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Reductions in retrobulbar and retinal capillary blood flow strongly correlate with changes in optic nerve head and retinal morphology over four years in open-angle glaucoma patients of African descent compared to patients of European descent

Brent Siesky, PhD[1], **Alon Harris, MS, FARVO, PhD**[1], **Joseph Carr, MD**[1], **Alice Verticchio Vercellin, MD**[1], **Rehan Hussain, MD**[1], **Priyanka Parekh Hembree, MD**[1], **Scott Wentz, MD**[1], **Michael Isaacs, MD**[1], **George Eckert, MAS**[2], and **Nicholas A. Moore, MD**[1]

[1]Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, IN

[2]Department of Biostatistics, Indiana University, Indianapolis, IN

Abstract

Purpose—To investigate the relationship of changes in ocular blood flow with optic nerve head and retinal morphology in open-angle glaucoma patients of African versus European descent over four years.

Materials and Methods—In this study, 112 patients with open-angle glaucoma were examined at baseline, 79 (59 European descent, 20 African descent) of which were followed for four years. Retinal capillary blood flow was assessed with Heidelberg retinal flowmetry. Retrobulbar blood flow was measured by color Doppler imaging. Retinal structural changes were examined with optical coherence tomography and Heidelberg retinal tomography-III. Mixed-model analysis of covariance was used to test for the significance of change from baseline to four-year follow-up, and Pearson correlation coefficients were calculated to evaluate linear associations.

Results—In open-angle glaucoma patients of African descent, structural changes of the optic nerve head demonstrated a strong association with the end diastolic velocities and resistive indices of the short posterior ciliary arteries over four years. In addition, there was a significantly larger increase in the avascular area of the inferior retina in patients of African descent, and this reduction in retinal capillaries strongly correlated with a reduction in macular thickness.

Conclusion—Reductions in retinal capillary and retrobulbar blood flow strongly correlated with changes in the optic nerve head and macular thickness over four years in open-angle glaucoma patients of African descent compared to European descent. This data suggests that ocular vascular health may be a more influential contributing factor in the pathophysiology of open-angle glaucoma in patients of African descent compared to European descent.

Address for correspondence: Alon Harris, MS, FARVO, PhD, Director of Clinical Research, Lois Letzer Professor of Ophthalmology, Professor of Cellular and Integrative Physiology, Department of Ophthalmology, Indiana University School of Medicine, 1160 West Michigan Street, Indianapolis, IN 46202, Phone: (317) 278-0177, Fax: (317) 278-1007, alharris@indiana.edu.

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Keywords

open-angle glaucoma; blood flow; optic nerve head; retina; race

INTRODUCTION

Open-angle glaucoma (OAG) is a leading cause of blindness worldwide, and it disproportionately affects persons of African descent (AD) compared to those of European descent (ED).[1–3] Being of AD is a known risk factor for the development of OAG, and more than six times as many people of AD compared with ED develop OAG.[1–4] In addition, compared with those of ED, OAG patients of AD present at younger ages, experience a more severe course of the disease, and undergo a faster rate of progression.[5–12] However, despite the well-documented disease disparity between persons of AD and ED, the underlying mechanisms that explain this disparity remain largely unknown.

Several studies have identified variables that are associated with progressive OAG in patients of AD. For instance, those of AD have a statistically significant greater optic disc area, deeper maximum cup depth, and thinner corneas compared to those of ED; these parameters have been reported to be associated with OAG and its structural progression.[11–15] Additionally, increased levels of oxygen in the anterior chamber have been found in individuals of AD, potentially leading to increased oxidative stress and subsequent risk for cellular injury.[16]

Elevated intraocular pressure (IOP) has been identified as a major risk factor for OAG, and AD patients often have a higher IOP as compared to those of ED.[11,13] Current treatments focus on reducing IOP to limit disease progression; however, it is well established that a subset of patients continue to progress despite meeting acceptable IOP goals. Furthermore, a subset of patients with ocular hypertension do not experience glaucomatous change or progression, suggesting that glaucoma progression is multifactorial in etiology and that other underlying factors, such as deranged ocular blood flow, may contribute to the pathogenesis of the disease.[17–18] Compromised vascular perfusion has been shown to be a contributing factor for OAG in many individuals.[19–20] Both systemic and localized vascular abnormalities, such as arterial hypertension, nocturnal hypotension, optic disc hemorrhage, migraines, and age-related changes of the vasculature have been linked to OAG.[21–23] Several large population-based studies have reported an association between decreased ocular perfusion pressure with an increase in OAG prevalence, incidence, and progression.[21–25] Furthermore, retinal, choroidal, and retrobulbar blood flow deficiencies have been associated with OAG.[26–29] However, the exact relationship between deranged ocular blood flow and OAG still remains unclear.

Bringing these concepts together, persons of AD experience more systemic vascular disorders (e.g., optic disc hemorrhage, peripheral vascular disease, cerebrovascular accidents, vascular nephropathy, coronary artery disease) than those of ED.[20,25,30–33] Thus, since ocular blood flow deficits have been identified as a contributory mechanism for OAG progression, it may be the vascular pathology in persons of AD that causes OAG to disproportionately affect this patient population.[34]

Previously, using retrospective data, we reported that OAG patients of AD had significantly lower retrobulbar blood flow velocities compared to those of ED.[35] These pilot findings were novel but limited by their retrospective and single visit logistics. Herein we present a comparative four-year longitudinal analysis describing the relationships between changes in retinal and retrobulbar blood flow with alterations in optic nerve head (ONH) and macular structure in OAG patients of AD and ED.

MATERIALS AND METHODS

A cohort of patients with OAG were prospectively examined at baseline and every six months over four years at the Glaucoma and Diagnostic Center at Indiana University School of Medicine. All patients signed an informed consent prior to the initiation of this study, which adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board committee at the Indiana University School of Medicine.

All participants were required to meet the following inclusion criteria: age 30 years or older and best-corrected visual acuity of 20/60 or better in the study eye. In addition, the clinical diagnosis of OAG had to be confirmed in the study eye by a fellowship-trained glaucoma specialist based upon criteria representative of glaucomatous optic disc or retinal nerve fiber layer structural abnormalities and/or automated perimetry visual field changes consistent with glaucomatous damage. Patients were excluded for the following reasons: evidence of pseudoexfoliation or pigment dispersion, history of acute angle-closure glaucoma or a narrow occludable anterior chamber angle, history of inflammatory eye diseases, history of intraocular trauma, severe or progressive retinal disease, any abnormality preventing reliable applanation tonometry, cataract surgery within the past year, resting pulse < 50 beats per minute, or uncontrolled cardiovascular, renal, or pulmonary disease. Participants were allowed to continue their preventative blood pressure and cholesterol-lowering medications. The data was categorized into groups of AD or ED based on self-reported race. Reporting of races other than AD or ED were excluded from this analysis.

One qualified eye was randomly designated as the observational study eye in each subject. To limit reproducibility bias with imaging, a single experienced operator with over ten years of experience, Brent Siesky (BS), performed all measurements in the same order and at the same time of the day for each patient. IOP was measured at each patient visit with Goldmann applanation tonometry. Perfusion within the peripapillary retinal capillary beds was assessed by confocal scanning laser Doppler flowmetry (CSLDF) (Heidelberg Retinal Flowmeter (HRF), Heidelberg Engineering, Heidelberg, Germany). CSLDF provided measurements of mean blood flow and blood flow velocity while creating a physical map of flow values contained within the retina. CSLDF also differentiated avascular tissue, measured as zero flow pixels (no detectable flow), from perfused tissue (presence of flow) and, therefore, provided a method for determining the functional capillary density of the fundus.[36–41] Pixels in poor focus from the rim, large blood vessels, saccades, and areas with unsuitable brightness, defined as any DC value <80 or >200, were excluded.[39]

Peripapillary retinal nerve fiber layer (RNFL) thickness, macular thickness, and optic nerve head (ONH) parameters were assessed by optical coherence tomography (OCT) (Stratus

software V.4.0, Zeiss Meditec, Dublin, California, USA).[42] The examination was performed and repeated until good-quality analyses (signal strength < 7) were obtained. Measurements were made along a circle concentric with the optic disc (Fast RNFL Thickness acquisition protocol) to assess RNFL thickness. The RNFL thickness and cup/disc vertical and horizontal ratios were calculated by OCT using the existing software. Topographic analysis of the ONH was performed using Heidelberg retinal tomography-III (HRT-III) (Heidelberg Engineering, Heidelberg, Germany). The parameters investigated in this study were cup area, rim area, cup/disc (C/D) area ratio, RNFL thickness, and linear C/D ratio. The linear cup/disc ratio is defined by HRT-III as the average of the cup/disc diameter ratios (square root of cup/disc area ratio). The HRT-III was utilized to supplement evaluation of subtle RNFL and ONH changes.[34,43]

Retrobulbar blood flow velocities and vascular resistance were measured with the Philips HDI 5000 color Doppler imaging (CDI) system with the microvascular small parts clinical option using a 7.5 Mhz linear probe (Philips Ultrasound, Bothell, Washington, USA). Peak systolic velocity (PSV) and end diastolic velocity (EDV) were determined for the ophthalmic artery (OA), central retinal artery (CRA), nasal posterior ciliary artery (NPCA), and temporal posterior ciliary artery (TPCA). The Pourcelot's resistive index (RI) was calculated (RI = (PSV−EDV)/PSV)) for each vessel. Retrobulbar blood flow velocities obtained by CDI were standardized by using a printout at each visit to ensure that velocities were taken from the same location in each vessel to increase reproducibility and specificity. Extensive details on these techniques are found in several previously published manuscripts.[44–46]

Statistical analysis involved performing a mixed-model analysis of covariance (ANCOVA) to test for significant change from baseline to four-year follow-up. The models were then extrapolated to test for whether the changes varied according to race. Pearson correlation coefficients were calculated to evaluate linear associations between changes in blood flow and structural progression after four years. Correlations were adjusted for years of glaucoma, use of glaucoma or hypertension medications, age 65 or older, body mass index category, diabetic status, and sex. Correlations were compared between groups using Fisher's z-tests. P values < 0.05 were considered statistically significant.

RESULTS

In this study, 112 OAG patients were enrolled according to the aforementioned inclusion criteria, and 79 patients with comprehensive blood flow and structural assessments were followed biannually over a period of four years. For AD participants, 20/29 (69%) completed all 8 visits over four years, while 59/83 (71%) ED patients completed all 8 visits through four years. Overall baseline characteristics of the populations are presented in Table 1. At baseline, there were no significant differences between persons of AD and ED with respect to IOP, visual field mean deviation, macular thickness, and ONH parameters ($p>0.05$). IOP was also not found to have a statistically significant influence on any measure of blood flow over the four-year period for either group ($p>0.05$). In addition, there was no significant difference between AD and ED regarding a history of hypertension, hyperlipidemia, cardiovascular disease, family history of cardiovascular disease, smoking

status, diabetes, or use of carbonic anhydrase inhibitors, prostaglandin analogues, alpha adrenergic agonists, or beta receptor blockers ($p>0.05$). Use of antihypertensive medications ($p=0.014$) and cholesterol-lowering medications ($p=0.030$) were more prevalent among participants of ED than AD.

Table 2 demonstrates the longitudinal changes in retrobulbar blood flow from baseline to four-year follow-up for patients of AD and ED; analysis indicates no significant differences throughout the study in retrobulbar blood flow between race groups. As depicted in Table 3, comparisons were made between structural measurements with HRT-III and OCT with changes in retrobulbar blood flow after four years. Changes in NPCA RI and EDV significantly correlated with changes in ONH morphology measured with OCT and HRT-III in patients of AD. This relationship was not present in those of ED, indicating a significant difference between the groups. In addition, changes in TPCA RI were significantly correlated with changes in OCT-measured ONH morphology, and TPCA EDV changes were significantly correlated with changes in HRT-III-measured ONH morphology in patients of AD, with a significant difference present between races.

Table 4 reports the retinal capillary blood flow of the patients assessed at four-year follow-up. The number of inferior retinal zero blood flow pixels increased over the four years in both AD and ED patients; however, only patients of AD demonstrated a significant increase over time ($p=0.001$). When comparing the changes in the inferior retinal zero flow pixels between races, AD patients experienced a significantly larger increase at four years ($p=0.034$). The superior retinal zero blood flow pixels increased in both AD and ED; however, only patients of ED displayed a significant increase from baseline to four years ($p=0.012$). No significant difference was observed between races when comparing the change in superior retinal zero flow pixels. Additionally, there were no significant differences in the superior and inferior retinal mean blood flow between the races.

Table 5 displays the correlations between zero blood flow pixels in patients monitored for macular thickness and macular volume changes. In AD patients, changes in the number of superior and inferior retinal zero blood flow pixels negatively correlated with macular thickness and volume. These correlations were weak in ED patients and did not reach statistical significance. These correlation outcomes were significantly different between patients of AD when compared to ED. Table 6 demonstrates the baseline and four-year changes in optic nerve head structural parameters for persons of AD and ED using OCT and HRT-III.

DISCUSSION

The higher rates of OAG and disease progression in persons of AD have been attributed to many possible causes, including elevated IOP commonly found within this population.[47–49] However, other studies have found no differences in IOP based on racial differences, suggesting that IOP-independent factors may contribute to the disproportionate glaucomatous changes in persons of AD.[5–12] Importantly, persons of AD are also known to have increased rates of systemic vascular diseases, such as hypertension and cardiovascular disease.[30–33] Results from the Ocular Hypertension Treatment Study suggest that these

increased rates of cardiovascular disease in AD persons may be linked to increased rates of glaucoma.[50]

Previously, we demonstrated, through a retrospective analysis, that patients of AD had a significantly lower retrobulbar blood flow in all vascular territories, supporting the hypothesis that vascular abnormalities may contribute to the pathogenesis of glaucoma differently in patients of AD.[35] Other studies have found decreased systemic and ocular blood flow to be correlated with glaucomatous structural damage in the retina and ONH.[51–53] This current four-year prospective analysis was designed to examine how changes over time in retrobulbar and retinal capillary blood flow relates to glaucomatous ONH and retinal structural changes in patients of AD compared to ED.

In this cohort of patients, changes during four years in both the EDV and the RI of the short posterior ciliary arteries, which feed the ONH, strongly correlated to morphological changes in ONH structure in patients of AD only. Many previous studies have found retrobulbar blood flow variables to be linked to glaucomatous damage. For instance, Calvo et al. reported that OA EDV and mean velocities were reduced in subjects who converted to glaucoma based on Moorfields Regression Analysis.[54] Jimenez-Aragon *et al.* found that the EDV and RI of the OA and CRA were significantly different between subjects who structurally progressed compared to those who did not progress.[55] Zeitz *et al.* showed that the EDV and PSV of the short posterior ciliary arteries were decreased in subjects who structurally progressed.[56] All of these reported findings support the concept of a potential retrobulbar blood flow influence on structural glaucomatous disease progression. Our study suggests that blood flow, specifically in the short posterior ciliary arteries, may be a contributory mechanism to structural glaucomatous changes of the ONH in patients of AD.

In our study population, we also found that inferior temporal retinal capillary density was significantly reduced in patients of AD compared to ED over a four-year period. As part of a comprehensive analysis of structural changes, we found this retinal capillary dropout to be strongly correlated with macular thinning in patients of AD. This finding is important in the realm of OAG because the macular inner retinal layer thickness has been reported to be useful for early detection and progression monitoring in glaucoma.[57] Our results parallel previous findings that suggest retinal blood flow is related to structural changes. For instance, ONH morphology changes in primary OAG patients and OAG patients of AD strongly correlate with retinal blood flow changes.[51,53] A previous study by Resch *et al.* found that reduced retinal blood flow was strongly correlated with ONH damage and visual field loss in OAG patients.[52] Our new data indicates that loss of retinal capillaries over time is another vascular contributory biomarker and newly identified mechanism that may account in part for the disproportionate glaucomatous progression observed in OAG patients of AD.

In this cohort of patients, there was no baseline difference between the two groups with respect to IOP, visual field mean deviation, or HRT-III and OCT structural changes, thereby, indicating that the differences between study groups observed over the four years were likely not related to IOP or disease severity differences present at baseline. However, we recognize that our study is not without limitations. One limitation of our study was that race was self-

reported. This may have affected the populations into which the participants were separated; however, prior research has shown that self-reported race strongly correlates with more technical measures of racial classification that utilize genetic information.[58] A second limitation is the larger number of ED than AD patients, which could potentially limit the scope of comparisons between groups. However, all available data from the cohorts were included without selection bias. In addition, the four-year follow-up with repeating measurements every six months by the same observer (BS) adds strength to the analysis. Furthermore, while our study demonstrates a correlation between changes in ocular blood flow with ONH and macular structure changes in AD patients with OAG, it was not designed to establish causation. Finally, our study lacked control groups of healthy persons without evidence of OAG.

Persons of AD experience a disproportionate rate of OAG disease and progression. While many factors likely play a role in this disparity, our data shows that over a multi-year timeframe ONH and retinal structural changes strongly correlate with changes in retrobulbar and retinal blood flow in OAG patients of AD. This suggests that ocular blood flow may be a stronger contributing factor in the pathophysiology of OAG in AD patients compared to patients of ED. The differing influence of the observed blood flow changes over time on glaucomatous disease progression between groups may be due to persons of AD having compromised vascular autoregulation in tissues around and within the optic nerve compared to their ED counterparts. Although our study has established differences over time in the ocular vasculature in patients of AD and ED, and its possible contribution to glaucomatous structural progression, the physiological and/or pathological mechanisms behind these vascular differences remain unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographics and glaucoma medications for open-angle glaucoma patients of African and European descent

	African Descent	European Descent
Total participants	29	83
Average Age (SD)	63 (±11)	65 (±11)
Age ≥ 65	15	47
Male	8	36
Non-insulin dependent diabetes mellitus	4	17
BMI ≥ 25	24	50
Hypertension medication use	13	38
Intraocular Pressure (SD)	16.9 (±3.8)	15.9 (±4.5)
Glaucoma medications*		
Carbonic anhydrase inhibitors (e.g. Dorzolamide)	8	11
Prostaglandin analogues (e.g. Latanoprost)	15	53
α adrenergic agonist (e.g. Brimonidine)	8	13
Beta receptor blockers (e.g. Timolol)	13	21

*Patients may be using more than one glaucoma medication

Note: There was no significant difference between AD and ED patients regarding a history of hypertension, hyperlipidemia, cardiovascular disease, family history of cardiovascular disease, smoking status, diabetes, or use of carbonic anhydrase inhibitors, prostaglandin analogues, α adrenergic agonist, or beta receptor blockers ($p>0.05$).

Table 1 legend: SD-standard deviation; BMI-body mass index

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Table 2

Longitudinal changes in retrobulbar blood flow velocity over four years in OAG patients of African and European descent.

	African Descent (AD)						European Descent (ED)						
	Baseline		4-year		Change		Baseline		4-year		Change		Comparison of change between races
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	p-value	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	p-value	p-value
OA PSV	29	21.72 (18.64, 25.33)	18	20.42 (17.14, 24.33)	−1.39 (−5.25, 1.92)	0.429	83	22.86 (20.44, 25.57)	59	22.80 (20.27, 25.64)	−0.06 (−2.11, 1.82)	0.949	0.503
OA EDV	29	5.23 (4.51, 6.05)	18	4.43 (3.60, 5.45)	−0.95 (−2.12, 0.04)	0.060	83	5.64 (5.04, 6.30)	59	4.71 (4.12, 5.38)	−1.11 (−1.79, −0.49)	**0.000**	0.893
OA RI	29	0.760 (0.784, 0.733)	18	0.789 (0.819, 0.754)	0.033 (0.077, −0.005)	0.090	83	0.752 (0.771, 0.731)	59	0.792 (0.812, 0.771)	0.048 (0.074, 0.025)	**0.000**	0.567
CRA PSV	29	8.17 (7.29, 9.05)	18	8.20 (7.10, 9.30)	0.03 (−0.99, 1.04)	0.958	83	7.88 (7.23, 8.54)	60	7.75 (7.02, 8.47)	−0.14 (−0.70, 0.43)	0.629	0.777
CRA EDV	29	2.19 (1.92, 2.51)	18	2.03 (1.74, 2.37)	−0.18 (−0.62, 0.19)	0.365	83	2.25 (2.04, 2.48)	60	2.06 (1.86, 2.29)	−0.21 (−0.45, 0.02)	0.074	0.923
CRA RI	29	0.716 (0.689, 0.743)	18	0.743 (0.714, 0.773)	0.028 (−0.009, 0.064)	0.141	83	0.698 (0.679, 0.718)	60	0.724 (0.704, 0.744)	0.025 (0.004, 0.047)	**0.018**	0.925
NPCA PSV	29	7.50 (6.72, 8.28)	18	8.16 (7.36, 8.95)	0.65 (−0.15, 1.46)	0.109	82	7.43 (6.86, 8.00)	60	7.60 (7.05, 8.15)	0.17 (−0.28, 0.62)	0.4595	0.295
NPCA EDV	29	2.32 (2.06, 2.62)	18	2.60 (2.26, 2.99)	0.25 (−0.10, 0.55)	0.156	82	2.38 (2.18, 2.60)	60	2.27 (2.06, 2.49)	−0.12 (−0.35, 0.09)	0.278	0.076
NPCA RI	29	0.680 (0.653, 0.707)	18	0.668 (0.637, 0.698)	−0.013 (−0.050, 0.025)	0.506	82	0.661 (0.641, 0.681)	60	0.691 (0.670, 0.712)	0.030 (0.009, 0.052)	**0.006**	0.050
TPCA PSV	29	7.79 (7.02, 8.55)	18	8.32 (7.42, 9.22)	0.53 (−0.33, 1.40)	0.224	83	7.59 (7.03, 8.15)	60	7.82 (7.22, 8.42)	0.23 (−0.25, 0.72)	0.337	0.546
TPCA EDV	29	2.34 (2.08, 2.64)	18	2.51 (2.20, 2.85)	0.15 (−0.19, 0.45)	0.362	83	2.35 (2.16, 2.56)	60	2.27 (2.08, 2.48)	−0.08 (−0.29, 0.11)	0.416	0.230
TPCA RI	29	0.689 (0.716, 0.660)	18	0.695 (0.722, 0.665)	0.006 (0.045, −0.029)	0.758	83	0.681 (0.701, 0.660)	60	0.703 (0.722, 0.683)	0.024 (0.047, 0.002)	**0.036**	0.432

Bold P-values indicate statistical significance ($p<0.05$).

Note: OA blood flow assessment was unable to be obtained at four-year follow-up in one ED patient due to poor image quality.

Table 2 legend: CRA-central retinal artery; EDV–end diastolic velocity; NPCA–nasal posterior ciliary artery; OA-ophthalmic artery; OAG–open-angle glaucoma; PSV-peak systolic velocity; RI–resistive index; TPCA–temporal posterior ciliary artery.

Table 3

Correlations between changes in retrobulbar blood flow velocity with changes in optic nerve head morphology in OAG patients of African and European descent.

		NPCA									
		RI					EDV				
Technique	Measurement	AD		ED		Comparison AD vs. ED	AD		ED		Comparison AD vs. ED
		r	p	r	p	p	r	p	r	p	p
OCT	Cup area	0.63	**0.01**	−0.01	0.92	**0.01**	−0.57	**0.02**	0.04	0.78	**0.02**
	Rim area	−0.68	**0.00**	−0.12	0.36	**0.02**	0.63	**0.01**	0.14	0.31	**0.05**
	Cup/Disc area ratio	0.76	**0.00**	−0.05	0.71	**0.00**	−0.72	**0.00**	0.02	0.86	**0.00**
	Cup/Disc horizontal ratio	0.62	**0.01**	0.09	0.51	**0.04**	−0.69	**0.00**	−0.09	0.48	**0.01**
	Cup/Disc vertical ratio	0.74	**0.00**	−0.06	0.66	**0.00**	−0.73	**0.00**	0.09	0.52	**0.00**
	RNFLT	−0.43	0.07	−0.07	0.62	0.17	0.35	0.15	−0.03	0.84	0.17
HRT-III	Cup area	0.64	**0.00**	−0.05	0.68	**0.00**	−0.47	0.05	0.08	0.57	**0.05**
	Rim area	−0.60	**0.01**	0.04	0.79	**0.01**	0.52	**0.03**	−0.02	0.87	**0.04**
	Rim Volume	−0.60	**0.01**	−0.01	0.93	**0.02**	0.47	**0.05**	0.02	0.89	0.09
	Cup/Disc area ratio	0.76	**0.00**	−0.03	0.82	**0.00**	−0.61	**0.01**	0.01	0.93	**0.01**
	Linear cup/disc ratio	0.76	**0.00**	−0.05	0.70	**0.00**	−0.61	**0.01**	0.04	0.79	**0.01**
	RNFLT	−0.53	**0.02**	0.02	0.88	**0.04**	0.44	0.07	0.00	0.99	0.10
		TPCA									
		RI					EDV				
		AD		ED		Comparison AD vs. ED	AD		ED		Comparison AD vs. ED
		r	p	r	p	p	r	p	r	p	p
OCT	Cup area	−0.55	**0.02**	0.26	**0.04**	**0.00**	−0.39	0.13	0.18	0.18	**0.04**
	Rim area	0.46	0.06	0.03	0.82	0.12	0.40	0.11	0.11	0.40	0.30

	Cup/Disc area ratio	−0.55	**0.02**	0.06	0.64	**0.02**	−0.44	0.08	−0.04	0.76	0.15
	Cup/Disc horizontal ratio	−0.58	**0.01**	0.12	0.35	**0.01**	−0.46	0.06	0.02	0.86	0.08
	Cup/Disc vertical ratio	−0.55	**0.02**	0.13	0.32	**0.01**	−0.44	0.08	0.10	0.44	0.05
	RNFLT	0.25	0.32	0.06	0.64	0.50	0.18	0.48	−0.11	0.43	0.32
HRT-III	Cup area	−0.29	0.26	0.09	0.49	0.18	−0.50	**0.04**	0.11	0.40	**0.02**
	Rim area	0.23	0.35	−0.01	0.92	0.38	0.31	0.22	−0.05	0.72	0.21
	Rim volume	0.36	0.14	−0.01	0.95	0.18	0.39	0.11	−0.08	0.54	0.09
	Cup/Disc area ratio	−0.38	0.12	−0.02	0.91	0.20	−0.57	**0.01**	0.05	0.71	**0.02**
	Linear cup/disc ratio	−0.41	0.09	−0.04	0.79	0.16	−0.61	**0.01**	0.05	0.72	**0.01**
	RNFLT	0.40	0.10	0.12	0.37	0.29	0.50	**0.03**	−0.08	0.55	**0.03**

Bold P-values indicate statistical significance (p<0.05).

Table 3 legend: AD–African descent; ED–European descent; EDV–end diastolic velocity; HRT-III–Heidelberg retinal tomography-III; NPCA–nasal posterior ciliary artery; OAG–open angle glaucoma; OCT–optical coherence tomography; r-correlation coefficient; RI–resistive index; RNFLT-retinal nerve fiber layer thickness; TPCA–temporal posterior ciliary artery.

Table 4

Longitudinal changes in retinal capillary blood flow from baseline to four-year follow-up in OAG patients of African and European descent.

HRF	Retinal Area	Race	Baseline Mean (n)	4-year Mean (n)	Mean change from baseline to follow-up	p-value	Comparison of change between races (p-value)
Zero Pixel Blood Flow *	Superior Retina	AD	0.193 (29)	0.214 (19)	0.019	0.214	0.856
		ED	0.199 (83)	0.224 (61)	0.023	**0.012**	
	Inferior Retina	AD	0.172 (28)	0.228 (20)	0.042	**0.001**	**0.034**
		ED	0.189 (83)	0.204 (59)	0.013	0.143	
Mean Blood Flow **	Superior Retina	AD	449.79 (29)	458.15 (19)	8.21	0.815	0.460
		ED	411.45 (83)	392.08 (61)	−20.33	0.285	
	Inferior Retina	AD	487.46 (28)	430.44 (20)	−64.57	0.092	0.429
		ED	397.34 (83)	374.95 (59)	−23.73	0.176	

Bold P-values indicate statistical significance ($p<0.05$).

Note: At four-year follow-up, the superior retinal HRF recording was unable to be obtained in one AD patient due to poor image quality. Also two patients of ED were unable to be assessed for HRF inferior retinal flow due to poor image quality.

Table 4 legend: AD-African descent; ED-European descent; HRF-Heidelberg Retinal Flowmetry; n-number of participants; OAG-open angle glaucoma.

* Zero pixel blood flow represents the % (shown as a decimal) avascular area of the total peripapillary retinal area measured with no detectable blood flow.

** Mean blood flow represents the average recorded retinal capillary blood flow in the respective peripapillary superior and inferior retina.

Table 5

Correlations between changes in zero blood flow pixels and changes in macular thickness over four years in OAG patients of African and European descent.

Retinal Area Zero Blood Flow Pixels	Macular Region	African Descent (AD)			European Descent (ED)			Comparison AD vs. ED
		n	r	p-value	n	r	p-value	p-value
Superior Retina	outer superior	18	−0.61	**0.006**	59	−0.09	0.476	**0.034**
	inner superior	18	−0.51	**0.031**	59	0.01	0.944	0.051
	outer inferior	18	−0.76	**0.000**	59	−0.05	0.700	**0.001**
	inner inferior	18	−0.64	**0.002**	59	−0.21	0.120	0.060
	outer nasal	18	−0.58	**0.010**	59	0.03	0.827	**0.017**
	inner nasal	18	−0.50	**0.032**	59	−0.16	0.235	0.174
	outer temporal	18	−0.60	**0.007**	59	−0.19	0.150	0.083
	inner temporal	18	−0.27	0.289	59	0.02	0.864	0.307
	macular volume	18	−0.61	**0.006**	59	−0.12	0.361	**0.044**
Inferior Retina	outer superior	18	−0.69	**0.001**	57	0.04	0.743	**0.002**
	inner superior	18	−0.55	**0.017**	57	−0.15	0.281	0.109
	outer inferior	18	−0.80	**0.000**	57	−0.10	0.452	**0.001**
	inner inferior	18	−0.65	**0.003**	57	−0.17	0.211	**0.039**
	outer nasal	18	−0.66	**0.002**	57	−0.21	0.124	**0.049**
	inner nasal	18	−0.54	**0.020**	57	−0.05	0.708	0.059
	outer temporal	18	−0.58	**0.010**	57	0.06	0.670	**0.014**
	inner temporal	18	−0.24	0.344	57	−0.04	0.780	0.479
	macular volume	18	−0.64	**0.004**	57	−0.07	0.629	**0.019**

Bold P-values indicate statistical significance ($p<0.05$).

Table 5 legend: n-number of participants; r-correlation coefficient.

Table 6

Longitudinal changes in optic nerve head morphology from baseline to four-year follow-up in OAG patients of African and European descent.

		Race	Baseline Mean (n)	4-year Mean (n)	Mean change from baseline to follow-up	p-value	Comparison of change between races (p-value)
OCT	Cup area	AD	1.183 (29)	1.455 (19)	0.271	**0.015**	0.968
		ED	1.136 (83)	1.402 (64)	0.266	**0.001**	
	Rim area	AD	1.188 (29)	0.998 (19)	−0.190	0.082	0.197
		ED	1.025 (83)	0.994 (64)	−0.031	0.600	
	Cup/Disc area ratio	AD	0.494 (29)	0.590 (19)	0.096	**0.028**	0.335
		ED	0.528 (83)	0.576 (64)	0.049	**0.042**	
	Cup/Disc horizontal ratio	AD	0.68 (29)	0.77 (19)	0.10	**0.005**	0.262
		ED	0.71 (83)	0.76 (64)	0.05	**0.005**	
	Cup/Disc vertical ratio	AD	0.674 (29)	0.731 (19)	0.057	0.084	0.508
		ED	0.694 (83)	0.727 (64)	0.032	0.075	
	RNFLT	AD	75.34 (29)	75.71 (20)	0.36	0.894	0.976
		ED	71.39 (83)	71.85 (64)	0.46	0.765	
HRT-III	Cup area	AD	0.909 (29)	0.920 (20)	0.010	0.825	0.578
		ED	0.852 (82)	0.834 (66)	−0.017	0.479	
	Rim area	AD	1.334 (29)	1.242 (20)	−0.092	0.089	**0.047**
		ED	1.191 (82)	1.219 (66)	0.028	0.345	
	Rim volume	AD	0.320 (29)	0.299 (20)	−0.021	0.356	**0.038**
		ED	0.237 (82)	0.269 (66)	0.033	**0.012**	
	Cup/Disc area ratio	AD	0.412 (29)	0.433 (20)	0.021	0.324	0.206
		ED	0.419 (82)	0.410 (66)	−0.009	0.447	
	Linear cup/disc ratio	AD	0.625 (29)	0.638 (20)	0.013	0.437	0.390
		ED	0.624 (82)	0.621 (65)	−0.003	0.747	

	Race	Baseline Mean (n)	4-year Mean (n)	Mean change from baseline to follow-up	p-value	Comparison of change between races (p-value)
RNFLT	AD	0.211 (29)	0.202 (20)	−0.009	0.506	0.162
	ED	0.163 (82)	0.176 (66)	0.013	0.102	

Bold P-values indicate statistical significance ($p<0.05$).

Table 6 legend: AD-African descent; ED-European descent; n-number of participants; OAG-open angle glaucoma; HRT-III–Heidelberg retinal tomography-III; OCT–optical coherence tomography; RNFLT-retinal nerve fiber layer thickness.