

Retinal Vessel Diameters and Incident Open-Angle Glaucoma and Optic Disc Changes: The Rotterdam Study

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PURPOSE. It remains unclear whether reduced retinal blood flow and smaller arterioles, reported to exist in patients with open-angle glaucoma (OAG), are a cause or a consequence of ganglion cell loss. We examined whether baseline retinal vessel diameters were related to incident (i)OAG or incident optic disc changes in a population-based sample.

METHODS. In the prospective population-based Rotterdam Study, baseline diameters of retinal arterioles and venules (1990–1993) were measured in digitized images of 3469 persons (aged 55 years and older) at risk for OAG. The follow-up examinations took place from 1997 to 1999. iOAG was based on the presence of incident glaucomatous visual field loss and/or incident glaucomatous optic neuropathy. Changes in neuroretinal rim, cup area, or vertical cup-to-disc ratio were calculated with a semiautomated image analyzer in 2782 persons.

RESULTS. After a mean follow-up time of 6.5 years, 74 participants had iOAG. At baseline, the mean arteriolar diameter was $147.5 \pm 14.2 \mu\text{m}$ (SD) and the venular, $222.9 \pm 20.0 \mu\text{m}$. Neither arteriolar diameters (odds ratio [OR] per SD decrease: 0.82; 95% confidence interval [CI]: 0.66–1.03) nor venular ones (OR per SD increase: 1.20; 95% CI: 0.95–1.53) were significantly related to iOAG. Baseline retinal vessel diameters

did not predict changes in the optic disc. Additional adjustment for cardiovascular risk factors did not alter these results.

CONCLUSIONS. The data show that baseline retinal vessel diameters did not influence the risk of iOAG or incident optic disc changes. These data provide no evidence for a retinal vascular role in the pathogenesis of OAG. (*Invest Ophthalmol Vis Sci.* 2005;46:1182–1187) DOI:10.1167/iovs.04-1459

Open-angle glaucoma (OAG) is characterized by progressive loss of retinal ganglion cells and their axons, resulting in glaucomatous optic neuropathy (GON), with corresponding glaucomatous visual field loss (GVFL). Despite being the second leading cause of incurable visual impairment in the Western world, little is known about the etiology of OAG.^{1,2} Age,¹ intraocular pressure (IOP),³ myopia,⁴ African origin,⁵ and family history⁶ are some of the factors associated with OAG.

Other possible risk factors are those related to the perfusion of the optic nerve head or the retinal ganglion cell layer.^{7–9} Data concerning the relationship between vascular risk factors and OAG remain controversial,⁹ as is the association between blood pressure measured at the brachial artery and prevalent OAG.^{10,11} Peripheral vascular markers may not represent local vascular abnormalities in patients with OAG. To overcome this problem, investigators have used blood flow measurements in the ophthalmic and posterior ciliary arteries in patients with OAG,^{12–16} showing 10% to 20% decreased ocular blood flow compared with age-matched control subjects.^{16,17} Some of these cross-sectional and case–control studies involved a small sample of, or highly selected, clinic-based patients. To our knowledge, prospective data on the relationship between retinal vascular factors and incident (i)OAG are not available. Because of these limitations, an important etiological question remains unanswered: whether an impaired retinal circulation plays a causative role in the pathophysiology of OAG.⁹

Recently, a semiautomated system was developed to measure retinal vessel diameters.¹⁸ We have reported that smaller arteriolar diameters are associated with higher blood pressures and larger venular diameters with atherosclerosis and inflammation.¹⁹ We tested in the present study the hypothesis that smaller arteriolar or larger venular diameters at baseline increases the risk of iOAG in a prospective population-based cohort. Furthermore, we investigated whether these diameters were related to incident optic disc changes.

METHODS

Study Population

The present study was part of the Rotterdam Study, a population-based, cohort study on chronic diseases in the elderly.^{1,20} A total of 7983 persons aged 55 years and older living in a district of Rotterdam agreed to participate. Because the ophthalmic part became operational after the screening of at-random, invited participants had started, 6780 participants underwent the ophthalmic examination.¹ The study was conducted according to the Declaration of Helsinki, and the Medical

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Ethics Committee of the Erasmus Medical Center approved the study protocol. Written informed consent was obtained from all participants. Baseline home interviews and examinations were performed from 1990 to mid-1993. The follow-up examinations took place from mid-1997 to the end of 1999.

The ophthalmic examination, both at baseline and follow-up, comprised Goldmann applanation IOP²¹; visual field (VF) testing; and, after pharmacological mydriasis, direct and indirect ophthalmoscopy and simultaneous stereoscopic fundus photography of the optic disc in both eyes with a telecentric fundus camera (20° field; Topcon Optical Co., Tokyo, Japan).¹

Retinal Vessel Measurements

After optic disc photographs were digitized with a high-resolution scanner, the digitized image with the best quality (left or right eye) was analyzed for each participant with a semiautomated system (Retinal Analysis, Optimate, WI; Department of Ophthalmology and Visual Science, University of Wisconsin-Madison) by four trained graders masked to the end points.¹⁹ We used the improved Parr-Hubbard formula to compute the summary arteriolar and venular diameters.²² Because eyes may have a different magnification due to refractive errors, we additionally adjusted these summary vessel measures for the refraction, using Littmann's formula to obtain corrected measures.²³ The arteriolar-to-venular ratio (AVR) was taken as the ratio of the arteriolar to venular diameters.

Optic Disc Morphometry

The optic disc transparencies were also analyzed independently from the retinal vessel measurements with a semiautomated image-analysis system (ImageNet; Topcon Optical Co.), to calculate the areas (in square millimeters) of the optic disc, cup, and neuroretinal rim, the minimal rim width and the vertical cup-to-disc ratio (VCDR).²⁴ The system's hardware, its software modules, and the reproducibility of measurements are described elsewhere.²⁵⁻²⁷ The same eye was taken for both the retinal vessel diameters and optic disc measurements.

Glaucoma Diagnosis

We considered OAG to be present in persons who had, at least in one (and the same) eye, an open anterior chamber angle, no history or signs of angle closure or secondary glaucoma, and the presence of GON and/or GVFL.¹

We defined GON using measurements obtained by image analysis, whenever available.¹ Possible GON was defined as a VCDR ≥ 0.7 , asymmetry between eyes ≥ 0.2 , minimum rim width < 0.10 . Probable GON was defined as a VCDR ≥ 0.8 , asymmetry between eyes ≥ 0.3 , or minimum rim width < 0.05 . When the image-analysis data were absent, funduscopy VCDR was used, leading to a slightly different definition of probable GON based on the distribution in the population: instead of VCDR ≥ 0.8 , it was VCDR ≥ 0.9 .¹ Minimum rim widths were not assessed funduscopically and were, in these cases, not taken into account.

The VF of each eye separately was screened with a 52-point suprathereshold test that covered the central field with a radius of 24°. If the test was unreliable, or a reliable test showed VFL in at least one eye, this test was repeated on that eye. When the second test again was unreliable, or VFL was still present, Goldmann kinetic perimetry was performed on both eyes.²⁸ Glaucomatous VFL was defined as VFL compatible with OAG after exclusion of all other neuro-ophthalmic causes. Definite OAG was defined as the presence of GVFL in combination with possible or probable GON. Probable OAG was either the presence of GVFL in the absence of GON or the presence of probable GON in the absence of GVFL.¹

Incidence of OAG was defined as having no OAG in both eyes at baseline and acquiring probable or definite OAG in at least one eye at follow-up. Excluded from this incidence definition were those who had possible GON at baseline and had probable GON at follow-up,

because this increase may be quite small and due to variability in measurement of GON.

Assessment of Confounders

The average of two blood pressure measurements in sitting position at the right brachial artery with a random-zero sphygmomanometer was taken. Mean perfusion pressure was calculated with the following equation: $\frac{2}{3} \times$ diastolic blood pressure + $\frac{1}{3} \times$ systolic blood pressure – IOP. Nonfasting serum total cholesterol was determined by an enzymatic procedure and high-density lipoprotein (HDL) was measured similarly after precipitation of the non-HDL fraction.²⁹ The ratio of the total to HDL cholesterol was taken. Diabetes mellitus was considered present if participants reported use of antidiabetic medication or when random or postload serum glucose level was > 11 mM.³⁰ Intima-media thickness was measured in the common carotid arteries by ultrasonography.³¹ Information on smoking (categorized as current, former or never) was obtained during the baseline home interview.

Study Sample

Of the 6780 participants in the ophthalmic part of the Rotterdam Study, 6436 persons had optic disc photographs, and, in 5674 persons, fundus transparencies were gradable for retinal vessel measurements. Excluding 157 persons with prevalent OAG, 5517 participants were at risk for iOAG. During follow-up, 838 participants died. A further 1210 refused or were unable to participate at the follow-up examination, leaving 3469 participants for the current analyses.

Also, 2782 participants had gradable stereo disc transparencies taken both at baseline and follow-up in at least one (the same) eye to calculate changes in optic disc morphometry with the image-analysis system (ImageNet; Topcon).

Data Analyses

To assess whether participants were different from nonparticipants or those who died, mean differences were calculated for the continuous variables by using analysis of covariance and odds ratios (ORs) for the categorical ones by logistic regression models. The mean differences and the ORs were adjusted for age and gender.

ORs with corresponding 95% confidence intervals (CIs) for iOAG were calculated by analyzing retinal vessel diameters, both linearly (per standard deviation) and in quartiles, adjusted for age, gender, and follow-up time, and adjusted in addition for other known cardiovascular risk factors. For additional adjustments, we included those cardiovascular risk factors that we had shown to be associated with retinal vessel diameters¹⁹ and that also have been implicated in the pathogenesis of glaucoma.⁹ Although IOP is an important risk factor for glaucoma, it was not included for additional adjustment because it was not related to the retinal vessel diameters. Quartiles were selected to secure enough cases in each category.

Because, retinal vessel measurements were performed in the eye with the best-quality fundus transparency, it could happen that the vessel measurement was performed in one eye, whereas iOAG developed in the other. In these cases, vessels were measured in the eye with iOAG, for an eye-specific subanalysis.

Incident optic disc changes were defined as the difference between follow-up and baseline measurements in neuroretinal rim area, cup area, or the VCDR. Analysis of covariance models were used to compute the age- and gender-adjusted mean changes in neuroretinal rim area, cup area, and VCDR for the different quartiles of retinal vessel diameters. The statistical significance level was set at $P \leq 0.05$, and the calculations were performed with commercially available software (SPSS Windows, ver. 11.0; SPSS Inc., Chicago, IL).

RESULTS

Table 1 shows the baseline characteristics of the study population. After a mean of 6.5 years of follow-up (range, 5.2–9.4) a total of 74 participants had iOAG, of whom 52 had probable

TABLE 1. Baseline Characteristics

	Participants	Nonparticipants*	Adjusted Differences†‡ (95% CI)	Died§	Adjusted Differences¶ (95% CI)
Number	3469	1210		838	
Age (Y)	65.4 (6.6)	70.1 (8.2)	4.7 (4.2-5.2)¶	75.1 (8.6)	9.8 (9.3-10.4)¶
Gender (% female)	57.6	67.9	1.41 (1.23-1.63)¶	51.0	0.62 (0.52-0.73)¶
Diabetes mellitus (%)	6.5	10.2	1.38 (1.08-1.75)¶	21.4	2.78 (2.18-3.56)¶
Smoking (%)					
Current	21.9	25.6	1.68 (1.43-1.98)¶	28.2	2.38 (1.95-2.90)¶
Past	45.6	38.1	0.82 (0.71-0.95)¶	39.2	0.65 (0.54-0.78)¶
Diastolic blood pressure (mm Hg)	73.6 (10.8)	74.3 (11.7)	1.6 (0.8-2.3)¶	73.2 (12.8)	0.9 (-0.1-1.8)
Systolic blood pressure (mm Hg)	135.6 (20.7)	142.0 (22.7)	3.6 (2.1-5.0)¶	144.9 (24.3)	3.4 (1.6-5.2)¶
Carotid intima-media thickness (mm)	0.77 (0.14)	0.80 (0.15)	0.01 (0.00-0.02)¶	0.87 (0.17)	0.04 (0.02-0.05)¶
Serum total cholesterol (mmol/L)	6.68 (1.17)	6.71 (1.19)	0.04 (-0.04-0.12)	6.34 (1.28)	-0.17 (-0.27- -0.07)¶
Serum HDL cholesterol (Mmol/L)	1.36 (0.35)	1.38 (0.36)	0.01 (-0.02-0.03)	1.28 (0.38)	-0.04 (-0.06- -0.01)¶
Intra-ocular pressure (mm Hg)	15.5 (2.97)	15.6 (3.10)	0.14 (-0.07-0.35)	15.3 (3.21)	-0.12 (-0.38-0.13)
Retinal arteriolar diameters (µm)	147.5 (14.2)	146.8 (14.5)	0.2 (-0.8-1.2)	144.7 (14.8)	-0.8 (-2.0-0.4)
Retinal venular diameters (µm)	222.9 (20.0)	220.8 (21.1)	0.6 (-0.7-2.0)	219.8 (22.9)	1.4 (-0.3-3.1)
Arteriolar-to-venular ratio	0.66 (0.06)	0.67 (0.06)	-0.001 (-0.005-0.003)	0.66 (0.06)	-0.007 (-0.012- -0.002)¶

Presented as unadjusted means (SD) or percentages. Adjusted differences are presented as mean differences for continuous and ORs for categorical variables with 95% CI.

*Unable or refused at follow-up.

† Age and gender adjusted if applicable.

‡ Nonparticipants versus participants.

§ Persons who died before the follow-up examination.

¶ Deceased persons versus participants.

¶: Significant ($P < 0.05$) compared with participants.

TABLE 2. Odds Ratios of iOAG per Standard Deviation Difference in Baseline Retinal Vessel Diameters*

	Model I	Model II¶
Generalized arteriolar narrowing†	0.82 (0.66-1.03)	0.91 (0.70-1.17)
Generalized venular dilatation‡	1.20 (0.95-1.53)	1.15 (0.89-1.49)
Arteriolar-to-venular ratio§	0.98 (0.77-1.24)	1.05 (0.81-1.37)

* OR with corresponding 95% CI $n = 3469$.

† OR per standard deviation decrease in retinal arteriolar diameters.

‡ OR per standard deviation increase in retinal venular diameters.

§ OR per standard deviation decrease in arteriolar-to-venular ratio.

|| Model I: adjusted for age, gender, and follow-up time.

¶ Model II: additionally adjusted for diabetes mellitus, smoking, total-to-HDL cholesterol ratio, mean perfusion pressure, and intima-media thickness.

and 22 definite iOAG. In persons with iOAG, the mean arteriolar diameter at baseline was $149.8 \pm 14.0 \mu\text{m}$ (SD), venular $225.6 \pm 17.4 \mu\text{m}$, and AVR 0.67 ± 0.06 , and in those without iOAG the mean results were 147.5 ± 14.2 , 222.9 ± 20.1 , and 0.66 ± 0.06 , respectively. Table 2 shows that neither retinal arteriolar nor venular diameter nor the AVR was related to the risk of iOAG. Categorizing retinal vessel diameters into quartiles did not show a consistent trend toward a higher risk of iOAG (Table 3). Additional adjustments for other cardiovascular risk factors did not affect these results.

In the 74 persons with iOAG, 8 had bilateral disease. In 40 of the persons the vessel measurements had already been performed on the eye with iOAG. For an eye-specific analysis, we also measured the retinal vessels in 26 of the remaining 34 persons who had gradable images in the same eye in which iOAG was diagnosed. In these 66 cases, neither arteriolar narrowing (OR: 0.84; 95% CI: 0.66-1.07), nor venular dilatation (OR: 1.16; 95% CI: 0.92-1.48), nor AVR (OR: 0.96; 95% CI: 0.76-1.23) was related to iOAG.

The mean area of the neuroretinal rim at baseline was $1.81 \pm 3.98 \text{ mm}^2$ (range, 0.79-3.98), the area of the cup was $0.58 \pm 0.34 \text{ mm}^2$ (range, 0.02-2.11), and the mean VCDR was 0.49 ± 0.13 (range, 0.04-0.78). At follow-up, the mean change in area of the neuroretinal rim was $0.029 \pm 0.21 \text{ mm}^2$, in area of the cup was $0.021 \pm 0.16 \text{ mm}^2$, and in VCDR was 0.004 ± 0.07 . Table 4 presents the relationship between quartiles of retinal vessel diameters and the change in these optic disc parameters. Baseline retinal vessel diameters were not related to incident optic disc changes.

DISCUSSION

In this prospective study in community-dwelling elderly people, our main finding was that both retinal arteriolar and venular diameters at baseline were not related to an increased risk of OAG. In line with these observations, the retinal vessel diameters did not predict incident optic disc changes.

A potential limitation of our study is the reduced number of participants at follow-up, owing to the large number of deaths that occurred during follow-up in this elderly cohort. If persons who died before the follow-up examination had OAG before death more often than those who survived, this would have biased the results toward the null value. However, we have previously shown that people who have OAG are not at an increased risk of death, excluding the possibility that survival bias explains our negative findings.³² Furthermore, persons who died before the follow-up examination and those who refused to participate showed statistically significant differences from the participants in cardiovascular profile, but the retinal vessel diameters were not different, suggesting a limited

role for selective nonresponse. This loss to follow-up probably resulted in the imprecision of an underlying association, leading to larger confidence intervals. Hence, we cannot rule out the possibility that we were unable to detect small effects due to the small number of incident cases. Another limitation was that photographs were not taken synchronized on the cardiac cycle, leading to variation in vessel diameter due to pulsatility.³³ However, because photography was independent of any characteristics of the participants, this would have caused random misclassification.

Strengths of the present study are its prospective population-based design, a large number of community-dwelling elderly persons, accurate and objective quantification of retinal vessel diameters, and standardized definitions for iOAG.

In systemic hypertension, the increased peripheral vascular resistance may impair ocular perfusion.³⁴ In the Rotterdam Study, blood pressure was associated with prevalent high-tension OAG (OR per standard deviation increase in pulse pressure: 1.32; 95% CI: 1.03-1.69), but not with prevalent normal-tension OAG (OR: 0.97; 95% CI: 0.82-1.15) (Hulsman et al., personal communication, November 2004). The increased risk of high-tension OAG was partly due to the positive correlation between blood pressure and IOP.^{7,11} However, it remains unclear whether high blood pressure, independent of its effect on IOP, is related to OAG.³⁴ No such relationship was established in either the Barbados Eye Study (OR: 1.29; 95% CI: 0.65-2.59),¹¹ or the Baltimore Eye Survey (OR: 1.32; 95% CI: 0.60-2.92).⁷ Alternatively, hypotension rather than hypertension has been proposed to be deleterious to the optic nerve function.^{9,34} A decreased diastolic perfusion pressure was related to prevalent OAG (OR: 3.29; 95% CI: 2.06-5.28).¹¹ It remains to be determined, however, to what extent systemic blood pressure is representative of the local perfusion of the optic nerve head and the retinal ganglion cell layer.¹¹

Few studies thus far have examined the relationship between retinal vessel abnormalities and OAG. One study showed that patients with OAG had significantly smaller arteriolar diameters ($n = 281$; mean: $91 \pm 20 \mu\text{m}$), measured on optic disc photographs, than age-matched control subjects ($n = 173$; mean: $104 \pm 18 \mu\text{m}$).¹² In a population-based cross-sectional study, prevalent OAG cases ($n = 59$; mean: $183 \mu\text{m}$) also had smaller arteriolar diameters compared with control cases ($n = 3065$; mean: $194 \mu\text{m}$).³⁵ Conversely, in another

TABLE 3. ORs of iOAG in Quartiles of Baseline Retinal Vessel Diameters*

	Model I†	Model II‡
Retinal arteriolar diameters		
4 (largest)	1.0 (Reference)	1.0 (Reference)
3	0.72 (0.39-1.35)	0.75 (0.38-1.48)
2	0.61 (0.32-1.18)	0.69 (0.34-1.40)
1 (smallest)	0.70 (0.39-1.35)	0.91 (0.46-1.79)
Retinal venular diameters		
1 (smallest)	1.0 (Reference)	1.0 (Reference)
2	2.17 (1.04-4.52)	1.81 (0.85-3.85)
3	2.23 (1.07-4.66)	1.98 (0.93-4.20)
4 (largest)	1.98 (0.93-4.22)	1.48 (0.66-3.31)
Arteriolar-to-venular ratio		
4 (largest)	1.0 (Reference)	1.0 (Reference)
3	1.47 (0.78-2.76)	1.66 (0.84-3.28)
2	1.24 (0.64-2.39)	1.45 (0.71-2.95)
1 (smallest)	0.78 (0.38-1.63)	0.92 (0.41-2.07)

* OR with corresponding 95% CI. $n = 3469$.

† Model I: adjusted for age, gender, and follow-up time.

‡ Model II: additionally adjusted for diabetes mellitus, smoking, total-to-HDL cholesterol ratio, mean perfusion pressure, and intima-media thickness.

TABLE 4. Mean Change of Optic Disc Dimensions in Quartiles of Baseline Retinal Vessel Diameters*

	Cup Area (mm ²)	Rim Area (mm ²)	VCDR†
Retinal arteriolar diameters			
4 (largest)	0.030 (0.018–0.042)	0.024 (0.008–0.039)	0.005 (0.000–0.010)
3	0.014 (0.002–0.026)	0.028 (0.013–0.043)	0.003 (–0.002–0.008)
2	0.019 (0.007–0.031)	0.027 (0.012–0.043)	0.005 (0.000–0.009)
1 (smallest)	0.021 (0.009–0.033)	0.037 (0.022–0.052)	0.005 (0.001–0.010)
Test for trend	<i>P</i> = 0.33	<i>P</i> = 0.67	<i>P</i> = 0.97
Retinal venular diameters			
1 (smallest)	0.024 (0.012–0.036)	0.032 (0.016–0.047)	0.005 (0.000–0.010)
2	0.016 (0.003–0.027)	0.034 (0.019–0.050)	0.003 (–0.002–0.008)
3	0.013 (0.001–0.024)	0.034 (0.019–0.050)	0.001 (–0.004–0.006)
4 (largest)	0.033 (0.021–0.045)	0.016 (0.000–0.031)	0.008 (0.003–0.013)
Test for trend	<i>P</i> = 0.08	<i>P</i> = 0.28	<i>P</i> = 0.25
Arteriolar-to-venular ratio			
4 (largest)	0.024 (0.012–0.036)	0.026 (0.011–0.042)	0.004 (–0.001–0.009)
3	0.013 (0.001–0.025)	0.036 (0.020–0.051)	0.002 (–0.003–0.007)
2	0.018 (0.007–0.030)	0.031 (0.016–0.046)	0.004 (–0.001–0.009)
1 (smallest)	0.029 (0.017–0.041)	0.023 (0.008–0.039)	0.008 (0.003–0.013)
Test for trend	<i>P</i> = 0.29	<i>P</i> = 0.70	<i>P</i> = 0.50

* Age and gender adjusted mean changes with corresponding 95% CI. (*n* = 2782).

† VCDR, vertical cup-to-disc ratio.

study involving digital scanning laser fluorescein angiography, no differences in either arteriolar or venular diameters were observed in patients with OAG compared with control subjects, although retinal arteriovenous circulation time was substantially prolonged.³⁶ Clinically, it is also known that reduced retinal blood perfusion, such as in central retinal artery occlusion or nonarteritic anterior ischemic optic neuropathy, often does not lead to glaucomatous cupping.^{14,37} Our prospective data provide evidence against a retinal vascular cause in the pathogenesis of retinal ganglion cell loss and the subsequent development of GVFL. Only in the categorized analysis did it seem that larger venular diameters were related to iOAG. However, there was no clear trend, and this association disappeared after additional adjustments. The results of the linear models for iOAG (Table 2) and the models for optic disc changes (Table 4) also support the view that this association is a spurious finding.

For proper interpretation of these results, local differences in ocular circulation should be discussed.^{9,38} The inner part of the retina (including the retinal ganglion cell layer) and the surface layer of the optic nerve head are vascularized by the retinal arterioles, whereas the main sources of blood supply to the optic nerve head are the short posterior ciliary arteries, either directly or from the circle of Haller and Zinn.³⁸ It has been reported that the autoregulation in the short posterior ciliary arteries seems to be less efficient than in the retinal circulation.⁹ Also, in contrast to the retinal vessels, the optic nerve head vasculature has no proper blood-tissue barrier, making it more sensitive to fluctuating levels of vasoactive molecules (such as angiotensin-II).⁹ Because of these differences, the short posterior ciliary arteries may be more vulnerable to vascular damage than the retinal vessels. This notion is supported by several studies suggesting that, in OAG, impairment in blood flow is more prominent in the short posterior ciliary arteries than in the retinal arteries.^{13,15,39}

Animal models have also suggested that the retinal circulation may not be causally related to OAG.⁴⁰ Administration of endothelin-1, a vasoconstrictive agent that reduces, among others, the retinal blood flow, resulted in loss of retinal ganglion cells and their axons in rats,⁴⁰ probably mediated by apoptosis.⁴¹ However, this type of vascular injury did not lead to optic disc cupping.⁴⁰ It has been suggested that remodeling of the extracellular matrix, irrespective of the origin of retinal ganglion cell loss, is the hallmark of optic disc cupping.⁴⁰

Activation of quiescent astrocytes (for example by an increase in IOP) could lead to an increased expression of metalloproteinases, enzymes that play an important role in remodeling the optic disc and eventually leading to cupping.⁴²

In conclusion, we have shown that baseline retinal vessel diameters did not increase the risk of iOAG or incident glaucomatous optic disc changes. The results reported herein provide no evidence for a retinal vascular role in the pathogenesis of OAG. Further prospective studies should be conducted to confirm these findings and to elucidate the possible role of vascular factors in the pathophysiology of OAG.

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