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Study of OCT based biomarkers as a predictor of visual outcome in diabetic macular edema

Anupriya Aggarwal¹, Rajwinder Kaur^{1*}, Ritesh Singla¹, Tanvir Sidhu²,
Priyanka Gupta¹, Priyanka Dahiya¹¹Dept. of Ophthalmology, Adesh University, Bathinda, Punjab, India²Dept. of Community Medicine, Adesh University, Bathinda, Punjab, India

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ABSTRACT

Purpose: To determine the association between optical coherence tomography (SD-OCT) based biomarkers and visual acuity (VA) in diabetic macular edema (DME).**Materials and Methods:** This cross-sectional study was conducted at a tertiary care teaching hospital between January 2021 and July 2022. The study included 54 eyes (30 patients) with DME. Based on the early treatment diabetic retinopathy study (ETDRS) grading system, these were classified as mild (n=1), moderate (n=31), severe (n=14), and very severe (n=8) non-proliferative diabetic retinopathy (NPDR). The demographics, VA recorded using ETDRS chart and ETDRS scoring system, slit lamp biomicroscopy findings, colour fundus pictures and biomarkers determined using macular scans on SD-OCT were noted. Six eyes with proliferative diabetic retinopathy (n=4) and considerable media opacity (n=2) were excluded. The data was entered into Microsoft Excel spreadsheet 2021 and IBM's SPSS 26 statistical program was used to calculate the results.

VA and biomarkers, which included central macular thickness, disorganisation of retinal inner layers (DRIL), ellipsoid zone disruption (EZD), choroidal thickness were measured on SD-OCT.

Results: The mean age was 59.4±9.4 years, and male to female ratio was 1.3:1. Mean uncorrected and best corrected VA were 46 and 61 letters, 55.12±1.76 and 67.25±10.05 letters for moderate NPDR, 43.07±3.95 and 52.14±17.83 letters for severe NPDR, and 26.50±16.53 and 36±16.38 letters for very severe NPDR, respectively. VA deteriorated with increasing disease severity. Poorer VA was associated with increased average foveal and macular thickness and increased mean horizontal disruption of the inner retinal layers (DRIL). Average choroidal thickness positively correlated with increasing DR severity.**Conclusion:** Poorer VA was associated with increasing DR severity, increased central retinal thickness, increased mean horizontal DRIL and increased average foveal choroidal thickness. We found no statistically significant correlation between VA and ellipsoid zone disruption.This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.For reprints contact: reprint@ipinnovative.com

1. Introduction

Diabetes mellitus (DM) is a group of chronic, metabolic diseases characterized by hyperglycaemia resulting from defects in either insulin secretion or insulin action.¹ Diabetic retinopathy (DR) is the most common

microvascular complication of diabetes, with a prevalence of 22.27% among affected individuals,² and diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetic retinopathy.³ Although varying prevalence is observed, the Diabetes Control and Complications Trial (DCCT) reported that 27% of type 1 diabetes (DM1) patients developed macular edema within nine years of onset⁴ and the Wisconsin Epidemiologic

* Corresponding author.

E-mail address: rajujerry26@gmail.com (R. Kaur).

Study of Diabetic Retinopathy (WESDR) reported increase in prevalence from 3% within 5 years of diagnosis to 28% after 20 years with type 2 diabetes.⁵

DME arises from the diabetes-induced breakdown of the blood-retinal barrier (BRB), manifested as retinal thickening caused by the accumulation of intra-retinal fluid, primarily in the inner and outer plexiform layers.³ It causes distortion and blurring of vision, which is a reduction in visual acuity (VA). It can occur at any stage of diabetic retinopathy.⁵ Although Increased macular thickness in DME is detectable on biomicroscopic examination and coloured fundus photographs, the advent of Spectral Domain-Optical Coherence Tomography (SD-OCT), which has better resolution and repeatability, has made it possible to characterise pathology in the retina layer by layer and detect early DME.⁶ Various studies have established correlation between VA and retinal morphological features like disorganization of the inner retinal layers (DRIL), ellipsoid zone disruption (EZD) and average foveal thickness in DME.^{7–10}

This study has been designed to assess these biomarkers on SD-OCT and correlate them with visual acuity. This will also help predicting the visual outcome of the patients undergoing treatment for DR and DME.

2. Material and Methods

The ophthalmology department of a tertiary care teaching hospital conducted this cross-sectional study between January 2021 and July 2022. The study adhered to the tenets of the Declaration of Helsinki and received ethical approval from the Institutional Research Ethics Committee. This study included all patients diagnosed with non-proliferative diabetic retinopathy (NPDR) with DME based on clinical examination, fundus photography, OCT, and fundus fluorescein angiography (FFA). Patients aged over 18 years, after obtaining prior informed consent were included. Patients with any other retinal pathology such as degenerative or vascular retinal diseases, ischemic maculopathy, inflammatory ocular diseases or any other retinal pathology secondary to systemic diseases other than diabetes mellitus, any media opacities in whom OCT imaging was not possible or known allergy to fluorescein dye, renal failure or any other contraindication to fluorescein angiography were excluded. After applying the inclusion and exclusion criteria, an eye diagnosed with NPDR with DME was taken as a study unit.

After taking informed written consent, a detailed ophthalmological examination was performed in all the patients which included uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) recorded on ETDRS chart, detailed slit-lamp biomicroscopy, fundus examination with indirect ophthalmoscope. The vision recorded on an ETDRS chart was then translated into ETDRS letters and Log Mar. This was followed by fundus

photographs captured on Visucam (Carl Zeiss Meditec) and OCT imaging with Heidelberg Spectralis in eye under examination. Single line and raster scanning protocols were used for image acquisition in all patients. This consisted of a single horizontal and vertical line scan through the fovea followed by a 6 mm X 6 mm macular raster scan with 7 raster lines. The parameters which were recorded on OCT were:

1. Central Macular Thickness (CMT)- The macula was divided into nine regions with three concentric rings centred on the fovea according to the ETDRS chart. Foveal thickness was defined as macular thickness within the innermost 1 mm ring, and mean macular thickness was defined as the average macular thickness from all nine regions of the ETDRS map. As Appukuttan et al¹¹ suggested, 220-300 μm was taken as the normal range for central foveal thickness for all the study patients.
2. DRIL - DRIL was defined as the inability to distinguish between the ganglion cell layer-inner plexiform layer complex, inner nuclear layer, and outer plexiform layer.⁶ Sun et al¹⁰ described the method to determine the horizontal extent of DRIL in each of the 7 B-scans. The foveal scan was selected first, followed by the three scans immediately superior and inferior. The horizontal measurements from all these scans were summed to derive an average global DRIL measure for each subject.:
3. EZD - Ellipsoid zone disruption was measured using the same protocol as described previously for measurement of DRIL. The extent of EZD was graded as:
 - (a) Grade 0- Intact EZ
 - (b) Grade 1- EZD localized to 1mm macular cube
 - (c) Grade 2- EZD localized to 3mm macular cube
 - (d) Grade 3- EZD localized to 6mm macular cube
4. Choroidal thickness (CT)- The choroidal thickness was measured using the same protocol described previously for CMT measurement on an ETDRS map in which the macula was divided into nine regions with three concentric rings centred on the fovea.

The outcome measures analysed were uncorrected and best-corrected visual acuity, CMT, DRIL, EZD and CT.

3. Results

All raw data was then entered into a Microsoft Excel spreadsheet 2021 and analysed using the appropriate statistical techniques with SPSS 26, an IBM product. The distribution of DM type, duration, treatment, other systemic diseases and NPDR severity were noted. Categorical data was presented as numbers and percentages while the quantitative data was presented as the mean $\pm$ SD

(Standard Deviation). Pearson's chi-squared test was used to determine whether there was a statistically significant difference between the expected observed frequencies in one or more categories. T-test and ANOVA analysis were used to differentiate means among the two or more groups. We considered a P value of ≤ 0.05 as statistically significant in this analysis.

Table 1 shows the descriptive and ocular characteristics of study population. A total of 54 eyes of 30 patients with NPDR with DME were included. Majority of subjects were male (56.6%, n=17) and 13 subjects (43.3%) were females. The mean (SD) age of participants was 59.4 ± 9.4 years. All of the patients included in the study had type 2 diabetes. 86.6% of the patients were on oral hypoglycaemic medications; the rest were on either insulin therapy (6.66%) or combined insulin and oral therapy (6.66%). According to ETDRS classification, one eye (1.9%) had mild NPDR, 31 eyes (57.4%) had moderate NPDR, 14 eyes (25.9%) had severe NPDR, and very severe NPDR was present in 8 eyes (14.8%). Regarding the type of DME pattern, the spongy type was the most common DME pattern seen (n=28, 51.9%).

Mean uncorrected and best corrected VA were 46 and 61 letters, 55.12 ± 1.76 and 67.25 ± 10.05 letters for moderate NPDR, 43.07 ± 3.95 and 52.14 ± 17.83 letters for severe NPDR, and 26.50 ± 16.53 and 36 ± 16.38 letters for very severe NPDR, respectively. On comparing VA with DR severity, better visual acuity was associated with a less severe stage of DR ($p=0.000$). Average foveal and macular thickness was highest in very severe NPDR ($507.55 \pm 133.47 \mu\text{m}$, $550.5 \pm 172.85 \mu\text{m}$) and lowest in mild NPDR ($329.2 \mu\text{m}$, $341 \mu\text{m}$), as shown in Table 2.

Half of the examined eyes with DME (n = 25, 50%) showed the presence of DRIL. No DRIL was found in eyes with mild NPDR. The mean horizontal measure of DRIL was $886 \pm 668.88 \mu\text{m}$ in very severe NPDR, while the value in moderate NPDR and severe NPDR was $322.94 \pm 424.688 \mu\text{m}$ and $423.43 \pm 417.127 \mu\text{m}$ respectively (Table 2). Additionally, compared to severe and moderate NPDR, very severe NPDR had the highest average foveal choroidal thickness. When average foveal and macular thickness ($p=0.042$, 0.02), DRIL ($p=0.034$), and average foveal choroidal thickness ($p=0.000$) were compared among the various grades of NPDR, one-way ANOVA showed statistically significant difference (Table 3).

The degree of association between VA and central retinal thickness was assessed. Poorer UCVA and BCVA were associated with increased average foveal thickness ($r = -0.331$, $p = 0.014$; $r = -0.465$, $p = 0.000$ respectively) and increased average macular thickness ($r = -0.384$, $p = 0.004$; $r = -0.502$, $p = 0.000$ respectively) establishing a negative correlation. Similarly, a negative correlation was established in assessing degree of association between VA and the mean horizontal measure of DRIL. Eyes with increased

Table 1: Demographic and clinical characteristics of the study population

Characteristics	No. (%)
Participants= 30	
Age	
30-45 years	2 (6.66)
46-60 years	13 (43.33)
61-75 years	15 (50)
Duration of DM	
≤ 5 years	4 (13)
6-10 years	8 (26)
11-15 years	11 (36)
16-20 years	4 (13)
21-25 years	2 (6)
> 26 years	1 (3)
Eye Involved	
Right eye	28 (51.9)
Left eye	26 (48.1)
Type of DME	
Spongy type	28 (51.9)
Cystic spaces	11 (20.4)
Serous retinal detachment (SRD)	5 (9.3)
Spongy type + SRD	7 (13)
Cystic spaces + SRD	3 (5.6)

Table 2: Distribution of OCT biomarkers

Variable	Mean $\pm$ SD
Average foveal thickness (μm)	
Mild NPDR	329.2
Moderate NPDR	366.26 ± 84.23
Severe NPDR	446.7 ± 95.76
Very severe NPDR	507.55 ± 133.47
Average macular thickness (μm)	
Mild NPDR	341
Moderate NPDR	403.68 ± 119.42
Severe NPDR	499.35 ± 550.5
Very severe NPDR	550.5 ± 172.85
DRIL-mean horizontal measure (μm)	
Mild NPDR	None
Moderate NPDR	322.94 ± 424.688
Severe NPDR	423.43 ± 417.127
Very severe NPDR	886 ± 668.88
Ellipsoid zone	
Intact	39 ± 72.22
Grade 1 disruption	1 ± 1.9
Grade 2 disruption	9 ± 16.7
Grade 3 disruption	5 ± 9.3
Average foveal choroidal thickness (μm)	
Mild NPDR	347
Moderate NPDR	306.29 ± 58.444
Severe NPDR	360.5 ± 73.868
Very Severe npdr	412.63 ± 56.475

mean horizontal DRIL showed poorer UCVA ($r = -0.375$, $p = 0.006$) and BCVA ($r = -0.385$, $p = 0.004$) (Table 4).

The Ellipsoid zone was intact in the majority of patients (72.22%, $n = 39$), while EZD was found in 27.88% ($n = 15$) Patients. Among them, grade 1 EZD was present in 1.9% of eyes ($n = 1$), grade 2 EZD in 16.7% of eyes ($n = 9$), and grade 3 EZD in 9.3% of eyes ($n = 5$). One-way ANOVA was performed to compare UCVA and BCVA according to EZD. The f value was 0.410 and 1.645, respectively, with 1 degree of freedom. The difference was found to be statistically non-significant.

Average foveal choroidal thickness in very severe NPDR was highest with value of $412.63 \pm 56.475 \mu\text{m}$ while $360.5 \pm 73.868 \mu\text{m}$ and $306.29 \pm 758.444 \mu\text{m}$ in severe and moderate NPDR, respectively. Increased average foveal choroidal thickness was seen in severe NPDR with DME. One-way ANOVA applied to compare average foveal choroidal thickness between severity groups showed statistically significant difference (degree of freedom = 3, $f = 7.052$, $p = 0.000$) (Table 3).

4. Discussion

DR is a progressive disease with microvascular alterations that lead to retinal ischemia, retinal permeability, neovascularization, and macular edema.³ DME is the most common cause of vision loss in patients with diabetic retinopathy. This study aimed to determine the association between retinal morphology on SD-OCT and VA in DME. The diagnosis and severity of DR were established with indirect ophthalmoscopy after pupillary dilatation, fundus photographs and FFA. Cases with PDR and ischemic maculopathy were excluded after considering their FFA findings.

Only one eye (1.9 percent) had mild NPDR, 31 eyes (57.4 percent) had moderate NPDR, 14 eyes (25.9 percent) had severe NPDR, and eight eyes (eight) had very severe NPDR (14.8 percent). The study's findings suggest that both uncorrected and best-corrected visual acuity deteriorated as the severity of DR increased, as shown in Table 3. Hisham Alkuraya et al¹² published similar statistically significant outcomes in their study comparing the severity of DR and visual acuity in DME patients ($p = 0.002$). Jeffrey R. Willis et al¹³ established that the functional burden associated with vision increased as DR severity increased ($P = .02$).

We found that UCVA and BCVA worsened as the central retinal thickness increased. Eyes with increased average foveal and macular thickness had poorer VA. This correlation was statistically significant and consistent with the findings of Hisham Alkuraya et al.¹² who established that the retinal thickness reflects the visual acuity with the best correction in eyes with DME. Sng CCAet al¹⁴ showed that diabetic participants with moderate or severe DR had greater foveal and temporal outer macula thickness than those with no or mild DR ($P = 0.003$). Figure 1 A shows

an SD-OCT image showing the increased central macular thickness and a spongy type of DME pattern.

DRIL is characterised as unable to distinguish between the ganglion cell layer- inner plexiform layer complex, the inner nuclear layer, and the outer plexiform layer. DRIL can be associated with or without a centre-involved DME. DRIL is measured on OCT B-scans by looking at the central 1 mm retinal zone. Disorganization of more than 50% or $>500 \mu\text{m}$ of this area is considered significant and is linked to a worse visual prognosis in eyes with active or resolved edema. Additionally, it has been proposed that DRIL represents the loss of horizontal, amacrine, or bipolar cells within the inner retinal layers.¹⁰ A centrally located DRIL and an increased horizontal mean measure were associated with lower VA outcomes in eyes with DME (UCVA: $r = -0.375$, $p = 0.006$; BCVA: $r = -0.385$, $p = 0.004$) (Table 4). These findings are consistent with prior studies that identified DRIL as a predictor of VA outcomes in eyes with DME that improved after treatment.^{10,15,16} We also found that increased mean horizontal DRIL was associated with increased average foveal and macular thickness ($r = 0.665$, $p = 0.000$; $r = 0.475$, $p = 0.000$). The null Hypothesis is rejected as the correlation has been found to be significant. Hence, UCVA and BCVA both have negative correlation with various variables predicting the severity of DR. Figure 1 B,C show SD-OCT images of diabetic macular edema with DRIL along with hyperreflective dots and hard exudate.

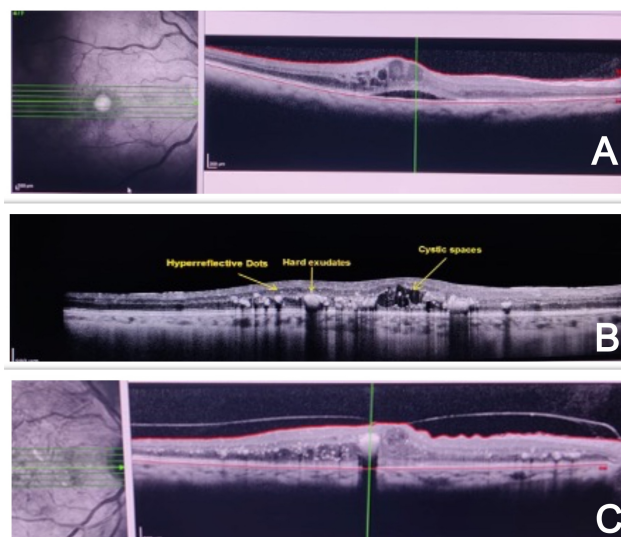


Figure 1: A): Spectral-domain optical coherence tomography image showing serous retinal detachment along with spongy type of DME with increased CMT; B): Spectral-domain optical coherence tomography image showing cystic spaces, DRIL, EZD, hyperreflective dots and hard exudates; C): Spectral-domain optical coherence tomography image showing disruption of inner retinal layers along with multiple hyper-reflective dots and hard exudate with back-shadowing

Table 3: Distribution and correlation of variables with severity of DR

Variable	Mild NPDR (ETDRS letters)	Moderate NPDR (ETDRS letters)	Severe NPDR (ETDRS letters)	Very severe NPDR (ETDRS letters)	Significance (degree of freedom)
UCVA, mean±SD	46	55.12±11.76	43.07±13.95	26.50±16.53	.000 (10.871)
BCVA, mean±SD	61	67.25±10.05	52.14±17.83	36±16.38	.000 (12.894)
Average foveal thickness (μm), mean±SD	329.2	366.26±84.23	446.7±95.76	507.55±133.47	.042 (2.933)
Average macular thickness (μm), mean±SD	341	403.68±119.42	499.35±188.32	550.5±172.85	.002 (5.854)
Dril- mean horizontal measure (μm), mean±SD	-	322.94±424.688	423.43±417.127	886± 668.88	0.034 (3.136)
Average foveal choroidal thickness (μm), mean±SD	347	306.29±58.444	360.50±73.868	412.63±56.475	.000 (7.052)

Table 4: Correlation of variables with visual acuity

Variable	UCVA		BCVA	
	r value	p value	r value	p value
Average foveal thickness (μm)	-.331*	.014	-.465**	.000
Average macular thickness (μm)	-.384**	.004	-.502**	.000
DRIL- mean horizontal measure (μm)	-.375**	.006	-.385**	.004

**Correlation is significant at the 0.01 level (2-tailed).

In 39 eyes (72%), ellipsoid zones were discovered to be intact, while 15 eyes (28%) showed EZD (Table 2). The integrity of the retinal photoreceptors and RPE is directly correlated with the integrity of the outer retinal layers. The correlation between EZD and UCVA or BCVA was not statistically significant. However, a statistically significant correlation between the presence of EZD and visual acuity was shown in studies like those by Bing Li et al.¹⁷ Lucy J. Kessler et al.,¹⁸ and Gupta SK et al.¹⁹ but this correlation was not seen in our investigation. 31.5 percent (n=17) of eyes with DME had hyperreflective dots, while 59.3 percent (n=32) had hard exudates. Hyperreflective dots are deposits within the walls of intra-retinal microaneurysms in DME patients and can be seen in any type of DME. Studies have denoted them as a morphologic sign of lipid extravasation in diabetics. These can be seen scattered throughout all retinal layers and can form confluent plaques in the outer plexiform layer.¹² Hyperreflective spots are lipoproteinaceous (albumin and fibrin) deposits in the outer retinal layers characterized by back shadowing, and sizes larger than 30 μm can be seen on retinal OCT. Quantitative information may be useful to monitor progression of hard exudates and treatment response in diabetic maculopathy.²⁰ Figure 1 C shows example of OCT image showing EZD, hyperreflective dots and hard exudates with back shadowing.

We found that increase in average choroidal thickness correlated with increasing severity of NPDR (p=0.000) (Table 3). Jee Taek Kim et al.²¹ found similar statistically significant results when comparing the mean sub-foveal and parafoveal choroidal thickness between eyes with, without or treated DME (p 0.05). Additionally, they correlated elevated VEGF levels to an increase in choroidal thickness, which dilated choroidal veins. Hiroaki Endo et al.,²² who evaluated total central choroidal thickness in eyes with and without DME, found significantly thicker total CCT layer in DME+ as compared to no DME (P < 0.05). It has also been proposed that baseline sub-foveal choroidal thickness serves as a predictor of response to anti-VEGF therapy.²³

5. Limitations

An important limitation of the present study is its cross-sectional design. We are unable to predict the impact of various OCT markers that were identified on retinal function over a longer period. Even while our investigation could lead to some encouraging findings, conducting a much larger scale multicentric study would be suggested to solidify these conclusions.

6. Conclusion

In summary, OCT provides valuable information on the retinal morphological changes associated with centre-

involving diabetic macular edema. Poorer VA was associated with increased DR severity, central retinal thickness, mean horizontal DRIL, and average foveal choroidal thickness. In eyes with baseline centre-involved DME, DRIL appears to be a strong predictive biomarker for VA. The development of DME or the progressive thickness of the choroidal layer with DR may reflect the disease's parallel progression.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Author biography

Anupriya Aggarwal, Junior Resident

Rajwinder Kaur, Professor  <https://orcid.org/0000-0003-3430-6553>

Ritesh Singla, Professor

Tanvir Sidhu, Professor

Priyanka Gupta, Associate Professor

Priyanka Dahiya, Assistant Professor

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