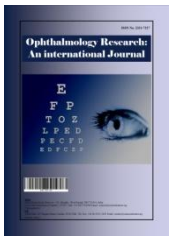

Ophthalmology Research: An International Journal

14(3): 6-17, 2021; Article no.OR.68428
ISSN: 2321-7227

Assessment of Subfoveal Choroidal Thickness with SD-OCT in Eyes with Different Stages of Age-Related Macular Degeneration (AMD)

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Authors' contributions

This work was carried out in collaboration between both authors. Author EP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author GK managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/OR/2021/v14i330193
Editor(s):
(1) Dr. Ahmad M Mansour, American University of Beirut, Lebanon.
Reviewers:
(1) Mithun Thulasidas, Sankara Eye Hospital, India.
(2) Izumi Yoshida Toho, University Sakura Medical Center, Japan.
(3) Petr Kolar, Slovak Medical University, Slovakia.
Complete Peer review History: http://www.sdiarticle4.com/review-history/68428

Original Research Article

Received 13 March 2021
Accepted 23 May 2021
Published 28 May 2021

ABSTRACT

Purpose: The aim of the study was to compare the subfoveal choroidal thickness (SFCT) with the use of Spectral-Domain OCT in eyes with AMD of different stages.
Methods: The participants comprised of 30 age-matched normal eyes as controls (Group 1), 19 with early-AMD eyes (Group 2), 14 with intermediate-AMD eyes (Group 3) and 29 with advanced (neovascular) AMD eyes (Group 4). All subjects underwent routine ophthalmologic examination. The choroid images, which included the subfoveal choroidal thickness images, obtained using Spectral-Domain Optical Coherence Tomography (and the technique of Enhanced Depth Imaging-EDI). All of the participants volunteered in this study and remained anonymous due to the protection of their personal data.
Results: 92 eyes with age greater than 65 years old were included. The mean subfoveal choroidal thickness was 260.93 ± 46.54 μm in age-matched normal eyes, 255.10 ± 44.85 μm in early AMD eyes, 230.92 ± 45.70 μm in intermediate AMD eyes and 206.82 ± 44.43 μm in advanced (neovascular) AMD eyes. There were statistically significant differences in the measurement results

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between the 4th Group with the 1st Group (P<0.0001) and 2nd Group (P=0.0006) respectively, meaning that SFCT was greater in normal and early AMD eyes.
Conclusion: Decreasing subfoveal choroidal thickness was demonstrated in the progression of AMD, especially in the advanced AMD eyes compared to normal or early AMD eyes.

Keywords: Age-related macular degeneration; spectral-domain optical coherence tomography; subfoveal choroidal thickness; classification of AMD.

1. INTRODUCTION

Age-Related Macular Degeneration (AMD) [1,2,3,4] is the leading cause of blindness in the developed world (both in the United States and in Western Europe) in people over the age of 60 [5]. Although the definition of age-related macular degeneration varies from study to study, the extensive presence of drusen (extracellular deposits between the pigment epithelium and the Bruch membrane) with or without pigmentary lesions are unquestionably characteristics of the disease. In its early stages, AMD develops slowly and asymptomatically, usually for a number of years. Aging is the primary risk factor for the development of this pathological eye disease. As we know, with age, significant biological changes occur in the eye and especially in the retina, as a tissue that does not undergo mitosis. These changes, although they may contribute to the pathogenesis of AMD, do not inevitably lead to the disease development.

Normal aging therefore results in a range of changes in the posterior pole region, many of which are clinically undetectable, involving the external retina, the pigmented epithelium, the Bruch membrane, and the choroid. More specifically, the Photoreceptors are reduced in density (rods are more vulnerable) [6,7,8]. In the Pigmented epithelium are observed a decrease in melanin granules and an increase in lipofuscin granules with a consequent decrease in the volume of the functional cytoplasm [9]. For Bruch's membrane there is an increase in its thickness (from approx. 2μm in the first decade of life to about 4.5-5.0μm in the tenth decade of life) [10], extracellular petal deposits (basal linear deposits & basal laminar deposits), fat filtration and reduction of its permeability [10,11]. In the Choroid progressive degenerative changes are observed such as reduction in the diameter of their lumen and the general reduction in their number, leading to a reduction in choroidal blood flow [12]. The above changes, therefore, are a result of age and may not be part of the manifestation spectrum of AM.

Classification of AMD [12,13]

Pathological changes associated with AMD can be classified as non-neovascular (dry) or neovascular (fluid). The most recent (2013) and widely accepted classification by most eye health researchers and professionals is as follows [13]:

- *Early age-related macular degeneration*

  Presence of multiple small drusen (<63μm) or medium sized drusen (≥63μm and <125μm) without evidence of advanced macular degeneration (advanced AMD-described below).

- *Intermediate age-related macular degeneration*

  Extensive presence of medium-sized drusen (≥63μm and <125μm) or presence of large-sized drusen (≥125μm) without evidence of advanced macular degeneration (Fig. 3.2).

- *Advanced age-related macular degeneration*

  Advanced AMD is characterized by the presence of one of the following two:

  i. Geographical atrophy or
  ii. Neovascular-type age-related macular degeneration.

2. MATERIALS AND METHODS

All participants were aged > 65 years and were examined by the same examiner each time between 7 p.m. and 9.30 p.m. at the Ophthalmology Clinic of GNA Korgialeniou-Benaki. Of the 57 patients, 25 were female and 32 were male (Fig. 1).

The study involved 57 Greek nationality patients, all of whom were older than 65 years. All patients underwent a complete ophthalmological examination, which included: refractive examination with optimal corrected visual acuity,

ophthalmoscopy, color fundus photography with non-mydriatic fundus camera and optical coherence tomography OCT with and without the Enhanced Depth Imaging technique (Enhanced Depth Imaging). The above measurements were performed at the ophthalmology clinic of GNA Korgialenio-Benakeio by the same examiner each time, at the same time of day, between 7 p.m. and 9.30 p.m.

After a thorough evaluation, the eyes (out of 57 patients) that were considered eligible for the study were 92. Eyes with additional retinal pathologies, except for Age Macular Degeneration (AMD), which are known to affect the thickness of the choroid of studying were excluded. Also, patients who have had ocular surgery for vitrectomy or patients with a history of ocular pathologies such as glaucoma, ocular inflammation, retinal detachment, refractive error > 3 D, or ocular hypertensive (arteriosclerotic) retinopathy, were also excluded. In addition, ocular pathologies that prevent the imaging of the choroid such as cataracts or retinal hemorrhage (and in particular the presence of bleeding under the macula) led to the exclusion from the study of the above patients. Eyes of patients with Geographic Atrophy (GA), late-stage of dry age-related macular degeneration (AMD) were also not included in the study due to the different mechanism and potential treatment compared to the Exudative Macular Degeneration. Finally, the subgroup of patients with Polypoidal Choroidal Vasculopathy (PCV) was excluded from this study due to the different pathophysiological characteristics of their eyes when compared to the general form of Exudative Wet Macular Degeneration.

According to Frederick L. Ferris III et al. [13], in 2013 the clinical classification system for age-related macular degeneration (AMD) is presented in the following table.

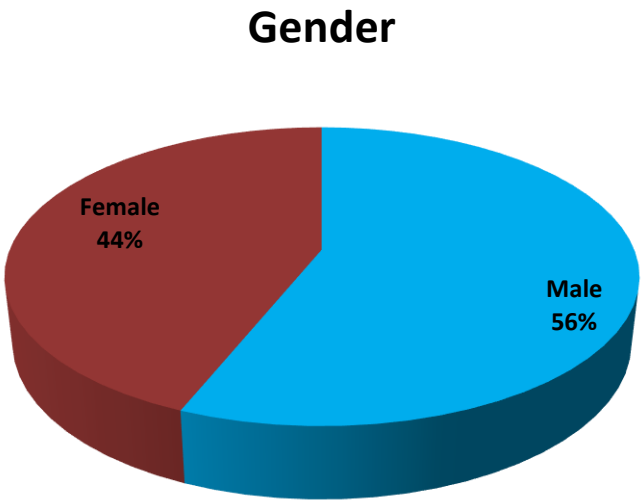

Fig. 1. Gender of the participants

Table 1. Clinical classification system for age-related macular degeneration (AMD) [13]

Classification of AMD	Definition (lesions assessed within 2 disc diameters of fovea in either eye)
No apparent aging changes	No drusen and No AMD pigmentary abnormalities
Normal aging changes	Only drupelets (small drusen ≤ 63μm) and No AMD pigmentary abnormalities
Early AMD	Medium drusen > 63μm and ≤ 125 μm and No AMD pigmentary abnormalities
Intermediate AMD	Large drusen > 125μm and/or Any AMD pigmentary abnormalities
Late AMD	Neovascular AMD and/or Any geographic atrophy

In this study the eyes with perfectly normal fundus with no apparent aging changes and the eyes of patients with normal aging changes invisible drusen after ophthalmoscopy and small drusen (<63μm) with no AMD pigmentary abnormalities were considered to be without clinically relevant increased risk of developing advanced stage AMD, were enter as control patients (Group) —Group 1. Therefore, taking into account the above criteria decision the study groups were formed as follows:

Group 1: eyes without clinically significant increased risk of developing advanced stage AMD or with small drusen (<63μm)
Group 2: eyes with early stage AMD with their main characteristic the presence of medium size drusen (> 63μm and ≤125μm)
Group 3: eyes with intermediate stage AMD with their main characteristic the large drusen (> 125μm)
Group 4: eyes with advanced stage AMD with their basic characteristic the existence of neovascular type AMD [14,15]

In the present study the technology used to measure the thickness of the choroid under the central fovea (fovea centralis) in patients with various stages of Age Macular Degeneration was that of optical coherence tomography. More specifically, the Spectralis SD-OCT system (Heidelberg Engineering, Carlsbad, CA) was used with the complete HEYEX 2 software, Heidelberg Eye Explorer. The optical coherence tomography (OCT) essentially achieves stratified images (either two or three dimensional) by calculating the time and intensity of delay of reflected or diffused light from the internal structure of the tissues [16,17]. It is a non-invasive and intact imaging method, which during its conventional use has an axial resolution of 10 μm, thus enabling the imaging of the retinal layers. In order to enable the imaging of the choroid, in the present study, the technique of Enhanced Depth imaging provided by the specific SD-OCT machine was used. In particular, shots were taken with a 19-line raster (7mm x 7mm rectangular box) using the EDI technique, followed by the selection of the most representative sections that passed through the central fovea. Finally, the thickness of the choroid under the macula was measured on the selected OCT image (manually, each time by the same researcher) as the vertical distance from the outside of the superflex line, representing the pigmented epithelium (point of intersection of the retinal pigment epithelium (RPE) with the Bruch membrane to the sclero-choroidal junction (Fig. 3).

Fig. 2. Groups of AMD stages according to 2013 Classification

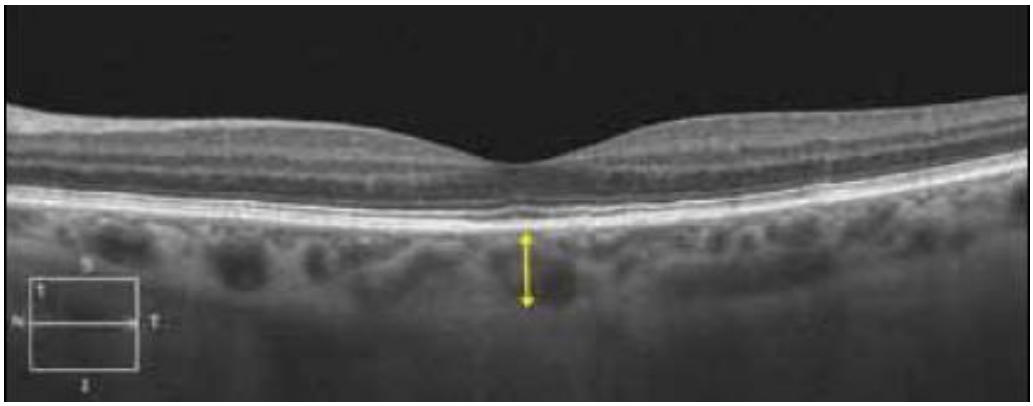

Fig. 3. Optical Coherence Tomography Section with the Enhanced Depth Technique (EDI-OCT image) in a normal eye. The yellow vertical arrow represents the thickness of the choroid under the central fovea

3. RESULTS

The mean value of the choroid thickness under the central fovea for Group 1 of this study that essentially represents the control group (normal eyes and eyes without clinically relevant increased risk of developing advanced stage AMD) was 260.93 μm ± 46.54 (minimum 186 μm - maximum 360μm), for Group 2 representing the early AMD eyes was 255.10 μm ± 44.85 (minimum 189 μm - maximum 327 μm), for Group 3 representing the intermediate AMD eyes were 230.92 μm ± 45.70 (minimum 152μm - maximum 321 μm) and finally for Group 4 representing the late / advanced AMD eyes (eyes with neovascular type AMD) were 206.82 μm ± 44.43 (minimum 121 μm - maximum 297 μm) (Table 2).

The Kolmogorov-Smirnov test was used in order to observe that in each group the sample follows a normal distribution. Finally, in each pair an independent two sample t test was performed (provided that they have the same variance) and the degree of significance was set at p = 0.005. In the present study, the null hypothesis of the t-test was that the mean of the choroid thickness measurements under the central fovea between the two groups compared each time is the same. In rejecting our null hypothesis and therefore having a statistically significant difference, it is concluded that the difference in the mean thickness of the choroid under the central fovea is not attributed to the sampling error.

3.1 Statistical Analysis of the Results

The SPSS version 15 (SPSS Inc., Chicago, Illinois, USA) statistical software was used. Comparing the results with independent two sample t test for Group 1 and Group 2 the difference between these two groups was -5.82181 with 95% CI of difference: -32.9038 to 21.2476, with Test statistic t -0.433 and Two-tailed probability P = 0.6670. As it can be seen from the result (P = 0.6670 and therefore P> 0.005), our null hypothesis in this case is not rejected and therefore it is concluded that there is no statistically significant difference between the average thickness of the choroid under central fovea between normal eyes (controls) Group 1 and those with early stage AMD Group 2.

Comparing the results with independent two sample t test for Group 2 and Group 3 the difference between these two groups was -24.1767 with 95% CI of difference -56.6554 to 8.3021, with Test statistic t -1.518 and Two-tailed probability P = 0.1391. As it can be seen from the result (P = 0.1391 and therefore P> 0.005), our null hypothesis in this case is not rejected and therefore it is concluded that there is no statistically significant difference between the average thickness of the choroid under central fovea between the eyes with early AMD eyes and those with intermediate AMD eyes, although there is a decrease in the average thickness of the eyes in Group 3 compared to those in Group 2. Comparing the results with independent two sample t test for Group 3 and Group 4 the difference between these two groups was -24.1010 with 95% CI of difference -53,5722 to 5,3703, with Test statistic t -1.652 and Two-tailed probability P = 0,1063. As it can be seen from the result (P = 0.1063 and therefore P> 0.005), our null hypothesis in this case is not rejected and therefore it is concluded that there

also is no statistically significant difference between the average thickness of the choroid under the central fovea between the eyes with intermediate AMD eyes and those with advanced AMD eyes, although there is a decrease in the average thickness of the eyes in Group 3 compared to those in Group 4.

Comparing the results with independent two sample t test for Group 1 (controls) with Group 4 (advanced-neovascular AMD eyes) the difference between these two groups was -54,1057 with 95% CI of difference -77,8430 to -30,3685, with Test statistic t -4,564 and Two-tailed probability P < 0,0001. In this case, as it can be seen from the result (t = -4,564, P <0.0001 and therefore P <0.005), our null hypothesis is rejected and it is therefore concluded that there is a statistically significant difference between the average thickness of choroid under the central fossa between the normal eyes (controls) and those with advanced neovascular AMD. This result is also observed in the following graph (Fig. 4), which shows a significant reduction in the average thickness of the eyes in Group 1 compared to those in Group 4. In fact, this differentiation is not attributed to the sampling error. The above result, is consistent with the results of other recent studies [13,14,15], while at the same time highlighting the measurement of choroidal thickness below the central fovea using OCT as a possible diagnostic criterion of AMD.

Comparing the results with independent two sample t test for Group 1 (controls) with Group 3 (Intermediate AMD eyes) the difference between these two groups was -30.0048 with 95% CI of difference -60.2377 to 0.2282, with Test statistic t -2.003 and Two-tailed probability P = 0.0517. As it can be seen from the result (P = 0.0517 and therefore P> 0.005), our null hypothesis in this case is not rejected and therefore it is concluded that there is no statistically significant difference between the average thickness of the choroid under central fovea between the normal eyes (controls) and those with intermediate AMD eyes (intermediate AMD eyes), although there is a significant reduction in the average thickness of the eyes in Group 3 compared to those in Group 1.

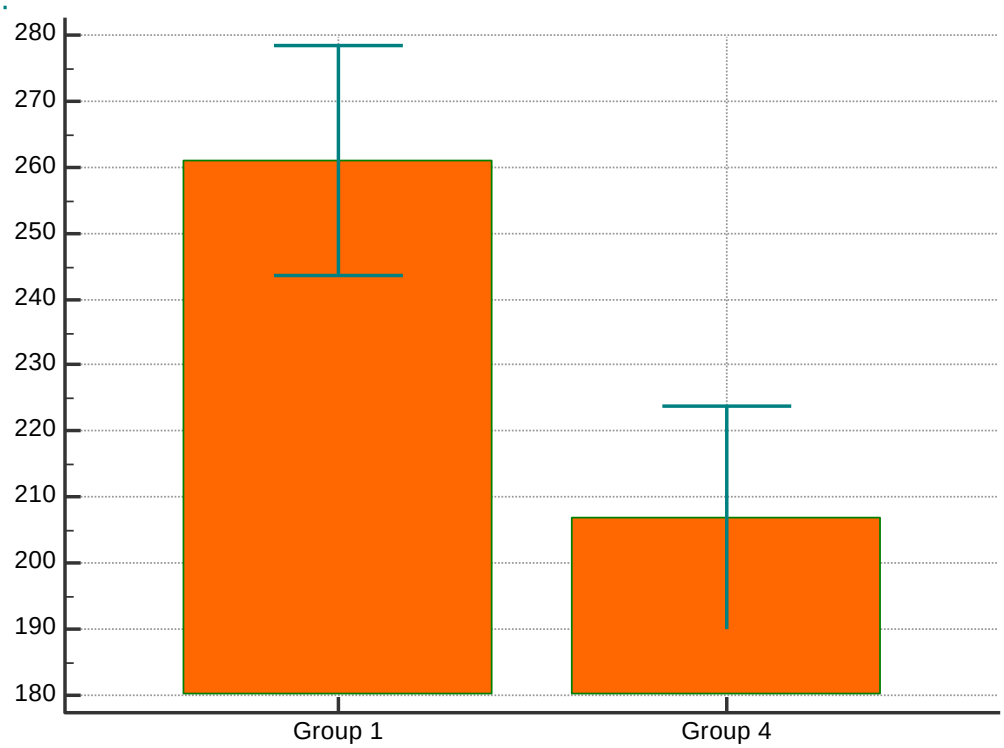

Fig. 4. Box Plot graph where on the y axis the thickness of the choroid is represented under the central fovea and on the x axis the pair of Groups examined (Groups 1 and 4)

Table 2. Mean value of the choroid thickness under the central fovea for each group of patients in this study

	Sample size	Min	Max	Arithmetic mean	95% CI for mean	Variance	Std	Kolmogorov-Smirnov test for normality
Group 1	30	186.00	360.00	260.9333	243.5538 to278.3129	2166.2713	46.5432	D=0.1080 accept Normality (P>0.10)
Group 2	19	189.00	327.00	255.1053	233.4863 to 276.7242	2011.8772	44.8540	D=0.1159 accept Normality (P>0.10)
Group 3	14	152.00	321.00	230.9286	204.5400 to 257.3172	2088.8407	45.7038	D=0.1057 accept Normality (P>0.10)
Group 4	29	121.00	297.00	206.8276	189.9256 to 223.7296	1974.4335	44.4346	D=0.0699 accept Normality (P>0.10)

Comparing the results with independent two sample t test for Group 2 (early AMD eyes) with Group 4 (advanced-neovascular AMD eyes)) the difference between these two groups was -48.2777 with 95% CI of difference -74.7744 to -21.7809, with Test statistic t -3.668 and Two-tailed probability P = 0.0006. In this case also, as it is perceived from the result (t = -3,668, P = 0.0006 and therefore P <0.005), our null hypothesis is rejected and therefore it is concluded that there is a statistically significant difference between the average of its thickness choroid under the central fovea between the eyes with early AMD and those with advanced AMD. This result is also observed in the following graph (Fig. 5), which shows a significant reduction in the average thickness of the eyes in Group 2 compared to those in Group 4. In fact, this differentiation cannot be attributed to the sampling error.

Comparing the means of the four stage Groups it is obvious that there is a relation between the choroid under the central fovea (SFCT) and the progress of the disease.

More statistic comparisons were conducted with all four groups according to Spearman rank correlation coefficient (Table 3.) and ANOVA with Bonferroni method applied (Table 4.).

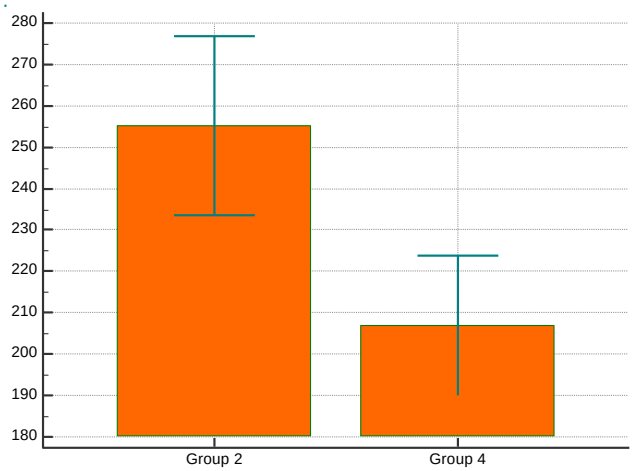

Fig. 5. Box Plot graph where on the y axis the thickness of the choroid is represented under the central fovea and on the x axis the pair of Groups examined (Groups 2 and 4)

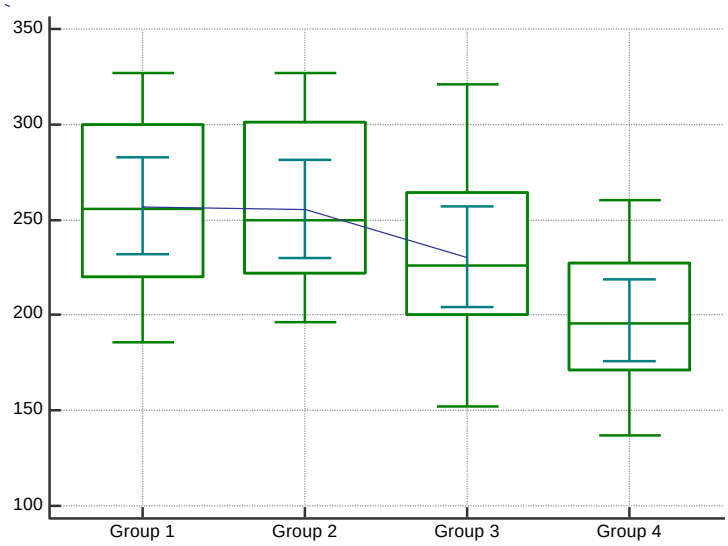

Fig. 6. Box Plot graph on the y axis the thickness of the choroid is represented under the central fovea and on the x axis the means of all Groups examined

Table 3. Comparison of the 4 groups according to Spearman rank correlation coefficient

		Group 1	**Group 2**	**Group 3**	**Group 4**
Group 1	Correlation Coefficient		-0,1180,631619	0,0510,863614	-0,0090,964129
	Significance Level Pn				
Group 2	Correlation Coefficient	-0,1180,631619		-0,2240,440514	-0,0020,992919
	Significance Level Pn				
Group 3	Correlation Coefficient	0,0510,863614	-0,2240,440514		-0,1540,599114
	Significance Level Pn				
Group 4	Correlation Coefficient	-0,0090,964129	-0,0020,992919	-0,1540,599114	
	Significance Level Pn				

Table 4. Comparison of the 4 groups with ANOVA Bonferroni corrected
Within-subjects factors

Factor	Mean	Std. Error	95% CI
Group_1	257,2143	11,7048	231,9276 to 282,5009
Group_2	255,7857	11,8146	230,2619 to 281,3096
Group_3	230,9286	12,2149	204,5400 to 257,3172
Group_4	197,2857	9,9545	175,7803 to 218,7912

Pairwise comparisons

Factors		Mean Difference	Std. Error	P [a]	95% CI [a]
Group_1-	Group_2	1,429	16,938	1,0000	-51,198 to 54,056
-	Group_3	26,286	15,333	0,6611	-21,353 to 73,925
-	Group_4	59,929	16,032	0,0149	10,116 to 109,742
Group_2-	Group_1	-1,429	16,938	1,0000	-54,056 to 51,198
-	Group_3	24,857	19,512	1,0000	-35,767 to 85,481
-	Group_4	58,500	15,469	0,0137	10,436 to 106,564
Group_3-	Group_1	-26,286	15,333	0,6611	-73,925 to 21,353
-	Group_2	-24,857	19,512	1,0000	-85,481 to 35,767
-	Group_4	33,643	17,267	0,4397	-20,007 to 87,293
Group_4-	Group_1	-59,929	16,032	0,0149	-109,742 to -10,116
-	Group_2	-58,500	15,469	0,0137	-106,564 to -10,436
-	Group_3	-33,643	17,267	0,4397	-87,293 to 20,007

4. DISCUSSION

In the present study, the thickness of the choroid under the central fovea was measured during the development (various stages) of Age-Related Macular Degeneration. The study included normal eyes (aged comparable to pathological ones), as well as eyes with early, intermediate and advanced (neovascular) stage of AMD according to the internationally accepted clinical classification of AMD of 2013. According to the literature, we know that the metabolic requirements of the retina for oxygen are very high and are satisfied by the underlying choroid. It is also well known and commonly accepted that with age there are various changes in both the retinal photoreceptors and the choroid and mainly in its blood flow, which is mainly reduced due to a reduction in blood volume in the choroidal circulation and not due to its velocity. Furthermore, the continuous technological development of ophthalmic imaging systems and their software and more specifically of SD-Optical Coherence Tomography (SD-OCT) using the technique of Enhanced Depth Imaging (EDI) (as well as other techniques) allowed us to study more deeply (anatomically and functionally) and more thoroughly the choroid, both under normal conditions and in conditions of eye disease. In this way, changes in the thickness of the choroid were observed both in normal eyes and in pathological conditions of the macula. Some studies, such as that conducted by Fein et al. [18,19,20], have shown that the eyes of patients with both dry and neovascular type AMDs show significantly thinner choroidal under the central fovea compared to normal-aged eyes. At the same time, other studies have shown variability in choroidal thickness below the central fovea in patients with early-stage IHD, or no deviation from normal [21].

In the present study, the Enhanced Depth Imaging (EDI) technique provided to us by the SD-OCT Spectralis ophthalmic imaging system was used, and the thickness of the choroid under the central fovea was measured manually by the same researcher for its various groups. Age-related macular degeneration, which represent the progression of the disease. Therefore, the measurements of choroidal thickness and the comparative study that followed them, showed its downward trend passing from the eyes with early stage AMD (Group 2) to the eyes with intermediate stage AMD (Group 3), as well as from the eyes with intermediate stage AMD (Group 3) in the eyes with advanced neovascular AMD (Group 4), which, however, did not show statistical significance.

However, measurements of choroidal thickness under the central fovea revealed a statistically significant and appreciable decrease in the group of advanced stage AMD (Group 4) when compared to both normal eyes (Group 1) and eyes with early stage AMD (Group 2), which

cannot be attributed to a sampling error. This result is in agreement with those of other recent studies, a fact that may place the measurement of choroid thickness under the macula using the imaging system of Optical Coherence Tomography (OCT), as a diagnostic criterion of the AMD.

In summary, the Enhanced Depth Imaging technique in OCT (EDI-OCT), as well as other techniques, such as Swept-Source OCT, provide easy structural analysis of the choroid and biometric measurements concerning it. This study showed a downward trend in the average thickness of the choroid under the central fovea as the AMD develops and progresses to its advanced stage with the presence of neovascular membranes. Further studies are clearly needed both to confirm the above findings, so that the assessment of chorionic thickness under the central fovea (SFCT) is likely to contribute to the diagnostic process of AMD and its stages, as well as to be able to determine the most likely correlation of choroid thickness with choroidal circulation under both normal and pathological conditions (eg study of the choroid vascular network and its changes in the various stages of AMD and its possible correlation with the changes in SFCT observed in our study).

5. CONCLUSION

The results between Group 1 and Group 4 and those between Group 2 and Group 4 are of particular importance, as it is understood that there is a difference in the average thickness of the choroid under the central fovea (SFCT) with a decrease in the group of eyes with neovascular AMD not only in relation to normal eyes (controls) but also in relation with eyes with early stage AMD. Therefore, the measurement of SFCT may be a quantitative parameter in the future, which in combination with others may even contribute to the categorization of the eyes in the various stages of AMD.

CONSENT

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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