Association between Central Retinal Thickness and Low Luminance Visual Acuity in Early Age-Related Macular Degeneration

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Complete List of Authors:	Puell, María; Complutense University of Madrid, Optometry and Vision Science Hurtado-Ceña, Francisco; Clínica Rementería Pérez-Carrasco, María; Complutense University of Madrid, Optometry and Vision Science Contreras, Inés; Clínica Rementería; Hospital Ramón y Cajal, Opthalmology, Instituto Ramón y Cajal de Investigaciones Sanitarias (IRYCIS)
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Abstract:	Purpose/Aim: To examine whether central retinal thickness (CRT) is related to mesopic visual acuity (VA) and low luminance deficit (LLD, difference between photopic and mesopic VA) in eyes with early and intermediate age-related macular degeneration (AMD). Materials and Methods: In a cross-sectional study, 50 pseudophakic subjects older than 63 years were divided into three groups (no AMD, early AMD and intermediate AMD). Spectral domain optical coherence tomography (SD-OCT) was used to measure CRT in the 1 mm-central-area. Best-corrected distance VA was measured under photopic or mesopic luminance conditions and LLD calculated. Subjects were stratified by VA impairment to compare CRTs across these groups. Relationships were examined by stepwise multiple linear regression. Results: No significant differences in mean CRT, photopic and mesopic VA or LLD were detected between the groups no AMD, early AMD and intermediate AMD. However, mean CRTs were 20 microns and 18 microns thicker in the eyes with impaired mesopic VA (> 0.3 logMAR) and impaired LLD (≥ 0.3 logMAR) compared to the eyes with non-impaired VA or LLD respectively (both $p < 0.01$). CRT and mesopic pupil size were independent predictors of mesopic VA ($p = 0.001$). CRT emerged as the only independent predictor of LLD ($p = 0.004$). Conclusions: Increased CRT was linked to worse retinal function when measured under mesopic conditions in eyes without AMD and eyes with early to intermediate AMD. SD-OCT imaging combined with VA measurements under low luminance conditions could be a useful tool to detect early AMD.

Retinal thickness and mesopic visual acuity in AMD

ABSTRACT

Purpose/Aim: To examine whether central retinal thickness (CRT) is related to mesopic visual acuity (VA) and low luminance deficit (LLD, difference between photopic and mesopic VA) in eyes with early and intermediate age-related macular degeneration (AMD). **Materials and Methods:** In a cross-sectional study, 50 pseudophakic subjects older than 63 years were divided into three groups (no AMD, early AMD and intermediate AMD). Spectral domain optical coherence tomography (SD-OCT) was used to measure CRT in the 1 mm-central-area. Best-corrected distance VA was measured under photopic or mesopic luminance conditions and LLD calculated. Subjects were stratified by VA impairment to compare CRTs across these groups. Relationships were examined by stepwise multiple linear regression. **Results:** No significant differences in mean CRT, photopic and mesopic VA or LLD were detected between the groups no AMD, early AMD and intermediate AMD. However, mean CRTs were 20 microns and 18 microns thicker in the eyes with impaired mesopic VA (> 0.3 logMAR) and impaired LLD (≥ 0.3 logMAR) compared to the eyes with non-impaired VA or LLD respectively (both $p < 0.01$). CRT and mesopic pupil size were independent predictors of mesopic VA ($p = 0.001$). CRT emerged as the only independent predictor of LLD ($p = 0.004$). **Conclusions**: Increased CRT was linked to worse retinal function when measured under mesopic conditions in eyes without AMD and eyes with early to intermediate AMD. SD-OCT imaging combined with VA measurements under low luminance conditions could be a useful tool to detect early AMD.

KEYWORDS: Age-related Macular Degeneration; Central Retinal Thickness; Visual Acuity; Mesopic Vision; Low Luminance Deficit; Retina.

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INTRODUCTION

Age-related macular degeneration (AMD) is a neurodegenerative disorder characterised by changes in the retinal pigment epithelium (RPE). In some patients progressive RPE atrophy with or without neovascularization may lead to severe loss of central visual acuity (VA).[1] To assess early damage and disease progression, both structural retinal imaging and functional vision tests are important.

New imaging techniques such as spectral-domain optical coherence tomography (SD-OCT) offering high-resolution of retinal structures have become indispensable tools for the diagnosis of retinal diseases and specifically of AMD.[2] While it is relatively well known that thinning of retinal layers takes place in advanced stages of AMD,[1] only limited data are available with regard to structural changes that may be detected by high-resolution retinal imaging in intermediate or early AMD stages.[3,4] Currently, interest mounts in trying to correlate macular morphology changes determined by OCT and visual function for the diagnosis of AMD.[5–9] [10,11] [12,13] Relationships between retinal morphology and VA, as the standard functional endpoint for clinical trials, have been mainly explored in advanced AMD stages.[7,8,13] However, data are lacking for early to intermediate non-neovascular AMD.[5,6]

In the early stages of AMD, foveal function, as measured by standard VA, often remains preserved.[14] Prior research has suggested that mesopic or low luminance VA, low contrast VA, and the low luminance deficit (LLD) or difference between photopic and mesopic VA may be diminished in early and intermediate AMD.[15–19] In addition, impaired mesopic VA worse than 0.30 logMAR (20/40)) in healthy older eyes has been identified as a risk factor for incident AMD developing 3 years later.[20]

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Mesopic VA could be therefore affected both by aging and AMD. To establish whether structural changes in the retina could be related to changes in mesopic VA, this study examines relationships between central retinal thickness (CRT) measured by SD-OCT and VA measured under photopic and mesopic luminance conditions in older eyes with and without early to intermediate AMD. Our study sought to add to the current body of knowledge of the effects of macular morphology changes in AMD on visual acuity. This widely accepted visual function test allowing for direct assessment of functional impairment is important for clinical trials. This knowledge could help to promptly identify subjects at a high risk of developing AMD or of AMD progression so that suitable follow-up or prevention measures can be implemented.

METHODS

Subjects

This was a cross-sectional, single-centre study conducted at the eye clinic Clínica Rementería in Madrid, Spain. The participants enrolled (n=51) were adults older than 63 years who were divided into three groups (no AMD (n=21), early AMD (n=14), and intermediate AMD (n=16)). To avoid confounding factors such as the influence of the aging lens on visual acuity,[21] especially under low luminance conditions when optotype contrast is reduced,[22] only pseudophakic subjects implanted with a monofocal intraocular lens (IOL) 6 to 12 months prior to enrolment and with no posterior capsule opacification (PCO) were enrolled.

In each subject, the right eye was selected unless it did not meet the inclusion criteria, in which case the left eye was included. Study eyes were required to have a best-corrected VA (BCVA) of 0.10 logMAR (≥ 20/25 Snellen) or better and a refractive error of less than ± 1.50 diopters (D) sphere or ± 1.50 D cylinder.

Exclusion criteria were: retinal disease (e.g. macular oedema or vitreoretinal disease), glaucoma and amblyopia. Further, subjects were excluded if they were diabetic, pseudophakic with a multifocal IOL or had undergone retinal surgery.

An extensive ophthalmologic examination was carried out in all participants. This comprised subjective refraction, measurement of BCVA with the ETDRS chart, anterior segment slit-lamp biomicroscopy and a dilated fundus examination, including fundus photographs acquired with the Visucam 500 (Carl Zeiss Meditect AG, Germany).

SD-OCT scans obtained with a Cirrus HD-OCT (Carl Zeiss Meditec, Jena, Germany) were carefully examined by a retina specialist (IC). Eligible participants were divided into groups based on their fundus features. AMD was graded according to the Beckman classification system [23] as no AMD, early, or intermediate AMD. In brief, no AMD was defined as the absence of or few drupelets (small drusen ≤63 μm) and no AMD pigmentary abnormalities. Early AMD was defined as the presence of medium drusen (63 to 125 μm) and no AMD pigmentary abnormalities. Intermediate AMD was defined as the presence of large drusen (>125 μm) and/or any AMD pigmentary abnormality. Individuals with advanced AMD (geographic atrophy or neovascular AMD) were excluded from this study. Fundus autofluorescence (FAF) images were also acquired with the TRC-50DX retinal camera (Topcon Medical Systems, Tokyo, Japan). The presence of reticular pseudodrusen or subretinal drusenoid deposits (RPD) was assessed by FAF and SD-OCT.

Our study protocol fulfilled the tenets of the Declaration of Helsinki and received approval from the Ethics Committee of the Hospital Clínico San Carlos (17/355-E). Written informed consent was obtained from each participant.

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Spectral-Domain Optical Coherence Tomography

Central retinal thickness (CRT) was measured by SD-OCT using the standard macular 512 x 128 cube scan protocol of the Cirrus HD-OCT (Carl Zeiss Meditec, Jena, Germany). In the macular thickness analysis, the software takes the most hyperreflective band of the retinal pigment epithelium as the outer border of the retina. Retinal thickness measurements were obtained in the subfields described in the Early Treatment of Diabetic Retinopathy Study (ETDRS) after pupil dilation. These ETDRS subfields are defined by three concentric rings (central, inner and outer) centred on the fovea of diameters 1, 3 and 6 mm. The only variable included in this study was overall retinal thickness measured in the central 1 mm diameter circle.

Visual Acuity

BCVA was measured monocularly using an ETDRS chart placed in an illuminator cabinet 4 m from the patient. Measurements were made under photopic (385 cd/m^2) and mesopic (1 cd/m^2) luminance conditions. Mean photopic luminance was reduced to 1 cd/m^2 using neutral density filters. These filters were fixed to a cardboard frame attached to the illuminator cabinet by means of small magnets so that the frame could be easily removed. Further, the frame was covered by an opaque fabric to reduce stray light. A MAVO-SPOT (Gossen Lighting Control, Nuremberg, Germany) was used to measure the luminance of the test. Each subject was first tested under normal room lighting conditions (photopic luminance). The room lighting was then switched off and after 10 minutes of mesopic adaptation to allow the pupil to dilate, the subject was tested again under mesopic luminance conditions. Participants were encouraged to guess letters. Each letter read correctly on each line was given a score of 0.02 log units. The drop produced in mesopic VA when compared with photopic VA (LLD) was registered as the increase in logMAR units.

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In addition, to control for the spatial resolution reducing effects of retinal illumination, pupil size was measured with an infrared pupillometer (Colvard, Oasis Medical, Glendora, California) under photopic and mesopic conditions.

Statistical Analysis

The Shapiro-Wilk test was used to check the normality of data. One eye in the intermediate AMD group identified as an outlier of more than 3 times the interquartile range for VA was removed. Thus, only 50 eyes were entered in subsequent analyses.

For normally distributed variables, the three study groups were compared by one-way analysis of variance (ANOVA) while the Kruskal-Wallis test was used for non-normally distributed continuous variables. Differences across groups in categorical variables such as gender, were assessed with the Chi-square test.

CRTs were compared between two groups of subjects classified according to visual acuity impairment level using a Student's t test. Categories for VA impairment were defined according to previous studies [20] as follows: photopic VA >0.0 logMAR (worse); mesopic VA >0.3 logMAR; and LLD (difference between photopic and mesopic VA) ≥0.3 logMAR (3 lines on the ETDRS chart).

Independent variables correlated with the VA variables were identified by forward stepwise linear regression (photopic VA, mesopic VA and LLD) across all eyes. In order to control for optical and morphological factors, CRT measurement, age, sex, refractive error, pupil size, presence of RPD, and AMD group (no AMD, early AMD and intermediate AMD), were entered as independent predictors in the model while each VA variable served as the dependent variable. Significance was set at a p-value less than 0.05.

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RESULTS

Table 1 provides the characteristics of the three study groups. No significant differences in mean CRT, photopic VA, mesopic VA and LLD were detected between AMD groups. Eleven out of 50 eyes (22%) were confirmed to have RPD.

According to our VA impairment classification, 33 eyes (66%) and 25 eyes (50%) were classed as having impaired photopic VA and impaired mesopic VA respectively, and 26 eyes (52%) as having impaired LLD. There were no significant differences between the proportions of eyes in the no AMD and AMD groups classified as having impaired photopic VA (no AMD (13 [62%]) early AMD (9 [64%]) and intermediate AMD (11 [73%]) (p = 0.765)), impaired mesopic VA (no AMD (11 [52%]) early AMD (6 [43%]) and intermediate AMD (8 [53%]) (p = 0.819)) or impaired LLD (no AMD (11 [52%]) early AMD (6 [43%]) and intermediate AMD (9 [60%]) (p = 0. 652)).

The distributions of CRT in the subjects stratified by VA impairment are shown in Figure 1. Mean CRT in those with normal photopic VA (259.1 ± 19.7 μm) was not significantly different to the value recorded in the group of subjects with impaired photopic VA (264.6 ± 23.1 μm) (t = 1.091; p = 0.4078). However, regardless of AMD status, mean CRT was 20.2 microns thicker in the impaired mesopic VA group (272.8 ± 23.0 μm) than in the normal mesopic VA group (252.6 ± 15.5 μm) (t = 3.638; p = 0.0007). Also, mean CRT was 17.6 microns thicker in the LLD deficit group (271.2 ± 24.2 μm) than in the no LLD deficit group (253.6 ± 15.0 μm) (t = 3.051; p = 0.0037).

Forward stepwise multiple linear regression analyses were conducted in which the dependent variables were each of the VA variables and the independent variables were AMD group (no AMD, early AMD and intermediate AMD), age, sex, refractive error, pupil size, CRT and RPD. The results of the models with significant outputs are summarized in Table 2. Photopic pupil size was a predictor of photopic VA, and CRT

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and mesopic pupil size were predictors of mesopic VA. CRT was found to be an independent predictor of LLD. CRT measures were not significantly associated with photopic VA. Positive beta coefficients represent the change in VA per each micron of increased CRT. Accordingly, the estimated effect of a 10-micron increase in CRT on mesopic VA and LLD was 0.02 logMAR (1 letter) across all eyes. Age, sex, refractive error, RPD or AMD group variables were not found to be significant predictors of the VA variables. Figure 2 shows the relationships observed between CRT and mesopic VA (r =+0.34, p = 0.0158) and LLD (r= +039, p = 0.0048).

DISCUSSION

In this study, relationships were examined between CRT and mesopic VA in eyes without AMD, or with early and intermediate AMD. Its main finding was that across all eyes an increased CRT was associated with a worse mesopic VA and greater low luminance deficit (a drop in mesopic VA when compared to photopic VA).

In addition, CRT did not differ among normal eyes and those with early or intermediate AMD. This finding is consistent with data from the first systematic study (German AugUR Study) on retinal layer thicknesses measured with the Spectralis SD-OCT device in nearly 1000 individuals aged ≥70 years. Correlations were examined with early AMD stage (mild, moderate and severe) and no significant changes were found in total retinal layer thickness in the central circle (see their supplementary tables).[3] Another Spectralis SD-OCT study revealed similar findings.[4] Comparisons of CRT measurements provided by the different OCT devices must be made with caution as the Cirrus OCT device takes the middle of the RPE layer as the outer retinal boundary, while the Spectralis SD-OCT uses Bruch's membrane for this segmentation.[24]

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In the present study, no significant differences were found in mean photopic and mesopic VA and LLD in normal eyes, eyes with early AMD and eyes with intermediate AMD. All eyes were pseudophakic as they had been implanted with monofocal IOLs. This inclusion criterion was designed to correct for the confounding effect of the ageing lens on VA measurements. The lack of differences in CRT and photopic VA between normal eyes and those with early or intermediate AMD may be explained by the fact that structural changes in early and intermediate AMD take place extrafoveally in most cases.[25] In other studies, significant differences were detected in mean mesopic VA and LLD in early AMD versus normal eyes,[15] [18] [19] but differences in lens state (e.g. LOCS III classification grade 1 or 2) between groups were not controlled for in such studies. In agreement with data recorded in older eyes with and without early AMD,[18] we classified similar proportions of normal, early AMD and intermediate AMD eyes as having impaired mesopic VA (worse than 0.3 logMAR (20/40)) and impaired LLD (a drop of 3 lines or more in the ETDRS chart).

When CRTs were compared across the groups of subjects classified according to VA impairment, we found that mean CRTs were 20 microns and 18 microns thicker in the groups of eyes with impaired mesopic VA and impaired LLD compared with the non-VA impaired and non-LLD impaired groups respectively ($p < 0.01$ for both). These differences cannot be attributed to the reproducibility of SD-OCT measurements as the repeatability of Cirrus HD-OCT CRT measurements in eyes with AMD has been reported as high.[26] To control for potential confounding factors in our study, a stepwise multiple regression analysis was conducted. No significant association was detected between photopic VA and CRT measurements, confirming previous findings in early to intermediate AMD.[5] In advanced AMD, weak or

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moderate correlations have been detected between photopic VA and CRT in neovascular AMD [13] and between many outer retinal layers and photopic VA in dry AMD.[6] In the present study, CRT and mesopic pupil size emerged as independent predictors of mesopic VA (p = 0.001) and CRT emerged as the only independent predictor of LLD (p = 0.004). Notwithstanding, the LLD variability explained by the model was low (16%). It should be noted that only clinical VA or recognition acuity (ETDRS chart) was measured here. While some authors have reported that recognition and resolution acuities (Landolt-C chart) do not clinically differ in normal observers,[27] in patients with AMD, computer-controlled resolution acuity tests yielded higher acuity estimates than ETDRS tests.[28] This means we would expect a stronger relationship between resolution VA and retinal structure rather than recognition VA. In a previous study in healthy subjects, we noted that a greater CRT was related to worse LLD in older eyes [29] and the effect estimated of a 10-micron increase in CRT on LLD was 1 letter (0.02 logMAR). The same effect was found in the present study across all eyes. Our findings are consistent with a report that an increased thickness of the total retina is significantly associated with a reduction in mesopic and scotopic sensitivity (microperimetry) in patients with intermediate AMD.[30] The latter authors also found a link between reduced sensitivity and the increased thickness of the retinal pigment epithelium–drusen complex and a central decrease in outer nuclear layer and photoreceptor-segment thickness.[30]

Although we did not measure individual retinal layer thicknesses, the increase observed in CRT in the group of eyes with impaired mesopic VA and impaired LLD cannot be only explained by a small increase in localized layers such as RPE. The German AugUR Study found that RPE/Bruch's membrane complex was thicker and photoreceptor layers were thinner in eyes with early AMD compared to no AMD (no

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significant layer thickness differences were found for other retinal layers measured).[3] Also, significant slight thickening of the RPE and outer retina in the central retina was found in early and intermediate AMD groups [4] and outer nuclear layer thickening in some macular areas in intermediate non-neovascular AMD eyes.[31] The reported thickening of some layers combined with the thinning of other layers amounts to little compared with the mean CRT increase of 18-20 microns found in our study. This novel finding also supports the hypothesis that the increase in CRT in the group of eyes with impaired mesopic VA and impaired LLD could perhaps be due to a continuous low-grade inflammatory process in the retina, causing a discrete increase in retinal thickness with clinical manifestations (in the early and intermediate AMD groups) or without clinical manifestations (in the no AMD group). Although in our study, the amount of central foveal thickening was associated with the extent of impaired low luminance visual function, the relationship was independent from AMD status. Low-grade inflammation, or para-inflammation, takes place in the healthy aging retina in physiological conditions [32] and chronic inflammation, or dysregulated para-inflammation, contributes to the initiation and progression of almost all age-related retinal diseases. [32,33] This mild inflammatory process could lead to RPE thickening.[3,4,31] Further, inflammation may involve osmotic swelling of Müller cell bodies, thickening the macular area.[32,34] In experimental studies, it has been observed that perifoveal Müller glial cells become activated with consequent hypertrophy in the earlier stages of retinal degeneration.[35] However, little is known about the role of Müller cells in AMD. It has been also reported that reactive microglial cells accumulate in the outer nuclear layer and subretinal space around drusen deposits.[36] Taking into account the results of the present study and considering that impaired mesopic VA in healthy

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older eyes was found to be a risk factor for incident AMD developing years later, [20] we propose that clinicians should consider adding VA measurement under low luminance conditions in patients with early AMD to the battery of clinical tests. This information combined with OCT could help to identify subjects at a high risk of developing AMD or of AMD progression.

A limitation of our study could be the number of eyes in each AMD category but considering that the p values found for mean differences between CRT and VA variables were very high ($p > 0.4$), it is very likely that even if the sample size were to be increased, there would still be no significant differences among the groups. Another limitation is that only overall retinal thickness was analysed and only by one grader. In real-world practice, CRT remains the main measurement that ophthalmologists take into account when evaluating patients due to the difficulty of accurate segmentation and interpreting results. It is possible that by including other OCT findings, such as RPE and photoreceptors, the resultant models would show better predictive power. One question for future research is the extent to which mesopic VA and its association with CRT could be useful to detect subjects at risk of developing AMD or progressing to advanced AMD. The longitudinal assessment of a larger number of subjects with impaired VA is needed to confirm whether structure-function changes could serve for this purpose.

In conclusion, increased CRT is linked to worse retinal function when measured under mesopic conditions in eyes without AMD and eyes with early to intermediate AMD. SD-OCT imaging combined with visual acuity measurements under low luminance conditions may be useful in a clinical setting.

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DECLARATION OF CONFLICTING INTERESTS

The Authors declare that there is no conflict of interest and have no proprietary interest in any of the materials mentioned in this article.

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TABLES

Table 1. Baseline characteristics of the study participants. Mean ± SD (min, max).

	No AMD	Early AMD	Int. AMD	p
No. of eyes (n)	21	14	15	
Age (years)	74.8 ± 6.0 (64, 84)	76.3 ± 4.7 (69, 84)	76.2 ± 5.1 (70, 84)	0.640
Sex (male/female)	10/11	7/7	6/9	0.848
Spherical equivalent (D)	-0.11 ± 0.67 (-1.50, +1.00)	-0.12 ± 0.28 (-0.75, +0.38)	-0.08 ± 0.70 (-1.25, +1.50)	0.829
Photopic pupil size (mm)	3.39 ± 0.46 (3.00 - 4.00)	3.82 ± 0.67 (3.00 - 5.00)	3.10 ± 0.28 (3.00 - 4.00)	0.001
Mesopic pupil size (mm)	4.31 ± 0.49 (3.50 - 5.00)	4.79 ± 0.78 (3.50 - 6.00)	4.20 ± 0.49 (3.50 - 5.00)	0.021
Photopic VA (logMAR)	0.03 ± 0.06 (-0.10 - 0.10)	0.03 ± 0.07 (-0.10 - 0.12)	0.04 ± 0.04 (0.00 - 0.10)	0.946
Mesopic VA (logMAR)	0.31 ± 0.13 (0.05 - 0.52)	0.30 ± 0.14 (0.12 - 0.54)	0.36 ± 0.10 (0.16 - 0.54)	0.416
LLD-VA (logMAR)	0.28 ± 0.12 (0.01 - 0.46)	0.27 ± 0.12 (0.08 - 0.46)	0.32 ± 0.10 (0.14 - 0.52)	0.416
CRT (µm)	264.5 ± 21.3 (227 - 306)	264.3 ± 23.4 (231 - 308)	258.8 ± 22.5 (220 - 301)	0.716

VA = visual acuity; CRT = central retinal thickness; Int. = intermediate

Retinal thickness and mesopic visual acuity in AMD

TABLE 2. Forward stepwise multiple regression models showing the predictor variables.

Dependent variable	Predictor variable	β	β (95% CI)	R^2	F	P
Photopic VA	Pupil	-0.0429	-0.0686; -0.0172	19%	11.27	0.0016
Mesopic VA	Pupil	-0.0736 (p=0.008)	-0.1267; -0.0206	25%	7.82	0.0012
	CRT	0.0024 (p=0.002)	0.0009; 0.0039			
LLD-VA	CRT	0.0021	0.0007; 0.0035	16%	9.45	0.0035

Pupil = pupil size (photopic or mesopic in each case); CRT = central retinal thickness; β = standardized beta estimate; CI: confidence interval.

FIGURE LEGENDS

FIGURE 1. Box plots of central retinal thickness (microns) according to (A) photopic visual acuity impairment (>0.0 logMAR), (B) mesopic visual acuity impairment (>0.3 logMAR) and (C) low luminance visual acuity deficit (≥0.3 logMAR) recorded in all eyes.

FIGURE 2. Relationships between central retinal thickness and mesopic visual acuity (left) and low luminance deficit (right) in the no AMD (●), early (○) and intermediate (▼) AMD groups. In both graphs, the solid regression line represents the intermediate AMD group, the long-dashed line the early AMD group, and the short-dashed line the “no AMD” group.

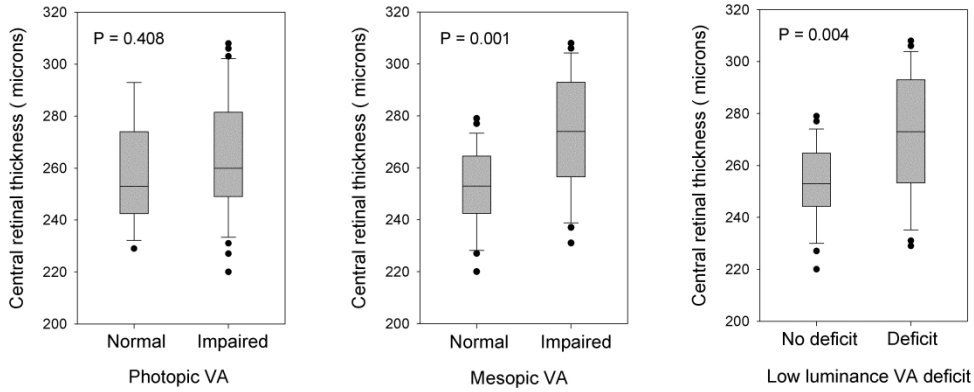

FIGURE 1. Box plots of central retinal thickness (microns) according to (A) photopic visual acuity impairment (>0.0 logMAR), (B) mesopic visual acuity impairment (>0.3 logMAR) and (C) low luminance visual acuity deficit (≥0.3 logMAR) recorded in all eyes.

173x102mm (600 x 600 DPI)

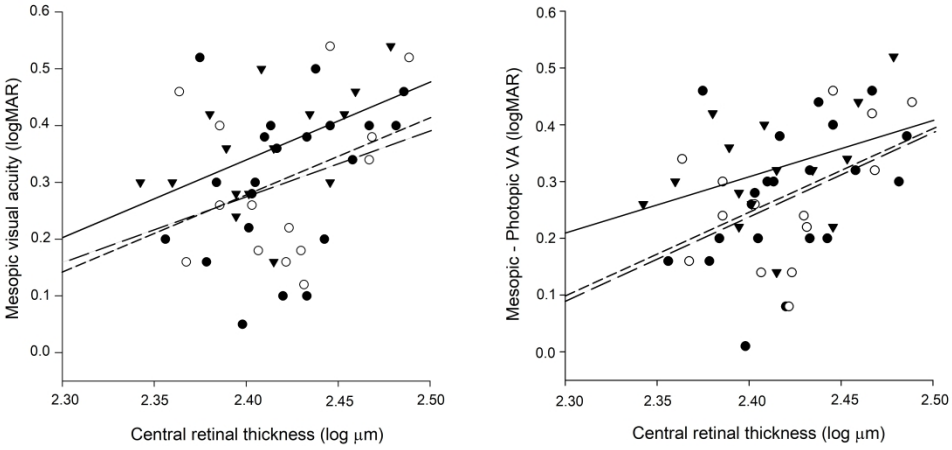

FIGURE 2. Relationships between central retinal thickness and mesopic visual acuity (left) and low luminance deficit (right) in the no AMD (●), early (○) and intermediate (▼) AMD groups. In both graphs, the solid regression line represents the intermediate AMD group, the long-dashed line the early AMD group, and the short-dashed line the "no AMD" group.

244x119mm (600 x 600 DPI)