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Retinal Vascular Geometry and Glaucoma: The Singapore Malay Eye Study

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Purpose: To determine the associations of geometric measurements (tortuosity, branching angle, and fractal dimension) of retinal vessels with glaucoma.

Design: Population-based, cross-sectional study.

Participants: Persons aged 40 to 80 years who participated in the Singapore Malay Eye Study (n = 3280; 78.7% response rate).

Methods: Quantitative retinal vascular parameters (tortuosity, branching angle, and fractal dimension) were measured from digital retinal fundus photographs using a computer-assisted program following a standardized grading protocol. Glaucoma was diagnosed according to the International Society of Geographic and Epidemiological Ophthalmology classification system.

Main Outcome Measures: The associations among retinal vascular parameters with glaucoma, the main glaucoma subtype primary open-angle glaucoma (POAG), and ocular hypertension (OHT).

Results: A total of 123 persons (4.4% of the 2789 participants) had glaucoma in the final analysis, 87 (70.7%) of whom were diagnosed with POAG. After adjusting for age, sex, body mass index, diabetes, hypertension, smoking, axial length, and intraocular pressure (IOP), decreased retinal arteriolar tortuosity (odds ratio [OR], 1.73; 95% confidence interval [CI], 1.38–2.18, comparing lowest vs. highest quartiles), decreased retinal venular tortuosity (OR, 1.59; 95% CI, 1.29–1.97), and narrower retinal venular branching angle (OR, 1.22; 95% CI, 1.00–1.48) were associated with glaucoma. Similar associations were found between these retinal vascular parameters and POAG. Decreased retinal vascular fractal dimension was associated with OHT (OR 1.37; 95% CI, 1.04–1.82).

Conclusions: Certain features of retinal vascular geometry are associated with glaucomatous optic neuropathy independently of vascular risk factors and IOP.

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Glaucoma is the leading cause of irreversible blindness worldwide.[1] There is increasing evidence that vascular disease may play a role in the pathogenesis of glaucoma. Systemic hypertension, vascular spasticity, impaired ocular blood flow, and acute hypotension have been proposed as potential risk factors for glaucoma from both clinical[2–4] and epidemiologic studies.[5,6]

A detailed assessment of the retinal vasculature may provide further clues regarding the relationship between early microvascular changes and glaucomatous optic neuropathy. Therefore, recent studies have investigated the link between retinal vascular caliber (or vessel diameter) and glaucoma, reporting that narrower caliber is associated with glaucomatous optic neuropathy[7,8] and thinner retinal nerve fiber layer thickness.[9]

However, retinal vascular caliber is only a single parameter of the retinal vasculature. Newer global parameters, including tortuosity, bifurcation/branching angle, and fractal dimension, describe the geometric pattern of the retinal vasculature and are indicative of the status of microcirculation and the level of ocular perfusion.[10,11] Previous studies have linked these geometric retinal vascular parameters with ischemic heart disease,[12] hypertension,[13–15] diabetic retinopathy,[16–20] cigarette smoking,[12] chronic anemia,[21] general cognitive ability,[22] and prematurity of the retina in preterm children.[23] In addition, a recent report showed that reduced retinal vascular tortuosity (straighter vessels) was associated with a thinner neuroretinal rim of the optic disc.[24] Nonetheless, the associations between retinal vascular geometric parameters and glaucoma have not been examined. This study determines the relationship of a range of retinal vascular geometric measures (tortuosity, branching angle, and fractal dimension) with glaucoma in a population-based study.

Materials and Methods

Study Population

The Singapore Malay Eye Study was a population-based, cross-sectional study of 3280 Malay men and women, aged 40 to 80

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years, living in Singapore. The study design and details of sample recruitment have been described previously.[25,26] Of 4168 eligible individuals, 3280 participants took part in our study (78.7% participation rate). The study followed the principles of the Declaration of Helsinki, and ethics approval was granted from the institutional review board of the Singapore Eye Research Institute. Written informed consent in the Malay language or English was obtained from each participant.

Study Measurements

All participants underwent a standardized interview and systemic and ocular examinations, including collection of blood samples at a centralized study clinic.[25,26] Body mass index was calculated as weight (in kilograms) divided by the square of height (in meters). Blood pressure was measured with a digital automatic blood pressure monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc., Milwaukee, WI), and hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or use of antihypertensive medication. Nonfasting venous blood samples were drawn and sent for analysis of serum glucose and hemoglobin A1C. Diabetes mellitus was defined as a nonfasting glucose level $\geq$11.1 mmol/l, use of diabetic medication, or self-reported history of diabetes.

Slit-lamp biomicroscopy (model BQ-900; Haag-Streit, Köniz, Switzerland) was performed to identify abnormalities of the anterior segment, including evidence of secondary glaucoma, ischemic sequelae of previous acute primary angle closure, and signs of previous surgery before pupil dilatation. Noncontact partial coherence laser interferometry (IOLMaster V3.01, Carl Zeiss Meditec AG, Jena, Germany) was used to measure axial length.

Glaucoma Assessment

Intraocular pressure (IOP) was measured with a Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland) before pupil dilation. Gonioscopy was performed with a Goldmann 2-mirror gonioscope (model 903, Haag-Streit, Köniz, Switzerland). After pupil dilation, the optic disc was evaluated with a +78 diopter lens at $\times$10 with measuring graticule. The vertical cup-to-disc ratio (VCDR) was then calculated. Finally, automated perimetry (SITA 24-2; Humphrey Visual Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA) was performed with near refractive correction by trained study technicians on 1 of 5 participants before examination by study ophthalmologists and all participants with suspected glaucoma.

Diagnostic Definition of Glaucoma

Glaucoma was defined according to International Society of Geographical and Epidemiological Ophthalmology criteria[27,28] based on 3 categories. Category 1 cases were defined as optic disc abnormality (VCDR/VCDR asymmetry $\geq$97.5 percentile or neuroretinal rim width between 11 and 1 o'clock or 5 and 7 o'clock $<$0.1 VCDR), with a corresponding glaucomatous visual field defect. Category 2 cases were defined as having a severely damaged optic disc (VCDR or VCDR asymmetry $\geq$99.5th percentile) in the absence of adequate performance in a visual field test. In diagnosing category 1 or 2 glaucoma, it was required that there was no other explanation for the VCDR finding (dysplastic disc or marked anisometropia) or visual field defect (retinal vascular disease, macular degeneration, or cerebrovascular disease). Category 3 cases were defined as subjects without visual field or optic disc data who were blind (corrected visual acuity, $<$3/60) and who had previous glaucoma surgery or had IOP $>$99.5th percentile.

In the glaucoma cases, primary open-angle glaucoma (POAG) was diagnosed according to the medical history, the evidence of glaucoma as defined in this article, and the status of the anterior chamber angle. An open anterior chamber angle was diagnosed if the posterior trabecular meshwork was seen for at least 180 degrees of the angle circumference during static gonioscopy.[29] Ocular hypertension (OHT) was defined as IOP $>$21.5 mmHg without glaucoma.[27] Final identification, adjudication, and classification of glaucoma cases were performed by a glaucoma specialist (T.A.).

Quantitative Measurements of Retinal Vascular Geometry

Digital fundus photography was taken using a 45-degree digital retinal camera (Canon CR-DGi with a 10D SLR digital camera backing; Canon, Tokyo, Japan) after pupil dilation using tropicamide 1% and phenylephrine hydrochloride 2.5%. Two retinal images of each eye were obtained, one centered at the optic disc and one centered at the fovea. The spatial resolution of each image was 3072$\times$2048 pixels, and the images were stored without compression before analysis. We used a semiautomated computer-assisted program (Singapore I Vessel Assessment [SIVA], v. 1.0) to quantitatively measure the following retinal vascular geometric parameters from digital photographs: retinal vascular branching angle, retinal vascular fractal dimension, and retinal vascular tortuosity (Fig 1).[14,15] Trained graders, masked to participant characteristics, executed the SIVA program to measure the retinal vasculature. The measured area was standardized and defined as the region from 0.5 to 2.0 disc diameters away from the disc margin. The SIVA program automatically identifies the optic disc, places a grid with reference to the center of optic disc, identifies vessel type, and measures retinal vascular tortuosity. Graders are responsible for the visual evaluation of SIVA automated measurement and manual intervention if necessary following a standardized grading protocol. All visible vessels coursing through the specified zone were measured. The reliability of retinal vasculature measurements using the SIVA program has been reported in detail.[30] In brief, a subset of 50 retinal images from 50 Singapore Malay Eye Study participants was randomly selected and independently measured by 2 graders using the SIVA program to determine intergrader reliability. These measurements were then repeated by the same graders after 2 weeks to assess intragrader reliability. Intragrader and intergrader reliability were moderate to high for both measurements, with coefficients of variation ranging from 17.7% to 0.33%.

Retinal vascular tortuosity is defined as the integral of the curvature square along the path of the vessel, normalized by the total path length.[11] A smaller tortuosity value indicates a straighter vessel. The estimates were summarized as retinal arteriolar tortuosity and retinal venular tortuosity, representing the average tortuosity of arterioles and venules of the eye, respectively.

Retinal vascular branching angle is defined as the first angle subtended between 2 daughter vessels at each vascular bifurcation (ω).[31] The estimates were summarized as retinal arteriolar branching angle and retinal venular branching angle, representing the average branching angle of arterioles and venules of the eye, respectively.

Retinal fractal dimension is calculated from a skeletonized line tracing of the retinal vascular bed, using the box-counting method, a "global" measure that summarizes the whole branching pattern of the retinal vascular tree.[32] A larger value indicates a more complex branching pattern.

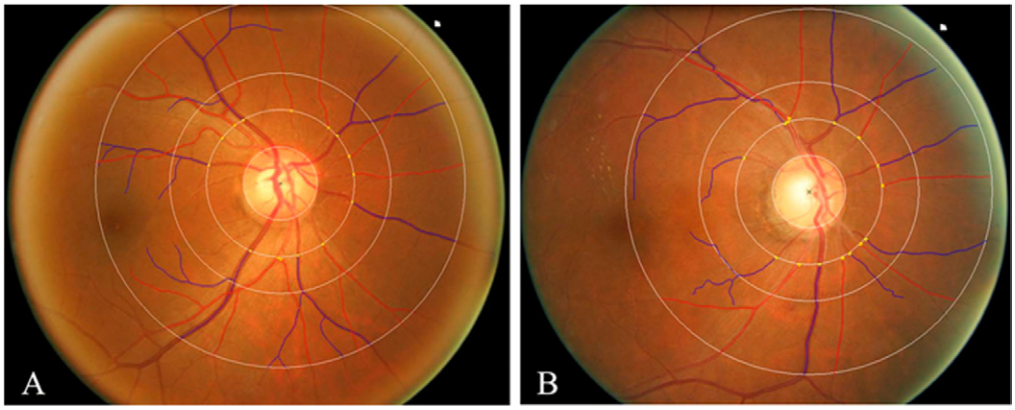

Figure 1. The geometry measurement of the retinal vasculature of a normal **(A)** and glaucomatous **(B)** fundus. The measured area is defined as a region from 0.5 to 2.0 disc diameters away from the disc margin. The center line of the vessels was traced by Singapore I Vessel Assessment software automatically. The retinal vascular tortuosity is derived from the integral of the curvature square along the path of the vessel, normalized by the total path length. Retinal vascular branching angle is defined as the first angle subtended between 2 daughter vessels at each vascular bifurcation. Fractal dimension is calculated from the skeletonized line tracing. **A,** The tortuosity values for arteriole and venule are 5.83×10^{-4} and 3.33×10^{-4}, respectively, the branching angles for arteriole and venule are 77.4 and 90.6 degrees, respectively, and the fractal dimension is 1.44. **B,** The tortuosity values for arteriole and venule are 0.38×10^{-4} and 0.96×10^{-4}, respectively, the branching angles for arteriole and venule are 74.8 and 78.8 degrees, respectively, and the fractal dimension is 1.38.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (v. 17.0; SPSS Inc., Chicago, IL). Findings were reported as means or proportions, with differences tested by independent *t* test, analysis of variance, or chi-square tests. The differences in mean vascular tortuosity, branching angles, and fractal dimension between groups for glaucoma, IOP, and VCDR also were tested using analysis of variance. To test the hypothesis that retinal vascular geometric parameters are associated with different outcomes (presence of any glaucoma, POAG, and OHT), logistic regression models were constructed to determine odds ratios (ORs) and 95% confidence intervals of these outcomes by comparing the lowest versus the highest quartile of the tortuosity, branching angles, and fractal dimensions. We initially adjusted for age and sex in model 1 and further adjusted for smoking, axial length, body mass index, hypertension, diabetes, and IOP in model 2. In this study, we selected only the right eye from each participant for analysis.

Results

Fundus photography was performed on 3264 participants (99.5% of the total study population). After excluding 475 participants with ungradable right eye images, 2789 participants were included for the final analysis (85.0% of the total 3280 participants). Compared with participants included in this analysis, excluded participants were older and more likely to have hypertension, diabetes, higher body mass index, and higher systolic blood pressure and to be nonsmokers (data not shown).

Table 1 (available at http://aaojournal.org) shows the distribution of retinal vascular tortuosity, branching angles, and fractal dimension in the study population when stratified by age groups and sex. The mean values of the arteriolar tortuosity, venular tortuosity, arteriolar branching angle, venular branching angle, and fractal dimension were 2.96 ± 1.46 ($\times10^{-4}$), 4.57 ± 2.40 ($\times10^{-4}$), 76.9 ± 11.2 degrees, 79.6 ± 10.3 degrees, and 1.41 ± 0.05, respectively. All of these retinal vascular geometric measurements decreased with age (all P for trend <0.001). When compared with women, men had a significantly smaller mean venular tortuosity value ($P = 0.004$), but no significant sex differences were evident for other vascular geometric measurements (all $P > 0.05$).

A total of 123 persons had glaucoma in this study population. Of these 123 patients, 91 were diagnosed with category 1 and 32 were diagnosed with category 2. No patients were diagnosed with category 3 of the International Society of Geographical and Epidemiological Ophthalmology classification. Primary open-angle glaucoma was the major glaucoma subtype (n = 87; 70.7%). Compared with eyes without glaucoma, eyes with glaucoma had significantly lower retinal arteriolar tortuosity ($P < 0.001$), venular tortuosity ($P < 0.001$), arteriolar branching angle ($P = 0.020$), venular branching angle ($P = 0.005$), and fractal dimension ($P < 0.001$) (Table 2). Eyes with OHT had significantly smaller venular branching angles ($P = 0.027$) and fractal dimension ($P = 0.002$). In addition, retinal arteriolar (P for trend 0.037) and venular tortuosity (P for trend <0.001) measures were lower in eyes with larger VCDR, whereas retinal arteriolar (P for trend <0.001) and fractal dimension (P for trend 0.013) were lower in eyes with higher IOP (Table 2).

Table 3 shows the odds of any glaucoma, POAG, and OHT in relationship to lower retinal vascular geometric measurements (compared with the lowest vs. the highest quartile). After adjusting for age, sex, diabetes, hypertension, smoking, body mass index, axial length, and IOP, straighter retinal arterioles and venules were both associated with increased odds for any glaucoma (OR, 1.73 and 1.59 for arteriolar and venular tortuosity, respectively) and POAG (OR, 1.88 and 1.61 for arteriolar and venular tortuosity, respectively). Narrower venular branching angle was associated with any glaucoma (OR, 1.22) and POAG (OR, 1.29). Lower fractal dimension was associated with OHT (OR, 1.37).

Discussion

This study found that certain retinal vascular geometric characteristics, quantitatively measured by a computer-as-

Table 2. Distribution of Retinal Vascular Tortuosity, Branching Angle, and Fractal Dimension by Any Glaucoma, Primary Open-Angle Glaucoma, Vertical Cup-to-Disc Ratio, and Intraocular Pressure

Ocular Outcomes/ Parameters	n	Tortuosity ($\times 10^{-4}$)				Branching Angle (°)				Fractal Dimension	P
		Arteriolar	*P*	*Venular*	*P*	*Arteriolar*	*P*	*Venular*	*P*		
All persons	2789	2.96 (1.46)	–	4.57 (2.40)	–	76.9 (11.2)		79.6 (10.3)	–	1.41 (0.05)	–
Any glaucoma											
Present	123	1.92 (1.56)		2.84 (2.20)		74.5 (11.8)		77.0 (12.1)		1.37 (0.10)	
Absent	2666	3.01 (1.42)	<0.001	4.65 (2.37)	<0.001	77.0 (11.1)	0.020	79.7 (10.2)	0.005	1.41 (0.04)	<0.001
POAG											
Present	87	1.79 (1.46)		2.85 (2.29)		75.3 (11.7)		76.5 (12.4)		1.37 (0.10)	
Absent	2702	3.00 (1.43)	<0.001	4.62 (2.38)	<0.001	77.0 (11.1)	0.181	79.7 (10.2)	0.005	1.41 (0.05)	<0.001
OHT											
Present	58	2.74 (0.95)		4.90 (6.00)		75.2 (12.3)		76.8 (12.2)		1.39 (0.05)	
Absent	2731	3.00 (1.43)	0.192	4.61 (2.38)	0.231	77.0 (11.1)	0.218	79.7 (10.2)	0.027	1.41 (0.05)	0.002
VCDR											
First quartile	868	3.00 (1.51)		4.92 (2.87)		77.0 (11.3)		79.8 (10.5)		1.40 (0.05)	
Second quartile	523	3.01 (1.24)		4.56 (2.02)		76.8 (11.2)		79.6 (10.1)		1.40 (0.04)	
Third quartile	848	3.02 (1.41)		4.58 (2.34)		77.4 (10.9)		79.7 (10.0)		1.41 (0.04)	
Fourth quartile	540	2.79 (1.55)	0.037	4.02 (1.83)	<0.001	76.2 (11.2)	0.472	79.0 (10.8)	0.216	1.40 (0.06)	0.830
IOP											
First quartile	813	3.09 (1.60)		4.60 (2.13)		77.3 (11.6)		79.3 (10.3)		1.40 (0.05)	
Second quartile	679	3.02 (1.41)		4.58 (2.61)		76.5 (11.0)		80.2 (10.0)		1.41 (0.05)	
Third quartile	767	2.91 (1.39)		4.59 (2.15)		76.5 (10.9)		79.7 (9.6)		1.41 (0.05)	
Fourth quartile	530	2.78 (1.31)	<0.001	4.47 (2.81)	0.415	76.6 (11.2)	0.351	79.2 (11.6)	0.802	1.40 (0.05)	0.013

IOP = intraocular pressure; OHT = ocular hypertension; POAG = primary open-angle glaucoma; VCDR = vertical cup-to-disc ratio.
Data are presented as mean (standard deviation).
P valus are based on independent *t* test or analyses of variance.

sisted program, are associated with glaucoma independently of age, sex, vascular risk factors, and other confounders. Eyes with decreased retinal arteriolar and venular tortuosity (straighter vessels) and smaller venular branching angle were more likely to have glaucoma, and eyes with decreased fractal dimension were associated with OHT.

Quantitative assessment of microvascular structure from retinal images provides information about the status of the retinal microcirculation.[33] In a previous study, narrower retinal vascular caliber was associated with glaucoma,[8] larger VCDR,[8] and retinal nerve fiber layer thickness[9] independent of IOP. Our findings further support IOP-independent vascular geometric changes seen in eyes with glaucomatous optic neuropathy. However, whether these changes result in or are a consequence of altered retinal circulation in glaucomatous eyes cannot be determined by this cross-sectional study and require longitudinal data.

Tortuosity or curvature of the retinal vessels is a key parameter describing the geometric pattern of the retinal vasculature, which may indicate the optimality state of the microcirculation and the level of ocular perfusion.[34] Vascular tortuosity may be associated with tissue hypoxia as a complex response mechanism mediated by secretions from vascular endothelial cells. These endothelial cells lining the vessel wall play an important role in autoregulating blood flow by secreting mediators, such as nitric oxide[35] and endothelin.[36] These chemicals are thought to stimulate angiogenesis, which subsequently increases vascular tortuosity and promotes better tissue perfusion.[37,38] Our findings showing that decreased retinal vascular tortuosity was associated with glaucoma are consistent with our previous report showing that straighter retinal vessels were associated with thinning of the neuroretinal rim. These results may indicate a potential role for endothelial dysfunction in the pathogenesis of glaucoma.[39,40]

Branching angle and fractal dimension also reflect the circulatory optimality of vessels. An optimal branching angle is associated with greater efficiency in blood flow with lower energy spent.[31] Because the retinal vasculature exhibits fractal-like structural characteristics, such as self-similarity, fractal analysis may offer a more natural and complete description of retinal vessel structure and geometry.[10,33,41] Branching angle has been found to be impaired in atherosclerosis,[42] altered blood flow,[43] and endothelial dysfunction.[35] Lower retinal fractal dimension was shown to be associated with prevalence of proliferative diabetic retinop-

Table 3. Relationship of Retinal Vascular Tortuosity, Branching Angle, and Fractal Dimension with Glaucoma, Primary Open-Angle Glaucoma, and Ocular Hypertension

Geometric Parameters (Lowest vs. Highest Quartile)	Any Glaucoma, OR (95% CI)	*P*	POAG, OR (95% CI)	*P*	OHT, OR (95% CI)	*P*
Tortuosity						
Arteriolar						
Model 1	1.58 (1.31–1.90)	<0.001	1.84 (1.46–2.32)	<0.001	1.01 (0.80–1.29)	0.910
Model 2	1.73 (1.38–2.18)	<0.001	1.88 (1.46–2.42)	<0.001	1.03 (0.81–1.32	0.792
Venular						
Model 1	1.61 (1.34–1.93)	<0.001	1.60 (1.30–1.98)	<0.001	1.24 (0.98–1.58)	0.017
Model 2	1.59 (1.29–1.97)	<0.001	1.61 (1.28–2.02)	<0.001	1.21 (0.93–1.57)	0.153
Branching angle						
Arteriolar						
Model 1	1.13 (0.95–1.34)	0.178	1.08 (0.89–1.32)	0.423	1.02 (0.80–1.29)	0.892
Model 2	1.07 (0.88–1.30)	0.521	1.03 (0.83–1.26)	0.819	1.01 (0.78–1.31)	0.916
Venular						
Model 1	1.19 (1.01–1.41)	0.042	1.23 (1.00–1.50)	0.048	1.07 (0.84–1.35)	0.597
Model 2	1.22 (1.00–1.48)	0.047	1.29 (1.04–1.60)	0.020	1.07 (0.83–1.39)	0.585
Fractal dimension						
Model 1	1.09 (0.91–1.30)	0.339	0.98 (0.80–1.20)	0.858	1.33 (1.03–1.72)	0.028
Model 2	1.01 (0.82–1.24)	0.932	0.90 (0.72–1.11)	0.325	1.37 (1.04–1.82)	0.027

CI = confidence interval; OHT = ocular hypertension; OR = odds ratio; POAG = primary open-angle glaucoma.
Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, smoking status, axial length, body mass index, diabetes, hypertension, and intraocular pressure (except in analysis of OHT).

athy[17] and higher systemic blood pressure,[32] whereas greater retinal fractal dimension was associated with early diabetic retinopathy.[16,17] The relationship between vascular branching angle and fractal dimension with glaucoma has not been examined previously. In this study, eyes with glaucoma or POAG had smaller (narrower) retinal venular branching angles compared with those without these glaucomatous states. These findings may reflect potential alterations in blood flow or endothelial dysfunction among patients with glaucoma.

The strengths of our study include its population-based sample, quantitative assessments of retinal vascular geometry with relatively high reproducibility, and use of a standardized study protocol including assessment of glaucoma. Limitations also should be noted. The cross-sectional nature of our data does not provide temporal information about these associations to determine whether retinal vascular geometric changes are antecedent or consequent to glaucomatous optic neuropathy. Further longitudinal studies are clearly needed. Second, caution should be exercised in interpreting the results regarding glaucoma subtypes because these analyses were limited by study power. Finally, a number of images (15%) were ungradable and therefore excluded from the analysis. Although such exclusion was inevitable, given the differences in the baseline characteristics (e.g., age, prevalence of hypertension, diabetes) between included and excluded subjects, exclusion of participants with ungradable images might have introduced bias to our findings.

In conclusion, subtle alterations in global retinal microvascular geometric parameters are associated with glaucomatous optic neuropathy. Our study further demonstrates that retinal vascular geometric changes may represent a novel marker indicative of glaucoma-related retinal microvascular damage.

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