The Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study: Study Design and Baseline Factors

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• PURPOSE: To describe the study design of the Confocal Scanning Laser Ophthalmoscopy (CSLO) Ancillary Study to the Ocular Hypertension Treatment Study (OHTS) and to examine the associations between optic disk topography, and baseline demographic, clinical, and ocular factors at study entry.

• DESIGN: A randomized clinical trial.

• METHODS: Participants in this ancillary study were recruited from seven of the 22 OHTS clinical centers. Each participant completed imaging annually using a CSLO, the Heidelberg Retina Tomograph (HRT). Associations between HRT topographic optic disk measurements and intraocular pressure (IOP), baseline photographic estimates of horizontal and vertical cup-to-disk diameter ratios by the OHTS Optic Disk Reading Center, baseline visual field indices, and demographic and clinical factors were assessed using linear mixed effects models.

• RESULTS: Four hundred thirty-nine participants had good quality images and were included in this baseline analysis. No associations between HRT topographic optic disk measurements and diabetes, systemic hypertension, cardiovascular disease, IOP, or visual function were found. The HRT topographic optic disk measurements were associated with baseline stereophotographic estimates of horizontal and vertical cup-to-disk diameter ratios. The strongest associations were found between stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios, and HRT cup-to-disk area ratio (r = .85 and .84, respectively), rim-to-disk area ratio (r = −.85 and −.84, respectively), mean cup depth (r = .84 and .83, respectively), and cup area (r = .83 and .80, respectively). After adjusting for optic disk area, all HRT topographic optic disk measurements remained associated with stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios.

• CONCLUSIONS: The CSLO ancillary study to the OHTS is the first multicenter clinical trial to use CSLO imaging to monitor changes in the optic disk. At study

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entry, HRT topographic measurements corresponded well with both horizontal and vertical stereophotographic-based estimates of cup-to-disk diameter ratio in ocular hypertensive participants. (Am J Ophthalmol 2004;137:219–227. © 2004 by Elsevier Inc. All rights reserved.)

THE OCULAR HYPERTENSION TREATMENT STUDY (OHTS), sponsored by the National Institutes of Health/National Eye Institute, 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 or optic nerve deterioration in participants with ocular hypertension at moderate risk for developing primary open angle glaucoma.[1] The 5-year results of this trial demonstrated that topical ocular hypotensive medication delays or prevents the onset of glaucomatous optic disk deterioration or visual field damage by more than 50%.[2,3] In OHTS, the presence of disk changes during follow-up was determined by evaluation of serial stereoscopic optic disk photographs.

Several instruments have been developed to provide objective measurements of the optic disk and retinal nerve fiber layer. One of these, the confocal scanning laser ophthalmoscope (CSLO) is being investigated as part of a prospective OHTS ancillary study designed to evaluate the effectiveness of the CSLO in detecting the presence and progression of glaucomatous optic disk damage and to determine whether optic disk topographic measurements are an accurate predictor of visual field loss.[1]

The aim of the present report is to describe the study design of the CSLO ancillary study to the OHTS, and to report baseline findings on the association of optic disk topography at entry into the OHTS CSLO ancillary study with baseline demographic, clinical and ocular factors including intraocular pressure (IOP), visual field indices, and horizontal and vertical cup-to-disk diameter ratio estimates from stereoscopic photographs at study entry.

METHODS

THE OHTS DESIGN, INCLUSION AND EXCLUSION CRITERIA, and participant characteristics have been described in detail elsewhere.[1] In brief, eligible subjects with ocular hypertension ranging from 24 mm Hg to 32 mm Hg in at least one eye and 21 mm Hg to 32 mm Hg in the fellow eye were enrolled. At study entry, each participant was required to have two normal, reliable automated, achromatic 30-2 visual fields (Zeiss-Humphrey Systems, Dublin, California, USA), as determined by certified masked readers at the Visual Field Reading Center. Reliable visual fields were defined as fewer than 33% false positives, false negatives, and fixation losses. Normal visual fields were classified based on STATPAC 2 criteria for global indices within the 95% age-specific population norms and glaucoma hemifield test within the 97% age-specific population norm.[4,5] Stereoscopic optic disk photographs were assessed by two independent, masked, certified graders at the Optic Disk Reading Center. To be eligible for the study, the color stereoscopic optic disk photographs obtained as either full-frame 35-mm pairs or split-frame simultaneous pairs had to be judged as normal. Participants 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 disk hemorrhage, or an asymmetry between the two eyes in the cup-disk ratios greater than 0.2.[1] Horizontal and vertical cup-disk ratios by contour were estimated visually from stereoscopic optic disk photographs. If the reader estimates of cup-to-disk ratio differed by more than 0.2 disk diameters (DD), they attempted to reach a consensus; if they could not, the cup-to-disk ratio was adjudicated by a glaucoma specialist.[6] The assessment of cup-to-disk diameter ratios by the Optic Disk Reading Center is highly reproducible.[6]

Participants in the OHTS CSLO ancillary study were recruited from seven of the 22 OHTS centers (Henry Ford Medical Center, Troy, Michigan; University of California, Davis, California; Devers Eye Institute, Portland, Oregon; University of California, San Diego, California; Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania; Jules Stein Eye Institute, University of California, Los Angeles, California; and New York Eye and Ear Infirmary, New York, New York). Informed consent for the ancillary study was obtained from study participants after approval by the Institutional Review Board at each institution.

The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, GmbH, Dossenheim, Germany) is a confocal scanning laser ophthalmoscope that provides topographical measures of the optic disk and peripapillary retina. Details describing this instrument have been presented elsewhere.[7–11] In brief, the topographical image is derived from 32 optical sections at consecutive focal depth planes. Each image consists of 256 × 256 pixels with each pixel corresponding to retinal height at its location. All HRT operators were certified by the CSLO Reading Center at the University of California, San Diego, before acquiring images for the OHTS CSLO ancillary study. The HRT examinations were obtained annually after pupillary dilation at the time of scheduled OHTS fundus examination and optic disk photography. Three 10-degree images centered on the optic disk were obtained on both eyes and three 15-degree images were obtained on the right eye. A mean image for each image series was computed using HRT software version 2.01. Keratometry measurements were used to correct all images for magnification error. Corrective lenses were used during image acquisition when astigmatism was greater than one diopter.

All quality assessment, image processing, and data analysis of the CSLO images took place at the University of

California, San Diego CSLO Reading Center. The quality of images obtained by each operator and site was monitored throughout the study by reviewing each image series (images at 32 consecutive focal planes) for clarity, appropriate focus and depth adjustment, and minimal eye movement. In addition, each mean topography image was monitored for adequate reproducibility (standard deviation < 50 μm). Participant database entries were reviewed for complete recording of patient information (including refractive error and keratometry reading). The optic disk margin defined as the inner margin of the scleral ring, was outlined on the mean topography image by a trained technician while viewing stereoscopic optic disk photographs of the optic disk taken within 12 months of the baseline images. Each outline of the optic disk was reviewed for accurate placement by a second trained technician with differences of opinion resolved by consensus. All CSLO Reading Center personnel were masked as to the identity and treatment status of the participants in this study.

Many topographical measurements are calculated by the HRT software during image analysis and have been described elsewhere.[12–14] In this study, mean cup depth, maximum cup depth, height variation contour, mean height contour, cup shape, disk area, cup area, cup-to-disk area ratio, horizontal and vertical cup-to-disk diameter ratios, cup volume (below the disk surface), rim area, rim volume (above the reference plane), rim-to-disk area ratio, retinal nerve fiber layer thickness, retinal nerve fiber layer cross sectional area, and reference plane height were evaluated along with the discriminant analysis formula, the HRT classification in the current HRT software version 2.01.[14] The HRT classification is the result of a linear discriminant function using age, cup shape, rim volume, and height variation contour. In this study, the HRT classification is analyzed both as a continuous variable and as a dichotomous variable ("outside normal limits" and "within normal limits"). It should be noted that the HRT horizontal and vertical cup-to-disk diameter ratios are measured at the center of the disk, and not necessarily at the center of the cup.[15]

Information on ocular characteristics including refractive error, corneal curvature, intraocular pressure, visual field mean deviation (MD), visual field pattern standard deviation (PSD), visual field corrected pattern standard deviation (CPSD), and Optic Disk Reading Center stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios was supplied by the OHTS Coordinating Center.[1] In addition, baseline demographic and clinical characteristics were recorded, including marital status, education, ethnicity, family history of glaucoma, and participant history of high blood pressure, heart disease, diabetes, age, race, sex, and refractive error.

For statistical analysis, differences in demographic and ocular characteristics between CSLO ancillary study participants (those providing informed consent) and participants in OHTS who chose not to be part of at the ancillary study were assessed using two-sample independent t test and χ^2 analysis.

The model used for studying the relationship between demographic and clinical characteristics, and quantitative HRT variables accounted for the fact that 99% of participants (434/439) contributed two eyes to the analysis. This was carried out using a linear mixed effects model with subject specific intercepts as random effects (for quantitative HRT variables) and fixed effects as described later or generalized estimating equations with binomial family, logit link, and exchangeable error structure for the predicted glaucoma diagnosis. Plots of residuals against fitted values were inspected to assure that there were no gross violations of assumptions of the mixed model. Calculations used the "lme" function[16] of the "nlme" package[16] (version 3.1-36) and the "geepack" package (version 0.2-4) under "R" (version 1.6.2).[17]

Univariate analysis was performed by inspecting scatterplots of HRT parameter values against IOP, stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios and visual field indices with the "loess" regression line superimposed (to allow detection of substantial departure from linearity) and by calculating the Pearson correlation coefficient. The Holm adjustment[18] was used to account for multiple comparisons. This method is similar to the familiar Bonferroni correction, but avoids some of the excessive conservatism of the latter.

As the first HRT image was not necessarily obtained at the baseline OHTS visit, the possible effect of the time lag between stereophotograph examinations and the HRT image acquisition was studied using linear mixed models in which "lag" from stereophotographic horizontal and vertical cup-to-disk diameter ratios interaction terms was included. These terms were set up in two different ways: in one case the time between baseline stereophotograph and the HRT was used, and in the other a dichotomy, splitting at the median, was used. In addition, plots of the time lag against residuals of HRT measurements from the fit given by regression on stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios were studied for possible lack of homogeneity of variance.

RESULTS

OF THE 1,636 RANDOMIZED PARTICIPANTS IN THE OCULAR Hypertension Treatment Study, 599 participants were from the seven sites participating in the CSLO ancillary study. Four individuals transferred from other sites to CSLO sites. A total of 451 of the 599 subjects (75.3%) consented to participate in the CSLO ancillary study to the OHTS; 148 did not consent to participate. Demographic, clinical, and ocular characteristics of the 451 participants and the 148 nonparticipants were similar (Table 1). However, the ancillary study participants

TABLE 1. Demographic and Ocular Characteristics of Participants and Nonparticipants in the CSLO Ancillary Study to the OHTS

Demographic Variables	Participants (n = 451)	Nonparticipants (n = 148)	*P* Value
Sex, n (%)			.63
Female	260 (58)	89 (60)	
Male	191 (42)	59 (40)	
Age, years			.51
Mean ± SD	54.4 ± 9.3	55.0 ± 9.7	
Marital status, n (%)			.71
Single	62 (14)	23 (15)	
Married	289 (64)	87 (59)	
Divorced/separated	75 (17)	28 (19)	
Widowed	25 (5)	10 (7)	
Education, n (%)			.01
Grade 6 or less	7 (2)	3 (2)	
Grade 7–11	16 (4)	10 (7)	
Grade 12/graduate equivalency degree	87 (19)	46 (31)	
1+ years of college	240 (53)	61 (41)	
1 + years of graduate school	100 (22)	28 (19)	
Race, n (%)			.07
African American	75 (17)	35 (23)	
Other	376 (83)	113 (76)	
Clinical characteristics, n (%)			
Previous topical ocular hypotensive medication,	137 (30)	38 (26)	.27
Family history of glaucoma	179 (40)	55 (37)	.55
High blood pressure	144 (32)	56 (38)	.38
Heart disease	17 (5)	10 (7)	.33
Diabetes	39 (9)	16 (11)	.46
Ocular Characteristics (mean ± SD)			
Intraocular pressure, mm Hg*	25.2 ± 2.4	25.4 ± 2.7	.50
Refractive error, D*	−1.12 ± 2.44	−0.99 ± 2.41	.47
Photograph based horizontal cup-disk diameter ratio*	0.36 ± 0.20	0.36 ± 0.19	.72
Photograph based vertical cup-disk diameter ratio*	0.39 ± 0.19	0.39 ± 0.19	.76
Visual field MD, dB*	0.31 ± 1.47	0.36 ± 1.46	.67
Visual field PSD, dB*	1.97 ± 0.47	1.98 ± 0.40	.79
Visual field CPSD, dB*	1.18 ± 0.70	1.13 ± 0.67	.40

CPSD = corrected pattern standard deviation; CSLO = Confocal Scanning Laser Ophthalmoscopy; MD = mean deviation; OHTS = Ocular Hypertension Treatment Study; PSD = pattern standard deviation.

*Average of the two eyes used.

tended to be more highly educated than the nonparticipants. Seventy-five (16.6%) of the participants, and 35 (23.6%) of the nonparticipants were African American. The demographic characteristics of the 451 subjects participating in this ancillary study were similar to the 1,636 subjects participating in the OHTS.[1]

Demographic and ocular characteristics of the 451 participants in the CSLO ancillary study to the OHTS are presented in Table 1. The age (mean ± standard deviation [SD]) of the participants at their initial HRT examination was 54.4 ± 9.3 years. Eye-specific measures reported in Table 1 are the average 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 two or three IOP readings taken during the baseline/randomization examination,[1] was 25.2 ± 2.4 mm Hg (average of right and left eyes) for the entire ancillary study sample; 63% of all participants had baseline IOP measurements greater than 24 mm Hg in both eyes. The mean (± SD) stereophotograph based estimates of the horizontal and vertical cup-to-disk diameter ratios (by contour; average of values for the right and left eyes) were 0.36 ± 0.19 and 0.39 ± 0.20, respectively. The Humphrey visual field thresholds of the two qualifying visual fields for both eyes were averaged; the mean corrected pattern standard deviation (CPSD) was 1.20 ± 0.71 dB, pattern standard deviation (PSD) was 1.99 ± 0.46 dB, and mean deviation (MD) was 0.26 ± 1.40 dB. Overall, 40% of the participants reported a family history of glaucoma and 30% reported previous use of topical ocular hypotensive medication before study enrollment (Table 1).

Of these 451 subjects enrolled in the CSLO ancillary study, 11 discontinued participation or became inactive before initial HRT imaging was completed. In addition, the baseline images of one participant were of insufficient quality to be included in this analysis. Therefore, a total of 439 participants are included in this analysis.

In addition, before funding was initiated, two study centers began imaging participants, using only 15-degree images in both eyes. Therefore 10-degree images were not obtained for some participants at the first OHTS CSLO ancillary study visit. To utilize the HRT images closest to the baseline stereophotographs, the first acceptable quality 10-degree or 15-degree mean topography image for each eye was included.

For most HRT measurements, the 10- and 15-degree field values were strongly correlated (all correlations were above 0.84) in eyes in which both were measured on the same date. Scatterplots were symmetrical about the line of identity for all HRT measurements except for mean height contour and reference plane height. Therefore, we believe that the 15-degree field image was a reasonable surrogate for the 10-degree field image for the eyes in which the

TABLE 2. Mean Topographic Optic Disk Parameter Measurements by Sex

Measurement	Overall (n = 873 eyes)	Male (n = 367 eyes)	Female (n = 498 eyes)	*P* Value*	Holm *P* Value
Corneal curvature (mm)	7.75 ± 0.26	7.79 ± 0.26	7.72 ± 0.26	.005	.898
Disk area (mm^2)	1.93 ± 0.40	1.96 ± 0.41	1.90 ± 0.39	.127	1.0
Reference plane height (mm)	0.32 ± 0.10	0.32 ± 0.09	0.32 ± 0.10	.96	1.0
Cup area (mm^2)	0.56 ± 0.37	0.60 ± 0.41	0.53 ± 0.37	.048	1.0
Cup volume (mm^3)	0.32 ± 0.22	0.33 ± 0.21	0.30 ± 0.22	.174	1.0
Mean cup depth (mm)	0.23 ± 0.10	0.24 ± 0.11	0.23 ± 0.10	.545	1.0
Cup shape	−0.20 ± 0.07	−0.20 ± 0.08	−0.20 ± 0.07	.730	1.0
Rim area (mm^2)	1.37 ± 0.29	1.36 ± 0.29	1.37 ± 0.29	.575	1.0
Rim volume (mm^3)	0.36 ± 0.14	0.34 ± 0.14	0.37 ± 0.14	.006	1.0
Cup/disk area ratio	0.27 ± 0.15	0.29 ± 0.14	0.26 ± 0.15	.106	1.0
Rim/disk ratio	0.73 ± 0.15	0.71 ± 0.16	0.74 ± 0.15	.106	1.0
Horizontal cup-to-disk diameter ratio	0.51 ± 0.21	0.52 ± 0.21	0.50 ± 0.21	.299	1.0
Vertical cup-to-disk diameter ratio	0.41 ± 0.21	0.44 ± 0.22	0.40 ± 0.22	.077	1.0
RNFL thickness (mm)	0.25 ± 0.07	0.24 ± 0.06	0.26 ± 0.06	.002	.329
RNFL cross-section (mm^2)	1.21 ± 0.33	1.17 ± 0.32	1.24 ± 0.33	.013	1.0
Mean height contour (mm)	0.08 ± 0.08	0.08 ± 0.07	0.07 ± 0.08	.021	1.0
HRT classification 1	1.14 ± 1.68	1.05 ± 1.67	1.21 ± 1.68	.292	1.0
HRT classification 2					
Outside normal limits	210 (24%)	102 (28%)	116 (23%)	.13	
Within normal limits	663	265	382		
Standard deviation of mean topography image (microns)	18.30 ± 7.9	19.0 ± 7.3	17.7 ± 7.9	.078	1.0

HRT = Heidelberg Retina Tomograph; RNFL = retinal nerve fiber layer.
**P* values related to differences by sex are adjusted for the lack of independence between two eyes.

earliest HRT used only a 15-degree field. Of the 873 eyes included in this analysis, 722 (83%) were 10-degree fields and 151 (17%) were 15-degree fields.

Mean HRT topographic optic disk parameter measurements from the first OHTS CSLO ancillary study visit of the 439 participants with good quality images are presented by sex in Table 2. Modest differences in cup area, height variation contour, mean height contour, retinal nerve fiber layer (RNFL) cross sectional area, RNFL thickness, and rim volume by sex were found. However, none of these differences remained statistically significant after Holm adjustment of the *P* values. The HRT classification is a discriminant function developed to differentiate between normal and glaucoma eyes.[14] Overall, 24% of the eyes were classified as outside normal limits using this classification criteria; no differences were found by sex.

No difference in optic disk topographic measurements was found between participants with and without diabetes, high blood pressure, and cardiovascular disease (data not shown). Similarly, there was no association between optic disk topographic measurements and demographic characteristics including marital status, and education ($P > .05$ in all cases before Holm adjustment). Age was significantly associated with one HRT parameter—RNFL cross sectional area ($P = .022$ after Holm adjustment). Refractive error was also associated with one HRT optic disk parameter—RNFL thickness ($P = .034$ after Holm adjustment for multiple comparisons). Differences in topographic optic disk parameter measurements by race were found, and are the topic of a separate manuscript.[19]

Univariate correlations (Pearson) between IOP, stereophotographic estimates of horizontal and vertical cup-to-disk diameter ratios, and HRT topographic optic disk measurements are presented in Table 3. There was no association between mean baseline IOP measures and the 18 HRT topographic optic disk measurements evaluated. There also was no association found between visual field MD, PSD, or CPSD and any of the HRT topographic optic disk parameter measurements (Table 4).

Most HRT topographic optic disk measurements were strongly associated with stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios in both the univariate (Table 3) and multivariate analysis (Table 5). The strongest univariate correlations were found between stereophotographic-based horizontal and vertical cup-to-disk diameter ratios and HRT cup-to-disk area ratio ($r = .85$ and $r = .84$, respectively), rim-to-disk area ratio ($r = -.85$ and $r = -.84$, respectively), mean cup depth ($r = .84$ and $r = .83$, respectively), and cup volume ($r = .83$ and $r = .81$, respectively), cup area ($r = .83$ and $r = .80$, respectively), horizontal cup disk diameter ratio ($r = .80$ and $r = .78$, respectively), and vertical cup disk diameter

TABLE 3. Univariate Correlations Between Intraocular Pressure (IOP), Horizontal and Vertical Cup-to-Disk Diameter, Ratios, and Topographic Optic Disk Parameters.

	Pearson *R*		
CSLO Measurement	IOP	Horizontal Cup-to-Disk Ratio From Stereo-photographs	Vertical Cup-to-Disk Ratio From Stereo-photographs
Disk area (mm^2)	0	.52	.50
Reference plane height (mm)	−.02	.33	.36
Cup area (mm^2)	.01	.83	.80
Cup volume (mm^3)	.01	.83	.81
Mean cup depth (mm)	0	.84	.83
Maximum cup depth (mm)	.02	.72	.74
Cup shape	−.04	.50	.46
Rim area (mm^2)	−.01	−.34	−.35
Rim volume (mm^3)	−.03	−.35	−.34
Rim/disk ratio	−.01	−.85	−.84
Cup/disk area ratio	.01	.85	.84
Horizontal cup disk ratio	−.01	.80	.78
Vertical cup disk ratio	.03	.79	.81
RNFL thickness (mm)	−.02	−.16	−.13
RNFL cross-section (mm^2)	−.01	.03	.05
Mean height contour (mm)	0	.54	.55
Height variation contour (mm)	−.02	−.07	−.04
HRT classification value 1	0	−.58	−.56

CSLO = Confocal Scanning Laser Ophthalmoscopy Study; HRT = Heidelberg Retina Tomograph; RNFL = retinal nerve fiber layer.

TABLE 4. Univariate Association Between Visual Field MD, CPSD, and PSD, and Topographic Optic Disk Parameters

	Pearson *R*		
CSLO Measurement	MD	PSD	CSPD
Disk area (mm^2)	−.04	−.05	−.02
Reference plane height (mm)	0	−.04	.01
Cup area (mm^2)	−.05	−.01	.03
Cup volume (mm^3)	−.03	−.02	.04
Mean cup depth (mm)	−.02	−.01	.03
Maximum cup depth (mm)	.03	−.02	.02
Cup shape	−.09	.02	.03
Rim area (mm^2)	.01	−.06	−.06
Rim volume (mm^3)	.03	−.04	−.05
Rim/disk ratio	.05	0	−.03
Cup/disk area ratio	−.05	0	.03
Horizontal cup disk ratio	0	−.05	0
Vertical cup disk ratio	−.06	−.01	.03
RNFL thickness (mm)	.06	−.04	−.02
RNFL cross-section (mm^2)	.05	−.06	−.03
Mean height contour (mm)	−.05	−.02	.03
Height variation contour (mm)	.06	−.01	.02
HRT classification value	.05	−.02	−.06

Abbreviations as in Table 3.

ratio ($r = .79$ and $r = .81$, respectively). After adjusting for disk area in the multivariate analysis, all HRT topographic optic disk measurements except height variation of contour and RNFL thickness (Holms adjusted P value = .408 and .060, respectively) were strongly associated with stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios.

As the OHTS clinical trial began before the funding for the OHTS CSLO ancillary study was approved, not all participants completed their imaging at the OHTS baseline visit. One study center was added 2 years later to increase African-American participation. Of the 439 participants with good quality images included in this analysis, 102 (23%) had images obtained at the baseline visit, 157 (36%) at the 6-month or 12-month visit, 127 (29%) at the 18-month or 24-month visit, 44 (10%) at the 30-month or 36-month visit, and 9 (2%) at later visits.

Since the baseline stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios was not necessarily based on photographs obtained at the same visit as the HRT images, we examined whether the time interval between the photographs and HRT images influenced the results in the multivariate model. None of the interactions of HRT measurements with time lag between the stereophotograph and HRT examinations (as a linear by linear term, or as dichotomous factor times linear term) attained $P < .05$ after Holm correction except maximum cUp Depth (using the dichotomous factor only). Inspection of residual plots showed no apparent trends with respect to the time lag.

We also examined whether the time interval (lag) between the visual field and HRT image influenced the relationship between HRT measurements and IOP, MD, PSD, and CPSD. We found no influence of time lag on the relationship between HRT measurements and IOP, MD, PSD, and CPSD.

DISCUSSION

THE CSLO ANCILLARY STUDY TO THE OHTS IS THE FIRST multicenter clinical trial to use CSLO imaging to monitor changes in optic disk topography. Our study demonstrated in a large, well-characterized cohort of ocular hypertensive patients that HRT measurements are strongly associated with stereophotographic estimates of horizontal and verti-

TABLE 5. Multivariate Analysis* of the Relationship Between Horizontal and Vertical Cup-to-Disk Diameter Ratio Measurements and HRT Topographic Optic Disk Parameters

CSLO Measurements	Horizontal Cup-to-Disk Diameter Ratio From Stereophotograph (R)		Vertical Cup-to-Disk Diameter Ratio From Stereophotograph (R)	
	Regression Coefficient	*P* Value†	Regression Coefficient	*P* Value†
Disk area	1.00	<.0001	.82	<.0001
Reference plane height	.16	<.0001	.154	<.0001
Cup area	1.20	<.0001	1.04	<.0001
Cup volume	.71	<.0001	.59	<.0001
Mean cup depth	.41	<.0001	.35	<.0001
Maximum cup depth	.76	<.0001	.69	<.0001
Cup shape	.18	<.0001	.15	<.0001
Rim area	−1.20	<.0001	−1.04	<.0001
Rim volume	−.42	<.0001	−.34	<.0001
Rim/disk area ratio	−.61	<.0001	−.54	<.0001
Cup/disk ratio	−.61	<.0001	.54	<.0001
RNFL thickness	−.05	.005	−.03	.060
Horizontal cup disk ratio	.80	<.0001	.71	<.0001
Vertical cup disk ratio	.83	<.0001	.78	<.0001
RNFL cross-section	−.27	.002	−.19	.03
Mean height contour	.21	<.0001	.18	<.0001
Height variation contour	−.06	.039	−.03	.408
HRT classification value	−6.46	<.0001	−5.52	<.0001

Abbreviations as in Table 3.

*Multivariate regression analysis included a random effect for participant so that *P* values take into account that two eyes from most participants were used in the analysis. In addition, all measurements except disk were adjusted for disk area.

†Holm *P* values presented to adjust for multiple comparisons.

cal cup-to-disk diameter ratios. In addition, we found that these associations remained after adjusting for disk area, IOP, and age. These results confirm previous reports of strong agreement between stereophotographic estimates of cup-to-disk ratios and HRT measurements in studies in normal participants and glaucoma patients.[15,20] In contrast to previous reports that included glaucoma patients with large cup-to-disk ratios, the current study found associations among ocular hypertensive patients with normal appearing optic discs at baseline, within a relatively narrow distribution of stereophotograph based cup-to-disk diameter ratio measurements (mean horizontal, 0.36 [95% confidence interval = 0.35 to 0.38]; mean vertical, 0.39 [95% confidence interval = 0.37 to 0.40]).

The HRT measurements with the strongest associations with stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios were cup-to-disk area ratio, rim-to-disk ratio, mean cup depth, and cup area and volume, thereby suggesting that HRT topography measurements reflect standardized assessment of stereophotographs. The HRT does provide linear measurements of both horizontal and vertical cup-to-disk diameter ratios. These HRT horizontal and vertical cup-to-disk diameter ratio measurements were also strongly associated with stereophotographic-based horizontal (r = .80 and .83, respectively) and vertical (r = .71 and .78, respectively) cup-to-disk diameter ratio estimates. It should be noted that the square root of the HRT cup-to-disk area ratio measurement reflects the horizontal and vertical cup-to-disk diameter ratios assessment so that a cup/disk area ratio of 0.27 can be expected when cup disk diameter ratios are approximately 0.52.

Stereophotograph based horizontal and vertical cup-to-disk diameter ratios were significantly smaller ($P < .001$ and = .046 respectively) than the HRT horizontal and vertical cup-to-disk diameter ratios. One explanation for these differences may be that the HRT diameter measurements are derived from the center of the disk, and not necessarily from the center of the cup. Another explanation for these differences may be due to differences in the location of the optic disk margin and reference plane used to estimate the cup disk ratios. In this study, the optic disk margin was outlined as the inner margin of the scleral ring, which may not correspond exactly to the qualitative estimate of the optic disk border used by the graders of the stereophotographs. The reference plane used by graders to qualitatively estimate cup disk ratios in stereophotographs may also be different than the reference plane that the HRT uses to calculate its cup-to-disk diameter ratios.

No association was found between HRT measurements and most demographic and clinical factors. Modest associations were found with sex and age before but not after

correction for multiple comparisons. These results are similar to previous reports of no effect of sex on optic disk topography in normal subjects.[12] Previous reports evaluating the relationship between HRT optic disk measurements and age are inconsistent, and when found are generally small.[23,24]

In this study of ocular hypertensive patients with normal visual fields at entry into the OHTS, no association was found between HRT topographic optic disk parameter measurements and MD, PSD, and CPSD visual field indices. The visual field indices were based on the mean of the first two baseline fields. Associations between HRT topographic optic disk measurements and visual field indices have been reported in studies that included eyes with glaucomatous visual field damage.[25–29] However, as this study was limited to ocular hypertensive patients with baseline visual field indices within a relatively small range of normal values, a strong association between visual field indices and optic disk topography was not expected.

Similarly, we found no association between IOP and HRT topographic optic disk measurements. This lack of association may be due in part to the relatively narrow range of IOP values (21 mm Hg to 36 mm Hg) in these study participants. Several investigators have reported change in HRT topography with change in IOP.[30–33] However, these reports of a significant relationship between IOP and HRT topographic measurements were based on change in IOP due to medical or surgical intervention, and not based on cross-sectional comparisons of IOP and HRT topography.

The HRT classification, a linear discriminant function identified 210 (24%) eyes as outside normal limits. There are several possible explanations for this finding. First, many of these eyes may be correctly identified as outside normal limits, and will reach end point in the longitudinal analysis. Another explanation is that the results are false positives. Using glaucomatous visual field damage as the gold standard, several cross-sectional studies have found that the sensitivity and specificity of the HRT classification ranges from 65% to 83% and 83% to 89%, respectively.[14,34,35] Based on these sensitivity and specificity estimates, it is likely that a proportion of the eyes classified as "outside normal limits" may be false positives.

There are some possible limitations to this study. First, HRT imaging did not occur at the time of baseline photography, IOP, and visual field testing in all participants. Approximately 33% of participants completed HRT imaging within 1 year of their baseline stereophotographs. Our analyses of time lag between stereophotograph and HRT imaging suggest that the effect of the time lag is not strong. Furthermore, changes in the optic disk that could have occurred between the time of baseline photography and the first HRT imaging session should have reduced the association between stereophotographic estimates of horizontal and vertical cup-to-disk diameter ratios and HRT topographic measurements. Therefore, our estimates of the association between the stereophotographic estimates of horizontal and vertical cup-to-disk diameter ratios and HRT topographic optic disk measurements are likely to be conservative or underestimates of the true association. We found no evidence of an influence of time lag on the relationship between HRT measurements and IOP, PSD, MD, and CPSD. Second, we used 10-degree and 15-degree images interchangeably in the analyses. Our analysis suggested that the HRT measurements obtained using 10-degree and 15-degree images were highly correlated. Therefore, our use of both 10-degree and 15-degree images would likely have minimal influence on the results. We verified this claim by completing all analyses using only 10-degree field of view images (data not shown), and found nearly identical results. Third, trained technicians outlined the disk margin using the commercially available HRT software while viewing stereoscopic photographs of the optic disk to aid in identifying the location of the inner margin of the scleral ring. It is possible that a bias was introduced by using stereophotographs to mark the disk margin, resulting in stronger correlations between topographic optic disk measurements and stereophotographic assessment of horizontal and vertical cup-to-disk ratios. However, in a study comparing the disk size of eyes when the outlining of the disk margin was completed with and without the use of stereophotographs, interobserver variation in optic disk size and HRT measurements was reduced using stereophotographs.[36] Therefore, is not clear what effect, if any, our procedures for marking the disk margins had on the results of this study.

In summary, this report describes the study design of the CSLO ancillary study to the OHTS, and demonstrates that HRT topographic measurements are associated with stereophotographic assessment of horizontal and vertical cup-to-disk diameter ratios, even in participants with normal appearing optic discs. These results suggest that HRT optic disk measurements describe features that are reflected in standardized assessment of cup-to-disk diameter ratios from stereophotographs.

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