Evaluation of choroidal thickness in cases with age-related macular degeneration

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Received: 2014-03-11 Accepted: 2014-08-06

年龄相关性黄斑变性的脉络膜厚度评价

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摘要

目的:通过光学相干断层扫描(optical coherence tomography, OCT; RTVue 100-2; V 5.1, Optovue, Fremont, CA, USA)测量比较非新生血管性与新生血管性年龄相关性黄斑变性(age-related macular degeneration, AMD)黄斑中心凹下脉络膜厚度(subfoveal choroidal thickness, SFCT),并分析脉络膜厚度(choroidal thickness, CT)对AMD新血管形成的影响。

方法:本研究为回顾性、横断面研究。以单侧眼患有新生血管性AMD且对侧眼患有非新生血管性AMD的24例患者(48眼)作为研究组,选取年龄与眼轴长度相匹配的40例健康眼作为对照组。非新生血管性AMD亚组研究对象是黄斑区有玻璃疣和/或色素变化眼,而新生血管性AMD亚组研究对象是由于脉络膜新生血管而致视网膜下或视网膜内有渗出液和/或脂性渗出眼。运用OCT垂直测量外侧高反射线(视网膜色素上皮层)到脉络膜巩膜交界面间的距离。选取7个不同点进行脉络膜厚度测量,测量区域为距黄斑中心凹颞侧和鼻侧1500μm范围,测量间距为500μm。测量结果在亚组间进行统计学对比研究。

结果:研究组患者平均年龄为72.4±8.97(60~82)岁,对照组受试者平均年龄为71.2±8.8(58~81)岁。新生血管性AMD组中平均SFCT明显大于非新生血管性AMD组的厚度($P<0.05$)。非新生血管性AMD组中,平均SFCT与平均鼻、颞侧脉络膜厚度比较,差异无统计学意义($P>0.05$);而新生血管性AMD组中,平均SFCT与平均鼻、颞侧脉络膜厚度比较,差异有统计学意义($P<0.05$)。

结论:运用OCT对脉络膜厚度进行测量,有助于理解AMD的病理生理机制。然而,仍需要大型前瞻性研究来探求新生血管性AMD中SFCT增厚的原因。

关键词:脉络膜厚度;年龄相关性黄斑变性;光学相干断层扫描

引用:Unsal E, Eltutar K, Osmanbasoglu OA, Zırtıloglu S, Kızılay O, Gungel H. 年龄相关性黄斑变性的脉络膜厚度评价. 国际眼科杂志 2014;14(9):1561-1566

Abstract

• AIM: To compare subfoveal choroidal thickness (SFCT) between cases with non-neovascular age-related macular degeneration (AMD) and neovascular AMD by optical coherence tomography (OCT) and to evaluate the contribution of choroidal thickness (CT) measurements to the understanding of pathogenesis of neovascularization in AMD.

• METHODS: Fourty-eigth eyes of 24 patients who had neovascular AMD in one eye and non-neovascular AMD in the other eye were included in this retrospective, cross-sectional study as study group. Forty eyes of healthy, age and axial length matched individuals were selected as the control group. Eyes with drusen and/or pigmentary changes were included in the non-neovascular AMD subgroup. Eyes with subretinal or intraretinal fluid and/orlipid exudation due to the choroidal neovascularization were included in the neovascular AMD subgroup. OCT measurements were performed with RTVue 100-2 (V 5.1, Optovue, Fremont, CA, USA) perpendicularly from the outer part of the hyperreflective line (retinal pigment epithelial layer) to the line corresponding to the choroido-scleral junction. Choroidal thickness was measured at 7 different points, 500μm intervals up to 1500μm temporal and nasal to the fovea in the study group and compared statistically between subgroups.

• RESULTS: The mean age of patients was 72.4±8.97 (60-82)y. The mean age of healthy individuals was 71.2±8.8 (58-81)y. Mean SFCT of neovascular AMD group were significantly thicker than non-neovascular AMD group ($P<0.05$). In non-neovascular AMD group, there was no statistically significant difference between the mean SFCT and the mean temporal-nasal choroid thickness ($P>0.05$). In neovascular AMD group, there was a statistically significant difference between the mean SFCT and the mean temporal-nasal choroid thickness ($P<0.05$).

• CONCLUSION: Choroidal thickness measurements with OCT device can make a contribution to the understanding the phatophysiology of AMD and large prospective studies should be conducted to understand why SFCT was thicker

in neovascular AMD.

• KEYWORDS: choroidal thickness; age-related macular degeneration; optical coherence tomography
DOI:10.3980/j.issn.1672-5123.2014.09.01

Citation: Unsal E, Eltutar K, Osmanbasoglu OA, Zırtıloglu S, Kızılay O, Gungel H. Evaluation of choroidal thickness in cases with age-related macular degeneration. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2014;14(9):1561-1566

INTRODUCTION

It is assumed that the oxygen used by retina is supplied 5% by retinal artery and 95% by choroid vessels[1]. The choroid accounts for 85 percent of ocular blood flow and play a major role in the oxygenation, nourishment and viability of retinal pigment epithelium and the outer retinal layers, which have the highest metabolic activity. A healthy choroid is essential for outer retinal layers. Until recently, choroid can be evaluated only by indocyaningreen angiography, laser flowmeter and ultrasonography. Even though these techniques show us choroidal vessel abnormalities and blood flow changes, they can not show three-dimensional anatomy of choroid layers and retinal pigment epithelium.

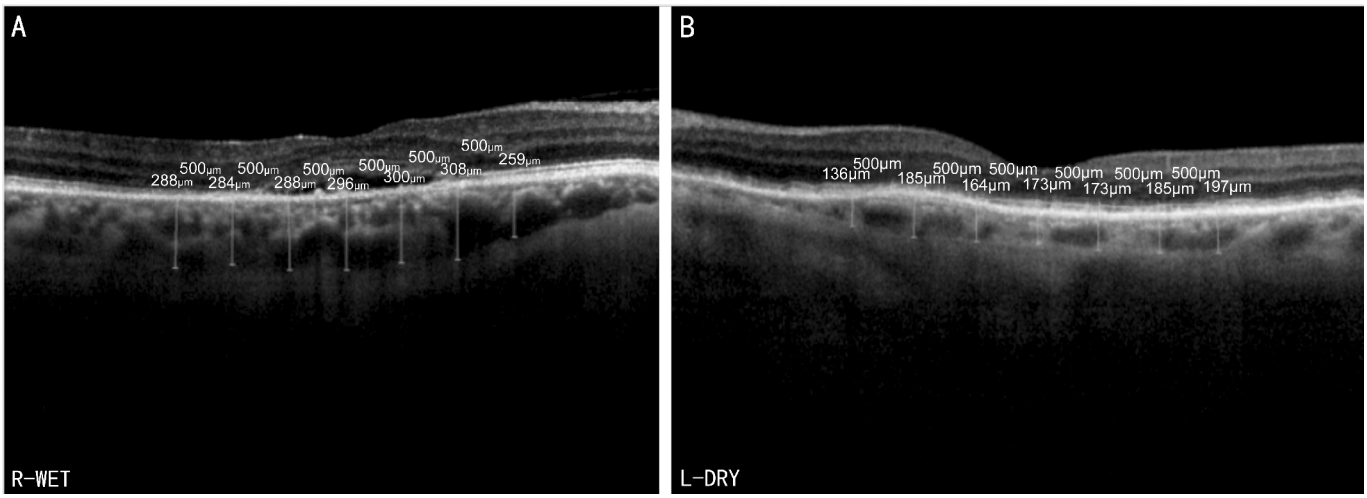
Optical coherence tomography (OCT) is an noninvasive imaging modality, which is used in acquiring high-resolution sections of retina. Recently, enhanced-depth imaging spectral domain optical coherence tomography (EDI) is described. This EDI software automatically captures the cross-sectional image with the choroid close to the zero delay line to maximize the sensitivity on the outer limit of the choroid[2,3]. Previously, the reason of inadequate choroidal imaging was that passing of the beam through the retinal pigment epithelium insufficiently. Now, this enhanced software allows to detect structural changes "beyond the retinal pigment epithelium (RPE)", like the choroid and lamina cribrosa[2]. In age-related macular degeneration (AMD), OCT indicating lesions and their size brings into connection with angiographies, makes it easy to decide the treatment of choice and helps us to follow-up cases. It is very helpful to indicate neovascular features of choroidal neovascular membrane (CNVM) like macular edema, subretinal fluid and pigment epithelial detachment (PED). Also after advances in antiangiogenic treatment, OCT is more useful than fundus fluorescein angiography in monthly cilinical routine examinations to decide repeated injections. Even though the etiology of AMD is still not known, there are some theories like aging of RPE, genetic and ocular perfusion defects. The decrease of choroidal blood flowing at the foveal region in non-neovascular AMD patients supports this ischemic theory secondary to perfusion defects[4-8]. Also many studies have been published before regarding the physiological and pathological changes arise from perfusion defects of choriocapillaris in AMD[9-13].

In literature, there are many studies: evaluating choroidal thickness measurements of patients with non-neovascular AMD of four different stages[14], comparing choroidal thickness measurements between neovascular and non-neovascular AMD patients with control group[15,16], comparing choroidal thickness measurements between "eyes with neovascular AMD with antivascular endothelial growth factor (anti-VEGF) treatment history and without anti-VEGF treatment history" and other eyes of the same patients with non-neovascular AMD[17], comparing choroidal thickness measurements between eyes with non-neovascular AMD and other unaffected eyes of the same patients, and comparing choroidal thickness measurements between "eyes with neovascular AMD with subgroups of intraretinal and subretinal edema, detachment of retinal pigment epithelium and fibrous scar formation" and other unaffected eyes of the same patients[18]. In our study we planned to evaluate the choroidal thickness (CT) of the eyes with non-neovascular AMD with OCT and compare it with the same patients fellow eyes with neovascular AMD that share the same genetic background and are exposed to same environmental factors. The purpose of this study is to compare choroidal thicknesses with OCT measurements between neovascular and non-neovascular AMD; and to evaluate contribution of choroid to the pathology of AMD.

SUBJECTS AND METHODS

Subjects Fourty-eigth eyes of 24 patients with the diagnosis of neovascular AMD in one eye and non neovascular AMD in the other eye were included in this retrospective and cross-sectional study and accepted as study group. Control group consists of 40 eyes of 20 healthy individuals of the same age, whose visual acuity was 20/20 and does not have any retinal or choroidal pathology. Informed consent was obtained from every patient. The study was performed in accordance with the tenets of Helsinki Decleration. The study protocol was approved by the Clinical Research Ethics Committee of Istanbul Training and Research Hospital.

Methods In the first visit, detailed systemic and ophthalmological medical history of patients were taken and routine ophthalmological examination including visual acuity measurement with Snellen chart, slit lamp examination, intraocular pressure measurement with Goldmann applanation tonometry and dilated fundus examination with 90 D lens were done. At first visit and during the follow-up, fundus fluorescein angiographic (FA) examinations were done when needed. Eyes without exudative disease, including only drusen and/or pigmentary abnormalities regardless of the amount and size (also confirmed by FA as no leakage or pooling) were included in the non-neovascular AMD subgroup. Eyes with subretinal and/or intraretinal fluid-lipid exudation or membrane dense plaques secondary to choroidal neovascular membrane (CNVM) which is developed from choriocapillaris in the subfoveal region were included in the neovascular AMD subgroup. Eyes with neovascularization were treated with current therapies with bevacizumab and/or ranibizumab. The exclusion criteria included any ocular illnesses such as the presence of macular abnormality other



Figures 1 Representative images are shown OCT images of the same patient with neovascular. AMD in the right eye (A) and non-neovascular AMD in the left eye (B).

than AMD, glaucoma, previous ocular surgery or trauma, refractive error (RE) ranging outside -3.00-+3.00 diopters and inability to cooperate during screening by OCT examination. Eyes with corneal or vitreal opacity or cataract which can deceive CT measurements were also excluded from the study. Eyes with subretinal fibrosis, disciformscar and geographic atrophy and also eyes with massive retinal, subretinal or subretinal pigment epithelial hemorrhage that avoided accurate choroidal visualization were not included.

OCT measurements were performed with the same OCT device (V 5.1, RTVue 100-2, Optovue, Fremont, CA, USA) by the same person with the "chorioretinal line" mode after pupillary mydriasis (>5mm) only in the morning (9.00a.m.-11.00a.m.). Only measurements with 60 or higher reliability index, which is specified by the manufacturer of OCT device, were included in the study. Central macular thickness was measured automatically with the software of the system using MM5 mode. A fovea-centered horizontally 0.3mm long line is used for the choroidal evaluation. Measurement was performed perpendicularly from outer part of the hyperreflective line (retinal pigment epithelial layer) to the line corresponding to choroido-scleral junction, vertically. Choroidal thickness was measured using the manual calipers provided by the device software. SFCT measurement (M) and measurement of choroidal thicknesses at every 500μm temporal and nasal to the foveal center was performed and named as choroidal thicknesses as T500 (500μm temporal distance from central fovea), T1000 (1000μm temporal distance), T1500 (1500μm temporal distance), N500 (500μm nasal distance), N1000 (1000μm nasal distance) and N1500 (1500μm nasal distance) (Figure 1).

Ocular axial lengths were measured using interferometry (IOL Master 500 Carl Zeiss Meditec, Jena, Germany). Cases, which have 0.3 mm or more axial length difference between right and left eye were also excluded from the study.

Statistical Analysis Statistical analyses were made using commercially-available software SPSS version 15.0 (SPSS Inc., Chicago, IL). For the statistical analyses, the mean±SD of the differences was calculated. CT at 7 different localizations compared between neovascular and non-neovascular eyes of the same patient.

The suitability of variables for normal distribution was examined by using the Shapiro-Wilk test. The statistical analysis was done using one-way analysis of variance (ANOVA) for intergroup comparison, Post-hoc test, using Tukey's method were adopted. Paired sample t-test was used to compare the dependent variables which are normally distributed. $P<0.05$ value is accepted as statistically significant.

RESULTS

The mean age of patients was 72.4±8.97 (60-82) y in the study group. The mean age of control group was 71.2±8.8 (58-81) y. There was no statistically significant difference between groups regarding the age ($P=0.876$). The mean axial length was 23.20±0.91mm in eyes with non-neovascular AMD, 23.19±0.90mm in eyes with neovascular AMD and 23.08±0.94mm in control group. There was no significant difference between axial lengths in between groups and subgroups ($P>0.05$).

In eyes with non-neovascular AMD, measurements of mean SFCT, T500, T1000, T1500, N500, N1000, N1500 were 221, 216, 226, 220, 222, 212, 213μm respectively. In eyes with neovascular AMD, they were 310, 286, 272, 265, 276, 266, 259μm respectively (Table 1). In control group, they were 259, 257, 249, 244, 253, 245, 230μm, respectively (Table 1). The mean SFCT of neovascular AMD group was significantly thicker than non-neovascular AMD group ($P<0.05$) (Table 2, Figure 2).

In non-neovascular AMD group, there was no statistically significant difference between the mean SFCT and the mean temporal-nasal choroid thicknesses ($P>0.05$). In neovascular AMD group, there was a statistically significant difference between the mean SFCT and the mean temporal-nasal choroid thickness in all temporal and nasal distances ($P<0.05$), except T500 ($P=0.063$) (Table 3).

Table 1 Mean choroidal thicknesses Mean CT (μm)

Location (μm From Fovea)	Neovascular AMD	Non-neovascular AMD	Control
SFCT	310±90. 16	221±36. 87	259±19. 25
T500	286±56. 26	216±40. 79	257±16. 68
T1000	272±33. 42	226±35. 76	249±14. 59
T1500	265±45. 88	220±35. 49	244±15. 87
N500	276±57. 24	222±37. 83	253±14. 75
N1000	266±57. 24	212±49. 08	245±13. 17
N1500	259±55. 81	213±36. 05	230±14. 89

AMD: age-related macular degeneration; SFCT: subfoveal choroidal thickness; T500: 500μm temporal distance from central fovea; T1000: 1000μm temporal distance; T1500: 1500μm temporal distance; N500: 500μm nasal distance; N1000: 1000μm nasal distance; N1500: 1500μm nasal distance.

Table 2 Comparisons of Choroidalthicknessesamonggroups

Location (μm From Fovea)	(Neovascular AMD)-(Non-neovascular AMD)	(Neovascular AMD)-control	(Non-neovascular AMD)-control
	P	*P*	*P*
SFCT	0. 000	0. 007	0. 064
T500	0. 000	0. 014	0. 001
T1000	0. 000	0. 005	0. 007
T1500	0. 000	0. 033	0. 016
N500	0. 000	0. 047	0. 010
N1000	0. 000	0. 095	0. 012
N1500	0. 000	0. 010	0. 137

AMD: age - related macular degeneration; SFCT: subfoveal choroidal thickness; T500: 500μm temporal distance from central fovea; T1000: 1000μm temporal distance; T1500: 1500μm temporal distance; N500: 500μm nasaldistance; N1000: 1000μm nasal distance; N1500: 1500μm nasal distance; *P*: values were performed byone-way ANOVA tests.

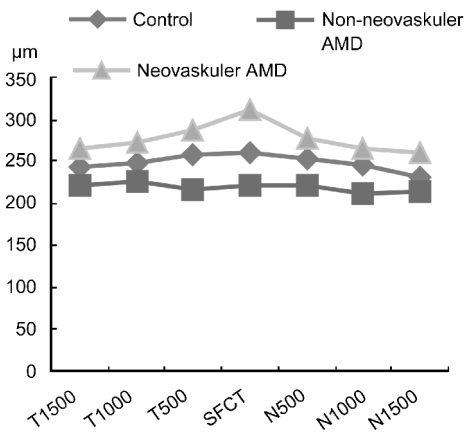


Figure 2 Mean choroidal thicknesses (μm) in cases with neovascular AMD, non - neovascular AMD and healthy subjects AMD: age - related macular degeneration; SFCT: Subfoveal choroidal thickness; T500: 500μm temporal distance from central fovea; T1000: 1000μm temporal distance; T1500: 1500μm temporal distance; N500: 500μm nasal distance; N1000: 1000μm nasal distance; N1500: 1500μm nasal distance.

DISCUSSION

Mean choroidal thickness of neovascular AMD group was found to be thicker than non-neovascular AMD group in this current study. There was no difference between SFCT and choroidal thickness of nasal and temporal quadrants of eyes with non-neovascular AMD. Regarding eyes with neovascular AMD, there was a statistically significant difference between the mean SFCT and the mean temporal - nasal choroid thicknesses in all temporal and nasal distances, except T500. In the previous reports, the CT was found to be thicker in the subfoveal area and was becoming thinner as we got nasal and temporal to the fovea in healthy younger subjects[19, 20]. However, in this study, we found no significant difference between the SFCT and nasal-temporal choroid thicknesses in the group of non-neovascular AMD patients. This was may be related to the thinner measurements of SCFT (about 221μm) according to the healthy control subjects (259μm). The eyes with neovascular AMD, SFCT was statistically thicker according tothe non-neaovascular subgroup and that can be explained by enhanced metabolic needs secondary to CNVM activity.

Table 3 Comparisons of choroidal thicknesses between SFCT and other locations

Parameters	*P*
Non-neovascular AMD	
SFCT- T500	0. 226
SFCT- T1000	0. 377
SFCT- T1500	0. 760
SFCT- N500	0. 889
SFCT- N1000	0. 182
SFCT- N1500	0. 291
Neovascular AMD	
SFCT- T500	0. 063
SFCT- T1000	0. 041
SFCT- T1500	0. 023
SFCT- N500	0. 014
SFCT- N1000	0. 001
SFCT- N1500	0. 000

AMD: age-related macular degeneration; SFCT: subfoveal choroidal thickness; T500: 500μm temporal distance from central fovea; T1000: 1000μm temporal distance; T1500: 1500μm temporal distance; N500: 500μm nasal distance; N1000: 1000μm nasal distance; N1500: 1500μm nasal distance; *P*: Paired sample *t*-test.

Earlier reports provide evidence of AMD-related morphologic changes asobliteration of choriocapillaris inmacular area[21], luminal narrowing and loss of the cellularity of choriocapillaries[12], and choroidal thinning, especially the choriocapillaris layer[13].

Chen *et al*[7] reported that patients with AMD have decreased vision, and delayed choroidal perfusion with fluorescein angiography (FA); and they mentioned that choroidal vascular dysfunction may have a role in AMD[7]. Pauleikhoff *et al*[8] and Boker *et al*[10] reported choroidal perfusion abnormalities with FA, and mentioned that these abnormalities may be caused by hypofluorescence secondary to fluorescence blockade in AMD with increased pigmentation or due to decreased choroidal circulation. Holz *et al*[22] determined that slow choroidal filling is a risk factor for geographicatrophy in patients with AMD and ischemia has an important role in

etiology of this situation. Prunte and Niesel[23] reported that lengthened arterial filling time and decreased choroidal blood flow is seen in indocyaninegreen angiography of patients with non-neovascular AMD. Metelitsine *et al*[6] determined in their prospective studies about foveolar choroidal circulation and CNVM that, decreased foveolar blood flow and volume is a sign of highly risk for developing CNVM in future. In AMD, CNVM development can be related with decreased choroidal circulation. This sign indicates us hypoperfusion and probable ischemia can be a stimulating factor for CNVM.

Harris *et al*[9] reported that decreased choroidal blood circulation and volume on Doppler laser flowmetry indicated AMD progression. Friedman *et al*[11, 24] showed in their study that sclera of AMD patients is rigid; and with color Doppler ultrasound imaging, blood circulation of central retinal artery and short posterior ciliary arteries is decreased and pulsation of them is increased. They indicated that decreasing compliances of sclera and choroidal vessels can cause an increase in resistance of choroidal vessels. In patients with AMD, a decrease in choroidal blood flow with Doppler imaging indicates AMD progression.

Jonas *et al*[18] compared three sub-groups with neovascular AMD, non-neovascular AMD and control patients regarding CT and found that there was no significant difference between all three sub-groups. Also Rahman *et al*[17] reported that there was no significant difference between neovascular AMD and early non-neovascular AMD. Unlike other studies Chung *et al*[15] reported that, SFCT of eyes with neovascular and early non-neovascular AMD was decreased compared to control group patients with the same age. McCourt *et al*[25] reported that the mean SFCT was 209.9μm in eyes with neovascular AMD, 162.4μm in eyes with non-neovascular AMD, 305.7μm in control group and found that the mean SFCT of both neovascular and non-neovascular AMD was significantly decreased compared to control group. Kim *et al*[16] also reported eyes with non-neovascular AMD, the mean SFCT was decreased compared to control group but there was no significant difference between eyes with neovascular AMD and control group. In this current study, the mean SFCT was 310μm in eyes with neovascular AMD eyes, 221μm in eyes with non-neovascular AMD.

Lee *et al*[14] evaluated correlation with SFCT and progress or severity of non-neovascular AMD. They indicated SFCT decreases while AMD progresses. There was a negative correlation between SFCT and geographic atrophy area, and they indicated SFCT can be used for following-up the progress of geographic atrophy.

There are many studies that indicate choroidal thickness[25,27] and choroidal blood flow[28,29] that they decrease with age. To eliminate age factor, we included the patients who have neovascular AMD in one eye and non-neovascular AMD in the other eye. It is known that refractive errors and axial length change CT[26, 27, 30]. For this reason, patients within -3.00 to +3.00 D of refractive error (RE) were included in this study. There was no significant difference between axial lengths of sub-groups.

In our study, there were some limitations. Eyes with neovascular AMD were from patients treated with bevacizumab and/or ranibizumab. There are some studies[31, 32] that indicate SFCT decreases with this treatment and some others[17] indicate that SFCT does not decrease by this treatment. Also we did not consider the time between intravitreal treatment and CT measurement with OCT and how many injections were applied. In some studies, it was incidated that optical opacities like cataract could change measurements of retina and it was layers like retinal nerve fiber layer (RNFL)[33-36]. So we excluded patients with corneal, lens or vitreous opacities. Tan *et al*[30] and Usie *et al*[37]. determined that CT is changing with circadian (diurnal) rhythm about 20-30μm; but we measured CT with OCT only in the morning hours (between 9.00a.m.-11.00a.m.).

In this study, weinterpreted CT as it was directly proportional to choroidal blood flow. But it might not be like that. We excluded eyes with geographic atrophy, which has partially capillary occlusion in macula.

In this study, CT was thinner in eyes with non-neovascular AMD than eyes with neovascular AMD. This detection confirms the theory that CT starts thinning in early AMD, choroid blood flow decreases and RPE cells and outer retinal layers can not be fed, and later those cells express neovascular growth factors. If those neovascular growth factors pass the threshold the disease progresses to neovascular AMD, but when those factors do not pass the threshold eyes become atrophic. Decreased choroidal blood flow causes residual materials like drusen not to be cleaned, and to accumulate in the macula.

Choroid measurements with OCT can be useful for understanding pathophysiology of disease in neovascular and non-neovascular cases. Large prospective studies should be conducted to understand why SFCT was thicker in neovascular AMD.

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