Association of Disorganization of Retinal Inner Layers (DRIL) and Macular Ischemia in Center Involved Diabetic Macular Edema

Soliman Ahmed Z[2], Radwan Salma H[2], Zhang Lei[3], Van Kuijk Frederik J[1], Koozekanani Dara D[1]*

[1]Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis, MN, United States

[2]Southwest Eye Institute, Elpaso, TX, United States

[3]Biostatistical Design and Analysis Center, Clinical and Translational Science Institute, University of Minnesota, Minneapolis, MN, United States

*Corresponding Author: Koozekanani Dara D, Associate Professor, Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis, MN, United States.

Abstract

Purpose: To investigate whether the worse visual outcomes associated with Disorganization of Retinal Inner Layers (DRIL) in patients with center involved diabetic macular edema (ci-DME) can be partly explained by the coexistence of diabetic macular ischemia (DMI).

Methods: Retrospective, longitudinal cohort study over 8 months in which Snellen visual acuity (VA) testing, fluorescein angiography (FA) and spectral domain optical coherence tomography (SDOCT) macular imaging were performed. Masked graders measured the foveal avascular zone (FAZ), Optic nerve (ON) area in FA images. The FAZ/ON ratio was calculated to adjust for the patient's refractive error. This ratio was used as a surrogate for DMI. DRIL extent in SDOCT images of the central 1500 μm of the macula was recorded.

Results: Thirty-six eyes of 30 participants with ci-DME were included. At baseline, the association of VA with SDOCT and angiographic variables was dependent upon DRIL severity. In eyes with DRIL involving more than 50% of the horizontal scan, VA was associated with the total DRIL length, FAZ/ON ratio, and central retinal subfield thickness (CST) (Rho [95% CI], 0.62 [0.37, 0.80], 0.71 [0.52, 0.82] and 0.49 [0.23, 0.75], respectively). At 8 months, VA was only associated with baseline DRIL length and FAZ/ON ratio (Rho [95% CI]: 0.41[0.14, 0.69], and 0.47 [0.22, 0.69], respectively). No association was detected between baseline CST and VA (Rho [95% CI]: -0.02 [-0.3, 0.3]). Intra- and inter-grader agreement showed Spearman rank correlation coefficients ranging from 0.80 to 0.88 for DRIL measurements and from 0.74 to 0.80 for FA measurements.

Conclusions and Relevance: Worse visual outcomes in eyes with center-involved DME were found to correlate with the extent of both DRIL and DMI. The relationship between these two biomarkers need to be explored further.

Keywords: Retinal Inner Layers; Macular Ischemia; Diabetes Mellitus (DM); Diabetic Macular Edema (DME); Diabetic Macular Ischemia (DMI)

Introduction

Diabetes Mellitus (DM) continues to affect an increasing proportion of the population, and secondary vision loss from diabetes concerns both patients and health care providers alike. The most common cause of visual acuity loss in DM is diabetic macular edema (DME).

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Several studies have confirmed the positive correlation between diabetic macular ischemia (DMI) and visual loss in eyes with DME [1-4]. However, the impact of DMI on visual acuity after treatment, even with a favorable anatomic outcome, has been controversial. Both Douvali., *et al*. and Chung., *et al.* reported a negative impact of DMI on visual improvement after intravitreal ranibizumab and bevacizumab administration, respectively [5,6]. On the other hand, other studies including an Early Treatment Diabetic Retinopathy Study (ETDRS) report, found no clear correlation between the presence of DMI and decreased treatment efficacy [7,8].

Several spectral domain ocular tomography (SDOCT) findings have been reported to correlate with DMI detected by fluorescein angiography (FA). These include cyst size, retinal thickness, continuity of the external limiting membrane and inner segment/outer segment junction, and foveal detachments [9-13]. Additionally, identification of ganglion cell layer boundaries has been found to be more difficult in the presence of advanced foveal avascular zone (FAZ) outline loss [9].

Recently, a newly described SDOCT feature, disorganization of the inner retinal layers (DRIL) has been of particular interest because its presence and severity have been found to be related to visual outcomes in patients with DME [14] after edema resolution [15]. DRIL is defined as the inability to delineate the inner retinal layer boundaries within the central 1500 micron region on SDOCT. DRIL reflects changes to the inner retina, at least as visualized by SDOCT, but its precise causes are not yet known. It may represent ischemic changes, as it has been detected in regions of capillary non-perfusion located outside the FAZ in patients with Diabetes as well as other conditions such as retinal vein occlusion and acute retinal necrosis [10,16-18,33].

The primary aim of this study was to explore the relationship between DRIL and DMI to further evaluate DMI as a potential pathophysiologic mechanism leading to its occurrence. In particular, we explored the relationship between both FAZ enlargement and visual acuity with DRIL and whether these correlations changed as DRIL extent changed over time. Finally, we evaluated whether the vision loss associated with presence of DRIL on SD OCT was correlated with the macular perfusion status as represented by FAZ/ON ratio measured on FA.

Research Design and 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, which waived the need for patient consent.

Using diagnostic codes, records of all patients with DME seen over a 24 months period were reviewed. Those who underwent SD OCT and FA imaging at the same visit were collected.

The medical records of all patients with center-involved diabetic macular edema (ci-DME) who underwent baseline fluorescein angiography (FA) and high resolution spectral domain optical coherence tomography (SDOCT) images at baseline and at follow up visits during the study period were reviewed. Images were acquired using the Spectralis HRA/OCT, Heidelberg Retinal Angiograph (Heidelberg engineering, Heidelberg Germany). The date of the last follow-up was June 1, 2014. Study participants had to be 18 years or older with best spectacle corrected VA of 20/500 or better in the study eye using a Snellen chart. The diagnosis of ci-DME was defined as Spectralis SDOCT central subfield thickness (CST) ≥320μm for males and ≥ 305 μm for females [9]. Exclusion criteria included macular edema due to non-diabetic causes, significant media opacity such as dense cataract or vitreous hemorrhage precluding acquisition of high quality images and patient inability to cooperate with a dilated retinal examination.

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, and duration of diabetes. The Logarithm of Minimal Angle of Resolution (logMAR) VA was calculated and used for comparison and statistics in order to allow for arithmetic rather than geometric evaluation of VA.

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Image analysis

Each image was assigned a unique study code prior to image analysis. Images were randomized using SAS software to assign images for each grader. Image analysis was performed by 2 experienced graders (SHR and AZS) using Adobe Photoshop CS6 (Adobe Systems, Inc). The graders were masked to all clinically relevant information. Observations were entered into standardized data collection forms recorded in Microsoft Excel (Microsoft Corp.). Using spearman correlations, inter and intra observer agreement for the graders ranged from 0.80 to 0.88 for DRIL measurements as established in a previous study [15] and ranged from 0.74 to 0.80 for FA measurements.

In brief, the following protocol was used in the current study:

1. **FA image analysis:** FA was performed with an intravenous infusion of 5 ml fluorescein sodium 20%. An early arterial phase FA image was preselected for each study eye; the FAZ was defined as the largest, innermost, dark, capillary free area bounded by foveal capillary ends [10]. The FAZ area was delineated by accurate (as much as possible) tracing of the capillary ends. In cases where the FAZ outline was not continuous, graders approximated the missing parts of FAZ boundaries [21]. FA images with markedly irregular FAZ outline precluding measurements were not included in the study. The optic nerve (ON) head area was also measured and the FAZ/ON ratio was calculated to account for the patient's refractive error. Adobe Photoshop was used in recording FAZ and ON areas using the area measuring tool.

2. **OCT image analysis:** In the current study, we followed the same protocol for OCT image analysis described in our aforementioned study [15]. In brief, a 20 x 15 degree area (5.9 x 4.4 mm) centered on the fovea was scanned with 19 B-scans and 16 automated real time means (ART) per scan on the high-resolution mode. The distance between the scans was 250 microns with a scanning angle of 20 degrees. The minimum acceptable image quality included in the study was 25 decibels (db). 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. One scan immediately above and below the foveal scan were included in the analysis for a total of 3 scans. An overlay measuring 1500 μm was placed over the center of each of the 3 scans.

DRIL measurements within the 1500 μm were then recorded by 2 experienced graders using the ruler tool in Adobe Photoshop CS6 (Adobe Systems, Inc). The horizontal extent of DRIL in the 3 central scans was averaged and the mean was recorded.

The SDOCT B-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, followup images were overlaid on the baseline scans using Adobe Photoshop CS6 (Adobe Systems, Inc) to ensure analysis of the same location. The mean total horizontal length of DRIL within the central 1500 microns area, denoted the total DRIL length, was recorded at baseline and subsequent visits, and was correlated with the baseline FAZ/ON, central subfield retinal thickness (CST) and logMAR VA at baseline and at 8 months (Figures 1 and 2).
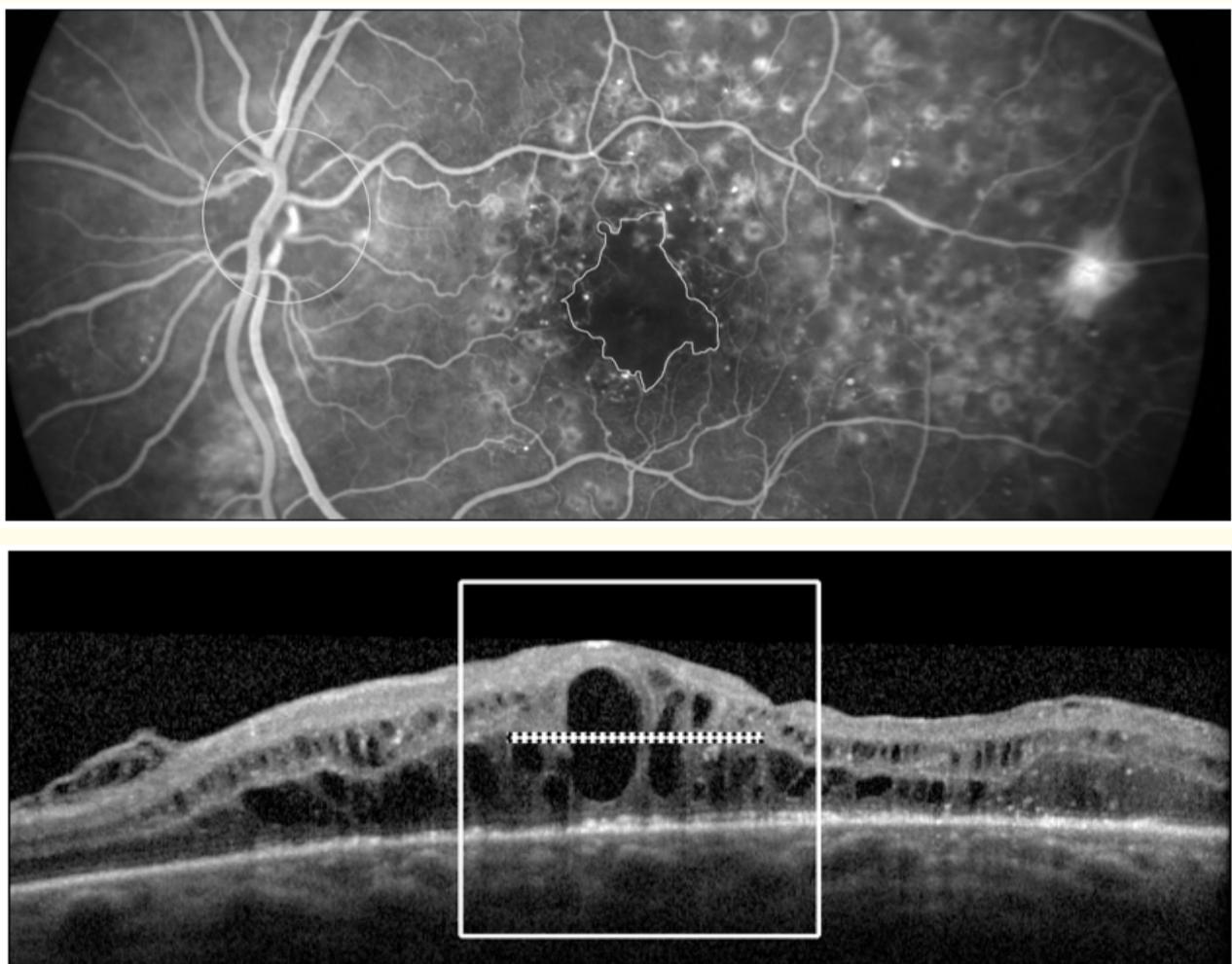

Figure 1: Representative baseline FA image (upper) and the corresponding SDOCT image (bottom) of DME in an eye with DRIL. The FAZ and region of DRIL are marked in each image; the FAZ/ON ratio : 0.95 and DRIL: 1200 microns. FAZ: Foveal Avascular Zone Area; ON: Optic Nerve Head Area; DRIL: Disorganization of Retinal Inner Layers.
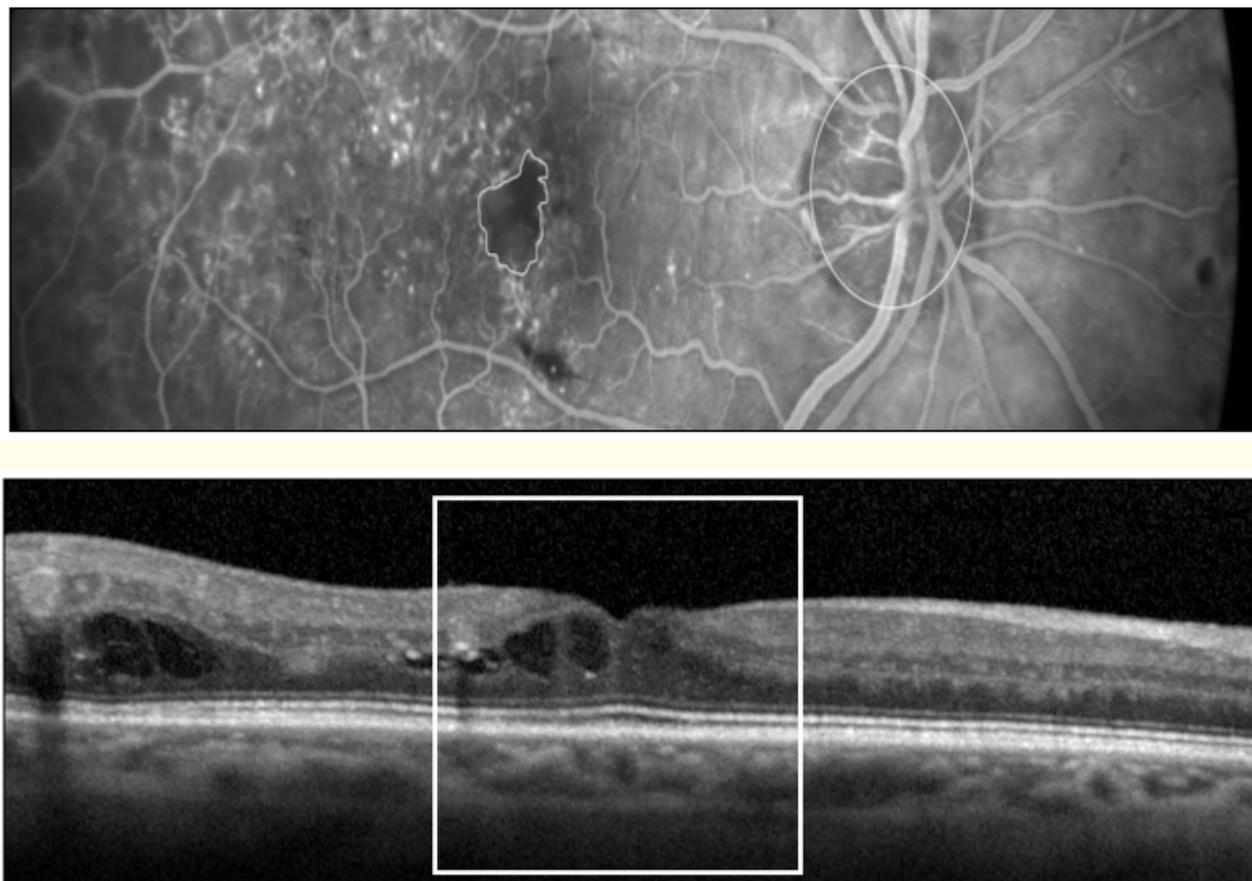
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Figure 2: *Representative baseline FA image (upper) and the corresponding SDOCT image (bottom) of DME in an eye with no baseline DRIL; the FAZ/ON ratio : 0.50. FAZ: Foveal Avascular Zone Area; ON: Optic Nerve Head Area; DRIL: Disorganization of Retinal Inner Layers.*

Statistical analysis

Statistical analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC). Graphs were plotted in R (http://www.r-project. org). The relationships between baseline measured OCT parameters, logMAR VA, and FAZ area were assessed by Spearman correlation coefficient (Rho). Bootstrap method [22] was used to construct the 95% confidence interval (CI) of Spearman correlation coefficient. One thousand bootstrap samples of patients were drawn (preserving clustering by patients); for each bootstrap sample, Spearman correlation coefficient was computed, and 95% bootstrap CI was constructed from the 2.5% and 97.5% percentiles. The associations between logMAR VA at 8 months and OCT parameter and FAZ area adjusting for baseline logMAR VA were also assessed by partial Spearman correlation coefficient. The 95% bootstrap confidence was computed. Separate, sub-analyses were also done for subjects with baseline DRIL > 50% (i.e. total DRIL length occupying greater than 50% of the measured area of interest) and for those with baseline DRIL < 50% (i.e. total DRIL length occupying less than 50% of the measured area of interest). Note that the subgroup with DRIL < 50% did not include those with no baseline DRIL. The relationship between the resolution pattern of the DRIL [11] with the baseline FAZ measurement and CST was explored by Linear Mixed Models adjusting for baseline logMAR VA. Group comparisons were adjusted for multiple comparisons using the Tukey-Kramer method.

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Results

Using the inclusion criteria described in the methods section, 60 eyes of 40 participants were identified. Of those, a total of 24 eyes were excluded due to lack of serial OCT images for 8 months (19 eyes), very irregular FAZ outline precluding measurements (3 eyes) or poor OCT image quality (< 20 db) (2 eyes).

Thirty-six eyes of 30 participants were analyzed. These included 9 eyes (25%) with no baseline DRIL, 9 eyes (25%) with baseline DRIL < 50% and 18 eyes (50%) with baseline DRIL > 50%.

Patient demographics and study eye characteristics are outlined in tables 1 and 2 respectively.

Study Participant characteristics Mean ± SD (N) or N (%)		
N	30	
Age (years)	60 ± 10	
HbA1c%	7.5 ± 0.5	
Duration of DM (years)	15 ± 8.5	
Ethnicity	White	25 (83%)
	Non-white	5 (17%)
Gender	Male	22 (73%)
	Female	8 (27%)

Table 1: *Study Participant characteristics.*

Baseline Study eye characteristics Mean ± SD (N) or N (%)		
N	36	
DRIL	> 50%	18 (50)
	< 50%	9 (25)
	No baseline DRIL	9 (25)
FAZ/ON	0.85 ± 0.50	
Log MAR VA	0.39 ± 0.12	
CST (μ)	421 ± 40	

Table 2: *Baseline Study eye characteristics.*

Baseline analysis

1. For all subjects, there was a strong association between FAZ/ON ratio and DRIL length, with Spearman correlation coefficients (Rho) values [reported with 95% CI] of (0.89 [0.80, 0.96]). In contrast, this association was not found between FAZ/ON ratio and CST (0.20 [0.00, 0.39]). Also, for all subjects, the baseline logMAR VA was associated with total DRIL length, FAZ/ON ratio and CST, with Rho [95% CI] (0.67 [0.51, 0.81], 0.64 [0.51, 0.76], and 0.53 [0.33, 0.68], respectively).

2. For eyes with DRIL > 50%, logMAR VA was highly associated with the total DRIL length and the FAZ/ON ratio, and CST (Rho [95% CI], 0.62 [0.37, 0.80], 0.71 [0.52, 0.82], and 0.49 [0.23, 0.75], respectively

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3. For eyes with DRIL < 50%, logMAR VA was only found to be associated with CST (Rho [95% CI], 0.44 [0.19, 0.69]). Interestingly, there was no association noticed between logMAR VA and total DRIL length or FAZ/ON ratio (Rho [95% CI]: 0.30 [-0.15, 0.67], and 0.20 [-0.14, 0.50], respectively).

The importance of these findings will be discussed further in the discussion section, and are shown in figure 3.
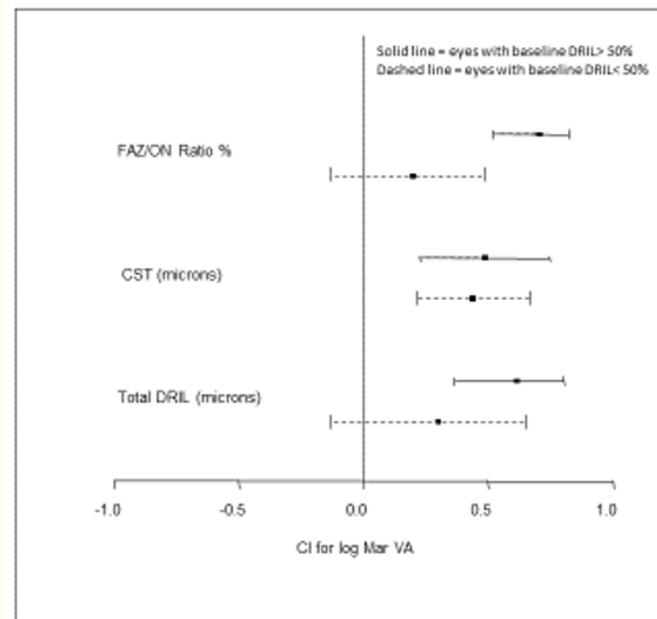

Figure 3: *Correlation of baseline logMAR VA with measured baseline biomarkers in eyes categorized by DRIL involvement. The plot shows Spearman correlation coefficient (CI) for each biomarker (scaled as indicated); those whose CI crosses the zero line are not significantly related to baseline logMAR VA.*
FAZ: Foveal avascular zone area, ON: optic nerve head area, DRIL: disorganization of retinal inner layers. CST: center subfield thickness.

At 8 months:

1. For all subjects, after adjusting for baseline VA, LogMAR VA at 8 months was associated only with baseline DRIL length and FAZ/ON ratio (Rho [95% CI]: 0.41[0.14, 0.69], and 0.47 [0.22, 0.69], respectively)*.* There was no association found with baseline CST (Rho [95% CI]: -0.02 [-0.3, 0.3]*).*

2. We further analyzed the DRIL resolution patterns in this study as has been reported in an earlier publication [15]. Of the 36 eyes, 9 eyes (25%) had no baseline DRIL, 8 eyes (23%) had baseline DRIL which resolved by 8 months (resolvers), and 19 eyes (52%) had baseline DRIL which failed to resolve by the study's end (non-resolvers). After adjusting for baseline VA, there was a significant difference in the baseline FAZ/ON ratio between the subjects with no baseline DRIL and the non-resolvers group (least squares [LS] mean [SE], 0.46 [0.14] vs. 1.07 [0.11], respectively) *(P =0.05)* despite the fact that there was no significant difference in baseline CST between the two groups. (least squares [LS] mean [SE], 385.8 [32.7] vs. 410.2 [31.63], respectively) *(P = 0.77)*. (Figure 4A and 4B) The mean FAZ/ON ratio was also higher in the resolvers than those with no baseline DRIL (LS mean [SE], 0.84 [0.13] vs. 0.46 [0.14], respectively) *(P = 0.23)* despite the fact that baseline CST was not statistically different among the two groups. (LS mean [SE], 385.90 [32.7] vs. 410.15 [31.63], respectively) *(P = 0.85).* All analyses in this study were adjusted for age and gender. In addition, groups have reported in a previous study [23] that no correlation was found between DRIL and the type or duration of DM, grade of diabetic retinopathy or HbA1c. Additionally, different treatment modalities have been used to treat these patients. However, the scope of this study was not to determine the efficacy of a particular treatment but rather to investigate whether the previously proven association between DRIL and poorer VA can be explained by underlying DMI.
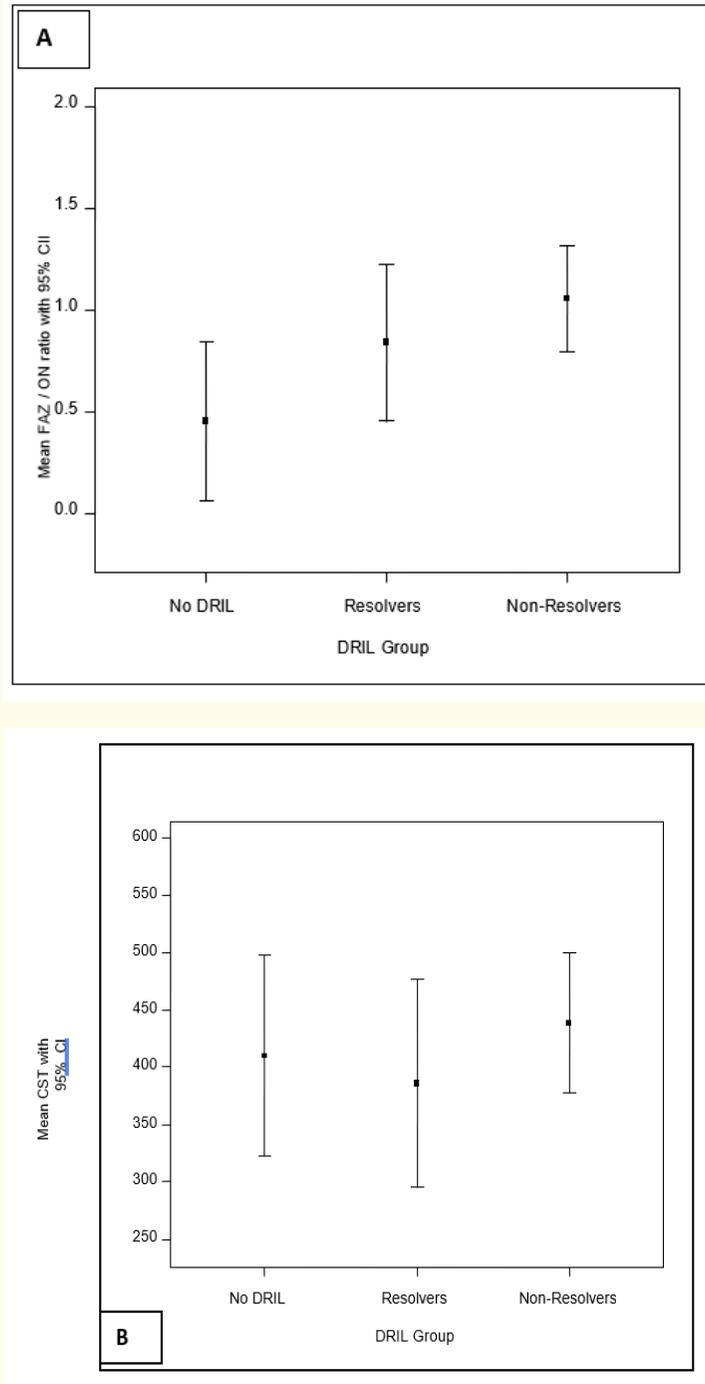
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Figure 4: Comparison of FAZ/ON ratio (A) and CST (B) by DRIL resolution pattern. FAZ: Foveal Avascular Zone Area; ON: Optic Nerve Head Area; CST: Central Subfield Thickness; DRIL: Disorganization of Retinal Inner Layers.

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Discussion

In this retrospective, longitudinal study, we performed quantitative analyses of FA and SDOCT images obtained from a cohort of patients with type 2 DM with different levels of retinopathy. In particular, we explored whether the vision loss associated with DRIL on SD-OCT images was correlated with the macular perfusion status as represented by FAZ/ON ratio measured on FA. We found strong correlations between baseline DRIL and the FAZ/ON ratio, but no such correlation for CST. Furthermore, in prior work, we found that VA improvement after DME resolution correlated with the pattern of DRIL resolution: those whose DRIL failed to resolve (termed non-resolvers) had less improvement than those whose DRIL did resolve (termed resolvers) [15]. In the current report, over an 8 months follow up period, the DRIL non-resolvers had more FAZ enlargement at baseline than either the resolvers or those with no baseline DRIL. It has been proposed by several groups that FAZ size can be an indicator of macular inner retinal perfusion [9,16,17,20,21]. Our findings correlating DRIL with FAZ/ON ratio as well as the variation in FAZ/ON ratio with DRIL resolution patterns strengthen the association between FAZ size and the presence of inner retinal damage. These findings suggest that DRIL may be an indirect indicator of ischemia and are in line with the findings reported by others using OCT angiography which showed good agreement with FA in detecting DMI [30,32]. Fluorescein angiography was used in the current study, despite its invasive nature, as it is still considered the gold standard for evaluation of macular perfusion in eyes with DME [21].

Moreover, we found that both baseline DRIL and FAZ/ON ratio were significantly related to both baseline VA as well as VA at 8 months. Baseline CST did not significantly correlate with VA at 8 months despite correlating with baseline VA. Sub-analyses suggest these relationships are driven primarily by the extent of DRIL. In particular, at baseline, strong associations between VA and both DRIL length and FAZ/ON ratio were found only in eyes with baseline DRIL > 50%. In contrast, in eyes with baseline DRIL < 50%, baseline CST correlated best with VA, with no correlation found between VA and DRIL length or FAZ/ON ratio. This interesting finding might partially explain the inconsistent, and sometimes paradoxical, correlation between CST and VA seen in previous reports [5,13,24-26]. Our data suggests that in eyes with increased DRIL extent, sufficient retinal damage may occur to make the CST less relevant. It is not clear whether there is actually a threshold level for DRIL, although other groups have used 50% of the measured scan region as an empiric level [23]. Data from the same report as well as data from our recent work [15] suggested that the measured amount of DRIL correlates with visual acuity, with higher levels of DRIL corresponding to worse acuity.

Limitations of this study include those inherent to its retrospective nature and the relatively small number of patients. Nevertheless, similar baseline associations between FAZ/ON ratio and DRIL length were observed after including the 19 eyes that didn't have serial SDOCT imaging on follow up in the baseline analysis (unpublished data). Additionally, measuring the FAZ area in the presence of macular edema is challenging [20,27]. However, in an attempt to increase grading uniformity, both graders independently graded 10 images at the beginning of the study and then sat down together to address any discrepancies.

Nevertheless, the exact underlying mechanism of vision loss in this patient population is still unclear.

Conclusion

This work expands our understanding of DRIL, its potential correlation with macular ischemia and how that might influence subsequent visual acuity in patients with ci-DME. DRIL measured on SDOCT is a potential biomarker of visual recovery in eyes with center-involved DME (ci-DME) [15,23] and so a better understanding of this biomarker could help guide clinical care. If our results are validated in larger prospective studies, integrating the extent of baseline DRIL with the information obtained from FA would provide a better estimate of the likelihood of vision improvement after therapy for ci-DME. Additionally, the introduction of OCT angiography [28-31] with its capability to non-invasively capture structural and angiographic data in a three dimensional image have shown a correlation between FAZ area and VA and will potentially expand our understanding of the correlation between DMI and DRIL. Further prospective studies are needed to validate our results and help identify the extent of DRIL that represents a "tipping point" at which the visual function might be irreversibly compromised.

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Acknowledgement and Disclaimer

Authors' Contributions

S.H.R. designed the study, performed data analysis and wrote the manuscript. A.Z.S. analyzed data and wrote the manuscript. L.Z. performed statistical analysis. F.V. contributed to the discussion and reviewed/edited the manuscript. D.D.K. contributed to study design and reviewed/edited the manuscript.

S.H.R. and D.D.K. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest

There is no conflict of interest to be reported.

Author's Contribution

Soliman Ahmed Z and Radwan Salma H both have contributed equally.

Bibliography

1. Jonas JB., *et al.* "Predictive factors for visual acuity after intravitreal triamcinolone treatment for diabetic macular edema". *Archives of Ophthalmology* 123.10 (2005): 1338-1343.

2. Arend O., *et al.* "The relationship of macular microcirculation to visual acuity in diabetic patients". *Archives of Ophthalmology* 113.5 (1995): 610-614.

3. Sim DA., *et al.* "The effects of macular ischemia on visual acuity in diabetic retinopathy". *Investigative Ophthalmology and Visual Science* 54.3 (2013): 2353-2360.

4. Klein R., *et al.* "Visual impairment in diabetes". *Ophthalmology* 91.1 (1984): 1-9.

5. Douvali M., *et al.* "Effect of macular ischemia on intravitreal ranibizumab treatment for diabetic macular edema". *Ophthalmologica* 232.3 (2014): 136-143.

6. Chung EJ., *et al.* "Effects of macular ischemia on the outcome of intravitreal bevacizumab therapy for diabetic macular edema". *Retina* 28.7 (2008): 957-963.

7. "Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. Early Treatment Diabetic Retinopathy Study Research Group". *Archives of Ophthalmology* 113.9 (1995): 1144-1155.

8. Mitchell P., *et al.* "The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema". *Ophthalmology* 118.4 (2011): 615-625.

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9. Dmuchowska DA., *et al.* "Can optical coherence tomography replace fluorescein angiography in detection of ischemic diabetic maculopathy?" *Graefe's Archive for Clinical and Experimental Ophthalmology* 252.5 (2014): 731-738.

10. Yeung L., *et al.* "Correlation between spectral domain optical coherence tomography findings and fluorescein angiography patterns in diabetic macular edema". *Ophthalmology* 116.6 (2009): 1158-1167.

11. Otani T and Kishi S. "Correlation between optical coherence tomography and fluorescein angiography findings in diabetic macular edema". *Ophthalmology* 114.1 (2007): 104-107.

12. Scarinci F., *et al.* "Association of Diabetic Macular Nonperfusion With Outer Retinal Disruption on Optical Coherence Tomography". *JAMA Ophthalmology* 133.9 (2015): 1036-1044.

13. Lee D-H., *et al.* "The relationship between foveal ischemia and spectral-domain optical coherence tomography findings in ischemic diabetic macular edema". *Investigative Ophthalmology and Visual Science* 54.2 (2013): 1080-1085.

14. Sun JK., *et al.* "Disorganization of Retinal Inner Layers as a Predictor of Visual Acuity in Eyes with Center Involved Diabetic Macular Edema". *JAMA Ophthalmology* 132.11 (2014): 1309-1316.

15. Radwan SH., *et al.* "Association of Disorganization of Retinal Inner Layers With Vision After Resolution of Center-Involved Diabetic Macular Edema". *JAMA Ophthalmology* 133.7 (2015): 820-825.

16. Nicholson L., *et al.* "Diagnostic accuracy of disorganisation of the retinal inner layers (DRIL) in detecting macular capillary nonperfusion in diabetic retinopathy". *Clinical and Experimental Ophthalmology* 43.8 (2015): 735-741.

17. Byeon SH., *et al.* "Foveal ganglion cell layer damage in ischemic diabetic maculopathy: correlation of optical coherence tomographic and anatomic changes". *Ophthalmology* 116.10 (2009): 1949-1959.e8.

18. Suzuki J., *et al.* "Analysis of retinal findings of acute retinal necrosis using optical coherence tomography". *Ocular Immunology and Inflammation* 14.3 (2006): 165-170.

19. Browning DJ., *et al.* "Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema". *Ophthalmology* 114.3 (2007): 525-536.

20. Conrath J., *et al.* "Foveal avascular zone in diabetic retinopathy: quantitative vs qualitative assessment". *Eye (London)* 19.3 (2005): 322-326.

21. "Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group". *Ophthalmology* 98.5 (1991): 807-822.

22. Borsci S., *et al.* "The Bootstrap Discovery Behaviour (BDB): a new outlook on usability evaluation". *Cognitive Processing* 12.1 (2010): 23-31.

23. Sun JK., *et al.* "Neural Retinal Disorganization as a Robust Marker of Visual Acuity in Current and Resolved Diabetic Macular Edema". *Diabetes* 64.7 (2015): 2560-2570.

24. Jittpoonkuson T., *et al.* "Correlation between fluorescein angiography and spectral-domain optical coherence tomography in the diagnosis of cystoid macular edema". *British Journal of Ophthalmology* 94.9 (2010): 1197-1200.

25. Maheshwary AS., *et al.* "The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema". *American Journal of Ophthalmology* 150.1 (2010): 63-67.e1.

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26. Shin HJ., *et al*. "Association between photoreceptor integrity and visual outcome in diabetic macular edema". *Graefe's Archive for Clinical and Experimental Ophthalmology* 250.1 (2011): 61-70.

27. Conrath J., *et al*. "Semi-automated detection of the foveal avascular zone in fluorescein angiograms in diabetes mellitus". *Clinical and Experimental Ophthalmology* 34.2 (2006): 119-123.

28. Spaide RF. "Volume-Rendered Optical Coherence Tomography of Diabetic Retinopathy Pilot Study". *American Journal of Ophthalmology* 160.6 (2015): 1200-1210.

29. Spaide RF. "Volume-rendered angiographic and structural optical coherence tomography". *Retina* 35.11 (2015): 2181-2187.

30. Bradley PD., *et al*. "The Evaluation of Diabetic Macular Ischemia Using Optical Coherence Tomography Angiography". *Investigative Ophthalmology and Visual Science* 57.2 (2016): 626-631.

31. Balaratnasingam C., *et al*. "Visual Acuity is Correlated with the Area of the Foveal Avascular Zone in Diabetic Retinopathy and Retinal Vein Occlusion". *Ophthalmology* 123.11 (2016): 2352-2367.

32. Moein HR., *et al*. "Optical Coherence Tomography Angiography to Detect Macular Capillary Ischemia in Patients with Inner Retinal Changes after Resolved Diabetic Macular Edema". *Retina* 38.12 (2018): 2277-2284.

33. Berry D., *et al*. "Association of Disorganization of Retinal Inner Layers with Ischemic Index and Visual Acuity in Central Retinal Vein Occlusion". *Ophthalmology Retina* 2.11 (2018): 1125-1132.