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The Relationship Between Artificial Intelligence–Assisted OCT Angiography–Derived Foveal Avascular Zone Parameters and Visual-Field Defect Progression in Eyes with Open-Angle Glaucoma

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Purpose: To investigate clinical factors associated with foveal avascular zone (FAZ) parameters obtained using OCT angiography (OCTA) with assistance from a previously developed artificial intelligence (AI) platform in eyes with open-angle glaucoma (OAG).

Design: Retrospective longitudinal.

Participants: This study followed up 885 eyes of 558 patients with OAG for $\geq$ 2 years; all eyes underwent $\geq$ 5 Humphrey visual-field (VF) tests and had 3.0 $\times$ 3.0 mm macular OCTA scans available.

Methods: Average total deviation (TD) in the superior, superocentral, inferocentral, and inferior sectors of the Humphrey 24-2 program was calculated. We collected 3.0 $\times$ 3.0 mm macular OCTA images from each patient and used a previously developed AI platform with these images to obtain FAZ parameters, including FAZ area, FAZ circularity index (CI), and FAZ perimeter. Multivariable linear mixed-effects models were used to analyze the relationship between FAZ parameters, TD or TD slope in each quadrant, and systemic factors, adjusting for potential confounding factors, including axial length.

Main Outcome Measures: Ophthalmic and systemic variables, FAZ parameters, and TD or TD slope in each quadrant.

Results: The multivariable model showed that FAZ parameters were correlated with both TD and TD slope in the inferocentral quadrant ($\beta = -0.244$ - 0.168, $P < 0.001$). Both upper-half and lower-half FAZ parameters were better associated with TD-inferocentral and TD-inferocentral slope than TD-superocentral or TD-superocentral slope in terms of β size and statistical significance, indicating that there was no evident vertical anatomical correspondence between TD in the central quadrant and FAZ parameters. Foveal avascular zone area enlargement was associated with female gender ($\beta = 0.242$, $P = 0.003$). Loss of FAZ circularity was associated with both aging and comorbid sleep apnea syndrome (SAS) (yes: 1, no: 0) ($\beta = -0.188$, $P < 0.001$; $\beta = -0.261$, $P = 0.031$, respectively). Foveal avascular zone perimeter elongation was associated with aging and female gender ($\beta = 0.084$, $P = 0.040$; $\beta = 0.168$, $P = 0.042$, respectively).

Conclusions: Artificial intelligence-assisted OCTA-measured FAZ enlargement and irregular shape might be good markers of ocular hypoperfusion and associated inferocentral VF defect progression in eyes with OAG.

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The foveal avascular zone (FAZ) is an area within the fovea centralis that lacks retinal blood vessels.[1] Fluorescein angiography has traditionally been the gold standard for detecting the FAZ in vivo.[2] Enlargement or irregularity of the FAZ has been linked to ocular ischemia, which has been implicated in the pathogenesis of conditions including, among others, diabetic retinopathy and branch retinal vein occlusion.[3,4] However, evaluation of the FAZ

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in clinical practice has mainly been limited to these 2 diseases, likely due to the invasive and time-consuming nature of fluorescein angiography.[5]

Recently, OCT angiography (OCTA) has emerged as a noninvasive technique for visualizing the retinal and choroidal vasculature without the need for dye injection, making it more practical for use in a broader range of ocular diseases, including glaucoma.[6,7] It has been suggested that FAZ abnormalities may be associated with parafoveal scotoma in eyes with glaucoma.[8–10] Glaucoma is the second leading cause of blindness worldwide, and the only evidence-based treatable risk factor is elevated intraocular pressure (IOP).[11] However, glaucoma is now recognized as a multifactorial disease, and ocular blood flow (BF) impairment is one of the most potentially important risk factors and treatment targets.[12,13] The relationship between FAZ irregularities and the pathophysiology of glaucoma, however, is not well understood. To address this gap in knowledge, we need studies with large sample sizes of glaucoma patients who have undergone OCTA and visual field (VF) testing, given the potential presence of various subgroups within the glaucoma population. One issue with this approach is that it is not practical to manually process a large number of OCTA images to obtain FAZ parameters. To overcome this challenge, we have recently developed an artificial intelligence (AI) platform that automatically and concisely segments the FAZ region in OCTA images and calculates 3 FAZ parameters: FAZ area, FAZ circularity index (CI), and FAZ perimeter.[14]

In this study, we set out to collect macular OCTA images and apply our AI platform to them. We sought to include a relatively large number of open-angle glaucoma (OAG) patients for whom follow-up data from Humphrey VF testing were available. Considering our previous finding that the contribution of BF impairment to VF defects varies depending on the quadrant,[15,16] we investigated sectoral differences in the relationship between FAZ abnormalities and VF defect severity and progression. In addition, we attempted to determine whether there is vertical anatomical correspondence between FAZ abnormalities and glaucomatous VF defects in the central quadrant. Furthermore, we investigated the systemic factors that influenced FAZ abnormalities in eyes with OAG.

Methods

Subjects

This retrospective longitudinal study reviewed the medical records of 3400 eyes of 1839 patients who underwent macular OCTA at Tohoku University Hospital in Miyagi, Japan, between April 2016 and April 2022. At their initial visit to our hospital, each patient underwent a medical history review that included hypertension, diabetes mellitus, dyslipidemia, heart disease, sleep apnea syndrome (SAS), and smoking history, and baseline data were obtained for visual acuity and IOP. We also recorded the results of slit lamp, gonioscopic, and dilated funduscopic examinations. The selection process for including eyes in this study is illustrated in Figure 1. The diagnosis of OAG, including primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG), was made by a glaucoma specialist based on the presence of glaucomatous changes to the optic disc with corresponding VF defects that met the Anderson–Patella criteria,[17] untreated baseline IOP, and the absence of any other disease that might affect the VF (e.g., corneal opacity, clinically evident cataract [lens nucleus grade $>$ 2 in the Emery–Little classification], hypertensive/diabetic retinopathy, optic neuritis, or brain infarction). A total of 2021 eyes of 1170 patients had an OAG diagnosis and no other ocular disease potentially affecting the VF data and were included. Additional inclusion criteria were (1) age between 20 and 85 years, (2) axial length $<$ 28 mm, and (3) availability of $\geq$ 5 Humphrey VF test results (none of which were obtained after glaucoma surgery) during $\geq$ 2 years of follow-up. A total of 944 eyes of 604 patients with OAG met these criteria. Then, we manually excluded OCTA images in which FAZ was not successfully segmented or could not be detected; this was usually due to poor image quality. We also excluded patients who underwent continuous positive airway pressure treatment during follow-up, based on information from our database, as continuous positive airway pressure may affect the speed of VF defect progression.[18,19] When both eyes of a patient met the inclusion criteria, both eyes were included in the analysis. This process resulted in the enrollment of 885 eyes of 558 patients with OAG. The patients were managed during follow-up at the discretion of the attending glaucoma specialist with reference to their target IOP, based on the Japan Glaucoma Society guidelines for glaucoma.[20] The procedures in this study were approved by the institutional review board of the Tohoku University Graduate School of Medicine (No 2021-1-265) and were conducted in accord with the tenets of the Declaration of Helsinki. All patients provided informed written consent to have data from their medical records used in research.

Measurement of Clinical Variables

Intraocular pressure was measured with Goldmann applanation tonometry, central corneal thickness was measured with anterior-segment OCT (CASIA, Tomey Corporation), axial length was measured using the IOL Master (Zeiss Meditec) or OA-2000 (Tomey), and circumpapillary retinal nerve fiber layer thickness (cpRNFLT) was measured using swept-source OCT (DRI-OCT, Triton, Topcon, Inc). The accompanying software was used to divide the peripapillary area into 4 sectors: superior, temporal, inferior, and nasal. Circumpapillary retinal nerve fiber layer thickness was measured in each sector. The VF was measured using the 24-2 Swedish interactive threshold algorithm standard program of the Humphrey Field Analyzer (Carl Zeiss Meditec). Only reliable measurements, i.e., those with fixation errors $<$ 20%, false positives $<$ 33%, and false negatives $<$ 33% were included in the dataset, and VF data after glaucoma surgery were excluded as described. The site-specific VF was evaluated in reference to the modified version of the VF sector map established by Garway-Heath et al.[15,21] This study focused on the superior, central, and inferior VF

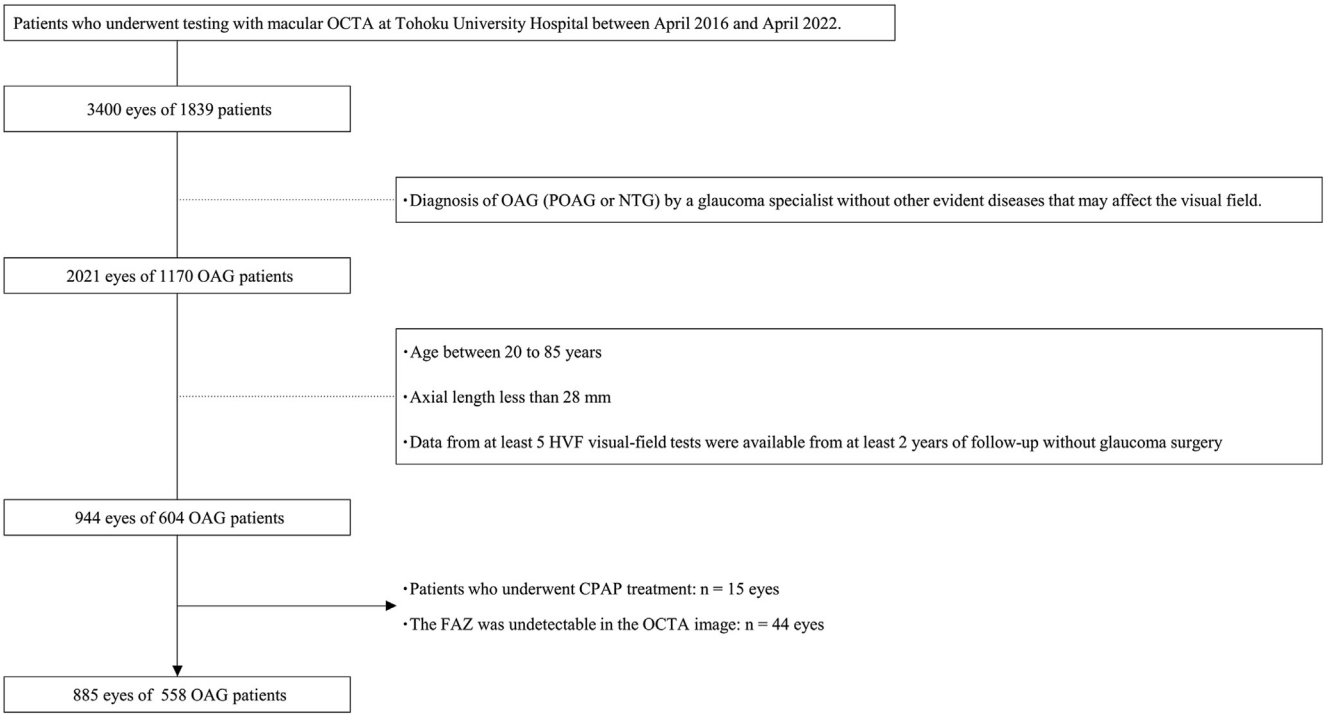

Figure 1. Selection scheme for eyes included in this study. The dotted lines indicate the inclusion criteria, and the horizontal arrows indicate the exclusion criteria. CPAP = continuous positive airway pressure; HVF = Humphrey visual field; FAZ = foveal avascular zone; NTG = normal-tension glaucoma; OAG = open-angle glaucoma; OCTA = OCT angiography; POAG = primary open-angle glaucoma.

sectors; the anatomical correspondence between total deviation (TD)/TD slope and OCT-derived cpRNFLT have also been previously described.[15] In this study, we additionally divided the central quadrant into the superocentral and inferocentral quadrants for 2 reasons: first, there may be a vertical difference in the relationship between VF defects and ocular BF, and second, because we wanted to investigate the anatomical correspondence between upper-half and lower-half FAZ parameters and TD in the central quadrant. Thus, in this study, we divided the central 6 measurement points into the superocentral (upper 3 points; orange area in Fig S2) and inferocentral quadrants (lower 3 points; green area in Fig S2). Average TD and TD slope were calculated in each sector. Prior to OCTA measurements, the pupils were dilated with 0.4% tropicamide, a muscarinic antagonist (Mydrin M; Santen Pharmaceutical Co, Ltd). After instillation, the patients sat in a dark, quiet room for 15 minutes to stabilize pupil dilation, blood pressure (BP), and pulse rate. OCT angiography, BP, and pulse rate were then measured (HBP-1300; Omron). Mean BP was calculated as follows:

$$mean\ BP = diastolic\ BP + \frac{1}{3}(systolic\ BP - diastolic\ BP)$$

OCTA and AI

In this study, we used an AI platform we recently developed to obtain the FAZ parameters.[14] Swept-source OCT was set to macular OCTA mode with the default settings to record slab images of the superficial retinal capillary plexus of the macula. A 3.0 mm × 3.0 mm region centered on the fovea was scanned and corrected for magnification errors using axial length parameters. ImageNet 6 V1.31 (Topcon, Inc) software, which accompanies the OCT machine, was used to generate the superficial retinal capillary plexus slab images by selecting the region starting from 2.6 μm below the internal limiting membrane to 15.6 μm beneath the inner plexiform/inner nuclear layer.[22]

The superficial retinal capillary plexus slab images were subsequently processed with a lightweight deep learning model (lightweight bottleneck narrowing with attention in Unet, LWBNA-Unet) that we developed for the detection and measurement of FAZ parameters. Briefly, LWBNA-Unet is a deep learning model based on Unet, which is frequently used for segmentation tasks. Pruning of filters, along with the introduction of layer-wise attention and contraction of channels at the bottleneck to allow only the high-level features necessary for the reconstruction of

$$upper\ or\ lower\ half\ FAZ\ CI = 4\pi \frac{2 \times upper\ or\ lower\ half\ FAZ\ area}{(2 \times upper\ or\ lower\ half\ FAZ\ perimeter)^2}$$

segmented features, make this model very lightweight and highly accurate. A comparison of the precision of measurements of FAZ area from LWBNA-Unet and ImageNet 6 shows that LWBNA-Unet provides measurements closer to manually measured, ground-truth data than ImageNet 6. Our AI-based platform outputs segmented images and corresponding parameters (such as area, perimeter, and shape index) of the whole image, as well as the upper and lower halves of the FAZ area. Foveal avascular zone CI is calculated using the following formula[23]:

$$FAZ\ CI = 4\pi \frac{FAZ\ area}{FAZ\ perimeter^2}$$

In the case of half circularity, the formula is as follows:

Statistical Analysis

All data are presented as the mean ± standard deviation. When values for clinical parameters were absent on the date that OCTA was conducted, the value measured at the closest date to the OCTA examination was used in the analysis. The relationship between FAZ parameters, TD in each quadrant, and TD slope in each quadrant was analyzed using a multivariable linear mixed-effects model. Fixed effects included age, gender (female: 1, male: 0), IOP, central corneal thickness, mean BP, pulse rate, axial length, and anatomically corresponding cpRNFLT, with the "subject" variable as a random effect. The same statistical method was applied to examine the relationship between TD and FAZ parameters in vertical anatomical correspondence. To investigate systemic factors affecting FAZ parameters, each FAZ parameter was set as a response variable, and systemic factors, such as age, gender, hypertension, diabetes mellitus, heart disease, SAS, smoking history, systolic/diastolic BP, and pulse rate, were set as explanatory variables, with "subject" as a random effect in a linear mixed-effects model. Systemic factors that reached $P < 0.1$ in the univariable analysis, in addition to axial length, were included in a subsequent multivariable linear mixed-effects model. All statistical analyses were performed using R software (version 4.1.3, R Foundation for Statistical Computing), with the significance level set at $P < 0.05$.

Table 1. Systemic Characteristics of Patients with Open-Angle Glaucoma

Parameter	Value
Number of patients (n)	558
Age (years)	59.55 ± 11.79
Male to female ratio (n)	299:282
Hypertension (n, %)	168 (30.1)
Diabetes mellitus (n, %)	48 (8.6)
Dyslipidemia (n, %)	152 (27.2)
Heart disease (n, %)	55 (9.9)
SAS (n, %)	56 (10.0)
Smoking history (n, %)	80 (14.3)
Systolic BP (mmHg)	125.69 ± 20.38
Diastolic BP (mmHg)	71.83 ± 13.70
Pulse rate (bpm)	73.56 ± 11.26
Oral CAI (n, %)	94 (16.8)

BP = blood pressure; CAI = carbonic anhydrase inhibitor; SAS = sleep apnea syndrome.

Table 2. Ocular Characteristics of Patients with Open-Angle Glaucoma

Parameter	Value
Number of eyes (n)	885
BCVA (logMAR)	−0.02 ± 0.22
IOP (mmHg)	13.29 ± 3.28
Axial length (mm)	25.46 ± 1.40
Central corneal thickness (μm)	515.68 ± 36.92
CpRNFLT (μm)	70.03 ± 15.40
MD (dB)	−9.57 ± 6.87
TD-superior (dB)	−11.29 ± 9.99
TD-superocentral (dB)	−10.58 ± 11.36
TD-inferocentral (dB)	−4.78 ± 7.90
TD-inferior (dB)	−9.08 ± 8.65
MD slope (dB/year)	−0.43 ± 0.59
TD-superior slope (dB/year)	−0.46 ± 0.83
TD-superocentral slope (dB/year)	−0.51 ± 1.13
TD-inferocentral slope (dB/year)	−0.30 ± 0.93
TD-inferior slope (dB/year)	−0.39 ± 0.72
FAZ area (mm^2)	0.37 ± 0.13
FAZ circularity index (AU)	0.65 ± 0.10
FAZ perimeter (mm)	2.66 ± 0.54
Prostaglandin analogs (n, %)	812 (91.8)
β blockers (n, %)	690 (78.0)
CAI (n, %)	649 (73.3)
α1 inhibitors (n, %)	80 (9.0)
α2 stimulators (n, %)	567 (64.1)
Rho-associated protein kinase inhibitors (n, %)	327 (36.9)

AU = arbitrary unit; BCVA = best-corrected visual acuity; CAI = carbonic anhydrase inhibitor; CpRNFLT = circumpapillary retinal nerve fiber layer thickness; dB = decibels; FAZ = foveal avascular zone; IOP = intraocular pressure; logMAR = logarithm of minimum angle of resolution; MD = mean deviation; TD = total deviation.

Results

Of 885 eyes, 709 eyes (80.1%) were diagnosed as having NTG and 176 (19.9%) eyes as having POAG. The average follow-up period and total number of Humphrey VF tests were 7.51 ± 4.71 years and 14.53 ± 7.82 times, respectively. Tables 1 and 2 show the systemic and ocular characteristics of the patients with OAG enrolled in this study. The average values for FAZ area, FAZ CI, and FAZ perimeter were 0.37 ± 0.13 mm^2, 0.65 ± 0.10 arbitrary units, and 2.66 ± 0.54 mm, respectively.

Table 3 presents the results of a multivariable linear mixed-effects model examining the relationship between FAZ parameters and VF defects in each quadrant, adjusting for age, gender, IOP, central corneal thickness, mean BP, pulse rate, axial length, and anatomically corresponding cpRNFLT. The FAZ area was significantly associated with TD-inferocentral, TD-inferior, and TD-inferocentral slope ($\beta = -0.133$ to 0.197, $P < 0.006$). The relationship between upper- and lower-half FAZ parameters and VF defect severity or progression in the superocentral and inferocentral quadrants is shown in Table 4. Both upper- and lower-half

Table 3. Multivariable Linear Mixed-Effects Model Showing the Relationship Between FAZ Parameters and TD

Variables	FAZ Area (β, *P*)	FAZ CI (β, *P*)	FAZ Perimeter (β, *P*)
TD-superior	0.017, 0.536	0.023, 0.343	0.003, 0.899
TD-superocentral	−0.076, 0.160	0.076, 0.010*	−0.102, < 0.001*
TD-inferocentral	−0.197, < 0.001*	0.168, < 0.001*	−0.244, < 0.001*
TD-inferior	−0.097, 0.006*	0.064, 0.040*	−0.119, < 0.001*
TD-superior slope	0.009, 0.794	−0.029, 0.392	0.017, 0.634
TD-superocentral slope	−0.024, 0.505	−0.000, 0.994	−0.028, 0.438
TD-inferocentral slope	−0.133, < 0.001*	0.115, < 0.001*	−0.159, < 0.001*
TD-inferior slope	−0.045, 0.233	0.024, 0.474	−0.044, 0.218

CI = circularity index; FAZ = foveal avascular zone; TD = total deviation.
Age, gender, intraocular pressure, center corneal thickness, mean blood pressure, pulse rate, axial length, and circumpapillary retinal nerve fiber layer thickness were adjusted.
β indicates the standardized partial regression coefficient.
*Indicates statistical significance in single regression analysis.

FAZ parameters were more strongly correlated with VF defects in the inferocentral and inferocentral slope quadrants compared with the superocentral and superocentral slope quadrants (i.e., absolute β value was always larger and the *P* value was always significant for the correlation between FAZ parameters in both the upper and lower halves and TD variables in the inferocentral quadrant, compared with TD variables in the superocentral quadrant), suggesting that there was no clear vertical anatomical correspondence between 24-2 central quadrant VF defects and FAZ parameters.

As shown in Table 5, the multivariable model showed that enlargement of the FAZ area was associated with female gender ($\beta = 0.242$, $P = 0.003$). The loss of FAZ CI was associated with aging and the presence of SAS ($\beta = -0.188$, $P < 0.001$ and $\beta = -0.261$, $P = 0.031$, respectively). Foveal avascular zone perimeter elongation was associated with aging and female gender ($\beta = 0.084$, $P = 0.040$ and $\beta = 0.168$, $P = 0.042$, respectively).

A representative patient demonstrating the link between FAZ abnormalities and progression of inferocentral VF defects is shown in Figure 3. Foveal avascular zone size in this patient is relatively large (FAZ area: 0.46 mm^2, FAZ perimeter: 3.22 mm) and FAZ shape is irregular (FAZ CI: 0.55 arbitrary unit); there is VF defect progression in the inferocentral quadrant.

Discussion

This study retrospectively analyzed macular OCTA scan images from 885 eyes of 558 patients with OAG for whom longitudinal VF test data were available. We used an AI platform we previously developed to determine and calculate FAZ parameters. We found that FAZ enlargement or irregular shape were associated with both VF defect severity and progression in the inferocentral quadrant. When we divided the central VF into superior and inferior quadrants and the FAZ region into upper and lower halves, we found no evident vertical anatomical correspondence in terms of the correlation between VF defects and FAZ parameters. Foveal avascular zone abnormalities may be influenced by aging, gender, and the presence of SAS.

Intriguingly, we observed sectoral differences in the relationship between FAZ abnormalities and VF defect severity and progression; VF defects in the inferocentral quadrant might be related to vulnerability to FAZ enlargement or loss of circularity. There have been several reports indicating a close link between inferior or central VF defects and BF-associated factors.[24–28] Suzuki et al[25] showed that patients with NTG with signs of ischemic changes in brain magnetic resonance imaging had a relatively deeper depression in the inferior pericentral VF area. Additionally, inferior VF defects typically develop in

Table 4. The Relationship Between FAZ Parameters and TD for Vertical Anatomical Correspondence

	Upper Half			Lower Half		
Variables	*FAZ Area (β, P)*	*FAZ CI (β, P)*	*FAZ Perimeter (β, P)*	*FAZ Area (β, P)*	*FAZ CI (β, P)*	*FAZ Perimeter (β, P)*
TD-superocentral	−0.074, 0.019*	0.109, 0.002*	−0.098, 0.001*	−0.075, 0.017*	0.116, < 0.001*	−0.092, 0.003*
TD-inferocentral	−0.196, < 0.001*	0.155, < 0.001*	−0.239, < 0.001*	−0.196, < 0.001*	0.132, < 0.001*	−0.210, < 0.001*
TD-superocentral slope	−0.024, 0.504	−0.019, 0.583	−0.015, 0.676	−0.028, 0.446	0.026, 0.457	−0.037, 0.300
TD-inferocentral slope	−0.135, < 0.001*	0.078, 0.022*	−0.153, < 0.001*	−0.129, < 0.001*	0.086, 0.011*	−0.144, < 0.001*

CI = circularity index; FAZ = foveal avascular zone; TD = total deviation.
Age, gender, intraocular pressure, central corneal thickness, mean blood pressure, pulse rate, axial length, and circumpapillary retinal nerve fiber layer thickness were adjusted.
β indicates the standardized partial regression coefficient.
*Indicates statistical significance in single regression analyses.

Table 5. Systemic Factors Affecting FAZ Parameters in Patients with Open-Angle Glaucoma

	FAZ Area		FAZ CI		FAZ Perimeter	
	Univariable (β, P)	*Multivariable (β, P)*	*Univariable (β, P)*	*Multivariable (β, P)*	*Univariable (β, P)*	*Multivariable (β, P)*
Age	0.068, 0.086	0.026, 0.513	−0.178, < 0.001	−0.188, < 0.001*	0.124, 0.001	0.084, 0.040*
Female gender	0.376, < 0.001	0.242, 0.003*	0.203, 0.004	0.118, 0.106	0.262, < 0.001	0.168, 0.042*
Hypertension	−0.104, 0.240		−0.182, 0.021	0.001, 0.986	−0.004, 0.959	
Diabetes mellitus	−0.072, 0.621		−0.106, 0.423		−0.064, 0.652	
Dyslipidemia	0.131, 0.151		−0.101, 0.218		0.151, 0.089	0.086, 0.332
Heart disease	−0.020, 0.884		0.022, 0.861		−0.032, 0.812	
SAS	−0.186, 0.172		−0.353, 0.004	−0.261, 0.031*	−0.056, 0.673	
Smoking history	−0.258, 0.026	−0.129, 0.265	−0.070, 0.494		−0.225, 0.045	−0.106, 0.350
Systolic BP	−0.087, 0.028		−0.074, 0.036	−0.028, 0.444	−0.049, 0.200	
Diastolic BP	−0.121, 0.002	−0.071, 0.072	−0.070, 0.049		−0.081, 0.037	−0.047, 0.229
Pulse rate	−0.008, 0.840		−0.020, 0.567		−0.005, 0.904	

BP = blood pressure; CI = circularity index; FAZ = foveal avascular zone; SAS = sleep apnea syndrome.
In addition to the above systemic factors, which all reached $P < 0.1$ in a univariable analysis, axial length was also adjusted in the multivariable models.
β indicates the standardized partial regression coefficient.
*Indicates statistical significance in single regression analyses.

nonarteritic anterior ischemic optic neuropathy.[28,29] We previously reported that reduced optic nerve head (ONH)-tissue BF, as measured by laser speckle flowgraphy, in the superior to temporal quadrant (but not the inferior quadrant) was an independent risk factor for anatomically corresponding inferior to central VF defect progression in eyes with OAG.[15] We also reported that the superior to temporal quadrants of the ONH are a region where BF

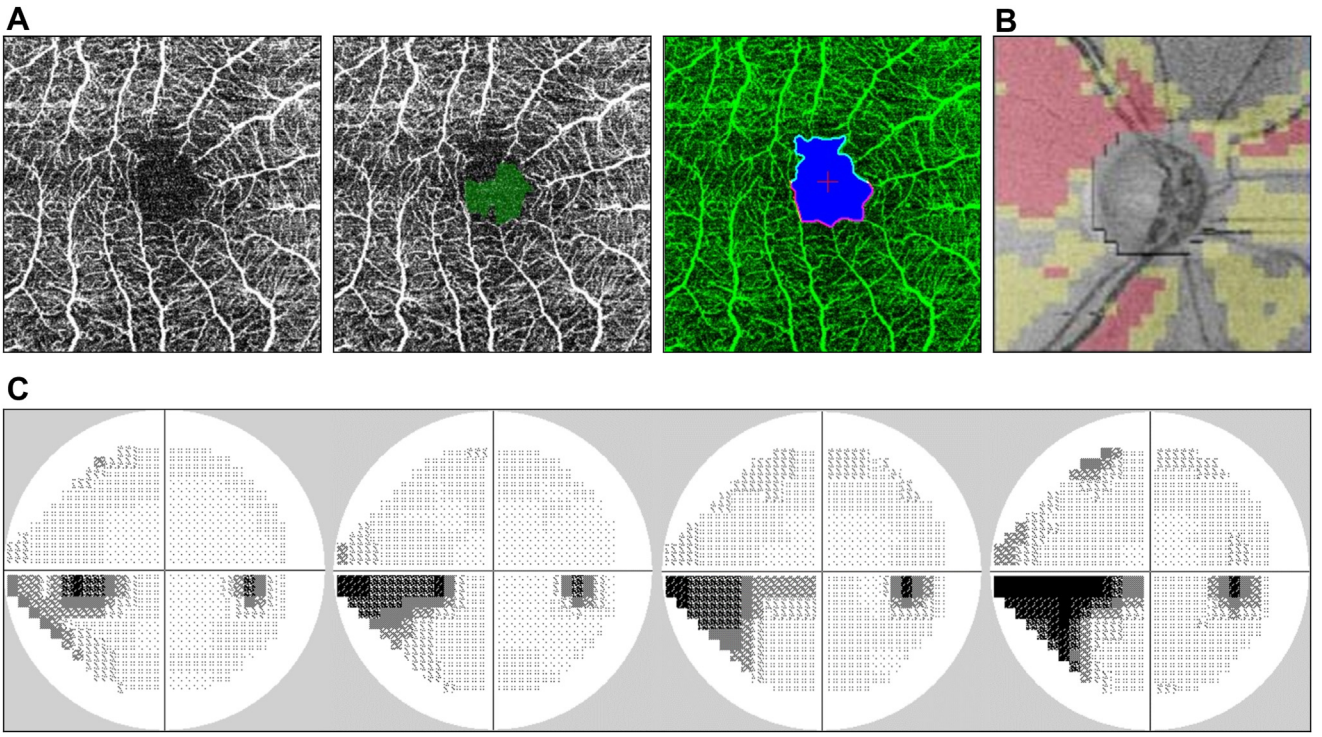

Figure 3. Representative 3.0 × 3.0 mm macular OCT angiography (OCTA) images, a deviation map report from a swept-source OCT disc scan, and grayscale images of Humphrey Field Analyzer results from the 24-2 Swedish interactive threshold algorithm. This patient is a 60-year-old male who presented with complication with sleep apnea syndrome. **A,** From left to right: raw 3.0 × 3.0 mm macular OCTA image, image with the foveal avascular zone (FAZ) segmented by the accompanying software, superimposed on the raw image, and the FAZ segmented by our artificial intelligence (AI) platform, superimposed on the raw image. The light green line indicates the upper half of the FAZ, and the purple line indicates the lower half of the FAZ. The purple cross indicates the center of the FAZ. The segmentation by our AI platform was superior to that of the OCT software, which is consistent with our previous findings.[14] **B,** Red indicates areas with circumpapillary retinal nerve fiber layer thickness in the lowest first percentile, and yellow indicates areas in the lowest fifth percentile. Damage to the retinal nerve fiber layer can be observed that is predominant superiorly and temporally. **C,** Visual-field defects, particularly in the inferocentral quadrant, progressed during the follow-up period.

impairment is likely to precede structural changes (i.e., neuron loss) in eyes with OAG.[16] These findings suggest that the inferior to central VF (corresponding to the superior to temporal ONH) is vulnerable to ocular BF impairment. As the FAZ is known to be sensitive to ocular ischemia, the results of this study support the concept that the inferocentral VF is vulnerable to ocular BF impairment. The underlying mechanism remains unclear, although we have previously speculated that the anatomical location of the watershed zone may provide some explanation.[15,16,30–32] The watershed zone is where the short posterior ciliary arteries anastomose and thus is potentially susceptible to ischemia. This zone is often located on the temporal side of the ONH,[33] which may explain the link between central VF defects and ocular BF impairment. Furthermore, another study suggests that there may be less anastomosis of the superior short posterior ciliary arteries, a finding that is consistent with the common occurrence of inferior VF defects in nonarteritic anterior ischemic optic neuropathy.[29,32] In addition to ONH BF reduction in the superior to temporal quadrants, FAZ abnormalities may also be a potential biomarker of mild chronic ocular ischemia.

We found that both the upper and lower halves of the FAZ were more strongly correlated with VF defects in the inferocentral and inferocentral slope quadrants compared with the superocentral and superocentral slope quadrants. Both our results and those previously reported suggest that parafoveal VF defects are associated with FAZ abnormalities,[8–10] and since the FAZ is located at the center of the retina, possible interpretations of this association are that central VF defects are caused by FAZ abnormalities or that FAZ abnormalities are the result of neurodegeneration in the central retina. However, our results challenge this interpretation, because if this were the case, then anomalies in the upper FAZ would be associated with lower central VF defects, and anomalies in the lower FAZ would be associated with upper VF defects. In fact, given that the actual diameter of the FAZ is approximately 1.5 degrees, which does not normally extend to the 4 central measurement points of the Humphrey Field Analyzer 24-2 program even in eyes with parafoveal scotoma,[34–36] it is unlikely that FAZ enlargement directly affects or is affected by this region. Rather, as the inferior to central VF may be vulnerable to BF impairment, possibly due to the aforementioned reason (i.e., watershed zone distribution around the ONH), and the FAZ is also an area sensitive to ocular ischemia, we interpret FAZ abnormalities as a potential biomarker of the condition of the eye in chronic BF impairment. Nevertheless, the results of Kwon et al[8] show a vertical correspondence, which is contrary to our results. This discrepancy may be related to differences in sample size, the proportion of patients with NTG, and segmentation methods for both the FAZ and the VF. Despite this, we consider that this study supports the concept that the FAZ reflects ocular or systemic health status (especially BF status), rather than directly affecting visual function in the central measurement points of the 24-2 VF test.[37–42] A multicenter study with patients of more varied ethnicities will be needed to clarify this point in the future.

We identified several systemic factors that contributed to FAZ abnormalities in glaucoma patients. Aging was associated with the loss of FAZ CI and perimeter elongation but not with FAZ enlargement. Since aging was not associated with FAZ enlargement, the association with perimeter elongation may be secondary to irregular shape. As the loss of FAZ CI quantifies abnormalities in FAZ shape rather than size, it may be less affected by other size-related factors, such as gender or axial length,[43] and may potentially be a more direct marker of ischemia. The association of aging with the loss of FAZ CI is thus explainable, given that aging serves as a major risk factor for the development of atherosclerosis and compromised blood circulation.[44,45] Conversely, female gender was associated with an increase in both FAZ area and FAZ perimeter, but was not associated with changes in FAZ CI, even after adjusting for axial length. Women have been considered to have a lower risk of developing atherosclerosis than men,[46,47] and the absence of a correlation with FAZ CI may indicate that FAZ enlargement in women might be an anatomical gender difference rather than a pathological change. Though a larger FAZ is consistent with previous findings,[48] the reason for this is not known. Nevertheless, sex hormones have been suggested to be involved in this process.[39] It is important to note that both age and gender may influence FAZ parameters.

Interestingly, complication with SAS was associated with the loss of FAZ CI even after adjustment for age and gender. Sleep apnea syndrome is a disorder characterized by frequent pauses in breathing or periods of shallow breathing during sleep, and it has been suggested that it is linked to glaucoma pathophysiology.[49] Hypoxemia and activation of the sympathetic nervous system as a response to life-threatening airway obstruction leads to vascular endothelial dysfunction.[50,51] We previously demonstrated that BF impairment in the superior to temporal ONH is associated with complication with SAS, and showed that this SAS-induced impairment of ocular BF contributes to inferior to central VF defects with anatomical correspondence.[15] This study indicates that SAS-induced chronic reduction in ocular BF might be associated with the deterioration of FAZ shape, which is also linked to inferocentral VF defects. When observing FAZ shape irregularities in eyes with glaucoma, it is important to consider the possibility that the patient may have SAS complications.

This study has several limitations. First, as this study is a single-center retrospective study, it may be missing important clinical data and our results may be subject to bias. For example, we relied on patient interviews to gather medical history, which may have led to underestimation or overestimation of the impact of disease complications on FAZ parameters. Additionally, patient demographic factors introduced further biases. Our study was conducted in a Japanese university hospital, a setting where NTG is commonplace.[52] This could have influenced the results by allowing IOP-independent factors such as vascular parameters to have a more significant role than is usually the case in glaucoma pathophysiology among our patients, particularly when compared to those with typical high-tension glaucoma. Our sample was also skewed by comprising

solely glaucoma patients with a slight bias toward older age (59.55 ± 11.79 years). Consequently, our data did not reflect the correlation between age and FAZ area that was observed in 2 earlier studies, which included healthy subjects with a wider age range (42 ± 25 years and 48 ± 20 years).[53,54] Given these considerations, we advocate for future research to broaden the participant population to include healthy subjects and more subjects with high-tension glaucoma, to provide a more comprehensive understanding of this topic. Second, as patients with progressive VF defects often receive additional eye drops, it is possible that these medications may have influenced the results of the present study. Nevertheless, the association between FAZ and the VF would likely have been even stronger if the patients had not been using anti-glaucoma eye drops, as these medications lower IOP (i.e., increase ocular perfusion pressure) and some have a BF-improving effect.[55–57] A prospective multicenter study is necessary to minimize these biases in future research. Third, although we have shown that there was no evident vertical anatomical correspondence between FAZ parameters and TD in the central measurement points of the 24-2 VF test, it is possible that the FAZ abnormalities were the cause of changes in central retinal function in, for example, TD in the central measurement points of the 10-2 VF test. Nevertheless, our results suggest that FAZ abnormalities might at least be a marker of central VF defects in the points of the 24-2 test. Further investigation of 10-2 test and macular OCTA data from a sufficient number of subjects will be needed to clarify this point in the future. Fourth, we used a strict multivariable model to determine factors affecting FAZ parameters. Nevertheless, other factors that were significantly correlated with FAZ parameters in a univariable model might also be associated with FAZ size or shape. For example, lower diastolic BP was associated with larger FAZ area and perimeter in a univariable model. Diastolic BP is important for tissue perfusion,[58] and in the eye, ocular perfusion pressure is defined by the balance with IOP.[59,60] Shoji et al[61] showed that after IOP is lowered with trabeculectomy, microvasculature that was undetectable in preoperative OCTA images becomes visible, reducing the FAZ area. This may indicate that low perfusion pressure leads to reduced BF in this ischemia-sensitive region. We need a prospective multicenter study to determine other factors potentially associated with FAZ parameters. A fifth limitation of our study is that we combined the patients with POAG and NTG into a single OAG group. This decision was made because IOP at the time of OCTA measurement was within the normal range even in the POAG group (15.4 ± 4.18 mmHg), making it difficult to obtain accurate results for high-tension glaucoma. Instead of separate analyses, we included the variable "POAG diagnosis (reference, NTG)" as an explanatory factor in the multivariable linear mixed-effects model shown in Table 5, which represents the main results of this study (Table S6). We need to recruit more typical patients with high-tension glaucoma who undergo OCTA in the future to elucidate the differences between these 2 types of glaucoma.

In conclusion, AI-assisted measurements of FAZ enlargement and irregular shape derived from macular OCTA scans may serve as a useful marker of ocular hypoperfusion and associated inferocentral VF defect severity and progression in eyes with OAG. Systemic factors including age, gender, and complication with SAS may affect the size or shape of the FAZ in eyes with OAG. Therefore, the combination of AI, OCTA, and evaluation of systemic factors might be useful for glaucoma care in patients with progressive inferocentral VF defects.

Footnotes and Disclosures

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No animals were used in this study.

Author Contributions:

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Data Collection: Ninomiya, Kiyota, Sharma, Himori

Analysis and interpretation: Ninomiya, Kiyota, Omodaka, Yasuda, Kunikata, Nakazawa

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Abbreviations and Acronyms:
AI = artificial intelligence; **BF** = blood flow; **BP** = blood pressure; **CI** = circularity index; **cpRNFLT** = circumpapillary retinal nerve fiber layer thickness; **FAZ** = foveal avascular zone; **IOP** = intraocular pressure; **LWBNA-Unet** = lightweight bottleneck narrowing with attention in Unet; **NTG** = normal-tension glaucoma; **OAG** = open-angle glaucoma; **OCTA** = OCT angiography; **ONH** = optic nerve head; **POAG** = primary

open-angle glaucoma; **SAS** = sleep apnea syndrome; **TD** = total deviation; **VF** = visual field.

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