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Original Article

Importance of ellipsoid zone line in the treatment of diabetic macular edema.

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Abstract:

Introduction: Diabetic macular edema (DME) is a worst manifestation of diabetic retinopathy (DR). Current advanced techniques may reverse DME, usually evaluated by the improvement in visual acuity (VA). In clinical practice VA is not improved even after marked decrease in the macular thickness. Structures abnormalities for example to ellipsoid zone (EZ) may account for post treatment visual outcome.

Objectives: To evaluate the relationship between Ellipsoid Zone line (EZ Line) and best corrected visual acuity (BCVA) after treating diabetic macular edema in type II diabetic patients.

Methodology: For this prospective and observational study patients of type II diabetes mellitus with clinically significant macular edema (CSME) without proliferative diabetic retinopathy were recruited. The BCVA was recorded by Snellen Acuity Chart and discriminant values of macular thickness and EZ line defect were evaluated using Ocular Coherence Tomography at the time of presentation and during follow-up period. SPSS 22 version was used for results analysis

Results: At 6th months follow-up, overall improvement in interruption of EZ line was good but statistically significant (P≤ 0.001) was found in sub class II a. The mean reduction in central sub foveal thickness (CSFT) was found significant (P≤ 0.001) in all class of EZ line but the mean value of BCVA in class I EZ line (70±SD18, P≤ 0.001) was better than class II (45±SD18, P-value = 0.021); and we did not find any correlation between the BCVA and level of interruption of EZ line after progressive decrease in CSFT (r = 0.210, P-value = 0.021).

Conclusion: It has been concluded the by the quantitative measurement of retinal layer with OCT we can say that EZ line continuity is closely linked to visual outcome in eyes with macular edema.

Keywords: Ellipsoid Zone Line, CME, Integrity of IS OS junction, CSFT

Introduction:

In twenty first century the diabetes mellitus is a serious public health issue that leads to decrease vision due to diabetic retinopathy (DR). Diabetic macular edema is another worst manifestation of diabetic retinopathy. Diabetic macular edema (DME) is another worst manifestation of diabetic retinopathy(DR).[1,2] Advancement in the techniques of laser photocoagulation[3] and different pharmacological interventions can reverse the DME[4] that is usually evaluated by the improvement in visual acuity (VA)[5] in clinical practice, but sometime marked decrease in the macular thickness could not

improve the VA despite the successful treatment.[6,7] It means not only the macular thickness some other microstructural abnormalities like subretinal fluid, intraretinal exudates, vitreomacular interface abnormalities and damage to ellipsoid zone (EZ) line that is a junction of photoreceptors inner segment (IS) & outer segment (OS) also hamper the post treatment visual outcome.[8] By the quantitative assessment of these abnormalities with help of new generation optical coherence tomography (OCT) we can predict the visual outcome prior to any type of treatment. [9] Correlation of integrity of EZ line at fovea with the VA in the vascular diseases has been defined by several studies,[10]Advance version of OCT is a best tool to evaluate the status of EZ line (photoreceptors inner/outer segment junction), can be recognized as the second hyper-reflective line just below external limiting membrane (ELM) and just above the retinal pigment epithelium (RPE).[11]

Rationale of study:

In cases of diabetic macular edema, although integrity of EZ line remains invisible yet it may predict outcome of visual outcome after treatment of macular edema. It is therefore logical to investigate integrity of EZ line and its relationship to visual outcome after treating diabetic macular edema.

Objective:

To investigate the integrity of the EZ line in relationship to visual outcome after treating the diabetic macular edema.

Methodology:

This prospective study conducted at Institute of Ophthalmology, Liaquat University of Medical and Health Sciences Jamshoro between July 2020 to June2021. During this period 100 consecutive patients were enrolled. Prior permission for this research was taken from Local Ethics Committee of the Institute. Written consent was obtained from all participants and each subject informed that the study will be carried out in accordance with local and regional regulations under good clinical practice and there are no additional risk/hazards of this research.

Inclusion Criteria:

- Patients older than 40 years with type II diabetes.
- Diabetic macular edema; diffuse or cystoid.
- Best Corrected Visual Acuity 6/60 to 6/18.
- Intra ocular pressure less than 20 mmHg.
- Clear optical zone.
- Round, reacting, regular pupil without iris neovessels.

Exclusion Criteria:

- Significant media opacity due to; corneal opacity & moderate to dense cataract.
- Macular edema other than DME, Exudation beneath fovea & Macular ischemia
- Proliferative diabetic retinopathy.
- Abnormalities of vitreo-macular junction like; Epiretinal membrane, and/or vitreomacular traction.
- History of (H/O) anterior and /or posterior uveitis.
- Laser or prior eye surgery like; vitrectomy and cataract surgery within the past 6 months.
- Glaucoma / ocular hypertension.
- Treated with any type of intravitreal injection (IVI)

Following clinical evaluations were performed:

- The BCVA was recorded by Snellen Acuity Chart and converted to ETDRS letter score.
- Applanation tonometer with slit lam biomicroscope was used to record intra ocular pressure (IOP) and
- Colored fundus photograph & macular thickness, and the integrity of ellipsoid zone line that was taken with Ocular Coherence Tomography.

Recruited patients were randomly selected and subjected to surgical intervention with IVI anti-vascular endothelial growth factors (AVEGF) and mETDRS grid laser photocoagulation (GLP). The intravitreal AVEGF (Bevacizumab: 1.25 mg/0.05 ml) was injected for 3 consecutive months and then as per need. Post IVI antibiotic eye drops one drop four time in a day and post GLP non-steroidal anti-inflammatory eye drops one drop QID was advised. The Swept Source –Ocular Coherence Tomography; DRI-OCT. Topcon, Tokyo, Japan was used to obtain good quality images of central macula because it has an axial resolution of 5µm and transvers resolution 20µm.It has excellent tissue penetration because it uses a short cavity swept laser with a tunable wavelength (1050 nm). High speed scanning 100000 A-scans/sec eliminates chances of artifacts. SS-OCT also has ability to provide a wide field image up to 12 × 12 mm.

Measurements of Macular Thickness

After recent advances in the technologies of OCT the retinal layers can be measured quantitatively to monitor the disease progression or treatment efficacy. We used three dimensional (3D) square scan and radial scan. The 3D square of 7 mm × 7 mm, consists of multiple horizontal line scans, that comprises 256 B/512 A-scans that

generates the ETDRS grid to assess macular thickness in central sub field of macula.

The ellipsoid zone was evaluated by considering the continuity of the EZ line in the central fovea, any interruption in the line, can be distinguished loss of back reflection line between ELM and RPE was measured by using the inbuilt caliper.

The integrity of EZ line was evaluated throughout the length of scan and damage to line was classified as follows: Class I: Intact EZ line thought scan (Figure 1). Class II: Interrupted EZ line (Figure: 2,3,4) Class II sub classified as C II A: mild interruption of EZ line (300 µm to 500µm), C II B: moderate interruption of EZ line (500µm to1000µm); and C II C: Sever interruption of EZ line (1000µm to ≥1500µm).

The thickness of macular region calculated with SS-OCT in all 3 concentric rings of ETDRS map (7×7mm) and were recorded from the scans of each subject. The innermost 1 mm ring is the fovea while the 3 mm inner and 6 mm outer ring are further divided into four equal regions. The color of map shows the average retinal thickness (ART) in each circles and monitored by different colors, Warm colors define the thicker and cool colors indicate thinner retinal areas. The central 1 mm average CSFT has high diagnostic value and it associates with visual outcome. Best corrected visual acuity and OCT was done to all patients before treatment and during follow-up period 1st, 3rd and 6th months.

Statistical Analysis

SPSS Version 20 was used for data management and evaluation. All values are expressed as the mean ± standard deviation percentages. BCVA was recorded by Snellen Acuity method than theses converted to ETDRS letter score with the help of Gregori et al[12] procedure, to facilitate statistical calculation. Correlation between two groups with respect to numeric variables were done by Student's t-tests. The chi-square test was used to compare between the groups with respect to categorical data. The relationship between the numeric variables was evaluated by using the Spearman correlation coefficient. P-values < 0.05 were considered significant.

Results:

The demographic and base line clinical characteristics are shown in table no 1. The mean age of patients who got IVI AVEGF was 49.45 ±7.93 years and of those who went for GLP the mean age was 52.09 ±7.36 years. The mean period of diabetes was 13.12 (SD±3.42) years. Out of fifty 26 (52%) males and out of fifty 24 (48%) females went for IVI AVEGF and out of another fifty 23 (46%) male and 27 (54%) females were treated with mETDRS grid laser photocoagulation (GLP).

Table 1: Baseline Demographic and Mean Data of Clinical Characteristics.

Characteristics	AVEGF Group	Grid Laser Group
Age (years)	49.45(±8.23)	52.09(±6.93)
Gender Male n (%) Female n (%)	 26 (52) 24 (48)	 23 (46) 27 (54)
Disease duration (year)	12.48(±2.91)	17.68(±2.49)
HbA1c (%)	08.15(±0.78)	07.96(±0.76)
IOP (mmHg)	17.68(±2.49)	18.20(±3.19)
Blood pressure (mmHg) Systole Diastole	 143(±17.11) 90 (±08.10)	 140(±15.90) 89(±08.10)

n = Number, % = Percentage, ± = Standard Deviation

EZ Line Results

In this study, before treatment we found 50% case of EZ line in class I (intact EZ line) and 50% in Class II (interrupted EZ line). In class II 40% EZ line was mildly interrupted, 28% cases were moderately interrupted and 32% were found in sub Class II c. In class II of EZ line sixteen eyes showed improvement in the defect, six eyes worsening in the defect, 28 eyes with no change, at 6th months follow-up after treatment (Table2).

Table 2: Baseline and Mean Improvement in EZ Defect

Classification of Ellipsoid Zone	Baseline n (%)	Improved n (%)	Not improved n (%)	Worsen n (%)
Class I: Intact EZ	50 (50)	----	-----	----
Class II: Interrupted EZ				
C II A: Mild	20 (40)	10(20)	10(20)	-----
C II B: Moderate	14 (28)	04(08)	08(16)	02(04)
C II C: Severe	16 (32)	02(04)	10(04)	04(08)

Table 3: Baseline and Mean Central Sub Foveal Thickness and Best Corrected Visual Acuity

Classification of Ellipsoid Zone	CSFT µm ±SD			BCVA (ETDRS letter score) of Ellipsoid		
	Baseline	Changed	p value	Baseline	Improved	p value
Class I: Intact EZ	504 ±189	310 ±130	≤ 0.001	47	70	≤ 0.001
Class II: Interrupted EZ						
C II A: Mild	507 ±189	235 ±128	≤ 0.001	47	65	≤ 0.001
C II B: Moderate	463 ±159	281 ±143	0.002	42	62	0.004
C II C: Severe	462 ±165	220 ±140	0.004	40	45	0.021

BCVA Results

Baseline mean BCVA of Class I EZ line was 47 (±SD18) letters, (ranged from 4 to 76 letters) improved to 70 (±SD 17) letters and was statistically significantly (P≤ 0.001) as compare to Class II EZ line after each visit (Table3)

Comparison of Integrity of EZ Line and CSFT with BCVA

At 6th months follow-up, overall improvement in interruption of EZ line was good but statistically significant (P≤ 0.001) was found in sub class II a (mild interruption) (Table 2). The mean reduction in CSFT was excellent (P≤ 0.001) in all class of EZ line but the mean value of BCVA in class I EZ line (70±SD18, P≤ 0.001) was better than the severely interrupted EZ line (45±SD18, P = 0.021); however, there was no correlation between the BCVA and level of interruption of EZ line after progressive decrease in central subfield foveal thickness (r = 0.210, P-value = 0.021). But we found good association between the BCVA (r =0.613, P-value < 0.001) and the improvement in interrupted EZ line (r = 0.498, P-value < 0.001) (Table 3).

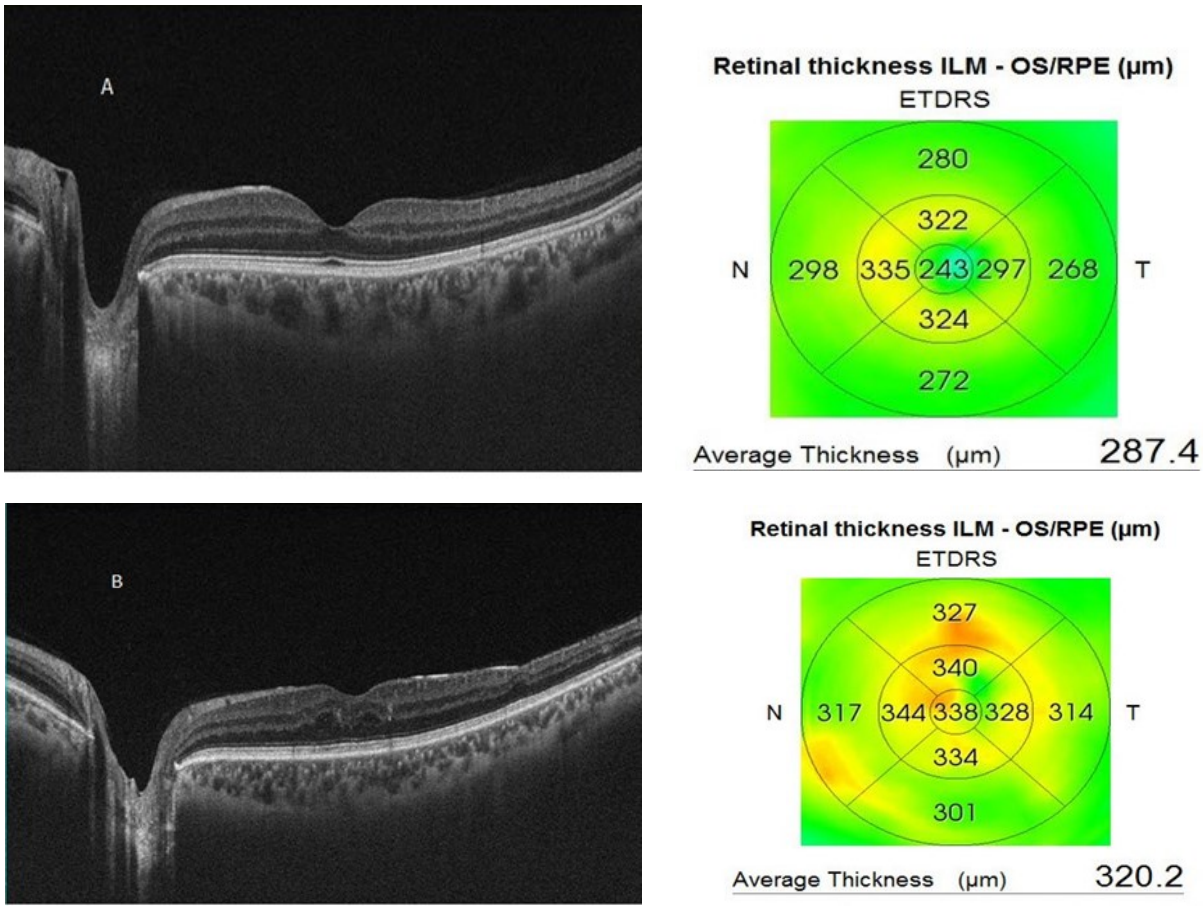

Figure I: SS OCT: A) showing normal retina. B) showing DME with intact EZ line

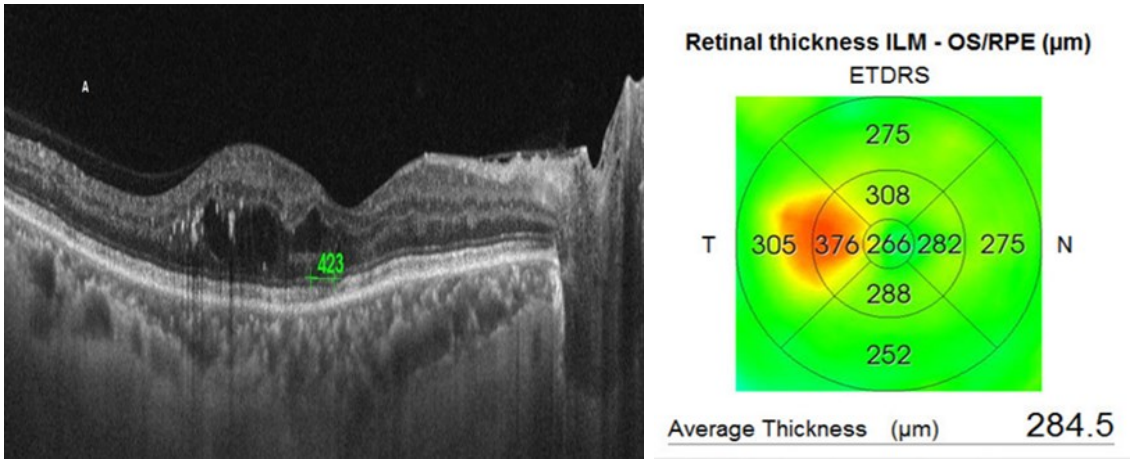

Figure 2: SS OCT: showing DME with interrupted EZ line Class II A

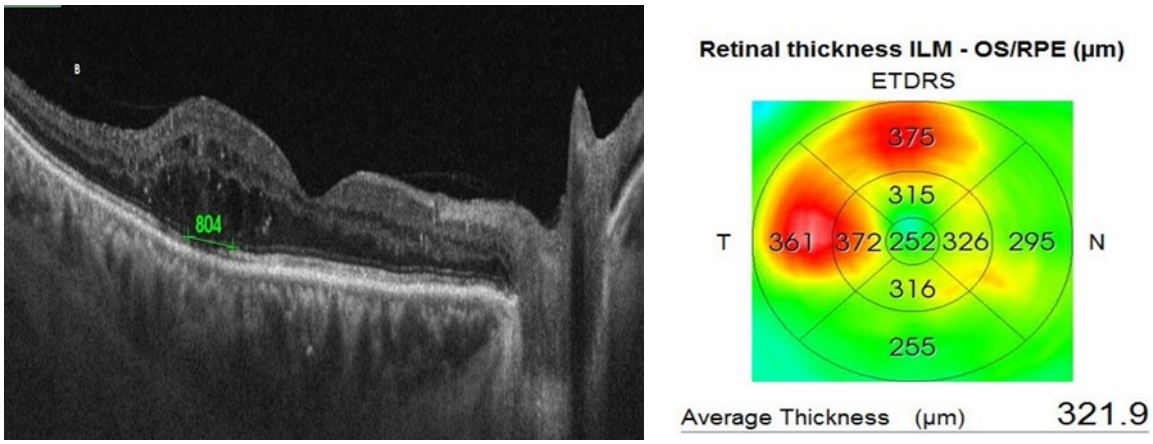

Figure 3: SS OCT: showing DME with interrupted EZ line Class II B.

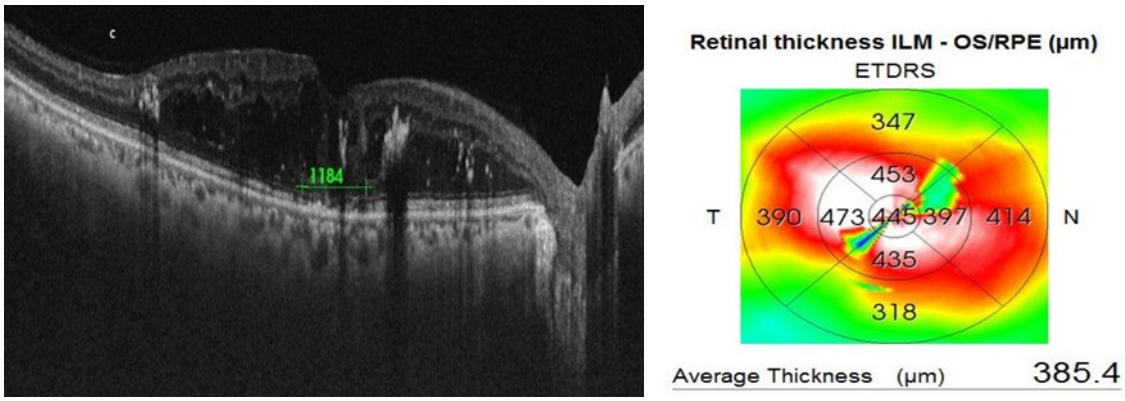

Figure 4: SS OCT: showing DME with interrupted EZ line Class II C

Discussion:

Different studies on Epidemiology of diabetes eye diseases stated that the most familiar reason of decrease vision in diabetic patients is DME[13] and it has bed effects on quality of life in working age group.[14] Different treatment modalities can decrease the macular thickness of DME[3] but some time we are unable to improve vision, which suggests that not only macular volume, there are several other factors also affect vision6. With the help of new techniques of OCT, we can evaluate the status of retinal structure at fovea that also define the functional efficacy after different intervention for DME.[15] It is commonly known that the phototransduction occurs at ellipsoid zone that is previously known photoreceptors IS OS junction. The approximate thickness of this area is about 30–40 μm. The subfoveal disruptions of this zone and variations in macular thickness are correlated with visual outcome that have been observed in different vascular disease,[16]but it is not clear to which extent of disrupted EZ can be restored after applying different treatment options, and which degree of disruption or macular thickness variability is functionally relevant and leads to permanent visual loss.[17]

According to David J et al[18] and Bing Li[19] more reliable assessment test for retinal thickness (RT) is central subfield OCT because it has high capability to reproduce the scan and correlated to the VA. Alasil et al and Hsiao CC also supported this statement but he has one objection and said that CST measurement is subjected to poor fixation.[20,21] Lan C Han and Fatemeh stated that central 1 mm scan is more reliable to assess the change in CSFT because there is very little chance of artifacts and has high correlation with vision.[22,23] In this study we also assessed the RT with 1-mm central scanned area to analyze the change in CSFT but we did not found any high correlation between CSFT. Dysfunction photoreceptor of may be a significant predictor of visual outcome of various retinal diseases.[10] After different interventions for DME some studies have shown the restoration of photoreceptors layers and agreed that the EZ is a biomarker of post treatment visual outcome,[24,25]but some have controversial statement.[26]

According to Mori, Y et al[26] the decrease in central subfield thickness was not correlated with VA improvement (ρ = 0.215, P = 0.093), and also not with damaged EZ (ρ = 0.209, P = 0.103)". He stated that the healing of this area (ρ = 0.463, P < 0.001) contributes to VA improvement after anti VEGF injection for DME at 12th months follow-up.[26] Results of current study are consistent with findings of Hu Y et al.[27]

The results of Nehal M and associate are similar, he used log Mar and for current we used ETDRS letter score. During early follow-up period he found a correlation between the VA (r = 0.538, P-value < 0.001) and the grade of IS OS defect (r =0.603, P-value < 0.001). the mean change in the VA of improved group was good than those in the non-improved group (P-value = 0.001) at 6 months.[6] In our study the mean reduction in CSFT was significant (P≤ 0.001) in all class of EZ line but the mean value of BCVA in intact class of EZ line (70±SD18, P≤ 0.001) was better than the severely interrupted EZ line (45±SD18, P-value = 0.021); however, the visual outcome was not correlated with the level of interruption of EZ line after progressive decrease in central subfield foveal thickness (r = 0.210, P-value = 0.021). But we also found good correlation of BCVA (r =0.613, P-value < 0.001) with the improvement in interrupted EZ line (r = 0.498, P-value < 0.001).

Tomoaki[28] and T Noriko[29]also researched the integrity of EZ line and their data showed that the disruption of this line associated with visual acuity in DME that is best predictor for visual outcome than increase in macular volume, their results are correlated with our study. Anjali et al found very excellent association between disrupted photoreceptors' junction (EZ line) & final vision (P = .0312) in DME patients. He also suggested a borderline correlation ship (P = .07) between macular volume and visual acuity[30] our results are correlated to this study but we used I mm central scanned area for average subfield foveal thickness instead of macular thickness.

After evaluating previous prospective studies and results of this study we agreed that BCVA has strong association with EZ line than CSFT after decrease in macular edema and we can use the OCT findings of EZ line as a predictor for visual out come in clinical trials and in clinical practice.

Conclusion:

The With help of recent advances in the techniques of OCT we can evaluate change in the foveal structural

like; CSFT, External limiting membrane and EZ line. Before decision of treatment options we can say that the best-corrected visual acuity can be more affected by the integrity of the EZ line than CSFT in DME.

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Conflict of interest:
The authors declare no conflict of interest.

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