

Racial Differences in Optic Disc Topography

Baseline Results From the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study

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Objective: To examine racial differences in optic disc topography among ocular hypertensive participants in the Ocular Hypertension Treatment Study.

Methods: Four hundred thirty-nine participants from 7 Ocular Hypertension Treatment Study centers who had good-quality baseline images obtained using a quantitative 3-dimensional confocal scanning laser ophthalmoscope, the Heidelberg Retina Tomograph (Heidelberg Engineering, Dossenheim, Germany), were included in this study. The first 10°- or 15°-field of view mean topographic image acquired was included in all analyses. Differences in Heidelberg Retina Tomograph topographic optic disc parameter measurements by self-identified race were assessed using a mixed-effects linear model to control for confounders and for the use of both eyes in the model.

Results: By self-attribution, 74 (17%) of the 439 participants were of African origin, 329 (75%) were white, 24 (5%) were Hispanic, and 12 (3%) were Native American, Native Alaskan, Asian, Pacific Islander, or unknown. The African American participants had statistically significantly ($P < .001$) larger mean (SD) optic disc areas than the other participants, 2.17 (0.41) mm² vs 1.87

(0.38) mm², respectively. African American participants had a larger cup area, cup volume, cup depth, neuroretinal rim area, rim volume, and smaller rim–optic disc area ratios than the other participants. No difference between African American and the other participants was found for cup shape and retinal nerve fiber layer thickness. After controlling for optic disc area, none of the differences between African American and the other participants found in the univariate analysis remained statistically significant ($P > .10$).

Conclusions: This study demonstrated in a large cohort of subjects with ocular hypertension, that African Americans have significantly larger optic discs, optic cups, neuroretinal rims, and cup-disc ratios than other racial groups. Furthermore, this study found that differences in topographic optic disc parameters between African Americans with ocular hypertension and other racial groups are largely explained by the larger optic disc area in the African Americans. These results highlight the need to consider race and optic disc size when evaluating the appearance of the optic disc in glaucoma.

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THE OCULAR HYPERTENSION Treatment Study (OHTS) is a multicenter, randomized clinical trial designed to evaluate the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of glaucomatous visual field loss and/or optic nerve deterioration in participants with ocular hypertension at moderate risk for developing primary open-angle glaucoma.¹ A secondary aim of the OHTS is to identify risk factors, including age, race, and cup-disc ratio, that predict which participants with ocular hypertension are most likely to develop primary open-angle glaucoma.¹ Given that glaucoma is the leading cause of blindness in African Americans and the prevalence of glaucoma has been found to be 4 to 5 times higher in Af-

rican Americans than in white subjects,²⁻⁷ the OHTS was designed so that 25% of the participants would be African American. The OHTS provides a unique opportunity to answer important questions about the development of glaucoma in African Americans with ocular hypertension.

In recent years, several new instruments have been developed that show promise for improving our ability to detect early glaucomatous damage and to follow progression of the disease. One of these instruments, the confocal scanning laser ophthalmoscope (CSLO), has been shown to provide objective, reproducible measurements of optic disc topography.⁸⁻¹³ The OHTS CSLO Ancillary Study was designed to evaluate the effectiveness of the CSLO in detecting the presence and progression of glaucomatous optic disc

Author affiliations are listed at the end of this article. A complete list of the members of the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study appears on page 27.

changes and to determine whether optic disc topographic measurements are an accurate predictor of visual field loss.¹ One of the specific aims of the OHTS CSLO Ancillary Study is to compare the racial differences in optic nerve topography among patients with ocular hypertension. This article describes the design of the OHTS CSLO Ancillary Study and compares the baseline optic disc topography of African American participants with other OHTS CSLO Ancillary Study participants.

METHODS

SUBJECTS

The OHTS design, eligibility criteria, and participant characteristics have been described in detail elsewhere.¹ In brief, to be eligible for participation in the study participants were required to have 2 normal and reliable visual field tests (Humphrey 30-2; Carl Zeiss Meditec, Dublin, Calif), qualifying intraocular pressure (IOP) readings between 24 and 32 mm Hg in one eye and between 21 and 32 mm Hg in the fellow eye, and normal color stereoscopic optic disc photographs for both eyes. Intraocular pressure was measured at least twice according to a standard protocol. Reliable visual fields were defined as less than 33% false-positive results, less than 33% false-negative results, and less than 33% fixation losses. Normal visual fields were classified based on clinical review at the Visual Field Reading Center and by STATPAC II (Carl Zeiss Meditec) criteria for global indices for corrected pattern standard deviation (CPSD) within the 95% age-specific population norm and a glaucoma hemifield test result within the 97% age-specific population norm.¹⁴ Prior to randomization, 2 independent, masked, certified readers at the OHTS Optic Disc Reading Center judged the color stereoscopic optic disc photographs as normal. Individuals were excluded from the study if the photographs documented a localized notch or thinning of the neuroretinal rim, a diffuse or localized area of pallor, an optic disc hemorrhage, or an asymmetry in the cup-disc ratios greater than 0.2, between the 2 eyes.¹

Twenty-two study centers participated in the OHTS. Participants were randomized to either the close observation or the medication groups. Randomization was stratified by clinic and race.

OHTS CSLO ANCILLARY STUDY DESIGN

Seven of the 22 OHTS centers (Henry Ford Medical Center, Troy, Mich; University of California, Davis, Sacramento; Devers Eye Institute, Portland, Ore; University of California, San Diego, La Jolla; Scheie Eye Institute, University of Pennsylvania, Philadelphia; Jules Stein Eye Institute, University of California, Los Angeles; and New York Eye and Ear Infirmary, New York) participated in the OHTS CSLO Ancillary Study. Informed consent for the OHTS CSLO Ancillary Study was obtained from all ancillary study participants after institutional review board approval at their respective institutions. Four hundred fifty-one persons with ocular hypertension provided informed consent for participation in the OHTS CSLO Ancillary Study.

HEIDELBERG RETINA TOMOGRAPHIC IMAGE ACQUISITION, PROCESSING, AND ANALYSIS

The Heidelberg Retina Tomograph (HRT) (Heidelberg Engineering, Dossenheim, Germany) uses confocal scanning diode laser technology to provide topographical measurements of the optic disc and peripapillary retina. Details describing this

instrument⁸⁻¹² and the quality assessment, image processing, and data analysis of the CSLO images at the CSLO Reading Center have been presented elsewhere.¹⁵

In brief, only operators certified by the CSLO Reading Center at the University of California, San Diego, acquired images for the OHTS CSLO Ancillary Study. The HRT examinations were obtained once each year after the pupils were dilated for the annual dilated fundus examination and photographing of the optic disc. Three 10° image series centered on the optic disc were obtained for both eyes and a mean image was computed using HRT software version 2.01. In addition, three 15° image series were obtained for the right eye. Magnification error was corrected using the participant's keratometry measurements. Corrective lenses were removed for HRT examination, unless the participant has an astigmatism exceeding 1.0 diopter (D). At an astigmatism of more than 1.0 D, corrective lenses were used during image acquisition.

All images were processed and reviewed for quality at the CSLO Reading Center.¹⁵ For this analysis, the first acceptable quality 10° or 15° mean topographic image for each eye was included.¹⁵ The optic disc margin was outlined on the mean topography image by a trained technician (A.R.S.) while viewing stereoscopic optic disc photographs of the optic disc taken within 12 months of the baseline images. Each outline of the optic disc was reviewed for accurate placement by a second trained technician (K.A.D.) with disagreements resolved by consensus.

Topographical parameters included with HRT software and investigated in this study were as follows: mean cup depth, maximum cup depth, height in contour, height variation contour, mean height contour, cup shape, disc area, cup area, cup-disc area ratio, cup volume (below surface), rim area, rim volume (above reference plane), rim-disc ratio, retinal nerve fiber layer thickness, retinal nerve fiber layer cross section, and reference plane height. Cup shape is a measure of the overall 3-dimensional shape of the optic disc cupping calculated as the third moment of the frequency distribution of depth values relative to the curved surface of measurements located within the outlined disc margin. We also examined values from the discriminant analysis formula of Mikelberg et al¹⁶ (the HRT classification in current HRT software version 2.01). The HRT classification discriminant function value is used to classify an eye as "outside normal limits" or "within normal limits."

BASELINE INFORMATION FROM THE COORDINATING CENTER

Information on baseline clinical characteristics including previous topical ocular hypotensive medication; family history of glaucoma; and participant history of hypertension, heart disease, and diabetes mellitus was analyzed to evaluate possible differences by racial group. Similarly, baseline ocular characteristics including refractive status, corneal curvature, IOP, visual field mean deviation, visual field pattern standard deviation (PSD), visual field corrected pattern standard deviation (CPSD), and Optic Disc Reading Center stereophotographic assessment of horizontal and vertical cups-disc diameter ratio were compared in the African American and other racial groups.

STATISTICAL ANALYSIS

Preliminary analyses showed an apparently nonlinear relationship between optic disc area and other variables. A cubic B-spline¹⁷ with only boundary knots seemed to account for the nonlinearities in optic disc area effects and was used to represent them in analyses in which optic disc area is considered a covariate. To control for confounders, differences in HRT topographic optic disc parameters by race were assessed using a

Table 1. Demographic and Ocular Characteristics of the 451 Participants in the OHTS CSLO Ancillary Study*

Demographic Variables	African American Participants (n = 75)	Other Racial Participants (n = 376)	Total (N = 451)	P Value†
Sex				
Male	53 (71)	207 (55)	260 (58)	.02
Female	22 (29)	169 (45)	191 (42)	
Age, mean (SD), y	54.4 (8.5)	54.4 (9.4)	54.4 (9.3)	.89
Marital status				
Single	15 (20)	47 (12)	62 (14)	<.001
Married	27 (36)	262 (70)	289 (64)	
Divorced or separated	25 (33)	50 (13)	75 (17)	
Widowed	8 (11)	17 (5)	25 (5)	
Educational level		(n = 450)		
Grade 6 or less	0	7 (2)	7 (2)	<.001
Grade 7-11	7 (9)	9 (20)	16 (4)	
Grade 12 or GED certificate	25 (33)	62 (17)	87 (19)	
1+ y College	32 (43)	208 (55)	240 (53)	
1+ y Graduate school	11 (15)	89 (24)	100 (22)	
Clinical characteristics				
Previous topical ocular hypotensive medication	24 (32)	113 (30)	137 (30)	.70
Family history of glaucoma	25 (33)	154 (41)	179 (40)	.18
Hypertension	42 (56)	102 (27)	144 (32)	<.001
Heart disease	6 (8)	11 (4)	17 (5)	.16
Diabetes mellitus	13 (17)	26 (7)	39 (9)	.04
Ocular characteristics, mean (SD)				
Intraocular pressure, mm Hg‡	25.0 (2.3)	25.3 (2.4)	25.2 (2.4)	.36
Refractive error, D‡	-1.10 (2.46)	-1.12 (2.44)	-1.12 (2.44)	.92
Photograph-based horizontal cup–disc diameter ratio‡	0.42 (0.18)	0.35 (0.19)	0.36 (0.20)	<.001
Photograph-based vertical cup–disc diameter ratio‡	0.46 (0.19)	0.38 (0.19)	0.39 (0.19)	<.001
Visual field, dB				
MD‡	-0.02 (1.76)	0.38 (1.39)	0.31 (1.47)	.002
PSD, dB‡	2.06 (0.79)	1.95 (0.37)	1.97 (0.47)	.007
CPSD, dB‡	1.23 (0.91)	1.17 (0.65)	1.18 (0.70)	.34

Abbreviations: CPSD, corrected pattern standard deviation; CSLO, confocal scanning laser ophthalmoscopy; GED, General Educational Development; MD, mean deviation; OHTS, Ocular Hypertension Treatment Study; PSD, pattern standard deviation.

*Data are given as the number (percentage) of participants unless otherwise indicated.

†Calculated comparing the African Americans with the other racial group.

‡Values indicated the average of the 2 eyes used.

mixed-effects linear model¹⁸ in which “participant” is treated as a random effect (and “eye” is nested within participant) and in which there are fixed effects for race and optic disc area. This model was fitted using the restricted maximum likelihood criterion, and conditional F tests were used to assess the significance of the fixed effects. Note that the model used in both the unadjusted and adjusted analyses explicitly accounts for the correlation of measurements taken on the 2 eyes of each participant. Calculations used the “lme” function¹⁸ of the “nlme” package¹⁸ (version 3.1-36; see <http://cran.us.r-project.org/src/contrib/PACKAGES.html#nlme>) and the “geepack” package (version 0.2-4) under “R” (version 1.6.2).¹⁹

RESULTS

DEMOGRAPHIC AND OCULAR CHARACTERISTICS

By self-attribution, 337 (75%) of the 451 participants with informed consent were white, not of Hispanic origin; 75 (17%) were black, not of Hispanic origin; 25 (5.5%) were Hispanic; and the balance were Native American, Native Alaskan, Asian, Pacific Islander, or other. **Table 1** lists the demographic and ocular characteristics of the overall sample and by race, grouped by African Ameri-

can and all other races combined. The mean (SD) age of the overall sample at enrollment was 54.4 (9.3) years. African Americans were more likely to be female and have hypertension than the other participants.

Baseline ocular characteristics that were used to establish eligibility are noted because their range is truncated in the sample. Eye-specific measurements reported in Table 1 are the averages of both eyes. The baseline IOP for analytic purposes is the mean baseline IOP measurement, which was taken at the baseline-randomization examination after eligibility had been established in the qualifying assessment period for the OHTS. The baseline IOP measurement, which represents 2 or 3 IOP readings per eye taken during the baseline-randomization examination,¹ was (mean [SD]) 25.2 (2.4) mm Hg (average of right and left eyes) for the entire sample, 25.0 (2.3) mm Hg for African Americans, and 25.3 (2.4) mm Hg for all of the other participants. Sixty-four percent of participants in the OHTS CSLO Ancillary Study had baseline IOP measurements greater than 24 mm Hg in both eyes. The mean (SD) horizontal and vertical cup–disc diameter ratio (average of values for the right and left eyes) as determined by Optic Disc Reading Center assessment of color stereophotographs was significantly greater (both $P < .001$) for Afri-

can Americans (0.42 [0.18] and 0.46 [0.19], respectively) than for the other participants (0.35 [0.19], and 0.38 [0.19]), respectively. The Humphrey 30-2 visual field thresholds of the 2 qualifying visual fields were averaged. While the CPSD of the qualifying visual fields did not differ by race, the PSD for African Americans (mean [SD], 2.06 [0.79] dB) was significantly different from that for the other participants (1.95 [0.37] dB, $P = .007$), as was the mean (SD) deviation (-0.02 [1.76] dB and 0.38 [1.39] dB, $P = .002$), respectively.

Overall, 40% of the OHTS CSLO Ancillary Study participants reported a family history of glaucoma and 30% reported previous use of topical ocular hypotensive medication prior to study enrollment. Neither of these factors differed significantly by race. Significantly more African Americans than other participants reported a history of diabetes mellitus ($P = .04$) and hypertension ($P < .001$). In addition, African Americans differed from the other participants in this sample for sex ($P = .02$), marital status ($P < .001$), and educational level ($P < .001$) (Table 1). These results are similar to those reported for the 1636 participants in the OHTS.¹

OPTIC DISC TOPOGRAPHY

Of the 451 consenting participants, 11 participants discontinued participation or became inactive before HRT imaging was completed. In addition, 1 participant did not have good-quality 10° images available for this analysis. Therefore, a total of 439 participants are included in this analysis of whom 74 (17%) are African American. As the OHTS clinical trial began before the funding for the OHTS CSLO Ancillary Study was approved, and 1 study center was added 2 years later to increase African American participation, not all participants completed their imaging at the baseline OHTS visit. In addition, before funding was initiated, only 15° images were obtained on both eyes, so that in some cases, 10° images were not obtained at the first OHTS CSLO Ancillary Study visit. Of the 439 participants with good-quality 10° or 15° images included in this analysis, 102 (23%) had images obtained at the baseline visit, 157 (36%) at the 6- or 12-month visit, 127 (29%) at the 18- or 24-month visit, 44 (10%) at the 30- or 36-month visit, and 9 (2%) at later visits. The proportion of African Americans who had images obtained on or before the 12-month visit after randomization was similar to that of the other participants, 54% and 59%, respectively.

Topographic optic disc parameter measurements from the 439 participants with usable images are given in **Table 2**. The mean SD of the mean topography image, a measure of image quality, was good in both African American and other eyes, 17.1 (8.1) μm , and 18.5 (7.9) μm , respectively. A mean SD of less than 50 μm was used as 1 measure of the quality of the acquired images.¹⁵ Statistically significant differences were found between African Americans and other participants for most topographic optic disc parameters. African American participants had significantly larger optic disc areas than the other participants, 2.17 (0.41) mm^2 and 1.87 (0.38) mm^2 , respectively ($P < .001$) (**Figure**). As indicated by the cup area, cup volume, and mean cup depth measurements in the univari-

ate, unadjusted analysis, African American eyes tended to have significantly larger and deeper cups ($P \leq .008$) than the other participants. The African Americans also had significantly larger cup-disc ratio ($P = .048$), neuroretinal rim area ($P < .001$), and volume ($P = .02$) measurements than the other participants. The rim-disc area ratio was smaller in African American eyes than the other participants' eyes. No difference between African Americans and other racial groups was found for the mean values of cup shape ($P = .66$), retinal nerve fiber layer thickness ($P = .56$), HRT classification value ($P = .09$), mean height contour ($P = .08$), and reference plane height ($P = .07$). However, after adjusting for optic disc area in the model, the differences in the other topographic optic disc parameter measurements between African Americans and the other racial groups are greatly reduced and no longer reach statistical significance (Table 2).

COMMENT

Our study demonstrated in a large, well-characterized cohort of ocular hypertensive participants that African Americans have significantly larger optic discs, neuroretinal rims, optic cups, and cup-disc ratios than the other groups. Furthermore, this current study established that after adjusting for optic disc area, differences in topographic optic disc parameters such as cup area, cup volume, rim area, rim volume, and rim-disc ratio between African Americans with ocular hypertension and other racial groups are reduced and no longer statistically significant.

These results in subjects with ocular hypertension confirm previous reports in healthy participants²⁰⁻²⁴ and patients with glaucoma²⁵ that showed African Americans have significantly larger optic discs, optic cups, and cup-disc ratios than other racial groups. The difference between African Americans and other racial groups in cup-disc area ratio measured with the HRT corresponds to differences in horizontal and vertical cup-disc diameter ratio found by assessment of stereophotographs at the OHTS Optic Disc Reading Center.¹ In addition, these OHTS HRT results also confirm reports that rim-disc ratio tends to be smaller in African American eyes,²⁴ despite larger disc areas in African American eyes. In contrast to these previous reports, the current study found that the differences in topographic optic disc parameters between ocular hypertensive African Americans and the other groups are largely explained by the larger optic disc area in the African Americans.

It could be argued that adjusting for other optic disc parameters, such as rim area or cup area also will explain the racial differences in optic disc parameter measurements. However, unlike disc area, cup and rim area are also features that are used to detect glaucoma, and both change with increasing severity of the disease. Furthermore, several studies have shown that correction for optic disc size is clinically useful for detecting glaucoma.^{26,27} For these reasons, we adjusted for optic disc area in the analysis model.

Earlier reports recommended that different criteria for normal appearance of the optic disc be used for African Americans and whites²⁰ since African Americans

Table 2. Mean Ocular and Topographic Optic Disc Parameter Measurements by Race*

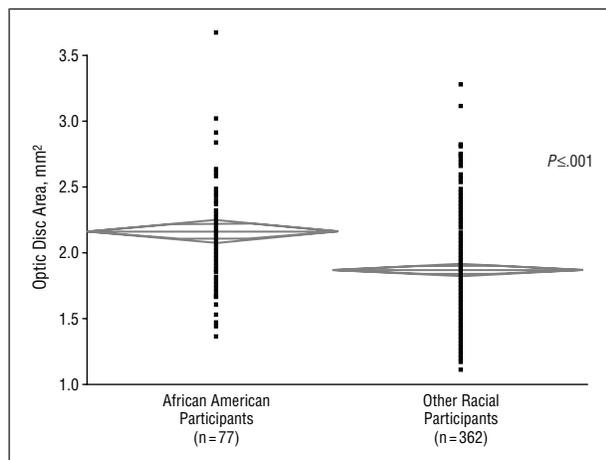
Factor	African American Participants (n = 148 Eyes)	Other Racial Participants (n = 725 Eyes)	Unadjusted P Value†	Adjusted Mean Difference‡	Adjusted P Value‡
Corneal curvature, mm	7.83 (0.27)	7.73 (0.26)	<.004	0.077	.02
Refraction, sphere	-0.95 (2.61)	-1.13 (2.41)	.59	0.121	.70
Standard deviation, μm	17.1 (8.1)	18.5 (7.90)	.11	-1.92	.03
Optic disc area, mm^2	2.17 (0.41)	1.87 (0.38)	<.001	NA	NA
Reference plane height, mm	0.34 (0.10)	0.32 (0.10)	.07	0.015	.21
Cup area, mm^2	0.69 (0.39)	0.53 (0.36)	<.001	-0.029	.36
Cup volume, mm^3	0.41 (0.23)	0.30 (0.22)	<.001	0.023	.26
Mean cup depth, mm	0.26 (0.10)	0.23 (0.10)	.008	0.006	.61
Cup shape	-0.19 (0.08)	-0.20 (0.07)	.66	-0.015	.07
Cup-disc area ratio	0.31 (0.15)	0.27 (0.15)	.048	-0.013	.38
Rim area, mm^2	1.48 (0.31)	1.34 (0.27)	<.001	0.029	.35
Rim volume, mm^3	0.38 (0.15)	0.35 (0.13)	.02	0.016	.31
Rim-disc ratio	0.69 (0.15)	0.73 (0.15)	.048	0.013	.38
RNFL thickness, mm	0.25 (0.06)	0.25 (0.07)	.56	0.011	.14
RNFL cross-sectional area, mm^2	1.30 (0.33)	1.19 (0.33)	.001	0.061	.10
Mean height contour, mm	0.09 (0.08)	0.07 (0.08)	.08	0.005	.61
HRT classification value	1.42 (1.94)	1.08 (1.61)	.09	0.352	.08
HRT classification					
Outside normal limits, No. (%)	38 (26)	180 (25)	.88	0.681	NA
Normal, No.	110	537			

Abbreviations: HRT, Heidelberg Retina Tomograph; NA, not applicable; RNFL, retinal nerve fiber layer.

*Data are unadjusted and adjusted for optic nerve size and given as mean (SD) unless otherwise indicated.

†Unadjusted P values are corrected for the lack of independence between the 2 eyes.

‡Values are adjusted for lack of independence between the eyes and the optic disc size.



The distribution of optic disc area in eyes of African Americans is significantly larger than in the eyes of the other racial participants. Only right eyes are included. Diamonds represent 95% confidence intervals.

generally have larger optic discs than other racial groups. The current study confirmed these recommendations and also highlighted the growing evidence of the importance for differential assessment of the optic nerve head based on optic disc size.^{26,28-30} A substantial number of participants not of African American race also had large optic discs. The challenge to the ophthalmologist is how best to judge the size of the optic disc during a clinical examination. An accurate assessment of disc area based on the clinical examination can be difficult to obtain since both magnification of the eye and the lens used can influence the size of the optic disc as viewed by the clinician. Several slitlamp methods for estimating optic disc

size have been proposed.³¹⁻³³ These methods can provide clinically useful classification of optic discs as small, medium, or large, but do not provide a reproducible or accurate estimate of the size of the optic disc.³³ Confocal scanning laser ophthalmoscopy provides objective and quantitative information on disc size and other topographic optic disc parameter measurements that can assist the clinician in determining whether the disc is glaucomatous or not.

There are conflicting reports on whether optic disc size influences susceptibility to glaucomatous damage at a given level of IOP.²⁸ Over 30 years ago it was hypothesized that greater pressure is exerted on a large disc than it is on a smaller one at a given level of IOP.³⁴ More recent reports have provided evidence supporting this hypothesis.^{20,22} Other investigators, however, have not found a relationship between optic disc size and susceptibility to glaucomatous damage.³⁵ Furthermore, studies have found that eyes with small optic discs possess fewer optic nerve fibers than eyes with larger optic discs.^{36,37}

Eyes with larger discs and more fibers have a larger anatomical reserve of neurons; they can lose more fibers before visual function is compromised. With its extensive follow-up of a well-defined ocular hypertensive population of diverse racial backgrounds and measurement of optic disc area, the OHTS CSLO Ancillary Study provides a unique opportunity to evaluate the complex relationship between IOP, optic disc area, race, and the development of glaucomatous optic neuropathy.

This study demonstrated in a large cohort of subjects with ocular hypertension that African Americans have significantly larger optic discs, optic cups, neuro-

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retinal rims, and cup-disc ratios than the other racial groups. Furthermore, this study established that differences in topographic optic disc parameters between African Americans with ocular hypertension and the other racial groups are largely explained by the larger optic disc area in the African Americans. These results highlight the need to consider race and optic disc size when evaluating the appearance of the optic disc in glaucoma.

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