Correlation Between Subfoveal Choroidal Thickness and the Severity or Progression of Nonexudative Age-Related Macular Degeneration

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Purpose. To investigate the correlation between subfoveal choroidal thickness (SFChT) and the severity or progression of nonexudative AMD.

Methods. One hundred seventy-six eyes of 114 patients with nonexudative AMD were included in this study. These eyes were divided into stages I through IV, based on the Age-Related Eye Disease Study (AREDS) classification of fundus findings. Using enhanced depth imaging from spectralis domain optical coherence tomography (SD-OCT), the central retinal thickness (CRT), SFChT, and parafoveal choroidal thickness (PFChT) were measured. The area of geographic atrophy (GA) was measured from fundus autofluorescence (FAF) images, and the progression of GA was calculated using RegionFinder software.

Results. The age-adjusted SFChT levels were lower at later stages of nonexudative AMD. These measurements were as follows: 266.68 ± 12.60 (stage I: 28 eyes), 263.34 ± 9.87 (stage II: 48 eyes), 200.55 ± 8.83 (stage III: 71 eyes), and 188.34 ± 13.72 (stage IV: 29 eyes) ($P = 0.0028$). The age-adjusted SFChT was also negatively correlated with the best corrected visual acuity (BCVA) (estimate, −0.001; $P = 0.0006$). Among 16 eyes with GA at baseline, SFChT showed a negative correlation with the baseline area of GA ($r = 0.5521$, $P = 0.0133$). In addition, GA progressed more rapidly during the mean follow up of 22.19 ± 9.08 months when the SFChT was lower at baseline ($r = 0.5658$, $P = 0.0112$).

Conclusions. Subfoveal choroidal thickness is closely related to the BCVA, the severity of nonexudative AMD, as well as the rate of GA progression. Subfoveal choroidal thickness may be a predictor of disease progression in GA cases.

Keywords: subfoveal choroidal thickness, nonexudative age-related macular degeneration, geographic atrophy

Nonexudative AMD is characterized by drusen and pigment changes in its early stages and by geographic atrophy (GA) at more advanced stages. Geographic atrophy results from uni- or multifocal atrophic patches of RPE as well as of the corresponding neuroretina and choriocapillary layer of the choroid.[1] Color fundus photography has been the gold standard for evaluating the severity and progression of AMD, as defined by the Age-Related Eye Disease Study (AREDS) classification system.[2,3] However, technical advances in imaging have now provided more information on the structural changes to the retina in AMD. Fluorescein angiography (FA), indocyanine green angiography (ICGA), spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF) are now widely used for evaluating and treating AMD patients.

To date, the pathogenesis of nonexudative AMD has not been well understood. Proposed mechanisms of RPE cell dysfunction include oxidative stress, inflammation, and alterations in choroidal blood flow.[4–7] Several authors have also suggested that the choroidal blood flow may be associated with the pathomechanism and progression of nonexudative AMD, but this hypothesis has not been validated because of the difficulty in measuring choroidal blood flow and thickness.[8,9] Recently however, the enhanced depth imaging (EDI) technique in SD-OCT has enabled the measurement of choroidal thickness.[10] In our present study, we investigated the correlation between subfoveal choroidal thickness (SFChT), and both the severity of nonexudative AMD and the progression of AMD.

Methods

A retrospective review was performed on 176 eyes from 114 patients with nonexudative AMD who visited the Department of Ophthalmology at the Asan Medical Center from November 2010 to September 2012. The design of this study followed the principles of the Declaration of Helsinki. All patients underwent a comprehensive ophthalmologic examination, including best-corrected visual acuity (BCVA), fundus examination, color fundus photography, FA, ICGA, FAF, and SD-OCT. Fluorescein angiography, ICGA, and FAF images were acquired using a Heidelberg Retina Angiograph 2 (HRA2; Heidelberg Engineering, Heidelberg, Germany) and SD-OCT imaging was performed using Spectralis system software (version 1.7.0.0; Heidelberg Engineering). Enhanced depth imaging optical coherence tomography was also performed on all eyes. Patients were excluded if they had a refractive error (RE) of 3 diopters (D) or higher, the presence or a past history of choroidal neovascularization, a history of any other retinal diseases, or a history of any retinal surgery. Pseudophakic patients with an unknown

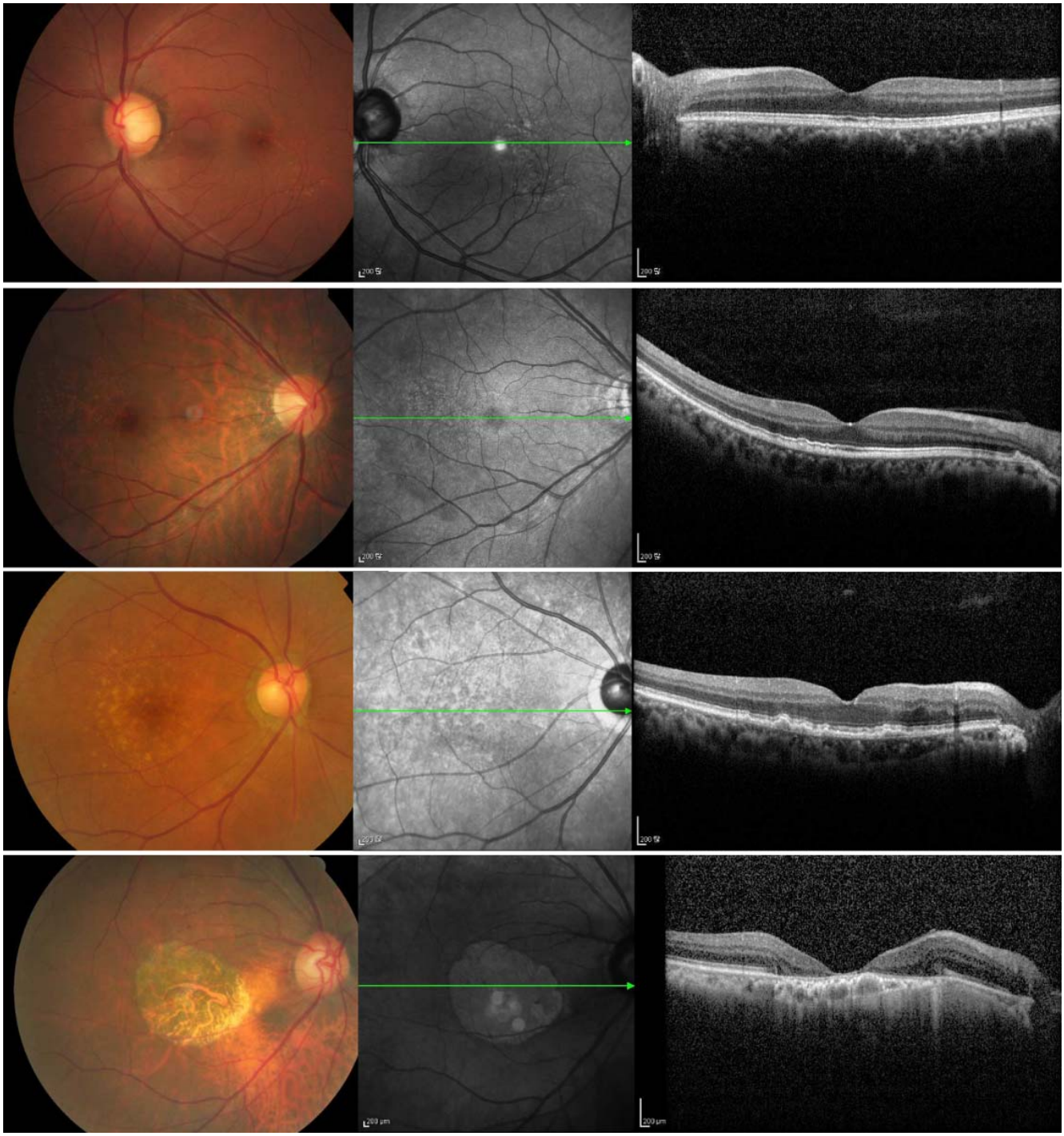

FIGURE 1. Fundus photography and SD-OCT findings in patients with dry AMD. Patients were categorized according to the AREDS classification of AMD as follows: (*first row*) stage I, showing a few small drusen; (*second row*) stage II, a few intermediate sized drusen with mild pigment changes; (*third row*) stage III, extensive intermediate drusen and a few large drusen; and (*bottom row*) stage IV, the presence of GA involving the center of the macula.

preoperative RE were also excluded as were patients with eyes showing a significant media opacity where good quality OCT scans or FAF images could not be attained.

Assessment of AMD Stages and Choroidal Thickness

All eyes included in our present study cohort were grouped into stages I through IV based on the Age-Related Eye Disease Study (AREDS) classification fundus findings as follows: stage I, no or a few small drusen (<63 μm in diameter); stage II, many small drusen or a few intermediate sized drusen (63–124 μm in diameter) or macular pigment changes; stage III, extensive intermediate drusen or at least one large drusen (≥125 μm in diameter), or a GA not involving the foveal center; and stage IV, the presence of GA involving the center of the macula (Fig. 1).[2] Staging was determined by two independent investigators in a blind manner and any discrepancies were resolved by consensus

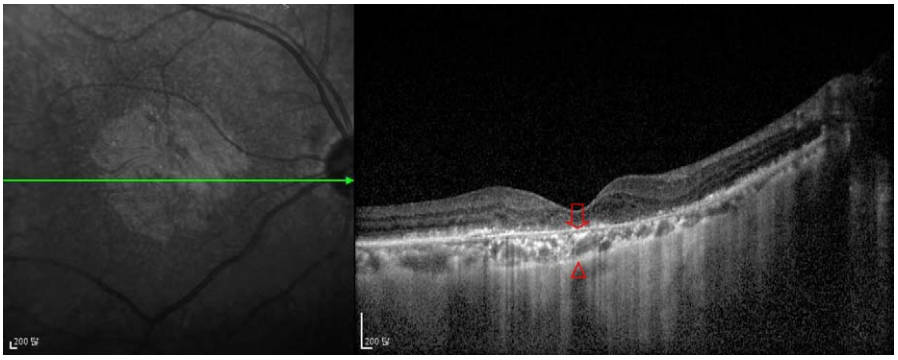

FIGURE 2. Measurement of SFChT in a GA patient using EDI-OCT. The vertical distance was measured manually at the fovea from the hyperreflective line of the Bruch's membrane (*arrow*) to the hyperreflective line of the choriosclera interface (*arrowhead*). In this case, the SFChT was 173 μm.

between these two observers. All eyes were assessed for choroidal thickness and we then evaluated the correlations between choroidal thickness and AMD stage.

Measurement of Choroidal Thickness Using EDI-OCT

The choroid was imaged by positioning a Heidelberg Spectralis OCT (Heidelberg Engineering) close enough to the eye to obtain an inverted image. The OCT images were obtained with the Heidelberg Spectralis OCT (Heidelberg Engineering) using a 19-scan horizontal raster protocol and a 9-mm vertical linear scan in EDI mode. All 19 B-scans were acquired in a continuous, automated sequence and covered a 30° × 15° area of the macula. Each scan was 9.0 mm in length and spaced 240-μm apart from each other. To measure the SFChT, the vertical distance was measured manually at the fovea, using the caliper tool in the OCT Heidelberg Eye Explorer software (Heidelberg Engineering), from the hyperreflective line of Bruch's membrane to the hyperreflective line of the choriosclera interface. (Fig. 2) The parafoveal choroidal thickness (PFChT) was measured at 1500-μm intervals horizontally and vertically from the foveal center using the same method. The SFChT and PFChT values were manually determined by two investigators who were masked to the color fundus findings, and the mean value of each was used. To assess the intraclass repeatability of the choroidal thickness, intraclass correlation coefficients (ICC) were calculated. The ICC values ranged from 0.92 to 0.97, with *P* values of less than 0.001 at each measured point.

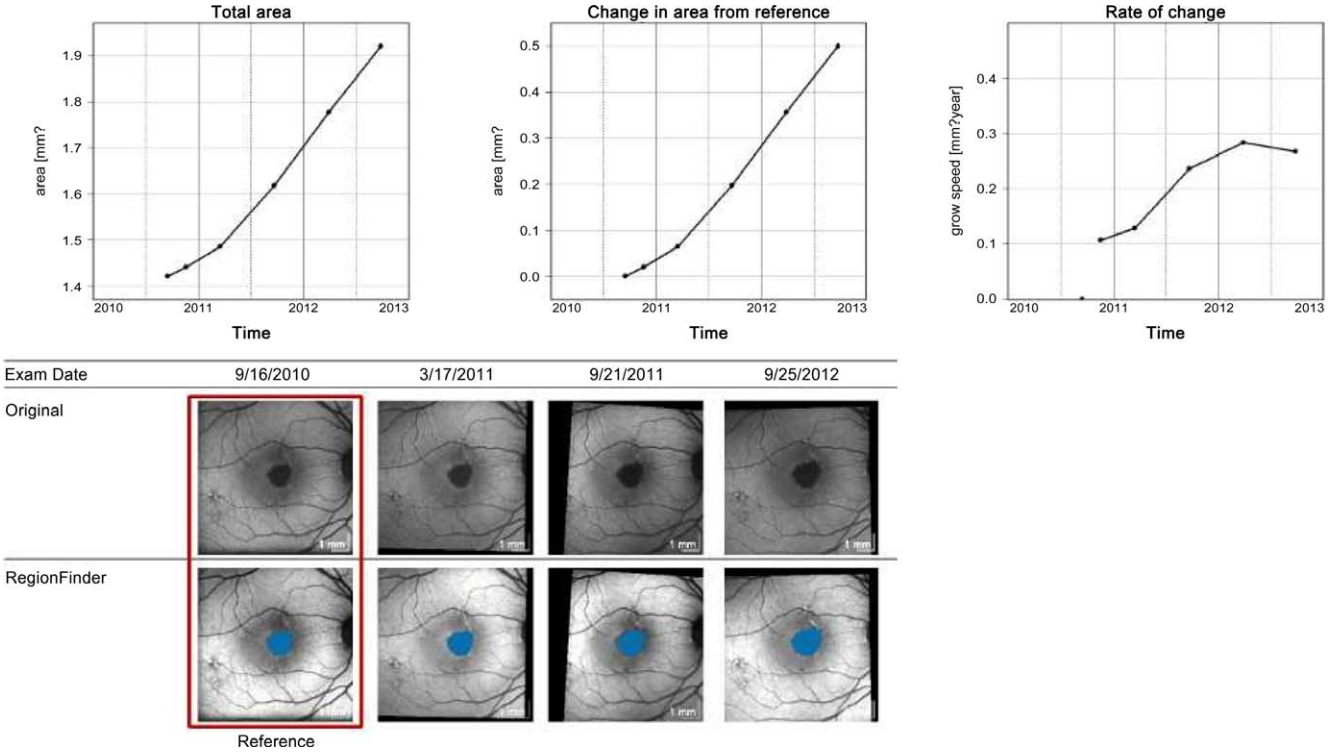

FIGURE 3. A representative case showing GA progression, assessed using RegionFinder software. The total GA area was measured via segmentation of the hypo-autofluorescent areas. During a follow-up period of about 2 years, the atrophic area showed continuous enlargement.

Table 1. Baseline Characteristics of the Study Population

	AREDS Classification, 176 Eyes				
	Stage I	**Stage II**	**Stage III**	**Stage IV, GA**	***P* Value**
Number, eyes/patients	28/20	48/33	71/41	29/20	-
Age, y, mean ± SD	58.96 ± 5.50	62.15 ± 9.14	67.75 ± 8.15	72.07 ± 6.94	<0.0001*
Sex, M:F	11:17	10:38	16:55	11:18	0.3235
BCVA, LogMAR, mean ± SD	0.03 ± 0.07	0.09 ± 0.17	0.16 ± 0.20	0.68 ± 0.50	<0.0001*
RE, D, mean ± SD	0.23 ± 1.20	0.31 ± 1.10	0.17 ± 1.17	0.30 ± 1.15	0.9150
CRT, μm, mean ± SD	256.4 ± 17.55	254.2 ± 21.25	247.4 ± 24.25	230.7 ± 35.66	<0.0001*

Statistical method used, ANOVA; $^*P < 0.05$ is considered to indicate statistical significance.

Assessment of GA Progression and Choroidal Thickness

Among the 29 GA eyes (stage IV) in our cohort, 16 eyes from 16 unilateral GA patients were included in subsequent analysis to evaluate the correlation between the baseline SFChT and GA progression. We excluded 13 eyes due to either a poor demarcation of the hypo-autofluorescent area or a lack of follow-up FAF data (2 or less follow ups). A retrospective longitudinal review was performed to evaluate GA progression. At all visits, the 16 GA patients underwent FAF and the GA area was calculated on the central FAF images by two independent investigators using semi-automated software (Region Finder, version 2.4.3.0; Heidelberg Engineering); the mean value was used. Fundus autofluorescence images were obtained using a 488-nm excitation wavelength and a barrier filter blocking wavelengths shorter than 500 nm from the excited retina. Images were acquired in high speed (768×768 resolution) mode. Autofluorescence images were acquired using the Automatic Real Time Mean (ART Mean) function set at approximately 30. The total sizes of the unifocal or multifocal GAs were measured by segmentation of the atrophic areas. The progression rate of GA over time was then calculated (Fig. 3). To assess the intraclass repeatability of the GA area measurement, ICCs were calculated. The ICC of the total size at baseline and the progression rate calculated using Region-Finder (Heidelberg Engineering) were 0.93 and 0.91, respectively, with *P* values of less than 0.001.

Outcome Measures and Statistical Analyses

We analyzed the correlation between choroidal thickness and AMD stages using a linear mixed model, which accounted for patient effects (both eyes of the same patient). We adjusted for covariates including age, sex, and RE. In addition, we analyzed the correlation between the disease progression rate and the

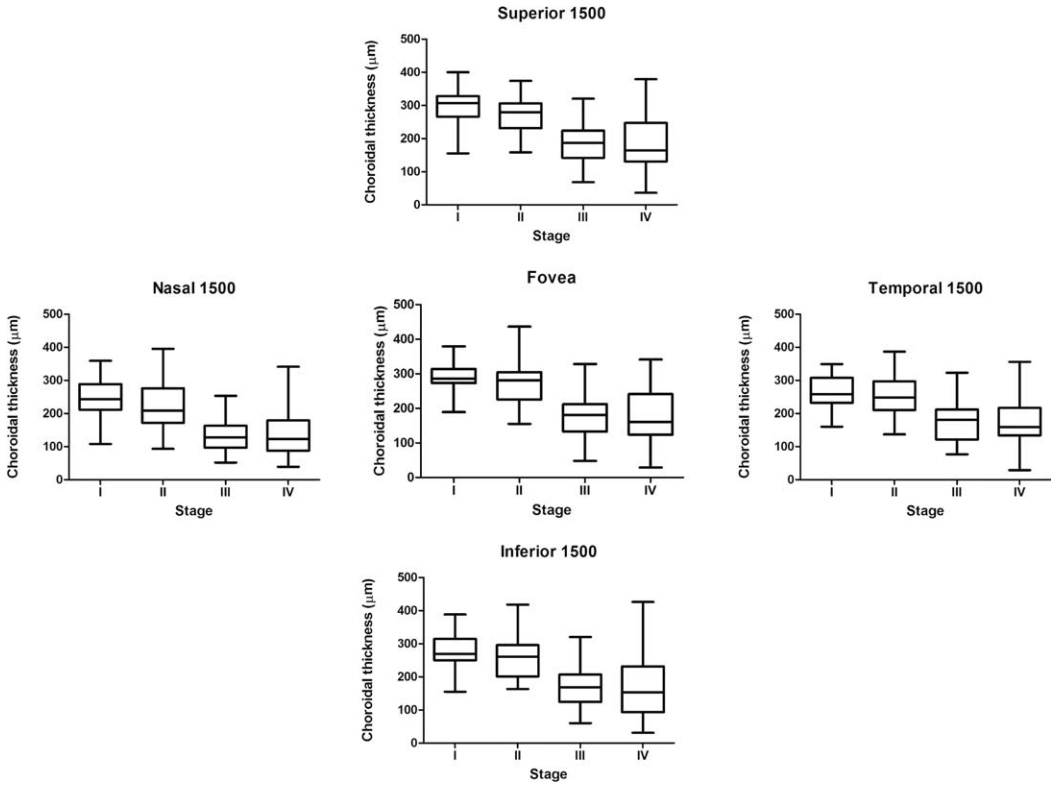

Figure 4. Mean choroidal thicknesses in each location at different AREDS stages. The choroidal layer is thickest at the subfoveal location. In comparison with eyes with stage I and stage II AMD, a significant reduction in choroidal thickness was evident in stage III and stage IV AMD at all locations (superior, 1500 μm; nasal, 1500 μm; fovea; temporal, 1500 μm; inferior, 1500 μm).

Table 2. Subfoveal Choroidal Thickness Differences at Each AMD Stage

Stage	I	II	III	IV
Number, eyes	28	48	71	29
SFChT, μm, mean ± SD	266.7 ± 12.60	263.34 ± 9.87	200.55 ± 8.83	188.34 ± 13.72

Subject eyes = 114; $n = 176$. Statistical method used: linear mixed model with adjustments for age, sex, and refractive error.

baseline SFChT and baseline atrophic area in GA patients, using Pearson's Correlation analysis. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 15.0; SPSS Inc., Chicago, IL).

Results

Table 1 lists the baseline characteristics of the 114 nonexudative AMD patients (176 eyes) included in our study cohort in accordance with the AREDS stages. The mean age was significantly higher in stage III and IV cases (67.75 ± 8.15 and 72.07 ± 6.94, respectively) compared with patients with stage I and II disease (58.96 ± 5.50 and 62.15 ± 9.14, respectively). The mean BCVA was also found to be significantly correlated with the AMD stage ($P < 0.001$). In contrast, the RE and the central retinal thickness (CRT) were not significantly correlated with the stage of AMD. The CRT of the stage IV patients was significantly lower than the other stage as stage IV indicates GA involving the center of the macula.

Correlation Between Choroidal Thickness and AMD Stage

The choroidal thickness is highest at the subfoveal location. The mean choroidal thickness at each AMD stage in our current study cohort is presented in Figure 4. Using linear mixed model analysis, we found no significant difference in choroidal thickness between stage I and stage II, but observed a significant reduction in choroidal thickness in stage III and IV AMD, compared with stage I and II, at all locations. We analyzed choroidal thickness between our AMD study groups with adjustment for age as the mean age at each disease stage was significantly different ($P < 0.001$). Our results showed that the choroidal thickness of stage III and IV cases was significantly lower than in patients with stage I and II AMD ($P < 0.001$; Tables 2, 3). In addition, our present data revealed an inverse correlation between SFChT and BCVA (estimate, –0.001; $P = 0.0006$).

Correlation Between Baseline SFChT and GA Progression

The mean baseline SFChT in our current patient population was 218.4 ± 77.88 μm, and the mean total area of the GA was 6.304 ± 4.39 mm^2. The baseline GA area was found to negatively correlate with the baseline SFChT ($r = –0.5521$, $P = 0.0133$) (Fig. 5, right panel). The mean follow-up period in our current patient cohort was 22.19 ± 9.08 months (range, 12–39). During the follow-up period, GA areas were calculated using RegionFinder software (Heidelberg Engineering) in which measurements were made 4 ± 1.4 times per eye (range, 3–7). Most of the eyes showed continuous enlargement of the GA area over time, and the calculated GA progression rate was 1.47 ± 1.46 mm^2/year (range, 0.06–5.38). Interestingly, the GA progression rate was also found to be significantly correlated with the baseline SFChT ($r = –0.5658$, $P = 0.0112$).

Discussion

In our current study, we found that the choroidal thickness decreases in the later stages of nonexudative AMD. In addition, we observed a significant correlation between SFChT and the size of the GA area, as well as between SFChT and AMD progression in eyes with GA. The choroid is a highly vascular structure that provides nutrients to the photoreceptors and removes waste products that arise in the RPE. Since the macula is the region of highest metabolic demand in the retina, the choroid is thought to be at its thickest under the fovea. In this regard, the SFChT has been used by many investigators as the main parameter representing the thickness of the choroidal layer. With aging, the choroid is known to undergo both structural and functional changes. In a previous study using a Doppler technique, it was shown that foveolar choroidal blood flow in healthy eyes significantly decreases with age.[8] A more recent study using Spectralis SD-OCT (Heidelberg Engineering) has reported that the SFChT decreases by approximately 1.56 μm each year.[10] Another study has also shown that the choroidal volume decreases by about 0.54 mm^3 every 10 years.[11] In addition, Ko et al.[12] reported the correlation between choroidal thickness and visual acuity using SD-OCT. Consistent with the results of their study, we also found that the foveal CT correlates negatively with the BCVA. The progressive reduction of the CT in the fovea related to age most likely leads to insufficient blood supply and metabolic supplements for the macula, and therefore it may be a possible explanation for loss of BCVA.

Choroidal structures are of particular interest when treating AMD patients because abnormalities in choroidal circulation have been hypothesized to contribute to the development of AMD. Spaide et al.[10] have reported that the thickness of the choroid shows a negative correlation with age and suggested that this is mostly related to loss of small choroidal vessels. Consistently, Grunwald et al.[8] using fluorescein angiograms, have reported previously that eyes with nonexudative AMD have a decreased blood volume and exhibit an abnormal flow compared with healthy eyes, with a further worsening of blood flow with increasing disease severity. This decreased blood flow has been postulated to be due to a combination of a narrowing of the choriocapillaris lumen, loss of cellularity, and thinning of the choroid, particularly the choriocapillaris layer. Our current observation of a significant thinning of the SFChT in advanced stage nonexudative AMD patients appears to be

Table 3. Statistical Analysis of Differences in Subfoveal Choroidal: Thickness Between AMD Stages

Comparison of Stage	P Value
I vs. II	0.8093
I vs. III	0.0029*
I vs. IV	0.0031*
II vs. III	0.0012*
II vs. IV	0.0022*
III vs. IV	0.4652

* Statistical significance was analyzed using a linear mixed model.

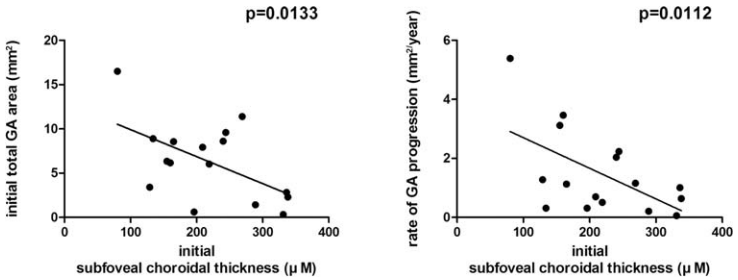

FIGURE 5. Scattergrams indicating the relationship between the SFChT and the initial GA area (*right panel*), and between the SFChT and the rate of GA progression (*left panel*). The plot shows a significant negative correlation by simple linear regression. The slopes of the *right panel* and *left panel* were –0.5521 and –0.5658, respectively.

consistent with this previously described anatomical change in the choroidal layer. Manjunath et al.[13] have also reported that the mean SFChT of nonexudative AMD patients is thinner than that of healthy eyes and is inversely correlated with age.

Previous studies have not conclusively demonstrated thinning of the choroidal layer in nonexudative AMD eyes due to technical limitations. Manjunath et al.[13] have demonstrated using Cirrus-HD OCT (Carl Zeiss Meditec, Dublin, CA) that eyes with nonexudative AMD show a variable range of choroidal thicknesses above and below the normal mean. However, their study included only 17 patients for whom the AMD stages were not classified, suggesting that some of their cases were of early AMD. Wood et al.[14] have reported no significant difference in choroidal thickness, measured by Spectralis SD OCT (Heidelberg Engineering), between early AMD eyes and healthy controls. Even in that earlier study however, patients with advanced AMD were excluded. Ko et al.[12] have reported the inverse relationship between the drusen area and choroidal thickness among patients including more advanced AMD of stage IIIs. In our present analyses, while eyes from AMD stage I or II patients showed no significant decrease in the SFChT, the SFChT was significantly reduced when the nonexudative AMD had progressed to stage III or IV. A failure to demonstrate a significant thinning of choroid among early-AMD eyes may suggest the potential time lag between the initial choroidal blood flow decreases in parallel with a subsequent anatomical thinning of the choroid in AMD eyes.

It is important to develop a prognosis once GA develops. Previous studies have shown that a specific type of diffuse trickling FAF pattern at the junctional zone may be associated with a rapid GA progression.[15–18] Sunness et al.[19] have reported that there is the close relationship between the baseline GA size and progression rate. However, there have been no previous studies of the relationship between choroidal thickness and the progression of GA. To measure the GA area, we employed a new automated program (RegionFinder; Heidelberg Engineering), which enables more accurate and reproducible measurements.[20] As expected among GA patients, the initial SFChT correlated well with the initial GA area, reflecting the severity of the disease itself. In addition, the progression of GA, represented by the rate of GA area increase over time, was found in our current analyses to be well correlated with the initial SFChT, as well as the initial GA area size. To our knowledge, our current study is the first to suggest that the initial SFChT measurement is a potential predictor of GA progression. Our conclusions are supported by the hypothesis that a thinning of the choroidal layer, as well as compromised choroidal circulation, contributes to the development of AMD.

Our present study is limited by the relatively small number of patients analyzed and its retrospective nature. Despite our small GA patient sample size, however, we believe that our subgroup of GA cases was adequately representative of GA patients in general. The mean GA progression rate among our subgroup was measured at 1.47 mm^2/year, which is consistent with the previously reported range of 1.5 to 2.1 mm^2/year.[15,18,19] Another noteworthy limitation of our present analyses is that we did not examine the relationships between the axial length and the SFChT. Previous reports have found that the choroidal thickness is closely associated with the axial length.[11,21–25] Since the RE was found not to be different between our current AREDS classification groups, we speculated that the potential influence of the axial length was not significant in our present study. Further investigations are needed to verify whether these findings are also observed if the eyes in AMD patients are adjusted for axial length.

In conclusion, our current findings reveal that choroidal thickness is closely related to not only the severity of nonexudative AMD, but also to the rate of GA progression among advanced AMD patients. With advances in imaging technology, SFChT can now be more accurately measured using EDI-OCT. Hence, the monitoring of the SFChT can be a predictor of disease progression in patients with nonexudative AMD, especially among cases with GA. A future study with a larger cohort and a longer-term prospective design will be necessary to confirm our hypothesis.

Acknowledgments

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