Published in final edited form as:
Br J Ophthalmol. 2014 November ; 98(11): 1551–1554. doi:10.1136/bjophthalmol-2013-304393.

Optic Nerve Head Morphology in Glaucoma Patients of African Descent is Strongly Correlated to Retinal Blood Flow

Priyanka Kanakamedala, M.D.[1], **Alon Harris, MS, PhD, FARVO**[1], **Brent Siesky, PhD**[1], **Ariel Tyring, M.D.**[1], **Michael Muchnik, B.S.**[1], **George Eckert, MAS**[2], and **Leslie Abrams Tobe, M.D.**[1]

[1]Eugene and Marilyn Glick Eye Institute, Department of Ophthalmology, Indiana, University School of Medicine, Indianapolis, Indiana, USA

[2]Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana, USA

Abstract

BACKGROUND/AIMS—To examine the relationship between change in optic nerve head (ONH) morphology and retinal blood flow in patients with open-angle glaucoma (OAG) of African (AD) and European descent (ED) over three years.

METHODS—112 patients with OAG (29 AD; 83 ED) underwent assessment of ONH morphology using Heidelberg retinal tomography (HRT-III) and retinal blood flow using confocal scanning laser Doppler. Repeated measures analysis of covariance was used to compare baseline and 3-year measurements and Pearson correlations were calculated to evaluate the relationships.

RESULTS—In OAG patients of AD, change in superior mean retinal blood flow was strongly, negatively correlated with change in cup/disc (C/D) area ratio ($r=-0.78$, $p=0.020$) and cup area ($r=-0.75$, $p=0.0283$) and strongly, positively correlated with change in rim area ($r=0.74$, $p=0.0328$) over three years. In OAG patients of AD, change in inferior mean retinal blood flow was strongly, negatively correlated with changes in C/D area ratio ($r=-0.88$, $p=0.0156$) and linear C/D ratio ($r=-0.86$, $p=0.0265$) over three years. In OAG patients of ED, these correlations were weak and did not reach statistical significance.

DISCUSSION—OAG patients of AD may have a stronger vascular component to their glaucoma pathophysiology than patients of ED.

Keywords

glaucoma; retina; optic nerve

INTRODUCTION

Glaucoma is a leading cause of blindness worldwide. Glaucoma disproportionately affects persons of African descent (AD), affecting six times more persons of AD than those of

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

European descent (ED).[1,2] Persons of AD also have a predilection for earlier development of open-angle glaucoma (OAG), increased disease severity and experience glaucoma progression more quickly, resulting in greater loss of visual function.[3–8] Despite the disparity in glaucoma progression between persons of AD and ED, the contributing mechanisms accounting for such differences in disease disparity have yet to be elucidated.

Although OAG is a leading cause of impaired vision worldwide, intraocular pressure (IOP) remains the only treatable risk factor for the disease. However, a high percentage of individuals with elevated IOP do not develop glaucoma while glaucoma progression often occurs despite meeting target IOP.[9] The involvement of other contributing factors including insufficient ocular blood flow and metabolism have been previously established in many patients. These vascular impairments include deficiencies of the retinal, choroidal and retrobulbar circulations.[10,11] Numerous clinical studies have also demonstrated that systemic and local vascular complications, including arterial hypertension, optic disc hemorrhage and aging of vasculature are associated with OAG.[10,12]

Importantly, the involvement of ocular blood flow in glaucoma may be especially present in persons of AD as they are known to higher rates of systemic vasculature abnormalities. The American Heart Association states that the death rate per 100,000 persons for cardiovascular disease was 28.7 for white males, 39.0 for black males, 20.1 for white females and 27.7 for black males.[13] Persons of AD have been noted to have a 2.5-fold increase in stroke risk compared to persons of ED.[14,15] Furthermore, in the African Descent and Glaucoma Evaluation Study (ADAGES), persons of AD were found to have higher blood pressure and a higher rate of diabetes mellitus.[16]

Due to the presence of increased systemic vasculature pathology and the increased severity and frequency of glaucoma in persons of AD, investigating changes in the retinal circulation in relation to changes in optic nerve head (ONH) structure over time may reveal a previously unreported contributing mechanism to AD OAG pathophysiology. To the best of our knowledge, we herein report the first prospective study that investigates how changing retinal capillary blood flow may contribute to glaucomatous changes in ONH morphology in patients of AD versus ED.

MATERIALS AND METHODS

112 patients with OAG (29 AD; 83 ED) were prospectively examined within the Department of Ophthalmology at the Indiana University School of Medicine over a period of 36 months. All patients signed an informed consent after explanation in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board.

The diagnosis of OAG was defined as optic disc cupping and repeatable reliable visual fields (SITA standard 24–2 perimetry) with glaucomatous damage prior to study entry, and confirmed by two separate visual field exams one week apart within the study (baseline exams). Diagnosis of OAG was confirmed in both criteria (prior to entry and at study entry) by a fellowship-trained glaucoma specialist (in the study eye): specifically, visual field

damage was consistent with glaucomatous damage (nasal step, arcuate field defect, or paracentral depression in clusters of test sites), and visual field loss in the upper hemifield that is different compared with the lower hemifield, i.e., across the horizontal midline (in early/moderate cases). The two cohorts were recruited as first comers who had qualified glaucoma (defined above) and were free from cardiovascular, renal, or pulmonary disease. Use of preventative blood pressure and cholesterol lowering medications were allowed in participants. IOP was measured with Goldmann applanation tonometry. Patient data were categorized into groups AD or ED based on self-reported race. Reporting of race other than AD or ED (i.e. Asian or Hispanic ethnicity) were excluded from this analysis.

Topographic analysis of the ONH was performed using the Heidelberg Retinal Tomograph version III (HRT3) (Heidelberg Engineering, Dossenheim, Germany), which provides topographic measurements of the optic nerve head. The dioptric ring of the HRT was adjusted to the spherical equivalent of any refractive error and cylindrical correction was added if needed. Topographic images were performed with an un-dilated pupil in most cases. If dilation was required it was achieved using tropicamide 0.5%. The drawing of the optic disc margins in all patients were manually traced by the same experienced ophthalmologist at baseline. The margin was drawn at the inner edge of the Elschnig's ring with at least 4–6 contour line points. The parameters investigated in this study were cup area, rim area, cup/disc (C/D) area ratio and linear C/D ratio. Linear cup/disc area ratio is defined by HRT3 as the average of the cup/disc diameter ratios (square root of cup/disc area ratio).

Confocal scanning laser Doppler flowmetry (Heidelberg Retinal Flowmeter (HRF), Heidelberg Engineering, Heidelberg, Germany) was used to measure perfusion within peripapillary retinal capillary beds. The HRF utilizes an infrared laser to scan the retina. The frequency and amplitude of Doppler shifts in the reflected light allow for determination of blood velocity and blood volume, respectively. This information is used to compute total blood flow and to create a physical map of flow values contained in the retina. Peripapillary retinal capillaries were sampled individually using pixel by pixel analysis in a 40×40 pixel area (~1,600 individual pixels per scan) for both supero-temporal and infero-temporal areas adjacent to the optic nerve. During the image acquisition, the refractive error of each eye was adjusted in the dioptric ring to produce the best image quality. Poorly focused pixels from the rim, large blood vessels, saccades and areas with improper brightness (any DC value <80 or >200) were excluded.

AD and ED patient cohorts were compared for differences in baseline measurements using analysis of covariance (ANCOVA). Repeated measures analysis of covariance (rmANCOVA) was used to evaluate changes from baseline to 3-year follow up. Pearson correlations were calculated to evaluate the associations between the changes in measurements between baseline and 3 years for each group. Correlations were adjusted for years of glaucoma, use of glaucoma medications, use of hypertension medication, age 65 or older, BMI category, diabetes, and sex. Correlations were compared between groups using Fisher's z-tests. P values < 0.05 were considered statistically significant.

RESULTS

Table 1 demonstrates the baseline characteristics of all 112 patients with OAG (29 AD; 83 ED) examined in this study. BMI, systolic BP, heart rate did not differ between AD and ED at baseline. Hypertension medications were similar in both groups (41% AD, 45% ED, p=0.77). Cholesterol medications were more prevalent among ED than AD (19% AD, 40% ED, p=0.03). Prostaglandin medication was not different in AD and ED (52% AD, 64% ED, p=0.25), however other glaucoma mediation were higher in AD than ED (62% vs. 34%, P=0.01). At baseline, there were no significant differences (P>0.05) between persons of AD compared to ED with respect to IOP, OPP, visual field mean deviation and pattern standard deviation, and ONH parameters. Changes in the measurements between baseline and 3-year follow-up are shown in Table 2. Over the 3 year study period IOP decreased in ED (p=0.001) while visual field PSD (p=0.004) and superior mean retinal flow (p=0.009) increased significantly in the AD group; however there were no statistically significant differences over time between groups. Additionally, no participants in either group were subsequently diagnosed with systemic cardiovascular disease over the 3-year study and there were also not any significant changes in ocular or systemic medication use from baseline.

Table 3 demonstrates the Pearson correlation values and their significance for ONH structure parameters in relation to mean retinal capillary blood flow. In OAG patients of AD, change in superior (area) mean retinal blood flow was strongly, negatively correlated with changes in C/D area ratio and cup area, and strongly, positively correlated with changes in rim area over three years with statistical significance. In OAG patients of AD, change in inferior (area) mean retinal blood flow was also strongly, negatively correlated with changes in C/D area ratio and linear C/D ratio over three years with statistical significance. In OAG patients of ED, these correlations were weak and did not reach statistical significance (p>0.05). The difference in strength of correlations between AD and ED groups was statistically significant for each relationship (p<0.05).

DISCUSSION

Although persons of AD have been found to have higher rates of glaucoma prevalence and progression compared to persons of ED, the contributory mechanisms explaining these differences have not yet been determined.[1–8] Risk factors independent of IOP, including vascular impairment, may help to explain this disparity as both impaired vascular function has been associated with glaucoma incidence, prevalence and progression [10,11,17–19] and persons of AD are known to have elevated systemic vascular disease. Persons of AD are known to have increased rates of systemic vascular diseases such as hypertension and cardiovascular disease compared to persons of ED.[13–16] This is an important aspect of glaucoma risk to evaluate in AD populations as studies have found decreased systemic and ocular blood flow to be correlated with glaucomatous structural damage in the retina and ONH.[10,11,18,19] Results from the Ocular Hypertension Treatment Study (OHTS) suggest that increased rates of cardiovascular disease in AD persons may be linked to increased rates of glaucoma.[20] Our study investigated OAG patients of AD and ED with respect to retinal capillary blood flow and it’s impact on glaucomatous ONH structural progression over time in patients currently free from these diseases.

In this cohort of patients, there was no difference at baseline between the two groups with respect to IOP, visual field mean deviation and pattern standard deviation, and HRT3 C/D area ratio, cup area, rim area and linear C/D ratio. This helps establish that the differences between study groups was not likely related to differing disease severity or IOP-related influence at baseline. Examining change over three years, persons of AD were found to have a strong, significant correlation between change in retinal capillary blood flow in both the superior and inferior temporal retina areas and change in ONH parameters including: C/D area ratio, cup area, rim area and linear C/D area ratio. These same associations were weak and not statistically significant in patients of ED, with the differences between the two groups reaching statistical significance in each parameter. It is interesting that the AD group had slightly increasing retinal flow over time as a group. This may represent a compensatory mechanism to protect retinal ganglion cells under duress, or may simply be a chance finding as the changes over time where not statistically different in comparison to the ED group. We feel the most important findings are the stark statistical differences in the relationships of retinal blood flow to structural damage of the ONH between Ad and ED patients. These data indicate the strong probability that alterations to retinal capillary blood flow may be more apparent in OAG patient of AD compared to their ED counterparts and may help explain non-IOP related relative risk.

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 (non-race specific).[18] In a similar study, Logan et al. found OAG patients with optic discs that had abnormal segments had retinal capillary blood flow values that were lower than those with a corresponding normal segment.[19] These studies suggest that retinal blood flow is related to glaucomatous ONH damage in some patients and taken in conjunction with our data, suggests the possibility that persons of AD might have a stronger retinal vascular component to their glaucomatous progression than persons of ED.

Recently our group, Siesky et al [21], conducted a retrospective study of retrobulbar blood flow parameters in AD and ED OAG patients. This study found a uniform reduction in retrobulbar blood flow in AD patients compared to ED patients within all retrobulbar blood vessels including the ophthalmic artery, central retinal artery, nasal short posterior ciliary artery and temporal short posterior ciliary artery. These results are in agreement with our data, suggesting that patients of AD may be at increased risk for vascular deficits in all ocular vascular beds and that these differences may subsequently put patients of AD at a greater risk for OAG pathology at similar IOP levels. While not conclusive, this analysis suggests a possible vascular contributory mechanism of structural glaucoma progression over time in patients of AD..

Our study has several limitations to acknowledge. Race was self-reported, however, self-described race has previously demonstrated a high correlation with more sophisticated measures of racial classification.[8] Our study also only assessed retinal capillary blood flow measurements and did not take into account the effect of other vessels involved in the supply of ocular tissues, although our previous retrospective investigation [21] suggests all ocular vascular beds may be susceptible. It also is important to note that use of preventative blood pressure and cholesterol lowering medications were allowed in participants, although blood

pressure treatments did not significantly differ between groups. Additionally, it is possible that visual field changes over time may differ from the ONH structural changes that we observed and would be a pertinent future direction of this research.

To the best of our knowledge, this study is the first of its kind to prospectively measure glaucomatous ONH progression in relation to changes in retinal capillary blood flow in AD versus ED OAG patients. As studies have previously found decreased retinal capillary blood flow to be associated with glaucomatous structural damage our findings further suggest that changes over time in the retinal circulation may be compromised in persons of AD and that this may contribute to glaucomatous ONH structural progression. This mechanism may help to explain, in part, the disparity in OAG disease between persons of AD and ED. More studies, including those that assess visual field progression, are needed to further elucidate causality in the disparity of OAG in AD and ED patients and are strongly encouraged.

Acknowledgments

FUNDING: This study was supported in part by the NIH/NEI grant 1R21EY022101-01A1.

References

1. Friedman DS, Wolfs RC, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol. 2004; 122:532–38. [PubMed: 15078671]
2. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol. 2004; 122:477–485. [PubMed: 15078664]
3. Racette L, Liebmann JM, Girkin CA, et al. African Descent and Glaucoma Evaluation Study (ADAGES): III. Ancestry differences in visual function in healthy eyes. Arch Ophthalmol. 2010; 128:551–59. [PubMed: 20457975]
4. Wilson R, Richardson TM, Hertzmark E, et al. Race as a risk factor for progressive glaucomatous damage. Ann Ophthalmol. 1985; 17:653–59. [PubMed: 4073724]
5. Sommer A, Tielsch JM, Katz J, et al. Racial differences in the cause-specific prevalence of blindness in east Baltimore. N Engl J Med. 1991; 325:1412–17. [PubMed: 1922252]
6. Martin MJ, Sommer A, Gold EB, et al. Race and primary open-angle glaucoma. Am J Ophthalmol. 1985; 99:383–87. [PubMed: 3985075]
7. Racette L, Wilson MR, Zangwill LM, et al. Primary open-angle glaucoma in blacks: a review. Surv Ophthalmol. 2003; 48:295–313. [PubMed: 12745004]
8. Tielsch JM, Sommer A, Katz J, et al. The Baltimore Eye Survey. Racial variations in the prevalence of primary open-angle glaucoma. JAMA. 1991; 266:369–74. [PubMed: 2056646]
9. Heijl A, Leske MC, Bengtsson B, et al. Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the early Manifest Glaucoma Trial. Arch Ophthalmol. 2002; 120(10):1268–79. [PubMed: 12365904]
10. Moore D, Harris A, Wudunn D, et al. Dysfunctional regulation of ocular blood flow: a risk factor for glaucoma? Clin Ophthalmol. 2008; 2:849–61. [PubMed: 19668439]
11. Weinreb, RN.; Harris, A., editors. Ocular Blood Flow in Glaucoma: The 6th Consensus Report of the World Glaucoma Association. Amsterdam, the Netherlands: Kugler Publications; 2009.
12. Harris AL, Kagemann, Ehrlich R, et al. Measuring and interpreting ocular blood flow and metabolism in glaucoma. Can J Ophthalmol. 2008; 43:328–36. [PubMed: 18443609]
13. Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Subcommittee (2012): Heart Disease and Stroke Statistics—A 2012 Update: A Report From the American Heart Assocation. Circulation. 125:e2–e220. [PubMed: 22179539]

14. Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. Am J Epidemiol. 1998; 147:259–68. [PubMed: 9482500]

15. Howard G, Lackland DT, Kleindorfer DO, et al. Racial differences in the impact of elevated systolic blood pressure on stroke risk. JAMA Intern Med. 2013; 173:46–51. [PubMed: 23229778]

16. Sample PA, Girkin CA, Zangwill LM, et al. The African Descent and Glaucoma Evaluation Study (ADAGES): design and baseline data. Arch Ophthalmol. 2009; 127:1136–45. [PubMed: 19752422]

17. Sergott RC, Aburn NS, Trible JR, et al. Color Doppler imaging: methodology and preliminary results in glaucoma. Surv Ophthalmol. 1994; 38:S65–S71. [PubMed: 7940149]

18. Resch H, Schmidl D, Hommer A, et al. Correlation of optic disc morphology and ocular perfusion parameters in patients with primary open angle glaucoma. Acta Ophthalmol. 2011; 89(7):544–9. [PubMed: 20003110]

19. Logan JF, Rankin SJ, Jackson AJ. Retinal blood flow measurements and neuroretinal rim damage in glaucoma. Br J Ophthalmol. 2004; 88(8):1049–54. [PubMed: 15258023]

20. Higginbotham EJ, Gordon MO, Beiser JA, et al. The Ocular Hypertension Treatment Study: topical medication delays or prevents primary open-angle glaucoma in African American individuals. Arch Ophthalmol. 2004; 122:813–20. [PubMed: 15197055]

21. Siesky B, Harris A, Racette L, et al. Differences in Ocular Blood Flow in Glaucoma Between Patients of African and European Descent. J Glaucoma. 2013 Epub ahead of print.

TABLE 1

Baseline measurements in persons of African Descent v. European Descent

	African Descent Mean (95% CI)	European Descent Mean (95% CI)	p-value
Sex (n=)	Male: 21	Male: 47	0.1340
	Female: 8	Female: 36	
Mean age (years)	66	66	0.9311
BMI	29.4 (28.2, 30.7)	29.0 (28.3, 29.8)	0.5822
Systolic BP	138.8 (129.8, 147.8)	134.4 (128.8, 140.0)	0.3733
Heart Rate	72.0 (67.0, 77.3)	71.2 (68.1, 74.4)	0.7757
IOP	16.98 (14.92, 19.04)	16.04 (14.76, 17.32)	0.4035
OPP	51.58 (46.75, 56.40)	50.15 (47.15, 53.14)	0.5885
VF MD	−3.67 (−2.18, −5.38)	−2.63 (−1.76, −3.57)	0.2122
VF PSD	3.57 (2.48, 4.99)	3.20 (2.54, 3.97)	0.5659
Superior Mean Retinal Flow	430 (383, 482)	399 (371, 428)	0.2336
Inferior Mean Retinal Flow	477 (414, 550)	393 (361, 429)	0.0135
HRT3 Cup Area	0.955 (0.714, 1.196)	0.946 (0.793, 1.099)	0.9469
HRT3 Rim Area	1.320 (1.136, 1.504)	1.202 (1.085, 1.319)	0.2444
HRT3 C/D Area Ratio	0.413 (0.328, 0.498)	0.420 (0.366, 0.474)	0.8888
HRT3 Linear C/D Ratio	0.630 (0.553, 0.707)	0.625 (0.576, 0.675)	0.9156

IOP=intraocular pressure, OPP=ocular perfusion pressure, VF=visual field, MD=mean deviation, PSD=pattern standard deviation, HRT3= Heidelberg Retinal Tomograph version III, C/D=cup/disk. Races were compared for differences in baseline measurements using analysis of covariance.

TABLE 2

Change from Baseline to 3-year follow-up in persons of African Descent v. European Descent

	African Descent Mean (95% CI)	European Descent Mean (95% CI)	p-value
BMI			
Systolic BP	−5.58 (−14.17, 3.02)	−1.62 (−6.57, 3.33)	0.4294
Heart Rate	2.06 (−2.14, 6.02)	0.61 (−1.79, 2.94)	0.5486
IOP	−1.33 (−3.11, 0.46)	−1.70 (−2.71, −0.70)	0.7148
OPP	0.03 (−4.17, 4.22)	1.89 (−0.49, 4.27)	0.4429
VF MD	0.00 (0.78, −0.73)	−0.30 (0.10, −0.68)	0.4456
VF PSD	0.72 (0.24, 1.14)	0.24 (−0.06, 0.51)	0.0836
Superior Mean Retinal Flow	74.70 (20.28, 121.79)	15.56 (−18.79, 47.05)	0.0734
Inferior Mean Retinal Flow	−17.19 (−95.79, 50.22)	23.61 (−8.77, 53.28)	0.2546
HRT3 Cup Area	0.042 (−0.038, 0.121)	0.022 (−0.024, 0.068)	0.6674
HRT3 Rim Area	−0.040 (−0.121, 0.041)	−0.016 (−0.063, 0.031)	0.6008
HRT3 C/D Area Ratio	0.019 (−0.015, 0.054)	0.009 (−0.011, 0.029)	0.6036
HRT3 Linear C/D Ratio	0.007 (−0.023, 0.037)	0.007 (−0.010, 0.025)	0.9832

IOP=intraocular pressure, OPP=ocular perfusion pressure, VF=visual field, MD=mean deviation, PSD=pattern standard deviation, HRT3= Heidelberg Retinal Tomograph version III, C/D=cup/disk. Races were compared for differences in changes using analysis of covariance.

TABLE 3

Pearson correlation values for Confocal scanning laser Doppler flowmetry in relation to Heidelberg Retinal Tomograph version III measurements of optic nerve head structure.

		African descent		European descent		Correlation Comparison
		Correlation (r-value)	***p-value***	***Correlation (r-value)***	***p-value***	***p-value***
Superior mean retinal flow	*C/D area ratio*	−0.78	0.0200	−0.19	0.2529	0.0052
	Cup area	−0.75	0.0283	−0.17	0.2876	0.0083
	Rim area	0.74	0.0328	0.20	0.2086	0.0143
Inferior retinal flow	*C/D area ratio*	−0.88	0.0156	−0.06	0.6923	0.0000
	Linear C/D ratio	−0.86	0.0265	−0.05	0.7584	0.0001

C/D=cup/disc. Pearson correlations were calculated to evaluate the associations between the changes in measurements between baseline and 3 years. Repeated measures analysis of covariance was used to compare the baseline and 3-year measurements, testing the changes within race and testing for whether the changes were different between races.