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Optical coherence tomographic biomarkers in diabetic retinopathy and diabetic macular Edema and co-relation with disease severity

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Abstract
Purpose: To evaluate Optical coherence tomographic (OCT) biomarkers in participants diagnosed with diabetes, diabetic retinopathy (DR) and diabetic macular edema (DME) and co relation with disease severity.
Methods: Demographics, visual acuity, SD-OCT, and colour fundus photographs of 110 individuals with diabetes, DR and DME (200 eyes) evaluated between December 2020 and October 2022 were analysed to evaluate disease severity corelation. Features captured on SD-OCT and thickness metrics. On SD-OCT we analysed the OCT scans (Macular cube 6 mm x 6 mm) for central subfield thickness and biomarkers: disorganization of the inner retinal layers (DRIL), presence of hyperreflective dots and foci and their location, intraretinal cystoid abnormalities and shape and presence of septae within the, integrity of the external limiting membrane and ellipsoid zone.
Results: 101 patients (200 eyes) were evaluated; 66 eyes had (33%) moderate NPDR, followed by 38 eyes (19%) with mild NPDR, 29 eyes (15%) with severe NPDR, 14 eyes (7%) very severe NPDR. Biomarkers like DRIL, Hyperreflective foci, ELM and EZ disruption ($p = 0.001$) and intraretinal cystoid spaces ($p = 0.003$) correlated positively with disease severity and negatively with VA.
Conclusion: SD-OCT imaging biomarkers can be utilised as an efficient tool in understanding the disease severity and inter individual differences in visual acuity when there is no difference in ETDRS-based grading of DR that is evident clinically.

Keywords: Small incision cataract surgery, trabeculectomy, glaucoma, intraocular pressure

Introduction

Diabetic retinopathy (DR) is a major complication of diabetes mellitus and a leading cause of visual impairment [1, 2].

Diabetic retinopathy (DR), a well-studied complication of diabetes mellitus (DM), affecting almost 35% of diabetic patients worldwide. DR is known to involve the entire neurovascular unit of the retina [3, 4], studies have identified retinal dysfunction and structural changes due to neuro retinal disruption, at times prior to the characteristic microvascular clinical findings of DR [5-7].

As prevalence of Diabetes mellitus is predicted to double by 2030, hence there is an urgent and vital need to elaborate the cellular mechanisms involved in neurovascular unit disruption, and to identify reliable endpoints of these cellular defects.

Diabetic retinopathy (DR) represents a spectrum of pathological changes that occur in the microvasculature of the eye in patients with diabetes mellitus. Diabetic macular edema (DME) is a characteristic feature of DR and an important cause of vision loss in people with diabetes [8]. In patients with DME, fluid accumulates within the macular tissue layers as a consequence of failure of the blood-retinal barrier. Typically DME causes blurring and distortion of vision, resulting in reduction in visual acuity (VA).

The introduction of time-domain optical coherence tomography (OCT) enabled a more precise non-invasive quantification of overall retinal thickness but it has only modest correlation with VA. Subsequently ultrastructural characterization of retinal pathology on layer-by-layer basis employing SD OCT enabled us to identify various biomarkers in various retinal pathologies and their involvement pattern were studied for their use in diagnosis and analysing disease process progression.

As per National Institutes of Health Biomarkers Definition Working Group defined Biomarker as “Characteristic that is objectively measured and evaluated as an indicator of

normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [9].
Some of the various biomarkers that have been studied on OCT include:

Disorganization of retinal inner layers Disorganization of retinal inner layers (DRIL)
The inability to distinguish between the ganglion cell layer–inner plexiform layer complex, inner nuclear layer and outer plexiform layer, measured on OCT B-scans by looking at the central 1 mm retinal zone. Disorganization of more than 50% or >500µm of this area is considered significant and is associated with worse visual prognosis in eyes with edema or resolved edema [10].

Integrity of ELM and EZ
ELM is first hyper-reflective band and is representative of the junctional complex between the glial Müller and photoreceptor cells [11] and serves as a barrier against macromolecules [12].
Studies have shown integrity of outer retinal layers as a direct indicator of the health of the retinal photoreceptors and RPE, that eyes with intact IS/OS junction have better visual gains post treatment.

Hyperreflective FOCI
First described by Bolz *et al*. as hyperreflective dots throughout all layers of retina, often within the septae between cystoid spaces, or confluent lesions in the outer retinal layers, or focal deposits within the vascular wall of microaneurysms.
HF are believed to represent extravasated protein and/or lipid deposits and as precursors of hard exudates, that tended to resorb along with intraretinal fluid after laser treatment
Later hypothesised to be lipid-laden macrophages migrating into cystoid spaces as a result of blood-retinal barrier (BRB) breakdown [13, 14].
In OCT angiography (OCTA), HRF presented decorrelation signals, as an expression of morphological changes in microglia/macrophages or intracellular organelles containing highly reflective material [15].
Glial cell proliferation represents one of the main alterations in diabetic retinopathy and microglia is essential to maintain retinal homeostasis and in inflammatory response [16].
Differentiating features between inflammatory HRF and other subtypes of hyperreflective material (i.e., retinal exudates, haemorrhages, and microaneurysms) on OCT B-scans include location within the inner retina, size ≤30 µm, absence of posterior shadowing, and reflectivity similar to the retinal nerve fiber layer.

Intra Retinal Cystoid Spaces
Elevated VEGF level in subjects of DR and DME, affects the inner blood retinal barrier leading to increased vascular permeability resulting in a decreased osmotic gradient, extracellular fluid accumulation, and cyst formation.
Intraretinal cystoid spaces can be categorized based on their size: small (200 µm), large (101–200 µm), or giant (>200 µm). Large cysts are associated with poor visual prognosis [17].
The septae/bridging retinal processes are said to be residual neural elements, connecting the outer and inner retina and hence aids in transmission of visual signals from the inner retinal layers to the optic nerve axons.
Studies showed that absence of these bridging retinal tissues is related poor prognosis post treatment. These eyes are not likely to show improvement after resolution of cysts leading to foveal atrophy and thinning [18, 19].

Materials and Methods
This was a single-site, cross-sectional observational study conducted at a tertiary referral centre.
The protocol was approved by the Institutional Review Board. Patients were evaluated from December 2020 to October 2022. Written informed consent was obtained from all patients before participation in the study. Subjects enrolled were grouped as diabetics with no DR, with mild NPDR, moderate NPDR, severe and very severe NPDR
Inclusion criteria for the diabetic group were: (1) age > 18 years and (2) diabetes as defined by the American Diabetes Association criteria for diagnosis (3) Those willing to give informed consent for the study.
Eyes were classified as having DME if they had SD OCT central subfield thickness (CST) ≥ 305 µm for men or ≥ 290 µm for women, thresholds established by previous Diabetic Retinopathy Clinical Research Network studies.
Exclusion criteria were significant media opacity precluding adequate image quality, cataract surgery within the previous 6 months, and history of uveitis, retinal vein occlusion, or other non-diabetic retinal pathology that might substantially impact VA, any drug intake that could impair vision, pregnancy or nursing, and inability to give informed consent or to complete testing.
All subject's demographic data were recorded including age, gender, additionally duration of diabetes, and haemoglobin A1c (HbA1c) was also assessed. Subjects further underwent a comprehensive ophthalmologic examination including VA, BCVA, including slit lamp examination, applanation tonometry, dilated funduscopic examination, Colour Fundus Photography and SD-OCT scan. All eyes were classified using the Early Treatment of Diabetic Retinopathy criteria.

Spectral-Domain Optical Coherence Tomography
Horizontal sections of Optical Coherence Tomography (OCT) images passing through the fovea were obtained with a 3D SD OCT (Topcon) instrument in OCT Section mode.
The images were used to evaluate the CRT, intraretinal cystoid space and subretinal fluid (SRF), and hyperreflective foci, presence of DRIL, integrity of ELM and EZ zone.
The CRT was defined as the distance between the internal limiting membrane and the presumed retinal pigment epithelium (RPE) at the fovea.
Retinal thickness was analysed using the ETDRS grid, which included the 1 mm central fovea, 3 mm inner ring, and 6 mm outer ring. The inner and outer rings were sectioned into superior, inferior, temporal, and nasal quadrants
The central 1 mm in diameter (foveal) area and four macular quadrants were evaluated in the foveal area, 7 B-scans were analysed (including 3 B-scans above and 3 scans below the scan passing through the foveal centre). A 1 mm diameter central overlay centred on the foveal depression on the central scan was placed on each of these scans to define the foveal area. This was the area without the inner retinal layers in the macular region. For the quadrants, we assessed 7 B-scans beginning 13line scans above and 13line scans below the central scan line. The retinal areas nasal and temporal to the central 1 mm section were evaluated, yielding superotemporal, superonasal, inferonasal and inferotemporal quadrant.
The following lesions were evaluated for presence, location,

and extent in the foveal area and 4 macular quadrants:
Intraretinal cysts (small cysts <250 µm, medium cysts ≥250 µm but <500 µm and large cysts ≥500 µm in diameter), Hyperreflective foci, ELM/EZ disruption
Eyes with an ELM line that appeared to be complete at the fovea in all scans were classified as ELM present and eyes with an undetectable ELM line in the fovea were classified as ELM disrupted

Statistical analysis
Statistical analysis were performed using SPSS for Windows version 24.
The relationship of VA to baseline variables and each OCT parameter of interest were evaluated by nonparametric analysis using student t test and λ^2 test. λ^2 test also was used to analyse the relationship between the integrity of the ELM line and the EZ zone (IS/OS line).
All values are expressed as the mean standard deviation. All BCVA measurements were converted to the logarithm of the minimal angle of resolution (log MAR) equivalents before statistical analysis. Student t tests and 2 tests were used to compare the 2 hyperreflective foci groups (foci absent in the outer retinal layers group vs foci present in the outer retinal layers group) regarding sex, age, duration of diabetes, HbA1C, total cholesterol, the presence of hypertension, log MAR VA, type of DR, the hyperreflective foci in the inner retinal layers of ELM line (Figure 1), and the integrity of the IS/OS and the ELM lines. The 2 test also was used to analyse the relationship between the integrity of the ELM line and the IS/OS line. Comparisons of the log MAR VA levels of the 3 groups that were classified based on the status of the IS/OS or ELM lines and comparison of the foveal thickness of the 3 ELM groups were carried out.
A P value < 0.05 was considered statistically significant.

Results
Descriptive characteristics of the study are shown in Table 1
101 patients (200 eyes) were evaluated, most common (71%) age group presenting was 60 to 70 years, mean (SD) age for men was 69 (8) and for women was 65 (7). The frequency of the DR severity stages in the 200 eyes (2 eyes were not graded because of poor-quality colour images) is shown in Table 1. Maximum, which is, 66 eyes had (33%) moderate NPDR, followed by 38 eyes (19%) with mild NPDR, 29 eyes (15%) with severe NPDR, 14 eyes (7%) very severe NPDR.
Associations between VA and retinal OCT biomarkers such as presence of DRIL, Intraretinal cystoid spaces, Hyperreflective Foci, ELM and EZ disruption was analysed.

Hyperreflective Foci
The presence, location and distribution of hyperreflective foci was analysed and it was found that of 20 eyes (40%) with normal fundus presented with hyperreflective foci in inner retinal layers.

66%, 79%, 24% eyes of Mild, Moderate and Severe NPDR: Presented with hyper reflective foci in inner retinal layers respectively. Whereas 17% of *moderate*, 59% of severe, 64% of very severe NPDR, 67% eyes of PDR presented with HF in both inner and outer retinal layers. BCVA (LogMAR) in eyes with HF in inner, inner & outer and in cystoid spaces was 0.78, 1.30 and 1.52 respectively. The log MAR VA was (p> 0.0001) worse in the group with hyperreflective foci in the outer retinal layers compared with the group without hyperreflective foci in the outer retinal layers.

ELM Integrity
ELM was disrupted in 111 eyes, Maximum ELM disruption was found in very severe NPDR (100%), followed by severe NPDR (96%), Moderate NPDR (85%) and 24% eyes with mild NPDR had disrupted ELM.; Log MAR mean being 1.8 & 1.69 for PDR and very severe NPDR, 1.19 for severe NPDR, 1.03 for moderate NPDR and 0.82 for mild NPDR.
Hence worsening of visual status was seen with ELM disruption (p>0.001) Table 2

EZ disruption was evaluated and it was disrupted 110 eyes, Maximum EZ disruption was found in very severe NPDR (100%) & PDR followed by severe NPDR (99%), Moderate NPDR (83%), 26% eyes with mild NPDR had disrupted ELM.
LogMAR mean being 1.8 & 1.69 for PDR and very severe NPDR, 1.24 for severe NPDR, 1.03 for moderate NPDR and 0.82 for mild NPDR. Mean visual aquity was least for the diagnosis category with maximum EZ disruption (p>0.001) Table 2

DRIL
DRIL was observed in 99% eyes with very severe and severe NPDR, 67% eyes with moderate NPDR (67%) and 21% eyes with mild NPDR.
Mean (SD) BCVA (LogMAR) value was 1.69 (0.14), 1.24 (0.12), 1.06 (0.06), 0.79 (0.13) for very severe, severe, moderate and mild NPDR with DME as shown in Table 2.
Worsening of visual acuity was seen in severe stages of DR and in eyes with DRIL (p> 0.001).

Association of DRIL with Integrity of ELM/EZ zones
It was found that odds of having DRIL was more in cases with disrupted ELM and disrupted EZ.

Intraretinal cystoid spaces 70 eyes presented with intraretinal cystoid spaces, out of which 53 eyes (78%) had septae and 17 eyes (24%) were without septae. The LogMAR VA in eyes with Intra retinal cystoid spaces with septae was much better than eyes with ICS without septae (1.25 vs1.38, p<0.003) (Table 2).

Table 1: Descriptive characteristics of the study group.

Characteristic	Value	
Age, mean (SD), y	65 (8)	
Male, No. (%)	69	
Female, No. (%)	31	
DM duration, mean (SD), y	18.50 (10.20)	
Ocular characteristic (n = 200)		
Diabetic retinopathy stage	**No. %**	**Mean BCVA**
Normal	25	0.29 (0.50)
Mild NPDR	19	0.75 (0.13)
Moderate NPDR	33	1.01 (0.10)
Severe NPDR	21	1.24 (0.12)

Abbreviations: DM, diabetes mellitus; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2: Association between VA and various OCT based retinal biomarkers in DR and DME

Biomarkers / LogMAR VA	VA	CI	P value
HF-Inner layers	0.78±0.32	0.72 – 0.84	0.001
HF- Outer /Inner and outer layers	1.30±0.30	1.24 – 1.42	
Septae In cystoid abnormalities			
Without septae	1.25±0.18	1.17 – 1.33	0.003
With Septae	1.38±0.18	1.24 - 1.51	
DRIL			
Yes	0.74±0.12	0.66-0.92	0.001
No	1.18±0.20	0.98-1.28	
ELM Disrupted			
Yes	1.18±0.28	1.12-1.22	0.001
No	0.51±0.28	0.45-0.57	
EZ Disrupted			
Yes	1.17±0.30	1.11 – 1.22	0.001
No	0.52±0.28	0.48 – 0.50	
DR severity stage			
Mild NPDR	0.76±0.13	0.72-0.80	
Moderate NPDR	1.01±0.10	0.99-1.00	
Severe NPDR	1.24±0.12	1.19-1.28	
Very severe NPDR	1.69±0.14	1.61-1.78	

Values are means ±standards deviations, Abbreviations: ELM, external limiting membrane; EZ, ellipsoid zone; DME, diabetic macula edema; DR, diabetic retinopathy; DRIL, disorganization of inner retinal layers; NPDR, Non Proliferative diabetic retinopathy; VA, visual acuity.

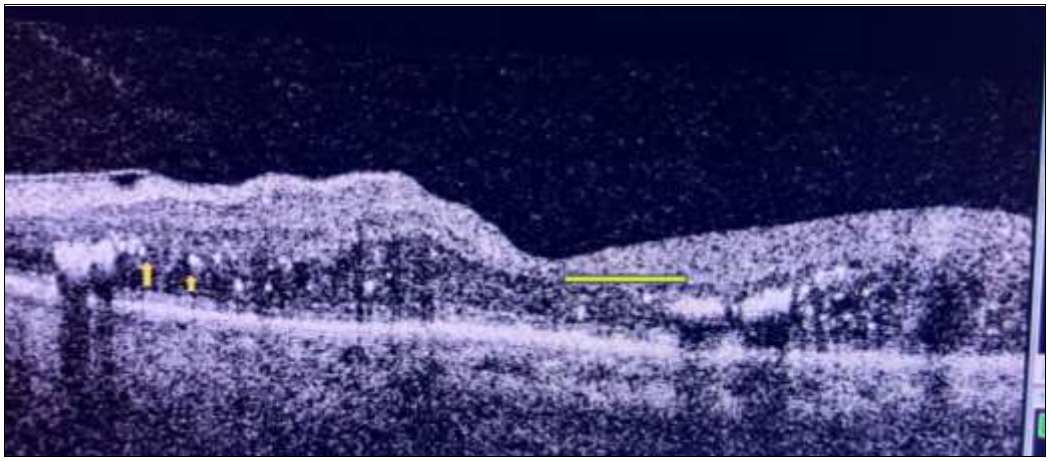

Fig 1: Spectral-Domain Optical Coherence Tomography Image showing various biomarkers

Spectral-Domain Optical Coherence Tomography Image showing hyperreflective foci (HF), disorganization of the retinal layers (DRIL)

Yellow arrows depicting hyperreflective foci, yellow line denotes DRIL

HF denoted by yellow arrows and white line denotes area of DRIL.

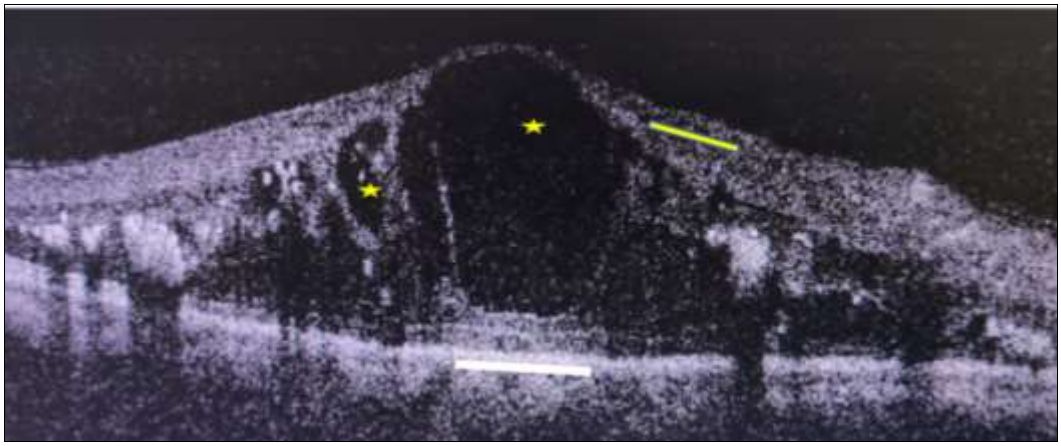

Fig 2: Spectral-Domain Optical Coherence Tomography Images of Disrupted Inner and Outer Retinal Layers and Intraretinal cystoid spaces (ICS) with bridging retinal processes Yellow star denotes ICS. Yellow vertical line shows DRIL, White vertical line shows disruption of ELM and EZ zones.

Discussion

The tomographic images of the retina graded systematically and associations between the presence and severity of a number of morphological features, including DRIL, HF, ELM disruption, the of fluid in DME was analysed and correlated with severity of DR and visual function.

Results from this study suggest that centrally located DRIL correlated with VA in eyes with center-involving DME and more severe stages of DR. It also showed strong correlation with disruption of ELM and EZ zones. Worsening of VA was seen with increasing DR severity and may be related to the presence of DRIL. These findings are similar to those of previous studies (20, 21, 22) showing DRIL to be a predictive marker for visual function outcomes in eyes with DME that resolved after treatment and its association with increasing severity of DR.

A study by Radha *et al*. also showed DRIL's association with increasing severity of DR [23].

It has been concluded that disorganization of the inner retina results from bipolar axons losing their integrity when their elastic limit is exceeded secondary to edema [24] and DRIL represents loss of bipolar, amacrine, or horizontal cells within the inner retinal layers [25].

Another significant finding was association of DRIL and outer retinal changes, since DRIL was strongly associated with ELM and EZ disruption, which were also strongly correlated with much severe degrees of DR and poor visual function. These findings were found to be consistent with other studies [26-29]. Maheshwary *et al*. also concluded that status of inner segment and outer segment and percentage of disruption as VA predictors.

It has been postulated that ELM corresponds to the adherence junction between the Müller cells and photoreceptor cells and acts as a barrier against macromolecules. Impaired retinal function secondary to breakdown of the blood-retinal barrier in DME leads to damage to the ELM and EZ.

In our study intact ELM was associated with better VA in comparison to disrupted ELM similar to studies by Saxena *et al*. [30].

We also evaluated the presence as well as location of hyper reflective foci, whether in inner layers or outer layers. Bolz and associates previously suggested that hyperreflective foci may represent subclinical features of lipoprotein extravasation that act as precursors of hard exudates [31].

Hyper reflective foci in the outer retinal layers might correspond to deposited lipoproteins, lipid-laden macrophages, debris of photoreceptors, and RPE hyperplasia [32].

In our study the presence of hyperreflective foci correlated with poor visual function and amongst that, more so in groups with HF in outer retinal layers and also corelated with disrupted ELM, suggesting HF as a part of pathological mechanism inducing photoreceptor damage following breakdown of blood retinal barrier causing ELM disruption.

So, disrupted ELM might permit these macromolecules to pass through this barrier and be deposited into the outer retinal layers, which is similar to the results of a previous report showing outer retinal discontinuity in eyes with retinal vein occlusion [33].

Cystoid spaces in DME forms secondary to Elevated VEGF levels affecting the inner blood–retinal barrier leading to increased vascular permeability and decreased osmotic gradient, extracellular fluid accumulation, and cyst formation. These cystic foci are associated with disturbed cellular function of the Müller cells glial cells whose cell bodies are in inner retinal layers, these cells are thought to act as metabolic pumps to keep the macula dehydrated and hence act neuro protectively in addition to providing mechanical stability and barrier function. Cystoid changes were also related to ELM and EZ disruptions, and associated with poor retinal function in terms of VA. This might be explained by previous studies showing outer plexiform layer (photoreceptor cells synapse to the secondary neurons) is affected by DME in the inner retinal layer [34], which can cause subsequent photoreceptor loss [35, 36].

Morphological categorisation of eyes with ICS into ICS with or without septae also revealed Better VA in presence of septae, which are considered to be remnant neurosensory components and hence thought to be a good prognostic indicator. Our findings support those of previous investigators [37].

Our study reports an association between DRIL and HF with ELM/EZ integrity and increasing severity of DR. Our finding of worsening of VA with increasing DR severity may be related to the presence of these biomarkers.

The strengths of this study are the systematic grading of colour and OCT images and homogeneous patient sample with DR and DME naive to anti–vascular endothelial growth factor treatment.

Limitation of the study is its cross-sectional design due to which OCT markers identifies could not be evaluated further in terms of their predictive significance and impact on visual function and their developmental correlation with each other.

Conclusion

SD-OCT imaging biomarkers can be utilised as an efficient tool in understanding the disease severity and inter individual differences in visual acuity when there is no difference in ETDRS-based grading of DR that is evident clinically.

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