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Severity of Diabetic Macular Edema does not influence Restoration of Retinal Photoreceptor Ellipsoid Zone after Intravitreal Bevacizumab Therapy

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Abstract

***Purpose:** To evaluate the influence of severity of diabetic macular edema (DME) in restoration of retinal photoreceptor ellipsoid zone (EZ) on spectral domain optical coherence tomography (SD-OCT),after intravitreal bevacizumab therapy (IVB), in patients without chronic kidney disease (CKD).*

***Materials and Methods:** Consecutive cases of type 2 diabetes mellitus (n=44), having EZ disruption on SD-OCT,between the ages of 40 and 65 years, were included. Cases with CKD were excluded.The cases were divided into six different clusters based on their macular thickness (central subfoveal thickness, CST); Cluster 1:250-300µm,Cluster 2:301-350µm, Cluster 3:351-400µm, Cluster 4:401-450µm, Cluster 5:451-500µm and Cluster 6:501-550µm. EZ disruption was graded on SD-OCT as following: Grade 0,Intact EZ ; Grade 1, Focal disruption (localized subfoveal involvement); Grade 2,Global disruption (generalized involvement within macular cube). Pretreatment CST was correlated with restoration of EZ, after three doses of IVB therapy on monthly basis. Data was analyzed statistically.*

***Results:** Decrease in logMAR VA was significant after IVB regimen from pre-treatment level of 1.78±0.07 to 0.42±0.05post intervention ($p<0.001$). Similarly, CST decreased significantly from pre-treatment level of 354.23±15.0 to 233.18±7.88 post intervention ($p<0.001$). EZ restoration in each cluster was found to be independent of the initial CST ($p>0.05$).*

***Conclusions:** Intravitreal bevacizumab regimen is associatedwith restoration of EZ, which is independent of pretreatment CST on SD-OCT, in cases of DME without CKD.*

Keywords: *Diabetic Retinopathy; Diabetic Macular Edema; Vascular Endothelial Growth Factor (VEGF); Bevacizumab; Intravitreal Therapy; Spectral Domain Optical Coherence Tomography (SD-OCT).*

Introduction

Ninety three million people are affected with diabetic retinopathy (DR). Among them, 21 million have treatable form of diabetic macula edema (DME) [1]. Overall prevalence of DME in patients with DR is 11 % - 21% [1-3].

Increase inVascular ndothelial growth factor(VEGF) has been found to be associated with increased central subfoveal thickness(CST) and retinal photoreceptor ellipsoid zone (EZ) disruption on spectral domain optical coherence tomography (SD-OCT)[4, 5].Central foveal thickness is significantly correlated with best-corrected visual acuity (BCVA) in healthy and diabetic eyes [6-8]. Macular thickening can be suspected if foveal thickness is greater than 252 µm and macular thinning can be suspected if foveal thickness is less than 172 µm on SD-OCT[6, 9, 10]. The median central subfoveal thickness cut-off selected for defining patients of DME and for data extraction has been observed to be 250 µm[10, 11].

Vascular endothelial growth factor (VEGF) is a biomolecule which is secreted from retinal pigment epithelial cells, pericytes, astrocytes,glial cells and endothelial cells which is part of a subfamily of growth factors, functioning as signaling proteins, and involved in angiogenesis[12]. The balance between VEGF and angiogenic inhibitors determines angiogenesis and proliferation in DR[13].

Our earlier work demonstrated that serum VEGF levels correlate with the severity of DR, increase in macular thickness and retinal photoreceptor EZ disruption[4]. Several publications in literatures highlighted that VEGF levels correlated significantly with DR[14, 15].

Anti-VEGF agents have been found to have beneficial effect in the management of DME. Many clinical trials have shown that intravitreal bevacizumab (IVB) administration is associated with decrease in CST and improvement in visual acuity (VA)[16-21]. Mori et al showed restoration of the foveal photoreceptors after administration of intravitreal ranibizumab injections to treat DME[22].

A tertiary care center-based, prospective, interventional study was undertaken to determine if the severity of DME, determined by CST on SD-OCT,influences the restoration of EZ after sequential IVB therapy for the first time.

Materials and Methods

The authors confirm adherence to the tenets of the Declaration of Helsinki. The study was undertaken after approval by Institutional Ethics Committee of King George's Medical University, Lucknow, Indiaand a written informed voluntary consent from all the study subjects. ***This study was registered with Clinical Trial Registry of India(CTRI) bearing registration number: CTRI/2019/03/018135.***

Patients

A total of 44 consecutive patients of Type 2 diabetes mellitus (DM), having DME between age group of 40-65 and having EZ disruption were included. Patients who did not give consent or had any other ocular or systemic disease affecting retinal vasculature and who received previous intravitreal injections, surgical or laser interventions or having renal dysfunction like chronic kidney disease (CKD)were excluded from the study.

Data Collection

Patient age and gender were documented. All study subjects underwent detailed fundus evaluation using slit lamp biomicroscopy, indirect ophthalmoscopy, fluorescein angiography and spectral domain optical coherence tomography(SD-OCT) examination and the baseline data was recorded. The outcome measures of the study were VA and OCT parameter (CST).The cases were divided into six different clusters based on their macular thickness (CST in µm); Cluster 1:250-300µm,Cluster 2:301-350µm, Cluster 3:351-400µm, Cluster 4:401-450µm, Cluster 5:451-500µm and Cluster 6:501-550µm. The outcome measures were assessed at pre-treatment (baseline) and post-treatment (after third dose IVB). VA was measured in logMAR using logMAR chart. SD-OCT parameter, CST, was assessed in micrometer (µm). In cases with bilateral involvement, eye with more severe DME

was included. The patients were administered three doses of IVB (1.25 mg in 0.05 mL) in the affected eye at monthly intervals.

*Spectral domain optical coherence tomography***.**The Cirrus HD-OCT (Carl Zeiss Meditech, Inc., CA, U.S.A.) was used to acquire a macular cube (128 ×512) and horizontal and vertical 5-line raster scans centered on the fovea.

Image Interpretation

The baseline SD-OCT image of each patient was compared with subsequent OCT image after injections and CST values and EZ disruption were noted.

The EZ, was defined as the second hyper-reflective band which clinically represents the retinal photoreceptor integrity[4, 22, 23]. EZ disruption was graded as Grade 0: Intact EZ, Grade 1: Focal disruption (Photoreceptor ellipsoid zone disruption indicating localized subfoveal involvement),Grade 2:Global disruption (Photoreceptor ellipsoid zone disruption indicating generalized involvement within macular cube) [23]. Data was collected at monthly intervals with analysis of pre- and post intervention data after three doses of IVB.

Analyses were performed on SPSS software (Windows version 17.0). Categorical groups were compared by chi-square ($\chi 2$) test. Pearson correlation analysis was done to assess association between the variables. A two-tailed ($\alpha=2$) $p<0.05$ was considered statistically significant.

Results and Discussion

The demographic characteristics of patients are summarized in Table 1.The subjects were divided into six different clusters based on their macular thickness (CST). Grades of EZ disruption, before and after intervention, were noted and analyzed in each cluster as depicted in Table 2. It was observed that restoration of EZ was independent of the initial macular thickness and the percentage restoration of EZ in each cluster was statistically insignificant ($p>0.05$) (Fig. 1).

Mean logMAR VA decreased significantly after IVB regimen from 1.78±0.07 at baseline to 0.42±0.05($p<0.001$), depicted in Table 3. Similar trend was observed in CST which decreased significantly from pre-treatment level of 354.23±15.0 to 233.18±7.88 post intervention ($p<0.001$), depicted in Table 4.

Vascular endothelial growth factor (VEGF) is a part of a subfamily of growth factors, functioning as signaling proteins, and involved in angiogenesis[12].VEGF induces retinal intercellular adhesion molecule-1 (ICAM-1) expression leading to early blood retinal barrier (BRB)breakdown, capillary non-perfusion, and endothelial cell injury and death[24].

In our earlier study, serum levels of VEGF were observed to increase significantly with an increase in CST due to breakdown of BRB. The levels of VEGF were also found to correlate with grades of disruption of EZ[4]. The amount and duration of VEGF exposure required for blood-retina barrier breakdown have been found to be less than that required for neovascularization[25]. Also in our another study, an increase in CST was found to be associated with an increase inEZ disruption, thus acting as a bioimaging biomarker for EZ disruption in DR[26]. Hence, an increase in CST and EZ disruption is indicative of an increase in VEGF activity in DME.

Several studies have demonstrated significant reduction of CST in patients of DME after anti-VEGF therapy[22, 27-29]. Anti-VEGF administration has been shown to be associated with restoration of foveal photoreceptors and EZ[21]. In the present study, we also observed that CST decreased and EZ was restored significantly after three injections of IVB in all the clusters. However, percentage of restoration of EZ was found to be independent of the pre-interventional CST values.

In our earlier study we had demonstrated that serum urea and creatinine act as surrogate markers for disruption of EZ in DR[30]. Thus, in our present study we had excluded patients of CKD as it acts as a confounding factor.

In the present study,clusters were indicative of high VEGF activity resulting in increased CST in DME. However, standard sequential-dose IVB regimen sufficed in decreasing CST, restoring EZ and improving VA. Absence of CKD provides a plausible explanation about increase in percentage of restoration of EZ after IVB.Pre-intervention CST values had no bearing on the restoration of EZ in this study.

Table 1. *Demographic characteristics (Mean ± SE) of patients (n=44)*

Variables	Mean ±SD
Age (years)	54.36±0.80
Sex:	20
Female	24
Male	6.10 ± 0.06
HbA1c (%)	
Fasting blood sugar (mg/dl)	89.00 ± 1.48
Post-prandial blood sugar (mg/dl)	128.50 ± 1.84
Serum urea (mg/dl)	30.38±1.23
Serum creatinine (mg/dl)	1.50 ± 0.04

Table 2. *Frequency distribution of EZ grade over various clusters of CST after intervention*

Clusters	CST Range (in microns)	Total Patients	Baseline (in %)	After 3rd dose (in %)
1	250-300	7	No disruption=0 (0.0) Focal disruption=6 (85.7) Global disruption=1(14.3)	No disruption=5 (71.5) Focal disruption=2 (28.5) Global disruption=0 (0.0)
2	301-350	8	No disruption=0 (0.0) Focal disruption=1 (12.5) Global disruption=7 (87.5)	No disruption=6 (75.0) Focal disruption=1 (12.5) Global disruption=1 (12.5)
3	351-400	4	No disruption=0 (0.0) Focal disruption=0 (0.0) Global disruption=4 (100.0)	No disruption=3 (75.0) Focal disruption=1 (25.0) Global disruption=0 (0.0)
4	401-450	4	No disruption=0 (0.0) Focal disruption=1 (25.0) Global disruption=3 (75.0)	No disruption=4 (100.0) Focal disruption=0 (0.0) Global disruption=0 (0.0)
5	451-500	4	No disruption=0 (0.0) Focal disruption=2 (50.0) Global disruption=2 (50.0)	No disruption=3 (75.0) Focal disruption=1 (25.0) Global disruption=0 (0.0)
6	501-550	17	No disruption=0 (0.0) Focal disruption=1 (5.8) Global disruption=16 (94.2)	No disruption=13 (76.4) Focal disruption=3 (17.7) Global disruption=1 (5.8)

Table 3. *LogMARVA (Mean ± SE, n=44) of patients over the course of interventions*

Period	VA
Baseline	1.78 ± 0.07
After 1st dose	1.09 ± 0.05
After 2nd dose	0.74 ± 0.04
After 3rd dose	0.42 ± 0.05

Table 4. *CST (Mean ± SE, n=44) of patients over the periods*

Period	CST (in µm)
Baseline	354.23 ± 15.00
After 1st dose	303.43 ± 11.04
After 2nd dose	278.52 ± 8.72
After 3rd dose	233.18 ± 7.88

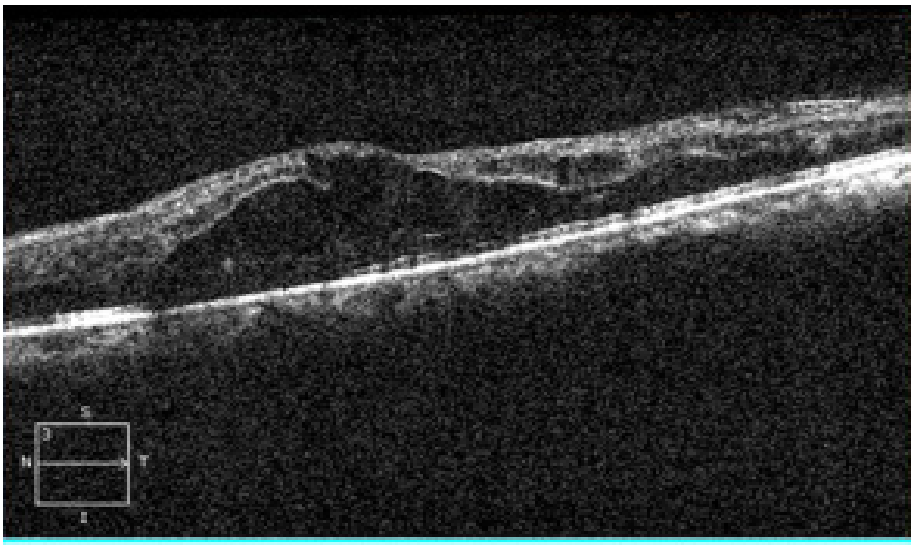

Figure 1(a). *DME Pre-treatment: showing global EZ disruption*

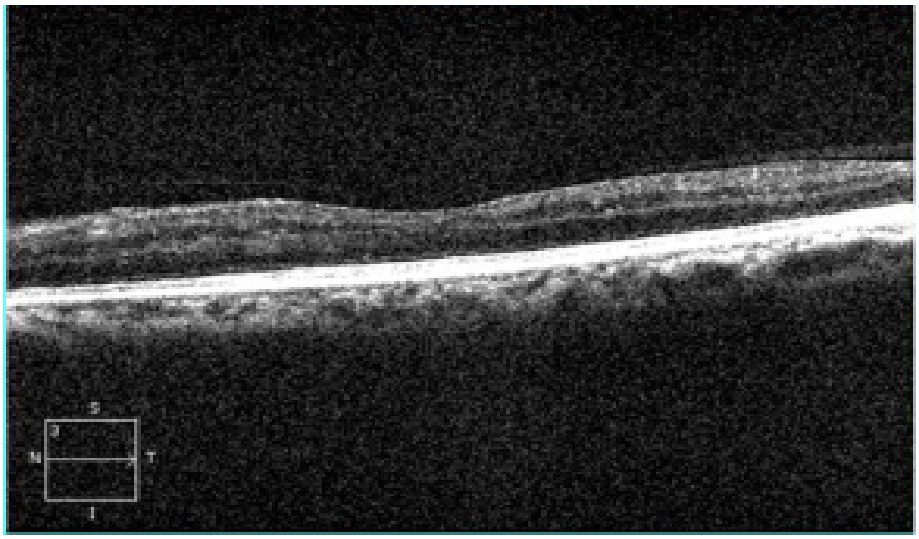

Figure 1(b). *DME Post-treatment: showing EZ restoration*

Conclusions

Intravitreal bevacizumab therapy restores retinal photoreceptor EZ, independent of initial macular thickness, in DME without CKD.

Conflict of Interest: Authors declare no conflict of interest.

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References

1. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;3:152-160.
2. Xie XW, Xu L, Wang YX, Jonas JB. Prevalence and associated factors of diabetic retinopathy. The Beijing Eye Study 2006. Graefe's Archive for Clinical and Experimental Ophthalmology. 2008;246(11): 1519-1526.
3. Wong TY, Klein R, Islam FM, Cotch MF, Folsom AR, Klein BE, Sharrett AR, Shea S. Diabetic retinopathy in a multi-ethnic cohort in the United States. American Journal of Ophthalmology. 2006;141(3): 446-455.
4. Jain A, Saxena S, Khanna VK, Shukla RK, Meyer CH. Status of serum VEGF and ICAM-1 and its association with external limiting membrane and inner segment-outer segment junction disruption in type 2 diabetes mellitus. Molecular Vision. 2013;19: 1760-1768.

5. Balla S, Zold E, Potor L, Lukucz B, Vajas A, Ujhelyi B, Nagy V. Analysis of intravitreal bevacizumab treatment for macular oedema due to retinal vein occlusion. European Journal of Ophthalmology. 2020 Sep 29:1120672120962051. doi: 10.1177/1120672120962051.

6. Chan A, Duker JS, Ko TH, Fujimoto JG, Schuman JS. Normal macular thickness measurements in healthy eyes using Stratus optical coherence tomography. Archives of Ophthalmology. 2006;124(2): 193-198.

7. Puliafito CA, Hee MR, Lin CP, Reichel E, Schuman JS, Duker JS, Izatt JA, Swanson EA, Fujimoto JG. Imaging of macular diseases with optical coherence tomography. Ophthalmology. 1995;102(2): 217-229.

8. Hee MR, Puliafito CA, Wong C, Duker JS, Reichel E, Rutledge B, Schuman JS, Swanson EA, Fujimoto JG. Quantitative assessment of macular edema with optical coherence tomography. Archives of Ophthalmology. 1995;113(8): 1019–1029.

9. Bandello F, Zarbin MA, Latanzzio R. Management of Diabetic Retinopathy. Developments in Ophthalmology. 2017;60: 131-142.

10. Temel E, Batıoğlu F. Optical coherence tomography angiography findings of diabetic patients with and without retinopathy. European Journal of Ophthalmology.2021 Jan 28:1120672121990562. doi: 10.1177/1120672121990562.

11. Virgili G, Menchini F, Murro V, Peluso E, Rosa F, Casazza G. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. Cochrane Database of Systematic Reviews. 2011;(7): CD008081.

12. Gupta N, Mansoor S, Sharma A. Diabetic retinopathy and VEGF. Open Ophthalmology Journal.2013;7:4–10.

13. Funatsu H, Yamashita H, Noma H, Shimizu E, Yamashita T, Hori S. Stimulation and inhibition of angiogenesis in diabetic retinopathy. Japan Journal of Ophthalmology.2001;45:577–584.

14. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. New England Journal of Medicine.1994;331:1480–1487.

15. Witmer AN, Vrensen GF, Van Noorden CJ, Schlingemann RO. Vascular endothelial growth factors and angiogenesis in eye disease. Progress in Retinal and Eye Research. 2003;22(1): 1-29.

16. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for macular edema from central retinal vein occlusion. Ophthalmic Surgery, Lasers and Imaging. 2005;36: 336-339.

17. Kriechbaum K, Michels S, Prager F, Georgopoulos M, Funk M, Geitzenauer W, Schmidt-Erfurth U. Intravitreal Avastin for macular oedema secondary to retinal vein occlusion: a prospective study. British Journal of Ophthalmology. 2008;92(4): 518-522.

18. Jaissle GB, Ziemssen F, Petermeier K, Szurman P, Ladewig M, Gelisken F, Völker M, Holz FG, Bartz-Schmidt KU. Bevacizumab zurTherapie des sekundärenMakulaödemsnachvenösenGefässverschlüssen [Bevacizumab for treatment of macular edema secondary to retinal vein occlusion]. Ophthalmologe. 2006;103(6): 471-475.

19. Priglinger SG, Wolf AH, Kreutzer TC, Kook D, Hofer A, Strauss RW, Alge CS, Kunze C, Haritoglou C, Kampik A. Intravitreal bevacizumab injections for treatment of central retinal vein occlusion: six-month results of a prospective trial. Retina. 2007;27(8): 1004-1012.

20. Hirashima T, Chihara T, Bun T, Utsumi T, Hirose M, Oh H. Intravitreal bevacizumab alone or combined with macular laser photocoagulation for recurrent or persistent macular edema secondary to branch retinal vein occlusion. Journal of Ophthalmology. 2014;2014: 173084.

21. Wilkins CS, Sobol EK, Lema GM, Lee JG, Rosen RB, Deobhakta A. Intravitreal dexamethasone insert in diabetic macular edema super-refractory to anti-vascular endothelial growth factor therapy. European Journal of Ophthalmology. 2021 Mar 23:11206721211004391. doi: 10.1177/11206721211004391.

22. Mori Y, Suzuma K, Uji A, Ishihara K, Yoshitake S, Fujimoto M, Dodo Y, Yoshitake T, Miwa Y, Murakami T. Restoration of foveal photoreceptors after intravitreal ranibizumab injections for diabetic macular edema. Science Reports. 2016;6: 39161.

23. Sharma SR, Saxena S, Mishra N. The association of grades of photoreceptor inner segment-ellipsoid band disruption with severity of retinopathy in type 2 diabetes mellitus. Journal of Case Reports Studies. 2014;2:502-508.

24. Joussen AM, Poulaki V, Qin W, Kirchhof B, Mitsiades N, Wiegand SJ, Rudge J, Yancopoulos GD, Adamis AP. Retinal vascular endothelial growth factor induces intercellular adhesion molecule-1 and endothelial nitric oxide synthase expression and initiates early diabetic retinal leukocyte adhesion in vivo. American Journal of Pathology. 2002;160(2): 501-509.

25. Tolentino MJ, Miller JW, Gragoudas ES. Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. Ophthalmology. 1996;103:1820-1828.

26. Ahuja S, Saxena S, Meyer CH, Gilhotra JS, Akduman L. Central subfield thickness and cube average thickness as bioimaging biomarkers for ellipsoid zone disruption in diabetic retinopathy. International Journal of Retina and Vitreous. 2018;4:41-43.

27. Comyn O, Sivaprasad S, Peto T, Neveu MM, Holder GE, Xing W, Bunce CV, Patel PJ, Egan CA, Bainbridge JW, Hykin PG. A randomized trial to assess functional and structural effects of ranibizumab versus laser in diabetic macular edema (the LUCIDATE study). American Journal of Ophthalmology. 2014;157(5) :960-970.

28. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. New England Journalof Medicine. 2015;372:1193–1203 .

29. Davidović SP, Nikolić SV, Curić NJ, Latinović SL, Drašković DO, Cabarkapa VS, Stošić ZZ. Changes of serum VEGF concentration after intravitreal injection of Avastin in treatment of diabetic retinopathy. European Journal of Ophthalmology. 2012;22(5): 792-798.

30. Saxena S, Ruia S, Prasad S, Jain A, Mishra N, Natu SM, Meyer CH, Gilhotra JS, Kruzliak P, Akduman L. Increased serum levels of urea and creatinine are surrogate markers for disruption of retinal photoreceptor external limiting membrane and inner segment ellipsoid zone in type 2 diabetes mellitus. Retina. 2017;37:344-349.

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