Clinical and Epidemiologic Research

Subfoveal Choroidal Thickness in Relation to Sex and Axial Length in 93 Danish University Students

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Purpose. To investigate the association between subfoveal choroidal thickness and ocular axial length, refractive error, and blood pressure in healthy young women and men.

Methods. Cross-sectional observational study of 93 eyes in 93 healthy Danish university students (mean age 24.9 ± 2.6 years). The submacular choroid was imaged using enhanced-depth imaging spectral domain optical coherence tomography. Subfoveal choroidal thickness was measured by visual inspection and manual fitting of the choroidal borderlines. Study parameters included history, best corrected visual acuity, objective refraction, interferometric ocular axial length, fundus photography, and blood pressure manometry.

Results. The mean subfoveal choroidal thickness was 342 (±118) μm, the mean age was 24.9 (±2.6) years and the mean refractive error of participants was −1.43 (±2.9) diopters (D). In a multiple regression model, subfoveal choroidal thickness decreased by 58.2 μm (95% confidence interval [CI], 42.2–74.2 μm; $P < 0.001$) per mm increase in axial length adjusted for age and sex and subfoveal choroidal thickness was 62 μm (95% CI, 21–104 μm; $P = 0.0039$) thicker in men than in women, adjusted for age and axial length. Arterial blood pressure had no statistical effect on subfoveal choroidal thickness.

Conclusions. In this study of healthy young participants choroidal thickness was 18% higher in men than in women when adjusting for age and axial length. This observation may help explain the effect of sex in conditions related to choroidal thickness such as myopia, central serous chorioretinopathy, and age-related macular degeneration. (*Invest Ophthalmol Vis Sci.* 2011;52:8438–8441) DOI:10.1167/iovs.11-8108

Recent developments have improved choroidal imaging by optical coherence tomography.[1,2] The interindividual variation in choroidal thickness is considerable, the range being 80 to 641μm in a study of healthy Japanese subjects.[3] While the high density and perfusion of the choriocapillaris may compensate for the modest vascularization of the retina, little is known about the role of the choroidal layers behind the choriocapillaris, which appear to account for most of the variation in total choroidal thickness. Hyperopia is associated with a thick choroid and myopia with a thin choroid.[4,5] Central serous chorioretinopathy[6] is associated with a thicker than average choroid while age-related macular degeneration[7] is associated with a thin choroid. The thicker choroid reported in patients with central serous chorioretinopathy has been linked to hyperpermeability and increased hydrostatic pressure in the choroidal circulation[6] which may be a central part of the pathogenesis of the disease. Likewise, it has been suggested that a thin choroid due to increased axial length and age may be paramount for the degenerative changes observed in high myopia.[4] Sex is a risk factor in all the aforementioned conditions—central serous chorioretinopathy being more common in men than in women[8] and myopia and age-related macular degeneration being more common in women.[9–14] In the present study, we therefore examined choroidal thickness in relation to ocular axial length, refractive error, blood pressure, and sex in healthy young women and men using enhanced-depth image spectral domain optical coherence tomography.

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Methods

Participants

Healthy volunteers for this cross-sectional observational study were recruited by posting a call for participants on the internal website for medical students of the Faculty of Health Sciences of the University of Copenhagen. A total of 97 participants responded. All study participants were in self-reported good health. Exclusion criteria included previous eye trauma, previous ocular surgery, congenital malformations of the eye, amblyopia, and inability to cooperate during a screening optical coherence tomography (OCT) examination. Right eyes were included unless exclusion criteria applied to that eye or the participant preferred to have the left eye dilated ($n = 22$). In three participants neither eye could be included because of previous refractive surgery (LASIK, $n = 2$; clear lens extraction, $n = 1$). One participant was excluded because the examination was made in an amblyopic eye. All participants gave their written informed consent. The study was approved by the local medical ethics committee and performed in accordance with the Declaration of Helsinki.

Procedures

All participants were asked about their medical history, current medication, current and previous ophthalmic disease or disorder, and treatments. All procedures were performed in one session. Visual acuity was recorded using Snellen and Early Treatment Diabetic Retinopathy Study charts and with the participants' own prescription correction. Objective refraction was measured using an autorefractometer (AR-660A; Nidek, Gamagori, Japan) before and 20 minutes after ocular surface application of tropicamide 1% (Alcon Denmark, Rødovre, Denmark) and phenylephrine hydrochloride 10% (Ophtha A/S; Actavis Nordic A/S, Gentofte, Denmark). Arterial blood pressure was measured in the sitting position after at least 5 minutes of rest. Ocular axial length was measured using interferometry (IOL-Master, version 3.01.0294; Carl Zeiss Meditec, La Jolla, CA) and calculated as the average of at least three scans.

The choroid was visualized using enhanced-depth imaging spectral domain optical coherence tomography (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany). The instrument was positioned close to the eye to produce an inverted image of the retina and

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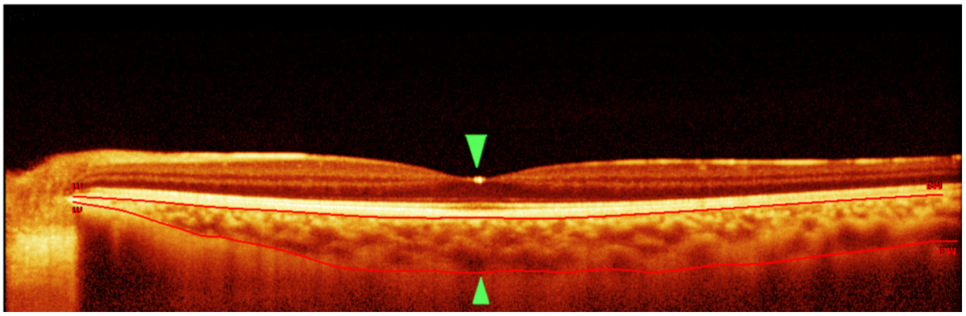

FIGURE 1. Heat spectrum color display of transfoveal enhanced-depth optical coherence tomogram from a healthy left eye with manually traced outlines of the choroid (*red lines*). Choroidal thickness reported in this study was measured at the center of the foveal depression (*green arrowheads*).

choroid. Eye tracking and automated real-time averaging features were used. Seven sections, each comprising 25 averaged raw scans were obtained within a 5 × 30-degree rectangle centered on the fovea. Choroidal thickness was measured subfovealy on the transfoveolar scan using the manufacturer's software (Heidelberg Eye Explorer version 1.6.1.0; Heidelberg Engineering), segmentation lines being moved manually to fit the outer border with the RPE/Bruch's membrane complex and the border with the sclera. Heat-spectrum color display was used to facilitate visual identification of the outer border (Fig. 1).

One unmasked grader (X.Q.L) measured the choroidal thickness in all participants. The layout of the segmentation lines marking the outer border of the choroid was saved in the built-in software of the OCT instrument and if needed discussed with I.C.M. who was masked to participants' refraction and axial length. Intergrader variability was tested between I.C.M. and X.Q.L. on 15 random participants. Mean difference (bias) was 5.33 μm; $P = 0.22$ (Student's *t*-test), with limits of agreement being −3.6 μm to 14.3 μm.

Statistical Analysis

Statistical analyses were made using commercially-available software (SAS version 9.1; SAS Institute, Cary, NC). Means and standard deviations were calculated for continuous variables and compared using two-tailed Student's *t*-tests. A general linear model (PROC GLM) was used to describe associations between choroidal thickness and axial length, refractive error, blood pressure, age, and sex. Linear regression models were tested for linearity, variance homogeneity, and normality of the distribution of residuals by visual inspection of relevant plots. Tests for interaction were performed by adding the cross product to the model. The level of statistical significance was set to $P < 0.05$, and estimates presented with 95% confidence intervals (CI). Spherical equivalent refraction was used for analysis and calculated as the algebraic sum of the value of the sphere and half the cylindrical value. The study was not designed to assess the effect of age but age was included in all analyses because previous studies have shown an effect of age on choroidal thickness.

RESULTS

Data analysis included 93 eyes from 93 participants (Table 1) of whom 33 were male (35%) and 60 were female (65%). The mean age was 24.9 ± 2.6 years (range, 19.6–33.4 years). All study eyes had a best-corrected visual acuity (BCVA) 0.8 or better and 88 eyes had BCVA 1.0 or better. Mean spherical equivalent refraction was −1.43 D (range, −11.25 D to 4.50 D; Fig. 2), women tending to be more myopic than men ($P = 0.26$; Table 1). Axial length for the entire study population had a mean value of 24.0 mm (range, 20.7 mm to 27.3 mm; Fig. 2) and fitted a normal distribution, women tending to have shorter eyes than men ($P = 0.16$; Table 1). The mean systolic blood pressure was higher in men than in women ($P = 0.0003$; Table 1) while the diastolic blood pressures were comparable (Table 1).

TABLE 1. Characteristics of the Study Population of 93 Healthy Danish Students

	Male	Female	*P*
n	33 (35)	60 (65)	
Age, y	25.4 (3.2)	24.6 (2.1)	0.15
Diastolic blood pressure, mm Hg	77.3 (10.3)	76.9 (10.5)	0.30
Systolic blood pressure, mm Hg	132 (13.6)	122 (10.9)	0.0003
Refractive error, D*	−0.98 (2.19)	−1.67 (3.07)	0.26
Axial length, mm	24.3 (1.15)	23.9 (1.29)	0.16
Choroidal thickness, μm	367 (102)	329 (125)	0.14

Data are presented as mean (SD) or *n* (%).
* Spherical equivalent refractive error.

None of the participants had a history of retinal or uveal disease and the posterior pole was unremarkable in all participants.

Mean subfoveal choroidal thickness was 342 μm ± 118 μm (range 73 μm to 691μm; Fig. 2). In a general linear regression model, subfoveal choroidal thickness decreased by 58.2 μm per mm axial length (95% CI, 42.2–74.2 μm per mm; $P < 0.0001$; $R^2 = 0.39$, adjusted for age and sex). In a similar analysis, subfoveal choroidal thickness was found to decrease by 25.4 μm/D myopia-shifted change in refraction (95% CI, 18.1–32.8 μm/D; $P < 0.0001$; $R^2 = 0.37$). The subfoveal choroid was 62.2 μm (95% CI, 20.5–104 μm) thicker in men than in women ($P = 0.0039$) when adjusting for age and axial length (Fig. 3).

There was no detectable effect of systolic or diastolic blood pressure on choroidal thickness and incorporation of blood pressures in the analyses did not change the results. No effect of age on choroidal thickness was observed in this limited age range study population.

Stepwise regression including both the axial length and the refraction in the same model was not performed in this study, because the variables are highly correlated and the association between choroidal thickness and axial length, adjusted for refraction, is not biologically relevant. The goodness of fit estimated by R^2 was slightly better when including axial length ($R^2 = 0.39$) than when including refraction ($R^2 = 0.37$) in the model.

There was no significant interaction between axial length and sex, between axial length and age, or between age and sex.

DISCUSSION

This study is the first, to the best of our knowledge, to report that for one and the same axial length the subfoveal choroid is thicker in men than in women. The 62-μm difference corresponds to 18% of the mean thickness of the choroid in our study population of 93 participants where choroidal thickness decreased by 58.2 μm per mm increase in axial length. Refraction and axial length were comparable in women and men.

The −58.2 μm/mm effect of axial length on subfoveal choroidal thickness was more than twice the −22.4 μm/mm found in a previous study of 43 participants spread over the

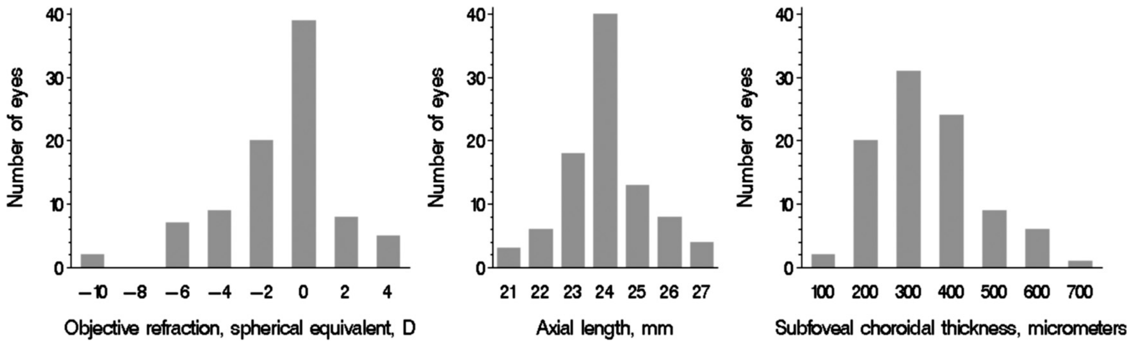

FIGURE 2. Distribution of objective cycloplegic refraction, axial length and subfoveal choroidal thickness in 93 healthy adults with a mean age of 24.9 ± 2.6 years.

wider age range of 23 to 88 years.[3] The subfoveal choroidal thickness of 342 ± 118 μm in the present study was comparable to the 354 ± 111 μm found in a previous study of the 43 healthy Japanese subjects[3] but higher than the 287 ± 76 μm found in a study of 34 healthy American subjects.[2] Mean axial lengths and refractive errors were comparable among the three studies, although ours differed by not excluding participants with myopia worse than −6 D.[2,3] Differences in age distribution may explain the differences in mean subfoveal thickness because choroidal thickness has been shown to decrease with age.[2–4]

Previous studies have reported sex-associated differences in axial length and intraocular pressure,[15] and morphometric optic disc parameters.[16] Sex-related differences in retinal thickness have also been reported using optical coherence tomography.[17–20] Reasons for the structural and physiological differences between men and women have been ascribed to the eyes being larger in men,[16] or to hormonal influence.[20]

In our study we found that men had a thicker choroid compared with women after adjusting for axial length and thus the sex-associated difference in choroidal thickness cannot be caused by men having larger eyes. Difference in hormonal exposure is a likely biological explanation. Indeed, identification of sex steroid receptor mRNAs in the choroid in the rat and in the rabbit as well as in the human retina and retinal pigment epithelium has been reported.[21] One study reported

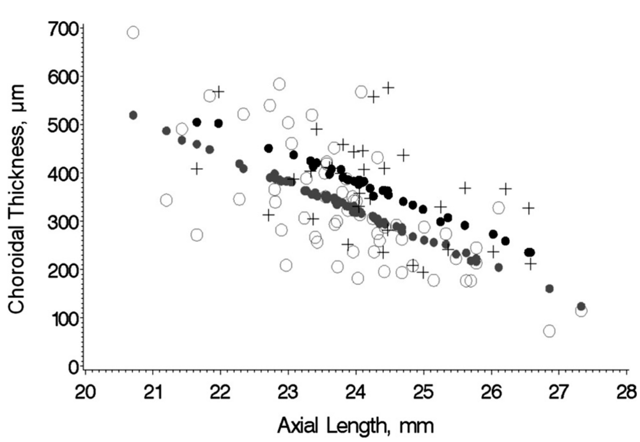

FIGURE 3. Choroidal thickness as a function of ocular axial length for women and men, adjusted for age. Raw data are shown as *circles* for women and *crosses* for men. A multiparametric analysis found that the subfoveal choroid was 62 μm (95% CI, 21–104 μm) thicker in men than in women ($P = 0.0039$) and that choroidal thickness decreased by 58.2 μm per mm increase in axial length (95% CI, −74.2 to −42.2 μm; $P < 0.0001$). *Filled markers* represent the age-adjusted predicted values for choroidal thickness in men (*black*) and in women (*gray*).

estrogen receptor subtype β mRNAs in human choroid[22] and it has been indicated that sex and hormonal status may influence choroidal blood flow.[23,24] Clear evidence of estrogen effects on the choroid however remains elusive.

This study confirmed that choroidal thickness decreases with increasing myopia and axial length. Studies in chicks and lower primates have shown that choroidal thickness changes after lid suturing or refractive defocusing,[25,26] findings that have been corroborated by a recent study in humans.[27] Consequently, the choroid must be considered as a potential accomodative organ in humans.

Near work affects the risk of myopia[28] and exposure to near work may be unbalanced between sexes. The occupational and educational homogeneity of our study population may explain why we have been first to demonstrate a sex effect on choroidal thickness.

Older studies of predominantly Western European populations have reported higher prevalences of myopia in women,[13,14] higher rates of progression of myopia in women, and higher prevalences of degenerative myopia in women than in men.[29] More recent population studies including the National Health and Nutrition Examination Survey (NHANES) and the Beaver Dam Study also reported higher prevalences of myopia and higher degrees of myopia in women[9,11] whereas another study reported a higher prevalence of high myopia in women but not of higher prevalence in women of lesser degrees of myopia.[30] Studies of myopia in twins have found that inclusion of sex gave the best fit when modeling the distribution of myopia.[31] Other studies in Japanese,[32] Chinese,[33] Iranian,[34] British,[35] and White and Black American[36] subjects found either no significant sex effect or women being slightly more hyperopic compared with men. The potential for a formal meta-analysis is limited by the degree to which essential descriptive factors such as age, educational background, and cumulative near-work have been documented in the studies.

In central serous chorioretinopathy the choroid has been found to be thicker than in healthy subjects[6] and choroidal thickness has been found to decrease after verteporfin photodynamic therapy.[37,38] Central serous chorioretinopathy occurs more frequently in men than in women,[8] an association that may hypothetically be explained, in the light of our study, by men having thicker choroids than women. In exudative age-related macular degeneration the choroid has been shown to be thinner than in normal controls,[7] suggesting that attenuation of the choroid may promote choroidal neovascularization. Again, our finding of a thinner choroid in women than in men fit the pattern of female sex being a risk factor for age-related macular degeneration.[12]

Blood pressure is of theoretical interest because previous studies have found an association between choroidal blood flow and systemic blood pressure and posture.[39,40] We found no effect of arterial blood pressure on choroidal thickness.

In conclusion, this study of subfoveal choroidal thickness in healthy young participants contributed the new finding that men had thicker choroids than women of comparable age and axial length and reproduced previously found associations between thinner choroids and longer axial lengths and more myopic refraction. The effect of choroidal thickness on the development of refraction and diseases of the posterior pole of the eye should be investigated in prospective studies.

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