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Analysis of choroidal thickness in dry type of age-related macular degeneration using spectral-domain optical coherence tomography

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Abstract

To evaluate and compare the choroidal thickness in old-aged (>45 years) patients with dry type of age related macular degeneration and age-matched normal population using spectral-domain optical coherence tomography. A cross-sectional study was conducted in a tertiary eye clinic center. The study consists of 2 study and 1 control groups. Fifty-three eyes of 27 patients and 56 eyes of 28 patients who were firstly diagnosed with dry type of age related macular degeneration were participated in the study groups and 64 eyes of 32 individuals without any retinal or choroidal disorder were participated in the control group. All 173 eyes underwent a detailed ophthalmologic examination including optical coherence tomography. An experienced observer measured choroidal thickness using spectral-domain optical coherence tomography. No statistically significant difference was established between the means of age among three groups. The distribution of choroidal thickness measurements demonstrated a normal distribution in all 3 groups. No statistically significant differences were found between the study groups in terms of mean choroidal thickness, but there were significant differences in mean choroidal thickness between the control group and both study groups. In our study, it was observed that choroidal thickness can be analysed by spectral-domain optical coherence tomography and choroidal thickness in patients with dry type of age related macular degeneration is appeared to be thinner than normal age-matched population.

Keywords: Age related macular degeneration, choroidal thickness, optical coherence tomography

Introduction

Age-related macular degeneration (AMD) is a degenerative retinal disease, presumably caused by both genetic and environmental factors [1]. AMD is a major cause of blindness in the elderly population and is the most common cause of irreversible vision loss in the developed world [2]. In clinical practice AMD can be classified into nonexudative (dry) and exudative (wet) types according to imaging tests and physical examination findings. Dry AMD is characterized by abnormal deposits known as drusen and progressive atrophy of photoreceptors and retinal pigment epithelial cells on the macula. Geographic atrophy (GA) represents the late stage of dry AMD and is typically defined as a round or oval area of 175 μ m or more at fundus photography. Due to the atrophy of outer retinal layers and retinal pigment epithelium (RPE), choroidal vessels are well visible at fundus examination. Visual acuity (VA) can still be good if the macula is spared, but VA impairment occurs in case of foveal involvement. Wet AMD is characterized by the formation of choroidal neovascular membrane (CNVM) that results in development of exudate, subretinal fluid, and hemorrhage. Although the exact pathophysiology of AMD is relatively poorly understood, researches have concentrated on the RPE/photoreceptor/Bruch's membrane complex, vascular endothelial growth factor (VEGF)-A, and the complement factor H (CFH) gene [3-5].

Besides, there is no satisfactory method to treat dry AMD yet. The Age-Related Eye Diseases Study (AREDS) concludes that patients with early or moderate dry AMD should consume adequate quantities of antioxidants [6]. With the promising results of anti-VEGF treatment of exudative ARMD, the application of photodynamic therapy (PDT) with verteporfin have been decreased [7-9].

Over the last years, optical coherence tomography (OCT) has become an important imaging modality in the field of ophthalmology [10]. OCT provides a high-resolution, cross-sectional, and 3-dimensional reconstructed view of the retina in vivo in a noninvasive, reproducible manner [11]. Although OCT is widely used to follow up the progression of macular thickness and response to treatment of wet AMD with anti-VEGF agents, currently little is known about the choroidal thickness of patients with AMD [12]. In comparison with the original time-domain OCT devices, newer Fourier spectral-domain (SD) OCT permits faster scanning speeds, up to 52 000 A-scans/second and provides better tissue resolution and more accurate qualitative - quantitative analysis in various macular diseases. These features allow SD-OCT devices to view intraocular structures such as choroidal tissue [13,14].

The choroidal thickness (ChT) in normal population and patients with retinal diseases has been measured by using eye tracking software, frame averaging, image inversion and increased

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wavelength for better choroidal signal penetration [15,16]. With the latest software upgrades of both the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) and Cirrus-HD OCT (Carl Zeiss Meditec, Dublin, California, USA) spectral-domain devices; now, clinicians have the opportunity to obtain choroidal thickness measurements routinely.

There are several studies that have investigated changes in choroidal structure and depth with increasing age and conditions such as high myopia and central serous chorioretinopathy (CSCR) [17-19]. However, the changes of choroidal thickness in patients with AMD has been little studied. So, in our study we aimed to evaluate and compare the thickness of choroid in patients with dry AMD and age-matched normal population using SD-OCT.

Material and Methods

The study was conducted at a single center in accordance with the tenets of the Declaration of Helsinki and written informed consent was obtained from the participants. The study was approved by the institutional review board. A cross-sectional and comparative study was performed. The study was composed of 3 groups. Fifty-three eyes of 27 patients with early dry AMD were included in the study group 1. The study group 2 was consisting of 56 eyes of 28 patients with intermediate dry AMD. Control group was composed of 64 eyes of 32 healthy individuals. The study groups were formed according to grades of AMD. Grades were defined using the Clinical Age-Related Maculopathy Staging system: grade 1, no AMD (no drusen or a few small drusen $< 63 \mu\text{m}$); grade 2, early AMD (intermediate-size drusen $63\text{--}124 \mu\text{m}$); grade 3, intermediate AMD (large drusen $\geq 125 \mu\text{m}$); grade 4, GA (with or without foveal involvement) [20]. Patients who had GA, exudative AMD, amblyopia, refractive errors $>\pm 6.0$ diopters (D), significant media opacity, CSCR, hypertensive-diabetic retinopathy, epiretinal membrane, macular edema or any other retinal disorder were excluded. In the control group, any individual who had any kind of retinal or choroidal disorders was excluded. In all groups any patient or individual who had history of retinal detachment, previous vitrectomy, previous intravitreal injection, intraocular surgery (including cataract surgery) within 1 year, history of ocular trauma and glaucoma were also excluded. All eyes in the study underwent a complete ophthalmologic examination including best-corrected visual acuity (BCVA), slit lamp anterior segment and fundus exam, color fundus photography, fundus fluorescein angiography (FFA), and OCT. VA was measured with Snellen chart and all Snellen VA measurements were converted to logarithm of the minimal angle of resolution (logMAR) for statistical analysis. Participants with BCVA < 0.30 logMAR were only included in the study.

An experienced observer measured choroidal thickness at 5 sites with high-definition horizontal 5-line raster scans by using SD Cirrus-HD OCT (Carl Zeiss Meditec, Dublin, California, USA). Mean ChT at each of the 4 locations other than fovea were measured at $1500 \mu\text{m}$ (1.5 mm) intervals nasal (N), temporal (T), superior (S) and inferior (I) to the fovea (F). ChT was measured manually using the enhanced-depth imaging (EDI) technique with the help of Cirrus Eye Explorer software version (Carl Zeiss Meditec, Dublin, California, USA) [21]. It was performed by placing the SD-OCT instrument close enough to the eye to obtain an inverted image. All images were obtained using an eye-tracking system, and 50-100

scans were averaged automatically to improve the signal-to-noise ratio in the dimmed light in the afternoon. The vertical distance between the hyperreflective line of Bruch's membrane and the choroid-scleral interface was defined as the subfoveal choroidal thickness (SFCT) (Figure 1). SFCT was measured with the aid of the horizontal and vertical line B-scan images through the center of the fovea.

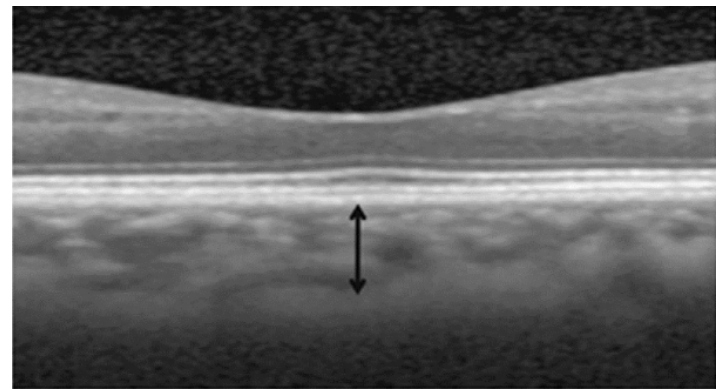


Figure 1. The vertical distance between the hyperreflective line of Bruch's membrane and the choroid-scleral interface the subfoveal choroidal thickness

All analyses were conducted using SPSS software (Version 18.0 for Windows, SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as 'mean $\pm$ SD'. The distribution of data was analysed with Kolmogorov-Smirnov test. Since data conformed to a normal distribution, the statistical analysis was performed with the help of one-way analysis of variance test (ANOVA), Independent t test and Pearson's correlation test. A p value of < 0.05 was considered statistically significant.

Results

The study group 1 included 11 males (40.7%) and 16 females (59.3%) and mean age was 51.42 ± 5.08 years. The study group 2 included 12 Males (42.9%) and 16 females (57.1%) and mean age was 53.66 ± 4.74 years. The control group included 10 Males (31.3%) and 22 females (68.7%) and mean age was 52.61 ± 5.12 years. No statistically significant difference ($p=0.38$) was found between the mean age of the groups. The mean of BCVA was 0.21 logMAR, 0.26 logMAR and 0.15 logMAR for the study group 1, 2 and control group, respectively.

The values of the mean ChT at 5 different sites are shown on Table 1. The pattern of ChT in the macula in the study group 1 and 2 demonstrated the thickest choroid located subfoveally, with nasal, temporal, superior and inferior thinning, maintaining a similar pattern seen in the control group. We did not observe any significant difference among the mean ChT in any sites between study group 1 and 2 ($P=0.236$, $P=0.166$, $P=0.330$, $P=0.822$, $P=0.763$ for subfoveal, nasal, temporal, superior and inferior locations, respectively). There was statistically significant difference ($P < 0.001$ for all sites) in the means of ChT in all locations between the control group and study group 1 and 2. The study group 2 had the lowest ChT values. The study group 1 had lower values than the control group.

In all groups, ChT measurements had strong intra-observer correlation at each of the 5 measurement locations (Table 1).

Study group 1 and 2 showed a statistically significant inverse correlation between age and SFCT ($r = -0.691$, $P < 0.001$; $r =$

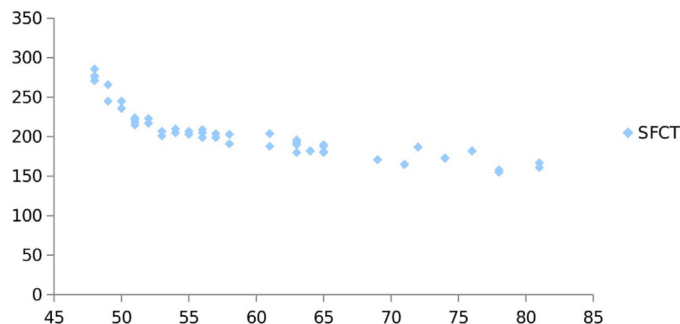
−0.638, $P < 0.001$; respectively) (See the Figure 2: The scatter plots for the study group 1). This relationship was weaker in the control group ($r = -0.593$; $P < 0.001$).

Table 1. Mean Choroidal Thickness and Intra-Observer Correlation of the Measurements

Location	Mean ChT (μm)–SG1	Mean ChT (μm)–SG2	Mean ChT (μm)–CG	P value*	Intra-observer correlation(r)**
Fovea	195.4±17.6	174.2±19.2	303.4±14.4	< 0.001	0.582/0.866/0.456
Nasal	189.3±15.0	172.6±15.8	300.4±14.4	< 0.001	0.601/0.727/0.588
Temporal	187.8±16.3	170.8±11.2	300.8±13.8	< 0.001	0.586/0.611/0.522
Superior	185.1±12.8	169.0±14.6	300.5±14.1	< 0.001	0.577/0.683/0.556
Inferior	182.8±14.4	167.3±10.8	300.9±13.8	< 0.001	0.574/0.640/0.496

SG1: Study Group 1, SG2: Study Group 2, CG: Control Group, *P values of choroidal thickness between the groups, Statistical analysis was calculated using the analysis of variance test; **For all r correlation values: $P < 0.001$ and the former value is for SG1 and the latter values were for SG2 and control group.

Age and SFCT Correlation



SCFT: Subfoveal choroidal thickness, x-axis for age and y-axis for SFCT

Figure 2. The scatter plots for the study group 1

Analysis also was performed to examine the relationship between BCVA and SFCT. No correlation was observed between SFCT and BCVA in the study group 1, 2 and control group ($r = -0.262$, $P = 0.052$; $r = -0.342$, $P = 0.064$ and $r = -0.176$, $P = 0.336$; respectively).

Discussion

Choroid is a highly vascular structure and provides nutrition to retina and removes waste products from the retinal pigment epithelium. Choroidal thickness varies with intraocular and perfusion pressure and choroidal metabolism is regulated by various vasoactive factors, including nitric oxide, endothelins, autonomic innervations and VEGFs [22–24]. Macula has the highest metabolic circulation in the retina, and this is thought to be the reason for the greatest choroidal thickness beneath the fovea.

Funk et al [25], observed increased VEGF-A in neovascular AMD which was induced by hypoxia and oxidative damage to the RPE. Consistent with the observed increased VEGF-A levels in neovascular AMD, anti-VEGF-A treatments have shown significant clinical benefit in patients with neovascular AMD [26].

ChT can be affected by age, refractive error, axial length, diurnal

variations, ocular perfusion pressure (OPP) and several other factors [27,28]. In the eye, OPP has been estimated using the systemic blood pressure and intraocular pressure (IOP) and has been considered an indirect indicator of choroidal blood flow and low OPP might cause a reduction in ocular blood flow, followed by choroidal blood flow insufficiency and hypoxia [29].

The structure and microcirculation of choroid is a major particular of interest in AMD. It is thought that AMD may be a vascular disease, a process beginning with insufficient perfusion of choroid leading to hypoxia and ischemia of the retinal pigment epithelium with the subsequent production of VEGF, which ultimately may result in the formation of choroidal neovascularization.30 It has shown that eyes with dry AMD have decreased blood volume and abnormal flow compared with normal eyes [31].

Optical coherence tomography (OCT) is a rapid, non-invasive imaging method capable of generating high-resolution optical cross-sections of the macula. OCT has also become a critical tool for assessing the morphological response of the retina and currently choroid to therapeutic interventions. OCT-derived measurements also have been used to determine the need for initial treatment and subsequent re-treatment in the management of AMD. These OCT-derived measurements of the SFCT are important outcome measures in clinical trials for choroidal pathologies [32].

Choroid has a dynamic and significant role in the pathogenesis of AMD. So choroidal thickness in AMD has been investigated. Therefore, in this study we aimed to compare ChT between normal eyes and eyes with dry AMD using the latest OCT imaging.

In a retrospective designed study, fifty-seven eyes of 47 patients with wet and dry AMD were evaluated to understand the relationship between choroidal thickness and AMD using SD-OCT.33 This study demonstrated that choroidal thickness can be measured by SD-OCT and variable choroidal thickness values exist among patients with the clinical diagnosis of wet and dry AMD. Most AMD patients in this study demonstrated thinner choroids than age-adjusted normal volunteers. Eyes with wet AMD demonstrated thinner average choroidal thickness than eyes with dry AMD. However, it was claimed that it is unclear at this time why in some eyes, choroidal thickness either increases or decreases with the disease and no direct correlation was found between choroidal thickness and duration of disease, number of intravitreal anti-VEGF injections, or visual acuity. In our study we aimed to compare the patients with only dry AMD and age-matched normal population. We excluded any other retinal or choroidal disease other than dry AMD to find a relationship between ChT and dry AMD using SD-OCT. We observed that there was a lower mean value of SFCT in the study group 1 and 2 with dry AMD than the control group of age-matched normal population. We also analysed the relationship between BCVA and subfoveal choroidal thickness. No correlation was found between BCVA and SCFT in both study groups and control group.

In another study, Spaide et al [34], issued a different topic, based on age-related choroidal atrophy. He observed overlap of choroidal atrophy with dry AMD in some patients. 28 eyes of 17 patients with a mean age of 80.6 ± 7.3 years were studied. The mean choroidal thickness of these eyes was less than 125 μm. The mean SFCT was 69.8 μm, and 35.7% (10 of 28) of the eyes were diagnosed with

late-stage AMD. It suggests that choroidal thickness decreases with increasing age and the choroidal circulation may play a role in the pathophysiology of AMD. With this regard, the study is parallel to our study, as we observed that there was a lower mean value of SFCT in patients with dry AMD.

Compared with normal eyes, eyes with dry AMD have decreased blood volume and abnormal flow and further worsening of blood flow with increasing disease severity [30,31]. This decreased choroidal blood flow in patients with AMD is thought to be a combination of narrowing of the choriocapillaries lumen, loss of cellularity, and thinning of the choroid, especially the choriocapillaries layer [35]. Moreover, eyes of patients with ARMD have been shown to have decreased nitric oxide and possibly this leads to vasoconstriction and hypoxia [36]. So, it is not unexpected that patients with dry AMD in our study had thinner average SFCT than age-matched normal volunteers, which may suggest a role for choroidal thinning in the pathogenesis or progression of AMD.

Ko A et al [37]. conducted an exploratory study using EDI mode of SD-OCT to determine if a correlation between ChT and drusen load exists in patients with dry ARMD. With this purpose, forty-four patients with dry AMD were recruited. The authors found an inverse correlation between choroidal thickness and drusen load. This finding suggests the conclusion of our study, which demonstrates an inverse relationship between choroidal thickness in patients with dry AMD and in age-matched normal population.

In a cross-sectional study, the authors aimed to compare retinal thickness and choroidal thickness in individuals (n = 16) with early AMD and in healthy controls (n = 16) using enhanced choroidal penetration, 3-dimensional OCT at 1060 nm [38]. They concluded a significant lower mean of retinal thickness but no significant difference of average SFCT in patients with AMD compared with control group. In contrast to this study we found a significant lower mean of SFCT in patients with AMD compared to age-matched normal population.

Kim JH et al [39]. retrospectively evaluated the variability in SFCT measurements in patients with AMD and CSCR using EDI-OCT. They revealed a significant positive correlation between SFCT and measurement variability including dry AMD. In particular, they stated a thin choroid in eyes with exudative and nonexudative AMD, which supports our study's findings.

Boonarpa N. et al [40]. reviewed a study to describe and evaluate a standardized protocol for measuring ChT using EDI OCT. They showed that the technique is accurate and reliable for routine clinical practice and research thus encouraged us to design this study.

Lains I. et al [41]. compared choroidal vascular features of eyes with and without subretinal drusenoid deposits (SDD), using swept-source optical coherence tomography. They concluded that in subjects with intermediate AMD, choroidal thickness and vessel volume are reduced in the presence of subretinal drusenoid deposits.

Spaide RF [42]. investigated the relationship between SFCT and disease manifestation in a series of eyes with nonexudative AMD. It was observed that a new form of drusen presentation could be

differentiated from typical soft drusen and was associated with thicker choroids. Disease manifestation in nonexudative AMD seems to be associated with choroidal thickness. Each of these has potential to lead to specific forms of late AMD.

Conclusion

In conclusion, the pathogenesis of dry AMD is closely related with choroidal structural and vascular abnormalities. Measurement of ChT in eyes of patients with dry ARMD compared with age-matched normal population using newest software technologies of SD-OCT (EDI mode) may have a useful role in understanding, analysing, follow-up and treatment response of in AMD. Therefore, in the present study the purpose was to evaluate and compare ChT in patients with dry AMD and normal age-matched population using EDI mode of SD-OCT. We concluded that ChT could be analysed by EDI mode of SD-OCT and ChT in the eyes of patients with dry AMD is appeared to be thinner than normal age-matched population.

This study has some limitations such as the number of patients, cross-sectional nature, absence of certified readers and scatter of light in very thick choroid. Further studies need to be carried out to understand the significance of choroidal thickness in dry or wet AMD with respect to visual function, disease progression and response to treatment over time.

Competing interests

The authors declare that they have no competing interest

Financial Disclosure

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