Assessment of SD-OCT imaging in cases of vitrectomy and membrane delamination for proliferative diabetic retinopathy

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Abstract

Purpose: To report our findings on morphological assessment of the vitreomacular interface and intraretinal architecture using SD-OCT before and after delamination of epiretinal membranes in patients with advanced proliferative diabetic retinopathy (PDR).

Design: Retrospective, noncomparative, interventional case series.

Participants: 14 patients with tractional retinal detachment (TRD) secondary to proliferative diabetic retinopathy had vitrectomy and membrane delamination.

Intervention: Pars plana vitrectomy (PPV) and delamination of pre-retinal membranes for tractional retinal detachment secondary to proliferative diabetic retinopathy (PDR) operated by two surgeons over one year period.

Main outcome measures: LogMAR distance visual acuity (VA), optical coherence tomography findings, including automated central 1-mm subfield retinal thickness (CFT), integrity of photoreceptor inner and outer segments (IS/OS) junction, integrity of external limiting membrane (ELM), presence of epiretinal membrane (ERM), subretinal fluid (SRF) and cystoid macular oedema (CMO).

Two-trained masked observers independently graded the OCT findings.

Key words: SD-OCT, epireretinal membrane, proliferative, diabetic retinopathy.

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OCT

SD-OCT was performed with the Cirrus HD-OCT system (Carl Zeiss Meditec) and Topcon 3D OCT-1000 (Topcon). The scans were taken three times to obtain scans with the highest signal intensity, no centration errors, and minimal segmentation errors. The proprietary Cirrus segmentation algorithm was used to produce retinal thickness maps.

The standard retinal subfields included one central subfield[1], inner and outer subfields (Fig. 1). The central subfield is bound by the innermost 1-mm-diameter circle. Two different readers analyzed all OCT scans in a masked manner. A disruption in the IS/OS or ELM was defined as the loss of the back-reflection line. The IS/OS junction and ELM disruption were measured in either direction from the foveal center. The IS/OS junction disruption was graded from 0 to 2. Grade 0 was given when an intact IS/OS layer was found, grade 1 was assigned for any focal disruption of the IS/OS junction, and grade 2 was assigned for total disruption of the

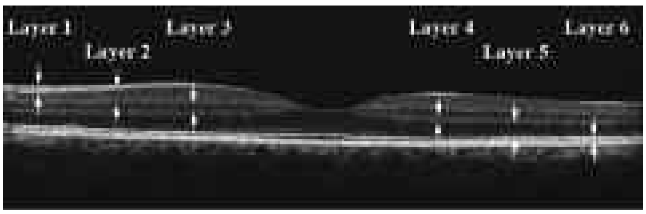


Figure 1(a). Normal Retinal Layers imaged by SD-OCT. A representative spectral domain optical coherence tomography image obtained in the left eye of one subject in the study. The 6 retinal were the nerve fiber layer (layer 1), ganglion cell layer + inner plexiform layer (layer 2), inner nuclear layer (layer 3), outer plexiform layer (layer 4), outer nuclear layer + photoreceptor inner segments (layer 5), and photoreceptor outer segments (layer 6).

IS/OS junction. Reduced back-scattering from the ELM, IS/OS, and the other outer retinal layers, which included the outer plexiform layer, the outer nuclear layer, the retinal pigment epithelium, and the choroid, was regarded to be the result of a shadowing effect, not disruption.

Each SD OCT image was analyzed using an image segmentation algorithm and thickness profiles of 6 retinal layers were automatically generated, as previously described. A representative SD OCT image obtained in one subject is shown in Fig. 1(a). Six retinal layers were identified by the automatic segmentation algorithm: nerve fiber layer (layer 1), ganglion cell layer + inner plexiform layer (layer 2), inner nuclear layer (layer 3), outer plexiform layer (layer 4), outer nuclear layer + photoreceptor inner segments (layer 5), and photoreceptor outer segments (layer 6).

Exclusions

Centration error was recorded when the central foveal subfield did not correspond to the true center based on both the topographic map and OCT B-scan data, and these eyes were excluded.

Statistical analysis

Visual acuity was recorded as the number of logMar letters correctly read by patient. The visual improvement, measured as the difference between pre-treatment and post- treatment, was used as the response variable for a stepwise regression. The pre-treatment central macular thickness and disruption of the IS-OS and ELM were used as predictors of post-operative visual acuity.

Results

7 pre-operative scans, 9 scans 1-3 months post-operatively and 14 scans >3 months post-operatively included in the analysis. Overall inter-observer agreement was 92.35%. Inter-observer agreement for the 1-3 months post-op group was 85.1% demonstrating substantial agreement with a Kappa statistic of 0.703 and significance p=0.00. Inter-observer agreement for the latest (>3 months) post-op group was 84.5% demonstrating substantial agreement with a Kappa statistic of 0.719 and significance p=0.00.

Mean pre-op VA is 1.12 and mean post-op VA is 0.91. On Table 1 is shown the pre-operative results for 7 patients demonstrating pre-operative VA according to macular characteristics. These findings were not significantly associated with a reduction in VA and unfortunately in some cases there seems to be an improvement in VA.

On Table 2 is shown the post-operative results for 9 patients 1-3 months post-operatively demonstrating post-operative VA according to a number of macular characteristics. No findings were significant.

On Table 3 is shown the post-operative results for 14 pa-

Variable	n	Mean VA logMar	Std. Dev	p value
Cystoid Macular Oedema				
CMO	7	1.1	0.79	-
No CMO	0	-	-	
Vitreomacular traction				
Present	3	0.9	1.07	[illegible]
Absent	4	1.3	0.37	
Subretinal Fluid				
SRF	0	-	-	-
No SRF	7	1.1	0.79	
IS/OS Junction				
IS/OS Continuous	1	2.1	-	F statistic=[illegible]
IS/OS Discontinuous	3	1.0	[illegible]	p=[illegible]
IS/OS Full disruption	3	[illegible]	[illegible]	
External limiting membrane				
Continuous	1	2.1	-	F statistic=[illegible]
Discontinuous	3	0.8	[illegible]	p=0.40
Full disruption	3	1.1	0.73	
Epiretinal Membrane				
ERM	4	1.0	0.88	[illegible]
No ERM	3	1.3	0.73	

Table 1. Pre-operative results for 7 patients demonstrating pre-operative VA according to macular characteristics. These findings were not significantly associated with a reduction in VA and unfortunately in some cases there seems to be an improvement in VA.

A) Reader's 1 results of scans 1-3 months post-operatively

Variable	n	Mean VA logMar	Std. Dev	p value
Cystoid Macular Oedema				
CMO	[illegible]	[illegible]	[illegible]	[illegible]
No CMO	[illegible]	[illegible]	[illegible]	
Subretinal Fluid				
SRF	2	[illegible]	[illegible]	[illegible]
No SRF	[illegible]	[illegible]	[illegible]	
IS/OS Junction				
IS/OS Continuous	[illegible]			F statistic=[illegible]
IS/OS Discontinuous	[illegible]	[illegible]	[illegible]	p=[illegible]
IS/OS Full disruption	[illegible]	1.28	[illegible]	
External limiting membrane				
Continuous	1	[illegible]		F statistic=[illegible]
Discontinuous	[illegible]	[illegible]	[illegible]	p=[illegible]
Full disruption	[illegible]	1.08	[illegible]	
Epiretinal Membrane				
ERM	[illegible]	[illegible]	[illegible]	[illegible]
No ERM	[illegible]	[illegible]	[illegible]	

B) Reader's 2 results of scans 1-3 months post-operatively

Variable	n	Mean VA logMar	Std. Dev	p value
Cystoid Macular Oedema				
CMO	[illegible]	[illegible]	[illegible]	[illegible]
No CMO	4	[illegible]	[illegible]	
Subretinal Fluid				
SRF	[illegible]	[illegible]	[illegible]	[illegible]
No SRF	[illegible]	[illegible]	[illegible]	
IS/OS Junction				
IS/OS Continuous	1	[illegible]	-	F statistic=[illegible]
IS/OS Discontinuous	5	[illegible]	[illegible]	p=[illegible]
IS/OS Full disruption	3	[illegible]	[illegible]	
External limiting membrane				
Continuous	1	[illegible]	-	F statistic=[illegible]
Discontinuous	[illegible]	[illegible]	[illegible]	p=[illegible]
Full disruption	[illegible]	[illegible]	[illegible]	
Epiretinal Membrane				
ERM	[illegible]	[illegible]	1.458	[illegible]
No ERM	[illegible]	[illegible]	[illegible]	

Table 2. Post-operative results for 9 patients 1-3 months post-operatively demonstrating post-operative VA according to a number of macular characteristics. No findings were significant. A. Reader's 1 results of scans 1-3 months post-operatively B. Reader's 2 results of scans 1-3 months post-operatively

Variable	n	Mean VA logMar	Std. Dev	p-value
Cystoid Macular Oedema				
CMO	5	0.59	0.502	0.567
No CMO	6	0.57	0.728	
IS/OS Junction				
IS/OS Continuous	5	0.46	0.321	F statistic= 6.01
IS/OS Discontinuous	5	0.52	0.205	p=0.0[illegible]
IS/OS Full disruption	4	1.53	0.665	
External limiting membrane				
Continuous	6	0.50	0.303	F statistic= 5.48
Discontinuous	3	0.40	0.179	p=0.022
Full disruption	5	1.39	0.634	
Epiretinal Membrane				
ERM	4	0.43	0.440	0.188
No ERM	10	0.53	0.655	

B) Reader's 2 results of scans >3 months post-operatively. ELM continuation was associated with a significant improvement in post-op VA. IS/OS continuation was also associated with an improvement in post-op VA.

Variable	n	Mean VA logMar	Std. Dev	p-value
Cystoid Macular Oedema				
CMO	7	0.67	0.529	0.631
No CMO	7	0.70	0.671	
Subretinal Fluid				
SRF	1	0.40	–	0.084
No SRF	13	0.79	0.658	
IS/OS Junction				
IS/OS Continuous	6	0.45	0.321	F statistic= 5.[illegible]
IS/OS Discontinuous	2	0.75	0.272	p=0.014
IS/OS Full disruption	4	1.45	0.732	
External limiting membrane				
Continuous	7	0.41	0.335	F statistic= 6.58
Discontinuous	3	0.72	0.153	p=0.012
Full disruption	4	1.48	0.732	
Epiretinal Membrane				
ERM	7	0.77	1.080	0.748

Table 3. Post-operative results for 14 patients >3 months post-operatively demonstrating post-operative VA according to a number of macular characteristics. The findings that were significant included IS/OS junction and ELM but please refer below for slight difference in trends in VA.

tients >3 months post-operatively demonstrating post-operative VA according to a number of macular characteristics. The findings that were significant included IS/OS junction and ELM but please refer below for slight difference in trends in VA.

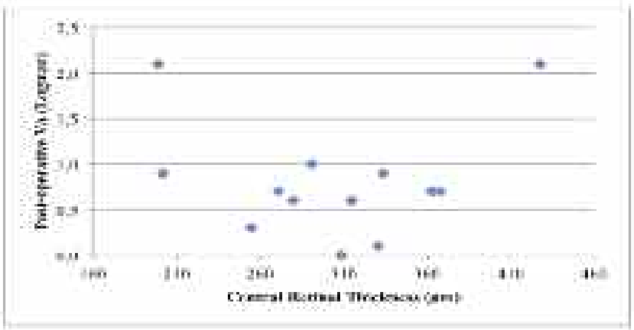


Figure 4. Scatter plot of >3 months post-op VA against Central Retinal thickness shows no specific trends. Pearson correlation coefficient 0.021 (p-value = 0.947). Mean CRT was 303.54 μm.

On Figure 4. is shown a scatter plot of >3 months post-op VA against Central Retinal thickness shows no specific trends. Pearson correlation coefficient 0.021 (p-value = 0.947). Mean CRT was 303.54 μm. and on Figure 5 a scatter plot of pre-op VA against post-op VA. Although this graph does not look particularly significant the Pearson correlation coefficient was 0.857 and $p<0.05$

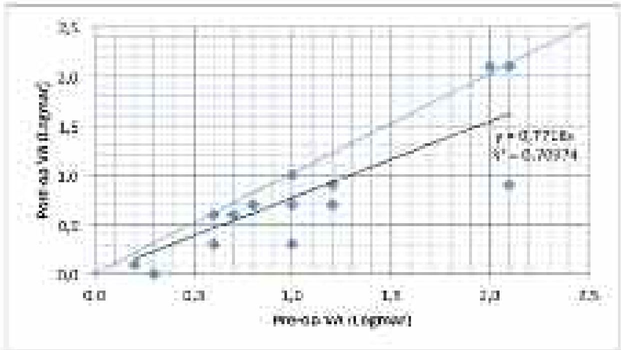


Figure 5. Scatter plot of pre-op VA against post-op VA. Although this graph does not look particularly significant the Pearson correlation coefficient was 0.857 and p<0.05

Conclusions

The integrity of the outer retinal microstructure appears to be an important biomarker of visual performance following PPV and membrane delamination for PDR. The IS/OS junction and ERM integrity correlate well with visual outcomes following surgery for PDR.

Introduction

Optical coherence tomography (OCT) is a well-established method of examining the retinal architecture in vivo. After the introduction of OCT, in vivo imaging of the retina of various retinal diseases came true. In particular, the ease with which these images can be acquired considerably changed the diagnostic strategy used by ophthalmologists.[2]

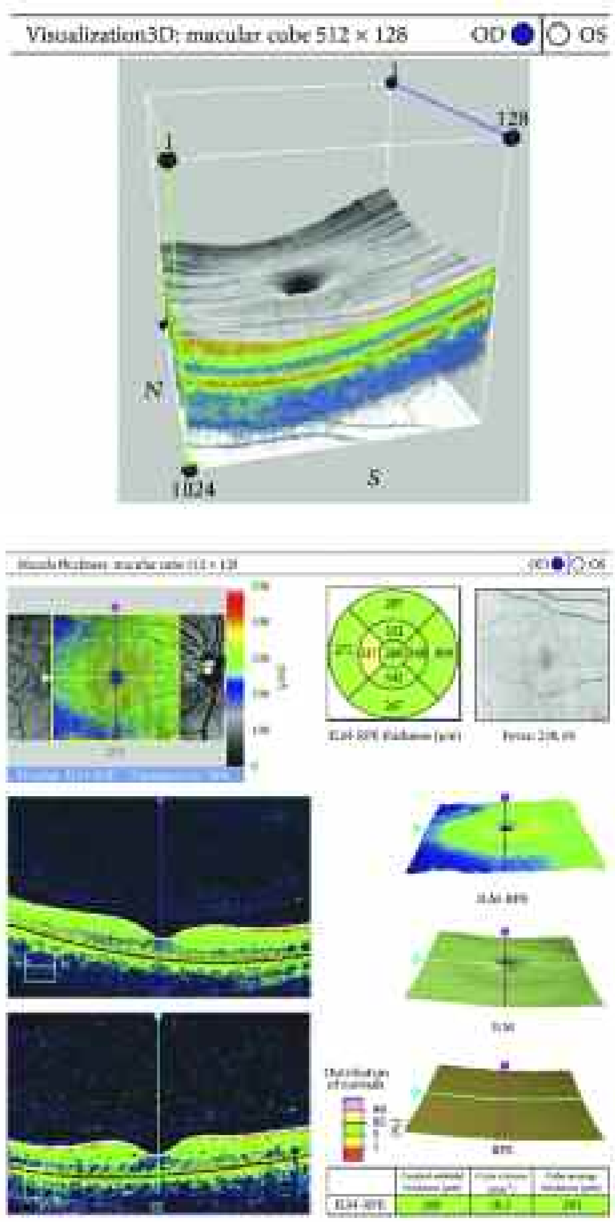
With most recent development of spectral-domain OCT (SD-OCT), pathological changes of the retina can be observed in much greater detail. SD-OCT technology uses low-coherence interferometry to detect light echoes, relying on a spectrometer and high-speed camera and based on the mathematical premise of the Fourier transformation.[3] Because application of the Fourier transformation has the effect of measuring all echoes of light simultaneously, as compared with sequentially in the case of time-domain OCT (TD-OCT), SD-OCT significantly increases the amount of data acquired in each session, resulting in a significant reduction of motion artefacts and an increased signal-to-noise ratio compared with TD-OCT. The axial resolution of TD-OCT was 10–20 μm. SD-OCT (5 to 6 μm of axial resolution) has improved the ability to detect intraretinal microstructures and to identify pathological changes in the retinal architecture in various diseases.[4]

OCT represents a major breakthrough in the diagnosis of retinal disease. As the technology allows to visualize the vitreoretinal interface, the intraretinal layers and the subretinal space together with the retinal pigment epithelial layer, many diseases can be diagnosed with a clear anatomical condition. The method can easily be repeated at multiple time points. 1Spectral domain OCT has a fast acquisition speed of 20,000-40,000 A-scans and an axial resolution of 5-7µm. Due to the fast scanning process, the modality allows a raster scanning providing data from all locations of the retina. The complete raster scanning may be used to compose a three-dimensional image of the entire macular area. The system allows a high detail representation of the anatomical changes in the single scan images and offers parameter for measurement of disease progression. It identifies the different retinal layers and high-definition OCT is able to identify ganglion cell loss and ischemia, as well as photoreceptors density predicting potential visual recovery. The good reproducibility of retinal thickness measurement with OCT allows its use for longitudinal objective monitoring of the macular edema, and for the assessment of treatment efficacy.[5]

Optical coherence tomography (OCT) is a non-invasive technology for measuring the thickness of the choroid, retina, and peri-papillary retinal nerve fiber layer. It provides helpful information for evaluating, diagnosing, and quantitatively monitoring the disease progression of several retinal pathologies.[6] Compared to conventional time-domain OCT (TD-OCT), the newly developed spectral-domain OCT (SD-OCT) has better resolution of B-scan images and faster data collection.[7,8]

SD-OCT clearly delineates two highly reflective lines in the outer retina, which are external limiting membrane (ELM) and photoreceptor inner and outer segment (IS/OS) junctions. These lines can serve as hallmarks for the evaluation of photoreceptor condition. The changes of these two lines on the SD-OCT images are due to the photoreceptor impairment and restoration.[9]

In Figures 1(b) and 1(c), the normal aspect of the macula is illustrated. Figure 1(b) represents the 3D visualization of a macular cube of 512 x 128 and Figure 1(c) shows the macular thickness. The images were obtained with the Cirrus OCT which is an SD-OCT device. In both images the foveal pit is evident, as well as the normal, regular arrangement of the retinal layers, resembling a histological section of the macula. The highly reflective tissues are given the red colour (retinal pigment epithelial band, internal limiting membrane), whereas the medium reflective layers of the neurosensory retina are represented in green. The macular thickness appears normal.



1(b) and 1 (c): Normal OCT images of the macula

Photoreceptor Impairment on Optical Coherence Tomographic Image

The retinal photoreceptor layer can be evaluated accurately using SD OCT by examining the integrity of the photoreceptor inner segment/outer segment junction. Disruption of this hyper reflective line just above the retinal pigment epithelium reveals damage to the macular photoreceptors, and several recent studies highlight the value of IS/OS junction integrity in retinal diseases including retinitis pigmentosa, central serous chorioretinopathy, acute zonal occult outer retinopathy, branch retinal vein occlusion, and macular hole treated with vitrectomy.[10-14] In each of these diverse retinal pathologic conditions, disturbance of the photoreceptors correlated with poor visual acuity or outcome.

With respect to epiretinal membrane (ERM), Shimozono et al.[15] studied 50 eyes with idiopathic ERM using SD-OCT. There were no eyes with ELM disruption. The IS/OS junction also retained its continuity in all cases, while the COST line was disrupted in 48%. The authors speculated that the tractional force generated by ERM can alter the interface between the outer segment tips and the RPE without severely damaging the outer segment itself or photoreceptor cell bodies. In contrast, in more vision-threatening diseases such as age-related macular degeneration the IS/OS junction, and even the ELM are disrupted in many cases.[16] Thus, there should be a hierarchy of vulnerability among the 2 lines; the IS/OS junction and the ELM can be disrupted when moderate, and severe photoreceptor damage, respectively, is caused.[15]

Limited information is available regarding the association between the foveal IS/OS junction line and function in patients following pars plana vitrectomy and membrane delamination for proliferative diabetic retinopathy.

Photoreceptor Restoration on Optical Coherence Tomographic Image

For the image assessment of the photoreceptor restoration on the OCT images, a lot of studies using OCT have reported on the relationship between the restoration of IS/OS junction and the recovery of the visual acuity after successful macular hole (MH) closure. Using TD-OCT, it has been reported that the presence of the IS/OS line on the OCT images is correlated with the recovery of good vision after MH surgery and is essential for normal visual function.[4]

After development of SD-OCT, SD-OCT images were analyzed in terms of the IS/OS junction and the ELM after idiopathic MH surgery. Ooka et al.[17] studied 43 eyes before and 1, 3, and 6 months after MH surgery. After MH surgery, the IS/OS or ELM line is restored from perifoveal region toward center of the closed MH on the OCT images. Therefore, measuring the length of defect in the IS/OS or ELM line can be useful in estimating the retinal restoration after MH surgery. The results of this study indicated that the length of the IS/OS junction defect was significantly correlated with the length of the ELM defect at all preoperative and postoperative times and that the restoration of the ELM was earlier than that of the IS/OS junction at all times and in all eyes. None of the eyes had a complete restoration of the IS/OS junction without a complete recovery of the ELM. These findings suggest that the restoration of the ELM is closely associated with that of the IS/OS junction, and the integrity of the ELM is necessary for the restoration of the IS/OS junction. At all postoperative times, the lengths of both the IS/OS and ELM defects were significantly correlated with both the visual acuity and the foveal sensitivity measured using MP-1. The restoration of the IS/OS junction and the ELM may reflect the morphological and functional recovery of the foveal photoreceptors in surgically closed MHs.

With respect to retinal restoration after ERM surgery, Shimozono et al.[15] studied 50 eyes that underwent vitrectomy for idiopathic ERM. There were no eyes with ELM disruption preoperatively and postoperatively. At baseline, the IS/OS junction retained its continuity in all cases. The disruption of the IS/OS junction temporarily increased at 1 month postoperatively and decreased to near the baseline level thereafter. Postoperatively, defect lengths of IS/OS was significantly correlated with the visual acuity.

As for retinal restoration after RD surgery, Wakabayashi et al.[18] evaluated foveal microstructural changes in eyes with anatomically successful repair of rhegmatogenous RDs using SD-OCT. In preoperative macula-off eyes, the postoperative visual acuity was significantly correlated with the integrity of the photoreceptor IS/OS and ELM lines detected by SD-OCT postoperatively. During the postoperative follow-up period, the IS/OS junction became restored in 64% of the eyes with the disrupted IS/OS junction and the continuous ELM line at the postoperative initial examination. In any eyes with the disrupted IS/OS and ELM at the initial examination, the photoreceptor layer did not become completely restored during the follow-up period. Thus, the authors concluded that the postoperative preservation of the ELM may predict the subsequent restoration of the photoreceptor layer in RD patients.

Regarding the histopathological findings of the detached retina after retinal reattachment, previous experimental studies have proposed that atrophy of the photoreceptors occurring soon after retinal reattachment may be irreversible in eyes with extended period of RD. However, the atrophy can stop or reverse in eyes with short time period of RD. Guérin et al.[19] investigated the recovery process of photoreceptor outer segments after retinal reattachment using the animal model of RD. RD leads to a reduction in photoreceptor outer segment absolute length. Increasing time of retinal reattachment is positively correlated with an increase in outer segment absolute length. Rod and cone outer segments regained approximately 40% of their control lengths after a 2-week reattachment period. By 30 days of reattachment, rod outer segments had regained 72% of their normal length, and cone outer segments had regained approximately 48%. After 150 days of reattachment, photoreceptor outer segment mean length was not statistically different from control areas. This histopathological finding of increase in the photoreceptor outer segment length after retinal reattachment suggested the direction of photoreceptor restoration from inside toward outside, being consistent with the SD-OCT findings after the repair of RD.

The process of the photoreceptor restoration after MH or RD surgery seems to be exact opposite of the process of photoreceptor impairment in RP or other retinal degenerative diseases. It is known that the photoreceptors continuously add and shed discs of the outer segments. This renewal of the outer segment has been suggested to be related to the recovery of the length of the foveal photoreceptor outer segments. The ELM is the first structure to recover after MH closure. The ELM is considered to consist of zonular adherence between photoreceptor inner segment and the Müller cell processes, and there is no zonula occludens in ELM. Thus, ELM is macromolecule-impermeant intermediate junction, and microscopic particles such as horseradish peroxidase can pass through the intercellular space of ELM. ELM is thought to have a supportive function in maintaining the alignment and orientation of the photoreceptor. Therefore, restoration of the ELM may be necessary for sequential photoreceptor outer segment repair, although the reason why the structure of ELM is most preserved in various retinal disease remains unclear. A continuous ELM has been considered to be a sign of intact photoreceptor cell bodies and the Müller cells, and the IS/OS junction rarely recovered without a recovery of the ELM. Reconstruction of the foveal ELM line in the early postoperative period can help to predict subsequent restoration of the foveal photoreceptor layer and the potential for better visual outcomes after MH surgery.[4] Bottoni et al.[20] reported that an intact outer nuclear layer at the fovea also seems to be necessary to achieve a complete restoration of the photoreceptor microstructure.

Histology and Optical Coherence Tomographic Image

Among two highly reflective lines depicted inside the RPE on the SD-OCT image, the ELM is considered to consist of zonular adherence between photoreceptor inner segment and the Müller cell processes. The ELM line typically is thinner and much fainter than the other two lines. The second line has been commonly ascribed to the boundary between the inner segments and outer segments of the photoreceptors (IS/OS).[4]

Most recently, Spaide and Curcio[9] evaluated the validity of commonly used anatomical designations for these hyperreflective lines. A scale model of outer retinal morphology was created using published information for direct comparison with SD-OCT scans. Their analysis showed a high likelihood that the SD-OCT lines attributed to the ELM (the first, innermost line) are correctly attributed. Comparative analysis showed that the second line, often attributed to the boundary between inner and outer segments of the.

Further studies regarding comparison between OCT images in vivo with histological correlative will be needed to understand what the change of OCT finding actually means. Only by making an accurate assessment of OCT findings, we can understand the precise changes of the photoreceptor in vivo in various retinal diseases.[4]

Proliferative diabetic retinopathy (PDR)

Proliferative diabetic retinopathy (PDR) is the most common blinding disease in the working age group. It is believed that the increase in incidence of diabetes will be exceeding the prognostic increase of 39% of the WHO. Thus, sequelae of diabetes such as diabetic maculopathy as well as PDR will increase in the future. Besides improved systemic treatment of the diabetes syndrome, the advent and the recent improvement in surgical treatment of PDR is and will be an important way to avoid blindness from PDR. The combination of pharmacologic agents and vitreoretinal microsurgery have added to improve the results of surgery today, even if there are no major randomized trials on this topic during the last 15 years.

Indications for vitrectomy in PDR include primarily severe non clearing vitreous haemorrhage, tractional retinal detachment, with or without involvement of the macula, combined tractional and rhegmatogenous retinal detachment, severe progressive fibrovascular proliferation, intense pre retinal haemorrhage, rubeosis iridis associated with vitreous haemorrhage, ghost cell glaucoma and macular edema in instances with a tractional component.

The aim of vitrectomy includes removal of opacities from the vitreous space, and the removal of tractional forces from the retinal surface. By doing this, fibrocellular proliferations on the retinal surface as well as fibrovascular proliferations from the optic disc and elsewhere have to be removed as much as possible. In the presence of macular edema, the removal of fine epimacular membranes should be attempted carefully.[21] A special group of patients have a combination of diabetic macular edema and PDR which can be approached at the time of vitreoretinal surgery as well. In these situations, it has to be taken into consideration that epiretinal membranes in diabetic retinopathy often have a multi-layered appearance. Therefore, in this situation it is advisable to remove not only the epiretinal tissue, but also the internal limiting membrane of the retina in order to relieve all necessary traction and gain the maximum in potential visual recovery.

Surgical correction of PDR is useful for improving vision. However, some cases show poor visual recovery even after complete removal of ERM. Several factors, such as preoperative visual acuity have been suggested as prognostic factors influencing the postoperative visual acuity. Recently, investigators have suggested that the macular microstructure, such as the macular thickness and appearance of the photoreceptor layer, may be associated with the postoperative visual acuity. However, the relatively low resolution of the scanning image of time-domain optical coherence tomography limits detailed delineation of the features of the photoreceptor layer. The introduction of spectral-domain OCT has improved the speed and sensitivity of the examination, allowing scanning at a higher resolution. Furthermore, SD OCT also has the ability to provide high registration and enables analysis of volume rendering by allowing 3-dimensional imaging, thereby enhancing the visualization of the intraretinal architectural morphologic features.[22]

Therefore, the aim of the present study was to report our findings on morphological assessment of the vitreomacular interface and intraretinal architecture using SD-OCT before and after delamination of epiretinal membranes in patients with advanced proliferative diabetic retinopathy (PDR) and to correlate these features with the functional outcomes.

Factors including IS/OS junction integrity, external limiting membrane (ELM) integrity, and CMT were investigated as potential predictive factors for vision improvement in eyes that underwent vitrectomy for delamination of epiretinal membranes in patients with advanced proliferative diabetic retinopathy (PDR).

Methods

Records of patients with PDR who underwent PPV for delimitation of epiretinal membranes were reviewed retrospectively. Patients with concurrent macular diseases such as macular degeneration or patients with significant cataracts were excluded.

The study complied with the tenets of the Declaration of Helsinki. All cases were identified through a search of the surgical record database at the Whipps Cross University Teaching Hospital (Medisoft). First the database was searched automatically for relevant diagnoses.

All data was collected and entered into spreadsheet software (Excel 2007, Microsoft Corp.).

Pars plana vitrectomies were performed at the Department of Ophthalmology, Whipps Cross University Hospital , London for delamination of membranes due to proliferative diabetic retinopathy for a period of one year, between August 2012 and July 2013.

Study protocol

The eligibility criteria for this study included 14 patients who underwent delamination of epiretinal membranes due to advanced proliferative diabetic retinopathy (PDR). Patients with diabetes mellitus type 1 and 2 were enrolled in the study. Eyes with dense cataract or other ocular diseases were excluded as well as eyes with no pre-operative and post-operative OCT images.

Examinations

Preoperatively and at 1 week, 1, 3 months and at last clinic visit postoperatively, all eyes underwent log MAR distance visual acuity testing, a careful biomicroscopic evaluation, measurement of the foveal area thickness using SD-optical coherence tomography. All regular examinations were independently graded by two OCT-trained masked examiners. The visual acuity was evaluated using the logMAR Thompson vision chart.

In the present series, SD OCT was performed for each eye using 5-line raster scans. Two examiners (E.P. and H.L.) who were blinded to information about the visual acuity of the patients interpreted the macular microstructure in the SD OCT images together. The photoreceptor layer was imaged as a hyper reflexive line showing the IS/OS junction above the retinal pigment epithelium. As intact IS/OS junction was defined as a continuous hyper-reflexive line. However, diagnosis of a disrupted IS/OS was made based on loss or irregularity of the hyper reflexive line corresponding to the IS/OS junction.

The IS/OS junction disruption was graded from 0 to 2. Grade 0 was given when an intact IS/OS layer was found, grade 1 was assigned for any focal disruption of the IS/OS junction, and grade 2 was assigned for total disruption of the IS/OS junction.

Macular edema at baseline and during the follow-up was assessed by OCT measurements to determine the automated central 1-mm subfield foveal thickness, which was defined as the distance between the inner retinal surface and the reti-

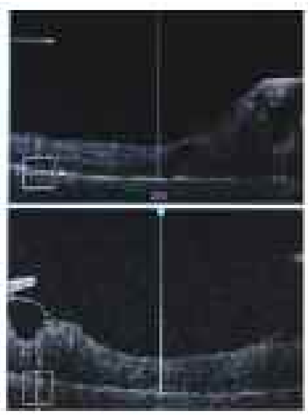


Figure 2a

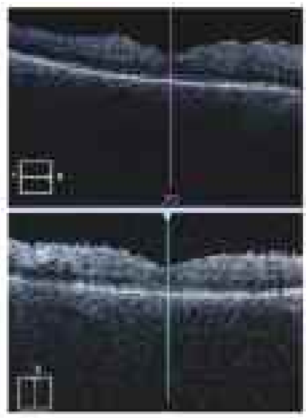


Figure 2b

Figure 2. OCTs of Case 1 are shown in images a and b.
2(a). shows the pretreatment OCT. VA: 6/30
2(b). 30 days following treatment there is a marked reduction in the CRT. VA: 6/24

nal pigment epithelium at the central fovea -the fovea was scanned in a vertical direction- the integrity of photoreceptor inner and outer segments (IS/OS), the presence of epiretinal membrane, subretinal fluid (SRF) and cystoid macular edema (CMO).

Representative images are shown in Figures 2 and 3.

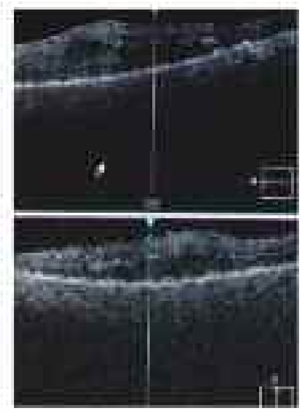


Figure 3a

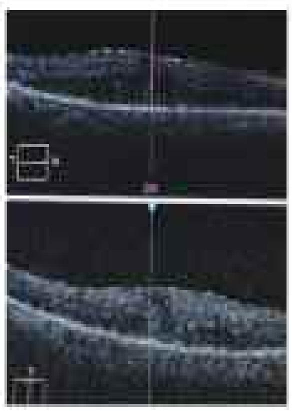


Figure 3b

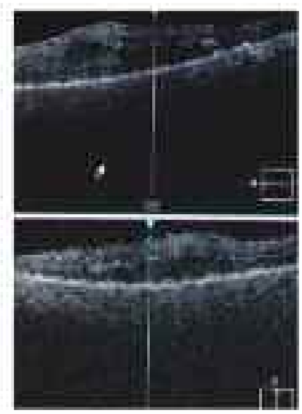


Figure 3c

Figure 3. Case 2. Changes in the ELM and photoreceptor IS/OS junction during follow-up. OCTs are shown in images a, b and c. Image 3(a). shows the pre-treatment OCT. VA:6/9 3(b). 2 months following treatment. VA: 6/24 and 3(c). 10 months after treatment shows marked reduction in the CRT. VA: 6/6

Surgical procedure

All operations were performed by two surgeons (HZ and CM) most under peribulbar anaesthesia. Vitrectomy surgery was performed using the Bausch and Lomb Stellaris vision enhancement system. A three-port pars plana vitrectomy was performed, and following core vitrectomy the posterior vitreous cortex was left attached. No triamcinolone was used for this manoeuver, in order to exclude a possible influence on the visual or morphological outcome.

In all patients who underwent ILM removal, it was obtained without the use of dyes. The membrane removal was extended over the whole edematous area to the vascular arcades, and was performed successfully in all eyes. Intraoperatively, panretinal argon endolaser coagulation was performed in eyes when needed for the treatment of severe non-proliferative or proliferative diabetic retinopathy. No focal or grid laser therapy was applied intraoperatively or within the follow-up period. Then, a careful examination of the retinal periphery by scleral indentation was carried out. Endolaser or cryocoagulation was performed for peripheral iatrogenic tears. No endotamponade was intended, but was necessary for peripheral tears.

Scissors delamitation was developed to permit removal of the diabetic membranes rather than segmentation into epicenters. Delamination means both blades of the scissors are introduced in the potential space between the membrane and the retina to several zones of adherence. Horizontal scissors, which are actually angled, were used for delamination at the inception of this technique. Curved scissors were developed to enable conformal delamination, greatly reducing the likelihood of the retinal damage with the scissors tips.[23]

There was no instance of endophthalmitis in this series.

Discussion

The most prevalent microvascular complication of diabetes mellitus is diabetic retinopathy.[6] An estimated 97% of insulin-dependent and 80% of non–insulin-dependent diabetics who have had the disease for at least 15 years have some degree of retinopathy. About 40% of insulin-dependent and 5% of non–insulin- dependent patients have proliferative diabetic retinopathy (PDR).[24] Pars plana vitrectomy (PPV) can improve anatomic features and functional visual acuity (VA) even for patients with advanced disease, and indeed has become a mainstay of therapy for complications of PDR.[6]

Proliferative diabetic retinopathy (PDR) is a major cause of blindness. Despite the recent development of sophisticated equipment for vitreous surgery and improvements in surgical techniques which significantly decrease the likelihood of blindness in patients with diabetes, many patients with PDR do not recover their vision. After vitrectomy for PDR, the surgical prognosis depends on the amount of residual proliferative tissues and iatrogenic retinal breaks. The surgical objective is to remove all proliferative membranes from the retina, and as a result, various surgical techniques have been proposed for PDR. The classic technique for PDR is a combination method of membrane segmentation[25,26] and delamination.[27] Our technique for PDR is referred to as the "en bloc excision technique" in cases with partial posterior vitreous detachment.[28,21] In this technique, the retrohyaloid space is entered in the quadrant of the chosen sclerotomy site and the delaminating instruments are inserted through a window in the posterior hyaloid membrane. In this manner, the adhesion sites around the vascular arcade are usually delaminated first. Surgical technique included standard three-port PPV, with combination of delamination and segmentation of gliotic tractional membranes using in some cases bimanual techniques.

The OCT technique was invented in the mid-1990s by Huang et al. and since then has become a well established diagnostic method in medicine[29], especially in ophthalmology. It is used mostly for imaging of human retinas in vivo through the iris of the eye, but also for examination of the geometry and diseases of the anterior chamber.

SD-OCT is likely to be used increasingly in standard practice as well as in clinical trials and research. The development of SD-OCT has allowed us to visualise foveal microstructures with unprecedented detail and to correlate them with visual function. Four highly reflective bands are clearly depicted in the outer retina on an SD-OCT image. The outermost line represents the RPE, and the innermost line represents the ELM, which consists of zonular adherence between photoreceptor inner segment and Muller cell processes.[30] A highly reflective band posterior to the ELM corresponds to the IS/OS junction of the photoreceptors. These microstructures are vulnerable to various macular pathologies, and therefore can serve as hallmarks for the evaluation of photoreceptor condition. Among them, the significance of the IS/OS junction has been best documented to date. The IS/OS junction reflects the integrity of the photoreceptor outer segments and its disruption has been proposed to lead to an impaired visual function in various diseases including PDR with ERM.

It is well known that some patients do not show sufficient improvement in visual acuity even after successful surgery. The deformation of the macula caused by the prolonged presence of the ERM before the surgery may explain the often inadequate improvement in the visual acuity, although such damage is difficult to detect by biomicroscopic examination. However, according to recent research using new tools, these controversies have been clarified. Using focal macular electroretinograms, Niwa and associates[31] reported that a reduction of the preoperative a wave, which originates mainly from the combined activity of the photoreceptors and off-bipolar cells, was correlated with the postoperative visual acuity. Various reports have shown favorable effects of pars plana vitrectomy (PPV) for treating DME with or without obvious abnormalities of the vitreoretinal interface.[32] Causes for this limited visual improvement include macular ischemia[33], photoreceptor dysfunction[34], and accumulated subfoveal hard exudates.[35]

Maheshwary et al. investigated spectral-domain optical coherence tomography (SD-OCT) in eyes with DME, and found a better correlation of the photoreceptor inner segment/outer segment (IS/OS) junction integrity with visual acuity than with central macular thickness (CMT).[36]

Several mechanisms might lead to photoreceptor changes. Breakdown of the BRB associated with diabetes might increase extravasation of the blood constituents (water, ions, proteins, lipids) and inflammatory cells and concomitantly exacerbate the pathomorphologic changes in the macula.[37]

Studies have shown that macular edema and thickness is the only one factor among many to affect visual acuity in patients with diabetic macular edema. Several prior studies using OCT had differing conclusions when correlating retinal thickness and visual acuity. The correlation coefficient between the retinal thickness and visual acuity was in a range of 0.28 to 0.73. Our current study showed a low correlation coefficient between retinal thickness and vision improvement. The reason for this poor correlation is likely to be the damage to the photoreceptor layer.[38]

Few data from randomized controlled trials are available concerning the therapeutic effect of vitrectomy and delamitation of membranes for proliferative diabetic retinopathy. Yanyali et al. observed a decrease in retinal thickness, without, however, significant improvement of visual acuity.[1] Vitrectomy has been reported to be effective in patients who have a thickened and taut posterior hyaloid membrane exerting traction on the retina.[39] Anatomical and visual outcomes are quite often unpredictable in vitrectomy for PDR. Anatomical results are often limited by the extent and degree of fibrous tissue, vitreoretinal adhesion,[40] and high rates of iatrogenic tears, which complicate the surgery.[41,42] No triamcinolone was used for the identification of vitreous remnants, in order to exclude any influence of drug remnants on the resorption of the macular edema. An incorrect intraoperative judgement of the posterior vitreous may have influenced the results. Even during surgery, it may be hard to distinguish a PVD from vitreoschisis, especially in patients with diabetic retinopathy.

Post-operative complications, including recurrent vitreous hemorrhage (VH), persistent detachment, whether tractional (TRD), rhegmatogenous (RRD), or combined TRD/RRD, iris neovascularization (INV) and neovascular glaucoma (NVG) are not uncommon and often lead to serious long-term visual impairment. We had a low rate of cataract formation post-operatively. This may be because many of our younger type I diabetic patients are phakic and possibly less prone to cataract progression, whereas many of our older type II diabetic patients were already pseudophakic. It is also well known that many patients will develop worsening lens opacification 1 to 2 years post-operatively. As some degree of post-operative haemorrhage occurs in virtually all cases, RD remains one of the principal complications of vitrectomy in diabetic patients. Persistent or recurrent haemorrhage is more likely the result of re-proliferation of fibrovascular tissue.[43] Reducing post-operative RDs significantly improves resultant VA[44], although we did not find TRD/RRD to be among the risk factors for poor visual outcome.

An important consideration with the growing literature regarding the IS/OS layer is how to evaluate disruption objectively and consistently. Currently, there are few data available addressing this issue. After a literature review, we found that most publications used trained observers to evaluate the IS/OS layer in a manner similar or identical to that of this study.[11-14]

Disruption of the IS/OS junction, namely, photoreceptor damage, as identified before surgery may be caused by mechanical traction induced by the ERM and may be irreversible even after successful removal of the ERM. ERM traction may cause irreversible mechanical plasmotomy of the photoreceptor cells.

It has been suggested that the integrity of the IS/OS layer could be an important predictor of vision in patients with retinitis pigmentosa, central serous chorioretinopathy, acute zonal occult outer retinopathy, branch retinal vein occlusion, and macular hole treated with vitrectomy.[10-13] Sakamoto et al. also showed a good correlation of photoreceptor layer integrity with visual acuity in a cross-sectional study of eyes with DME.[14]

In our study, pre-operative ELM integrity was a better predictor for vision improvement than CMT or IS/OS junction integrity. The ELM is not a true membrane, but is formed by a tangentially oriented series of adhesions, zonulae adherens, connecting apical processes of the Muller cells with inner segments of the photoreceptors. This layer may help to maintain the alignment and orientation of the photoreceptors. The ELM also acts as a diffusion barrier for the passage of proteins from the subretinal space to inner retina. Thus, the ELM is an OCT landmark of integrity of inner segments of the photoreceptors. Our study has shown that the integrity of this structure is the best predictor of vision improvement in eyes undergoing surgery for ERMs due to PDR.

Wakabayashi et al. demonstrated the significance of the ELM by showing the better correlation of the ELM with visual acuity in eyes that were repaired for retinal detachment.[18] Recently, Otani et al.[41] showed a close relationship of the photoreceptor IS/OS junction and ELM integrity with the visual acuity in eyes with DME. However, these studies did not evaluate these structures as predictive factors for visual improvement after treatment.[34]

Severe retinal edema or large cystic changes may reduce the visibility of outer retinal structures, including the outer plexiform layer or retinal pigmented epithelium (RPE). These false negatives should not be considered disruptions, but rather a shadowing effect.

It is unlikely that the ERM peeling maneuver directly affects outer retinal structures, and in our surgical experience we do not see any direct damage to ELM and IS/OS junction. Wakayabashi et al. showed that the eyes with damage to both IS/OS and ELM preoperatively did not achieve restoration of these structures after macular hole repair.[18] We also believe that the restoration of outer retinal structures may not be possible due to permanent damage to ELM caused by chronic edema. However, we certainly believe that vitrectomy for causative factors for DME may prevent further damage to the outer retinal structures; however, preoperative status of the outer retinal structures would predict the visual outcome after surgery.

Recently, ELM has been proposed as an adjunctive parameter to the IS/OS layer for assessing photoreceptor integrity especially in the eyes with complete loss of the IS/OS line.[16] In the present study, we found that the ELM became normalized before the outer foveal hyporeflective defects were resolved.

The reason for such a quick normalization of the ELM is not known. The ELM represents a series of junctional complexes between Muller cells and rod and cone photoreceptor cells. It might be that this junction is needed throughout the affected area before regeneration of photoreceptor outer segment can occur.

We also found no eyes with a disrupted ELM in the presence of an intact IS/OS line. Based on their findings, the integrity of the ELM seems critical for the potential restoration of the photoreceptor microstructure after retinal detachment, and we suggest that this integrity starts the healing process.

We also found that restoration of the ELM and IS/OS is important for the functional outcome. However, the simultaneous presence of ELM and IS/OS determined most of VA improvement, suggesting that a combined recovery of these anatomic layers is needed for a complete healing process.

Moreover, ELM integrity has been shown to have a better correlation with visual acuity than retinal thickness in eyes with cystoid macular edema secondary to venous occlusion, and in eyes with age-related macular degeneration.[16, 45]

Regarding the postoperative BCVA, our study showed that an intact IS/OS junction, as assessed before surgery, was strongly associated with better postoperative visual acuity and better visual recovery than a disrupted or irregular IS/OS junction, indicating that the preoperative integrity of the IS/OS junction may be a prognostic factor in patients undergoing ERM surgery. Preoperative assessment of the IS/OS junction may be an important procedure for precise determination of the indication for ERM surgery.

Limitation of our study is the absence of post-operative fluorescein angiography to identify macular ischemia and atrophy, which was found in other studies to be the most significant predictor of a poor outcome.[43, 46] A potential study weakness is that the assessment of the presence or absence of vitreomacular traction was made by the individual investigators based on their clinical judgment, without standardized criteria and without central reading center assessment or independent confirmation. However, the lack of centralized assessment may have more generalizability when applying these results to clinical practice, where there generally is no independent confirmation of vitreomacular traction. The lack of a concurrent control group also is a study weakness as well as the small numbers. and the short postoperative follow up period. Moreover, there is limited availability of preoperative OCT scans. Another limitation of this study include the subjective evaluation of the findings on SD OCT. Furthermore, the IS/OS junction may not be perpendicular to the direction of the incoming OCT beam accidentally, which appeared to weaken the backscatter. Development of OCT, enabling more objective examination of the IS/OS junction, is warranted for the future. In addition, although the SD-OCT images were analysed in a masked fashion, analysis was essentially subjective. More objective methodology for OCT assessment is warranted for the future.

In conclusion, our study underlines that examination with high-resolution optical coherence tomography allows three-dimensional visualization of the dynamics of epiretinal tractions that had not previously been obtainable. Epiretinal membranes can be clearly distinguished and their tractional effects can be traced through all retinal layers up to the pigment epithelium.[47]

The present study supports that recovery of the ELM and IS/OS is important for VA improvement. Additional new findings are that the ELM is the first structure to recover and an intact ELM seems to be necessary to achieve a complete restoration of the photoreceptor microstructure.

To the best of our knowledge, our study is the first to evaluate multiple OCT factors including CMT, IS/OS integrity, and ELM integrity as predictors of visual improvement after PPV for ERM delimitation due to PDR. Knowledge of which diabetic eyes are most likely to respond to treatment may be helpful for clinicians to plan therapy and for clinical trials design.

The integrity of the outer microstructure appears to be an important biomarker of visual performance following pars plana vitrectomy and membrane delamntation for PDR. The results also justify a larger randomized feasibility study to further characterize the efficacy and safety of this simple intervention.

In conclusion, the status of ELM on SD-OCT predicts vision improvement more accurately than the IS/OS junction and CMT in eyes after PPV for ERM delimitation due to PDR. We certainly believe that vitrectomy would prevent further damage to the outer retinal structures; however, preoperative status of the outer retinal structures would predict the visual outcome after surgery. High-resolution OCT should be the integral part of management for the better assessment of the outer retinal structures, which are important prognostic markers.

Prospective studies with a greater number of patients are required to obtain more developed approaches for evaluating the status of the photoreceptor layer and VA.

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