Published in final edited form as:

Am J Ophthalmol. 2010 July ; 150(1): 63–67.e1. doi:10.1016/j.ajo.2010.01.039.

The Association between Percent Disruption of the Photoreceptor Inner Segment/Outer Segment and Visual Acuity in Diabetic Macular Edema

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Introduction

Diabetic macular edema (DME) is a major cause of vision loss in patients with both insulin and non-insulin dependent Diabetes Mellitus.¹ It has long been accepted that macular edema can develop at all stages of retinopathy. Classically, patients have a gradual onset of blurry vision, and in more advanced cases, the macula becomes thickened and even cystic with profound visual loss. Due to the various clinical presentations of DME, specialized techniques such as spectral domain optical coherence tomography (SD-OCT) have become an important tool and an integral part of the diagnosis and management of this condition.¹

With the improved visualization of retinal architecture offered by OCT, many clinical studies have used this imaging technique to evaluate the effectiveness of various treatment modalities, and subsequent resolution of macular edema. Through these studies, authors have found that some eyes with DME have poor visual outcomes despite successful treatment and complete resolution of edema.¹ Moreover, a recent study by the Diabetic Retinopathy Clinical Research Network showed only a modest relationship between measured central retinal thickness and visual acuity in patients with DME.² The aforementioned observations imply that visual acuity is likely multi-factorial and maybe related to damage or disruption of the retinal architecture or direct photoreceptor damage.^{1,2}

The retinal photoreceptor layer can be accurately evaluated using SD-OCT by examining the integrity of the photoreceptor inner segment/outer segment (IS/OS) junction. Disruption of this hyper-reflective line just above the retinal pigment epithelium (RPE) reveals damage to the macular photoreceptors, and several recent studies highlight the value of IS/OS 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.^{3,4,5,6,7} In each of these diverse retinal pathologies, disturbance of the photoreceptors correlated with poor visual acuity or outcome.

Limited information is available regarding the association between the foveal IS/OS line and visual function in DME. One recent study retrospectively reviewed the relationship between the IS/OS layer on stratus OCT after the resolution of diabetic macular edema following pars plana vitrectomy (PPV). This paper reported that photoreceptor integrity is closely related to

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final visual acuity.¹ However, this study did not have the advantage of SD-OCT and was limited specifically to patients who underwent PPV for DME. In fact, the author states that a study using SD-OCT, with its ability to average multiple scans and reduce noise, would be beneficial to determine the relationship of photoreceptor status in the case of macular edema and visual outcome.¹

In this study, we examined the relationship between visual acuity and the integrity of the foveal photoreceptor layer in eyes with both previously treated and treatment-naïve DME by evaluating the IS/OS junction. We believe that similar to other macular pathologies, photoreceptor integrity is an important predictor of visual acuity in DME patients.

Methods

Records of patients with DME who underwent SD-OCT scanning were retrospectively reviewed. Only patients with evidence of edema clinically, FA leakage, or OCT thickening from DME were included in the study. Patients with macular edema from other causes including any history of uveitis, retinal detachment, recurrent ERMs, or vitreomacular traction were excluded. Additionally, patients with concurrent macular diseases such as macular degeneration, or patients with significant cataracts, graded above NO3 or NC3 according to the Lens Opacity Classification Scheme (LOCS III) were excluded.⁸

In total, 62 eyes with DME from 38 patients were identified for study evaluation. From the medical records of these patients best corrected visual acuity, using standardized calibrated ETDRS methodology, were recorded closest to the date of the SD-OCT scan. In addition information about patient age, gender, involved eye, insulin dependency, and any prior treatments for DME were recorded. Prior treatments included PRP, focal laser, PPV, triamcinolone injections, or bevaizumab injections. The status of the lens including lens grade if phakic or evidence of a posterior capsular opacity if pseudophakic was also noted.

Imaging

Diabetic macular edema was evaluated with scanning laser SD-OCT using either an OPKO-OTI (Toronto, Canada) or a Heidelberg Spectralis (Vista, CA). For each patient, horizontal and vertical SD-OCT images through the fovea were obtained for evaluation. Two experienced observers masked to visual acuities measured several variables. First, foveal thickness was calculated by using the calipers feature on the SD-OCT instrument with manual correction as needed.⁹ An average thickness value was obtained after reviewing both scans. Next, the photoreceptor IS/OS layer was evaluated 500 microns in either direction of the fovea. The IS/OS disruption was graded from 0–2. Grade 0 was given when an intact IS/OS layer was found, Grade 1 scored focal disruption of the IS/OS junction of 200 microns or less, and Grade 2 scored greater than 200 microns of disruption. Grades from each patient's horizontal and vertical scan were added to yield a global disruption scale. For example, a global disruption scale of 0 corresponded to no disruption in either scan, while a scale of 4 resulted from Grade 2 disruption horizontally and vertically. Lastly, the percentage of disruption along the IS/OS layer, again measured 500 microns in either direction from the foveal center, was recorded. The percentage disruption was averaged to generate a number between 0% (no IS/OS disruption) and 100% (total loss of the IS/OS layer in both horizontal and vertical scans). Figures 1 and Figure 2

Statistics

Visual acuity recorded as number of ETDRS letters was used as the outcome variable in univariate and multivariate analysis while tested predictors included central macular thickness, retinal volume, global disruption scale of outer retina, percentage disruption of the outer retina,

and history of previous treatments. In this study the majority of participating patients had both eyes in the study, therefore, the generalized estimating equation (GEE) was used to handle the intra patient correlation between the two eyes. All statistical analysis was performed using SAS version 9.2.

Results

62 eyes from 38 patients were studied including 12 women and 26 men, with a mean age of 67.9 years old. Mean visual acuity was 48.1 ETDRS letters ($20/50^{-2}$) and median was 53 ETDRS letters ($20/40^{-2}$).

Quality SD-OCT scans were obtained for each patient and none were eliminated from the study secondary to inability to grade the photoreceptor layer or due to a visually significant cataract. Mean macular thickness was 277 microns (median 251.5 microns) and mean macular volume was 312.2 microns (median 293.5 microns). 9 eyes out of the 62 eyes (14.5%) did not have a volume map at the time of OCT scan. This information was only available to us for patients who had undergone a set of horizontal raster scans allowing topographic and volume calculations by the SD-OCT. These patients were not incorporated into the multivariable analyses related to volume. 24 eyes out of the 62 eyes (38.7%) had no disruption while the remaining 38 eyes (61.9%) had a mean grade of disruption of 1.67 and a mean percentage disruption of 26.9%. 19 eyes (30%) had not had treatment while 43 eyes (69.8%) were treated with various methods.

Using number of ETDRS letters as the outcome measure, multivariate analysis was done using the generalized estimating equation to correct for inter eye associations within a given patient. Tested predictors for visual acuity included macular volume, percent disruption, and history of prior treatment. A statistically significant correlation between percent disruption and visual acuity was found with a p value of 0.0312 ($p < 0.05$). There was no significant difference in the treated versus untreated patients. The GEE analysis also found that visual acuity declines with increasing disruption of the IS/OS layer of the photoreceptors. The regression coefficient was -0.30 after adjusting for volume effect, indicating that for each percent increase of IS/OS disruption vision decreases by 0.3 ETDRS letters. (Figure 3) There was a strong trend suggesting a relationship between macular volume and visual acuity though borderline significance was found ($p = 0.07$) with a simple regression analysis.

Discussion

In 2007 The Diabetic Retinopathy Clinical Research Network published an article noting that a wide range of visual acuity may be observed for a given degree of retinal edema.¹⁰ If there is only a modest correlation between OCT measured central retinal thickness and visual acuity, what else is contributing to a patient's visual deterioration in the setting of edema? Speculation as to the reasons for limited visual acuity have been macular ischemia,^{11,12,13,14} photoreceptor dysfunction,^{15,16} and accumulated subfoveal hard exudates.⁸ Likely, the answer to this question is multi-factorial; however, the results of this study suggest that percentage disruption of the photoreceptor IS/OS layer on SD-OCT may be a significant predictor of visual acuity in patients with DME.

When analyzing statistical relationships between visual acuity and the predictors of macular volume, percent disruption, and history of prior treatment the only predictor that was statistically significant in multivariate analysis was percent disruption of the inner/outer segments. We elected to use macular volume instead of central retinal thickness as an indicator of edema severity. The Diabetic Retinopathy Clinical Research Network showed that total macular volume may be used when macular edema is more diffuse and represents a more global

measurement of macular edema.¹⁷ We also used percent disruption as our indicator of IS/OS disease and not a simple grading of presence or absence of disruption. We did this because preliminary statistical analysis indicated that these variables provided more information correlating better with outcomes.

The relationship between visual acuity and the percentage disruption held true in both treated and untreated eyes. Although treated patients that regained normal visual acuity were excluded from this study, the above data implies that whatever disruption of the IS/OS junction that might occur after laser treatments affect our disruption score to a minimal extent. The borderline significance found between macular volume and visual acuity was expected; however, our analysis of the predictive power of the IS/OS junction integrity is independent of other predictive parameters. We did find a relationship between macular volume and percent disruption of the IS/OS junction. Since IS/OS junction line integrity is an independent predictor of vision, clinicians can recall that for each percentage disruption a decrease by 0.33 ETDRS letters can be anticipated.

This study was limited by a small sample size and its retrospective nature. Patients also had different treatments for DME and the duration of edema for each patient at the time of the SD-OCT was variable. This mixture of patients does provide a broad overview of the spectrum of DME, and is more representative of the variability of clinical presentation. Another limitation of this study is that the SD-OCT scans were performed on two different machines (Heidelberg Spectralis and OPKO-OTI). Although there is some heterogeneity between the two scanners, both provide high resolution images.¹⁸

An important consideration with the growing literature regarding the IS/OS layer is how to objectively and consistently evaluate disruption. Currently, there is little data available addressing this issue. After a literature review, most publications used trained observers to evaluate the IS/OS layer in a manner similar or identical to this study.^{3,4,5,6,7,9} In an effort to substantiate grading reliability in this study all scans were re-graded in a masked fashion as described above. Kappa and the intraclass correlation coefficient (ICC) as a measure of reliability were computed. An ICC for the grading of the IS/OS was 0.9366 (95% CI 0.9335–0.96302), for percent disruption was 0.9415 (95% CI 0.9335–0.96302), and for the status of the IS/OS layer a kappa coefficient was 0.8307 (95% CI 0.6892–0.9723). These results show excellent repeatability, and suggest this method of IS/OS evaluation is an objective way to analyze photoreceptor status.

Several studies using OCT to evaluate photoreceptor IS/OS layer and visual acuity have shown that the status the outer retinal segment is significant in patients with retinitis pigmentosa, central serous chorioretinopathy, acute zonal occult outer retinopathy, branch retinal vein occlusion, and macular hole treated with vitrectomy.^{3,4,5,6,7} This study shows that in a heterogeneous population of patients with DME, not only is the status of IS/OS disruption important, but the percentage disruption is a predictor of visual acuity in a patient. It once again reinforces the importance of the IS/OS junction and its clinical relevance. Although intuitively accepted that increased photoreceptor damage leads to poor vision, this paper provides evidence for the above. In the future, studies will be needed to identify if different treatments help prevent or accelerate photoreceptor damage and if time of edema is related to percentage of photoreceptor damage.

In conclusion, we report that percentage disruption of the photoreceptor IS/OS layer evaluated by SD-OCT is a significant predictor of visual acuity in patients with DME. Assessing the status of the IS/OS junction on SD-OCT helps clinicians more accurately predict the visual outcome of patients with DME, and future studies will be needed to identify treatments that might help prevent photoreceptor damage in DME.

Acknowledgments

This study was supported by NIH grant EY07366 (WRF), an unrestricted grant from Research to Prevent Blindness (UCSD), and a Heed Ophthalmic Fellowship (SFO). The Authors indicate no financial support or financial conflict of interest. Involved in design (A.M, S.O, W.F); conduct of study (A.M, S.O, W.F); data collection (A.M, S.O, W.F); data management, analysis, and interpretation (A.M, S.O, W.F, L.C, F.M, R.Y); and manuscript preparation, review and approval (A.M, S.O, W.F, L.C, F.M, R.Y); This study was approved by the University of California San Diego Institutional Review Board, and was conducted in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. (HIPAA).

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Biography

Anjali S. Maheshwary, MD, received her medical degree from the Chicago Medical School with membership to Alpha Omega Alpha and completed a medical internship at the University of San Diego California. She is currently a resident at the Shiley Eye Center in La Jolla, California. Dr. Maheshwary is interested in pursuing a surgical retina fellowship with hopes of becoming a proliferative clinician-scientist.

Figure 1. Normal Retinal Layers Imaged by SD-OCT

Spectral domain OCT imaged with Heidelberg Spectralis. Note the improved delineation of each layer of the retina and the clearly distinguishable IS/OS junction. ILM=internal limiting membrane, RNFL: retinal nerve fiber layer, GCL: ganglion cell layer, IPL: inner plexiform layer, INL: inner nuclear layer, OPL: outer plexiform layer, ONL: outer nuclear layer, ELM: external limited membrane, IS/OS inner segment/outer segment junction, RPE: retinal pigment epithelium.

Figure 2. Examples of Photoreceptor IS/OS Layer Disruption on SD-OCT in Patients with Diabetic Macular Edema

Six SD-OCT Heidelberg Spectralis images through the fovea. The photoreceptor IS/OS layer was evaluated 500 microns in either direction of the fovea. The IS/OS disruption was graded from 0–2. Grade 0 was given when an intact IS/OS layer was found, Grade 1 scored focal disruption of the IS/OS junction of 200 microns or less, and Grade 2 scored greater than 200 microns of disruption. The percentage of disruption along the IS/OS layer, again measured 500 microns in either direction from the foveal center, was recorded. The percentage disruption was averaged to generate a number between 0% (no IS/OS disruption) and 100% (total loss of the IS/OS layer in both horizontal and vertical scans). The arrow head corresponds to the IS/OS junction: top right and left shows an intact IS/OS junction with Grade 0 disruption, the middle right and left shows a disrupted IS/OS junction with Grade 1 disruption, and the bottom right and left show a disrupted IS/OS junction with Grade 2 disruption

Figure 3. Relationship between Visual Acuity and Increasing IS/OS Disruption on SD-OCT in Patients with Diabetic Macular Edema

The scatter plot of patient visual acuity, expressed as the ETDRS letters read, over percentage of inner and outer segment disruption, judged from the spectral OCT, with a regression line. The graph demonstrates the decline of visual acuity with the increasing disturbance of the IS/OS layer of the photoreceptors. The regression coefficient was -0.30 after adjusting for volume effect, indicating that for each percent increase of IS/OS disruption vision decreases by 0.3 ETDRS letters.