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Assessment of Subfoveal Choroidal Thickness in Different Subtypes of Age Related Macular Degeneration

Yaşa Bağlı Maküla Dejenerasyonunun Farklı Alt Tiplerinde Subfoveal Koroid Kalınlığının Değerlendirilmesi

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ABSTRACT Objectives: To evaluate the alterations in subfoveal choroidal thickness (SFCT) in different subtypes of age related macular degeneration (AMD) in comparison with the age-related change in SFCT. **Material and Methods:** 178 eyes of 90 patients with AMD (AMD group) and 204 eyes of 102 subjects without any chorioretinal pathologies (control group) were included. Control group was divided into 3 consecutive age groups: A (20-34 years), B (35-49 years) and C (≥ 50 years). Choroidal thickness was measured at the subfoveal region using the enhanced depth imaging program of a SD-OCT. **Results:** In both groups, SFCT showed a negative correlation with age. SFCT decreased 25.8 μm for each decade in the control group. After adjustment for age, the mean SFCT in AMD group, both non-neovascular and neovascular forms, were significantly reduced compared with the eyes in control subjects of ≥ 50 years of age ($p<0.001$ for all). There was no difference in age-adjusted SFCT between eyes with non-neovascular and neovascular AMD ($p=0.710$). Among the eyes with non-neovascular AMD, those with geographic atrophy had a further reduction in SFCT ($p<0.001$). Among the eyes with neovascular AMD, those with subfoveal scarring had a further reduction in SFCT ($p<0.001$). In the AMD group, SFCT in the eyes with the signs of advanced AMD was significantly reduced compared with the eyes without the signs of advanced AMD ($p=0.006$). **Conclusion:** SFCT was reduced with increasing age and further reduced in patients with AMD, both in non-neovascular and neovascular forms. Progression of the AMD seems to be related with a further reduction in SFCT.

Keywords: Macular degeneration; choroid; choroidal neovascularization; geographic atrophy; tomography, optical coherence

ÖZET Amaç: Yaşa bağlı maküla dejenerasyonunun (YBMD) farklı alt tiplerinde subfoveal koroid kalınlığı (SFKK) değişikliklerinin, yaşa bağlı SFKK değişimi ile birlikte değerlendirilmesi. **Gereç ve Yöntemler:** Çalışmaya YBMD hastalığı olan 90 olgunun 178 gözü (YBMD grubu) ile herhangi bir koryoretinal patolojisi olmayan 102 olgunun 204 gözü (kontrol grubu) dahil edildi. Kontrol grubu üç ardışık yaş grubuna bölündü: A (20-34 yaş), B (35-49 yaş) ve C (≥50 yaş). Koroid kalınlığı subfoveal alanda SD-OCT cihazının "enhanced depth imaging" programı kullanılarak ölçüldü. **Bulgular:** Her iki grupta SFKK yaş ile negatif korelasyon gösterdi. Kontrol grubunda SFKK'da her dekadda 25.8 μm azalma tespit edildi. Yaşa göre düzeltme sonrasında SFKK'nın YBMD grubunda hem neovasküler hem de neovasküler olmayan tiplerinde kontrol grubunda ≥50 yaş olgulara göre azalmış olduğu görüldü (tümü için $p<0,001$). Neovasküler ve neovasküler olmayan YBMD tipleri arasında yaşa göre düzeltilmiş SFKK açısından fark yoktu ($p=0,710$). Neovasküler olmayan YBMD'li gözler içerisinde, coğrafi atrofi mevcut olanlarda SFKK'da daha fazla azalma tespit edildi ($p<0,001$). Neovasküler YBMD'li gözler içerisinde, subfoveal skarlaşma mevcut olanlarda SFKK'da daha fazla azalma tespit edildi ($p<0,001$). YBMD grubunda ileri YBMD bulgusu olan gözlerde SFKK'nın ileri YBMD bulgusu olmayan gözlere göre azalmış olduğu görüldü ($p=0,006$). **Sonuç:** SFKK yaşla birlikte azalmakta olup, YBMD hastalarında hem neovasküler hem de neovaküler olmayan gruplarda daha fazla azalmaktadır. YBMD hastalığındaki ilerlemenin azalmış koroid kalınlığı ile ilişkili olduğu görülmektedir.

Anahtar Kelimeler: Makula dejenerasyonu; koroid; koroidal neovaskülarizasyon; jeografik atrofi; tomografi, optik koherens

Choroid is the posterior part of the uvea lying between retina and sclera, which has been associated with the pathogenesis of many diseases affecting the posterior segment of the eye.[1-4] So, it is important to visualize the choroid in detail. Classical imaging techniques cannot provide cross-sectional imaging of the choroid and accurate measurement of the choroidal thickness.[5-7] In 2008, Spaide et al. described a new technique: Enhanced Depth Imaging (EDI).[8] This technique allows in vivo visualization of the choroid in detail and accurate measurement of the choroidal thickness using the standard spectral domain optical coherence tomography (SD-OCT) devices. Choroidal thickness measurements using EDI technique has a high repeatability and reproducibility.[8-10]

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly.[11-13] Choroidal changes in AMD are of increasing importance because it is thought that choroidal abnormalities may play an important role in the pathogenesis of AMD.[7,14,15] It is supposed that retinal degenerations and choroidal neovascularization may have an association with choroidal defects and the reduction of the oxygen supply to the retina may lead to AMD.[4,16]

In this study, we aimed to evaluate the change of choroidal thickness with age and the alterations of SFCT in patients with different subtypes and pathological characteristics of AMD.

MATERIAL AND METHODS

Ninety patients with AMD (AMD group) and 102 healthy subjects without any chorioretinal pathologies (control group) were enrolled in this observational study. Patients were excluded if they had high myopic or hyperopic refractive errors of greater than -6.0 or +6.0 diopters (D) or a history of glaucoma, ocular hypertension, uveitis, intraocular tumors and previous vitreoretinal surgery. Subjects in the control group had no chorioretinal pathologies and subjects in the AMD group had no chorioretinal pathologies other than AMD. Subjects older than 20 years of age were included in the control group to evaluate the association between age and choroidal thickness. Control group was divided into 3 consecutive age goups: A (20-34 years), B (35-49 years) and C (≥ 50 years). As a natural course of the disease, AMD is seen in the patients 50 years of age or older. So the subjects older than 50 years of age in the control group (Group C) were included in the comparisons of choroidal thickness between two groups. In control group, 204 eyes of 102 subjects were included. In AMD group, 178 eyes of 90 patients were included. Only one eyes of two patients in AMD group were included because of the phthisis bulbi in the fellow eye as a result of previous ocular trauma. This study was approved by the local Ethics Committee and informed consent was taken before each individual's participation in this study.

All subjects in both control and AMD groups underwent a complete ophthalmological examination including refractive error measurement by an autorefractometer (Topcon KR-8100 Auto Keratorefractometer, Topcon Corporation, Japan), intraocular pressure measurement by a non-contact tonometer (Canon Full Auto Tonometer TX-F, Canon, USA), best corrected visual acuity (BCVA) measurement with Snellen Charts and slit-lamp biomicroscopy for anterior segment and fundus examination. Macular optical coherence tomography (OCT) images and fundus fluorescein angiographic images in patients with AMD were obtained using an SD-OCT device (Spectralis®, Heidelberg Engineering, Heidelberg, Germany). Assignment to the subgroups (non-neovascular AMD, neovascular AMD and controls) was performed according to the results of posterior segment biomicroscopy, OCT and fundus fluorescein angiographic images. Eyes with geographic atrophy (GA) involving center of macula or signs of choroidal neovascularization were classified as "advanced AMD".

In both control and AMD groups, EDI-OCT images were obtained using the same SD-OCT device. Single line scans going directly through the center of the fovea comprised of 100 averaged images were taken using the automatic averaging and eye tracking features. Choroidal thickness was measured manually in the subfoveal region from the inner border of the sclera to the outer border of

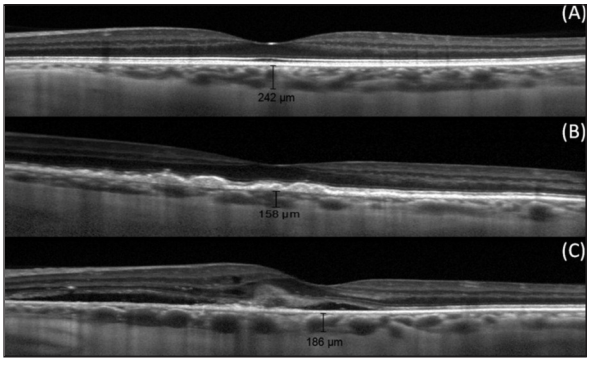

FIGURE 1: Representative images of the subfoveal choroidal thickness in a healthy eye (A), in an eye with non-neovascular AMD (B) and neovascular AMD (C).

the retinal pigment epithelium (RPE) vertically using the calipers of the software (Heidelberg Eye Explorer Software ver. 1.7.0.0). Figure 1 shows the representative images of the subfoveal choroidal thickness in a healthy eye (A), in an eye with non-neovascular AMD (B) and neovascular AMD (C). All measurements were performed by the same specialist.

Data were expressed as the mean ± standard deviation (SD). Normality was checked for each continuous variable. Pearson correlation was used for the analyses of correlation. One-way analysis of variance (ANOVA) was used for the multiple comparisons and Post-Hoc analysis was performed with Bonferroni correction. Linear regression analysis was used to describe the association between variables. Comparisons between control and AMD groups were performed with the analysis of covariances (ANCOVA) after adjustment for age as a covariate. Paired samples - t test was used to compare the SFCT between two eyes of the patients at different stages of AMD. Statistical analysis of the data was performed using SPSS 20.0 software and a p value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the age distribution in AMD and control groups (Table 1). In the AMD group 37 patients (41.1%) had non-neovascular AMD in both eyes, 36 patients (40.0%) had non-neovascular AMD in one eye and neovascular AMD in the fellow eye, 15 patients (16.7%) had neovascular AMD in both eyes and 2 patients (2.2%), who had a phthisic eye because of trauma, had non-neovascular AMD in the fellow eye. In five of the 36 patients, who had non-neovascular AMD in one eye and neovascular AMD in the fellow eye, SFCT could not be measured in the eye with neovascular AMD because of the thickness of the subfoveal fluid and fibrous tissue. These eyes were not included in the statistical analysis of SFCT. So, a total of 173 eyes were included in the statistical analysis; 112 had non-neovascular AMD (64.7%), 61 had neovascular AMD (35.3%). Sixteen of the 112 eyes with non-neovascular AMD (14.3%) had geographic atrophy involving center of macula. Thirty nine of the 61 eyes with neovascular AMD (63.9%) had subfoveal scarring.

In both AMD and control groups, SFCT showed a statistically significant negative correlation with age ($r=-0.362$, $p<0.001$ and $r=-0.576$, $p<0.001$, respectively). In the control group mean SFCT in three consecutive age groups A (20-34 years), B (35-49 years), C (≥50 years) were 347.45±62.07 µm, 301.52±61.66 µm and 258.60 ± 66.07 µm respectively and the difference was statistically significant (ANOVA, $p<0.001$). Post-Hoc analysis with Bonferroni correction revealed statistically significant differences in each pairs ($p<0.001$ for all). In linear regression analysis, SFCT decrased 25.8 µm for each decade (95% CI: -30.8 – -20.7 µm, $p<0.001$).

Subjects older than 50 years of age in the control group (Group C) were used in the statistical

TABLE 1: Age distribution of the patients with AMD and healthy control subjects.

	Number of Cases	Age (years) mean ± SD
AMD Group	90	72.88 ± 8.03 (range 50-88)
Control Group	102	46.18±16.45 (range 20-79)
A (20-34 years)	30	26.87±3.75 (range 20-34)
B (35-49 years)	30	41.83±4.47 (range 35-49)
C (≥ 50 years)	42	63.07±7.96 (range 50-79)

AMD: Age-related macular degeneration; SD: Standard deviation.

TABLE 2: Estimated means of subfoveal choroidal thickness after adjustment for age[a] in AMD group in comparison with the control group C (≥ 50 years of age).

	Estimated mean SFCT (µm)	Standard Error	95% CI	p[b]
Control Group				
C (≥ 50 years)	237.71	7.05	223.84-251.59	
AMD Group				
Overall	175.40	4.67	166.20-184.61	<0.001
Non-neovascular	176.55	5.70	165.33-187.78	<0.001
Neovascular	173.27	7.67	158.18-188.35	<0.001

[a]Age is the covariate in the models and evaluated at 69.66

[b]Significance in the analysis of covariances (ANCOVA)

AMD: Age-related macular degeneration; SFCT: subfoveal choroidal thickness; CI: Confidence interval.

comparisons of SFCT between AMD group and controls. However, because of the statistically significant difference between AMD group and control group C with regard to age (72.88±8.03 and 63.07±7.96 years, respectively, p<0.001), SFCT measurements between AMD and contol groups were compared using ANCOVA with the age as a covariate. After adjustment for age, the mean SFCT in the AMD group was significantly reduced compared with the group C (estimated means 175.40 µm and 237.71 µm, respectively; p<0.001) (Table 2). The mean SFCT of the eyes with non-neovascular AMD and neovascular AMD were also significantly reduced compared with the control group C after adjustment for age (p<0.001 for both) (Table 2). There was not a statistically significant difference in age-adjusted SFCT between eyes with non-neovascular AMD and neovascular AMD (p=0.710). Among the eyes with non-neovascular AMD, those with geographic atrophy involving center of macula had decreased SFCT compared with the eyes without geographic atrophy (p<0.001) (Table 3). Among the eyes with neovascular AMD, those with subfoveal scarring had decreased SFCT compared with the eyes without subfoveal scarring (p<0.001) (Table 3). In the AMD group, age-adjusted SFCT in the eyes with the signs of advanced AMD was significantly reduced compared with the eyes without the signs of advanced AMD (p=0.006) (Table 3). In the group of 31 patients with non-neovascular AMD in one eye and neovascular AMD in the fellow eye; there was not a statistically significant difference in SFCT between both eyes (paired samples-t test, p= 0.320) (Table 4). In the patients with non-neovascular AMD without geographic atrophy in one eye and neovascular AMD without subfoveal scarring in the fellow eye; there was not a statistically significant difference in SFCT between both eyes (mean SFCT 220.92±68.02 µm and 221.85±69.90 µm respectively, paired samples-t test, p= 0.957)

DISCUSSION

Since the advent of the EDI technique, many studies have been performed to determine the normal values of SFCT in the healthy eyes. Spaide et al. firstly described the EDI technique in 2008 and re-

TABLE 3: Estimated means of subfoveal choroidal thickness after adjustment for age in the eyes with different subtypes of AMD.

	Estimated mean SFCT (µm)	Standard Error	95% CI	p[d]
Non-neovascular AMD				
with geographic atrophy	108.07[a]	13.82	80.68-135.49	<0.001
without geographic atrophy	176.76[a]	5.62	165.61-187.91	
Neovascular AMD				
with subfoveal scarring	143.36[b]	8.05	127.24-159.48	<0.001
without subfoveal scarring	195.54 b	10.73	174.06-217.02	
AMD				
advanced AMD not presents	176.20 c	5.84	164.68-187.72	0.006
advanced AMD presents	151.63[c]	6.52	138.76-164.50	

[a,b,c]Age is the covariate in the models and evaluated at 72.70, 73.16 and 72.86 respectively

[d]Significance in the analysis of covariances (ANCOVA)

AMD: Age-related macular degeneration; SFCT: Subfoveal choroidal thickness, CI: Confidence interval.

TABLE 4: Comparison of the SFCT in the patients with non-neovascular AMD in one eye and neovascular AMD in the fellow eye.

	Mean SFCT (µm) ± Standard Deviation	p[a]
Eyes with non-neovascular AMD	187.35±71.04	0.320
Eyes with neovascular AMD	176.39±71.32	

[a]Significance in the paired samples - t test

AMD: Age-related macular degeneration; SFCT: Subfoveal choroidal thickness.

ported that the mean SFCT was 318 μm in the right eye and 335 μm in the left eye of the 17 healthy volunteers with a mean age of 33.4 years.[8] They used the Spectralis SD-OCT device for the choroidal imaging. In the present study, we used the same device and found that the mean SFCT was 297 μm in the 204 eyes of 102 healthy subjects with a mean age of 46.2 years. Likewise, other OCT devices can be used to visualize the choroid and measure the SFCT with the same technique. Manjunath et al. used Cirrus HD-OCT Device (Carl Zeiss Meditec Inc., Dublin, CA) and found a mean SFCT of 272 μm in the 34 eyes of 34 subjects without any chorioretinal pathologies with a mean age of 51 years.[9] Ikuno et al. used the experimental OCT device with 1060 nm wavelength light source and they reported that the mean SFCT was 354 μm in the 86 eyes of 43 healthy subjects with a mean age of 39 years.[17] Their result seems to be greater than the studies using SD-OCT devices. They suggested that greater results might be arised from the difference of the wavelength of the light source and the software or the difference of the patients' demographics.

The current literature reveals that the mostly pronounced factor associated with the SFCT is age.[17-22] In 1994, Ramrattan et al. reported the results of their autopsy study suggesting that the mean SFCT of the histologically analysed eyes was 193.5 μm at first decade and decreased to 84 μm at 10th decade.[23] However, results from histological studies may not reflect the exact choroidal thickness in vivo. Cessation of the blood circulation after death may affect the thickness of the choroid that is such a highly vascularized tissue and postmortem fixation may also damage and lead to shrinkage of the tissue.[6,14,24] Therefore, studies using EDI technique seems to be more helpful to evaluate the age and SFCT relation in the living body. In the present study SFCT showed a statistically significant negative correlation with age in both control and AMD groups and decreased 25.8 μm for each decade in the healthy individuals. Similarly, Margolis and Spaide reported that between 19-85 years, SFCT decreased 15.6 μm for each decade and Noori et al. reported that SFCT decreased 17.39 μm for each decade.[6,22] Both used Spectralis OCT device and EDI technique. Ikuno et al. used the 1060-nm OCT device to compare the relationship between choroidal thickness and age, refractive error, axial length and reported that the most associated factor with SFCT was age.[17] Because the choroidal tissue is highly vascularized, the decrease of the SFCT with age may be explained by the effect of small vessel diseases in the elderly like the other tissues in the body.[6] Moreover, microvascular damage may decrease the flow of oxygen and nutrients from the choroid to RPE and the outer segments of the retina.[6]

After the description of the EDI technique, Spaide defined the term "Age related choroidal atrophy" in 2009 and gave rise to an opinion that the decrease of choroidal thickness in elderly might be associated with the pathogenesis of AMD.[19] In the present study, SFCT in AMD patients, both with non-neovascular and neovascular forms, was significantly reduced compared with the healthy individuals. Similarly, Chung et al. reported that the mean SFCT was 224 μm in 20 eyes without any chorioretinal pathologies, 177 μm in 17 eyes with non-neovascular AMD and 171 μm in 30 eyes with neovascular AMD.[25] Sigler and Randolph, reported that early AMD is associated with decreased SFCT.[26] Choroidal thickness seems to be decreasing from the early stages of the AMD but yet it is not clearly known in which way this interaction occurs. It has been suggested that the reduction of the flow of oxygen from the choroid to the retina may lead to AMD.[4,15,16] The decrease of the choroidal thickness may play a role in the natural course of AMD.[14,27] But still there is a question that either the choroidal atrophy and hypoxia leads to AMD or the choroidal thinning is a secondary result of AMD, or both.

In the present study, we did not find any statistically significant difference in SFCT between eyes with non-neovascular and neovascular AMD. Furthermore, in the group of patients with non-neovascular AMD in one eye and neovascular AMD in the fellow eye; no statistically significant difference was observed between both eyes. Additionally, in the patients with non-neovascular

AMD without geographic atrophy in one eye and neovascular AMD without subfoveal scarring in the fellow eye; SFCT measurements were similar between both eyes. However, among the eyes with non-neovascular AMD, those with geographic atrophy had a further reduction in SFCT and among the eyes with neovascular AMD, those with subfoveal scarring had a further reduction. Factors mostly influencing the SFCT seems to be the presence of geographic atrophy and subfoveal scarring. SFCT in the eyes with the signs of advanced AMD was significantly reduced compared with the eyes without the signs of advanced AMD. Therefore, one can suppose that the progression of the disease is associated with reduced SFCT.

As seen in the present study, both in healthy eyes and eyes with AMD, SFCT measurements can be performed easily with the EDI technique. But, this technique has some limitations that have to be mentioned. Firstly, media opacities like corneal scars, cataract, and vitreous hemorrhage block the light and the choroid cannot be imaged.[24] Besides, highly elevated pigment epithelial detachments, subretinal and/or intraretinal fluids, choroidal neovascular membranes and subfoveal scars may decrease the penetration of the light to the deeper tissues and choroid cannot be imaged in detail. In our study, SFCT could not be measured in five eyes with neovascular AMD because of the thickness of the subfoveal fluid and fibrous tissue. Another limitation of the EDI technique is that the SFCT measurements have to be performed manually. Although high repeatability and reproducibility of the SFCT measurements with this technique have been reported, possible automated measurement with the software may be timesaving and more accurate.[8-10]

In conclusion, the mean SFCT reduces with increasing age. We have also found a significant reduction in the SFCT of eyes with AMD, both in neovascular and non-neovascular subgroups. Additionally, the severity of the disease seems to be related with a further reduction in SFCT.

Ethical Approve

This study was approved by the Ethics Committee of Necmettin Erbakan University Meram Medicinal Faculty.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Conception and Design: *Selman Belviranlı, Nazmi Zengin;* ***Acquisition of Data:*** *Selman Belviranlı, İsmail Doğru;* ***Analysis and Interpretation of Data:*** *Selman Belviranlı, Nazmi Zengin, Günhal Şatırtav, Gülfidan Bitirgen;* ***Statistical Analysis:*** *Selman Belviranlı, Gülfidan Bitirgen;* ***Drafting of the Manuscript:*** *Selman Belviranlı, İsmail Doğru, Gülfidan Bitirgen;* ***Critical Revision of the Manuscript:*** *Selman Belviranlı, Nazmi Zengin, Günhal Şatırtav;* ***Final Approval of the Manuscript:*** *Selman Belviranlı, Nazmi Zengin, Günhal Şatırtav, İsmail Doğru, Gülfidan Bitirgen.*

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