

Current Understanding of the Pathophysiology of Disorganization of the Retinal Inner Layers and Relationship to Visual Acuity

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ABSTRACT

In clinical practice, visual acuity (VA) outcomes after treatment may be associated with multiple optical coherence tomography (OCT) variables including central subfield thickness (CST), ellipsoid zone (EZ) disruption, epiretinal membrane, vitreoretinal interface abnormalities, and disorganization of retinal inner layers (DRIL). Since CST has shown only a modest correlation with VA, additional OCT-based prognostic factors can be useful. DRIL is an OCT derived variable that may be a prognostic factor. Ischemia and inflammation may explain the pathogenesis of DRIL but are not well understood. Visual transmission pathways may be interrupted and affect VA. This review highlights the various studies on DRIL and VA, specifically within diabetic macular edema (DME), diabetic retinopathy, retinal vein occlusion, and Uveitic macular edema (ME). Based on the current literature review, DRIL's prognostic value in predicting VA is not well elucidated but shows potential to be utilized in clinical practice.

Keywords: Disorganization of inner retinal layers, Macular edema, Retinal vein occlusion, Visual acuity

INTRODUCTION

Macular edema (ME) occurs secondary to damage or inflammation of the endothelium of the small blood vessels of the retina and interruption of the tight junctions resulting in increased vascular permeability and pooling of fluid in the macula. It can occur as a consequence of diabetic retinopathy (DR), ocular surgeries, neovascular age-related macular degeneration, retinal vein occlusion (RVO),

and uveitis amongst other less common entities. ME can cause symptomatic distortion of vision and decreased visual acuity (VA) that can become permanent if left untreated. Therefore, biomarkers that can aid in predicting VA improvements with the treatment of ME would be important for clinicians.^[1]

The use of optical coherence tomography (OCT) in the setting of ME has allowed further studies to identify if predictive factors exist, and if so, which factors could assist in predicting VA outcomes in the treatment of ME. Perhaps the most commonly studied and followed OCT variable is central subfield thickness (CST), although there is an only modest correlation between CST and VA in diabetic ME (DME) and with a high degree of variability.^[2,3] A prospective cross-sectional study performed by the DRCR in 2007 included 251 eyes of 210 DME patients and evaluated the relationship between CST and VA. This study also reported a

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moderate correlation between CST and VA changes ($r = 0.44$) and found that retinal thickness accounts for up to 27% of the variability in measured VA suggesting that factors other than CST may have greater importance as determinants of VA.^[3] A review paper written by Keane and Sadda on OCT in the diagnosis and management of DR reported that CST has been rapidly embraced in clinical and research settings despite limited evidence of correlation with VA.^[4]

Given the ease of identifying and obtaining CST, it still demonstrates limitations in determining VA; therefore, other aspects of OCT have been investigated to determine their viability as biomarkers for VA and treatment outcomes, including ellipsoid zone (EZ) disruption, epiretinal membrane (ERM), vitreoretinal interface abnormalities, and disorganization of retinal inner layers (DRIL). A review paper on multimodal imaging in DME by Acon and Wu reported that OCT variables such as EZ integrity, ERM, CST, and DRIL have been evaluated as prognostic factors in VA.^[5]

Studies have determined that there is only a moderate correlation between VA and EZ integrity or ERM.^[6,7] Maheshwary *et al.* studied 38 DME patients (62 eyes) in a retrospective case series exploring the correlation between EZ integrity and VA in DME. They reported a moderate Spearman correlation coefficient (r) between EZ integrity and VA in DME ($r = -0.30$, $P = 0.0312$). Wong *et al.* studied a prospective cohort of 89 DME patients (104 eyes) who received ranibizumab for the treatment of DME. They reported the effects on vitreoretinal interface abnormalities and concluded that there is a statistically significant but weak correlation between increasing degrees of ERM and VA decline ($R^2 = 0.15$, $P < 0.01$).^[7]

A retrospective cross-sectional study including 13 eyes of 9 patients with existing or resolved DME was a first to study the correlation between DRIL and VA.^[8] This early study also reported that DRIL extent $>500 \mu\text{m}$ in a $1000 \mu\text{m}$ foveal scan specifically had VA loss despite edema resolution. Since then, an increasing number of follow-up studies evaluating DRIL's prognostic value and association with VA have been performed.^[9-12] A number of these studies have shown promise for the use of DRIL as an OCT parameter with stronger correlations with VA outcomes than CST. Herein, the aim of this review is to summarize the current understanding of the pathophysiology of DRIL and its relationship to VA.

DEFINING DRIL

The normal laminar inner retinal structure consists of the internal limiting membrane, retinal nerve fiber layer, ganglion cell layer, inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and the outer nuclear layer. DRIL is defined as the horizontal extent in microns for which any boundaries between the IPL, INL, and OPL could

not be identified on OCT scan.^[9,10] The presence of DRIL on OCT is assessed independently, and not graded differently in the presence of other spectral domain optical coherence tomography (SDOCT) pathologies including but not limited to the presence of intraretinal cysts or retinal edema.^[9] There has not been a uniform methodology between the studies to calculate the severity level of DRIL based on the horizontal extent and the horizontal length at which an eye is considered to have DRIL.

The pathogenesis of DRIL and its relationship to VA is not fully understood. The inability to segment inner retinal layer boundaries may represent an anatomical interruption in the visual transmission pathway secondary to the destruction of cells within the inner retinal layers possibly disrupting neural transmission from photoreceptors to the retinal ganglion cells.^[9] Pelosini *et al.* studied a cohort of 81 diabetic and uveitic patients (129 eyes) to determine if the volume of retinal tissue between the inner and outer retina layers could be useful as an indicator of VA. They reported that CST predicted only 14% of VA changes. However, they observed that changes consistent with DRIL predicted 80% of VA changes.^[13] These authors suggested that the neurosensory retina has a degree of elasticity that if exceeded, leads to snapping of bipolar axons compromising the visual transmission pathways. This could explain why the VA may not recover completely following the resolution of cystoid ME (CME).

It has also been hypothesized that ischemia may instigate the development of DRIL and compromise the inner retinal circulation as it has been observed in DME, RVO, acute retinal necrosis, and blunt ocular trauma.^[14-17] Nicholson *et al.* reported a positive association of macular capillary nonperfusion on fluorescein angiography (FA) with areas of DRIL in eyes with DR.^[14] Balaratnasingam *et al.* reviewed eyes with DR and RVO and found a correlation between DRIL length and the foveal avascular zone (FAZ) on OCT angiography.^[18] Finally, inflammation has been implicated in the development of DRIL as well. Inflammation and secondary vascular leakage have been associated with chronic inner retinal neurodegeneration.^[19] The relative contribution of ischemia and inflammation to the pathogenesis of DRIL is not clear, and further studies are needed to understand DRIL pathophysiology.

DRIL IN DME

DRIL has demonstrated prognostic value in predicting VA changes in current or resolved DME (Table 1).^[9,10] Sun *et al.* reported in their bivariate analysis that greater baseline DRIL extent was associated with worse baseline VA ($0.04/100 \mu\text{m}$, 95% confidence intervals [CI] $0.02-0.05$, $P < 0.001$).^[9] In multivariate modeling, only greater baseline DRIL extent was associated with worse baseline VA when accounting for CST. Increasing DRIL extent over 8 months was also

Table 1: DME studies table

Author	Type of study	Number of patients	How DRIL was measured	Focus of study	Length of follow-up	Major findings
Sun <i>et al.</i>	Retrospective longitudinal cohort study	96	DRIL extent was measured from 7 scan OCT images (3 B-scans immediately above and below the foveal center) by an experienced grader masked to VA	DRIL's predictive value for VA in DME	8 months	Baseline DRIL extent was highly associated with baseline VA 4 month DRIL extent changes were highly predictive of 4-month VA changes
Das <i>et al.</i>	Cross-sectional observational case series	80	DRIL was measured in the same way as in Sun <i>et al.</i> except there were two graders instead of one	Potential of various markers in predicting DR progression and VA gain in DME patients	None	DRIL, RTF, MRT, ELM disruption, and EZ disruption had a statistically significant association with baseline VA
Shikari <i>et al.</i>	Cross-sectional study	49	Same as Sun <i>et al.</i>	Association between VA and DRIL extent and location in DME	None	Greater horizontal DRIL extent was associated with worse VA even when adjusting for CST
Radwan <i>et al.</i>	Retrospective longitudinal cohort study	55	DRIL extent was measured from 5 scan OCT images (2 B-scans immediately above and below the foveal center) by two experienced graders masked to VA	Association between DRIL and VA after resolution of ME in patients with nondiabetic ME or DME	8 months (center-involved ME that resolved within an 8 months period)	In univariate analysis, VA after edema resolution was associated with baseline VA, horizontal DRIL extent, ELM disruption, and EZ disruption In multivariate analysis, horizontal DRIL extent was the only remaining variable associated with VA after edema resolution
Santos <i>et al.</i>	Prospective analysis	18	Same as Radwan <i>et al.</i>	Effects of anti-VEGF treatment on various OCT measurements in DME patients	1 week	Baseline CRT and sites of LOR were significantly associated with VA changes after 1 week of anti-VEGF treatment Baseline DRIL and EZ were not associated with VA changes after 1 week of anti-VEGF treatment

(Contd...)

Table 1: (Continued)

Author	Type of study	Number of patients	How DRIL was measured	Focus of study	Length of follow-up	Major findings
Fickweiler <i>et al.</i>	Prospective 6-month multicenter randomized controlled trial	119	The horizontal DRIL extent was measured as a percentage of the 1-mm central zone of the fovea (only considered if DRIL >50% of the 1-mm zone)	Association between DME and VA in patients in Netherlands receiving monthly injections of bevacizumab or ranibizumab for 6 months	6 months	Baseline DRIL and SRD were significantly associated with VA changes at 6 months

DRIL: Disorganization of retinal inner layers, VA: Visual acuity, DME: Diabetic ME, DR: Diabetic retinopathy, RTF: Retinal thickness at the fovea, MRT: Maximal retinal thickness, ELM: External limiting membrane, EZ: Ellipsoid zone, CST: Central subfield thickness, OCT: Optical coherence tomography, CRT: Central retinal thickness, LOR: Lower than normal optical reflectivity, VEGF: Vascular endothelial growth factor, SRD: Serous retinal detachment

associated with VA worsening over 8 months (0.03/100 μm , 95% CI 0.02–0.05, $P < 0.001$). None of the baseline OCT variables were significantly related to VA changes from baseline to 8 months. However, multivariate linear regression demonstrated that VA reduction in 8 months was significantly correlated with 4-month DRIL increase ($P = 0.004$) and CST increase ($P = 0.03$). When using a model generated from the 4-month DRIL extent changes that account for VA changes from baseline to 4 months, the mean difference between predicted and actual change was 0.10 logMAR VA ($r = 0.80$).

Radwan *et al.* reported in bivariate analyses comparing baseline VA to various OCT variables at baseline.^[10] CST, horizontal DRIL length, EZ disruption length, external limiting membrane (ELM) disruption length, and presence of subretinal fluid showed statistically significant associations ($P = 0.03$, $P = 0.006$, $P = 0.002$, $P = 0.007$, and $P = 0.031$, respectively). VA after edema resolution was associated with baseline VA, total length extent of DRIL, ELM disruption, and EZ disruption ($P = 0.001$, $P = 0.001$, $P = 0.046$, $P = 0.003$, and $P = 0.003$, respectively). In a multivariate model including baseline VA, the only OCT variable that continued to be associated with subsequent VA was total horizontal DRIL length (0.0003/ μm , 95% CI 0–0.0006, $P = 0.03$).

Das *et al.* reported that DRIL had a high degree of correlation with VA (–4.6 early treatment DR study [ETDRS] letters per 100 μm , 95% CI –8.0 to –1.3 letters, $r = -0.53$, $P = 0.009$).^[20] Other values with statistically significant correlations include retinal thickness at the fovea (RTF) ($r = -0.27$, $P = 0.005$), maximal retinal thickness (MRT) ($r = -0.4$, $P = 0.01$), ELM disruption ($r = -0.41$, $P = 0.01$), and EZ disruption ($r = 0.44$, $P = 0.003$).

Shikari *et al.* reported that greater average extent of DRIL across the 7 B-scans of each eye was significantly related to

worse VA ($P = 0.005$).^[21] This relationship was significant even when adjusting for CST.

Fickweiler *et al.* reported in a multivariate analysis that serous retinal detachment (SRD) and DRIL were statistically significantly associated with a change in VA at month 6 ($P = 0.01$ and $P < 0.05$, respectively).^[22] The frequency of injections in these patients was consistent in this study compared to other studies.

Despite multiple study results supporting a correlation between VA and DRIL in DME, other studies such as one prospective cross-sectional study by Santos *et al.* suggest that DRIL does not have a predictive value for VA.^[23] After the 1st week of anti-vascular endothelial growth factor (VEGF) treatment, the participants in Santos's study were split into three groups (good responders [>8 ETDRS letters gained], moderate responders [>5 and <8 ETDRS letters gained], and poor responders [<5 ETDRS letters gained or loss of VA]). The baseline central retinal thickness (CRT), sites of lower than normal optical reflectivity (LOR), horizontal DRIL extent, and horizontal EZ disruption were measured for each of the three groups. Only the CRT and LOR had statistically different baseline values for these groups ($P = 0.026$, $P = 0.026$, respectively) while DRIL and EZ baseline values for these groups were not statistically different ($P = 0.686$, $P = 0.600$).

DRIL IN DR

The relationship between DRIL and VA in DR has been analyzed in some studies (Table 2). Joltikov *et al.*, in a cross-sectional study, studied the association between DRIL and retinal function in 75 patients with and without non-proliferative DR, without DME.^[24] In this study, 57

Table 2: DRIL in diabetic retinopathy studies table

Author	Type of study	Number of patients	How DRIL was measured	Focus of study	Length of follow-up	Major findings
Joltikov <i>et al.</i>	Cross-sectional study	75	Same as Sun <i>et al.</i>	Association between DRIL and retinal function in diabetic patients with and without nonproliferative diabetic retinopathy	None	Diabetic subjects with DRIL have reduced retinal function (reduced VA) and have decreased retinal thickness
Onishi <i>et al.</i>	Cross-sectional study	20	Same as Sun <i>et al.</i>	Examine the relationship between ischemia and DRIL in patients with DRIL and diabetic retinopathy	None	Regions of the retina with DRIL demonstrated significant perfusion deficits compared with adjacent control areas without DRIL

DRIL: Disorganization of retinal inner layers, VA: Visual acuity

participants with diabetes mellitus and 18 healthy controls underwent OCT scans and their demographic data were recorded. DRIL was identified in 9 of the 57 diabetic patients and none of the healthy control patients. The DRIL subjects had a higher body mass index and longer duration of diabetes than diabetic patients without DRIL ($P = 0.03$ and $P = 0.009$, respectively). The patients with DRIL had reduced ETDRS VA ($P = 0.003$). In addition, these patients had a 6% reduction in total retinal thickness ($P = 0.03$) and a 7% reduction in inner retinal thickness ($P = 0.05$) compared to the healthy control patients and diabetic patients without DRIL, which suggests that DRIL may be an indicator of retinal stress.

Onishi *et al.*, in a cross-sectional study, examined the relationship between ischemia and DRIL in 20 patients presenting with a history of DR and DRIL.^[25] In these patients, OCT scans with DRIL were compared with OCT scans of adjacent regions without DRIL as control. They reported that OCT angiography of eyes with DRIL on OCT demonstrated significant perfusion defects compared to adjacent control areas ($P < 0.001$).

DRIL IN RVO

The relationship between DRIL and VA in RVO has also been analyzed in many studies summarized in Table 3. Mimouni *et al.* reported greater DRIL extent at baseline correlated with worse baseline BCVA (0.04/100 μm DRIL, 95% CI, 0.01–0.07, $P = 0.003$).^[12] In multivariate analysis, baseline DRIL ($P = 0.03$) and EZ disruption ($P < 0.001$) correlated with baseline BCVA. The patient population in this study was initially treatment naïve and subsequently received monthly injections. At baseline, 83% of the patients presented with DRIL. Over the course of receiving anti-VEGF injections for 8 months, the proportion of these patients with DRIL decreased over time to 71% at 4 months and 62% at 8 months, respectively ($P < 0.001$). A subanalysis of BRVO and central

RVO (CRVO) patients reported in a stepwise multivariate regression analysis that reduction of DRIL during 4 months was the only factor predictive of an 8 months VA change (0.01–0.06/100 μm DRIL reduction in both groups, 95% CI 0.01–0.06, $P = 0.04$ and $P = 0.02$, respectively). Change in DRIL at 8 months was associated with a change in BVCA at 8 months (0.03/100 μm DRIL reduction, 95% CI 0.01–0.05, $P = 0.001$). In a stepwise multivariate regression analysis, the extent of change in DRIL ($P = 0.002$) was the only parameter that remained significant.^[12] However, Eldeeb *et al.* expressed concern about the definition of DRIL used in this study.^[26] The definition used in this study was similar to Sun *et al.* but the boundary lines marked in some figures of this study did not match with the layers described in the definition. Eldeeb *et al.* elucidated that the boundaries used in this study may instead be based on the vascular anatomy of the retina based on the superficial or middle capillary plexuses. In addition, in the study's multivariate analysis, confounding variables such as baseline VA were not accounted for in the analysis. Further, Călugăru and Călugăru, in another response to the study, were concerned about selection bias.^[27] This study included RVO patients with both ischemic and nonischemic occlusions and included patients in all age ranges. Concern arose around how results of the study may have been affected given the differing underlying etiologies for development of RVO in patients older or younger than 50 years old.

Balaratnasingam *et al.* collected multiple SDOCT and OCT angiography markers. They reported significant correlations between VA and FAZ ($P < 0.001$) and DRIL and VA ($P < 0.001$).^[18] In addition, they found a moderate positive correlation between DRIL length and FAZ area (PCC = 0.3961, $P < 0.001$). While Balaratnasingam's study includes eyes with both DR and RVO, it includes a relatively small number of eyes with RVO in comparison.

In Babiuch *et al.*'s study, multivariate models accounting for age, baseline DRIL, ETDRS, and CST were generated for both the BRVO and CRVO/HRVO cohorts at the 6 months

Table 3: RVO studies table

Author	Type of study	Number of patients	How DRIL was measured	Focus of study	Length of follow-up	Major findings
Mimouni <i>et al.</i>	Retrospective cohort study	136	Same as Das <i>et al.</i> with the presence of DRIL extent being defined as >20 μ m	Correlation between DRIL and VA in RVO patients with ischemic or nonischemic occlusions before and after receiving anti-VEGF treatment	8 months	DRIL and EZ disruption had a statistically significant correlation with baseline VA. DRIL change at 8 months was associated with VA change at 8 months. DRIL changes at 4 months in the BRVO/CRVO subgroups had predictive value for VA changes at 8 months.
Balaratnasigam <i>et al.</i>	Cross-sectional study	95	Same as Sun <i>et al.</i>	Correlation between the area of FAZ and DRIL with VA in patients with DR (65 eyes), branch RVO (19 eyes), and central RVO (11 eyes)	None	FAZ and DRIL had a statistically significant correlation with VA.
Babiuch <i>et al.</i>	Retrospective cohort study	147	DRIL extent was measured from 3 scan OCT images (1 B-scan immediately above and below the foveal center) and each region was assigned a DRIL score of 0–3 based on DRIL presence (+1) or absence (0)	Prognostic potential of baseline DRIL and DRIL burden throughout treatment on VA for patients with treatment naïve branch RVO (72 eyes) and central or hemispheric RVO (75 eyes)	12 months	Baseline DRIL was correlated with lower baseline VA in the branch RVO group. DRIL presence in BRVO was predictive of VA gain up to 6 months. DRIL scores in central or hemispheric RVO were predictive of VA changes in both 6 and 12 months.
Berry <i>et al.</i>	Retrospective, longitudinal cohort study	25	OCT scans of the central 1-mm were analyzed by two masked graders	Correlation between DRIL with ischemia and VA outcomes in CRVO patients who subsequently received treatment	Median follow-up time of 24 months	DRIL extent was the only OCT parameter associated with VA at both 6 months and final visits (median time for final visit=24 months).
Nakano <i>et al.</i>	Retrospective cohort study	60	Foveal scans	Evaluate the association between DRIL and	Unspecified	In univariate analysis, DRIL length at final visit

(Contd...)

Table 3: (Continued)

Author	Type of study	Number of patients	How DRIL was measured	Focus of study	Length of follow-up	Major findings
				VA after anti-VEGF treatment for ME due to BRVO		was significantly associated with final VA In multivariate analysis, only age and EZ disruption were significantly associated with VA
Chan <i>et al.</i>	Retrospective cohort study	84	Foveal scan	Associations and predictive value of OCT parameter and VA outcomes in ME secondary to CRVO	12 months	In multivariate analysis adjusting for baseline VA, worsening VA over 1 year was associated with 1-year increases in DRIL and EZ disruption A 3-month increase in DRIL and EZ disruption had predictive value in VA changes for 1 year

RVO: Retinal vein occlusion, DRIL: Disorganization of retinal inner layers, EZ: Ellipsoid zone, VA: Visual acuity, FAZ: Foveal avascular zone, DR: Diabetic retinopathy, OCT: Optical coherence tomography, CRVO: Central RVO, BRVO: Branch RVO

and 12-month mark to evaluate the predictive value of baseline DRIL and DRIL burden changes throughout treatment on VA.^[28] In the BRVO group, but not the CRVO group, baseline DRIL correlated with lower baseline ETDRS score (ANOVA; 66.7 no DRIL vs. 54.6 DRIL; $P = 0.002$). Absence of DRIL at baseline in the CRVO/HRVO group correlated with greater VA gains at 6 months, adjusting for baseline VA (ETDRS letter score change at 6-months: 19.50 no DRIL vs. 12.72 DRIL present; $P = 0.044$). Over 12 months, continued DRIL presence in BRVO was predictive of less VA gain up to 6 months (ETDRS letter score change at 6-months: 6.2 DRIL increase group vs. 18.6 DRIL decrease group vs. 2.9 DRIL stable group; $P = 0.025$). Increasing DRIL scores in CRVO/HRVO were predictive of reduced VA improvement at 6-months (ETDRS letter score change at 6-months: -0.12 DRIL increase group vs. 16.90 DRIL decrease group vs. 8.45 DRIL stable group; $P = 0.002$) and 12 months (ETDRS letter score change at 12-months: -1.91 DRIL increase group vs. 17.83 DRIL decrease group vs. 6.97 DRIL stable group; $P < 0.001$).

Berry *et al.* reported that neither the extent or presence of DRIL at baseline revealed an association with baseline VA.^[29] However, DRIL extent was correlated with worse VA at the 6-month ($r = 0.656$, $P = 0.001$) and final visits (median time for final visit was 24 months, $r = 0.509$, $P = 0.016$) after treatment. At final follow-up, DRIL extent was the OCT parameter most strongly correlated with baseline ischemic

index ($r = 0.418$, $P = 0.047$) and baseline enlarged FAZ ($P = 0.057$) on ultra-widefield FA. A multivariate regression analysis revealed DRIL extent at final follow-up as the only OCT parameter associated with VA ($P = 0.013$) and maintained significance after accounting for ME.

Nakano *et al.* evaluated the association between DRIL and VA after anti-VEGF treatment for ME due to BRVO.^[30] They determined that DRIL had a minor role in predicting VA after anti-VEGF treatment. It was not found to have a significant association in multivariable analysis. Chan *et al.* evaluated the predictive value of various OCT parameters in ME secondary to CRVO.^[31] In multivariate analysis, adjusting for baseline VA, worsening VA over 1 year was associated with 1-year increases in DRIL (point estimate, 0.06/100 μm , $P < 0.001$). A 3-month increase in DRIL (0.05/100 μm , $P = 0.003$) were the only factors predicting VA worsening over 1 year after controlling for baseline VA.

DRIL IN UVEITIC ME (UCME)

DRIL has been studied largely in DR, DME, and RVO, but has also been demonstrated in UCME (Table 4).^[9,10,12] Grewal *et al.*, in a secondary analysis of VISUAL-1 trial data with 42 UCME patients (56 eyes), analyzed the relationship between DRIL and VA in UCME.^[11] Horizontal and vertical DRIL

length, size of intraretinal cysts, ELM disruption length, EZ disruption length, and the presence of hyperreflective foci (HRF) were recorded. Their study reported an association horizontal DRIL length and baseline VA in univariate analysis (0.057/100 μm, 95% CI 0.026–0.089, $P < 0.001$). It also reported an association between VA across all visits and average horizontal DRIL length in univariate analysis (0.055/100 μm DRIL reduction, 95% CI 0.036–0.073, $P < 0.001$). However, DRIL did not have a statistically significant relationship with the VA in multiple regression analysis. The authors acknowledged that they were unable to study DRIL improvement and VA changes due to the limitation in sample size. Further studies are still needed to analyze the relationship between DRIL and VA changes.

DRIL IN OTHER CONDITIONS

There have been smaller-scale studies on the association between DRIL and conditions not discussed above (Table 5). Zur *et al.* evaluated the extent of DRIL and to investigate its predictive value for visual outcome in cases of idiopathic ERM that was treated by pars plana vitrectomy.^[32] DRIL was assessed as a severity score (no presence/mild/severe) and the primary outcome measure was the correlation of DRIL with outcomes after 3, 6, and 12 months. At baseline, 34.4% of patients presented without DRIL, 24.4% with mild DRIL, and 41.1% with severe DRIL. VA, CST, and MRT at baseline showed a statistically significant correlation with DRIL severity ($P = 0.003$, $P < 0.001$, and $P < 0.001$, respectively). DRIL severity

before surgery showed a statistically significant correlation with the change in VA, CST, and MRT over 12 months when comparing patients with severe DRIL to patients with mild or no DRIL at baseline ($P = 0.007$, $P < 0.001$, and $P < 0.001$, respectively). The patients with mild DRIL and without DRIL did not have statistically significant changes in VA, CST, and MRT. These preliminary study results suggest that severe DRIL may have an association on functional and anatomic outcomes post-surgery.

Guo *et al.* evaluated structural changes such as DRIL, EZ disruption, ELM disruption, and central macular thickness and its association with VA in idiopathic macular telangiectasia (MT) Type 1, a condition characterized by abnormally dilated and tortuous capillaries around the fovea for unknown reasons.^[33] This condition is relatively rare, and as such, the sample size in this study was minimal. They reported that baseline VA correlated with DRIL ($r = 0.707$, $P = 0.005$) in the 1-mm diameter foveal region and all of the MT Type 1 eyes in the study had DRIL. These results suggest that the presence of DRIL may be predictive biomarkers of VA in patients with MT Type 1.

LIMITATIONS OF DRIL ASSESSMENT

A major limitation of DRIL is in its detection and quantification. In a study by Sun *et al.*, the horizontal extent of DRIL was measured by three different graders with high intergrader agreement (Pearson correlation coefficient ranging from 0.80

Table 4: DRIL in uveitic our studies table

Author	Type of study	Number of patients	How DRIL was measured	Focus of study	Length of follow-up	Major findings
Grewal <i>et al.</i>	Secondary analysis of randomized clinical trial data	42	Same as Sun <i>et al.</i>	Correlations between various OCT parameters such as DRIL and VA in uveitic cystoid macular edema	80 weeks	In univariate analysis, horizontal DRIL extent was associated with baseline VA. In multivariate analysis, DRIL did not have a statistically significant relationship with VA.

DRIL: Disorganization of retinal inner layers, OCT: Optical coherence tomography, VA: Visual acuity

Table 5: DRIL in other conditions table

Author	Type of study	How DRIL was measured	Focus of study	Length of follow-up	Major findings
Zur <i>et al.</i>	Multicenter international retrospective case series	Foveal scans with three graders	Evaluate the extent of DRIL and to investigate its predictive value for VA in cases of idiopathic ERM that were treated by PPV and ERM peeling	12 months	DRIL severity was statistically significantly correlated with VA, CST, and MRT both at baseline and 12 months post-op
Guo <i>et al.</i>	Cross-sectional study	Foveal scan	Evaluate the structural changes associated with VA in patients with idiopathic MT Type 1	None	Decreased DCP and the presence of DRIL may be predictive biomarkers of VA in patients with MT Type 1

DRIL: Disorganization of retinal inner layers, CST: Central subfield thickness, VA: Visual acuity, MRT: Maximal retinal thickness, DCP: Deep capillary plexus, MT: Macular telangiectasia

to 0.86).^[9] Other studies used similar methods to measure horizontal DRIL extent.^[10,12,20] Abdulaal *et al.*, in a cross-sectional study with 18 DME patients (24 eyes), evaluated the reproducibility of DRIL in eyes with DME imaged by 2 SDOCT instruments (Zess Cirrus HD-OCT 4000D and Heidelberg Spectralis 6 mode) with high speed and high-resolution settings resulting in four types of scans per eye.^[34] In this study, DRIL was assessed using customized MATLAB software and found high intraclass correlation coefficients (ICCs) between the four types of scans (ICCs ranging from 0.77 to 0.93). These values are highly precise; however, the DRIL values were not confirmed against visual inspection, so the accuracy may be low. Most studies studying DRIL used graders as opposed to autonomous software to measure DRIL.^[9-12] Schmidt-Erfurth and Michl reported that the current definition of DRIL lacks the accuracy necessary to detect DRIL reliably leading to potentially low intergrader agreement.^[35] Other features such as the presence of HRF or cystic spaces that alter retinal boundaries could contribute to the visual appearance of DRIL. The researchers concluded that DRIL has not been characterized enough for standardized assessment, and there is a need for advanced image analysis to define DRIL.

There is a significant body of literature regarding DRIL and its association with current and resolved DME; however, additional studies to analyze the relationship between DRIL and VA in other disease states are needed to determine its viability as a biomarker. Even within DME, only a few smaller-scale studies have analyzed the relationship retrospectively between DRIL and VA. In addition, there have been no histopathologic studies of DRIL, which still renders the underlying etiology unclear.

FUTURE DIRECTION

Automated detection and quantification of DRIL would likely enable clinical advancements, enabling methodology for addressing DRIL when it is detected, or for preventing the formation of DRIL during treatment. This could potentially improve clinical outcomes in ME secondary to multiple etiologies. In addition, it has been shown that DRIL can resolve over time;^[9] so earlier and more precise detection might also yield improved clinical outcomes. Finally, histopathologic studies of DRIL may lend a clearer understanding of the underlying etiology of DRIL, (i.e., ischemia, inflammation, and inner retinal layer destruction secondary to ME) and further information as to how this biomarker can affect long-term VA outcomes and potentially aid in guiding treatment.

Conflicts of interest disclosures

See submitted conflicts of interest forms.

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