 1 mmHg higher	0.99 (0.95 to 1.03)	0.640				
Systolic pressure, 1 mmHg higher	0.99 (0.97 to 1.02)	0.731				
Peak IOP, 1 mmHg higher	1.08 (0.98 to 1.18)	0.117				
Mean IOP, 1 mmHg higher	1.05 (0.89 to 1.24)	0.536				
CCT, 1 μm thicker	1.00 (0.99 to 1.01)	0.695				
Average SSI, 1 unit higher	0.95 (0.89 to 1.03)	0.201	0.93 (0.85 to 1.02)	0.105	0.93 (0.85 to 1.02)	0.105
Baseline age, 1 year older	1.01 (0.96 to 1.06)	0.739				
Baseline corrected FAZ area, 0.1 mm^2 larger	1.19 (0.80 to 1.78)	0.386				

CCT = central corneal thickness; FAZ = foveal avascular zone; GCC = ganglion cell complex; IOP = intraocular pressure; MD = mean deviation; SD = standard deviation; SSI = signal strength index; VF = visual field. Values are shown in mean (95% confidence interval), unless otherwise indicated. Bold text indicates a statistically significant difference with $p<0.05$.