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Evolution of idiopathic epiretinal membrane studied by optical coherence tomography

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PURPOSE. *To study the evolution of idiopathic epiretinal membrane (IERM) as examined by optical coherence tomography (OCT) in the 1-mm-diameter circle centered on the fovea.*
METHODS. *In a case series study 71 subjects (71 eyes) with idiopathic epiretinal membrane and macular thickness greater than 220±10 μm were evaluated by OCT. The fellow healthy eye of 52 patients was used as the control group. The mean follow-up was 36 months. Measurements of macular thickness at baseline and at the final examination were performed. Best-corrected visual acuity was expressed as the number of letters read on the Early Treatment Diabetic Retinopathy Study chart.*
RESULTS. *Within the inner macular central circle of 1 mm diameter the thickness of the fovea increased by an average of 12.29% (p<0.001) during follow-up in the study group while in the control group the foveal thickness decreased by –0.44% (p=0.43). The mean increase of the fovea thickness was accompanied by a modest decrease of best-corrected visual acuity from a mean 43.26 letters at baseline to a mean 39.20 letters at the last examination (p<0.001).*
CONCLUSIONS. *In the study group the macular thickness increased during a mean follow-up period of 36 months. The average increase between the baseline and the final examination at the inner central circle of 1 mm diameter was 12.29%. Decrease of the macular thickness was not observed in any of the studied cases. The mean decrease of visual acuity was 9.4%. OCT also depicted with accuracy the changing morphology of the affected macula during the study period. (Eur J Ophthalmol 2008; 18: 980-8)*

KEY WORDS. *Idiopathic epiretinal membrane, Optical coherence tomography, Macular thickness, Visual acuity*

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INTRODUCTION

Epiretinal membrane (ERM) is the result of fibroglial proliferation on the surface of the retina (1-3). It may occur as a primary idiopathic disorder of the posterior pole independently of specific disease processes other than posterior vitreous detachment (4-7) or it can be associated with a variety of ocular diseases (8, 9). The prevalence of idiopathic epiretinal membrane (IERM) ranges from 7.1% to 10.3% in the age group from 60 to 80 years old (10). Idiopathic epiretinal membrane, when it happens, affects one or both eyes of subjects over 50 years of age and both sexes are equally affected. Some reports showed a higher prevalence of IERM in female subjects but this did not reach statistical significance (11).
The IERM may have a translucent or semitranslucent fibroglial appearance or may be thick and opaque (macular pucker) with visual dysfunction varying from mild to severe (12). Eyes with thin IERM commonly main-

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tain 20/50 visual acuity, while in cases with macular pucker the visual acuity is usually significantly affected and approaches the level of 20/200 (7, 13).

Until now the evolution of IERM or ERM has been mainly based on clinical appearance, biomicroscopy, fundus photography, and fluorescein angiography (4, 7, 13). So far optical coherence tomography (OCT) has been used to describe the characteristics of the IERM (14) or to study the structure and function of the macula before and after surgical intervention for the removal of the epiretinal macular membrane (15-17).

OCT is a noninvasive, noncontact imaging instrument, which is capable of producing high resolution cross sectional images of the retina (18-20). The technique contributed to the study of many retinal disorders and it has been extensively used in the quantitative assessment of macular edema (21-24).

The aim of this study is to describe the evolution of IERM in the macula by OCT in a series of patients who had no surgical intervention for removal of the membrane.

METHODS

In the study 85 eyes of 85 phakic subjects with clinical diagnosis of idiopathic epiretinal membrane were selected consecutively from two different hospitals. The patients were selected and investigated among a total of 223 patients with IERM examined initially and during the progress of the study. The fellow healthy eye of 52 patients was used as a control group since the remaining 19 eyes had cataract, pseudophakia, or retinal pathology. From the 85 subjects, 8 were dropped during follow-up due to cataract progression, 5 patients did not complete the follow-up, and 1 patient moved to another country. Therefore, 71 patients were included in our study. Twenty-eight patients had no lens opacity, 39 eyes had cataract grade I, and 4 cases had cataract grade II according to the LOCS II classification system.

Inclusion criteria

In the study we included the following:

- Patients who had IERM located at the macula and firmly attached without gaps to the retinal surface at the inner central circle of 1 mm diameter. At the outer circle of 3 mm diameter the IERM was firmly attached to the retinal surface with small gaps in some cases between the membrane and the inner retina.
- Patients who had coexisting abnormal foveal thickness exceeding 220±10 μm.
- Patients who had a follow-up period equal to or greater than 24 months.
- Patients who had no eye surgery or other current or previous eye disease except IERM accompanied by macular edema.
- Patients who had the ability to fixate on the OCT fixation target.
- Patients who had refractive error not exceeding the ±5.00 D spherical equivalent.

Exclusion criteria

We excluded the following:

- Patients who had IERM accompanied by pseudohole or lamellar macular hole.
- Patients who had coexisting vitreous membrane and vitreomacular traction evident on OCT examination.
- Patients who were pseudophakic.
- Patients who were phakic with lens opacities grade III or higher according to the LOCS II classification system in all three categories (nuclear, cortical, posterior subcapsular) (25).

Foveal and parafoveal morphology and thickness were studied by OCT every 6 months. However, for the purpose of the present investigation we included only the measurements at baseline and at the final examination.

At baseline and during the progress of the investigation biomicroscopy and OCT revealed that in all studied patients the membrane had a translucent or irregular wrinkling appearance. All patients had IERM grade 0 and I according to the Gass classification and in no case was obvious progression of the IERM by biomicroscopy noted during follow-up (12). Forty-eight eyes had a total posterior vitreous detachment (PVD) and in 23 eyes the vitreous was completely attached to the macula.

Best-corrected visual acuity after refraction was expressed as the number of letters read on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (26). Visual acuity (VA) was examined

at baseline and at the last examination.

OCT examination was performed after pupil dilation with local application of 5% phenylephrine and 0.5% tropicamide. The macular thickness measurements were performed by Stratus OCT (OCT 3 Carl Zeiss, Meditec, Dublin, CA). Six radial scans, 30º degrees apart each, centered at the foveola were performed for each patient using the macular thickness protocol. The scans were considered of adequate quality if the OCT software would correctly identify the inner and outer boundaries of the retina as described below. In cases where those boundaries were miscalculated by the OCT software the scans were repeated until the correct ones were produced.

The calculation of macular thickness is performed between the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE). However, in cases of IERM where the membrane is thin and totally adherent to the retinal surface, it is almost impossible to distinguish it from the ILM. Therefore, in our study, the macular thickness was measured automatically as the distance between the IERM and the anterior boundary of the RPE. In calculating the macular thickness, the OCT software included also the thickness of the epiretinal membrane. IERM was visible on the OCT image as a highly reflective layer on the inner retinal surface (14). Images were selected to be of adequate quality and were characterized by the good demarcation of the vitreoretinal and chorioretinal interface. OCT in each scan was directed through the center of the fovea using the OCT's fixation target. OCT measurements were performed in each of the following areas: 1) central area within an inner circle of 1 mm diameter, 2) the center of the foveola, and 3) the perifoveal area and especially in the superior, temporal, nasal, and inferior quadrants within a circle of 3 mm diameter. The IERM was firmly attached to the macula in the inner 1 mm diameter circle in all studied cases. In the 3 mm diameter circle of the macula we observed gaps between the membrane and the retina in most cases (61/71).

Our measurements were mainly based on the increase of the foveal thickness in the 1 mm diameter central area, which is considered to be potentially more reliable (27). The reliability is based on the fact that the macular thickness in the foveal area of 1 mm diameter is determined by 512 data points instead of 6 data points for the center of the foveola (27). The central foveolar thickness was the average of 6 radial scan measurements centered at the foveola. The measurements of retinal thickness were performed by the same observers in the two different hospitals and between 11 AM and 3 PM local time, in order to avoid macular thickness diurnal variations (28). Measurements were analyzed by using Wilcoxon matched-pairs signed rank sum test. All tests were made assuming a level of statistical significance ($p<0.005$).

The study was conducted according to the declaration of Helsinki and all participants gave informed consent after the purpose of the study had been explained to them. The medical ethics committee of the hospitals approved the study.

RESULTS

The mean age of the subjects was 70.2 years (range: 55–83 years). Follow-up ranged from 24 months to 56 months (mean: 36 months). Forty-one subjects were female and 30 were male. In the study group we did not find any correlation between 1) the baseline foveal thickness and the age of the patients (correlation coefficient: –0.10 and $p=0.43$) and 2) the final foveal thickness and the age of the subjects (correlation coefficient: –0.10 and $p=0.39$). In the control group there

TABLE I - CHARACTERISTICS AND FOVEAL THICKNESS OF PATIENTS WITH IDIOPATHIC EPIRETINAL MEMBRANE

Characteristic	Value	p
Age, yrs, mean (SD)	70.23 (5.77)	
Sex, M/F, n (%)	30 (42.25)/41 (57.75)	
Fovea*		
[Mean (SD)]		
Baseline	325.29 (57.28)	
Final	363.81 (59.62)	
Difference	38.52 (23.55)	<0.001
Relative difference (%)	12.29 (7.69)	
VA†		
[Mean (SD)]		
Baseline	43.26 (6.71)	
Final	39.20 (7.54)	
Difference	–4.06 (2.87)	<0.001
Follow-up, mo, mean (SD) (range)	36.01 (9.28) (24–56)	

*Foveal thickness within an inner circle of 1 mm diameter in µm.
†Visual acuity (score of number of letters read measured by Early Diabetic Treatment Retinopathy Study Charts)

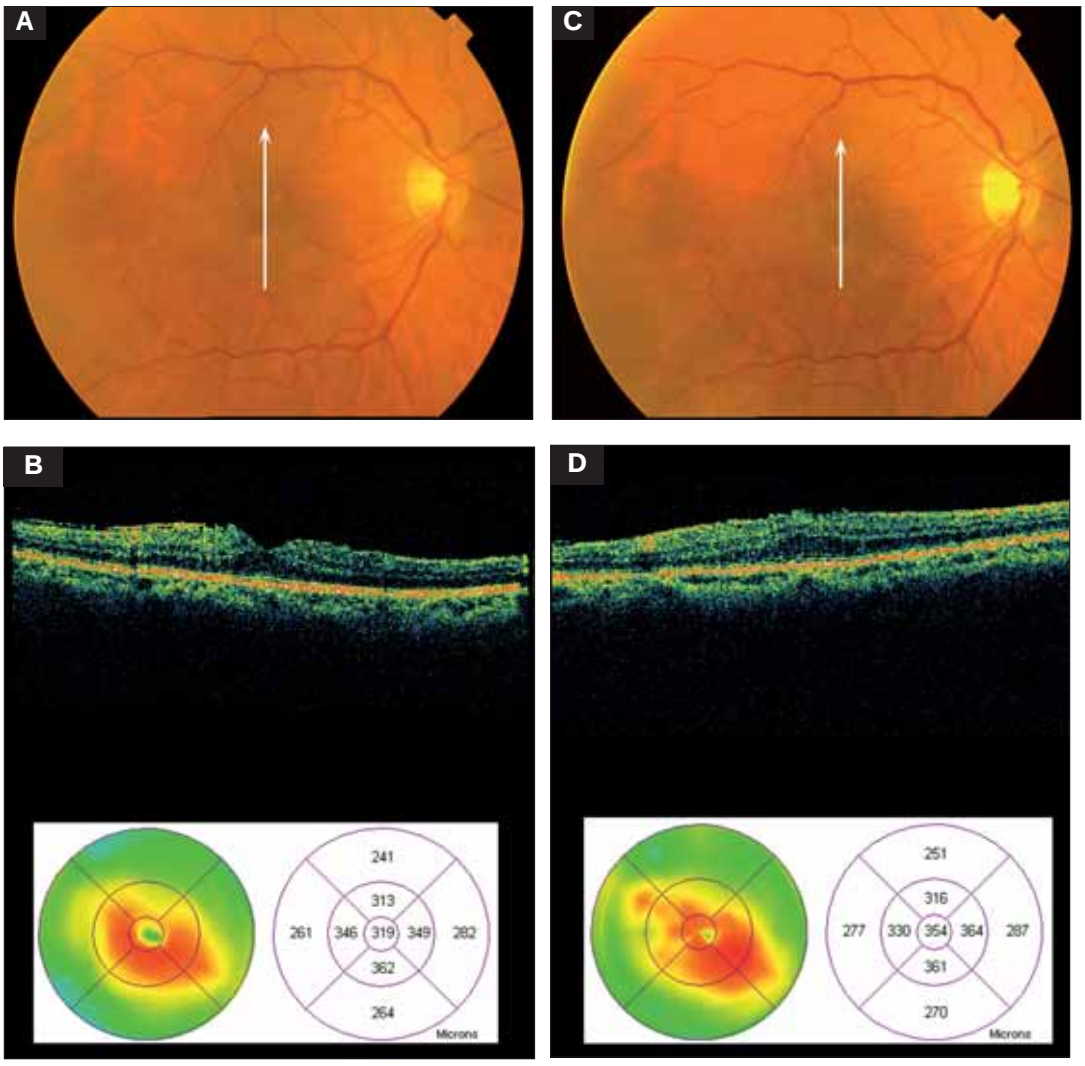

Fig. 1 - *Idiopathic epiretinal membrane of the right eye of a 72-year-old woman.* **(A)** *Fundus photograph showing the idiopathic epiretinal membrane and the direction of the optical coherence tomography scan at baseline.* **(B)** *Vertical transfoveal optical coherence tomography scan at baseline showing that the foveal thickness at the 1 mm diameter circle is 319 µm while the visual acuity is 40 letters according to the Early Treatment Diabetic Retinopathy Study chart.* **(C)** *Fundus photograph showing the idiopathic epiretinal membrane and the direction of the optical coherence tomography scan at the final examination.* **(D)** *Vertical optical coherence tomography scan through the fovea at the 1 mm diameter circle demonstrating the abolition of the foveal pit while the foveal thickness is 354 µm at the final examination. During the follow-up period the visual acuity decreased by 8 letters.*

was no correlation found between the macular thickness and the age of the subjects (correlation coefficient: 0.10 and p=0.47). In the study group the mean refraction was –0.32 diopters and there was not any correlation found between the macular thickness and the refraction (correlation coefficient: –0.09 and p=0.45). In the control group the mean refraction was –0.87 diopters and there was no correlation found between the macular thickness and the refraction (correlation coefficient: 0.13 and p=0.36).

The characteristics and the macular thickness of subjects with IERM in the 1 mm diameter inner circle of the fovea are given in Table I. There was a decrease of best-corrected visual acuity from a mean 43.26 letters at baseline to a mean 39.20 letters at the last examination as measured with the ETDRS chart (Tab. I). Overall, 9.9% (7) of patients retained their visual acuity, 63.4% (45) of cases lost up to 5 letters, and 26.7% (19) of eyes lost between 6 and 10 letters of visual acuity.

In the central area of 1 mm diameter the macular thickness increased by an average of 12.29% from a mean 325.29±57.28 (±SD) µm at baseline to a mean 363.81±59.62 (±SD) µm in the final examination (p<0.001) (Tab. I, Figs. 1–4). Overall, 33 eyes (46.5%) had an increase of macular thickness between 0% and 10%, 24 cases (33.8%) between 10.1% and 20%, and 14 patients (19.7%) had an increase of macular thickness 20.1% and over. In the central foveola the macular thickness increased from a mean 311±84.3 (±SD) µm at baseline to a mean 343±95.1 (±SD) µm in the final examination (average increase 10.4% [p<0.005]).

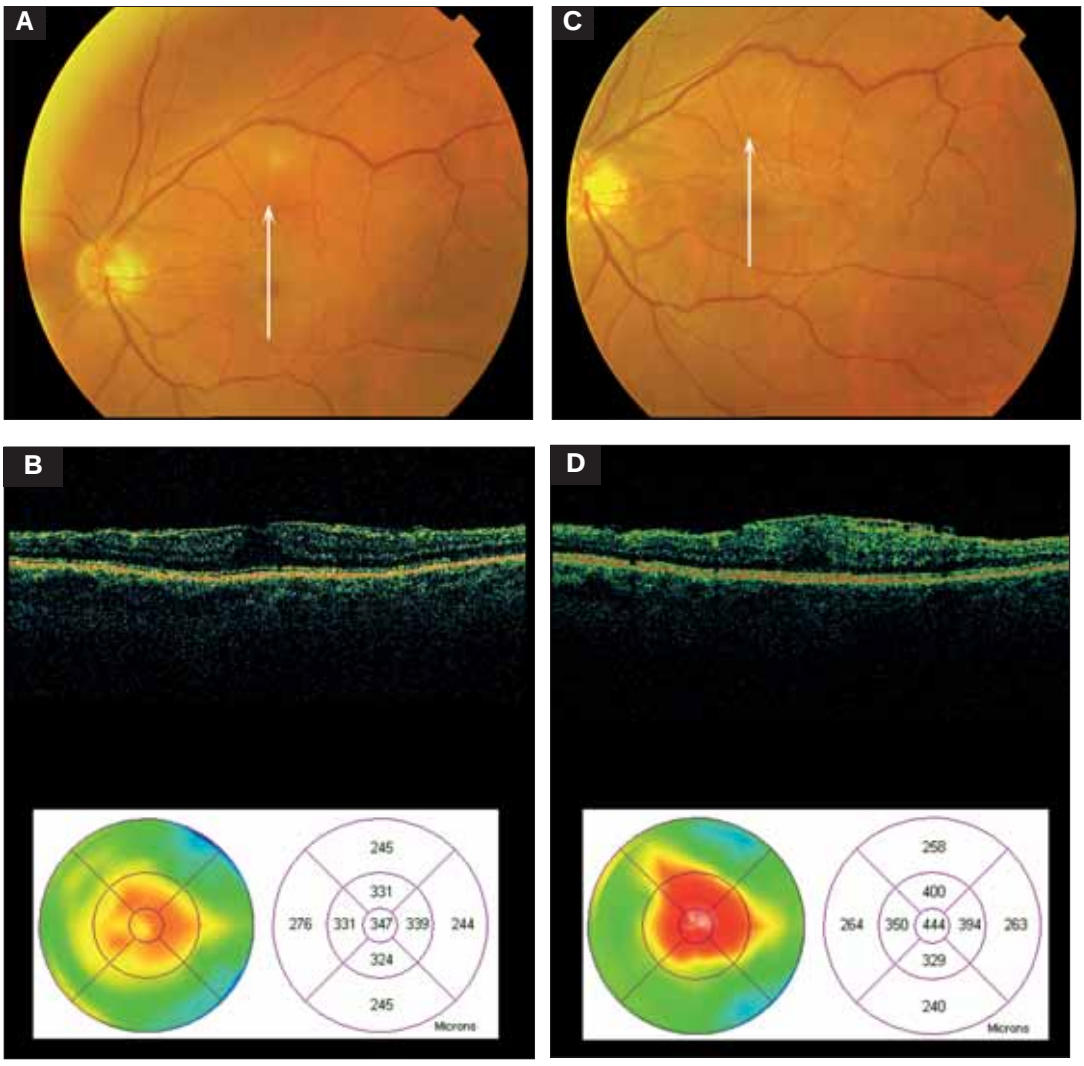

Fig. 2 - *Idiopathic epiretinal membrane of the left eye of a 60-year-old woman.* **(A)** *Fundus photograph showing the idiopathic epiretinal membrane and the direction of the optical coherence tomography scan at baseline.* **(B)** *Vertical transfoveal optical coherence tomography scan at baseline showing an increase of the foveal thickness (1 mm diameter inner circle: foveal thickness 347 µm). Best-corrected visual acuity is 35 letters by the Early Treatment Diabetic Retinopathy Study chart.* **(C)** *Fundus photograph showing the idiopathic epiretinal membrane and the direction of the optical coherence tomography scan at the final examination.* **(D)** *Vertical transfoveal optical coherence tomography scan at the final examination showing the abolition of the foveal pit and further increase by 27.95% of the foveal edema (1 mm diameter inner circle: foveal thickness 444 µm). Best-corrected visual acuity 30 letters measured by the Early Treatment Diabetic Retinopathy Study chart.*

In the control group the macular thickness of the central area of 1 mm diameter decreased by an average of –0.44% from a mean 167.38±18.1 (±SD) µm at baseline to a mean 166.54±17.67 (±SD) µm in the final examination, a difference statistically not significant (p=0.241). The central foveolar thickness was measured automatically by the computer software. In the study group the macular thickness between baseline and final examination in the superior, inferior, temporal, and nasal quadrants in a 3 mm diameter circle shows an average macular thickness increase ranging from 3.79% to 4.82% in all quadrants.

At baseline, 47 (66.2%) cases had alterations of the foveal contour with increased macular thickness while in 24 (33.8%) patients we observed loss of the foveal contour accompanied by diffuse macular edema. During follow-up 18 of 47 eyes with alterations of the foveal contour developed loss of the foveal contour accompanied by diffuse macular edema, while the remaining 29 of 47 cases preserved their foveal appearance. In the 24 patients with loss of the foveal contour initially, the existing diffuse macular edema increased or showed minimal alterations. Changes in the macular morphology were also observed in the form of cystoid intraretinal spaces confined to the area of diffuse macular edema in four cases and in the form of increased rate of loss of foveal contour from an initial 33.8% (24 cases) to a final 59.15% (42 patients). The macular morphology of the control group remained unchanged. Regression analysis to define the relation between macular thickness and visual acuity is given in Figure 4.

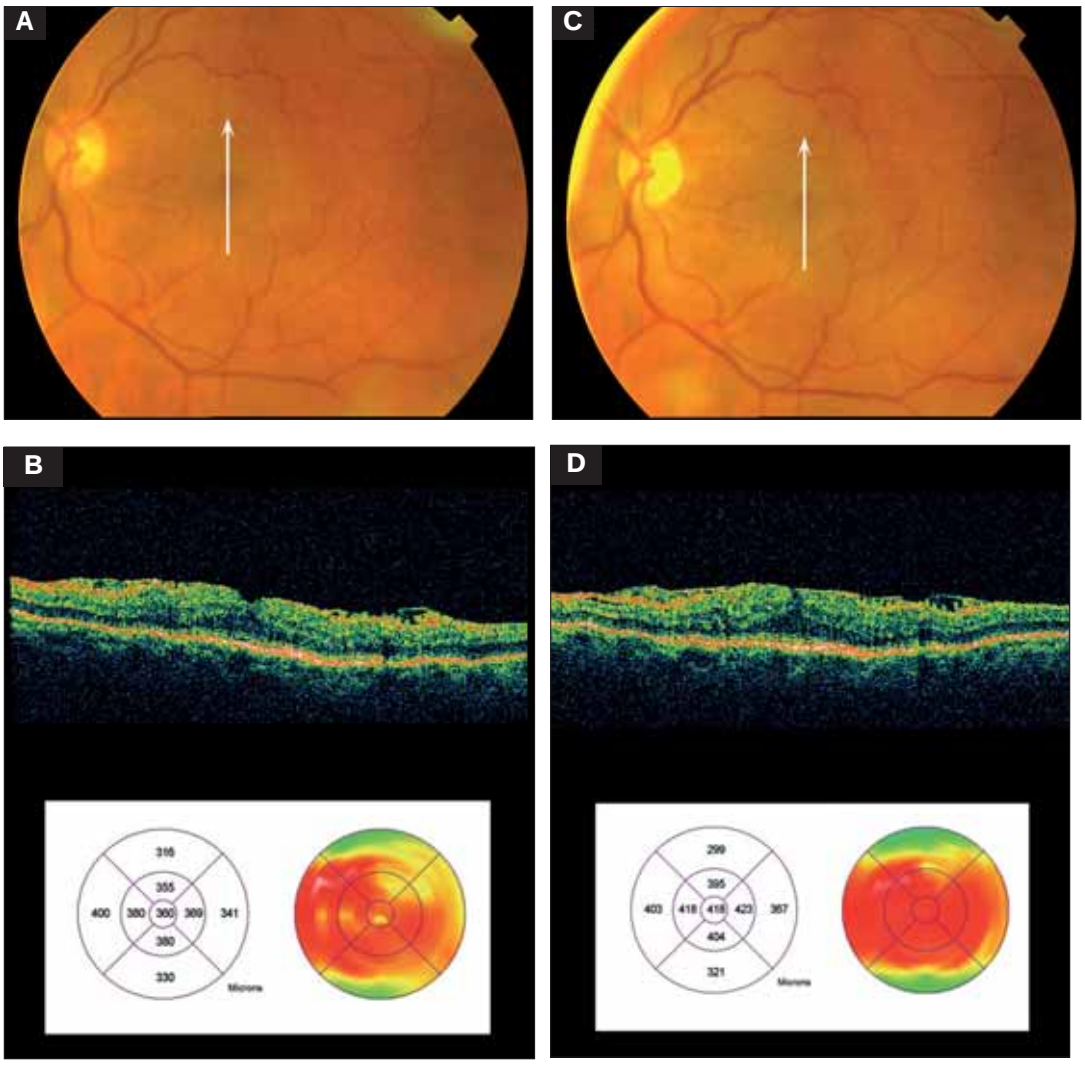

Fig. 3 - *Idiopathic epiretinal membrane of the left eye of a 68-year-old man.* **(A)** *Fundus photograph showing the idiopathic epiretinal membrane and the direction of the optical coherence tomography scan at baseline.* **(B)** *Vertical transfoveal optical coherence tomography scan at baseline shows an increased foveal thickness (360 µm) in the 1 mm diameter circle. Best-corrected visual acuity 45 letters (Early Treatment Diabetic Retinopathy Study chart).* **(C)** *Fundus photograph showing the idiopathic epiretinal membrane and the direction of the optical coherence tomography scan at the final examination.* **(D)** *Vertical transfoveal optical coherence tomography scan at the final examination shows that the foveal thickness has increased (418 µm) by 16%. Note also the abolition of the foveal pit. Best-corrected visual acuity was 35 letters (Early Treatment Diabetic Retinopathy Study).*

During the follow-up period we did not notice either decrease of the macular thickness or automatic separation of the IERM from the retinal surface. Two of the 23 patients with attached hyaloid at baseline were found to develop a PVD during follow-up.

DISCUSSION

We have shown that patients with IERM experience significant difference in macular thickening in the 1 mm diameter central area of the fovea between the first and the last examination. The macular thickness in this area increased by an average of 12.29% ± 7.69% (±SD) ($p<0.001$) in a period of observation ranging from 24 to 56 months (mean: 36 months). In the control group we found a mean decrease of foveal thickness during follow-up –0.44%, which was not statistically significant ($p=0.241$) (29). The average difference of 12.29%±7.69% (±SD) in the foveal thickness is in agreement with recent reports, which showed that in patients with clinically significant macular edema, changes of retinal thickness greater than 10% in the 1 mm central macular area are likely to represent real changes rather than be caused by inconsistency of the OCT software (30-32).

We also observed an increase of 10.4% in the central foveolar point, ranging from a mean 311±84.3 (±SD) µm at baseline to a mean 343.1±95.1 (±SD) µm at the final examination. However, our measurements were mainly based on the increase of the foveal thickness in the 1 mm diameter central area, which is consid-

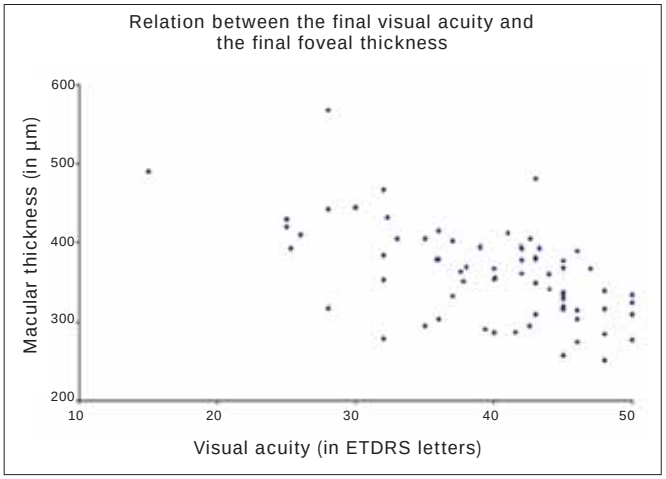

Fig. 4 - *Scatter plot of the final visual acuity (Early Treatment Diabetic Retinopathy Study chart) and the final macular thickness (1 mm diameter) in µm (correlation coefficient: –0.60 and p<0.001).*

ered to be potentially more reliable (27). This is due to the fact that the macular thickness in the foveal area of 1 mm diameter is determined by 512 data points instead of 6 data points for the center of the foveola (27). An increase ranging from 3.79% to 4.82% of the macular thickness was also observed in all four perifoveal quadrants in the 3 mm diameter area. Potential sources of variability in our measurements such as coexistence of vitreoretinal adhesions that could impair correct detection of retinal thickness were originally excluded. Pseudophakic eyes were also excluded since cataract surgery may alter vitreous configuration with concurrent alterations on IERM and macular morphology. Studies have shown that cataract extraction is associated with a risk of PVD, macular edema, and retinal detachment, possibly as a result of a disturbance to the vitreous during surgery (33). Moreover vitreous detachment has been observed in emmetropic eyes after uneventful phacoemulsification surgery in 75.88% of eyes (34).

"Off center" artifacts due to development of eccentric fixation over time may be observed infrequently (35). All our patients had relatively small changes in VA over time making eccentric fixation an event unlikely to occur. Moreover, in all cases the standard deviation of the retinal thickness at the inner central circle of the fovea as calculated by the software was <10% making the 1 mm diameter retinal thickness measurement more reliable (36). Additionally, the OCT operators gave particular attention in monitoring through the infrared camera the patient's fixation and the position of the scan lines relative to the foveal center during the scanning procedure, in an attempt to minimize any error. The same two experienced examiners performed all measurements.

The presence of IERM may cause artifacts in determining mainly the inner and to a lesser extent the outer retinal margin by the computer software (35). However, the ill-defined outer retinal margin was addressed in our study by repeating the scans until we were satisfied that the outer retinal margin was correctly placed. Regarding the inner retinal surface, the IERM was firmly attached without gaps between the membrane and the inner retina at the 1 mm diameter area in all our cases included in the study. At the 3 mm diameter area there were several small gaps between the IERM and the retinal surface resulting in miscalculation of the inner retinal margin. Therefore, those cases, even though were studied, were excluded from our calculations and the study was based on the measurements of the 1 mm diameter inner circle of the fovea.

Clinical observation based on biomicroscopy, photography, and fluorescein angiography showed that the disease may sometimes advance rapidly over a few months but more commonly it is stationary or progresses slowly with stable visual acuity (4, 7). The natural course of IERM was also investigated over a period of 5 years in the Blue Mountain Study (11). This study, which was exclusively based on fundus photographs and funduscopy, roughly showed that 1/3 of the studied cases progressed, 1/3 regressed, and 1/3 remained stable. Until now literature lacked information regarding the study of IERM evolution by OCT. OCT in our study adds some new information, which is related to the morphologic macular changes observed and to the consequent alterations to the macular thickness, findings which became evident in a shorter than 5 years period of observation. The main morphologic differences between baseline and final examination were the abolition of the foveal pit (Figs. 1–3) from an initial 33.8% (24 cases) to a final 59.15% (42 patients) and the changing pattern of the preexisting macular edema, in the form of intraretinal cystic spaces, in 4 cases. The main increase of macular thickness in the 1 mm diameter inner circle was 12.29%, which is considered statistically significant (p<0.001). Worth mentioning is also that in none of the studied

cases was decrease of the macular thickness noted, possibly because during the follow-up period we did not observe automatic separation of the IERM from the retinal surface in any case.

Forty-eight eyes in our study had a total PVD and in 23 eyes the vitreous was completely attached to the macula at baseline. Two of the 23 patients with attached hyaloid at baseline were found to develop a PVD during follow-up. IERM may occur in eyes with PVD and also in patients with attached vitreous. Clinical and pathologic studies have shown an especially high incidence of PVD in eyes with IERM. At the time of PVD, disruption of the ILM could allow fibrous astrocytes access to the retinal surface to proliferate and create an extracellular matrix (37). IERM can also be found in eyes with attached posterior hyaloid. Yamashita et al have shown that in cases of IERM visible on OCT and attached posterior hyaloid, after surgically induced PVD the preexisting IERM remained on the macula in 80% of their studied cases (38).

Regression analysis, which has been used to define the relation between macular thickness and visual acuity, has shown that a linear association exists between the final foveal thickness and the final visual acuity while the slope was negative ($p<0.005$, Fig. 4). Overall, the macular thickness increased by an average of 12.29% and in the same period of observation the visual acuity deteriorated by an average of 4.06 letters. Although retinal thickness does not always correlate with VA, it is considered that the presence and increase of macular edema during follow-up is an important factor in deciding whether to operate on a patient with IERM (39). Surgery has been advocated for IERM cases with VA 20/60 or worse (40-45) or with VA 20/50 or better (46). All those studies were based on biomicroscopic examination of the IERM. Do et al used clinical information and OCT to study eyes with IERM and they performed surgery on eyes based on VA (median 20/100) and on the preoperative macular edema (mean retinal thickness 348 μm) (39). Our OCT findings combined with the known clinical observations could further clarify IERM evolution and perhaps could assist the surgeon in deciding whether to operate on IERM patients based on the progress of the disease. However, more OCT studies are warranted in order to further increase our knowledge regarding the evolution of IERM.

The authors have no financial interest in any aspect of this study.

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