Association of Disorganization of Retinal Inner Layers With Vision After Resolution of Center-Involved Diabetic Macular Edema

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IMPORTANCE Macular edema (ME) prognosis and treatment response vary according to the underlying abnormalities. Biomarkers of visual acuity (VA) improvement could influence management decisions in different types of ME.

OBJECTIVE To investigate whether disorganization of retinal inner layers (DRIL) and other spectral-domain optical coherence tomography (SD-OCT)–derived variables are associated with subsequent VA after ME resolution in both nondiabetic and diabetic ME.

DESIGN, SETTING, AND PARTICIPANTS A retrospective, longitudinal cohort study in which Snellen VA testing and SD-OCT macular imaging were performed, was conducted at a tertiary referral eye center for retinal diseases. The medical records of all patients with ME from December 1, 2010, to December 31, 2012, were reviewed. The date of the last follow-up was June 1, 2013. Participants included 55 patients (70 eyes) with center-involved ME that had resolved during an 8-month period. Patients were grouped based on the source of ME (diabetic vs nondiabetic). Exclusion criteria included significant media opacity interfering with good-quality SD-OCT image acquisition. Masked graders analyzed the central 1500-μm macular region for changes, including cysts, DRIL length and extent, and outer retinal layers disruption. Intrgrader and intergrader agreement Spearman rank correlation coefficients ranged from 0.70 to 0.93 for quantitative measurement, and κ values ranged from 0.88 to 1.00 for qualitative grading.

MAIN OUTCOMES AND MEASURES Visual acuity and morphologic changes measured on SD-OCT.

RESULTS In both groups, VA after ME resolution correlated with baseline VA. In diabetic ME involving a multivariable model including baseline VA and DRIL, total length was associated with subsequent VA as determined by a parameter estimate (PE) of 0.0003 (95% CI, 0.0000-0.0006) (P = .02). The VA change during the 8-month period, after adjusting for baseline VA, was best associated with DRIL change (PE, 0.0002 [95% CI, 0.0000-0.0003]; P = .04). Participants whose DRIL resolved, both early and late, showed improvement in their VA deficit at 8 months (least squares mean [SE], 41.3 [28.5] and 40.9 [37.5], respectively) compared with nonresolvers, whether inconsistent or persistent, whose VA worsened. After adjustment for baseline VA, eyes with persistent DRIL showed the largest difference in VA deficit compared with those with no baseline DRIL (~89.6 [27.2] vs 49.7 [19.6], respectively; P = .006).

CONCLUSIONS AND RELEVANCE The presence of DRIL at baseline and its resolution pattern may be associated with subsequent VA after resolution of center-involved diabetic ME.
Macular edema (ME) is a common complication of many retinal diseases, including diabetes mellitus, retinal vein occlusion, uveitis, and the Irvine-Gass syndrome. Macular edema is often associated with vision loss, although the mechanism is not firmly established. Alteration of the blood-retinal barrier, release of inflammatory mediators, and ischemic processes have been postulated as possible mechanisms for vision loss.

Spectral-domain optical coherence tomography (SD-OCT) provides high-resolution noncontact imaging of the retinal substructure that can be used as a quantitative tool to evaluate ME. There is a need to discover a priori the features that are associated with a patient’s potential for vision recovery and the likelihood of a positive treatment response. Spectral-domain OCT-derived factors, including photoreceptor layer integrity and outer nuclear layer involvement with cystoid spaces, were found to correlate better with visual acuity (VA) than was macular thickness in ME. Recent disorganization of retinal inner layers (DRIL) was found to correlate more consistently with VA in both active and resolved center-involved diabetic ME (DME).

The present study evaluated several SD-OCT factors, including DRIL, to assess whether they correlate with subsequent VA after resolution of ME in patients with and without diabetes mellitus. In addition, the resolution patterns of DRIL were investigated.

Participants received different treatment modalities; the aim of this study was not to determine the efficacy of a particular treatment. The study was designed to investigate whether factors associated with subsequent VA after resolution of ME would vary by the source of ME.

**Methods**

This retrospective, longitudinal cohort study was conducted at the University of Minnesota Eye Clinic. The study design was consistent with the tenets of the Declaration of Helsinki and was approved by the institutional review board of the University of Minnesota, with waiver of the need for patient consent.

Patient eligibility was determined by reviewing the medical records for their most recent clinic visit. The medical records of all patients with ME from December 1, 2010, to December 31, 2012, were reviewed. The date of the last follow-up was June 1, 2013. Patients were included only if they had center-involved ME documented by SD-OCT imaging (Spectralis; Heidelberg Engineering) that resolved during an 8-month period with or without treatment. Study participants had to be at least 18 years or older with VA in the study eye with a Snellen measurement of 20/50 or better. The diagnosis of center-involved ME was defined as a baseline SD-OCT central subfield thickness (CST) of 300 μm or more for men and 305 μm or more for women. Patients were divided into 2 groups according to the source of the edema. Group A (43 eyes) comprised eyes with center-involved DME; group B (27 eyes) comprised eyes with ME from other causes. These other causes included central retinal vein occlusion (4 eyes), branch retinal vein occlusion (9 eyes), uveitis (7 eyes), cystoid macular edema following cataract surgery (5 eyes), epiretinal membrane with vitreomacular traction (1 eye), and idiopathic ME (1 eye). All patients in group A had a documented history of diabetes mellitus type 1 or 2 as defined by the American Diabetes Association. Group B patients had an established retinal diagnosis as determined by a retina specialist (including F.J.v.K. and D.D.K.) as well as documented center-involved ME. Exclusion criteria included significant media opacity, such as dense cataract or vitreous hemorrhage; poor-quality images; and patients’ inability to cooperate with examination or image acquisition of high-quality SD-OCT images.

All images were acquired by certified photographers. A 20° × 15° (5.9 × 4.4-mm) area centered on the fovea was scanned with 19 B-scans and 16 automated real-time means per scan on the high-resolution mode. The scans obtained at the baseline examination were registered and locked to a reference image to ensure that the same location was scanned at each subsequent visit. In patients for whom a reference image was not obtained, follow-up images were overlaid on the baseline scans (Adobe Photoshop CS6; Adobe Systems Inc) to ensure analysis of the same location.

Standardized study forms were used to record baseline and follow-up data at 1, 3, 6, and 8 months (or the closest visit if the exact interval was not available). Data recorded included age, sex, race/ethnicity, duration of diabetes (for group A), hemoglobin A1c level recorded from the most recent testing (group A), and the cause of ME (group B). Patients with missing follow-up visits were included in the study, although the values for the missing fields were not included in that specific correlation analysis. Records of all patients included in the study were reviewed, and their VA, CST, and all other subfield thickness values were recorded. The logMAR VA was calculated and used for comparison and statistical analysis to allow for arithmetic rather than geometric evaluation of VA.

**Image Analysis**

Two graders (S.H.R. and A.Z.S.) independently analyzed the SD-OCT images at baseline. Intergrader reliability was assessed on a random subsample of 70 images. In addition, each grader was asked to reanalyze a random sample of 10 previously graded images to calculate intragrader reliability. Spearman rank correlation coefficients ranged from 0.70 to 0.93 (0.80-0.88 for DRIL measurements, 0.83-0.93 for outer retinal layer disruptions, and 0.70-0.80 for cyst measurements). The κ values ranged from 0.88 to 1.00 regarding the presence or absence of visible cone outer segment tips, hard exudates, subretinal fluid, and epiretinal membrane. Image analysis was assessed on a random subsample of 70 images. In addition, each grader was asked to reanalyze a random sample of 10 previously graded images to calculate intragrader reliability. Spearman rank correlation coefficients ranged from 0.70 to 0.93 (0.80-0.88 for DRIL measurements, 0.83-0.93 for outer retinal layer disruptions, and 0.70-0.80 for cyst measurements). The κ values ranged from 0.88 to 1.00 regarding the presence or absence of visible cone outer segment tips, hard exudates, subretinal fluid, and epiretinal membrane. Image analysis was assessed on a random subsample of 70 images. In addition, each grader was asked to reanalyze a random sample of 10 previously graded images to calculate intragrader reliability. Spearman rank correlation coefficients ranged from 0.70 to 0.93 (0.80-0.88 for DRIL measurements, 0.83-0.93 for outer retinal layer disruptions, and 0.70-0.80 for cyst measurements). The κ values ranged from 0.88 to 1.00 regarding the presence or absence of visible cone outer segment tips, hard exudates, subretinal fluid, and epiretinal membrane.
Conducted using the protocol described by Sun et al with few modifications, as summarized below.

For each study eye, the foveal scan was identified as the central scan of the grid passing through the foveal area on the infrared image. Two scans immediately above and below the foveal scan were included in the analysis for a total of 5 scans (eFigure 1 in the Supplement). An overlay measuring 1500 μm was placed over the center of each of the 5 scans; this area was the region included in the analysis. Image analysis was then performed (Adobe Photoshop CS6; Adobe Systems Inc). The graders were masked to all clinically relevant information. Observations were entered into standardized data collection forms (Excel; Microsoft Corp). The graders were masked to the inner retinal layer boundaries within the central 1500-μm region. In addition to measuring the horizontal length of all features within each scan, each feature was given a score from 0 to 5 based on the number of scans in which that feature was present (the vertical extent). For patients with no or minimal DRIL (eFigure 3A in the Supplement), the individual retinal layer thicknesses were measured (MatLab software, version 2013b; MathWorks Inc) with manual correction as needed (eFigure 3B in the Supplement). In addition, changes in the horizontal length of DRIL, ELM disruption, and EZ disruption over time were recorded and correlated with changes in VA and CST.

### Statistical Analysis

The associations between baseline-measured SD-OCT variables, baseline VA, and VA after resolution of ME were explored in both groups. In addition, the correlation between changes in the measured SD-OCT variables and changes in VA during the study period was evaluated. Bivariate linear regression analyses were used to evaluate the correlation of each SD-OCT variable with the baseline and subsequent VA after edema resolution. Generalized linear mixed models with random effects were used to adjust for correlations between eyes from the same individual. Statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc).

### Results

Seventy eyes of 55 study participants were included. Based on the cause of the ME, patients were divided into 2 groups (A and B). Separate analyses were done for each group. A summary of patient and study eye characteristics is shown in the Table and in eTable 1 in the Supplement, respectively.

#### Group A: DME

Bivariate analyses for each baseline OCT variable and baseline logMAR VA showed an association with CST, total DRIL length, EZ disruption length, and presence of subretinal fluid, with parameter estimate (PE) values (reported with 95% CI) of 0.0010 (0.0001-0.002), 0.0003 (0.0001-0.0005), 0.0003 (0.0001-0.0005), and 0.0655 (0.0008-0.13), respectively (P = .03, P = .006, P = .002, and P = .031, respectively). The logMAR VA after edema resolution was associated with baseline logMAR VA, total length and total extent of DRIL, ELM disruption, and EZ disruption (PE [95% CI], 0.95 [0.64-1.24], 0.0005 [0.0003-0.0008], 0.065 [0.002-0.12], 0.0004 [0.0002-0.0006], and 0.0004 [0.0002-0.0006], respectively (P = .001, .0003, .0005, .0005, and .0005, respectively).
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Figure 2. Visual Acuity (VA) and Center Subfield Thickness (CST) in Disorganization of Retinal Inner Layers (DRIL) Groups

Table 2. No. of eyes

<table>
<thead>
<tr>
<th></th>
<th>With baseline DRIL</th>
<th>Lacking baseline DRIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes</td>
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<td>28</td>
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<tr>
<td>P value</td>
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<td>.02</td>
</tr>
<tr>
<td>Adjusted for VA</td>
<td>.07</td>
<td>.15</td>
</tr>
</tbody>
</table>

Graphs show mean (SE) values. A, Comparison of eyes with baseline DRIL vs eyes lacking baseline DRIL. Eyes with baseline DRIL had poorer VA. B, Center subfield thickness resolved in eyes with and without baseline DRIL.

Figure 3. Correlation Between Visual Acuity (VA) Change vs Spectral-Domain Optical Coherence Tomography Variable Changes in Eyes With Diabetic Macular Edema and Disorganization of Retinal Inner Layers (DRIL) at Baseline

The correlation between the change in logMAR VA with that in center subfield thickness (CST), DRIL, ellipsoid zone (EZ), and external limiting membrane (ELM) disruption in individuals with diabetic macular edema (group A, 28 eyes). P values were adjusted for baseline VA. Solid boxes indicate parameter estimate (PE); error bars, 95% CI.

P = .001, P = .046, P = .003, and P = .003, respectively) (eTable 2 in the Supplement). In a multivariate model including baseline logMAR VA, the only OCT variable that continued to be associated with subsequent logMAR VA was total length of DRIL (PE [95% CI], 0.0003 [0.00006]; P = .03 ) (Figure 1).

Eyes with DRIL at baseline had a poorer initial VA compared with eyes lacking DRIL at baseline (mean [SE] logMAR VA, 0.5 [0.06] vs 0.24 [0.08]; P = .008). This difference remained significant for all visits. The logMAR VA for the 2 groups at 8 months after resolution of ME was 0.45 (0.06) vs 0.16 (0.08); P = .003. The difference in means after adjusting for baseline VA was significant (P = .04) (Figure 2A). When we compared baseline CST between both groups, there was no significant difference (mean [SE], 376 [25] μm vs 424 [19] μm; P = .11), and the groups demonstrated similar resolution at 8 months (286 [25] μm vs 278 [19] μm; P = .80) (Figure 2B).

In eyes with baseline DRIL, the change in logMAR VA was associated only with the change in DRIL length after adjusting for baseline VA (PE [95% CI], 0.0002 [0 to 0.0003]; P = .04). There was no association with the change in CST, EZ disruption, and ELM disruption (PE [95% CI], 0.00002 [−0.0002 to 0.0002], 0.00005 [0 to 0.0001], and 0.00008 [0 to 0.0002] (P = .10, P = .22, and P = .10, respectively) (Figure 3).

DRIL Resolution Patterns in DME

Representative OCT images illustrating the different DRIL resolution patterns in eyes with and without baseline DRIL throughout the course of the study are shown in eFigure 4 in the Supplement. Four distinct DRIL resolution patterns were noted in patients with DME (group A):

• Early resolvers: eyes that showed resolution of more than 50% of the baseline DRIL length at the first or second visit and remained stable or improved by the end of the study.
• Late resolvers: eyes that showed resolution of more than 50% of the baseline DRIL length in the third or fourth visit and remained stable or improved by the end of the study.
• Inconsistent: eyes that showed resolution of more than 50% of the baseline DRIL length at any point with subsequent recurrence.
• Persistent: eyes that never showed resolution of more than 50% of the baseline DRIL length at any time point during the study despite resolution of DME.

The percentage reduction of VA deficit at 8 months (defined as the change in VA letter score on Snellen examination from baseline to 8 months divided by baseline VA deficit and multiplied by 100) was calculated. Eyes with early and late resolution of DRIL showed greater positive reduction in VA deficit...
Figure 4. Visual Acuity (VA) Prognosis in Different Disorganization of Retinal Inner Layers (DRIL) Resolution Patterns

The difference between the percentage reduction in VA deficit at 8 months in each of the 4 DRIL resolution patterns and that in eyes with no baseline DRIL adjusting for baseline VA. The patterns are described in the DRIL Resolution Patterns in DME subsection of the Results section of the text. Circles indicate means; error bars, SE.

<table>
<thead>
<tr>
<th>Group</th>
<th>No Baseline DRIL</th>
<th>Early Resolvers</th>
<th>Late Resolvers</th>
<th>Inconsistent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes</td>
<td>15</td>
<td>7</td>
<td>4</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

The mean baseline CST, DRIL length, DRIL extent, and total cyst area were higher in the nonresolvers (both persistent and inconsistent) compared with the resolvers (both early and late) (LS mean [SE], 431.20 [36.7] vs 402.85 [32.4], 788.33 [76.7] vs 426.63 [93.1], 3.64 [0.3] vs 2.63 [0.4], and 669.54 [154.5] vs 430.27 [191.0], respectively). However, the greatest difference was noted in baseline total DRIL length (P = .03) (Figure 5 in the Supplement). The significance of this result is discussed further in the Discussion section.

**Group B: Non-DME**

The logMAR VA after resolution of ME was highly associated with baseline logMAR VA (PE [95% CI], 0.581 [0.162-0.998]; P = .02). None of the OCT variables measured correlated with either baseline or logMAR VA after resolution of ME (eTable 3 in the Supplement).

**In Both Groups: DME and Non-DME**

Retinal segmentation was performed in eyes with no baseline DRIL in both diabetic and nondiabetic eyes. There was no statistically significant difference between the thicknesses of any of the layers in either the diabetic or nondiabetic eyes after adjusting for the CST (eFigure 6 in the Supplement).

**Discussion**

This study demonstrated that, for center-involved DME, strong correlations exist between baseline DRIL and subsequent VA after ME resolution. This correlation remained after adjusting for baseline VA. In addition, VA change over time was best associated with DRIL change over time, even after including baseline VA in the model. Moreover, the pattern of DRIL resolution appears to be predictive of subsequent VA and the likelihood of improvement. The same correlation between DRIL and VA did not exist for eyes with center-involved non-DME. There is cause to believe that DME may differ from ME due to other causes. For example, functional improvement is often seen after improvement of ME associated with inflammatory conditions, such as uveitis and postcataract cystoid ME. However, resolution of DME is not always associated with improvement in vision, and paradoxical responses can exist.

In the present study, baseline VA was the only predictor that highly correlated with subsequent visual outcome in both DME and non-DME. Similar findings were reported by the Diabetic Retinopathy Clinical Research Network13 and in the Standard Care vs Corticosteroid for Retinal Vein Occlusion study14 for retinal vein occlusion.

Coscas and Gaudric15 monitored a similar cohort of patients with DME and non-DME for 3 to 5 years. They concluded that visual prognosis largely depends on the cause of ME. They reported that the presence of cystoid spaces at baseline was associated with poorer vision and that the absence of a central cyst was associated with a better visual outcome.

Several studies demonstrated that photoreceptor layer integrity was associated with VA in central retinal vein occlusion. The smaller number of eyes with central retinal vein occlusion in our cohort (4 eyes) precluded a separate subset analysis. Thus, similar associations were not found in our study.

A similar correlation between VA after DME resolution and baseline DRIL has been reported. In our study, we further identified multiple resolution patterns of DRIL that correlated differently with reduction in VA deficit despite resolution of the ME in all cases. Eyes with a persistent or inconsistent pattern of DRIL resolution (nonresolvers) had less reduction of their VA deficit compared with eyes whose DRIL resolved early or late and did not recur (resolvers). In fact, resolvers had a reduction of their VA deficit similar to that in participants with no baseline DRIL. The baseline DRIL length was higher in the nonresolvers (persistent and inconsistent) compared with the resolvers (early and late). These patterns may explain why the baseline DRIL length and the percentage of change over time can predict VA after ME resolution. Eyes with higher baseline DRIL are more likely to fall into the nonresolvers group. Conversely, eyes with lower baseline DRIL may fall into the resolvers group.

It is not known exactly what DRIL demonstrated on OCT images may represent histologically. The images may indicate tissue that is damaged or less likely to recover. Pelosini and colleagues18 reported a strong correlation between subse-
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ORIGINAL INVESTIGATION RESEARCH

Study supervision: Soliman, Tokarev, van Kuijk, Koozekanani.

Administrative, technical, or material support: Statistical analysis: Radwan, Soliman, Koozekanani.

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Quent VA and the volume of tissue remaining within the 2 plexiform layers. They postulated that this tissue might represent viable connections between the photoreceptor and ganglion cell layers. Their study included 106 eyes with DME and only 23 eyes with ME due to other causes. However, they did not perform a separate analysis for the nondiabetic eyes. Thus, their conclusions were primarily derived from the DME eyes included in the study. These findings may support our results showing that increased DRIL length, and thus possibly less viable remaining tissue, is associated with worse visual outcomes in DME.

It is possible that some of the associated factors investigated in the present study were not sufficiently powered to detect a subtle association with subsequent VA. However, DRIL length and the patterns of DRIL resolution showed clear associations with subsequent VA for DME. This work expands our understanding of the significance of DRIL in center-involved DME by showing the effect of different resolution patterns on VA recovery, as well as the effects of DRIL in other abnormalities. To our knowledge, we are the first group to report the correlation between DRIL resolution patterns and VA after resolution of DME. Limitations of this study include those inherent to its retrospective nature. The study failed to detect any association between OCT variables and subsequent VA in eyes with non-DME; this failure may have occurred because we included multiple abnormalities in this group with no separate analysis performed for each underlying abnormality.

**Conclusions**

Prospective studies are required to validate our results and evaluate whether the resolution patterns of DRIL will continue to correlate with VA over longer follow-up periods. Furthermore, the association between DRIL resolution patterns and macular ischemia, observed on fluorescein angiography, is another area that needs to be explored. A study is currently under way to evaluate the presence of such an association.

**REFERENCES**