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Macular pigment optical density assessed by heterochromatic flicker photometry in eyes affected by primary epiretinal membrane

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Abstract:	Purpose To compare macular pigment optical density (MPOD) in healthy eyes vs eyes affected by primary epiretinal membrane (ERM) in different stages and to assess the relation between MPOD and optical coherence tomography findings. Methods Prospective cross-sectional study of 62 eyes from 62 patients affected by unilateral primary ERM. Contralateral healthy eyes from the same patients were used as a control group. Main outcome measures were MPOD, ERM stage, central foveal thickness (CFT), outer nuclear layer thickness (ONLT), integrity of outer retinal bands (ORB) and presence of Central Bouquet (CB) abnormalities. Results In the study group mean CFT was 444±75 μm and mean ONLT was 245±40 μm, while in the control group mean CFT was 230±21 μm and mean ONLT was 102±14 μm ($p<0.001$). Mean MPOD was 0.86±0.07 in eyes with ERM and 0.48±0.09 in contralateral healthy eyes ($p<0.001$). MPOD was associated with CFT ($p=0.006$) and ONLT ($p<0.001$) while no significant associations were observed between MPOD and ORB integrity ($p=0.14$) and CB abnormalities ($p=0.08$). Conclusions MPOD increased in eyes affected by primary ERM proportionally to CFT and, especially, ONLT. Probably, centripetal forces exerted by ERM contraction on the retinal surface lead to a progressive foveal packing of foveal Muller cells.
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To Professor Alexander J. Brucker

Editor in Chief

Retina

Dated: 28/08/2021

Dear Editor in Chief,

I am very glad to send you our manuscript entitled **“**Macular pigment optical density assessed by heterochromatic flicker photometry in eyes affected by primary epiretinal membrane” for publication as original article in your prestigious journal, “Retina”.

I state that the content of the manuscript has not been published or submitted for publication elsewhere. I also state that the protocol for the research project has been approved by University “G. d’Annunzio” Ethics Committee and that it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). In addition, I state that the subjects gave informed consent and their anonymity has been preserved.

I had full access to all the data in the study and I take responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit for publication.

Please note that the authors have no financial interest in any of the products mentioned in this paper.

Sincerely yours,

Luca Cerino

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Macular pigment optical density assessed by heterochromatic flicker photometry in eyes affected by primary epiretinal membrane

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RUNNING HEAD

MPOD variations in eyes with primary ERM

CONFLICT OF INTEREST/FUNDING STATEMENT

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KEYWORDS

Epiretinal membrane, Heterochromatic flicker photometry, Macular pigment optical density, Muller cell cone, Spectral domain – Optical coherence tomography

SUMMARY STATEMENT

Macular pigment optical density measured by heterochromatic flicker photometry increases in eyes with primary epiretinal membrane, proportionally to epiretinal membrane severity and, particularly, to outer nuclear layer thicknening. Probably, epiretinal membrane contraction induces a foveal packing of the Muller cell cone, that is responsible for outer nuclear layer thickening.

ABSTRACT

Purpose

To compare macular pigment optical density (MPOD) in healthy eyes vs eyes affected by primary epiretinal membrane (ERM) in different stages and to assess the relation between MPOD and optical coherence tomography findings.

Methods

Prospective cross-sectional study of 62 eyes from 62 patients affected by unilateral primary ERM. Contralateral healthy eyes from the same patients were used as a control group. Main outcome measures were MPOD, ERM stage, central foveal thickness (CFT), outer nuclear layer thickness (ONLT), integrity of outer retinal bands (ORB) and presence of Central Bouquet (CB) abnormalities.

Results

In the study group mean CFT was 444±75 μm and mean ONLT was 245±40 μm, while in the control group mean CFT was 230±21 μm and mean ONLT was 102±14 μm ($p<0.001$). Mean MPOD was 0.86±0.07 in eyes with ERM and 0.48±0.09 in contralateral healthy eyes ($p<0.001$). MPOD was associated with CFT ($p=0.006$) and ONLT ($p<0.001$) while no significant associations were observed between MPOD and ORB integrity ($p=0.14$) and CB abnormalities ($p=0.08$).

Conclusions

MPOD increased in eyes affected by primary ERM proportionally to CFT and, especially, ONLT. Probably, centripetal forces exerted by ERM contraction on the retinal surface lead to a progressive foveal packing of foveal Muller cells.

INTRODUCTION

Epiretinal membrane (ERM) is a vitreo-macular interface pathology characterized by fibrocellular proliferation above the retinal surface resulting in a sheet-like structure able to contract and lead to retinal wrinkling with subsequent visual impairment. ERM is classified as primary or secondary, depending on the absence or the presence of another ocular pathology responsible for its occurence.[1]

Based on optical coherence tomography (OCT) findings, many different ERM staging systems have been proposed.[2-4]

Muller cells play an important pathogenetic role in primary ERM formation and progression to advanced stages.[5-8]

Foveal macular pigment (MP) is composed of the xanthophylls lutein and zeaxanthin and, to date, it is thought to be mostly embedded inside foveal Muller cells.[9]

Due to the protective role of MP against age-related macular degeneration,[10] the detection and quantification of MP has gained a raising interest in evaluating macular health.

Macular pigment optical density (MPOD) can be assessed in vivo using heterochromatic flicker photometry (HFP) and many previous studies demonstrated its reliability.[11-13]

To our knowledge there are poor informations about the impact of vitreo-macular interface pathologies on MPOD. Romano et al[14] assessed MPOD variations in eyes affected by primary ERM or full-thickness macular hole (FTMH) and treated with macular peeling. For MPOD assessment the one-wavelength fundus reflectance method was used.

Bottoni et al,[15] using a two-wavelength autofluorescence technique, evaluated MPOD changes after successful FTMH surgery and examined the relationship between MPOD, Spectral Domain-Optical Coherence Tomography (SD-OCT) findings and best-corrected visual acuity (BCVA).

Aim of our study was to assess the differences in MPOD, measured by HFP, between healthy eyes and eyes affected by primary ERM in different stages.

METHODS

In this prospective comparative study, 62 eyes from 62 patients affected by unilateral primary ERM were compared with 62 contralateral healthy eyes from the same patients.

The relationships between MPOD, anatomical findings and visual function were examined.

All partecipants were selected among patients seen at Ophtalmology Clinic of University G. d'Annunzio (Chieti, Italy) from April 1, 2020 to July 31, 2021.

Enrolled subjects needed to have primary unilateral ERM with the other eye presenting no evidence of ERM on SD-OCT examination.

Additional inclusion criteria were age of 18 years or more and axial length (AL) inferior to 26mm.

Exclusion criteria for both study and control eyes were: previous ocular surgery or trauma, amblyopia, media opacities preventing reliable MPOD measurement, other retinal diseases, previous intermediate and/or posterior uveitis. Eyes with macular pseudoholes were also excluded.

All patients were carefully examined under the slit lamp after pupil dilation with Tropicamide 10mg/ml eye drops in order to stage cataract according to the Lens Opacification Classification System III (LOCS III): a cataract stage > NO2-NC2 or > C2 or > P2 in at least one eye was an exclusion criterion.

Particular attention was paid to exclude signs of uveitis and retinal vascular diseases, possible causes of secondary ERM. In the presence of any suspect finding (arterovenous crossings, retinal hemorrages, microaneurysms, etc.), when the patient was not aware to suffer from any systemic disease, an accurate investigational work-up for the possible underlying pathologies (Holter blood pressure monitoring, haematochemical tests, etc.) was performed.

Since there are disagreements about how cataract surgery affects MPOD measured by using HFP,[16,17] patients with one or both pseudophakic eyes were excluded.

The study and data collection methods received approval from the local institutional review board. Written informed consent for the research was obtained from patients in adherence to the tenets of the Declaration of Helsinki.

At baseline, patients underwent a comprehensive ophthalmic examination including BCVA assessment, slit-lamp biomicroscopy of the anterior and posterior segments of the eye, intraocular pressure measurement. BCVA was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) charts and it was reported in logarithm of the minimal angle of resolution (logMAR) values for the purpose of statistical analysis.

AL was measured using partial coherence laser interferometry (IOLMaster 700, Carl Zeiss Meditec, Jena, Germany).

All patients were imaged with SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Inc, Dublin, CA) after pupil dilation, using two different recording protocols. The macular cube 512 x 128-scan protocol, covering a 6 mm x 6-mm macular area centered on the fovea, was used to obtain the central foveal thickness (CFT), automatically measured from internal limiting membrane (ILM) to retinal pigmented epithelium (RPE) and displayed on the Macular thickness analysis report. When the examiner found an inadequate centration of the ETDRS grid due to a failure of the automatic Fovea Finder™ system in the presence of an alterated foveal profile, a manual detection of foveal centre was performed in order to obtain the exact value of CFT.

The HD Cross imaging protocol consisting of 10 scans - 5 horizontal and 5 vertical - centered on the fovea, was used to dispose of high definition images necessary to assess integrity and segmentation of retinal layers and to investigate the possible presence of Ectopic Inner Foveal Layers (EIFL)[2] and abnormalities of the Central Bouquet (CB).[7]

Multiple morphologic characteristics were recorded including the presence of foveal pit, the presence of EIFL, alterations of retinal layers' segmentation, the integrity of the hyper-reflective outer retinal bands (ORB) including external limiting membrane (ELM), ellipsoid zone (EZ) and interdigitation zone (IZ) (Figure 1) and the presence of CB abnormalities,[7] that are the cotton ball sign, the foveolar serous detachment and the acquired vitelliform lesion (Figure 2).

The built-in caliper tool on the HD Cross printout was used to measure manually the thickness of the outer nuclear layer (ONL) in the foveal region. The horizontal scan centered on the fovea was used to obtain ONL thickness (ONLT) accurately placing the caliper on the hyporeflective band extended between ELM and ILM,

perpendicularly to the RPE line. In the presence of EIFL, their inferior border on OCT scans was used as upper limit of the ONL, as shown in Figure 3.

ERMs were staged according to Govetto et al. OCT-staging system[2] (Figure 1).

ONLT was measured in stages 1, 2 and 3 due to the impossibility of correctly differentiating retinal layers in stage 4 ERMs.

All instrumental tests were performed by a single examiner (LC). For a precise ERM staging and CFT and ONLT measurement, SD-OCT images were evaluated by two independent and masked observers (LC and AAG) and re-assessed by a third experienced observer (PC) in order to resolve any disagreement.

MPOD assessment

MPOD was calculated by means of HFP using the Macular pigment Screener (MPS) II (Elektron Technology, Cambridge, UK). The MPS II measures how much blue light MP absorbs. MPOD values are provided on a scale of 0 to 1 – the lower the value, the higher the level of blue light hitting the foveal cones.

HFP requires patients to make flicker matches using two wavelengths of light, one of which (blue; 465nm) is absorbed by the MP and another (green; 530nm) which is not. The two lights are superimposed and start flickering with a rate higher than the critical flicker fusion rate. The frequency is gradually reduced at a rate of 6Hz/s and patients are instructed to press a button as soon as flicker is detected.

The process is repeated for different green-blue luminance ratios. MPOD is automatically calculated as the log ratio of the central to the peripheral blue light luminances corresponding to the minimal flicker frequency perceived.

All patients were tested using the Detailed test mode consisting of a central and a peripheral test: the former having a 1° circular central target and the latter during which the patient fixates on a larger 1.75° red spot located at 8° horizontal nasal eccentricity.

The software of the MPS II automatically analyzes the results and gives three possible outcomes: “accept”, “caution”, and “reject”. For example, it reports unacceptable results in case of too few data points or shallow graph, noisy data or flicker too high. When unacceptable results (i.e. ‘‘caution’’ or ‘‘reject’’) were observed, the test was interrupted and the subject was asked to repeat it on the following day. Every test was repeated twice (with 30-minute interval between measurements) to verify the repeatability of the instrument.

All subjects were able to perform the test and included for statistical analysis.

Statistical analysis

Statistical analyses were conducted using MedCalc Software Version 19.3.1 (MedCalc Software Ltd., Ostend, Belgium). A value of $p<0.05$ was considered statistically significant.

Quantitative continuous variables are presented as mean ± standard deviation. The D’Agostino-Pearson test was used to verify the normal distribution of data. Logarithmic transformation was applied when necessary to achieve normal distribution.

Frequency and percentage were calculated for categorical variables.

Differences between data sets were evaluated with paired samples t-tests.

To investigate the relationships between MPOD and BCVA and other continuous variables, a mixed effects linear regression analysis was applied.

A logistic regression analysis was performed to test the relationship between dichotomous variables (i.e. presence/absence of CB abnormalities and ORB disruption) and both BCVA and MPOD.

RESULTS

Sixty-two patients with unilateral primary ERM, 35 women and 27 men, (mean age 62.5±9.1 years) were included in the study.

SD-OCT examination resulted in a mean CFT of 444±75 μm and a mean ONLT of 245±40 μm in the study group, while mean CFT was 230±21 μm and mean ONLT was 102±14 μm in the control group ($p<0.001$). The eyes of the study group were distributed in the four OCT stages as follows:

- Stage 1: 13 eyes (21%);
- Stage 2: 27 eyes (43%);
- Stage 3: 16 eyes (26%);
- Stage 4: 6 eyes (10%).

Ten out of 62 eyes (16%) presented ORB disruption and a significantly higher prevalence was found in stages 3 and 4 compared to earlier stages ($p<0.001$).

CB abnormalities were found in 13 eyes, 8 presenting the cotton ball sign (13%), 3 the acquired vitelliform lesion (5%) and 2 the foveolar detachment (3%).

Mean MPOD was 0.86±0.07 in eyes with ERM and 0.48±0.09 in contralateral healthy eyes ($p<0.001$), while mean BCVA was 0.37±0.2 logMAR and 0 logMAR respectively.

Both MPOD and BCVA were different between ERM stages.

BCVA was significantly better in early stages 1 and 2, while it was poorer in advanced stages 3 and 4 ($p<0.001$).

On the other hand, MPOD was slightly lower in stage 1, reaching the maximum value (i.e. >0,9) in most of stage 2, 3 and 4 ERMs.

Results for each stage group are extensively developed in Table 1.

MPOD and BCVA were also associated with CFT ($p=0.006$ and $p<0.001$ respectively), as well as MPOD resulted strongly related to ONLT ($p<0.001$).

Outer retinal alterations were found to be related to BCVA, while no significant associations were observed between MPOD and ORB integrity ($p=0.14$) and CB abnormalities ($p=0.08$). Disruption of ORB was associated with lower BCVAs ($p<0.001$) and CB abnormalities showed intrinsic differencies with better visual acuities observed in eyes with the cotton ball sign and worse visual acuities found in eyes with acquired vitelliform lesions ($p<0.001$).

There was also a significant association between MPOD and BCVA themselves ($p<0.001$).

Data related to MPOD distribution in relation to the other continuous variables are presented in Figure 4.

DISCUSSION

Primary ERM is characterized by fibrocellular proliferation above the macular surface resulting in a contractile sheet-like structure that occurs in the absence of any underlying ocular pathology.[1]

In this process Muller cells, that uniquely extend across nearly the entire thickness of the retina, play an important pathogenetic role acting as retinal mechanoceptors sensitive to stretching forces exerted by posterior vitreous cortex on the retinal surface.[18] When stimulated, they release many cytokines that promote both cellular differentiation[19] and glial cells migration to the inner retinal surface.[5,18]

Glial cells are the most represented cell type in early primary ERMs while, in advanced stages, myofibroblasts are predominant.[5] It was shown that glial cells constituting ERMs mostly derive from Muller cells themselves, that are also able to transdifferentiate into contractile myofibroblasts.[6]

Muller cells are the only type of glial cells present in the fovea.[20] There are two types of foveal Muller cells[21]: the Muller cells of the foveal walls, with the typical z-shaped cellular projections crossing the ONL and the Henle fiber layer, and a group of 25-35 unique Muller cells more vertically oriented, whose cell bodies overlay the foveal area of high photoreceptor density, forming a plug of tissue called “Muller cell cone” (MCC).[9,20,21]

To date, it is thought that foveal MP is mostly embedded inside Muller cells of the MCC,[9] as macular autofluorescence in healthy eyes is highly attenuated at the foveal center with a progressive increase proceding centrifugally reflecting the gradient of MP whose density decreases continuously from the center of the foveola toward the periphery.[22] In addition, in eyes affected by lamellar macular holes, characterized by

a partial defect of the inner fovea – involving, therefore, the MCC – an increased foveal AF can be observed.[23]

MP is composed of xanthophylls that both act as filters, directly absorbing short wavelength visible light, and have an antioxidant effect, playing a protective role against ultraviolet radiation damage.[10]

Since Muller cells collect most of foveal MP and they are involved in primary ERM pathogenesis, we aimed at investigating MPOD variations in eyes affected by primary ERM at different stages and we related them to visual function and morphologic findings.

In healthy subjects, MPOD is affected by many different factors like age, body mass index and diet.[24] In order to avoid these confounding factors, we used contralateral healthy eyes as a control group.

We found an increased MPOD in eyes with primary ERM, due to the retinal wrinkling and the subsequent centripetal displacement of the MCC, leading to an increased concentration of foveal MP.

Conversely, Romano et al[14] observed a significantly reduced MPOD in eyes with idiopathic ERM compared with normal eyes. These apparently conflicting results are attributable to the different methods used to assess MPOD. Since the one-wavelength fundus reflectance method uses an imaging technique, ERM can obscure MP, being interposed between the fovea and the fundus camera. On the other hand, HFP is a subjective method and it is not affected by ERM thickness. These results also suggest that glial cells and myofibroblasts that constitute ERM, while originating from Muller cells, do not contain xanthophylls.

On SD-OCT examination, CFT and outer retinal layers abnormalities are the most studied parameters to define ERM severity, since an increased CFT is inversely related with BCVA as well as photoreceptor disruption is an important predictor of poor visual outcome.[25,26]

Our data set confirmed these findings with CFT and ORB integrity strongly related to BCVAs.

MPOD resulted directly related to CFT and, especially, to ONLT, corroborating the hypotesis of the MCC centripetal shift with subsequent thickening of the ONL that is responsible for the progressive foveal pit disappearance. On the other hand, disruption of the ORB did not affect MPOD.

In recent years, attention has shifted to the study of inner retinal layers in eyes with ERM.[27,28]

Govetto et al[2] described the EIFL defined as a continuous hypo- or hyper-reflective inner retinal band extending from the INL and IPL across the fovea. The frequent persistence of EIFL after surgery suggested that their formation could result from a traction-induced molecular reaction,[8] probably mediated by Muller cells. They[2] introduced a new four-stage OCT classification of ERM, later validated by different authors,[29,30] drawing attention to EIFL and retinal layers' segmentation.

Our data set confirmed a significant association between OCT stage and visual function.

In stage 1 ERMs, MPOD values resulted proportional to CFT until reaching a plateau in most of stage 2, 3 and 4 ERMs. On the other hand, MPOD retained a strong association to ONLT in all stages.

These findings suggest that once foveal pit gets flattened, the highest density of foveal Muller cells is achieved. Probably, ONL thickening is attributable to a centripetal displacement of the MCC (Figure 5), that would explain the increase of MPOD. Further increase in CFT, observed in stages 3 and 4, is attributable to EIFL that do not affect MP despite Muller cells probably play a role in their formation.

Additional indipendent parameters related to visual prognosis are the abnormalities of the CB[7] induced by tractive forces exerted on the foveal cells in vitreomacular interface disorders like ERM. CB is defined as a 100 µm wide circular area centered on the fovea, composed of the thinnest and most sensitive cones densely packed with specialized Muller cells.[9]

The cotton ball sign, the subfoveal serous detachment and the secondary vitelliform foveal lesionhave been recently considered as subsequent stages of the same process associated with a progressive reduction in BCVA. Both their appearence and their location suggest a pathogenetic role of foveal Muller cells with the severity of the lesion depending on the strenght and the chronicity of the traction exerted on the Muller cells of the CB.[7] Thus, we assessed the correlation between MPOD and CB abnormalities, but we did not find a significant correlation. Probably, in this process Muller cells only act as mechanoceptors transmitting mechanical forces to photoreceptors that progressively undergo degeneration.

In conclusion, our data set confirmed the validity of the Govetto et al[2] OCT staging system. of primary ERM and its relation to visual function. Also the Govetto et al[7] hypothesis of cotton ball sign, foveolar detachment and acquired vitelliform lesion as progressive stages of the same clinical spectrum is consistent with our findings.

We observed an increased MPOD in eyes affected by primary ERM and higher values were found in advanced stages, while both ORB and CB abnormalities did not affect MPOD. Probably, centripetal forces exerted by ERM contraction on the retinal surface lead to a progressive foveal packing of the MCC, that is the site where MP is mostly located. In fact, CFT and, especially, ONLT resulted in direct proportion to MPOD suggesting that ONL thickening in part is due to MCC central shift.

Since MPOD resulted strongly related to ERM severity, its measurement could become part of the pre-operative assessment of eyes affected by primary ERM. Further studies are required to establish its prognostic value.

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FIGURE LEGENDS

Figure 1. Spectral domain-optical coherence tomography scans showing epiretinal membranes (ERMs) in different stages. (A) Stage 1 ERM with well-defined retinal layers and preserved foveal depression. Outer retinal bands (ORBs) including external limiting membrane (blue arrow), ellipsoid zone (green arrow) and interdigitation zone (red arrow) are intact. (B) Stage 2 ERM with loss of foveal depression, while all retinal layers are still well-defined. A multifocal disruption of the ORBs (red stars) can be observed. (C) Stage 3 ERM characterized by the development of ectopic inner foveal layers (EIFL) crossing the fovea (green star) in the absence of the foveal pit while all retinal layers can be clearly identified. (D) Stage 4 ERM associated with EIFL, loss of foveal pit and disruption of retinal layers.

Figure 2. Spectral domain-optical coherence tomography scans showing epiretinal membranes (ERMs) associated with central bouquet abnormalities. (A) Stage 3 ERM with evidence of the cotton ball sign, defined as a small hyperreflective area located between ellipsoid zone (EZ) and interdigitation zone. (B) Stage 3 ERM with a subfoveal serous detachment of the neuroepithelium. (C) Stage 2 ERM associated with a large hyperreflective acquired vitelliform lesion, located between EZ and retinal pigment epithelium.

Figure 3. Thickness of the outer nuclear layer (ONL) in the foveal region was manually measured using the built-in caliper tool on the HD Cross printout of the Cirrus HD-OCT (Carl Zeiss Meditec, Inc, Dublin, CA). The caliper was accurately placed on the hyporeflective band extended between external limiting membrane and internal limiting membrane, perpendicularly to the retinal pigment epithelium line (A, B). In the presence of ectopic inner foveal layers, their inferior border was used as upper limit of the ONL (C).

Figure 4. Relation between macular pigment optical density (MPOD) and the main quantitative variables. (Top left) MPOD is significantly associated with central foveal thickness (CFT) ($p=0.006$) due to the centripetal displacement of the macular pigment (MP) induced by epiretinal membrane contraction. (Top right) There is a stronger association between MPOD and outer nuclear layer thickness (ONLT) ($p<0.001$) suggesting that the latter is mainly attributable to a centripetal shift of the Muller cell cone, while the further increase in CFT is due to ectopic inner foveal layers that do not affect MP. (Bottom) There is also a significant association between MPOD and best-corrected visual acuity (BCVA) ($p<0.001$), probably resultant from the progressive foveal thickening that is responsible for both MPOD increase and BCVA worsening.

Figure 5. Muller cell cone (MCC) displacement due to epiretinal membrane (ERM). The tissue of the MCC is shown in orange and the foveal Muller cells are illustrated as red lines. Tissue movements induced by ERM contraction are indicated by red arrows. (A) Healthy fovea with the normal distribution of the MCC. (B) Stage 1 ERM with a mild thickening of the outer nuclear layer (ONL) due to the centripetal shift of the MCC. (C) Stage 2 ERM in which foveal pit disappearance induced by ERM contraction is associated with a significant thickening of the ONL. The centripetal displacement of the MCC is more pronounced leading to an increased foveolar density foveal Muller cells.

Figure 1

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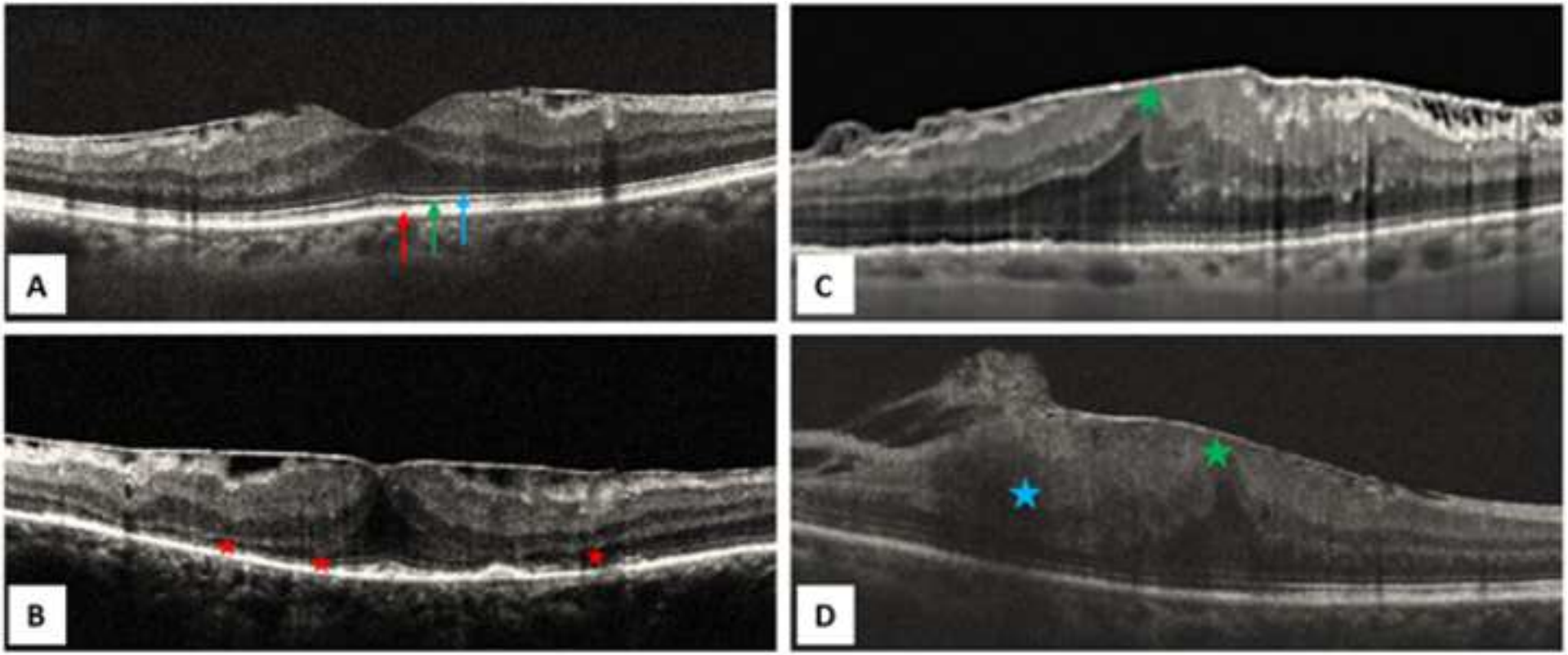

Figure 2

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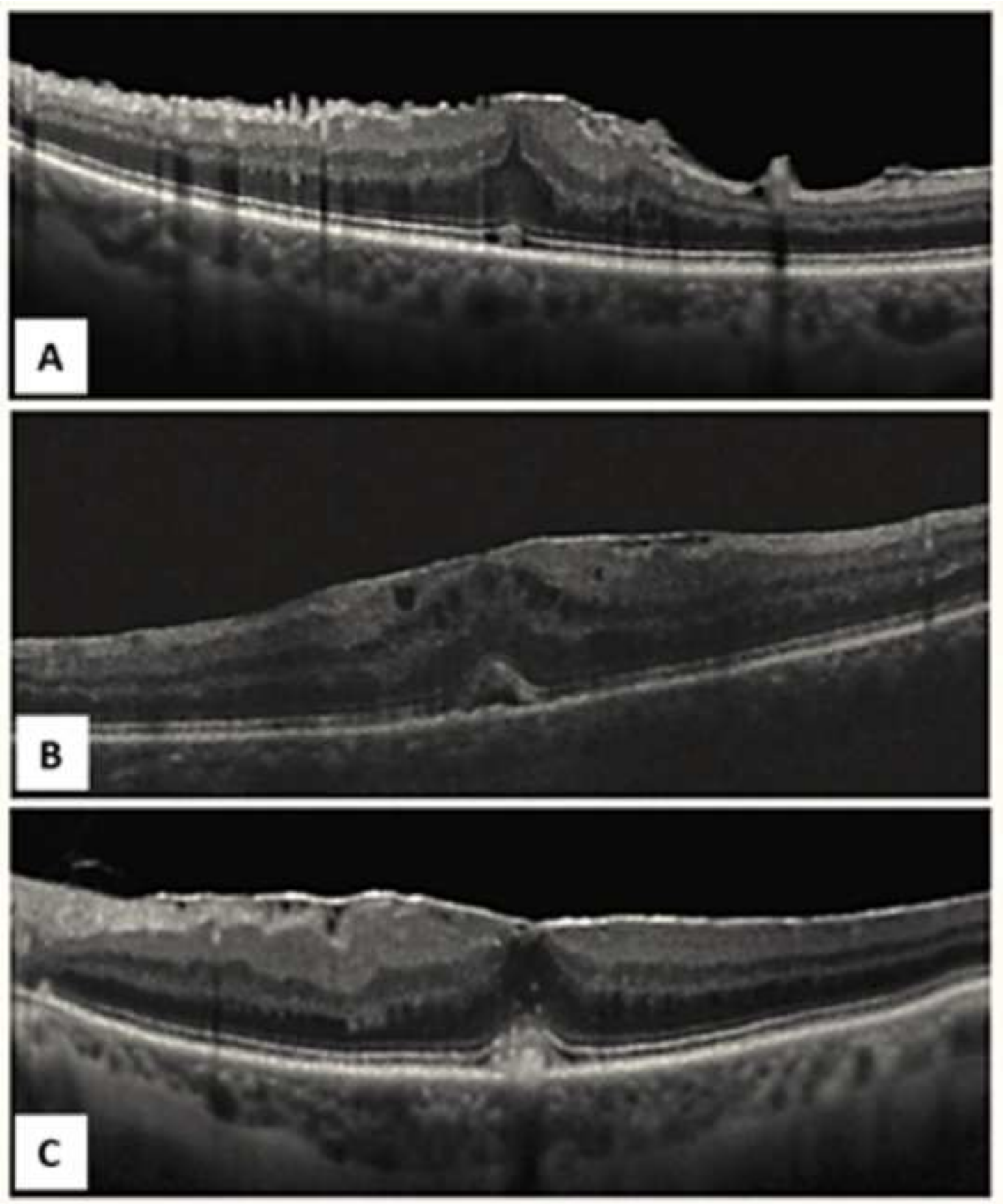

Figure 3

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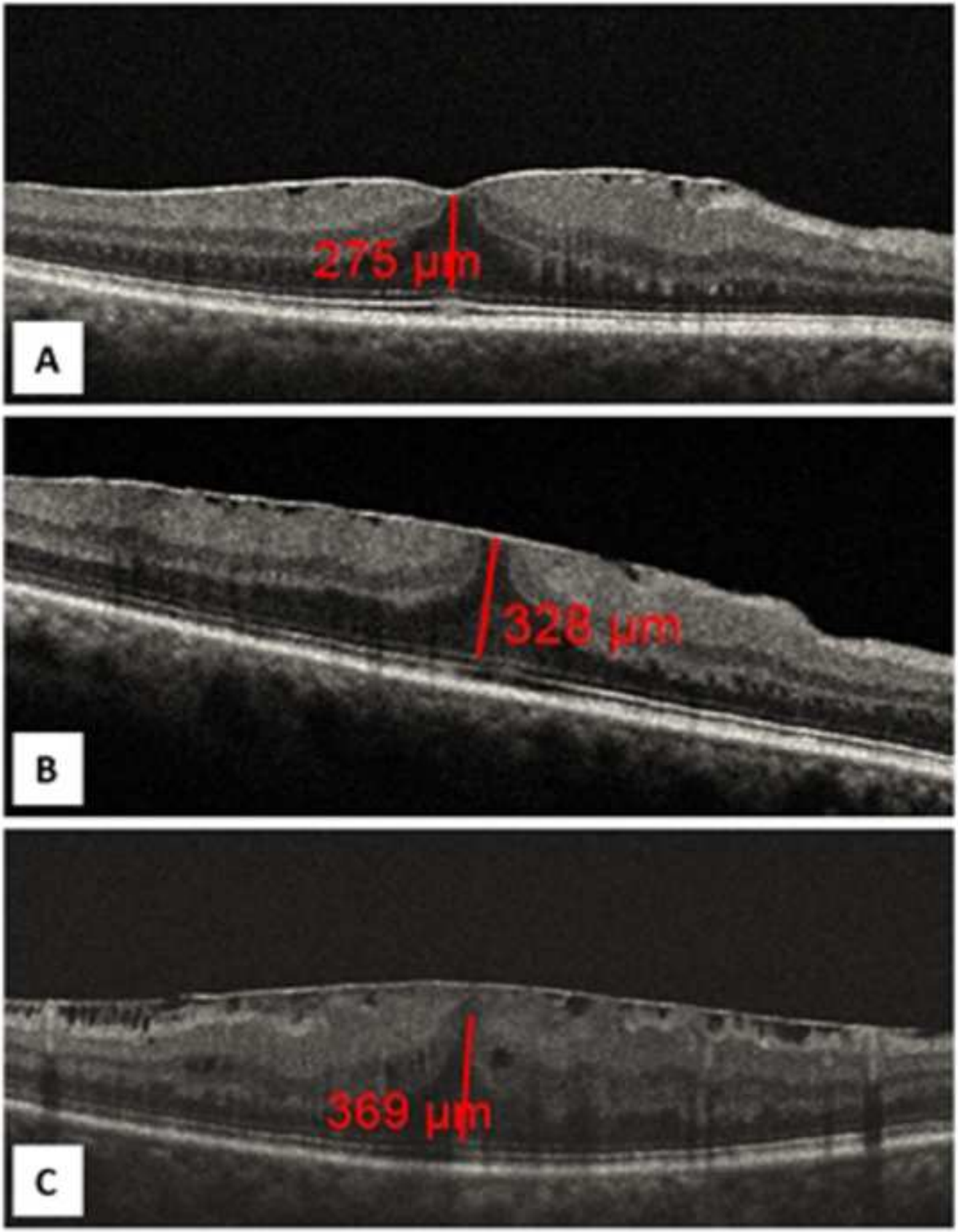

Figure 4

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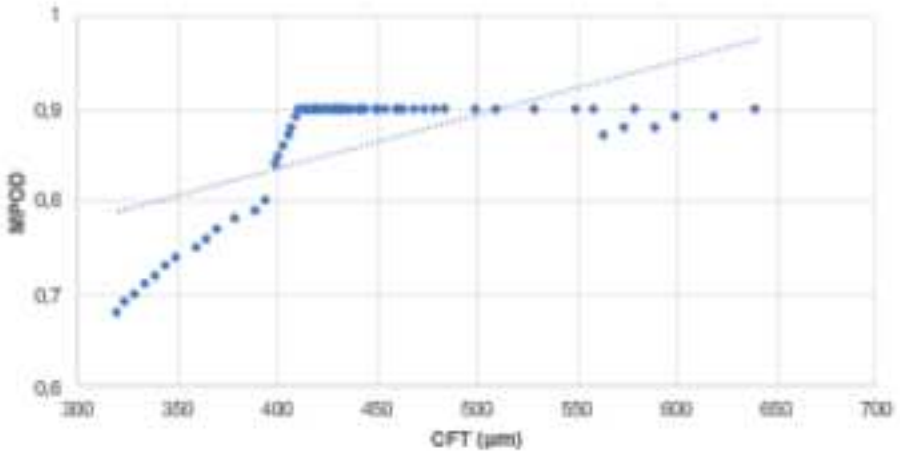

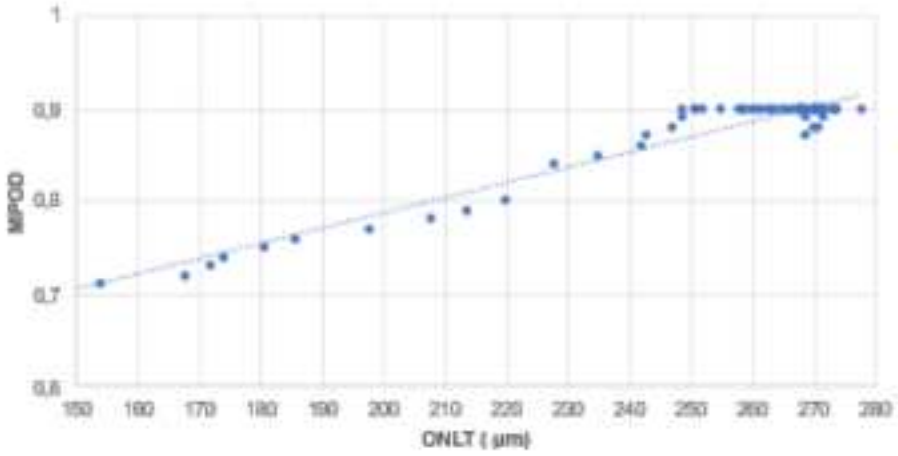

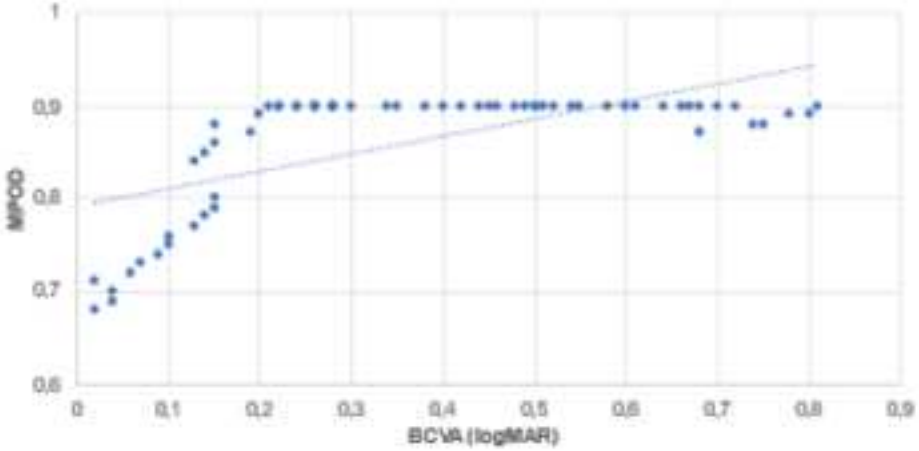

Figure 5

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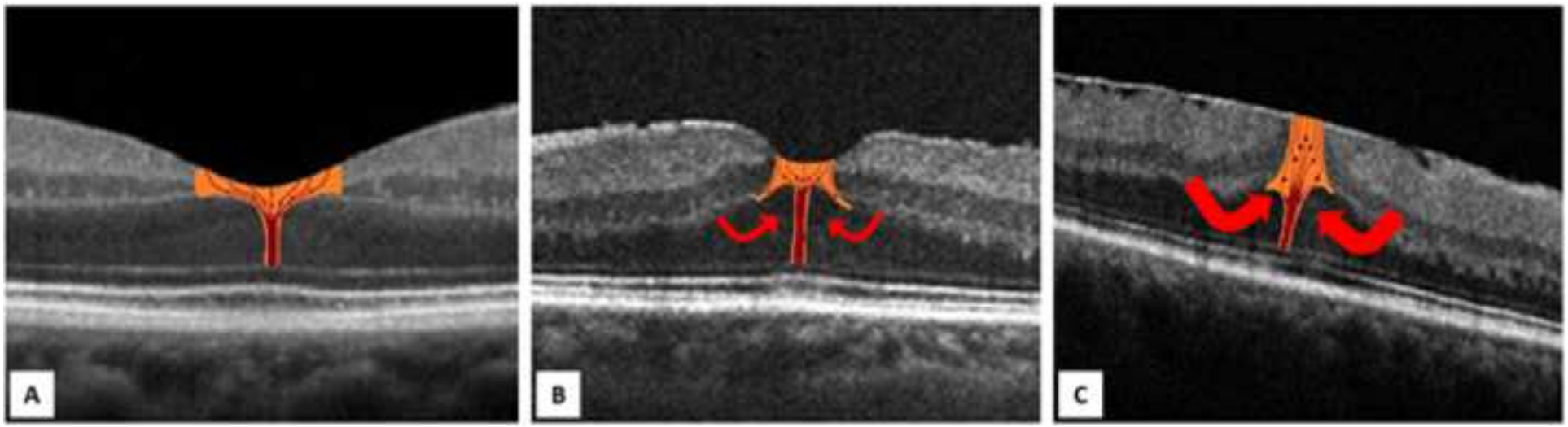

Table 1

Table 1. Characteristics of studied epiretinal membranes

	BCVA (logMAR)	**MPOD**	**CFT (µm)**	**ONLT (µm)**	**ORB disruption (n°)**	**CB abnormalities (n°)**
Stage 1 (13 eyes)	0.08±0.04	0.74±0.04	354±25	175±31	ELM disruption: 0 EZ disruption: 0 IZ disruption: 0	Cotton ball sign: 0 Foveolar detachment: 0 Acquired vitelliform lesion: 0
Stage 2 (27 eyes)	0.3±0.11	0.89±0.02	424±14	260±12	ELM disruption: 0 EZ disruption: 2 IZ disruption: 0	Cotton ball sign: 2 Foveolar detachment: 0 Acquired vitelliform lesion: 0
Stage 3 (16 eyes)	0.59±0.08	0.9±0.00	493±42	266±9	ELM disruption: 2 EZ disruption: 4 IZ disruption: 3	Cotton ball sign: 4 Foveolar detachment: 1 Acquired vitelliform lesion: 1
Stage 4 (6 eyes)	0.76±0.05	0.89±0.05	598±28	-	ELM disruption: 3 EZ disruption: 4 IZ disruption: 4	Cotton ball sign: 2 Foveolar detachment: 1 Acquired vitelliform lesion: 2

BCVA = best-corrected visual acuity. MPOD = macular pigment optical density. CFT = central foveal thickness. ONLT = outer nuclear layer thickness. ORB = outer retinal bands. CB = central bouquet. ELM = external limiting membrane. EZ = ellipsoid zone. IZ = interdigitation zone.