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Research Article

External Limiting Membrane and Ellipsoid Zone Integrity and Presenting Visual Acuity in Treatment-Naive Center Involved Diabetic Macular Edema

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Abstract

Purpose: To study the relationship between external limiting membrane (ELM) and ellipsoid zone (EZ) integrity and presenting visual acuity (VA) in patients with center involved diabetic macular edema (DME).

Methods: This cross-sectional study involved 81 eyes of 55 patients with center involved DME. Visual acuity (VA) was scored and converted to the LogMar. Optical coherence tomography (OCT) was undertaken for every patient. The relationship between ELM and EZ integrity and visual acuity was analyzed.

Results: All eyes with intact EZ had intact ELM while 59.3% of eyes with disrupted EZ showed intact ELM. Intactness of both layers was more common with diffuse retinal thickening (DRT) while disruption of both layers was more with combined cystoid macular edema (CME) and serous retinal detachment (SRD). Disruption of either EZ or ELM was associated with significant diminution of VA (P = 0.001, 0.011 respectively). Eyes with disruption of both ELM and EZ had significantly lower VA than eyes with both layers intact.

Conclusion: In treatment-naive center involved DME, disruption of ELM is less common than disruption of EZ. Nevertheless, a disrupted ELM is always associated with a disrupted EZ. Occurrence of both CME and SRD is associated with an increased incidence of ELM and EZ disruption. Disruption in both ELM and EZ is associated with a low visual acuity.

Keywords: *Optical Coherence Tomography; Visual Acuity; Diabetic Macular Edema; Ellipsoid Zone; External Limiting Membrane*

Abbreviations

ELM: External Limiting Membrane; EZ: Ellipsoid Zone; VA: Visual Acuity; DME: Diabetic Macular Edema; OCT: Optical Coherence Tomography; CME: Cystoid Macular Edema; DRT: Diffuse Retinal Thickening; SRD: Serous Retinal Detachment; DR: Diabetic Retinopathy; SD-OCT: Spectral Domain Optical Coherence Tomography; IS/OS: Photoreceptors Inner Segment/ Outer Segment; IV: Intravitreal; BCVA: Best Spectacle Corrected Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; LogMar: Logarithm of the Minimum Angle of Resolution; IOP: Intraocular Pressure; FA: Fluorescein Angiography; NPDR: Non Proliferative Diabetic Retinopathy; ART: Automatic Real Time; CST: Central Subfield Thickness; CSV: Central Subfield Volume

Introduction

Diabetic retinopathy (DR) is the top cause of new blindness in patients in the age range from 20 to 74 years [1-3]. Diabetic macular edema (DME) is the leading cause of visual impairment in DR with a prevalence of 2.7 to 11.0% [4-6].

There is a satisfactory agreement between slit-lamp biomicroscopy and optical coherence tomography (OCT) for DME detection [7]. OCT offers the added advantages of measuring macular thickness and determining the morphologic patterns of DME. However, correlation between macular thickness and visual acuity in DME is weak. This had motivated the search for other causes of visual affection [8-11].

The high resolution of the SD-OCT had allowed better imaging of outer retinal structures, especially the external limiting membrane (ELM) and ellipsoid zone (EZ), formerly named the photoreceptors IS/OS junction [12,13].

The ELM is not a true membrane, but a confluence of junctional complexes between Muller cells and photoreceptors inner segments. It maintains the integrity of the photoreceptors inner segments by forming a diffusion barrier between the subretinal space and the inner retina [14].

The closer proximity of the EZ to the ELM than expected for the IS/OS junction had convinced the (IN. OCT) Panel to change its name to ellipsoid zone. The EZ corresponds to the photoreceptor inner segment ellipsoid which is important for the photoreceptor function because of its high content of mitochondria [15-17].

Multiple studies have revealed that photoreceptor integrity and external limiting membrane integrity could be important predictor of visual function in DME [10,11].

The aim of this cross-sectional study was to study the relationship between both ELM and EZ and presenting visual acuity (VA) in patients with treatment-naive center involved DME.

Materials and Methods

This study involved 81 eyes of 55 patients with treatment-naive center involved DME detected on clinical examination by slit lamp biomicroscopy with non-contact lens.

We excluded patients with proliferative diabetic retinopathy, ischemic maculopathy, tractional macular detachment, significant cataract, corneal or any media opacity and also cases with previous panretinal photocoagulation, cataract extraction since less than 6 months, macular laser photocoagulation, intravitreal (IV) injection or vitrectomy.

A written informed consent was taken from each subject. The study was approved by the Ethics Research Committee, Faculty of Medicine, Alexandria University. Each patient was subjected to detailed history taking, including type and duration of DM, full ophthalmological examination including uncorrected and best spectacle corrected visual acuity (BCVA) measurement. Distance BCVA for each eye was measured using ETDRS chart at a distance of 4 meters. Visual acuity was converted to the logarithm of the minimum angle of resolution (LogMar). Measurement of intraocular pressure (IOP) was done by applanation tonometry and dilated fundus examination was performed using slit lamp biomicroscope and a non-contact fundus lens.

Fluorescein angiography (FA) was performed for all subjects using Heidelberg Retinal Angiograph 2 (Heidelberg Engineering, Heidelberg, Germany) or Topcon fundus camera 501 x (Topcon Medical Systems; Tokyo, Japan). FA images were analyzed according to the severity of non-proliferative diabetic retinopathy (NPDR) (mild, moderate, severe) and the type of macular leakage (focal, diffuse, cystoid) [16].

Optical coherence tomography (OCT) was done for all subjects using a SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Each B-scan consisted of 512 A-scans and was averaged 9 times applying the Automatic Real Time (ART) mode. A 20 X 20-degree scan pattern using 25 sections with an inter-scan distance of 240 μm was recorded. All OCT scans were centered on the fovea by providing a central, internal fixation mark. For each patient, a 20 degrees/6 mm long horizontal and vertical SD-OCT images through the fovea averaged 40 times using the ART mode were obtained for evaluation. Central subfield thickness (CST) and central subfield volume (CSV) within 1000 μm diameter of the central fovea were calculated automatically by the SD-OCT instrument.

Ellipsoid zone (EZ) and external limiting membrane (ELM) were assessed for reflectivity defects in the central 1000 microns of the vertical and horizontal SD-OCT images through the fovea and were categorized as disrupted or not. EZ or ELM disruption was defined as loss of the hyper-reflective band. We also graded the combined disruption of both layers as follows; intact both layers, disrupted EZ only and disrupted both layers.

Eyes with extensive shadowing effect due to hard exudates or severe macular edema hindering evaluation of the ELM or EZ were excluded from the study. The fovea was defined as the region without inner retinal layers. For verification of foveal position especially in cases with distorted anatomy as cases with NSRD, the ETDRS grid overlay was placed over the center of the foveal scan in the corresponding infrared images.

Statistical analysis of the data

Data were analyzed using IBM SPSS software package version 20.0. Chi-square test and Fisher's Exact test were applied to compare different groups regarding categorical variables. Kolmogorov-Smirnov test was used to test the normality of distribution of quantitative variables. For abnormally distributed data, Mann-Whitney test was applied for 2 groups comparisons. Correlations between quantitative variables were evaluated by spearman coefficients. Significance of the obtained results was judged at the 5% level [17].

Results

The study included 81 eyes of 55 cases, whose data is summarized in table 1.

Sex	
Male	25 (45.5%)
Female	30 (54.5%)
Age (years)	56.58 ± 7.19
Duration of DM (years)	12.63 ± 4.89
BCVA (LogMar)	0.65 ± 0.38
F. A	
Mild NPDR	8 (9.9%)
Moderate NPDR	39 (48.1%)
Severe NPDR	34 (42 %)
Macular oedema pattern in FA	
Diffuse	11 (13.6%)
Focal	62 (76.5%)
Cystoid	8 (9.9 %)
OCT Pattern of macular oedema	
Diffuse retinal thickening (DRT)	26 (32.1%)
Cystoid macular edema (CME)	25 (30.9%)
Serous retinal Detachment (SRD)	9 (11.1%)
CME + SRD	21 (25.9%)
EZ integrity in OCT	
Intact	54 (66.7%)
Disrupted	27 (33.3%)
ELM integrity in OCT	
Intact	70 (86.4%)
Disrupted	11 (13.6 %)
Combined ELM and EZ integrity in OCT	
Intact both	54 (66.7%)
Disrupted EZ only	16 (19.7%)
Disrupted both	11 (13.6%)
Central Subfield Thickness CST (µm)	385.70 ± 131.83
Central Subfield Volume CSV (mm^3)	0.30 ± 0.10
Macular Volume MV (mm^3)	9.99 ± 1.68

Table 1: *Distribution of the studied cases according to different parame.*

The most common OCT patterns was diffuse retinal thickening (DRT) (26 eyes) followed by cystoid macular edema (CME (25 eyes) and combined CME and serous retinal detachment (SRD) (21 eyes) while the least prevalent was SRD (9 eyes). Regarding the visual acuity, it ranged from counting fingers 2 meters (LogMar = 1.48) to 0.8 (LogMar = 0.1) with a median of LogMar 0.7.

Kappa test was used to the agreement between the 2 graders (A R, K N). There was an almost perfect agreement with a measured κ value of 0.865 for EZ and 0.949 for ELM. Both grader reanalyzed a random sample of previously graded images to calculate intragrader reliability and the κ values was 0.88 for EZ and 0.91 for ELM.

On assessing changes in outer retinal layers, intactness of the EZ and the ELM was more prevalent than their disruption, although intactness of the ELM was more common (70 eyes versus 54 eyes). For the combined layers changes, the most common pattern was intactness of both layers (50 eyes), while the least frequent was disruption of both layers (11 eyes).

There was a statistically significant relation between EZ integrity and ELM integrity (p = < 0.001). All eyes that had intact EZ (54 eyes) had an intact ELM while 59.3% of the eyes that had disrupted EZ (27 eyes) still had an intact ELM. Interestingly, no eyes had a disrupted ELM with an intact EZ. These findings are shown in table 2.

	EZ integrity in OCT				**c^2**	**^{FE}p**
	Intact (n = 54)		**Disrupted (n = 27)**			
	No.	**%**	**No.**	**%**		
ELM integrity in OCT						
Intact	54	100.0	16	59.3	25.457*	< 0.00*
Disrupted	0	0.0	11	40.7		

Table 2: *Relation between EZ and ELM integrity in OCT.*

c^2: Chi square test

FE: Fisher Exact test

**: Statistically significant at p ≤ 0.05.*

We also studied the distribution of the combined changes of EZ and ELM in different OCT patterns of DME. Intactness of both layers was most common in DRT while disruption of both layers was most frequent in combined CME and SRD and absent in DRT. These results are illustrated in table 3 and figures 1-4.

	Combined			**Total**
	Intact both	**Disrupted EZ only**	**Disrupted both**	
Serous Retinal Detachment (SRD)	3 (33.3%)	5 (55.5%)	1 (11.1%)	9
Cystoid macular edema (CME)	17 (68%)	4 (16%)	4(16%)	25
Diffuse retinal thickening	24 (92.3%)	2 (7.6%)	0 (0%)	26
CME+ SRD	11 (52.3%)	4 (19.0%)	6 (28.6%)	21
	55	15	11	81

Table 3: *Morphologic patterns of in diabetic macular edema on OCT * and Combined outer retinal change.*

Person Chi-square = 20.16; p = 0.003.

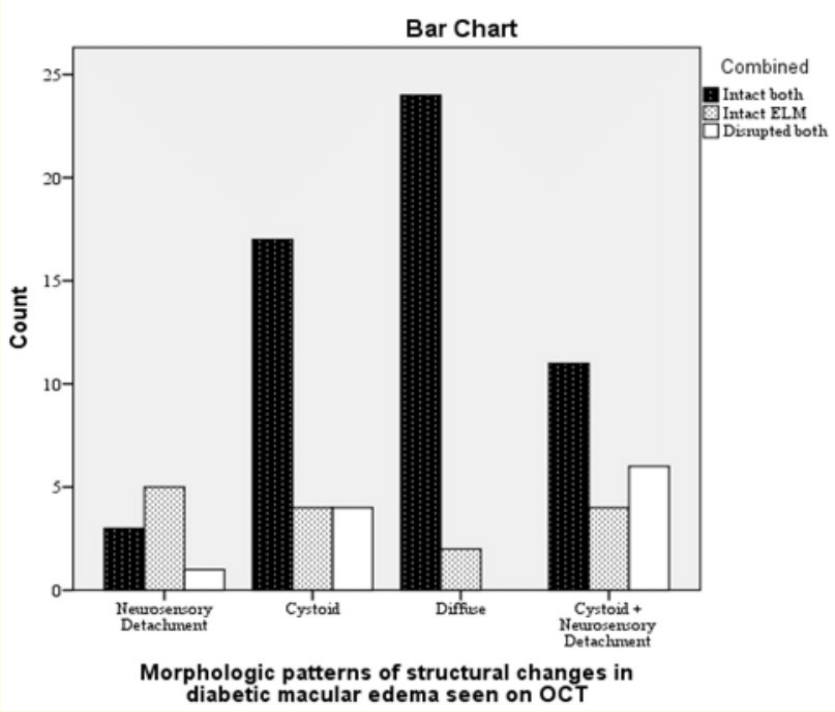
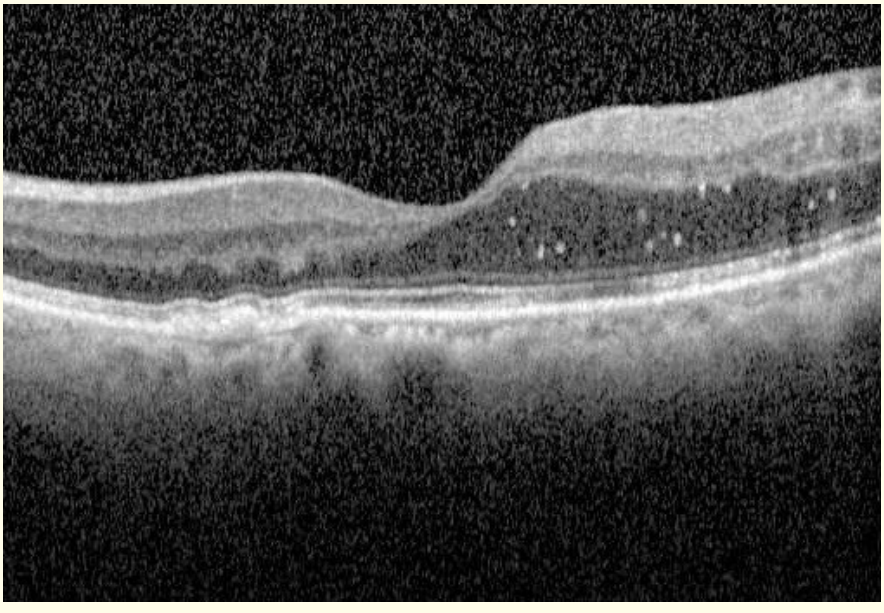


Figure 1: *Morphologic patterns in diabetic macular edema on OCT and Combined outer retinal changes.*



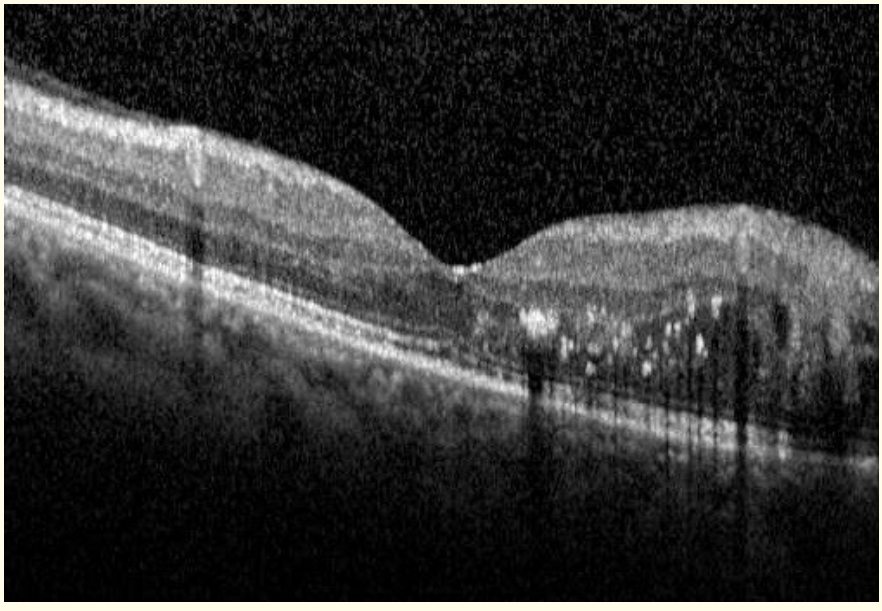
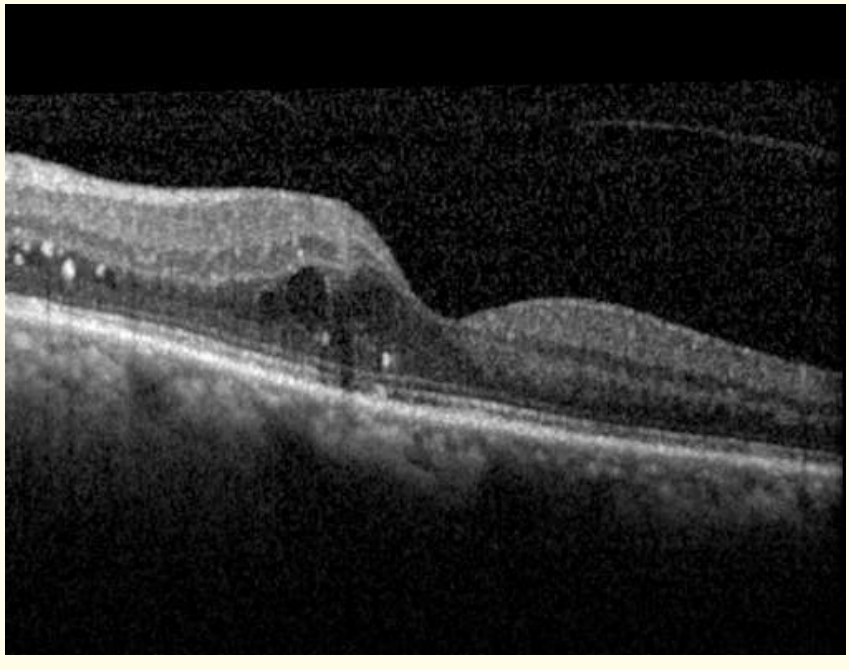


Figure 2: *SD-OCT Heidelberg Spectralis images of a 6 mm horizontal line scan through the fovea in eyes with diffuse retinal thickening. The central 1000 µ shows an intact ELM and EZ in a, an intact ELM with focal spots of EZ disruption in b. ELM: External Limiting Membrane; EZ: Ellipsoid Zone; SD- OCT: Spectral Domain Optical Coherence Tomography.*



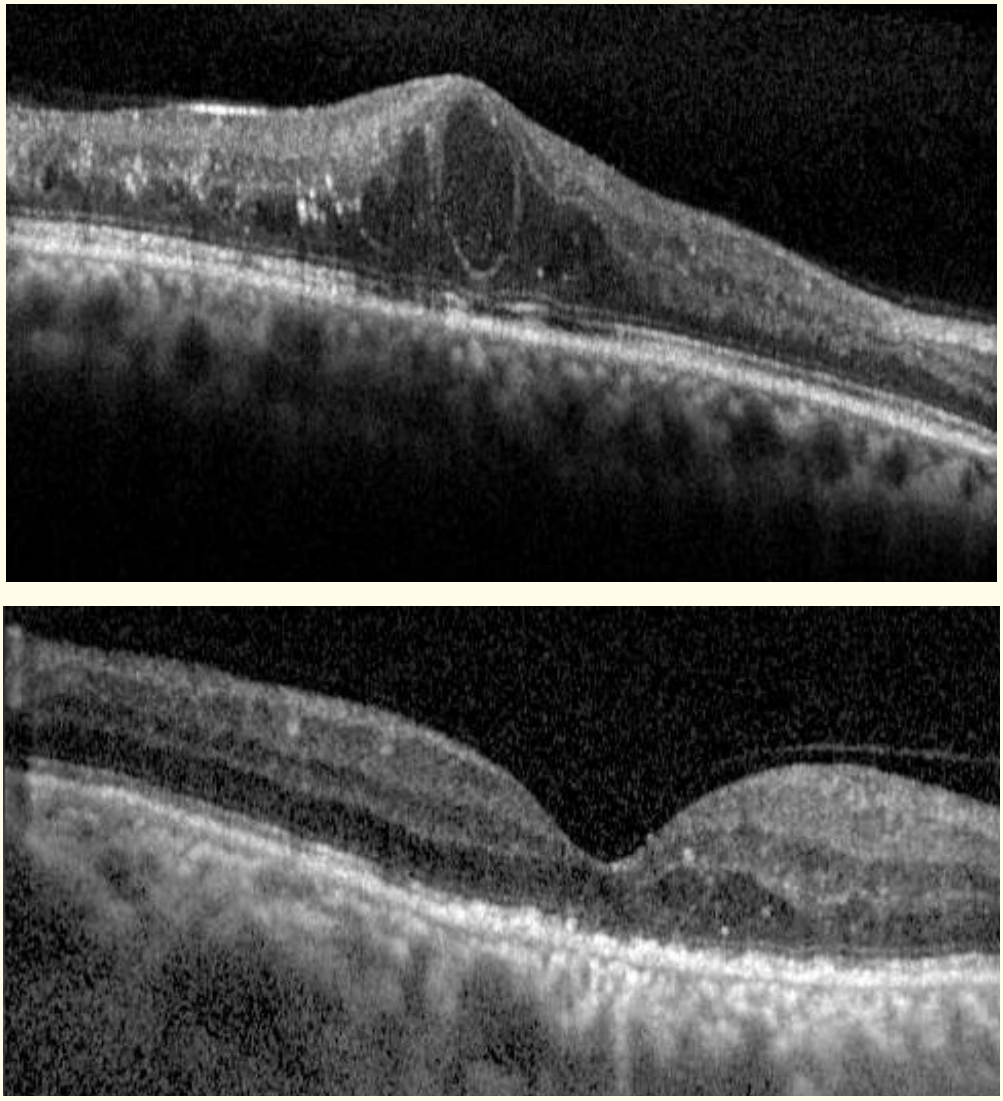


Figure 3: *SD-OCT Heidelberg Spectralis images of a 6 mm horizontal line scan through the fovea in eyes with cystoid macular edema. The central 1000 µ shows an intact ELM and EZ in a, an intact ELM with focal spots of EZ disruption in b and broad areas of ELM and EZ disruption in c. ELM: External Limiting Membrane; EZ: Ellipsoid Zone; SD- OCT: Spectral Domain Optical Coherence Tomography.*

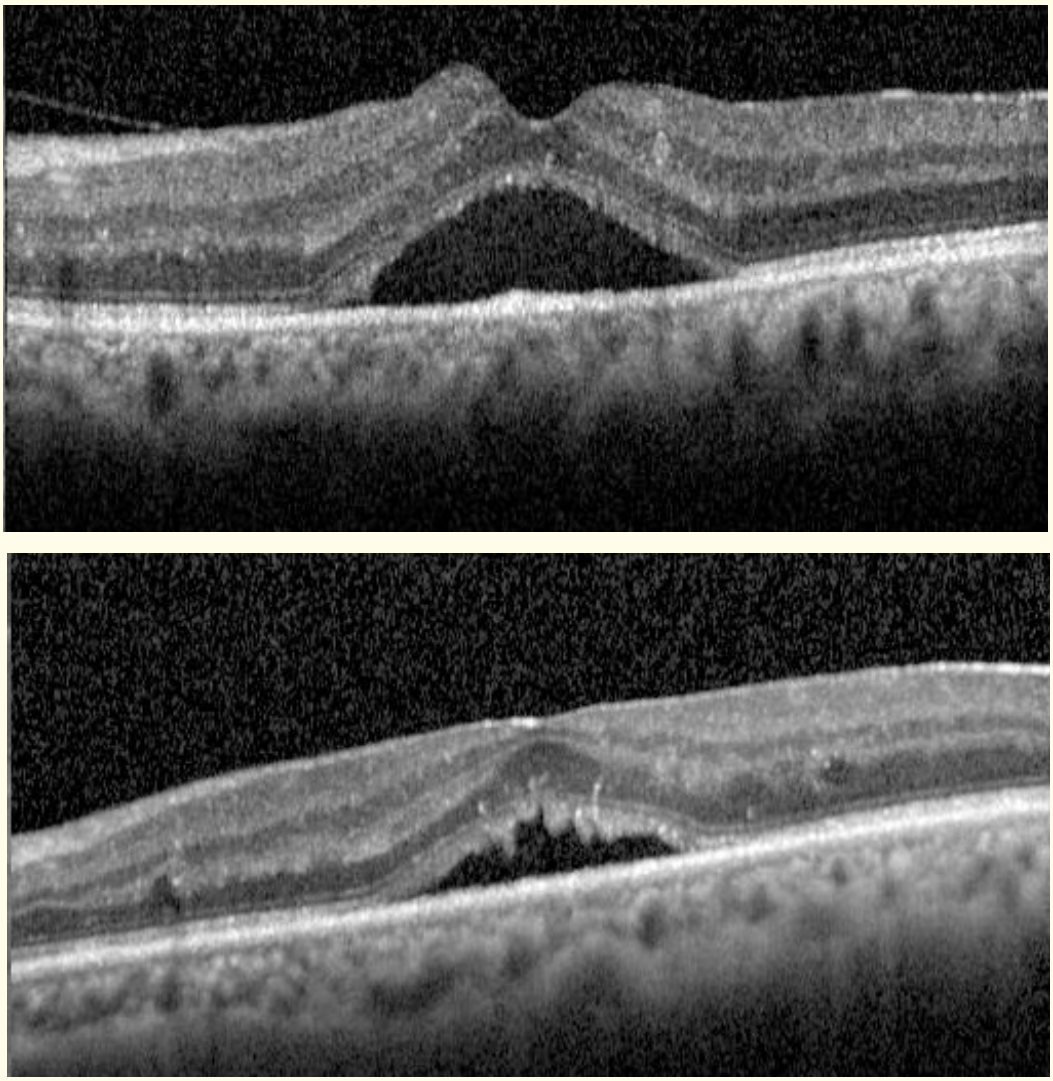


Figure 4: *SD-OCT Heidelberg Spectralis images of a 6 mm horizontal line scan through the fovea in eyes with serous retinal detachment. The central 1000 μ shows an intact ELM and EZ in a, and an intact ELM with focal spots of EZ disruption in b. ELM: External Limiting Membrane; EZ: Ellipsoid Zone; SD- OCT: Spectral Domain Optical Coherence Tomography.*

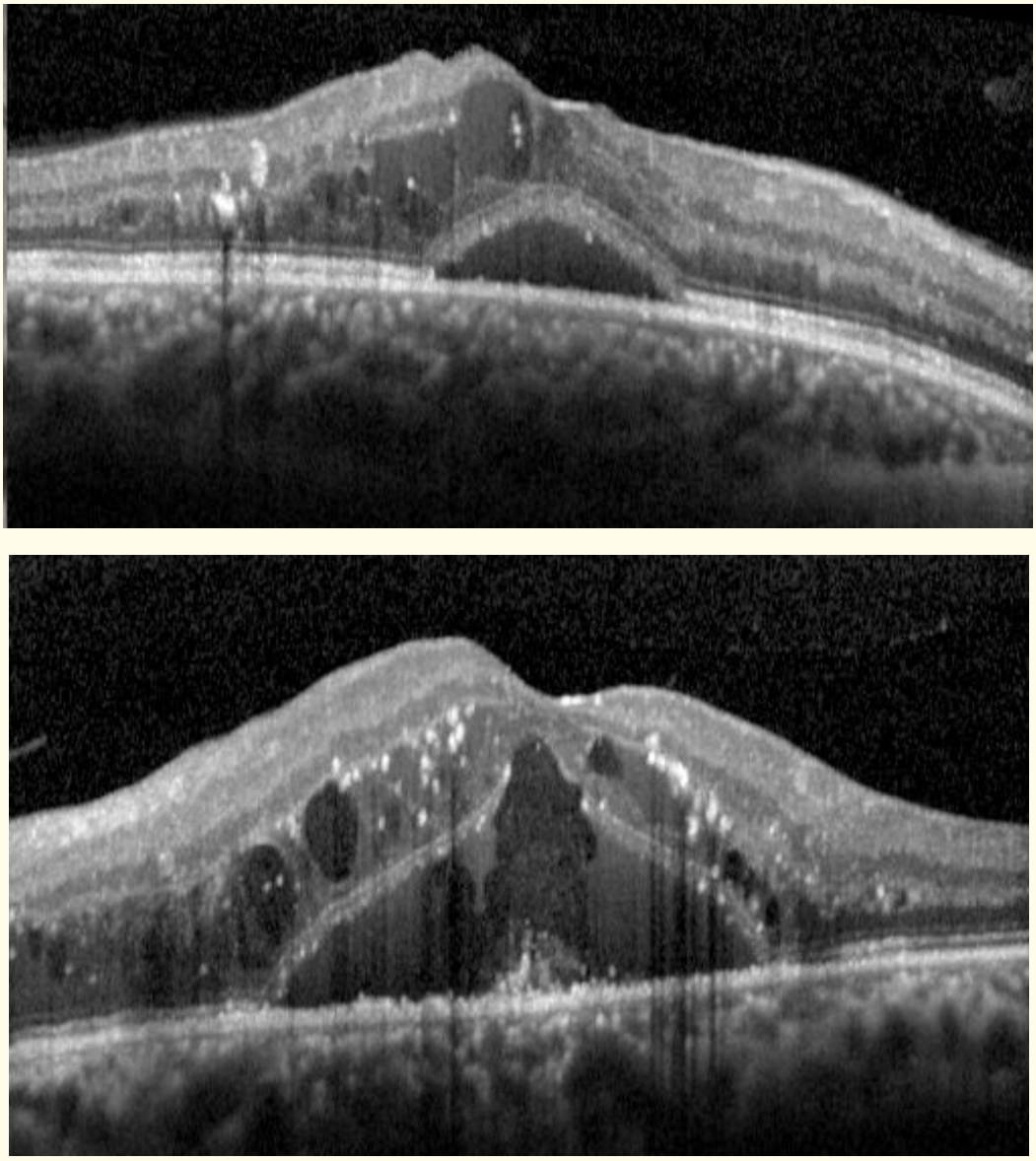


Figure 5: *SD-OCT Heidelberg Spectralis images of a 6 mm horizontal line scan through the fovea in eyes with combined cystoid macular edema and serous retinal retinal detachment. The central 1000 µ shows an intact ELM and EZ in a, an intact ELM with focal spots of EZ disruption in b and broad areas of ELM and EZ disruption in c. ELM: External Limiting Membrane; EZ: Ellipsoid Zone; SD- OCT: Spectral Domain Optical Coherence Tomography.*

Cases with disruption of either EZ or ELM were associated with significantly lower BCVA than cases with intactness of either layers (P = 0.001, 0.011 respectively). On analyzing the relation between vision and the combined change of EZ and ELM, BCVA was significantly lower with progressive disruption. Games Howell posthoc test revealed significant difference between disruption of both layers and intactness of both layers. These results are summarized in table 4.

	N	BCVA (LogMar)	Test	P
		Mean ± SD		
EZ integrity in OCT		0.55 ± 0.37	Z = 3.256*	0.001*
Intact	54	0.83 ± 0.32		
Disrupted	27			
ELM integrity in OCT			Z = 2.538*	0.011*
Intact	70	0.60 ± 0.36		
Disrupted	11	0.93 ± 0.37		
Combined integrity in OCT			F = 4.933*	0.016*
Intact both	55	0.57 ± 0.39		
Disrupted EZ only	15	0.74 ± 0.23		
Disrupted both	11	0.91 ± 0.36		

Table 4: *Relation between BCVA (LogMar) with EZ and ELM integrity in OCT.*

Z: Z for Mann Whitney test.

F: Welch test Games.

**: Statistically significant at p ≤ 0.05.*

There was a statistically significant relation between EZ integrity and each of ELM integrity (p = < 0.001), CST (p = 0.002), macular volume (MV) (p = 0.040) and central subfield volume (p = 0.003). There was a highly statistically significant relation between ELM integrity and both of CST (p = < 0.001) and central subfield volume (p = < 0.001). The correlation between different parameters is illustrated in table 5.

		ELM integrity in OCT	CST	Macular Volume	Central Subfield Volume (CSV)
EZ integrity in OCT (Intact = 0, Disrupted = 1)	r_s	0.561*	0.333*	0.229*	0.330*
	P	< 0.001	0.002	0.040	0.003
ELM integrity in OCT (Intact = 0, Disrupted = 1)	r_s	1.000	0.396*	0.193	0.396*
	P		< 0.001	0.084	< 0.001
CST	r_s		1.000	0.600*	0.998*
	P			<0.001	<0.001
Macular Volume	r_s			1.000	0.594*
	P				< 0.001

Table 5: *Correlation between different OCT parameters.*

r_s: Spearman coefficient.

**: Statistically significant at p ≤ 0.05.*

Discussion

OCT with its objective measurement of macular thickness and detailed view of retinal architecture had become fundamental in DME diagnosis and follow up [18]. However, macular thickness is only one of several factors affecting vision in DME [19]. Another important and potentially irreversible factor is photoreceptor dysfunction [20]. Poor vision with photoreceptors disruption could be related to underlying capillary nonperfusion [21].

Nevertheless, initial VA remains the most reliable indicator of visual recovery in DME. Cases presenting with severe visual loss rarely achieve complete visual recovery even with successful treatment. [22] Therefore, combining evaluation of initial VA and pre-treatment photoreceptors status could provide a more accurate assessment of expected visual improvement.

Although numerous studies had analyzed the photoreceptor status in DME, there is no agreement among researchers on a standard method of assessment. In our study, the EZ and the ELM integrity were separately evaluated in the central 1000 microns of the horizontal and vertical SD-OCT images and graded as disrupted or not. Several other studies also evaluated the central 1000 μm; while Maheshwary., *et al.* [23] graded the EZ disruption into less than or more than 200 μm, Shah., *et al.* [24] and Muftuoglu., *et al.* [20] calculated the percentage of damage of each layer and Hannouche *et al.* [25] only reported whether the ELM was intact or disrupted.

Others as Radwan., *et al.* [26] evaluated a longer 1500 μm in the central 5 scans and scored them based on the number of scans involved to account for the vertical extent. Otani., *et al.* [27] evaluated an even longer 1.8 mm transfoveal line. For more realistic evaluation, both studies of Jain., *et al.* [28] and Shin., *et al.* [22] combined the grading of EZ and ELM status into 3 situations: no disruption, ELM disruption only, and both layers disrupted.

Our results showed a statistically significant relation between EZ and ELM integrity (p = <0.001). All eyes that had intact EZ had intact ELM while 59.3% of the eyes that had disruption of the EZ still had intact ELM. This finding was similar to Shin., *et al.* [22] and Muftuoglu., *et al*. [20] studies which reported absence of eyes with intact EZ and disrupted ELM. Also similar to Otani., *et al.* study [27], in which the ELM and EZ scores were equal in 69% of eyes, while the ELM was more preserved in the rest of the eyes. Interestingly, at baseline in Muftuoglu., *et al*. study [20], the mean length of EZ disruption was almost doubled when cases also had a disrupted ELM. This suggested that ELM disruption occurred with more advanced photoreceptors damage and was therefore associated with a more severe EZ defect.

In our cases, intactness of both layers was most prevalent in DRT (92.3%) while disruption of both layers was most prevalent in combined CME and SRD (28.6%) and absent in DRT. Our results were similar to Seo., *et al*. [29] study, in which intactness of ELM or EZ was highest with DRT (82.6%, 60.8%) and disruption was most common with SRD (75%, 81.3%) followed by CME (43.8%, 56.3 %).

These findings could be explained by Shah., *et al.* proposal for photoreceptor disruption, which attributed the damage to either extensive chronic fluid accumulation in the outer layers or altered choriocapillaris diffusion from macular detachment [24,30-32]. In our sample, eyes with combined CME and SRD had both mechanisms at work. This could explain the increased likelihood of damage with that pattern.

In our study, a statistically significant relation was reported between presenting VA in log Mar and the integrity of ELM and EZ. In eyes with intact ELM, mean VA was 0.6 versus 0.9 in eyes with disrupted ELM and in eyes with intact EZ, mean VA was 0.5 versus 0.8 in eyes with disrupted EZ. Our results were similar to Otani., *et al*. study, [27] which showed a high correlation between ELM and EZ scores and the presenting VA and to Hannouche., *et al*. study [25] which only assessed the ELM.

On analyzing the relation between vision and the combined change of EZ and ELM in our cases, significant difference was found only between disruption of both layers and intactness of both layers. This finding was in agreement with Otani., *et al*. study [27], which showed that eyes with disrupted EZ always had better VA when the ELM was preserved and with Muftuoglu., *et al.* [20] and Shin., *et al.* studies [22], which not only reported significantly worse vision when both layers were disrupted, but also a better visual prognosis and more EZ restoration with good initial ELM.

As the ELM lies between the cell bodies and the inner segments of the photoreceptors, damage may begin by loss of outer segments with defects in the EZ and progress to loss of cell bodies with defects in the ELM. Therefore, changes in the integrity of the ELM may reflects more advanced cell body damage and lower survival potential [33]. These facts suggest that visual prognosis is affected more by ELM disruption than by EZ disruption.

There were some limitations for our study. First, its cross-sectional design and the relatively small sample size. Second, the qualitatively assessed the horizontal and vertical line scans transfoveal lines. Using the macular star and quantitative measurement of the defects may have resulted in a more detailed assessment and better correlation with VA. Third, the generalization of the results was limited by excluding eyes with severe shadowing effect, vitreomacular traction and macular ischemia.

Conclusion

In treatment-naive center involved DME, disruption of ELM is less frequent than disruption of EZ. Nevertheless, a disrupted ELM is always associated with a disrupted EZ. Occurrence of both CME and SRD in DME is associated with an increased incidence of ELM and EZ disruption. Disruption in both ELM and EZ is usually associated with a low visual acuity.

Conflict of Interest

Authors declare no conflict of interest.

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