Evaluation of Structural Changes of Choroid in Intermediate Age-Related Macular Degeneration

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ABSTRACT

Purpose: To evaluate the structural changes in the choroid by binarization method in intermediate age-related macular degeneration (AMD) and to examine the correlation between parafoveal external retinal and internal retinal thinning.

Material method: Enhanced depth imaging optical coherence tomography images of 50 patients diagnosed with intermediary AMD and age matched 30 healthy subjects were analyzed retrospectively.

Results: Compared to the control group in the AMD group; the central choroidal thickness, choroidal area, stroma area and lumen area were found to be significantly reduced. There was no significant difference in the choroidal vascular index (CVI) compared to the control group in intermediate AMD. In the AMD group, significant thinning was found in the parafoveal inner and outer retinal thickness compared to the control group. When the correlation between parafoveal inner and outer retinal thicknesses and choroidal parameters were evaluated individually in the AMD group, no significant correlation was found.

Discussion: In non-neovascular intermediate AMD cases, there was a decrease in inner and outer retinal thicknesses, central choroidal thickness, lumen and stroma area of the choroid, however, the decrease in CVI was not prominent. No correlation was found to support the hypothesis that inner retinal thinning develops due to choroidal and/or outer retinal changes.

Keywords: Intermediate age related macular degeneration, enhance dept optical coherence tomography, binarization, choroidal vascular index.

INTRODUCTION AND OBJECTIVE

Drusen and retinal pigment epithelium (RPE) changes are characteristics and distinguishing features of dry age-related macular degeneration (AMD). According to Age-Related Eye Disease Study (AREDS) classification, AMD is classified as follows: category, a few, small or no drusen; category 2 (early AMD), several drusen, a few intermediate drusen and/or pigmentary changes in one or both eyes; category 3, extensive intermediate drusen or one or more large drusen in one or both eyes.[1] The likelihood of late AMD development within 5 years ranges from 2% to 20% in patients with intermediate drusen while it ranges from 13% to 47% in patients with large drusen.[2]

The choroid provides metabolic support to retinal pigment epithelium (RPE) and outer retinal layer. High blood flow and oxygen transport from choroid to these layers are required to maintain normal photoreceptor metabolism. Usually, progressive involutional changes develop in choroid by aging. Somewhat atrophy is anticipated in choroid by advancing age; however, the atrophy in AMD was found to be greater than atrophy attributed to aging.[3] A significant association was detected between increase in the extent of drusen and reduction in choroidal blood flow.[4, 5]

Based on current knowledge, it is controversial whether decreased choroidal blood flow and choroidal changes are primary stimulus in AMD pathogenesis or they are consequence of AMD. If decreased choroidal blood flow is primary stimulus, it is anticipated that retinal layer involvement will develop secondary to reduced choroidal blood flow. In this study, we aimed to demonstrate structural choroidal changes using in vivo binarization method and to evaluate whether potential outer retinal involvement has effect on inner retinal thickness.

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MATERIAL AND METHOD

The study was approved by Ethics Committee on Clinical Research of XXX University, Medicine School (approval#02-65-18). The study was conducted in accordance with tenets of Helsinki Declaration. The study was supported in the context of Project 18A0230005 by Coordination Committee on Scientific Research Projects of XXX University.

We retrospectively reviewed Enhanced Depth Imaging-Optic Coherence Imaging (EDI-OCT) and fundus images from 50 patients diagnosed with intermediate AMD in our clinic and 30 healthy controls between 2015 and 2020. The diagnosis of intermediate AMD was made based on Age-Related Eye Disease Study (AREDS) classification by reviewing fundus images.[6] The exclusion criteria included previous history of vitrectomy, retinal laser or intravitreal injection; maculopathy etiology other than AMD, refractive errors >3 diopter, optic neuropathy, glaucoma or age<60 years. The images with manufacturer signal index<15 (range: 0-40) were also excluded.[7]

OCT images were captured using Confocal Scanning Laser Ophthalmoscope (cSLO) Multicolor Imaging + Spectral Domain OCT (Spectralis®, Multicolor module, Heidelberg Engineering Inc., Heidelberg, Germany). Parafoveal inner retinal thickness, parafoveal outer retinal thickness and central choroidal thickness (CCT) were measured using device software. The inner retinal thickness was defined as distance from anterior surface of internal limiting membrane (ILM) to anterior surface of external limiting membrane (ELM) while external retinal thickness was defined as distance from anterior surface of ELM to posterior surface of RPE.

Choroidal area (CA), lumen area (LA), stromal area (SA) and choroidal vascularity index (CVI) were calculated by ImageJ software (version 1.50a; National Institute of Health) using binarization method. Before binarization, OCT images were converted to 8-bit image. Niblack binarization method was used to calculate lumen and stromal area at choroid tissue. The lumen area was determined using threshold tool. After adding space between pixels, choroidal area, lumen area and stromal area were calculated using software in automated manner. White pixels were considered as stromal area while black pixels were considered as lumen area (Figure 1).[8] The CVI was defined as LA/Total CA. Inter-group comparisons were performed regarding CCT, CA, LA, SA, CVI, inner retinal thickness and outer retinal thickness. We also evaluated the correlation of inner and outer retinal thickness with CCA, CA, LA, SA and CVI.

Data were analyzed using SPSS for Windows version 15.0 (Statistical Package for the Social Sciences). T test was used to assess difference in mean values while Mann Whitney U test was used to assess difference in median values among groups. In continuous variables, Spearman's correlation test was used to assess correlation in case of skewed distribution while Pearson's correlation test was used in case of normal distribution. A p value>0.05 was considered as statistically significant in all analyses.

FINDINGS

Mean age was 71.02 ±1.3 years in the AMD group and 70.56±2.1 years in the control group, indicating no significant difference between groups (p=0.38).

When retinal parameters were assessed, it was found that parafoveal inner retinal thickness was 102.7±12.0 µm in the AMD group and 113.0±5.9 in the control group, indicating significant difference between groups (**p<0.001**). It was found that parafoveal outer retinal thickness was 206.2±17.0 µm in the AMD group and 213.3±9.8 µm in the

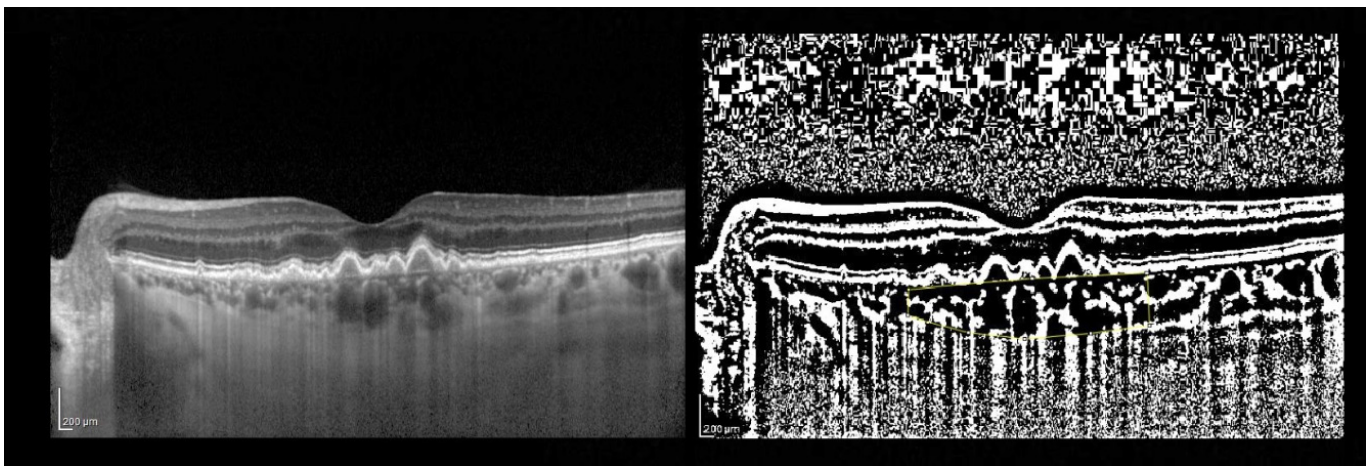

Figure 1: *A 72-years old female patient with intermediate AMD; black areas under retinal pigmentary epithelium show luminal area while white areas show stromal choroid tissue.*

control group, indicating significant difference between groups (**p=0.034**).

When choroidal parameters were assessed, it was found that CCT was 197.1±76.0 µm, in the AMD group and 280.3±89.3 µm in the control group, indicating significant difference (**p<0.001**). After binarization, CA was 0.58±0.2 mm^2 in the AMD group and 0.94±0.3 mm^2 in the control group (**p<0,001**); LA was 0.43±0.15 mm^2 in the AMD group and 0.70±0.22 mm^2 in the control group (**p<0.001**); SA was 0.15±0.05 mm^2 in the AMD group and 0.25±0.07 mm^2 in the control group (**p=0.024**), indicating significant differences between groups. The CVI was calculated as 0.74±0.26 in the AMD group and 0.73±0.19 in the control group, indicating no significant difference (p=0.48) (**Table 1**). No significant correlation was found between individual choroidal parameters and parafoveal inner or outer retina thickness in the AMD group (**Table 2**).

DISCUSSION AND CONCLUSION

In our study, a significant decrease was detected in parafoveal inner and outer retinal thicknesses and all choroidal parameters in intermediate AMD when compared to healthy controls. However, no significant difference was detected in CV between AMD group and healthy controls since there was simultaneous decrease in both lumen and stromal area in choroid. Thus, it isn't possible to suggest that vascularity was preferentially involved. Again, no significant difference was detected in correlations which were assessed to test the hypothesis that structural choroidal changes trigger reduction in inner and outer retinal thicknesses.

In previous years, many studies have been performed to investigate the relationship between AMD and choroidal thickness and it has been shown that choroidal is thinned by progression of dry AMD even at early disease.[9-11] In wet AMD, choroidal thickening has been reported.[12] However, choroidal thickness measurements limited one or few macular localization show smaller extent of structural changes in choroid. The binarization method, described in recent years, and the CVI, described by Agrawal et al.,[13] have changed our understanding about structural changes in choroid and pathogenesis and course of retinal diseases, respectively. The CVI is used as an index for changes in choroidal vascularity. Unlike measurement of choroidal thickness, the CVI isn't affected by age and ocular or systemic parameters; thus, it is a reliable parameter in quantification of vascular changes in choroid.[14, 15] Although automated segmentation software hasn't been developed, CVI can be measured manually using several software.

Table 1: *Retinal and choroidal parameters measured in AMD and control groups.*

	AMD n=50 (Mean ± SD)	**Control n=30** (Mean ± SD)	**P value**
Inner retinal thickness, µm	102.7±12.0	113.0±5.9	**p<0.001**
Outer retinal thickness, µm	206.2±17.0	213.3±9.8	**p=0.034**
CCT, µm	197.1±76.0	280.3±89.3	**p<0.001**
Choroidal area, mm^2	0.58±0.2	0.94±0.3	**p<0.001**
Luminal area, mm^2	0.43±0.15	0.70±0.22	**p<0.001**
Stromal area, mm^2	0.15±0.05	0.25±0.07	**p=0.024**
CVI	0.74±0.26	0.73±0.19	p=0.48

SD: Standard deviation. AMD: Age-related Macular Degeneration. CCT: Central Choroidal Thickness. CVI: Choroidal Vascularity Index

Table 2: *Correlation between retina and choroidal parameters in AMD group.*

P values*	**Inner retinal thickness**	**Outer retinal thickness**
CCT	0.259 (rho=0.180)	0.412 (rho=0.132)
CA	0.414 (rho=0.125)	0.299 (rho=0.158)
LA	0.355 (rho=0.141)	0.302 (rho=0.157)
SA	0.508 (rho=0.101)	0.340 (rho=0.145)
CVI	0.975 (rho=-0.050)	0.302 (rho=0.157)

*Spearman's rho correlation test. rho: correlation coefficient

In our study, no significant difference was detected in the CVI if thinning at choroidal lumen and stroma was comparable. In a study on structural changes of choroid in dry AMD, Corvi et al. found decrease in total choroidal area, lumen area and stromal area in dry AMD; when compared to controls; however, no change was detected in CVI. The decrease in the choroidal parameters continued progressively over 24-months follow-up and CVI remained unchanged.[16] In a study on Hindu patients, Koh et al. showed CVI reduction in AMD group when compared to controls.[17] However, the study included both patients with dry and wet AMD. It has been reported that there is an increase in choroidal thickness in the wet AMD unlike dry AMD. Thus, the results of the study may be affected by mix study population.

In our study, it was found that there was a decease in parafoveal inner and outer retinal thicknesses in intermediate AMD. The thinning in outer retinal layers can be affected by choroidal lumen area and resultant reduction in blood flow.[4, 5] Several hypotheses have been proposed to explain decrease in inner retinal layers in AMD. In one hypothesis, it is proposed that the thinning in inner retinal layer may occur due to alterations in superficial retinal capillaries leading decreased inner retinal perfusion and ischemia. However, the reason for changes in superficial retinal capillaries remains to be unknown. Another hypothesis is that synaptic malformation due to photoreceptor loss can trigger inner retinal degeneration by decreasing trans-neuronal input to inner retina via post-receptor degeneration resulting.[18-24]

To best of our knowledge, this is the first study investigating relationship between choroid parameters and retinal thickness in AMD in direct manner. Both parafoveal inner and outer retinal thicknesses were found to be decreased in intermediate AMD. No correlation was detected between parafoveal inner and outer retinal thickness in AMD; in addition, no relationship was found between retinal thicknesses and choroid parameters. These findings provides no support to the hypothesis that reduction in inner retinal thickness develops due choroidal and/or outer retinal alterations. This may be due to limited sample size in our study. Again, the losses in other retinal and choroidal parameters during follow-up may be correlated with each other. Thus, prospective, longitudinal series are needed to assess correlations between losses in retinal and choroidal parameters after a certain follow-up period in newly diagnosed patients. In recent studies, it was shown that there is an association between changes in choriocapillaris flow and pathogenesis and progression of AMD.[25] The CVI shows changes in Haller's and Sattler's layers rather than choriocapillaris. In our study, one limitation is that we failed to assess correlation between choriocapillaris flow and retinal changes.

In conclusion, CVI is a now, eye-opening concept about our understanding in retinal diseases. No reduction was detected in CVI due to parallel reductions in SA and LA in intermediate AMD. The transition from intermediate AMD to advanced AMD, in other words, CVI reduction or disease progression, may be due to greater reduction in luminal area than those in stromal area. The hypothesis involving decrease in choroidal area, luminal area and stromal area and outer retinal thickness; followed reduction in inner retinal thickness due to potential post-receptor degeneration is an important issue which may change follow-up and treatment protocols in AMD.

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