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Integrity of Outer Retinal Layers After Resolution of Central Involved Diabetic Macular Edema

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Abstract

Purpose—To evaluate the integrity of outer retina layers after resolution of central involved diabetic macular edema (DME) and to demonstrate the effect of various baseline factors for the final vision and final external limiting membrane (ELM) integrity.

Methods—Fifty-nine eyes of 48 patients with resolved DME were included. Several optical coherence tomography parameters including central subfield thickness (CST), maximum foveal thickness, foveal center point thickness and the extent of the ellipsoidal (ISe) layer and ELM damage were assessed at the time of DME and after resolution of DME. Eyes having laser scars near the fovea were excluded. Final visual acuity was classified as good (Snellen≥20/40, logMAR ≤0.3) or impaired (Snellen <20/40, logMAR>0.3) for the logistic regression analysis. Zero Inflated Poison Regression model was used to find the best predictors for post treatment ELM damage.

Results—External limiting membrane and ISe layers were disrupted in 16 (27.2%) eyes and 21 (35.5%) eyes at the final visit, respectively. Baseline ELM damage (p=0.001), baseline impaired vision (p= 0.013) and the most recent HbA1c level (p=0.018) were the best set of parameters for having impaired final visual acuity. Baseline vision, severity of diabetic retinopathy, absence of intravitreal injection, CST and history of extra-foveal macular laser (not within 1 mm of fovea) (p<0.001, for all parameters) were independent predictors for the final ELM damage.

Conclusion—Outer retinal layers may be damaged even after complete resolution of DME, where ISe damage appeared to be more common than ELM damage. Poorly controlled diabetic patients with damaged ELM and worse vision at the time of DME were more likely to have ELM damage and subsequent impaired vision after complete resolution of DME.

Keywords

Diabetic macular edema; ellipsoidal layer damage; external limiting membrane damage

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INTRODUCTION

Diabetic macular edema (DME) is the major cause of severe vision loss in patients with diabetic retinopathy (DR).[1,2] The prevalence of DME, which increases with the severity of DR,[2] has been reported to be 20.1% in type I diabetics and 25.4% in type II diabetic patients over a 10-year period.[3,4]

Diabetic macular edema is characterized by retinal thickening secondary to the breakdown of the inner-and outer blood-retinal barrier (BRB) and altered vitreo-macular interface.[5, 6] Although hyperglycemia is a well-known risk factor for the development of DME, the pathogenesis of edema is complex and multifactorial.[7] Hyperglycemia activates several metabolic pathways and increases the production of advanced glycation end-products and free radicals, which trigger up-regulation of inflammatory cytokines and growth factors such as interleukin (IL)-1, IL-6, vascular endothelial growth factor (VEGF).[5, 6] Subsequently, these factors deteriorate the BRB and the visual acuity (VA).

Spectral-domain optical coherence tomography (SD-OCT) with higher axial resolution and reduced speckle noise provides qualitative and quantitative analysis of outer retinal structures, including the external limiting membrane (ELM) and inner segment ellipsoidal band layer (ISe) (previously known as boundary of the inner segment and outer segment (IS/OS) junction). Important factor for the visual recovery in treated DME patients appears to be the resolution of macular edema with preservation of photoreceptor integrity. In fact, photoreceptor preservation appears to be important as a predictor of good vision in various other retinal diseases.[8]

Although concommitant disruption of the outer retinal layers at the time of DME has been evaluated in several studies,[8, 9, 10] the integrity of the outer retinal layers after DME resolution has not been well elucidated. There have been a few reports demonstrating the association between the preservation of the IS/OS junction and better final visual acuity following DME resolution.[11,12] However, in these studies, the integrity of the outer retinal layer damage was not quantified and the study population was limited specifically to patients who had either intravitreal (IV) triamcinolone injections or pars plana vitrectomy.[11,12]

Although diabetic macular edema (DME) may be treated effectively in many eyes, outer retinal structures may remain irreversibly damaged in some patients. In this study, we evaluate the status of the outer retinal layers in patients with successfully treated center involving DME and determine the best predictive factors for the final visual acuity and final status of the outer retinal layers.

METHODS

UCSD Institutional Review Board approval was acquired for the review and analysis of patient data. The study adhered the to the tenets of the Declaration of Helsinki eyes for research involving human subjects and complied with Health Insurance Portability and Accountability Act (HIPAA) of regulations.

We retrospectively reviewed the medical records of 234 consecutive patients who underwent SD-OCT scanning showing diabetic macular edema at the Jacobs Retina Center at the Shiley Eye Center, University of California, San Diego (UCSD) between October 2008 and March 2015. Only eyes with center involving DME (central subfield thickness ≥ 305 for women, ≥ 320 for men) confirmed by clinical examination, SD-OCT and fundus fluorescein angiography (FA), that demonstrated complete resolution of edema were included.

Exclusion criteria included evidence of macular ischemia based on FA findings, any history of uveitis, presence of concurrent retinal diseases such as macular degeneration or retinal vein occlusion, other causes of macular edema that occured following intraocular surgery, and visually significant cataract graded at more than N03 or NC3 according to the Lens Opacity Classification Scheme.

A total of 59 eyes of 48 patients met the criteria and were included the study. Data including patient age, gender, involved eye, the most recent HbA1c level, insulin dependency, and treatments for DME were recorded. Treatments included: macula laser (focal or grid), intravitreal injections- including triamcinolone (Kenalog, Merk&Co, Inc, NJ, USA), bevacizumab (Avastin, Genentech Inc, San Francisco, USA) or ranibizumab (Lucentis, Genentech Inc, San Francisco, USA) – and pars plana vitrectomy. The grading for the severity of the diabetic retinopathy was done based on clinical examination (W.R.F.) and confirmed with the imaging modalities, including color photography and fundus fluorescein angiography using the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale as non-proliferative DR (mild, moderate, severe) and proliferative DR by one masked observer (MA). Duration of DME was defined as the interval from the onset of DME to complete resolution of DME. The visual acuity was assessed using ETDRS chart and the best available vision was recorded at baseline and at the last follow-up. The visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis.

Imaging

All imaging modalities (FA, OCT) were done using Heidelberg Spectralis (Heidelberg Engineering, Carlsbad, CA, US) device. Two experienced retina specialists (IKM, RG) masked to VA reviewed all images. For each study eye, a 6 × 6-mm macular cube scan was preformed using the fast scanning mode comprising of 25 horizontal B-scans each made up of 512 A-scans. Horizontal and vertical scans cutting through the fovea were also preformed in each study eye. At the time of DME, the presumed fovea was defined as a region without inner retinal layers.[13] Subsequently, ETDRS grid overlay with a central 1-mm diameter was placed over the very center of the foveal scan in corresponding infrared images, and eyes with clearly visible laser scars located within or just beyond the border of the central circle were excluded. Fundus fluorescein angiography was also used to confirm that none of the laser scars were approaching the fovea.

The accuracy of delineation of appropriate layer on SD-OCT was confirmed by the observers (I.K.M, R.G.). The following parameters were obtained using the SD-OCT volumetric map: central subfield thickness (CST: mean retinal thickness within the central 1000-μm-diameter area), maximum foveal thickness (MaxFov: the maximum retinal

thickness of a point within the central 1000-μm-diameter area; Figure 1a, figure 1b). Additionally, foveal center point (FCP), the vertical distance between the innermost retina and RPE-Bruch complex was measured automatically in both axes, and the average thickness was obtained for the statistical analysis (Figure 1c). Baseline images were set as reference to allow for point-to-point correspondence between consecutive follow-up scans.

Evaluation of Outer Retinal Layers

The integrity of the ELM and the ISe at the presumed foveal center were evaluated both quantitatively and qualitatively during the presence of DME and after its resolution. A disruption in ELM and ellipsoidal inner segment was defined as loss of the back-reflection line in the respective layers.[14] The outer retinal layer disruption was graded from 0 to 2. Grade 0 was given when an intact ORL was found, grade 1 was assigned for focal disruption of the ORL of 500 μm or less, and grade 2 was assigned for more than 500 μm of disruption. Grades from each horizontal and vertical scans were added to yield a global disruption scale. Next, the photoreceptor layer, including the ELM, and inner ellipsoid layer was evaluated 500 μm in either direction of the fovea. The percentage ellipsoid and ELM layer disruption was averaged from horizontal and vertical scans to generate a number between 0% (no disruption) and 100% (total loss) as we previously described.[8, 15]

While evaluating the extent of the ELM and ISe damage, we observed that the presence of cysts and hyper-reflective material may give an appearance of outer retinal disruption on SD-OCT without true ELM or ISe disruption. We minimized this issue by reviewing several consecutive scans through the fovea and beyond, and excluded eyes with pseudo-outer retinal damage appearance if the damage—loss of back reflection line in outer retinal layers—was not visible in all scans cutting through the same area. We also verified this by checking the extent of the outer retinal damage in both horizontal and vertical scans. Based on our observation, when the appearance of outer retinal damage was a result of shadowing from overlying hyper-reflective material or cysts, both ISe and ELM would be involved, moreover, the length of the damage and horizontal diameter of the cysts would be consistent. Furthermore, the shadowing effect secondary to overlying hyper-reflective material, which was not considered as a real damage, did not consistently correspond to the same areas of ELM and/or ISe disruption; when proceeding to another scan using raster scans, the disruption like appearance shifted to just underneath the HRM (figure 1c, figure 2). Based on the above-mentioned observations, we excluded eyes with an outer retinal damage resulting from intraretinal cyst and/or hyperreflective material.

Evaluation of Intraretinal Cysts

The size of the cysts was measured manually within the central 1000 μm and graded according to its largest diameter as follows: grade 0, no cyst; grade 1: small cyst (<100 μm), grade 2: large cyst (>100 μm). If the number of the cysts were less than 3, it was regarded as single-few (S-F), if the number of the cysts were more than 3, it was regarded as multiple (M). Presence of subretinal fluid was also assessed in raster SD-OCT scans.

Statistical analysis

The normality was checked using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Final visual acuity was classified as good (Snellen≥20/40, logMAR ≤0.3) and impaired (Snellen <20/40, logMAR>0.3) for fitting a logistic regression model. The significant variables that were included in the final model showing the strongest predictors for having impaired vision (<20/40) after resolution of DME were selected based on univariate logistic models, where predictors with $p<0.05$ were included. Inter-dependency between two eyes in the same individual was controlled using generalized estimating equations analysis, which accounts for inter-eye correlation.

For the outer retinal structural analysis, since baseline ELM damage was found to be slightly more associated with final visual acuity than ISe damage, ELM was selected as a major representative of outer retinal layers and a zero inflated poison model was fit to explain ELM damage post DME resolution. This model has two parts, a logistic model that predicts the large proportion of eyes with zero damage and a Poison model that explains the amount of damage at the end of study. Baseline ELM damage was used as a predictor to help explaining high probability of not having final damage. Manual stepwise selection was used to select a final model; predictors were included if the p-value was smaller than 0.05. All statistics were done with SAS (SAS software version 9.4 (SAS Institute, Cary, NC, US).

RESULTS

This study included 59 eyes from 48 (20 female, 28 male) patients with a mean age of 61±13 (range: 31 to 90) years. Baseline demographics of the patients are given in Table 1. The mean duration of DME was 19.32±15.7 weeks (range: 4–73) in the overall study population.

External limiting membrane was found to be intact (Figure 3) in 43 eyes (72.8%), disrupted in 16 eyes (27.2%) with a mean of 35±32.2 (range: 2.9–100) disruption percentage after resolution of DME. Ellipsoidal layer was intact in 38 eyes (64.5%), disrupted in 21 (35.5%) eyes with a mean of 38.5±33.5% (range: 4–100) disruption after resolution of DME (Figure 4). When outer retinal layers were simultaneously evaluated, 10 eyes had intact ELM and disrupted ISe with a mean of 4.7±2.7% ISe damage and 11 eyes had disrupted ELM and ISe with a mean of 35.2 ±32.1% ELM damage and a mean of 49.1 ±31.6% ISe damage. No eyes had only ELM damage without ISe damage. The characteristics of the patients based on the integrity of outer retinal layers are shown in Table 2. The mean follow-up duration after complete resolution of DME was 12.68±16.3 weeks (range: 14–26). Follow-up duration was similar among the groups when eyes were categorized based on the final integrity of outer retinal layers.

The odds ratios of variables for the final visual acuity in univariate analysis is given in Table 3. Among the studied variables; duration of DME, HbA1c, age, the integrity of baseline structure, having multiple cysts and baseline visual acuity were found to be associated with having impaired final vision. Final visual acuity was also significantly correlated with final ELM damage (ICC:−0.65, $p<0.0001$). For the final model to predict eyes that would have impaired vision after resolution of DME; baseline ELM damage at the time of DME was the

most important predictor variable, responsible for 76% of the predictor power of the model, followed by baseline visual acuity (14% of predictive power), and Hb1Ac (10% of predictive power).

For the first part of the model to predict whether patient would end up with a post-DME ELM damage, baseline ELM damage was the only predictor variable (p=0.0031). Once patient had ELM damage, variables to predict the extent of the ELM damage are summarized in Table 4. While keeping all other characteristics constant, for each unit increase in baseline decimal visual acuity, the odds of post-DME resolution ELM damage decreased by a factor of 0.25 (95% CI: 0.16–0.41, p<0.001). The expected post-DME treatment ELM damage for eyes that had macula laser was 1.67 times higher than for the eyes that did not need macula laser (95% CI: 1.22–2.27, p<0.001). For diabetic retinopathy grade, moderate DR was associated with a 3.1 time higher expected post-DME resolution damage than mild DR; while severe DR was associated with a 9.2 times higher post-DME resolution ELM damage than mild DR. However, moderate DR was not significantly different from proliferative DR. Among these significant parameters, baseline visual acuity was the most important variable predicting the extent of final ELM damage— responsible for approximately 23% of the predictive power of the model, followed by severity of diabetic retinopathy (25% of predictive power), not having intravitreal injection (24% of predictive power), central subfoveal thickness (16% of predictive power), and macular laser (2.6% of predictive power).

Since laser was found to have an impact on final ELM damage despite excluding eyes with laser scars approaching the fovea, we did some further analysis to see if laser treated eyes had worse disease. Among the several parameters showing the severity of the edema and patients' demographics; eyes that had laser treatment had longer duration of DME (20.6±16 weeks versus 17.8±15.2 weeks, p=0.4) and higher percentage of baseline ELM damage (13±27% versus 4±8%). Insulin use was also more common (45% versus 27%) in these older patients (63±11 year versus 57±14 year) than those who did not have any laser.

DISCUSSION

Although diabetic retinopathy is mainly considered as a microangiopathy and the visual dysfunction of diabetic retinopathy is mostly resulted from a defect at the post-receptor level, which is the above the photoreceptor-RPE cell complex,[16] in this study among the 59 eyes of 48 patients with central involved DME 27% of eyes had external limiting membrane damage and 35% of eyes demonstrated ellipsoidal layer damage after resolution of DME. Although the integrity of these layers were significantly associated with the final visual acuity, baseline ELM damage was slightly more associated with the final vision. Moreover, ELM damage was most concurrent with a higher percentage of ellipsoid layer damage. This may confirm that changes in the integrity of the ELM may reflect photoreceptor cell bodies status, which may be a sign of advanced photoreceptor damage.

In the final model for the final visual acuity as an outcome, the baseline integrity of the ELM was found to be best predictor, followed by the baseline vision, and most recent HbA1c level, respectively. The more ELM damage at the time of DME the patient had, the lower the

visual acuity following DME resolution. Also, patients with better visual acuity at presentation were associated with a better final visual acuity after DME resolution. Each unit increase in baseline ELM damage was associated with a 11% increase in odds of having impaired vision (<20/50, Snellen), each unit increase in baseline HbA1c was associated with 1.7 times increase in odds of having impaired vision, and being in the impaired vision group at baseline (<20/50, Snellen) was associated with 10.5 times increase in odds of having impaired visual acuity at the end of study. These results suggest that poorly controlled diabetic patients with damaged ELM and worse baseline vision were more likely to have impaired vision even after complete resolution of DME. When the set of predictors discussed above are known, the others do not seem to have an important impact on final vision.

In the final model with final ELM damage as an outcome, we found that baseline vision was the most important predictor, responsible for approximately 32% of the predictive power of the model. Severity of diabetic retinopathy (25% of predictive power), not having intravitreal injection (24% of predictive power), central subfoveal thickness (16% of predictive power), and the prior use of macular (not within 1 mm of fovea) laser (2.6% of predictive power) were the other predictors for the final vision.

Similarly, in our previous report,[15] ELM was found to be a better predictor than the IS/OS junction for the vision improvement in eyes that underwent vitrectomy for persistent DME. In a previous report[12] with 48 eyes of 37 patients post-vitrectomy for DME, postoperative visual acuity in the IS/OS intact group was found to be significantly better than that in IS/OS disrupted group. However, in that study different from ours, other variables that might affect the integrity of photoreceptor layer, including preoperative IS/OS status, macula thickness measurements such as central subfoveal thickness were not evaluated. Also, the status of postoperative IS/OS line was categorized as intact or partially visible/absent, which might cause inaccurate results due to varying effect of disruption length on visual outcome.

Despite the presence of strong evidence showing the association between outer retinal layers and visual acuity,[10,11,12] there are several factors that may contribute the visual outcomes such as disorganization of inner retinal layers[17] and macular ischemia after DME resolution.[18] Furthermore, resolution of DME is not always associated with an improvement in vision, yet some paradoxical changes may exist. In order to partially overcome these issues, we excluded eyes with macular ischemia. However, it may not be possible to control all contributors in such a complex disease, additional factors might exist.

Diabetes may alter the ion flux and cause several molecular alterations within photoreceptors.[19,20] There are some reports showing the role of VEGF in neuronal function control, suggesting a decrease in VEGF expression would result in photoreceptor degeneration[21] Conversely, it has been found that an overexpression of VEGF in the retina also resulted in photoreceptor degeneration.[22] Thus, further studies are needed to more clearly evaluate the contributing factors for photoreceptor damage in diabetic macular edema.

Laser photocoagulation in close proximity to the fovea might contribute to poor visual outcome following DME resolution. Though use of focal or grid laser has become less common approaches for the treatment of DME after the advent of anti-VEGF drugs, laser treatment still remains a treatment option particularly for eyes with persistent DME.[23] In order to minimize any direct adverse effect of laser treatment, eyes with centrally located laser scars were excluded in the current study. Notwithstanding, laser was found to have very mild impact (2%) on the final integrity of the ELM layer. Since we reserved laser for eyes with persistent DME, we believe that this weak effect may be secondary to the severity of a chronic disease, rather than the effect from the laser itself.

This study has some limitations, such as the retrospective design with a small number of patients, and the employment of several treatment options with a varying follow-up duration. Moreover, the choice of treatment option was at the clinician's discretion, rather than employing a strict algorithm to all patients. Although these limitations may not allow us to show the individual effect of each treatment modality; in real-world conditions, it is not always possible to manage all DME patients using a single treatment approach. Despite these limitations, thorough documentation of DME with high resolution SD-OCT, analyzing various parameters and quantitating the outer retinal layer damage and controlling the 2 eyes of same subjects allowed us to evaluate the role of various factors on the final integrity of the ELM and subsequent vision. We believed that knowledge of the predictive factors for the outer retinal layer disruption and final visual acuity would give important information for clinicians to plan their treatment and to predict the prognosis of final visual acuity in eyes with diabetic macular edema.

In conclusion, our study showed that outer retinal layers could be disrupted even after complete resolution of DME. The integrity of those layers at the time of DME predicted the final integrity and subsequent visual acuity. Baseline worse vision, higher percentage of ELM disruption, and higher HbA1c level were associated with worse vision after resolution of DME. Final ELM damage could be predicted with baseline visual acuity, central subfoveal thickness and type of received treatment. Further studies with a high number of patients are needed to show the necessary treatment strategies to better maintain the health of photoreceptors.

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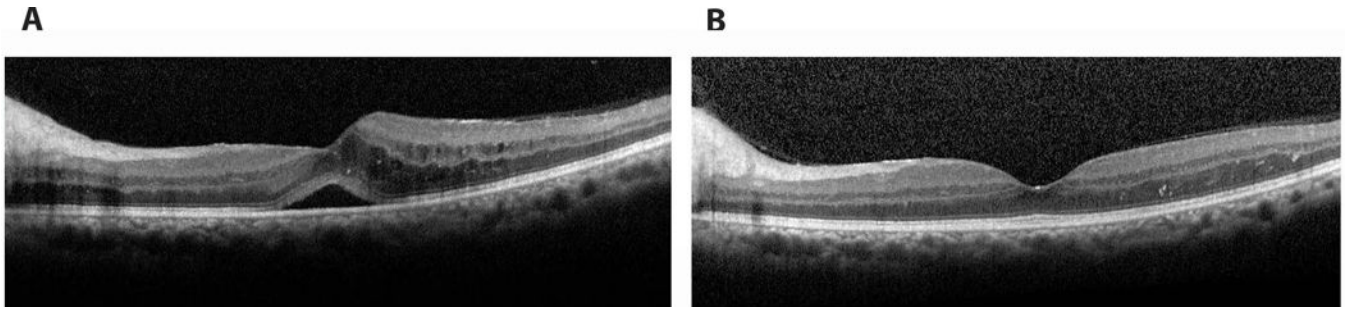

Figure 1. Evaluation of retina thickness parameters by spectral-domain optical coherence tomography at the time of DME

a shows the infrared image of a DME patient with an overlying Early Treatment Diabetic Retinopathy Study Circle.

b and c show the retina thickness map of the same patient with a central subfield thickness of 439 microns, and a maximum retinal thickness of 549 microns.

c: The vertical line represents the distance between internal limiting membrane and Retina Pigment Epithelium-Bruch membrane complex (foveal center point thickness). Hyper-reflective material is shown with *, note that the transmission defect (**) is not being considered as ellipsoidal layer damage.

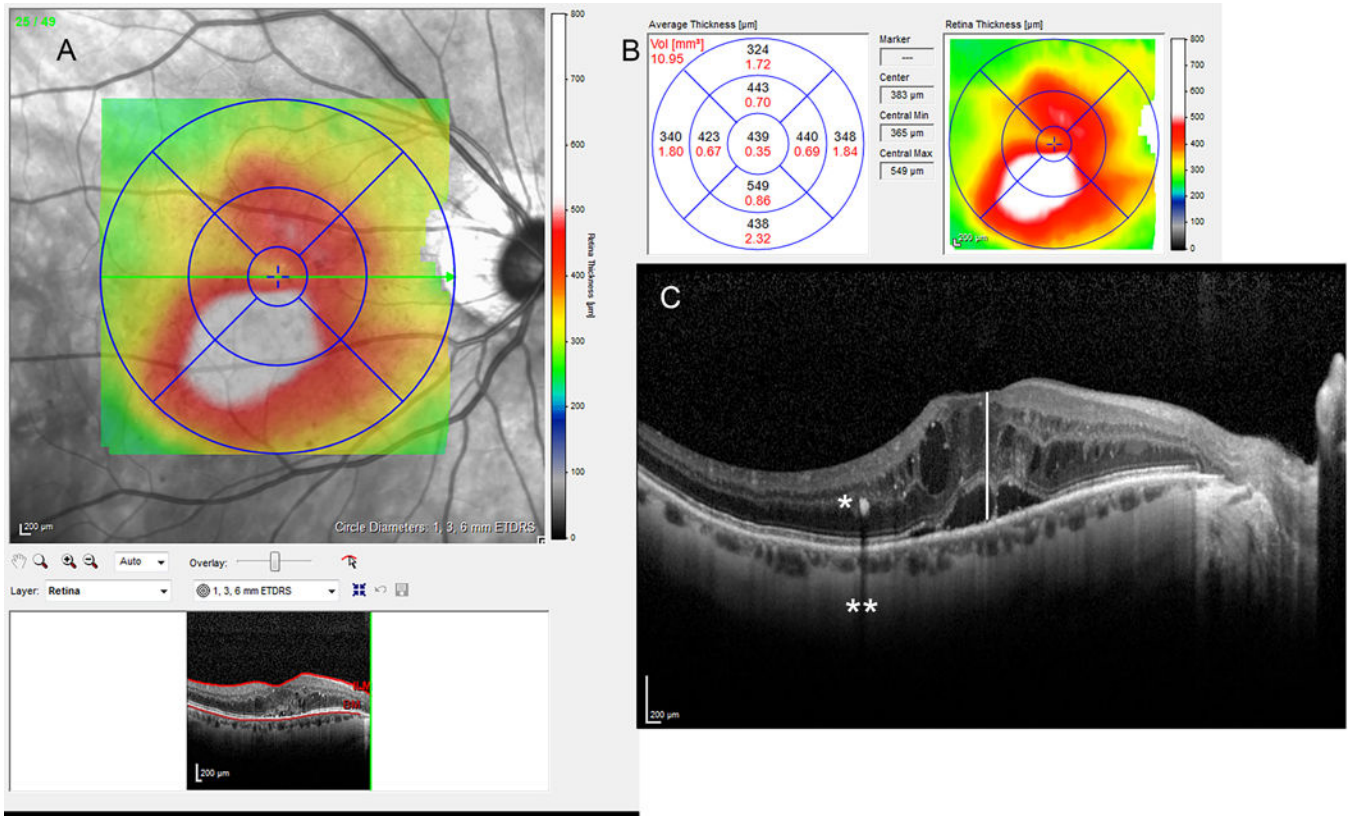

Figure 2.

Raster spectral-domain optical coherence tomography scans of a patient with mild DME and hyper-reflective material (HRM). External limiting membrane and ellipsoidal layers seem to be disrupted (Figure A), however, the shadowing effect secondary to overlying hyper-reflective material does not consistently correspond to the same areas of ELM and/or ISe disruption; when proceeding to another scan using raster scans (B, C), the disruption like appearance shifted to just underneath the HRM. This defect is not being considered as ellipsoidal layer damage.

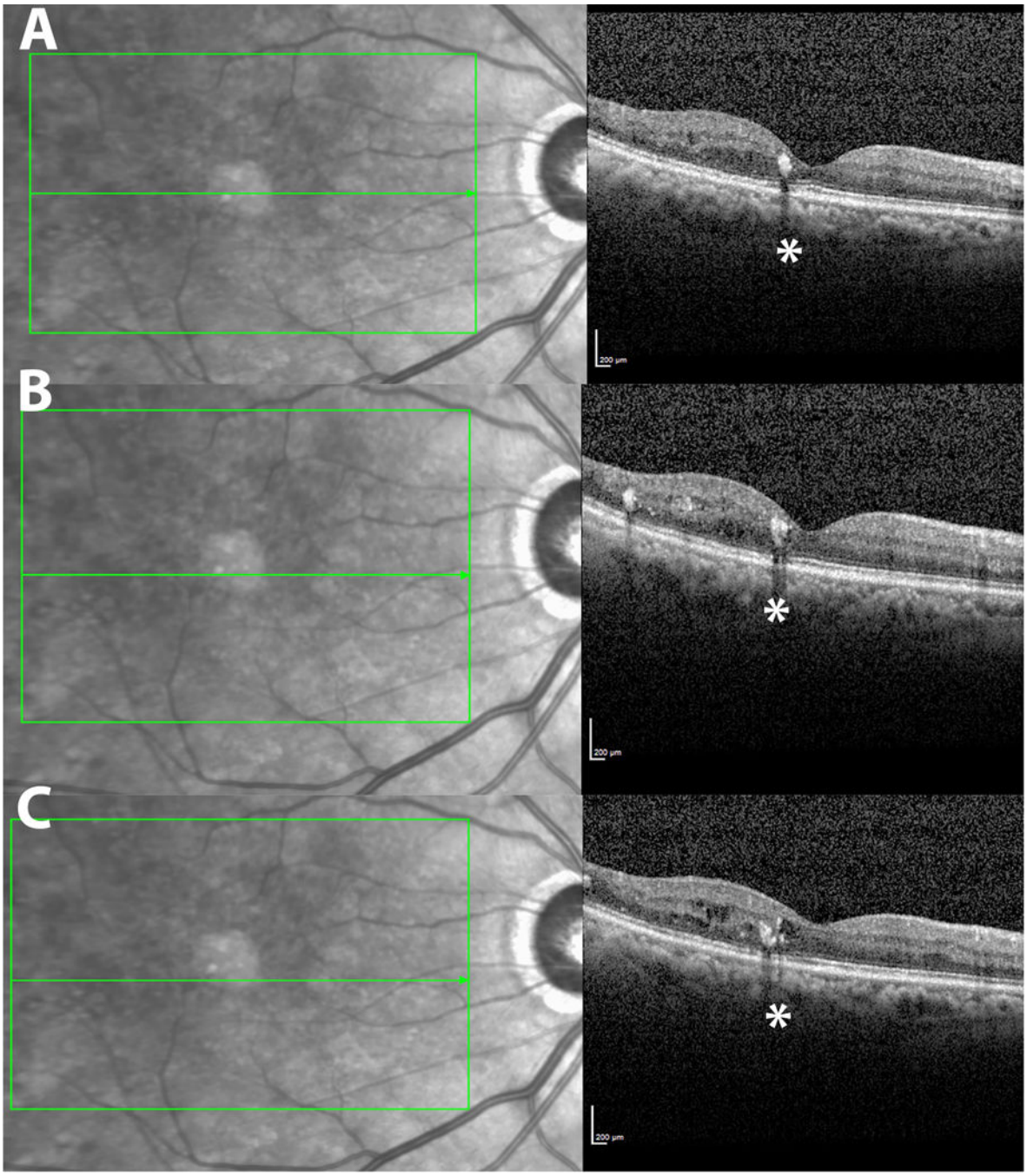

Figure 3.

Spectral-domain optical coherence tomography image of a diabetic patient with subretinal fluid and multiple small cysts (A). External limiting membrane and ellipsoidal layers are preserved both at the time of DME and after resolution of DME (B).

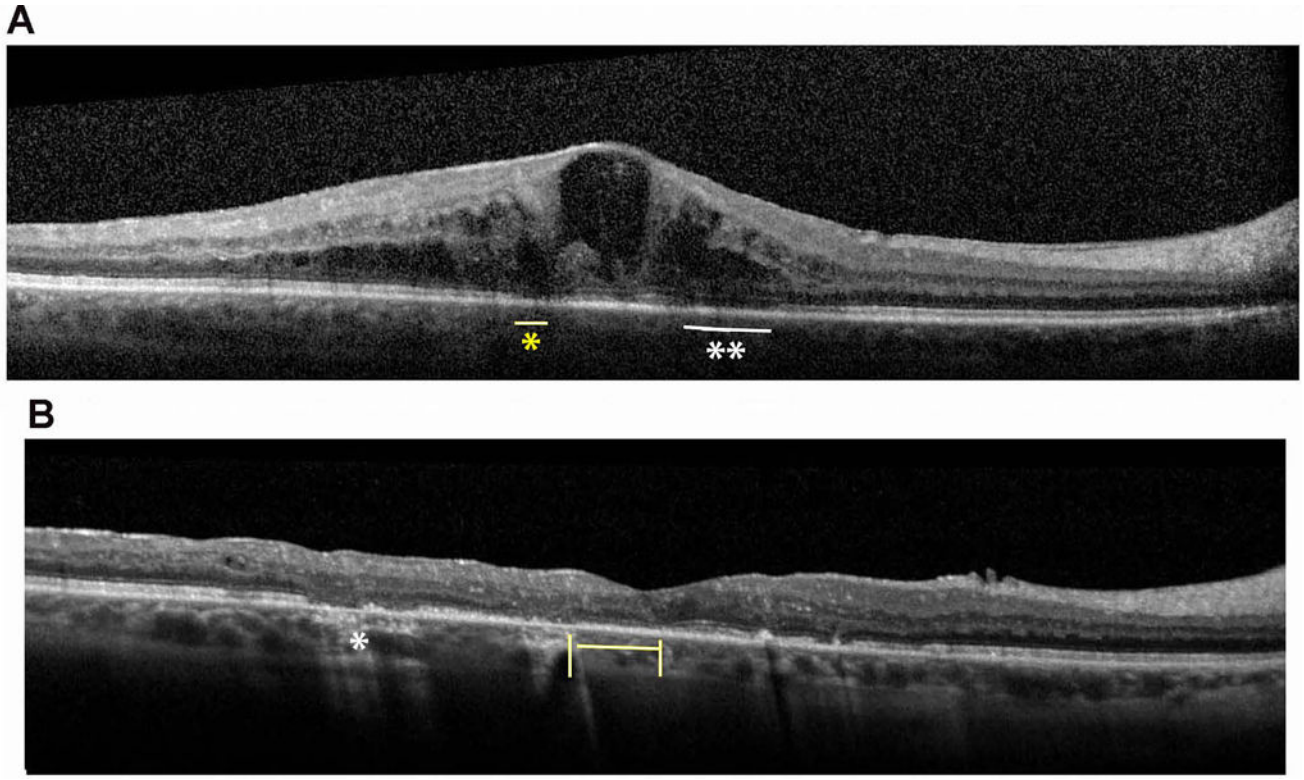

Figure 4.

Spectral-domain optical coherence tomography (SD-OCT) images of a 56-year-old male patient with a baseline BCVA of 20/63.

A. SD-OCT image showing a few large cysts and multiple small intraretinal cysts with outer retinal layer damage.

* (yellow line) Indicates the length of both external limiting membrane damage and ellipsoidal layer damage, whereas ** (white line) shows the extent of ellipsoidal layer damage at the time of diabetic macular edema

B. Image of the same patient obtained by eye-tracked feature of SD-OCT showing disruption of outer retinal layers particularly temporal to the fovea (yellow line indicates the extent of ellipsoidal layer damage) after the resolution of diabetic retinal edema. Vision improved to 20/50 following DME treatment including pars plana vitrectomy. Note, patient has some perifoveal outer retinal layer atrophy (*) corresponding to laser scar, and this atrophy is being disregarded in the evaluation of outer retinal layers since it is far from the center of the fovea.

Table 1

Baseline demographics of the patients with resolved diabetic macular edema

Variable	IS/OS (+), ELM (+) (group A)	IS/OS (−), ELM (+) (group B)	IS/OS (−), ELM (−) (group C)	p	p A–B	p A–C	p B–C
Number of eyes	38	5	16				
Age, years	58±13	66±7	64±13	0.17	–	–	–
DM type (I/II)	9/29	0/5	8/8	0.07			
Insulin use (yes/no)	23/15	3/2	9/7	0.91	–	–	–
HbA1c	7±0.8	7.5±0.7	8.4±2.3	0.06			
Hypertension (yes/no)	29/9	4/1	12/4	1	–	–	–
Hyperlipidemia (no/yes)	14/24	1/4	1/5	0.04	0.64	0.023	0.42
DM duration, years	17.2±9	17.4±5	18.5±7	0.82	–	–	–
DR grade (NPDR/PDR)	31/7	4/1	9/7	0.16	–	–	–

Group A=eyes with intact ellipsoidal layer and intact external limiting membrane at last follow-up, Group B=eyes with damaged ellipsoidal layer (inner/outer segment boundary junction) and intact external limiting membrane at last follow-up, Group C=eyes with both damaged ellipsoidal layer and external limiting membrane layer at last follow-up, DM=diabetes mellitus, HbA1c=glycosylated hemoglobin, DR=diabetic retinopathy, NPDR=non-proliferative diabetic retinopathy, PDR=proliferative diabetic retinopathy

Continuous parameters are presented as mean and standard deviation

–: non-applicable

Table 2

Characteristics of the eyes at the time of diabetic macular edema and after resolution of diabetic macular edema

Variable	IS/OS (+), ELM (+) (group A)	IS/OS (−), ELM (+) (group B)	IS/OS (−), ELM (−) (group C)	p	p A–B	p A–C	p B–C
Number of eyes	38	5	16				
Parameters at the time of DME							
BCVA, logMAR (Snellen)	0.2±0.2 (20/32)	0.4±0.2 (20/50)	0.6±0.4 (20/80)	0.011		0.007	0.43
Max Fov Thick, microns	424±70	485±40	496±144	0.066	–	–	–
CST, microns	348±59	390±37	427±143	0.026		0.023	0.32
FCP, microns	319±68	378±48	400±169	0.092	–	–	–
ELM damage, %	0.9±3.8	7.2±5.5	29±33	<0.001	0.001	<0.001	0.21
IS/OS damage, %	4.7±11.4	15.7±18.1	37±35.6	<0.001	0.013	<0.001	0.38
SRF (no/yes)	32/6	4/1	13/3	0.948	–	–	–
HRM (no/yes)	22/16	1/4	6/10	0.155	–	–	–
Cyst size (small/large)	24/13	1/4	5/10	0.034	0.02	0.029	0.04
Received Treatment							
Intravitreal injection (yes/no)	18/20	5/0	12/4	0.028			
No of anti-VEGF injections, mean	4.2±3.3	5.4±3.02	5.5±3.04	0.56			
No of TCA injections, mean	1±0	1.3±0.5	1.4±0.5	0.39			
Laser (yes/no)	19/19	2/3	10/6	0.43			
PPV (yes/no)	9/29	1/4	7/9	0.32			
DME duration, weeks	14±11	24±10.8	29±20	0.006	0.48	0.005	0.87
Parameters after resolution of DME							
BCVA, LogMAR (Snellen)	0.09±0.1 (≈20/25)	0.4±0.2 (20/50)	0.67±0.4 (≈20/100)	<0.001	0.004	<0.001	0.43
CST	279±20	265±15	233±25	<0.001	0.139	<0.001	0.01
FCP, microns	226±20	214±28	197±28	<0.001	0.09	<0.001	0.32
ELM damage, %	–	–	35±32	–	–	–	–
IS/OS damage, %	–	4.7±2.7	49±31.6	–	–	–	0.003

Group A=eyes with intact ellipsoidal layer and intact external limiting membrane (inner segment-outer segment boundary junction, IS/OS) at last follow-up, Group B=eyes with damaged ellipsoidal layer (inner/outer segment boundary junction) and intact external limiting membrane at last follow-up, group C=eyes with both damaged ellipsoidal layer and damaged external limiting membrane at last follow-up, SRF=subretinal fluid, HRM=hyper-reflective material, BCVA=best-corrected visual acuity, CST=central subfield thickness, FCP=foveal center point thickness, ELM=external limiting membrane, SRF=subretinal fluid, HRM=hyperreflective material, TCA=triamcinolone, DME=diabetic macular edema, PPV=pars plana vitrectomy, – non-applicable

Continuous parameters are presented as mean and standard deviation

Table 3

Univariate analysis for the final visual acuity

Continuous Variables		
	Odds Ratio (95% CI)	**P**
Duration of DM	1.000 (0.933–1.072)	0.99
Duration of DME	1.042 (1.001–1.084)	0.04
No of iv inj	1.053 (0.894–1.241)	0.53
MaxFov_DME	1.003 (0.998–1.009)	0.23
CST_DME	1.003 (0.998–1.008)	0.21
FCP_DME	1.004 (0.998–1.009)	0.15
HbA1c	1.487 (1.060–2.087)	0.02
Age	1.051 (0.992–1.113)	0.08
% of ISe damage during DME	1.063 (1.026–1.101)	<0.001
% of ELM damage during DME	1.112 (1.049–1.178)	<0.001
Categorical Variables		
	Odds Ratio (95% CI)	**P**
BCVA at baseline (impaired/Good)	9.77 (2.362–40.482)	0.002
DR grade		
Moderate NPDR versus mild NPDR	3.83 (0.534–27.496)	0.183
Severe NPDR versus mild NPDR	11.5 (1.305–101.35)	0.028
PDR versus mild NPDR	7.66 (1.250–47.018)	0.027
Hyperlipidemia (yes/no)	2.8 (0.523–14.987)	0.229
Macula laser (yes/no)	1.8 (0.4880–6.638)	0.377
Surgery (yes/no)	3.4 (0.945–12.230)	0.061
Receiving iv injection (yes/no)	3.34 (0.798–14.037)	0.098
Cyst (multiple/few)	4.37 (1.125–17.002)	0.033
Cyst (large/small)	2.22 (0.562–8.784)	0.255
SRF (yes/no)	0.75 (0.121–4.668)	0.757
HRM (present/absent)	3.289 (0.869–12.442)	0.08

CI=confidence interval, BCVA=best corrected visual acuity, DM=diabetes mellitus, no of iv inj=number of intravitreal injections, MaxFov_DME=maximal foveal thickness, DME= diabetic macular edema, CST=central subfield thickness, FCP=foveal center point, ISe=inner ellipsoidal segment layer, ELM=external limiting membrane, DR=diabetic retinopathy, NPDR=non-proliferative diabetic retinopathy, PDR=proliferative diabetic retinopathy, SRF=subretinal fluid, HRM= hyperreflective material

Table 4

Zero Inflated Poison model for the external limiting membrane layer damage after resolution of diabetic macular edema

Zero Inflation		
	Odds Ratio (95% CI)	**p**
% of ELM damage during DME	0.86 (0.78–0.95)	0.0031
Poison Model		
	Odds Ratio (95% CI)	**p**
DR grade:		
Severe DR vs mild DR	9.245 (5.5–15.5)	<0.001
Moderate vs mild DR	3.126 (2.2–4.3)	<0.001
PDR versus mild DR	3.104 (2.0–4.6)	<0.001
Moderate DR vs PDR	1.007 (0.7–1.4)	0.3764
Macula Laser (yes/no)	1.670 (1.2–2.2)	<0.001
IV injection (no/yes)	4.597 (3.0–6.8)	<0.001
CST	1.002 (1.001–1.003)	<0.001
BCVA at baseline	0.258 (0.16–0.41)	<0.001
Baseline ELM damage	0.998 (0.99–1.003)	0.496

ELM=external limiting membrane, DME=diabetic macular edema, DR=diabetic retinopathy, vs=versus, PDR=proliferative DR, BCVA=best corrected visual acuity, DM=diabetes mellitus, iv=intravitreal, CST=central subfoveal thickness, BCVA=best-corrected visual acuity