Lack of Association between Glaucoma and Macular Choroidal Thickness Measured with Enhanced Depth-Imaging Optical Coherence Tomography

Jean-Claude Mwanza, Jessica T. Hochberg, Michael R. Banitt, William J. Feuer, and Donald L. Budenz

PURPOSE. To compare choroidal thickness measurements among normal eyes, eyes with normal tension glaucoma (NTG), and those with primary open-angle glaucoma (POAG), and to correlate choroidal thickness with demographic and clinical ocular parameters.

METHODS. Choroidal thickness was measured with enhanced depth-imaging (EDI) optical coherence tomography (OCT) in one eye of 38 normal, 20 NTG, and 56 POAG subjects and compared among groups. The mean age was 69.3 ± 13.6 years (60.1 ± 13.4 years for normal subjects and 73.8 ± 11.3 years for glaucoma subjects; $P < 0.001$). Measurements were made at the fovea and in the temporal and nasal choroid every 0.5 mm up to 3 mm away from the fovea. Univariate and multivariate linear regression analyses were performed to assess the association between choroidal thickness and demographic and ocular parameters.

RESULTS. There were no differences in foveal, temporal, or nasal choroidal thickness between normal, NTG, and POAG subjects (all $P > 0.05$) after adjusting for age, axial length, and intraocular pressure. Similarly, glaucoma severity groups did not differ from each other in all choroidal thickness measurements (all $P > 0.05$). Age ($\beta = -1.78$; $P < 0.001$) was the most significant factor associated with subfoveal choroidal thickness in the entire group, followed by axial length ($\beta = -11.8$; $P = 0.002$).

CONCLUSIONS. Choroidal thickness does not differ among normal, NTG, and POAG subjects, suggesting a lack of relationship between choroidal thickness and glaucoma based on EDI OCT measurements. (*Invest Ophthalmol Vis Sci.* 2011;52:3430–3435) DOI:10.1167/iops.10.6600

The pathogenesis of glaucomatous optic neuropathy (GON) remains enigmatic despite being investigated for decades. Even more puzzling is the mechanism behind normal-tension glaucoma (NTG). Increased intraocular pressure (IOP) is the major risk factor for primary open-angle glaucoma (POAG) and the benefit of lowering IOP has been well documented.^{1,2}

However, the concept of NTG, coupled with evidence that elevated IOP is not always associated with GON and that oftentimes GON progresses after lowering IOP, challenges the mechanical pathogenetic theory based on elevated IOP. This has led to the theory that, in addition to elevated IOP, other factors may play an important role in glaucoma pathogenesis. Particularly worthy of note is the vascular/hemodynamic theory that considers GON as an ischemic injury resulting from diminished blood supply after reduced ocular blood flow at the level of lamina cribrosa.^{3–5}

There has been increasing interest in investigating the role of the choroid in the pathogenesis of GON. Previous studies have found an association between GON and impaired choroidal circulation or blood flow to the ONH.^{6–8} In addition, a limited number of studies, mostly histologic, have investigated the association between glaucoma and choroidal thickness with inconsistent findings.^{9–13} High-frequency ultrasonography has been used to measure choroidal thickness in chick and primate eyes.^{14,15} However, concerns regarding the related high-energy dispersion make this technique unsafe for use on the human ocular posterior segment. Laser Doppler interferometry is another technique that has allowed measurement of axial length both in chicks and in humans and of choroidal thickness in chicks to be made more accurately than ultrasonography,^{16–18} but reports on such measurements of choroidal thickness in humans are unavailable. Partial coherence interferometry can also measure choroidal thickness in humans and animals, but its use is limited because of substantial intra-subject variability.¹⁹ Optical frequency domain imaging (OFDI), also known as swept source OCT, has been shown to provide high-resolution images of the choroid,²⁰ but choroidal thickness has yet to be measured with this technique. In addition, OFDI has not been available for clinical use. Thus, despite considerable improvements in ocular posterior segment imaging, in vivo assessment of the choroid has remained difficult even with the advent of spectral domain (SD) OCT because of significant signal strength (SS) attenuation beyond the retinal pigment epithelium (RPE).^{21,22} Enhanced depth-imaging (EDI) OCT is a new method that uses low SS and low resolution but increased depth on conventional SD-OCT to acquire detailed cross-sectional images of the choroid and to measure its thickness.^{23,24} Initial publications of EDI OCT measurements demonstrate the thickness of the choroid to be greatest either subfoveally or temporally with a significant reduction closer to the optic nerve.²³ The choroid also appears to get thinner with increasing age and axial length.²⁵ Spaide²⁶ recently defined a new clinical entity called age-related choroidal atrophy; interestingly, glaucoma was present in 6 of 17 (35.3%) of the patients. The purpose of our study was twofold: to compare choroidal thickness measured with EDI OCT in normal eyes, eyes with NTG, and those with POAG, and to

From the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida.

Supported by National Institutes of Health Grant P30 EY014801, an unrestricted grant from the Research to Prevent Blindness, and a Horizon Grant from Allergan Corporation (JCM).

Submitted for publication September 18, 2010; revised December 19, 2010, and January 2, 2011; accepted January 10, 2011.

Disclosure: J.-C. Mwanza, Heidelberg Engineering (F); J.T. Hochberg, Heidelberg Engineering (F); M.R. Banitt, Heidelberg Engineering (F); W.J. Feuer, Heidelberg Engineering (F); D.L. Budenz, Heidelberg Engineering (F)

Corresponding author: Donald L. Budenz, Bascom Palmer Eye Institute, 900 NW 17th Street, Miami, FL 33136; dbudenz@med.miami.edu.

determine the effect of age, sex, ethnicity, axial length, IOP, and glaucoma severity on choroidal thickness.

SUBJECTS AND METHODS

Subjects

A total of 119 subjects (38 normal subjects, 20 with NTG, and 61 with POAG) were enrolled in this study from December 2009 to April 2010. Only one eye per subject was randomly selected for the study. Glaucoma (POAG and NTG) patients were consecutively recruited among outpatients at the Glaucoma Service, whereas normal subjects were recruited from general ophthalmology clinics of the Anne Bates Leach Eye Hospital, Bascom Palmer Eye Institute, at the Miller School of Medicine, University of Miami. All glaucoma subjects had recently undergone full ophthalmologic examination and reliable visual field analysis (Humphrey Visual Field Analyzer [Carl Zeiss Inc., Dublin, CA] using the Swedish Interactive Thresholding Algorithm standard 24-2 perimetry). All subjects were required to have best-corrected visual acuity of 20/40 or better, refractive error less than -6 diopters of sphere or 3 diopters of cylinder, clear media, no history of retinal disease (e.g., diabetic retinopathy, macular degeneration, retinal detachment) or laser therapy, optic nerve abnormalities including non-glaucomatous optic neuropathy, or ocular surgery within 1 month of enrollment date. History of treatment with medications that might affect retinal thickness (i.e., intravitreal anti-VEGF therapy) was also an exclusion criterion. Glaucoma subjects were included if they had an established diagnosis of NTG or POAG made by a glaucoma specialist based on glaucomatous optic disc damage and an abnormal visual field (VF) test result consisting of pattern SD $<5\%$, glaucoma hemifield test results outside normal limits, or both. At least two consecutive abnormal VF examinations were required, with the most recent test performed within 12 months of enrollment. Normal tension glaucoma was diagnosed in the presence of repeatable IOP ≤ 21 mm Hg, glaucomatous optic disc changes, and VF loss as above. Subjects were further classified as having mild ($MD > -6$ dB), moderate ($MD -12$ dB $\leq MD \leq -6$ dB), or severe ($MD < -12$ dB) glaucoma.²⁷ Other inclusion criteria for normal subjects were IOP ≤ 21 mm Hg and normal ophthalmoscopic appearance of the optic nerve (cup-to-disc ratio <0.5 in both eyes, cup-to-disc ratio asymmetry <0.2 , absence of hemorrhage, or localized or diffuse rim thinning). Normal subjects did not undergo VF testing. The study was approved by the Institutional Review Board (IRB) of the Human Subjects Research Office of the Miller School of Medicine, University of Miami, Miami, Florida, and written informed as well as HIPAA consents were obtained from each participant. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Image Acquisition and Processing

The same experienced operator (JTH) performed imaging on all subjects through dilated pupils with the same OCT instrument (Spectralis, software version 4.0; Heidelberg Engineering, Heidelberg, Germany). Spectralis OCT uses SD technology with an 870-nm wavelength superluminescent diode and performs 40,000 A-scans/s with an axial resolution of $7\text{ }\mu\text{m}$ and transversal resolution of $14\text{ }\mu\text{m}$. All images were acquired using a single retinal thickness horizontal B-scan centered on the fovea (number of A-scans/B-scan, 1536; scan angle, 30° ; scan length, 9 mm). The automatic real-time (100 frames) averaging mode was applied to maximize the signal-to-noise ratio and to ensure good quality images. To achieve good visualization of the choroid, EDI OCT was used as previously described by Spaide et al.²⁴ Briefly, after the patient's chin and forehead were correctly positioned, the instrument was pushed toward the eye while the patient maintained fixation on the internal fixation light until the retinal image was inverted near the top of the display window and the choroid, including the sclerochoroidal margin, was seen. Three consecutive scans were then acquired per eye. Image quality was judged based on signal-to-noise ratio, and

only scans with signal-to-noise ratios ≥ 20 dB were saved and considered for analysis.

After all eyes were imaged, two readers (JCM, MRB) who were masked to the identity, diagnostic and other ocular parameters of the subjects used the manual segmentation function to delineate the boundaries of the choroid. The manual function was used because Spectralis OCT does not provide an algorithm for automatic segmentation of the choroid. One segmentation line was placed on the RPE/Bruch's membrane interface, and another line was placed on the sclerochoroidal interface to represent the inner and outer boundaries of the choroid, respectively (Fig. 1). The retinal thickness algorithm function was then used to automatically generate the thickness of the choroid at the fovea and every 0.5 mm up to 3 mm away from the fovea in the nasal and temporal sectors. The first reader repeated this procedure three times to generate measurements for intraobserver variability, and the second reader independently made one measurement on a different day. In addition to Spectralis OCT retinal imaging, all eyes underwent measurement of axial length (IOLMaster; Carl Zeiss Meditec, Dublin, CA).

Statistical Analysis

All data were analyzed with statistical analysis software (SPSS, version 18; SPSS Inc., Chicago, IL). Differences in thickness values between groups were analyzed for statistical significance with one-way analysis of variance. Univariate and multivariate linear regressions were used to assess the relation between choroidal thickness and age, IOP, axial length, VF mean deviation (MD), study eye, sex, ethnicity, diagnostic group (normal, NTG, POAG), and glaucoma severity. Specifically, these variables were initially fitted in a univariate model and then entered in a multivariate analysis to determine independence of effects. Mean choroidal thickness was regressed against age to verify the hypothesis that choroidal RNFL thickness varies as a function of age. Intraobserver and interobserver agreements were evaluated with intraclass correla-

FIGURE 1. Illustrative scans from a 74-year-old normal subject (*top*) showing a thick choroid before and after manual segmentation (*upper line*, RPE/Bruch's membrane interface; *lower line*, sclerochoroidal interface), from another 72-year-old normal subject (*middle*) with a thin choroid, and a 79-year-old subject with moderate glaucoma (*bottom*).

tion coefficient (ICC) and Pearson's correlation coefficient, respectively. For all analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of Subjects

Of the 119 subjects who were enrolled initially, five (one with mild and four with severe POAG) were excluded from the final analysis because of poor image quality or inability of the investigator to clearly see the outer boundary of the choroid. Thus, 114 (38 normal, 20 NTG, and 56 POAG) subjects were included in the final analysis. Of 76 glaucoma subjects, 18 had undergone filtering surgery in the study eye, and 58 were taking topical IOP-lowering drugs. There were 53 men and 61 women, and 60 right and 54 left eyes. Distribution by ethnic origin was as follows: 38 subjects of Caucasian, 25 of African, 49 of Hispanic, and 2 of Asian descent. Among glaucoma subjects, 34 were mildly, 19 were moderately, and 23 were severely affected. The mean age was 60.1 ± 13.4 years (range, 31–84 years) for normal and 73.8 ± 11.3 years (range, 37–93 years) for glaucoma subjects ($P < 0.001$). Mean VF MD in the glaucoma group was -9.62 ± 7.84 dB. Mean axial length was 23.91 ± 1.54 mm, 23.79 ± 0.91 , and 23.91 ± 2.05 in normal, NTG, and POAG subjects, respectively ($P = 0.96$). IOP in normal (13.6 ± 3.05 mm Hg), NTG (12.05 ± 2.93 mm Hg), and POAG (14.4 ± 4.75 mm Hg) subjects did not differ significantly ($P = 0.09$).

Choroidal Thickness Measurements and Association with Demographic and Ocular Parameters

Choroidal thickness measurements at each location (fovea and extrafovea) significantly and positively correlated with measurements at all other locations (all $P < 0.001$). There were significant negative correlations between subfoveal choroidal thickness and age ($r = -0.31$; $P = 0.001$) and axial length ($r = -0.224$; $P = 0.017$; Fig. 2). Both age and axial length also correlated with nasal ($r = -0.252$, $P = 0.007$; $r = -0.33$, $P <$

0.001 , respectively) and temporal ($r = -0.276$, $P = 0.003$; $r = -0.279$, $P = 0.003$, respectively) choroidal thickness. IOP correlated with nasal choroid measurements only (all $P < 0.05$). These correlations were also run separately in normal ($n = 38$) and glaucoma ($n = 76$) subjects to determine whether the trend was the same. In normal subjects, all thickness measurements correlated with age ($r = -0.34$ and $P = 0.026$ for subfoveal; $r = -0.29$ and $P = 0.037$ for nasal; $r = -0.61$ and $P = 0.003$ for temporal; and $r = -0.51$ and $P = 0.007$ for average). Significant correlations were also found between axial length and both nasal ($r = -0.44$, $P = 0.006$) and average ($r = -0.354$, $P = 0.029$) choroidal thickness. None of the measurements correlated with IOP (all $P > 0.05$). In glaucoma subjects, in addition to age, subfoveal, nasal, temporal, and overall average choroidal thickness also significantly correlated with axial length. IOP correlated with thicknesses of the foveal ($r = -0.25$, $P = 0.029$) and nasal choroid ($r = -0.25$, $P = 0.028$) but not the temporal or average choroidal thickness. In the univariate analysis including age, sex, ethnicity, laterality, axial length, IOP, presence of glaucoma, normal or NTG or POAG, and severity of glaucoma as independent factors and subfoveal choroidal thickness as a dependent variable, significant negative associations were observed only for age ($\beta = -2.14$, $P < 0.001$) and axial length ($\beta = -11.27$, $P = 0.006$). Age and axial length were also negatively associated with temporal choroidal thickness ($\beta = -1.80$, $P < 0.001$ and $\beta = -11.83$, $P = 0.001$, respectively), nasal choroidal thickness ($\beta = -1.63$, $P = 0.001$ and $\beta = -14.14$, $P < 0.001$, respectively), and average choroidal thickness ($\beta = -1.74$, $P < 0.001$ and $\beta = -13.01$, $P < 0.001$, respectively).

When multivariate regression analysis was performed with the same dependent variables by using the forward method in the overall group of study participants (normal and glaucoma), age ($\beta = -1.87$, $P < 0.001$) was the most significant predictor of subfoveal choroidal thickness, followed by axial length ($\beta = -11.80$, $P = 0.002$; Table 1). When these two variables were excluded from the model, no other variable showed a significant impact on subfoveal and overall average choroidal thickness. After excluding age, only axial length ($\beta = -0.37$; $P <$

FIGURE 2. Scatter plot of simple linear regression analysis between age and subfoveal (A), nasal (B), and temporal choroidal thickness (C) and between subfoveal choroidal thickness and axial length (D).

TABLE 1. Multivariate Regression Analysis of Subfoveal Choroidal Thickness in Normal and Glaucomatous Eyes

Variables	Overall Group		Normal		All Glaucoma	
	β	P	β	P	β	P
Age	-1.78	<0.001	-1.45	<0.001	-2.97	<0.001
Axial length	-11.8	0.002	—	—	-17.000	<0.001

0.001) and IOP ($\beta = -0.21$; $P = 0.022$) were significant determinants of subfoveal choroidal thickness. In normal subjects, significant association was found between subfoveal choroidal thickness and age ($\beta = -1.45$; $P < 0.001$). Neither ethnicity nor presence or absence of glaucoma had a significant effect on any of the measurements (all $P > 0.05$). In the glaucoma group, age and axial length were significant determinants of both subfoveal and average choroidal thickness.

Between-Groups Comparisons of Choroidal Thickness

Table 2 presents age-, axial length- and IOP-adjusted general linear model average choroidal thickness values at the fovea and different locations from the fovea in the three groups of subjects. The comparison between normal and all glaucoma subjects (NTG and POAG) did not reveal any significant difference in subfoveal (214.68 μm vs. 216.16 μm ; $P = 0.92$), nasal (170.35 μm vs. 174.07 μm ; $P = 0.77$), and temporal (201.81 μm vs. 212.77 μm ; $P = 0.37$) choroidal thickness and all locations in the nasal and temporal choroid (all $P > 0.05$). The pooled within-group residual standard deviation was approximately 25–33 μm . Similarly, no statistically significant differences were observed in choroidal thickness measurements between normal, NTG, and POAG subjects, although NTG subjects tended to have thicker choroids (all $P > 0.05$). A second set of models constructed without adjusting for IOP gave very similar results. The nasal choroid was significantly thinner than the subfoveal and the temporal choroid, and the subfoveal choroid was thicker than the temporal one, but the differences did not reach significance levels in normal or glaucoma subjects. There was a tendency toward thicker choroids in subjects with severe glaucoma than in normal subjects and those with mild glaucoma, but the differences between groups did not reach statistical significance (all $P > 0.05$; Table 3, Fig. 3). No differences were observed in choroidal thickness measurements between ethnic groups (all $P > 0.05$). Intraobserver ICCs for foveal, nasal, and temporal choroidal thickness were all 0.99. Measurements from the two observers were highly correlated ($r = 0.93$ for foveal, $r = 0.94$ for nasal, and $r = 0.92$ for temporal choroid; all $P < 0.001$).

DISCUSSION

The role of the choroid among the complex network of factors contributing to the pathogenesis of GON is incompletely understood. To contribute to the understanding of the relationship between the choroid and glaucoma, studies have been carried out to measure the thickness of the choroid in glaucomatous eyes using histopathologic or in vivo imaging techniques. The conflicting results of those studies, coupled with recent advances in imaging of the ocular posterior segment, particularly with the advent of SD-OCT, was the impetus for reassessing the relationship between choroidal thickness and glaucoma. In addition, though there are recent reports on choroidal thickness measured with SD-OCT in normal eyes,^{23,26,28,29} myopic eyes,^{25,30} and eyes with central serous chorioretinopathy,^{31,32} we were not aware of previous reports on such measurements in glaucomatous eyes at the time of this manuscript's preparation.

The main finding of the present study is the lack of a difference in choroidal thickness among normal eyes, eyes with NTG, and eyes with POAG. This finding is significant and may reflect a lack of association between glaucoma and choroidal thickness. On average, the sample standard deviations of choroidal thickness measurements were approximately ± 50 μm in normal subjects and ± 60 μm in glaucoma subjects, whereas confidence intervals around the differences between the two groups was approximately ± 30 μm (Table 2). Therefore, whatever differences may exist between the groups are not large compared with the variability between measurements made on the subjects within each group. Previous studies have reported either increases or decreases in choroidal thickness in glaucomatous eyes. Cristini et al.⁹ used echography and exploited the properties of radiofrequency to measure the choroidal thickness in 48 normal eyes and 21 eyes with OAG. They found a 20% significant increase in choroidal thickness in glaucomatous compared with normal eyes and speculated that this increase resulted from the swelling of blood vessels. However, they failed to further elaborate on the origin of the swelling because their glaucomatous eyes were all hypertensive at the time of the measurements, with IOPs ranging between 30 and 45 mm Hg. Choroidal thickness measured with ultrasound also showed a significant increase in another study of 22 glaucomatous eyes.¹² Spraul et al.¹¹ performed a detailed histopathologic study on morphometric changes in choroidal vessels in eyes with advanced glaucoma. In the glaucoma subjects, the choroidal thickness and the diameter of the largest choroidal arteries were significantly increased, whereas the increase in diameter of choroidal veins failed to reach a statistical significance level compared to normal eyes. Conversely, Yin et al.¹³ found a decrease in choroidal thickness in glaucomatous eyes based on histologic observations of 25 glaucomatous and 18 normal eyes. In that study, glaucomatous eyes showed a thinner choroid that the authors attributed to a concomitant decrease in vessel density and shrinkage of choroidal

TABLE 2. Adjusted Mean Choroidal Thickness in Normal, NTG, and POAG Eyes

Location	Normal	Glaucoma*	NTG	POAG	P^1	P^2	95% CI†	RSD‡
Nasal	170.35	174.07	188.45	168.73	0.77	0.41	-21.89, 29.33	25.49
Subfoveal	214.68	216.16	239.04	207.66	0.92	0.19	-27.88, 30.85	32.56
Temporal	201.81	212.77	222.34	209.21	0.37	0.44	-13.04, 34.96	24.79
Average	187.55	195.82	206.50	191.84	0.48	0.43	-14.65, 31.18	25.13

Values are in micrometers. P^1 , P value between normal and all glaucomatous eyes; P^2 , P value between normal, NTG, and POAG eyes. 95% CI, 95% confidence interval.

* NTG and POAG combined.

† Confidence intervals of the difference between normal and glaucomatous eyes.

‡ Pooled within-groups residual standard deviations.

TABLE 3. Adjusted Mean Choroidal Thickness in Normal, Mild, Moderate, and Severe Glaucoma

Location	Normal*	Mild	Moderate	Severe	P†	95% CI‡	RSD§
Nasal	170.71	166.25	169.63	188.72	0.51	-14.08, 50.09	25.70
Subfoveal	214.94	213.52	219.21	217.12	0.99	-34.97, 39.33	32.82
Temporal	202.34	206.87	217.83	216.44	0.69	-16.18, 44.39	24.84
Average	188.03	188.96	197.29	203.95	0.64	-12.93, 44.76	25.24

Values are in micrometers.

* Normal means differ slightly from those of Table 2 because of adjustments with different groupings of glaucomatous eyes.

† Overall *P* value between groups.

‡ Confidence intervals of differences between normal and severe glaucoma.

§ Pooled within-groups residual standard deviations.

vessel diameters. The discrepancies between postmortem studies may be methodological and ascribed to differences in tissue handling, examination, and classification techniques. The increase in choroidal thickness reported by older imaging techniques is likely due to inaccuracy of the measurements compared with newer techniques such as SD-OCT. Indeed, ultrasonography has an axial resolution of approximately 200 μm with a limited penetration, resulting in poor resolution that makes it less suitable for morphologic tissue imaging.³³

The comparison between glaucoma groups in our cohort of patients unexpectedly showed that eyes with severe glaucoma tended to have thicker choroid than normal eyes and eyes with mild glaucoma. The reason for this is unknown, but Cristini et al.³⁴ hypothesized as follows: the reduction in the number of small choroidal vessels results in a decrease in blood flow and an increase in pressure within the remaining vessels, which, in turn, increases the IOP after vessel enlargement,¹¹ with the ultimate consequence being an increase in choroidal thickness. However, this theory does not explain the decrease in choroidal thickness despite reduced choroidal vessel diameters and delay in choroidal filling reported by Yin et al.¹³

Central and peripheral choroid thicknesses are known to be uneven. We have found that the subfoveal choroid was thicker than the temporal and nasal choroid and that the temporal choroid was thicker than the nasal choroid in all three groups of subjects. In nonhuman primates, choroidal thickness is approximately 95 μm at the fovea and 55 μm in the periphery.³⁵ In chickens, these numbers are approximately 250 μm and 100 μm , respectively.³⁶ Although they are in agreement with some previous studies,^{23,28,29} our observations differ from others that reported a thicker temporal choroid compared with the

choroid at the fovea.^{25,30} The explanation for this difference may lie in the interindividual variability in choroidal thickness and thus in study populations.

The finding that choroidal thickness decreases as age increases and that age is the most influential factor in choroidal thinning is in agreement with previous histologic^{13,37} and in vivo imaging studies.^{23,25,26,28,30} As a corollary of this observation, age is an important confounding factor that should be accounted for when interpreting the potential effect of a given pathology on choroidal thickness. Regression analyses indicated that subfoveal choroidal thickness decreased by 12.6 μm and 16.3 μm per decade of age in normal and glaucoma subjects, respectively. Other SD-OCT-based studies have reported decreases of 15.6 and 14 μm in normal eyes^{23,28} and 12.7 μm in myopic eyes.²⁵ A histologic study of 85 human eyes found a thinning rate of 11 μm per decade.³⁷ The fact that choroidal thickness decays were comparable in normal and glaucoma subjects further supports the main finding of the present study, which is that choroidal thickness and glaucoma are not related.

Axial length was also a significant determinant of choroidal thickness in the present study; eyes with longer axial lengths had thinner choroids. Nemeth et al.¹⁰ and Guthoff et al.³⁸ reported similar findings in their studies after measuring the thickness of the "posterior ocular coat" (i.e., retina through sclera without measurement of the choroid separately) using ultrasonography. This technique measured the thickness from the retina to the sclera rather than the choroid alone. Esmaeelpour et al.³⁹ recently measured choroidal thickness in healthy persons using a 1060-nm superluminescent diode OCT device and found axial length to be the most important determinant of choroidal thickness. On the contrary, the association between axial length and choroidal thickness could not be demonstrated in two recent studies using high-penetration OCT in healthy Japanese subjects²⁸ and Cirrus HD-OCT (Zeiss) in Japanese subjects with high myopia,³⁰ even if a negative correlation was found in the former study.

Although subfoveal choroidal thicknesses did not correlate with IOP, multiple regression analysis revealed a negative association between the two only when age was excluded from the equation. Although our results did not agree with the lack of association reported by Cristini et al.,⁹ they are in agreement with other reports.^{10,12} IOP did not correlate (Pearson correlation) and was not associated (linear regression analyses) with any of the measurements in normal subjects; IOP correlated only with nasal choroidal thickness in subjects with glaucoma. We are unable to postulate the clinical correlate of this finding.

The results of the present study should be interpreted acknowledging some limitations. First, the sample size was relatively small, particularly for normal subjects. Despite the small sample size, the 95% confidence intervals suggest that any true differences are smaller than the pooled within-group standard deviation.

FIGURE 3. Graph of mean subfoveal, nasal, and temporal choroidal thickness in normal subjects and subjects with mild, moderate, and severe glaucoma. The choroid tended to be thicker in severe glaucoma, but the comparison between groups was not statistically significant.

tions. In other words, differences between groups, if they existed, were small compared with differences within groups. Second, the current operating software of Spectralis OCT does not provide automatic segmentation of the choroid. Manual segmentation might introduce some inaccuracy. However, every effort was made to be as accurate as possible, using methodologies identical to those of other studies of choroidal thickness measurements made with the Spectralis OCT.^{23,31} The excellent correlation between and within observers in the present study suggests that the measurements were, at least, extremely reproducible. It is our hope that software to automatically segment the choroid will be made available in the near future.

To conclude, choroidal thickness does not seem to differ between normal, NTG, and POAG subjects based on EDI OCT measurements, suggesting a lack of association not only between choroidal thickness and glaucoma but also with glaucoma severity. However, there is a significant relationship between choroidal thickness and age and axial length.

References

1. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol*. 2000;130:429–440.
2. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:714–720.
3. Cioffi GA, Wang L, Fortune B, et al. Chronic ischemia induces regional axonal damage in experimental primate optic neuropathy. *Arch Ophthalmol*. 2004;122:1517–1525.
4. Duijm HF, van den Berg TJ, Greve EL. Choroidal haemodynamics in glaucoma. *Br J Ophthalmol*. 1997;81:735–742.
5. Fuchsjäger-Mayrl G, Wally B, Georgopoulos M, et al. Ocular blood flow and systemic blood pressure in patients with primary open-angle glaucoma and ocular hypertension. *Invest Ophthalmol Vis Sci*. 2004;45:834–839.
6. Galassi F, Sodi A, Ucci F, Renieri G, Pieri B, Baccini M. Ocular hemodynamics and glaucoma prognosis: a color Doppler imaging study. *Arch Ophthalmol*. 2003;121:1711–1715.
7. Grunwald JE, Piltz J, Hariprasad SM, DuPont J. Optic nerve and choroidal circulation in glaucoma. *Invest Ophthalmol Vis Sci*. 1998;39:2329–2336.
8. Nicoletta MT, Hnik P, Drance SM. Scanning laser Doppler flowmeter study of retinal and optic disk blood flow in glaucomatous patients. *Am J Ophthalmol*. 1996;122:775–783.
9. Cristini G, Cennamo G, Daponte P. Choroidal thickness in primary glaucoma. *Ophthalmologica*. 1991;202:81–85.
10. Nemeth J. The posterior coats of the eye in glaucoma: an echobiometric study. *Graefes Arch Clin Exp Ophthalmol*. 1990;28:33–35.
11. Spraul CW, Lang GE, Lang GK, Grossniklaus HE. Morphometric changes of the choriocapillaris and the choroidal vasculature in eyes with advanced glaucomatous changes. *Vision Res*. 2002;42:923–932.
12. Tane S, Kohno J, eds. *The Microscopic Biometry of the Thickness of the Human Retina, Choroid and Sclera by Ultrasound*. Rome: Kugler & Ghedini; 1987.
13. Yin ZQ, Vaegan, Millar TJ, Beaumont P, Sarks S. Widespread choroidal insufficiency in primary open-angle glaucoma. *J Glaucoma*. 1997;6:23–32.
14. Nickla DL, Wildsoet C, Wallman J. The circadian rhythm in intraocular pressure and its relation to diurnal ocular growth changes in chicks. *Exp Eye Res*. 1998;66:183–193.
15. Nickla DL, Wildsoet CF, Troilo D. Diurnal rhythms in intraocular pressure, axial length, and choroidal thickness in a primate model of eye growth, the common marmoset. *Invest Ophthalmol Vis Sci*. 2002;43:2519–2528.
16. Papastergiou GI, Schmid GF, Riva CE, Mendel MJ, Stone RA, Laties AM. Ocular axial length and choroidal thickness in newly hatched chicks and one-year-old chickens fluctuate in a diurnal pattern that is influenced by visual experience and intraocular pressure changes. *Exp Eye Res*. 1998;66:195–205.
17. Schmid GF, Papastergiou GI, Nickla DL, et al. Validation of laser Doppler interferometric measurements in vivo of axial eye length and thickness of fundus layers in chicks. *Curr Eye Res*. 1996;15:691–696.
18. Schmid GF, Petrig BL, Riva CE, et al. Measurement by laser Doppler interferometry of intraocular distances in humans and chicks with a precision of better than 20 pm. *Appl Opt*. 1996;35:3358–3361.
19. Brown JS, Flitcroft DI, Ying GS, et al. In vivo human choroidal thickness measurements: evidence for diurnal fluctuations. *Invest Ophthalmol Vis Sci*. 2009;50:5–12.
20. Lee EC, de Boer JF, Mujat M, Lim H, Yun SH. In vivo optical frequency domain imaging of human retina and choroid. *Opt Express*. 2006;14:4403–4411.
21. Stanga PE, Bird AC. Optical coherence tomography (OCT): principles of operation, technology, indications in vitreoretinal imaging and interpretation of results. *Int Ophthalmol*. 2001;23:191–197.
22. Wang RK. Signal degradation by multiple scattering in optical coherence tomography of dense tissue: a Monte Carlo study towards optical clearing of biotissues. *Phys Med Biol*. 2002;47:2281–2299.
23. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. *Am J Ophthalmol*. 2009;147:811–815.
24. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2008;146:496–500.
25. Fujiwara T, Imamura Y, Margolis R, Slakter JS, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes. *Am J Ophthalmol*. 2009;148:445–450.
26. Spaide RF. Age-related choroidal atrophy. *Am J Ophthalmol*. 2009;147:801–810.
27. Hodapp E, Parrish RK II, Anderson DR. *Clinical Decisions in Glaucoma*. St. Louis: Mosby-Year Book. 1993.
28. Ikuno Y, Kawaguchi K, Nouchi T, Yasuno Y. Choroidal thickness in healthy Japanese subjects. *Invest Ophthalmol Vis Sci*. 2010;51:2173–2176.
29. Manjunath V, Taha M, Fujimoto JG, Duker JS. Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography. *Am J Ophthalmol*. 2010;150:325–329.
30. Ikuno Y, Tano Y. Retinal and choroidal biometry in highly myopic eyes with spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2009;50:3876–3880.
31. Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina*. 2009;29:1469–1473.
32. Maruko I, Iida T, Sugano Y, Ojima A, Ogasawara M, Spaide RF. Subfoveal choroidal thickness after treatment of central serous chorioretinopathy. *Ophthalmology*. 2010;117:1792–1799.
33. Drexler W, Morgner U, Ghanta RK, Kartner FX, Schuman JS, Fujimoto JG. Ultrahigh-resolution ophthalmic optical coherence tomography. *Nat Med*. 2001;7:502–507.
34. Cristini G, Meduri R, Garbini GC, Giovannini A. A new method for determining the blood quantity in the eye in a unit of time. *Graefes Arch Clin Exp Ophthalmol*. 1975;19:1–11.
35. Krebs W, Krebs I. *Primate Retina and Choroid: Atlas of Fine Structure in Man and Monkey*. New York: Springer-Verlag; 1991.
36. Wallman J, Wildsoet C, Xu A, et al. Moving the retina: choroidal modulation of refractive state. *Vision Res*. 1995;35:37–50.
37. Ramrattan RS, van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, de Jong PT. Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging. *Invest Ophthalmol Vis Sci*. 1994;35:2857–2864.
38. Guthoff R, Berger RW, Draeger J. Ultrasonographic measurement of the posterior coats of the eye and their relation to axial length. *Graefes Arch Clin Exp Ophthalmol*. 1987;25:374–376.
39. Esmaeelpour M, Povazay B, Hermann B, et al. Three-dimensional 1060nm OCT: choroidal thickness maps in normals and improved posterior segment visualization in cataract patients. *Invest Ophthalmol Vis Sci*. 2010;51:5260–5266.