

Macular Thickness Variations with Sex, Age, and Axial Length in Healthy Subjects: A Spectral Domain–Optical Coherence Tomography Study

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PURPOSE. To assess the relationship between macular retinal thickness and volume and age, sex, and refractive error/axial length with spectral domain–optical coherence tomography (SD-OCT).

METHODS. One randomly selected eye of 198 consecutive ophthalmically normal subjects (104 men, 94 women) between July 2008 and January 2009, with corrected visual acuities better than 20/30 were included in this cross-sectional study. Complete ophthalmic examination, axial length measurement with a laser interferometer, and macular cube 512 × 128 scan by SD-OCT were performed.

RESULTS. The mean age was 55.6 ± 16.4 years (range, 17–83), average refractive error was -2.17 ± 4.82 (range, -23.50 – 3.75), and average axial length was 24.73 ± 1.98 mm (range, 21.52–32.51). The central subfield thickness, average inner macular thickness, and overall macular volume were significantly lower in the female subjects (partial correlation: $P = 0.009$, $P = 0.027$, and $P = 0.042$, respectively). As age increased, average inner macular thickness, average outer macular thickness, overall average macular thickness, and macular volume decreased significantly (partial correlation: $P = 0.002$, $P = 0.002$, $P = 0.002$, and $P = 0.000$, respectively). Refractive error had no significant influence in partial correlation analysis. Axial length correlated negatively with average outer macular thickness, overall average macular thickness, and macular volume (partial correlation: $P = 0.006$, $P = 0.044$, and $P = 0.003$, respectively).

CONCLUSIONS. In normal subjects, SD-OCT showed that retinal thickness is related to age, sex, and axial length, with regional variations. (*Invest Ophthalmol Vis Sci.* 2010;51:3913–3918) DOI:10.1167/iovs.09-4189

Assessment of macular thickness is important for the treatment and follow-up of a variety of ocular diseases. The introduction of optical coherence tomography (OCT) has enabled clinicians to reliably detect small changes in macular thickness and to quantitatively evaluate the efficacy of different therapeutic modalities. Several studies on the variations of

macular thickness measurements in normal subjects according to age and refractive error/axial length have been reported. Some studies^{1–3} have shown reductions in macular thickness with age, whereas others^{4–8} have found no significant correlation. In studies in which the first-generation OCT (OCT 1),⁹ second-generation Humphrey OCT 2000 (all commercial equipment mentioned in the article are manufactured by Carl Zeiss Meditec, Dublin, CA, unless otherwise noted),^{7,10} and retinal thickness analyzer (RTA) were used,^{4–6} the correlation between average macular thickness and myopia was found to be insignificant. More recent studies in which the third-generation Stratus OCT was used have shown average macular thickness¹¹ and macular volume¹² to be related to refractive error/axial length in normal subjects, as in histopathologic studies.^{13,14}

The disparity between these studies may stem from the relatively poor scanning resolution and small sampling density of the measuring devices used in the earlier studies. Both OCT 1 and Humphrey OCT 2000 allow 100 A-scans in a linear scan with axial resolution of 12 to 15 μm , and only two to four linear scans over the macular region were captured in previous studies.^{9,10} Even the Stratus OCT acquires images at a rate of only 400 A-scans per second, with an axial resolution of 10 μm . Recently, a new class of OCT instruments employing spectral (Fourier) domain technology has been developed. Cirrus HD-OCT is one such instrument, with a higher scan rate of 27,000 A-scans per second, with an improved axial resolution of 5 μm . The spectral domain OCT (SD-OCT) system provides more accurate measurements, with decreased artifacts¹⁵ and better repeatability.¹⁶ Both the Stratus OCT and the Cirrus HD-OCT systems employ intrinsic software algorithms to calculate retinal thicknesses averaged across standardized subfields in the macula. However, the Stratus OCT employs fewer A-scans that are heavily weighted toward the center, whereas the Cirrus HD-OCT employs significantly more A-scans that are evenly distributed over the scanned area. Furthermore, the Cirrus HD-OCT's fundus images help evaluate the scan quality and allow the centering of the measurement at the fovea, enabling more accurate retinal thickness measurements.¹⁷ In this study, we re-examined the relationships between macular retinal subfield thicknesses and age, sex, and refractive error/axial length using the more accurate SD-OCT scanning.

METHODS

Subjects

One randomly selected eye of consecutive ophthalmically normal subjects who visited the ophthalmology clinic of Gangnam Severance Hospital between July 2008 and January 2009 and met the eligibility criteria was included. Autorefracted corrected Snellen visual acuities (ACVA) better than 20/30 and no ophthalmic disease except mild cataract were included. All subjects underwent a full ophthalmic examination including ACVA, autorefraction (RK-3 autorefractor keratometer; Canon, Tokyo, Japan), intraocular pressure measurement

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with Goldmann applanation tonometry, slit lamp examination, indirect ophthalmoscopy, and axial length measurement (IOL Master). Patients who had undergone an uneventful cataract or refractive surgery (PRK, LASEK, LASIK, or phakic intraocular lens implantation) more than 6 months ago were included. In these patients, the original refractive error before surgery was recorded by reviewing the clinical records. Subjects with a history of ocular trauma; ocular surgery other than the uneventful cataract surgery or refractive surgery; evidence of pseudoexfoliation, uveitis, pigment dispersion syndrome, or corneal opacity; media opacity other than the mild cataract; intraocular pressure greater than 21 mm Hg; gonioscopic findings of angle closure; abnormal visual fields; and retinal disease, diabetes, or neurologic diseases were excluded. Eyes with any abnormal findings in SD-OCT, SD-OCT with signal strength <6, evidence of myopic degeneration involving any of the nine subfields, or de-centered images were also excluded. This study was conducted in accordance with the principles of the Declaration of Helsinki and performed with the approval of the institutional review board of Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea. Informed consent was obtained from each subject before enrollment.

Spectral Domain-Optical Coherence Tomography

SD-OCT was performed with the Cirrus HD-OCT system (software ver. 3.0) and macular cube 512 × 128 protocol. All scans were performed by two experienced ophthalmologists. The scans were taken three times to obtain scans with the highest signal intensity, no centration errors, and minimal segmentation errors. The proprietary Cirrus segmentation algorithm was used to produce retinal thickness maps, which were then averaged over nine retinal subfields in a 6-mm-

diameter circle centered at the true fovea location, as defined by the Age-Related Eye Disease Study.¹⁸ The standard retinal subfields are central, inner superior, inner nasal, inner inferior, inner temporal, outer superior, outer nasal, outer inferior, and outer temporal (Fig. 1). The inner subfields are bounded by the 3-mm-diameter circle. The central subfield is bounded by the innermost 1-mm-diameter circle. Two different readers analyzed all OCT scans and were each blinded to the other's analyses. Centration error was recorded when the central foveal subfield did not correspond to the true center based on both the topographic map and OCT B-scan data, and these eyes were excluded. Each of the 128 B-scans were scrutinized in each case and checked for the segmentation boundaries displayed. Retinal thickness parameters after manual correction were used for statistical analysis in 12 patients with minimal segmentation errors. The average of the four-quadrant macular thicknesses in the inner (1–3 mm) and outer (3–6 mm) rings were used for analyses. Overall average macular thickness and overall macular volume over the entire grid area were also obtained from the computational software output.

Statistical Analysis

The distribution of the study population with respect to age, sex, refractive error, and axial length were compared by Pearson correlation analysis and independent-samples *t*-test. Associations between macular measurements and age, sex, and refractive error/axial length were examined by partial correlation analysis. The results were considered to be statistically significant at *P* < 0.05. All analyses were performed using SPSS statistical software program (SPSS 11.0; SPSS Inc., Chicago, IL).

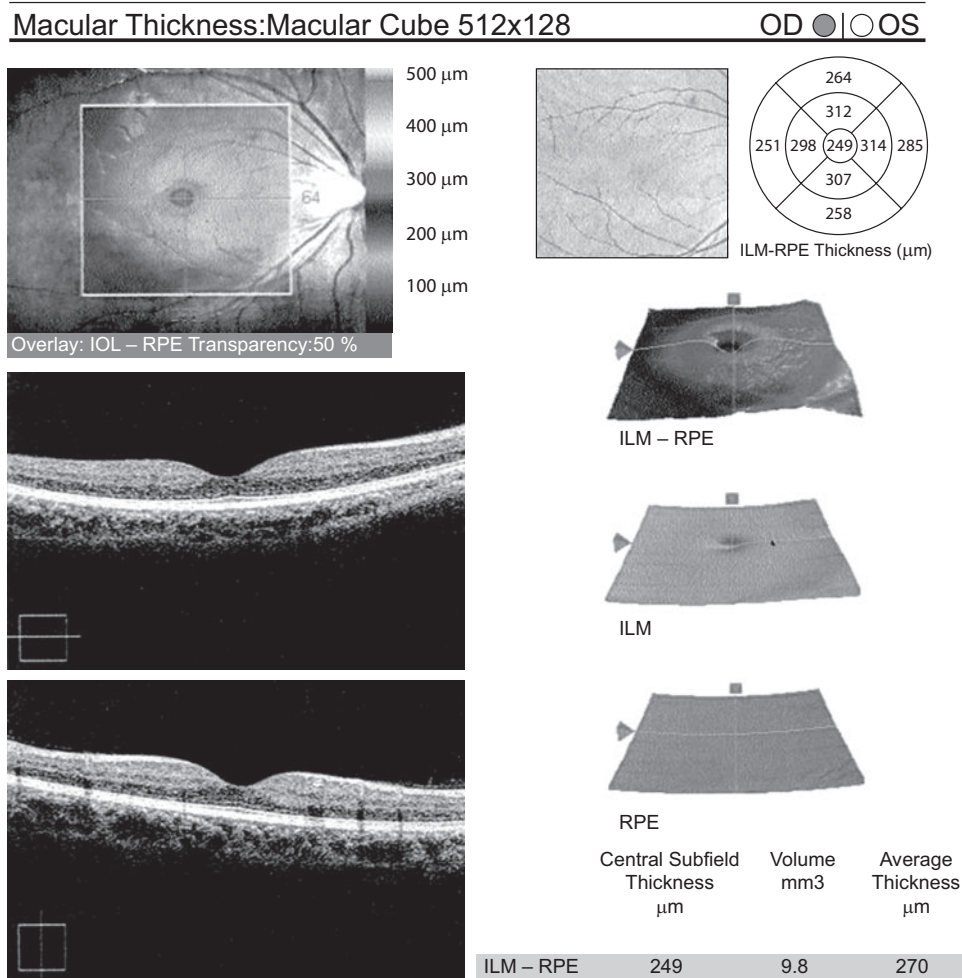


FIGURE 1. Macular cube 512 × 128 scan; *top left*: fundus image with scan cube overlay; *top right*: macular thickness map topology. The central innermost 1-mm-diameter circle represents the central subfield; inner superior, inner nasal, inner inferior, and inner temporal areas bounded by the 3-mm-diameter circle form the inner macula; outer superior, outer nasal, outer inferior, and outer temporal areas bounded by the 6-mm-diameter circle form the outer macula. *Middle and bottom left*: slice through cube front and cube side. *Middle right*: 3-D surface maps. *Bottom right*: central subfield thickness, overall average macular thickness, and overall macular volume over the entire grid area are displayed.

TABLE 1. Baseline Characteristics

	Overall*	Male*	Female*	P
Subjects, <i>n</i> eyes	198	104	94	
Age, y	55.6 ± 16.4	53.8 ± 15.2	57.5 ± 17.5	0.106†
Axial length, mm	24.73 ± 1.98	24.95 ± 1.94	24.49 ± 2.01	0.102†
Refractive error, D	-2.17 ± 4.82	-1.99 ± 4.08	-2.39 ± 5.58	0.584†
Central subfield thickness, μm	253.92 ± 24.18	259.37 ± 23.08	247.90 ± 24.05	0.009‡ (-0.196)§
Superior inner macular thickness, μm	317.45 ± 19.8	320.68 ± 18.15	313.88 ± 21	0.040‡ (-0.154)§
Nasal inner macular thickness, μm	320.24 ± 18.63	323.51 ± 18.43	316.62 ± 18.27	0.064‡ (-0.139)§
Inferior inner macular thickness, μm	311.66 ± 20.15	314.95 ± 19.6	308.01 ± 20.21	0.104‡ (-0.122)§
Temporal inner macular thickness, μm	304.17 ± 25.58	309.45 ± 16.95	298.32 ± 31.65	0.015‡ (-0.183)§
Average inner macular thickness, μm	313.38 ± 19.22	317.15 ± 17.44	309.21 ± 20.30	0.027‡ (-0.166)§
Superior outer macular thickness, μm	274.77 ± 14.98	274.34 ± 15.67	275.26 ± 14.25	0.911‡ (0.008)§
Nasal outer macular thickness, μm	291.86 ± 17.88	293.28 ± 17.33	290.3 ± 18.43	0.4‡ (-0.064)§
Inferior outer macular thickness, μm	264.43 ± 15.86	266.72 ± 14.89	261.9 ± 16.59	0.022‡ (-0.172)§
Temporal outer macular thickness, μm	257.86 ± 20.27	261.62 ± 16.03	253.7 ± 23.5	0.006‡ (-0.207)§
Average outer macular thickness, μm	272.23 ± 14.6	273.99 ± 13.98	270.29 ± 15.08	0.072‡ (-0.135)§
Overall average thickness, μm	275.66 ± 14.12	277.41 ± 13.60	273.72 ± 14.51	0.129‡ (-0.114)§
Overall macular volume, mm ³	9.74 ± 0.71	9.84 ± 0.62	9.64 ± 0.78	0.042‡ (-0.153)§

* Mean ± SD.

† Independent samples *t*-test between males and females.

‡ Partial correlation analysis adjusted by age, axial length, and refractive error.

§ Partial correlation coefficients.

RESULTS

A total of 198 eyes of 198 subjects (104 males and 94 females) were enrolled. The mean ACVA of study participants was 0.96 ± 0.08 (range, 20/30–20/20) and the mean age was 55.6 ± 16.4 years (range, 17–83). The average refractive error in spherical equivalents (SE) was -2.17 ± 4.82 D (range, -23.50–3.75) and the axial length was 24.73 ± 1.98 mm (range, 21.52–32.51; Table 1). Age distribution correlated negatively with axial length and positively correlated with refractive error (Pearson correlation and coefficients: $r = -0.442$, $P = 0.000$; and $r = 0.410$, $P = 0.000$). No significant difference was found between the sexes in age, axial length, or refractive error (independent-samples *t*-test: $P = 0.106$, $P = 0.102$, and $P = 0.584$).

Table 1 presents the macular subfield thicknesses stratified by sex. The central subfield thickness, average inner macular thickness, and overall macular volume were significantly lower in the women (partial correlation analysis adjusted by age, axial

length, and refractive error: $r = -0.196$, $P = 0.009$; $r = -0.166$, $P = 0.027$; and $r = -0.153$, $P = 0.042$, respectively).

As the subjects' mean age increased, average inner macular thickness, average outer macular thickness, overall average macular thickness, and overall macular volume decreased significantly (partial correlation analysis adjusted by sex, axial length, and refractive error: $r = -0.227$, $P = 0.002$; $r = -0.226$, $P = 0.002$, $r = -0.227$, $P = 0.002$; and $r = -0.347$, $P = 0.000$, respectively; Table 2; Fig. 2).

A high correlation was found between axial length and refractive error (Pearson correlation, $r = -0.871$, $P = 0.000$). However, refractive error had no significant influence on macular subfield thicknesses or macular volume in partial correlation analysis when adjusted by sex, age, and axial length (Table 2). Axial length correlated negatively with average outer macular thickness, overall average macular thickness, and overall macular volume (partial correlation analysis adjusted by age, sex, and refractive error: $r = -0.204$, $P = 0.006$; $r = -0.151$, $P = 0.044$; and $r = -0.222$, $P = 0.003$, respectively; Table 2; Fig. 3).

TABLE 2. Correlations between Macular Measurements and Age, Sex, and Axial Length

	Age		Refractive Error		Axial Length	
	r^*	P^*	r^\dagger	P^\dagger	r^\ddagger	P^\ddagger
Central subfield thickness	-0.041	0.584	-0.038	0.611	0.112	0.137
Superior inner macular thickness	-0.215	0.004	-0.054	0.472	-0.078	0.304
Nasal inner macular thickness	-0.195	0.009	0.010	0.894	-0.007	0.923
Inferior inner macular thickness	-0.252	0.001	0.044	0.564	-0.083	0.269
Temporal inner macular thickness	-0.177	0.018	-0.026	0.733	-0.056	0.461
Average inner macular thickness	-0.227	0.002	-0.010	0.897	-0.062	0.410
Superior outer macular thickness	-0.213	0.004	-0.125	0.097	-0.231	0.002
Nasal outer macular thickness	-0.219	0.003	-0.029	0.704	-0.102	0.175
Inferior outer macular thickness	-0.145	0.053	0.074	0.328	-0.154	0.040
Temporal outer macular thickness	-0.189	0.012	-0.046	0.540	-0.207	0.006
Average outer macular thickness	-0.226	0.002	-0.038	0.616	-0.204	0.006
Overall average macular thickness	-0.227	0.002	-0.013	0.859	-0.151	0.044
Overall macular volume	-0.347	0.000	-0.006	0.937	-0.222	0.003

P-values and correlation coefficients of partial correlation analysis.

* Adjusted for sex, refractive error, and axial length.

† Adjusted for sex, age, axial length.

‡ Adjusted for sex, age, refractive error.

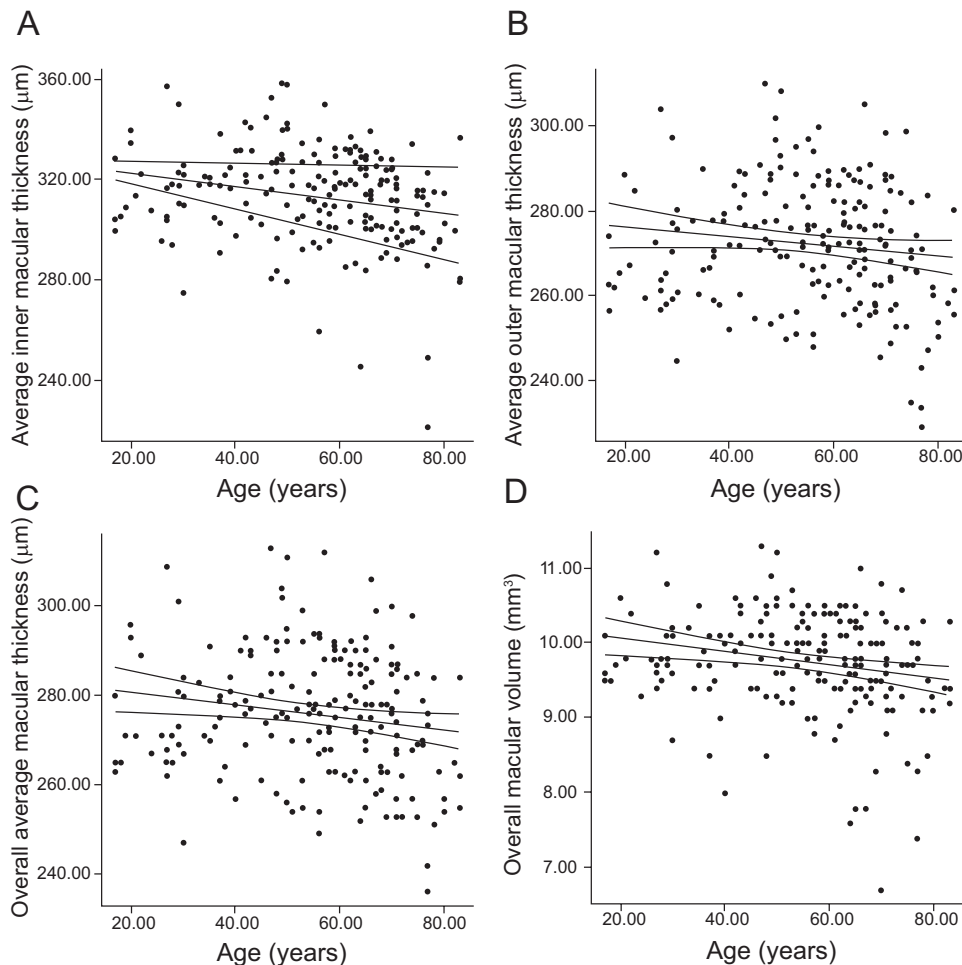


FIGURE 2. Age versus average inner macular thickness (A), average outer macular thickness (B), overall average macular thickness (C), and overall macular volume (D). *Solid line:* linear regression; *top and bottom lines:* the 95% confidence intervals for the regression line.

DISCUSSION

In this study, we noted that central subfield thickness, average inner macular thickness, and overall macular volume were all significantly lower in the female subjects. These findings are in line with those in previous reports,^{19–21} confirming the impact of sex on central retinal thickness measurements. The reduced foveal thickness in female subjects is compatible with the observation that they have a higher risk of developing macular holes,^{22,23} as the macular hole development has been suggested to begin with foveal thinning. A longitudinal follow-up study is needed to address the clinical significance of this finding.

The average inner, outer, overall macular thickness, and overall macular volume were shown to decrease with the subjects' mean age in this study. These results correspond to histologic human retina studies that have demonstrated a decrease in the density of photoreceptors, ganglion cells, and retinal pigment epithelial cells with age.^{24,25} Several studies in which the RTA,^{4–6} Humphrey OCT 2000,^{7,10} and Stratus OCT were used^{8,11} reported a lack of relationship between retinal thickness and age. However, a study with Humphrey OCT 2000¹ and recent reports with OCT 3^{2,3} presented results consistent with our study. In the studies with the Humphrey OCT 2000, Göbel et al.⁷ and Kanai et al.¹ analyzed the foveola, 1 mm superior, inferior, nasal, and temporal to the foveola with four linear scans, and only the latter group found reduced retinal thickness in four parafoveal points with age. Wakitani et al.¹⁰ analyzed the central 3-mm macular area in three circular areas measured with four linear Humphrey OCT 2000 scans,

but found no relationship with age. The Stratus OCT study by Chan et al.⁸ included only 37 eyes and did not consider the effect of axial length or sex. Lam et al.¹¹ used the fast macular thickness map protocol of Stratus OCT on 143 eyes with a relatively wide age spectrum (23–77 years) and a wide range of refractive error/axial length (+3.25 to –18.13 D/ 21.10–31.10 mm), but still found no relationship with age. Eriksson and Alm² and Manassakorn et al.,³ however, reported results similar to our study using the Stratus OCT. We believe that the three studies found a relationship with age by limiting the inclusion criteria to a refractive error of ± 3 D¹ or ± 6 D and astigmatism of ≤ 3 D.^{2,3} Eriksson and Alm² reported that retinal thickness in all nine ETDRS areas had a negative correlation with age. However, although they limited the range of participants' refractive error, they did not consider the influence of sex in their statistical analysis. Manassakorn et al.³ found significant association between age and macular thickness in all ETDRS areas except the center. They not only restricted the participants' refractive error, but they also confirmed no significant difference in sex distribution in the age groups. Therefore, their study is the most reliable in controlling all the factors that might influence macular subfield thickness analysis. Our results using the SD-OCT affirm that macular subfield thickness, except in the central subfield, and macular volume decrease with age.

In our study, as axial length increased, average outer macular thickness, overall average macular thickness, and overall macular volume decreased. This finding affirms histopathologic studies that have demonstrated increasing retinal thin-

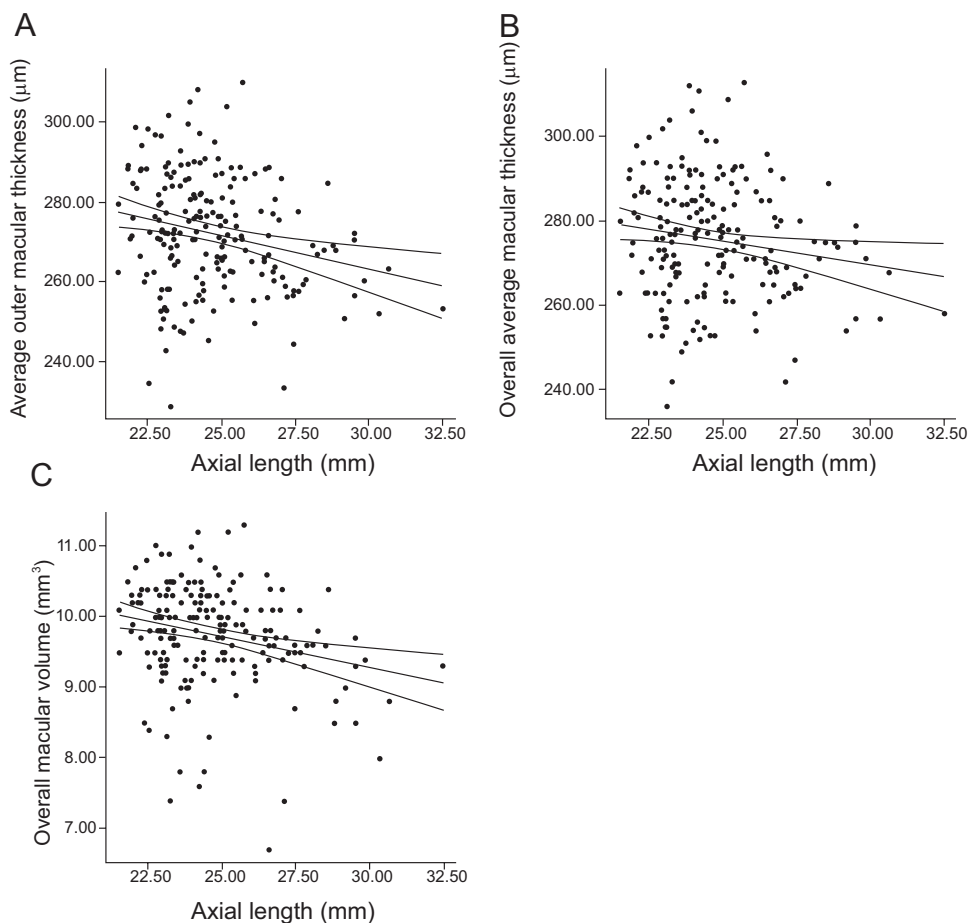


FIGURE 3. Axial length versus average outer macular thickness (A), overall average macular thickness (B), and overall macular volume (C). In all plots, the linear regression line (solid line) and 95% confidence intervals for the regression (curved lines) are given.

ning with myopia,^{13,14} and a clinical study that demonstrated more frequent chorioretinal atrophy in the posterior pole in eyes with longer axial length.²⁶ Results in several studies using Humphrey OCT 2000 did not show a relationship between axial length and average retinal thickness.^{7,10} However, these studies analyzed only a small central macular area within 2-mm⁷ and 3-mm¹⁰ diameters with four linear scans. Lim et al.⁹ used OCT 1 with larger scan lengths of 6 mm in young myopic subjects and obtained results similar to those in our study. The mean maximum retinal thickness of the four thickest parafoveal points correlated negatively with axial length. In a Stratus OCT study, Manassakorn et al.³ found no significant correlation between macular thickness and refractive error and did not mention a correlation with axial length. However, the refractive errors of the participants in this study were limited to between -6 and $+6$ D. When subjects with a wide range of refractive error were included, Stratus OCT demonstrated results consistent with our own. Lam et al.,¹¹ using Stratus OCT fast macular thickness map protocol, showed a negative correlation between outer and overall macular thicknesses and axial length. Refractive error and axial length had opposing effects on macular thicknesses and volume in their study, but the authors did not perform partial correlation analysis to discover the individual effects of refractive error. In another study in which Stratus OCT fast macular thickness map protocol was used to compare highly myopic eyes with nonmyopic eyes the researchers found that highly myopic eyes had lesser average inner, outer macular thickness, and macular volume.¹² All together, the results of our SD-OCT study corroborate the trend of these recent studies that outer macular thickness and volume decrease with increas-

ing axial length, even after adjusting the other factors that may have influence.

The main limitations of our study were the enrollment of subjects with mild cataract and using the autorefractor for measurement of the refractive error. Since media opacity obscures the signal to the retina and decreases the signal strength, we only included subjects with SD-OCT scans with signal intensity ≥ 6 . Van Velthoven et al.²⁷ stated that mild nuclear cataracts have no significant influence on the retinal thickness. Also as reported by Tappeiner et al.,²⁸ decrease of transmission to only 30% still allowed reliable analyses of the retinal layers which is required to speculate retinal thickness. We included only patients with mild cataract in this study, and the ACVA in these patients was comparable with that of the remainder of the patients with no ocular disease (0.95 vs. 0.97; $P = 0.129$). A subset analysis of patients with no cataract and acuity of 20/20 showed the same relationships (results not shown). Still, aging and cataracts have both been reported to induce refractive changes.²⁹ Inclusion of patients with mild cataract may have influenced the appearance that of refractive error contributes to macular thickness and volume. However, we made an effort to control this bias by performing partial correlation analysis of each of the factors. Autorefractor was chosen to minimize time, expense, and inconvenience for patients. Autorefractor may not be the most accurate method, but it provides measurements with small deviation in adults. We found that although the refractive error and axial length had a high negative correlation, the structural change of axial length was the more significant factor influencing macular thickness. Also of note, our study was cross-sectional and therefore may

not accurately present the decrease in macular retinal thickness with age.

In conclusion, we used SD-OCT scanning with improved resolution and significantly more A-scans to demonstrate that macular thickness is related to sex, age, and axial length in normal subjects with regional variations. Analysis of macular thickness in macular diseases and glaucoma should be interpreted in the context of these findings.

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