Article

Two-Year Choroidal Thickness Attenuation and Its Associations in Healthy Chinese Adults

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Purpose: Identifying clinical associations causing attenuation in choroidal thickness (CT) among healthy Chinese adults.

Methods: A 2-year longitudinal study was conducted in volunteers aged over 30 years from China. All participants had no history of eye disease or surgery. All subjects underwent swept-source optical coherence tomography to measure the CT in the macular region at baseline and at 2-year follow-up. The regression models were based on the generalized estimating equation.

Results: A total of 603 eyes of 336 healthy participants were included in the final analysis (mean [SD] age, 58.88 [8.82] years; 74.70% female). Mean (SD) choroidal thickness (MCT) was reduced significantly from 206.62 (72.42) to 194.02 (72.08) μm (difference, −12.60 μm; 95% confidence interval [CI], −13.62 to −11.57). Among the Early Treatment of Diabetic Retinopathy Study (ETDRS) grid, CT at the subfoveal sector showed the greatest 2-year reduction (difference, −14.55 μm; 95% CI, −15.87 to −13.22). The largest 2-year change was observed in the 50 to 59 years group (difference, −14.51 μm; 95% CI, −16.71 to −12.32). Multivariate regression showed female gender ($\beta = -2.85$; 95% CI, −5.65 to −0.56) and baseline MCT ($\beta = -0.040$; 95% CI, −0.056 to −0.024) were significantly and independently associated with greater 2-year CT decrease.

Conclusions: These results indicated that CT among Chinese healthy adults decreased during the 2-year follow-up, and the greater choroidal thinning rate was significantly associated with female gender and larger baseline MCT.

Translational Relevance: Longitudinal CT data of healthy adults provide a reference range when evaluating pathologic variations, especially for the age-related retinal-choroidal disorders.

Introduction

The choroid is the only provider of nutrients and oxygen to the outer retina, receives about 90% of the ocular blood, and acts as the primary scavenger to clear the retina. Normal choroidal vasculature is vital for the retinal function.[1] As a result, choroidal thickness (CT) could reflect retinal function to some degree. Swept-source optical coherence tomography (SS-OCT) is a new generation of OCT that utilizes a tunable swept laser as its light source. This newer technique allows deeper penetration and clearer visualization of the ocular structures beyond the retinal pigment epithelium (RPE) with higher speed, longer wavelength light source, and no signal roll-off.[2,3] Compared with enhanced depth imaging spectral-domain OCT (EDI SD-OCT), a more advanced evolution of SD-OCT to allow deeper choroid visualization,[4] the advantages for utilizing SS-OCT for CT measuring were obvious. First, the clearer boundary of the choroid–scleral interface on SS-OCT could produce 100% interobserver agreement,[5] which makes measurements of CT more reliable. In addition, unlike EDI, which measures the CT at either a single point under the fovea or at several predetermined retinal positions, the high-speed swept laser of SS-OCT can scan a broad range of choroid simultaneously, without movement of the OCT focus.[6]

Cross-sectional studies proved that CT is associated with age, axial length (AL), and other biometric factors in healthy eyes.[7–9] In addition, CT differs across the posterior pole.[10] Although longitudinal studies on CT change have been conducted among children and adolescents, to our knowledge, there is not any study on longitudinal changes of CT among healthy adults aged 30 years and above. Therefore, it is important to get normative data on CT in adults to provide a reference range when evaluating pathologic variations, especially for the aging-related retinochoroidal disorders.

To fill the knowledge gap, we carried out the first longitudinal study on CT measurement of healthy adults using SS-OCT. In this study, we aimed to describe the cohort characteristics of CT and to evaluate the CT changes over 2 years in eyes of healthy adults. Furthermore, we sought to determine the independent influence of baseline characteristics for longitudinal changes of CT and to elucidate the most relevant factors.

Methods

Participants

The study was performed at the Zhongshan Ophthalmic Center (ZOC), affiliated to Sun Yat-sen University in Guangzhou, China. Healthy volunteers were recruited from the community health center near ZOC from March to December 2018. The study was conducted according to the tenets of the Declaration of Helsinki. All participants signed informed consent. The Ethics Committee of ZOC approved the study protocol.

The inclusion criteria were as follows: (1) adults aged 30 to 80 years; (2) no history or evidence of eye disorders and no previous invasive eye treatments, including any type of injection or surgery; and (3) no systemic diseases. The exclusion criteria included (1) AL $\geq$26.0 mm, (2) best-corrected visual acuity $\leq$20/20, (3) intraocular pressure $\geq$21 mm Hg, (4) any retinal or RPE abnormality detectable with fundus photograph or OCT, (5) severe cataract, or (6) low OCT image quality because of unstable fixation, abnormal refractive media, or other causes.

The subjects underwent the same examinations at baseline, 1-year, and 2-year follow-up using the same protocols, devices, and dark rooms. The time window was 1 month. Only subjects who went through all examinations were included in the final statistical analysis. Complete medical history was taken through a detailed questionnaire survey. Briefly, basic information, lifestyle factors, and medical history of all participants were included in the survey. An experienced nurse measured height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in compliance with standardized procedures. Body mass index (BMI) was calculated as the weight (kg)/height (m^2). Complete ocular examinations were performed for all participants by experienced ophthalmologists in ZOC. All examinations were carried out under nonmydriatic conditions. The detailed protocol is described in the Supplementary Material.

SS-OCT Acquisition

An experienced technician performed all OCT scans. It was confirmed before the scan that none of the patients had consumed analgesic medications or had alcohol or drinks with caffeine for at least 24 hours before the procedure. All subjects underwent sequential scans with a commercial SS-OCT imaging system Triton (DRI-OCT-2 Triton; Topcon Inc, Tokyo, Japan) to obtain high-definition retina and choroid images. This system had a tunable laser as the light source with a center wavelength of 1050 nm to produce a scanning speed of 100,000 A-scans per second. A transverse resolution of 20 μm and an axial resolution of 8 μm were achieved within the tissue. A three-dimensional raster scan (7.0 × 7.0 mm, 512 × 256) protocol was adopted, with a scan density of 512 A-scans × 512 B-scans centering on the macula. Image quality score (IQS) was generated automatically by the built-in software (IMAGEnet1.23). OCT images with an IQS of <50, with eye movement or artifacts, decentration images, and images with segmentation failure, were excluded.

The images were first analyzed by the built-in layer segmentation software. CT was measured from the chorio-scleral border to the outer portion of the hyperreflective line corresponding to the RPE layer. The macula was divided by the Early Treatment of Diabetic Retinopathy Study (ETDRS) into the inner ring (1 to 3 mm) and the outer ring (3 to 6 mm). The whole area was then separated into nine subfields: the outer superior, inner superior, outer temporal, inner temporal, foveal center, outer nasal, inner nasal, outer inferior, and inner inferior. CT in each of the nine subfields and the mean CT (MCT) of all nine grids were automatically calculated (Fig. 1). Two trained retinal specialists reviewed each line of both RPE and the chorio-scleral border in all images of the three-dimensional data set to verify or manually adjust to the correct segmentation to acquire controlled calculations.
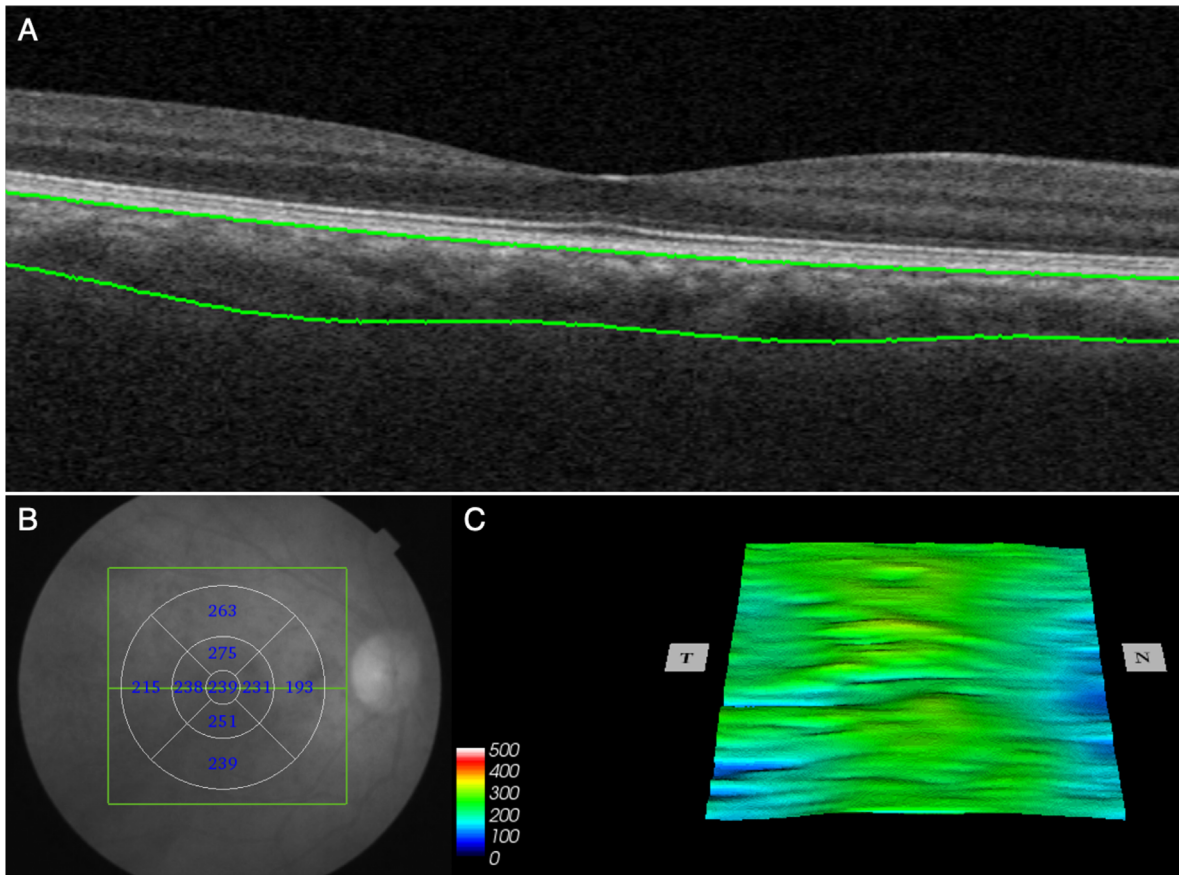
Figure 1. Illustration of CT measurements in EDTRS nine sectors by SS-OCT. The segmentation lines in A refer to as the choroidal layer. The individual grids are referred to as the foveal center, outer superior, inner superior, outer temporal, inner temporal, inner nasal, outer nasal, inner inferior, and outer inferior. N, nasal; T, temporal.

Statistical Analysis

The Kolmogorov–Smirnov test was applied to verify the normal distribution. Normally distributed data were presented as mean ± SD. Nonnormal distribution was reported as median ± interquartile range. The paired *t*-test was adopted to compare CT at baseline and that at 2-year follow-up. The 95% confidence interval (CI) in the various factors among the entire cohort as well as subgroups was calculated. Regarding the multiple comparison, post hoc testing using the Bonferroni correction was applied to reveal if the 2-year differences were statistically significant in each of the sectors on the standard ETDRS grid. $P < 0.005$ was considered statistically significant. Age, baseline MCT, and AL were subgrouped accordingly to present the distribution of CT change. Taking into account the correlations between the two eyes in a single person, univariate and multivariate regression analyses were performed based on the generalized estimating equation.[11] The association of demographic, systemic, and ocular parameters with the attenuation of MCT or subfoveal choroidal thickness (SFCT) over 2 years was

then calculated. Specifically, the "attenuation" was the arithmetic difference between the CT value measured at 2 years and at baseline. This difference was used as the dependent variable in the regression models. We dropped waist-to-hip ratio, SBP, and spherical equivalent considering their collinearity with BMI, DBP, and AL, respectively. Parameters with $P < 0.10$ in the univariable regressions were entered into the subsequent multiple regression analysis, adjusting for age, and performed on MCT and SFCT separately. The data were analyzed by a commercial analytical software program (Stata Version 16.0; StataCorp, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

Baseline Demographic Characteristics

Participants who met the inclusion criteria and enrolled in the 2-year follow-up visits with available
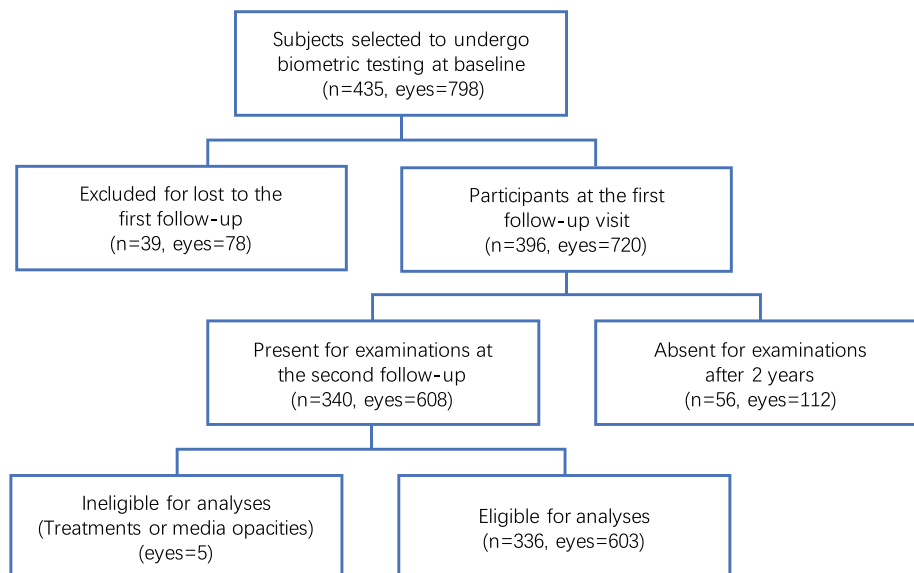
Figure 2. The schematic workflow. Eligible participants from two annual visits with a 2-year interval.

SS-OCT data were included in the analysis. Figure 2 shows the schematic workflow of including and excluding subjects. Briefly, 798 eyes of 435 healthy volunteers were recruited at the baseline examination. At the first and second follow-up visits, there were 39 and 56 participants without OCT images or lost to follow-up. Among the remaining 340 participants, at the 2-year follow-up visit, five eyes were excluded due to poor quality of choroid image on SS-OCT. A total of 603 eyes of 336 healthy participants were enrolled in the final analysis. The baseline demographics and clinical characteristics are shown in Table 1. The average age was 58.88 ± 8.82 years (range, 32–76), and 74.70% of the participants were female. Mean AL was 23.49 ± 0.88 mm.

Distribution and Longitudinal Change of CT among the ETDRS Grid

At the 2-year follow-up, there was a significant decrease in MCT (difference, −12.60 µm; 95% CI, −13.62 to −11.57, $P < 0.001$, Supplementary Fig. S1A). Post hoc testing using the Bonferroni correction showed that the 2-year differences were statistically significant in each of the sectors on the standard ETDRS grid. At baseline, the inner superior sector was the thickest with a CT of 231.00 ± 81.02 µm, followed by the foveal center (230.10 ± 86.96 µm), and the outer nasal sector was the thinnest (174.80 ± 82.75 µm) ($P < 0.001$). Significant attenuation of CT in the nine

Table 1. Baseline Characteristics of Study Participants

Characteristic	Value
No. of subjects	603
Age, y	58.88 ± 8.82
Female	251 (74.70%)
BMI, kg/m^2	23.13 ± 3.00
WHR	0.87 ± 0.06
SBP, mm Hg	125.85 ± 17.41
DBP, mm Hg	68.48 ± 9.55
SE, diopters	0.34 ± 1.97
IOP, mm Hg	16.07 ± 2.35
CCT, µm	541.73 ± 31.10
ACD, mm	2.48 ± 0.33
LT, mm	4.54 ± 0.33
AL, mm	23.49 ± 0.88

Data are expressed as mean ± SD or %.
ACD, anterior chamber depth; CCT, central corneal thickness; IOP, intraocular pressure; LT, lens thickness; SE, spherical equivalent; WHR, waist-to-hip ratio.

macular sectors of the ETDRS grid was found over the 2-year follow-up (Table 2). CT reduction across the nine sectors varied, with the most significant reduction found at the central fovea (mean 2-year difference: −14.55 µm; 95% CI, −15.87 to −13.22, $P < 0.001$), and the least found at the outer nasal sector (mean 2-year difference: −9.98 µm; 95% CI, −11.10 to −8.85, $P < 0.001$).

Table 2. Two-Year Change of Mean Choroidal Thickness on the Standard ETDRS Grid

Characteristic (µm)	Baseline (Mean ± SD)	2-Year (Mean ± SD)	Mean 2-Year Difference (95% CI)[a]
MCT	206.62 ± 72.42	194.02 ± 71.08	−12.60 (−13.62 to −11.57)[b]
Outer superior	226.30 ± 75.37	212.07 ± 74.40	−14.23 (−15.68 to −12.78)[b]
Inner superior	231.00 ± 81.02	217.41 ± 79.47	−13.59 (−15.14 to −12.04)[b]
Outer temporal	205.59 ± 69.53	192.55 ± 67.03	−13.04 (−14.24 to −11.84)[b]
Inner temporal	223.90 ± 78.48	209.82 ± 76.83	−14.08 (−15.38 to −12.78)[b]
Foveal center	230.31 ± 86.96	215.77 ± 85.24	−14.55 (−15.87 to −13.22)[b]
Inner nasal	217.87 ± 89.01	204.56 ± 87.41	−13.31 (−13.58 to −12.05)[b]
Outer nasal	174.80 ± 82.75	164.82 ± 81.73	−9.98 (−11.10 to −8.85)[b]
Inner inferior	217.17 ± 87.79	203.67 ± 86.30	−13.49 (−15.02 to −11.97)[b]
Outer inferior	197.46 ± 81.71	185.82 ± 79.88	−11.64 (−12.92 to −10.36)[b]

Regarding the multiple comparison, post hoc testing using the Bonferroni correction was applied. $P < 0.005$ was considered statistically significant.

[a] Paired *t*-test.
[b] $P < 0.001$.

The Association of Longitudinal MCT Changes with Age, Sex, Baseline MCT, and AL

The largest 2-year change was observed in the 50 to 59 years group (difference, −14.51 µm; 95% CI, −16.71 to −12.32) and progressively became less evident in the 60 to 69 and 70 to 79 groups (Table 3, Fig. 3). As for the gender, the change in MCT was greater in the female group (difference, −13.36 µm; 95% CI, −14.53 to −12.19). Moreover, the result showed that the greater the baseline MCT was, the greater the reduction in CT would be. The largest reduction was −15.40 µm, with the 95% CI ranging from −17.63 to −13.17. For baseline AL, the largest mean 2-year difference in MCT was observed in the third quantile subgroup (difference: −14.70 µm; 95% CI, −16.78 to −12.62). Similar results were found for SFCT (Supplementary Table S1, Supplementary Figs. S1B, S2).

Table 3. Stratified 2-Year Changes of MCT (µm) Measured by SS-OCT

| Characteristic	n	Baseline Measurement, Mean (SD) (µm)	Mean 2-Year Difference (95% CI) (µm)
Age group (y)			
30–49	107	237.09 (74.51)	−12.45 (−14.89 to −10.00)[a]
50–59	155	223.91 (66.17)	−14.51 (−16.71 to −12.32)[a]
60–69	293	195.17 (65.61)	−11.99 (−13.41 to −10.57)[a]
≥70	48	152.76 (81.82)	−10.45 (−13.81 to −7.08)[a]
Sex			
Male	158	213.07 (75.87)	−10.45 (−12.53 to −8.37)[a]
Female	445	204.33 (71.11)	−13.36 (−14.53 to −12.19)[a]
MCT at baseline (µm)			
First quantile	151	115.71 (25.78)	−8.59 (−9.87 to −7.30)[a]
Second quantile	151	179.46 (17.41)	−11.99 (−14.09 to −9.89)[a]
Third quantile	151	229.65 (13.80)	−14.43 (−16.72 to −12.13)[a]
Fourth quantile	150	302.30 (33.89)	−15.40 (−17.63 to −13.17)[a]
AL group (mm)			
First quantile	152	225.49 (72.65)	−12.26 (−14.27 to −10.26)[a]
Second quantile	153	209.58 (69.27)	−13.31 (−15.53 to −11.09)[a]
Third quantile	151	205.13 (71.14)	−14.70 (−16.78 to −12.62)[a]
Fourth quantile	147	185.55 (73.69)	−10.04 (−11.88 to −8.20)[a]

[a] $P < 0.001$.
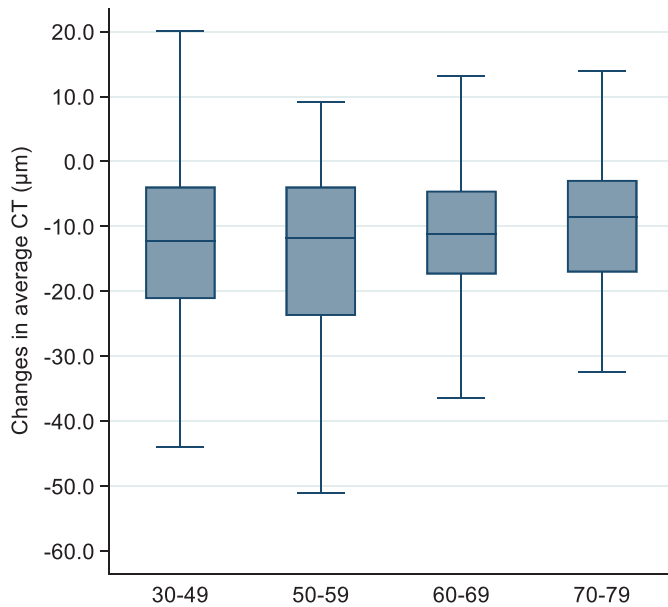
Figure 3. Two-year change in average CT (μm) across age groups with 10-year age intervals. The *shaded boxes* indicate the interquartile range, the *horizontal line* within the boxes indicates the median, and the *limit lines* indicate 95% CI.

Factors Associated with Longitudinal Changes in MCT and SFCT

Separate regression models were created for mean and subfoveal CT to determine which parameter showed the strongest association with CT change. Multiple regression analysis showed that female gender was associated with more decline in CT ($\beta = -2.85$, for being female versus male; 95% CI, -5.65 to -0.56; $P = 0.046$), and higher MCT at baseline was associated with the faster decline in MCT ($\beta = -0.040$, for each micron increase in baseline MCT; 95% CI, -0.056 to -0.024; $P < 0.001$) after adjusting for confounding factors. Similar results were found for SFCT: female gender was associated with more decline ($\beta = -4.05$, for being female versus male; 95% CI, -7.43 to -0.66; $P = 0.020$), and higher MCT at baseline was associated with the faster decline in SFCT ($\beta = -0.041$, for each micron increase in baseline MCT; 95% CI, -0.060 to -0.021; $P < 0.001$). Table 4 and Supplementary Table S2 show the results of adjusted simple and multiple regression analysis on MCT and SFCT with different variables, respectively.

Discussion

To our knowledge, this is the first 2-year longitudinal study on CT change in normal Chinese adults using SS-OCT. The study results showed that CT decreased in all sections of the ETDRS grid after 2-year observation, with the central foveal choroid decreasing the most and the outer nasal decreasing the least. Adjusted multivariate regression showed that female gender and higher baseline MCT were significant associations for faster CT attenuation.

Cross-sectional studies have proved that the thinning of the choroid is related to aging. However, the reported annual CT decrease differed greatly. To be specific, regression analysis by Margolis and Spaide[12] and Ikuno et al.[13] revealed a 15.6-μm and 14-μm SFCT decrease for each decade of life, respectively. The Beijing Eye Study demonstrated a 4.1-μm decrease in SFCT for each 1-year increase in age.[8] The Singapore Malay Eye Study 2 reported a 4.139-μm decrease in SFCT for each 1-year increase in age after adjusting for other factors.[14] The Montrachet Study showed that older age is independently associated with thinner SFCT.[15] The KLoSHA Eye study showed that

Table 4. Association Between Subject Characteristics and 2-Year Change of MCT (μm)

Characteristic	Univariate Adjusted Coefficient (95% CI)	*P*	Multivariate Adjusted Coefficient (95% CI)	*P*
Age (per 1 year)	0.068 (-0.070 to 0.21)	0.34	—	—
Female sex	-2.42 (-5.20 to 0.36)	0.089	-2.85 (-5.65 to -0.56)	**0.046**
BMI (per 1 kg/m^2)	0.19 (-0.21 to 0.60)	0.35	—	—
DBP (per 1 mm Hg)	-0.10 (-0.23 to 0.025)	0.11	-0.11 (-0.24 to 0.013)	0.079
IOP (per 1 mm Hg)	0.0017 (-0.49 to 0.49)	0.99	—	—
CCT (per 1 μm)	0.010 (-0.029 to 0.049)	0.61	—	—
ACD (per 1 mm)	1.18 (-2.47 to 4.82)	0.53	—	—
LT (per 1 mm)	1.28 (-2.36 to 4.91)	0.49	—	—
AL (per 1 mm)	1.16 (-0.18 to 2.50)	0.089	0.13 (-1.24 to 1.50)	0.86
Baseline MCT (per 1 μm)	-0.040 (-0.055 to -0.024)	<0.001	-0.040 (-0.056 to -0.024)	**<0.001**

P values are based on the generalized estimating equation. Bold indicates statistical significance.

SFCT and MCT decreased by 27.7 µm or 6.02 µm for each decade of life, respectively.[16] Moreover, cross-sectional studies might underestimate the changes in CT with aging in general. In the current longitudinal study, MCT and SFCT decreased by 12.60 µm and 14.55 µm for every 2-year increase in age, respectively. The inconsistency among the studies may be attributable to different baseline characteristics, such as age variation, different OCT instruments,[17] and the limitations of SD-OCT technology. The choroid has been reported to lose submacular vascularity with age, especially the arterioles.[18] Ruiz-Medrano et al.[19] and Zhao et al.[20] described that age-related CT decrease was mostly at the expense of Haller's layer, including large vascellum. Thus, the capacity of the choroid to remove metabolic wastes from the outer retina is declining.[21–23]

For topographic variations in CT, similar results as reported by previous studies were observed. Shin et al.[10] reported that the outer nasal macula area was the thinnest among the ETDRS grids. Touhami et al.[24] also demonstrated that the thinnest point was the nasal outer macula since the CT pattern was correlated with choroidal vein distribution. In the current study, the thinnest point was at the outer nasal sector (174.80 ± 82.75 µm). The thinner nasal choroid thickness could be ascribed to the choroidal watershed zones[25] and its closeness to the optic nerve head. Hence, this could be related to glaucoma or have contributed to peripapillary atrophy.[4] The results of the current study also demonstrated that the thickest point was at the fovea (230.31 ± 86.96 µm) and the inner superior sector (231.00 ± 81.02 µm). This could also relate to where the choroidal vein density was the highest.[24] In addition, the current study suggested that the decrease at the nine sectors differed after 2-year observation. Among all sectors, the foveal center decreased the fastest (mean 2-year difference: −14.55 µm; 95% CI, −15.87 to −13.22), and the outer nasal sector decreased the slowest (mean 2-year difference: −9.98 µm; 95% CI, −11.10 to −8.85). This could be attributed to the high metabolic demand of the choroid for the nutrient supply at the central fovea, which requires rapid and dense filling of the choriocapillaries and choroidal arteries,[26] resulting in the fastest consumption of the foveal choroid.

Some previous studies reported that females had thinner choroid and smaller choroidal volume than males.[27,28] Interestingly, the current longitudinal study suggested that choroidal thinning speed was significantly associated with gender. To be specific, CT had a greater decrease in female participants after 2-year observation. The previous study demonstrated the influence of gender on choroidal blood flow, indicating the role of estrogens.[28] In addition, a study reported that estrogen receptor subtype β was localized in human choroid.[29] Furthermore, some important human eye pathologies were found to be related to gender, such as myopic retinopathy. The Hisayama Study reported female gender as a significant risk factor for myopic retinopathy (odds ratio, 3.29; 95% CI, 1.09–9.92).[30] Vongphanit et al.[31] documented a higher prevalence of myopic retinopathy in females in an older Australian population. With a thinner choroid and faster thinning speed, women's eyes may be more susceptible to specific pathologic conditions and faster disease progressions.

A large number of previous cross-sectional studies have found a correlation between CT and AL. The Beijing Eye Study[8] on 3468 individuals showed that subfoveal CT decreased by 32 µm for every 1-mm increase in AL. The Singapore Malay Eye Study 2 demonstrated that longer AL was significantly associated with thinner choroid and smaller choroidal volume. After subgrouping the AL into four quantiles, the current study revealed that the longer the AL was, the thinner the CT would be. However, cross-sectional results cannot illuminate the effect of AL on the longitudinal changes of CT. The current longitudinal observation study among adults suggested that the 2-year attenuation rate of CT was not associated with AL. Baseline MCT was found to be negatively correlated to CT reduction. With the decrease of baseline MCT, the ability of the choroid to supply sufficient metabolites to the RPE and outer retina may also decrease.

The present study has the merit of being the first longitudinal study on choroidal thinning in large-scale Chinese adults that followed standardized examination protocols. However, there are some limitations to the current study. First, all participants in the current study were Chinese healthy subjects. Ethnic variations in CT have been reported in previous studies.[32,33] Hence, the variations in the rate of CT thinning in different races should be further verified. Second, the thickness of the choroid varies greatly with the degree of blood vessel filling, which could be affected by the cardiovascular status. Some studies found a diurnal fluctuation of CT. In 12 healthy subjects with a mean age of 30 years (range, 21–37 years), Tan et al.[34] observed that MCT was the thickest at 9:00 AM and decreased to the thinnest at 5:00 PM. Mansouri et al.[9] proved in 56 eyes of 28 healthy volunteers that the water drinking test could increase CT and choroidal volume, which mimicked peak diurnal intraocular pressure. These could lead to the measuring error from different time points and need to be further controlled in our future study. Third, the follow-up duration in the current study was only 2 years, which was relatively short. To

explore the long-term effect, a prospective cohort with a longer follow-up period is in progress.

In conclusion, in the current 2-year longitudinal study, the decrease in CT measured by SS-OCT was observed in Chinese healthy adults for the first time. Adjusted multivariate regression revealed female gender and larger baseline MCT to be independently correlated with faster CT attenuation. A larger-scale, longer-term, and cross-race verification is necessary to further validate the above findings.

Acknowledgments

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