

## Supplementary Online Content

Das R, Spence G, Hogg RE, Stevenson M, Chakravathy U. Disorganization of inner retina and outer retinal morphology in diabetic macular edema.

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This supplementary material has been provided by the authors to give readers additional information about their work.

**e Table 1- Grading of SD- OCT images in DME-definitions**

Grading	Question	Description
Presence of IRF	Yes-Cystoid or diffuse	Cystoid- accumulation of intra retinal fluid that has a cystoid appearance, which causes increased retinal thickness. (e Figure 1)
	No CG	Diffuse- accumulation of intraretinal fluid causing increased retinal thickness that does not have a focal appearance within the scans in the macular region (e Figure 1).
If cystoid, describe the cyst  Septae	Present  Absent	The presence of a linear hyperreflective line dividing the cyst as septae within the cysts. Example of large cyst with no septae is shown in e Figure 1.
Presence of subretinal fluid (SRF)	Yes/No	A homogeneous optically empty space situated between the neurosensory retina and the RPE (e Figure 2).
Symmetry of IRF around the fovea	Symmetrical	We evaluated this in general terms. We visually amalgamated The intra and/or sub retinal fluid was visually judged on whether this was (roughly) symmetrical on both sides of the fovea.
	Asymmetrical	We evaluated this in general terms. The intra and/or sub retinal fluid were visually judged on whether this was (roughly)

		asymmetrical on both sides of the fovea. (e Figure 3). □
Shape of the DME	Dome	Rounded shape (e Figure 1)
	Fusiform	Wide in the middle and tapering at both ends
Hyper reflective dots	Yes/No	Lesions of equal or higher reflectivity than the RPE band, located within the neurosensory retina and within SRD, often discrete and well-circumscribed, but sometimes seen attached to elevated RPE overlying drusen. Dots are $\leq 30\mu\text{m}$ in the vertical direction.
Hyper reflective foci	Yes/No	Lesions of equal or higher reflectivity than the retinal pigment epithelium (RPE) band, located within the neurosensory retina and within SRD, not so well circumscribed but sometimes seen attached to elevated RPE. Foci are $>30\mu\text{m}$ in the vertical direction.
ELM and EZ	Intact	All hyper-reflectivity bands are visible and morphologically intact in the foveal scans lying within 500 $\mu\text{m}$ of the foveal depression in all directions
	Disrupted	If there is disruption in the continuity of the hyper reflective layers. The extent of disruption of ELM and EZ over a region of 1000 $\mu\text{m}$ surrounding the center of the fovea was recorded (Figure 1).

DRIL	Yes/No	The horizontal extent in microns for which any boundaries between the ganglion cell–inner plexiform layer complex, inner nuclear layer, and outer plexiform layer could not be identified. The horizontal extent of DRIL in each of 7 B-scans was measured and added to derive a global DRIL measure for each eye (Figure 2).
Vitreous attachment	Yes/No	Attached at the macula without traction
		Attached at macula with traction
		Definitely detached at macula (can see vitreous face but not attached)
		Not known (either fully detached beyond the range of scan or fully attached and therefore not visible)
		CG
Other pathology	Yes	Macular hole
	No/CG	Epiretinal membrane (Figure 2)
Thickness at the fovea/presumed fovea		We selected one scan from the image set, which best shows, the foveal depression and measured all features present on this scan. The Retinal thickness at fovea (RTF) was measured from the Internal Limiting Membrane (ILM) to the inner edge of the interdigitation zone (IZ). The height of the

		sub retinal fluid (SRF) if present was recorded. Choroidal thickness at the fovea and 1000 microns temporal and nasal to fovea was measured. The choroid was measured from the bottom of the RPE/Bruch's complex until the signal falls off to background, or to the choroid/sclera junction.
Maximum retinal thickness (MRT)		We measured this if the site of MRT was not at the fovea and we recorded the maximum observed thickness of a particular layer in any of the OCT scans from the ILM to the inner edge of the IZ.

Abbreviations- SD-OCT, spectral domain optical coherence tomography; DME, diabetic macular edema; IRF, intraretinal fluid; CG, cannot grade; SRF, subretinal fluid; ELM, external limiting membrane; EZ, ellipsoid zone; DRIL, disorganization of inner retinal layers; RTF, retinal thickness fovea; MRT, maximum retinal thickness; CT, choroidal thickness.

**e Table 2- Relationship of visual acuity with age and systemic factors**

Factors	mean, +/-SD, years	$\beta^a$	P value <sup>b</sup>
Age	63 +/-11	-0.15	.16
Duration of DM	16.74 +/-10.84	0.08	.5
	<b>VA (letters) mean +/-SD</b>	<b>ANOVA</b>	
Hypertension n (%) Yes 51(63.7) No 29( 36.3)	54.6+/-15.4 56.9+/-13.3	F=0.43(1,78)	.5
Hyperlipidemia n (%) Yes 54 (67.5) No 26( 32.5)	55.9+/-14.55 54.5+/-15.2	F=0.15(1,78)	.4
Smoking n (%) Yes 33(41.3) No 47( 67.5)	53.8+/-16.05 56.6+/-13.7	F=0.72 (1,78)	.4

Abbreviations- VA, visual acuity; DM, Diabetes mellitus

<sup>a</sup> Results are reported from Linear regression

<sup>b</sup>  $P < .05$

**e Table 3- Associations between VA and retinal morphological features of DME and DR**

Variables	n (%)	VA mean +/-SD (letters)	ANOVA, P value	
<b>Type of DME</b>				
Intraretinal fluid (IRF)	72(70.6)	55.2+/-14.9	F=0.03(1,99), .8	
IRF and subretinal fluid (SRF)	29(28.4)	55.8 +/-14.4		
<b>Type of IRF</b>				
Diffuse	21(20.6)	55.2 +/-17	F=0.004(1,98), .9	
Cystoid	26 (25.5)	55.6 +/-13.4		
Mixed	54(52.9)	55.3 +/-14.6		
<b>Symmetry of IRF</b>				
Symmetrical	69 (67.6)	54.7 +/-14.4	F=0.49(1,99), .4	
Asymmetrical	32 (31.4)	56.9 +/-15.3		
<b>Shape of DME</b>			F=4.8(1,99), .03 <sup>a</sup>	
Dome	51(50)	53.7 +/-13.4		
Fusiform	32(31.4)	55.9 +/-14.3		
<b>Cysts in inner retina</b>	Yes	81(79.4)	55.2 +/-14.2	F=0.07(1,99), .7
	No	20(19.6)	57.2 +/-16.6	
<b>Septae in cysts</b>	Yes	59(57.8)	57.15 +/-13.5	F=4.2(1,79), .04 <sup>a</sup>
	No	22(21.6)	49.95 +/-15	
<b>DRIL</b>	Yes	23 (22.5)	46.1+/-14.9	F=13.2 (1, 99), <0.001 <sup>b</sup>
	No	78(76.5)	58.1 +/-13.5	
<b>ELM disrupted</b>	Yes	38(37.3)	46.1 +/-14.8	F= 13.2 (1,99), <. 001 <sup>a</sup>
	No	63(61.8)	61 +/-11.5	
<b>EZ disrupted</b>	Yes	42(41.2)	48.26 +/-14.8	F=20.09 (1,99), <.001 <sup>a</sup>
	No	59(57.8)	60.63 +/-12.4	
<b>DR severity stage</b>				
Mild NPDR	53(52)	57.96 +/-14.09	F=3.4 (1,99), .03 <sup>a</sup>	
Moderate NPDR	37(36.3)	55 +/-14.6		
PDR	10(9.8)	45.1+/-14.2		

Abbreviations- DME, diabetic macular edema; DR, diabetic retinopathy; IRF, intra retinal fluid; DRIL, disorganization of inner retinal layers; ELM, external limiting membrane; EZ, ellipsoid zone; NPDR, non proliferative DR; PDR, proliferative DR

<sup>a</sup> P<.05

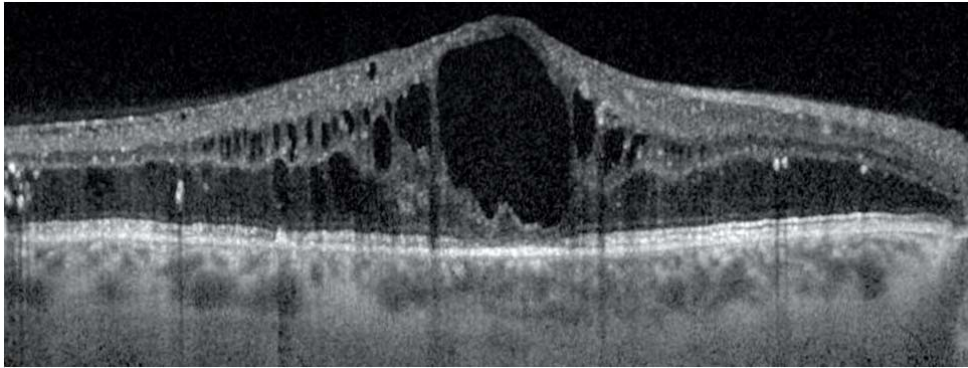
**e Table 4- Correlations between VA and OCT linear variables**

<b>Variable</b>	<b>VA</b> Pearson's correlation, p-value	<b>p-value</b>
RTF per 100 µm	-0.27**	<b>0.005</b>
MRT per 100 µm	-0.4*	<b>0.01</b>
Average global DRIL per 100 µm	-0.53**	<b>0.009</b>
ELM disruption at fovea per 100 µm	-0.41*	<b>0.01</b>
EZ disruption at fovea per 100 µm	-0.44**	<b>0.003</b>
CT at fovea per 100 µm	-0.11	0.2
CT temporal to fovea per 100 µm	-0.1	0.2
CT nasal to fovea per 100 µm	-0.4	0.1

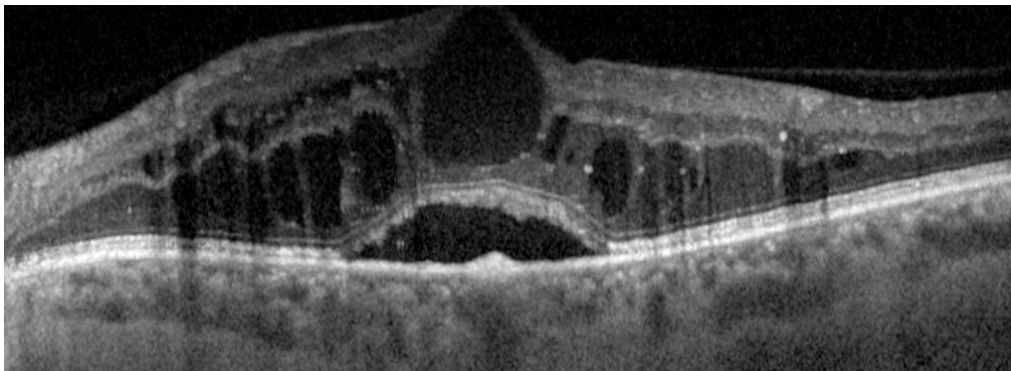
Abbreviations- VA, visual acuity; OCT, optical coherence tomography; RTF, retinal thickness at fovea; MRT, maximum retinal thickness; DRIL, disorganization of inner retinal layers; ELM, external limiting membrane; EZ, ellipsoid zone; CT, choroidal thickness \*\* significant at the level of 0.01, \*significant at level of 0.05



**e Figure 1- SD-OCT image showing both cystoid and diffuse DME**



**e Figure 2- DME with sub retinal fluid**



**e Figure 3- Asymmetrical shape of DME**

