

The Association of Grades of Photoreceptor Inner Segment-Ellipsoid Band Disruption with Severity of Retinopathy in Type 2 Diabetes Mellitus

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Citation: Sharma SR, Saxena S, Mishra N, Akduman L, Meyer CH (2014) The Association of Grades of Photoreceptor Inner Segment-Ellipsoid Band Disruption with Severity of Retinopathy in Type 2 Diabetes Mellitus. J Case Rep Stud 2(5): 502. doi: 10.15744/2348-9820.2.202

Received Date: May 20, 2014 Accepted Date: October 03, 2014 Published Date: October 07, 2014

Abstract

A prospective case-control study was undertaken to evaluate the association of inner segment-ellipsoid (ISel) band disruption with severity of diabetic retinopathy on spectral-domain optical coherence tomography. ISel disruption was graded as - grade 0: intact ISel; grade 1: focal disruption (subfoveal ISel disruption) and grade 2: global disruption (ISel disruption involving macular cube). Increased severity of diabetic retinopathy was found to be associated with increase in disruption of ISel ($r = 0.49$, $p < 0.001$). 'Global' disruption of ISel in proliferative diabetic retinopathy (PDR) ($n=40$) was significantly higher as compared non proliferative diabetic retinopathy (NPDR) ($n=40$) (Intact/Focal/Global: 5/25/10 (NPDR) vs. 0/11/29 (PDR), $\chi^2=19.70$; $p<0.0001$). Decrease in visual acuity was found to be significantly associated with increased disruption of ISel and severity of retinopathy.

Introduction

Diabetic retinopathy is an important cause of preventable blindness [1]. It a major microvascular complication in type 2 diabetes mellitus [2]. It leads to several structural changes in retina which correlates with severity of retinopathy [3].

Optical coherence tomography provides information akin to live *in-vivo* histology of the retina [4]. Recently Spaide et al and Curcio et al speculated that the outer highly reflective band next to retinal pigment epithelium was located at the ellipsoid in the inner segments which correlated between the retinal microstructure on the SD-OCT images and the histologic findings [5,6]. Thus it is more appropriate to consider the previously termed inner segment-outer segment (IS-OS) junction to be photoreceptor inner segment ellipsoid band (ISel). Photoreceptor ISel has been found to be visible on optical coherence tomography (OCT) due to its biological activity rather than the structure in an animal model [7]. Our recent study highlighted that an increase in serum vascular endothelial growth factor and intercellular adhesion molecule-1 levels is associated with an increase in the severity of diabetic retinopathy and the grade of subfoveal external limiting membrane (ELM) and ISel disruption [8].

In the present study we examined, in patients of type 2 diabetes mellitus, the association of 'focal' and 'global' grades of ISel disruption with the severity of diabetic retinopathy and change in visual acuity, using SD-OCT.

Methods

Our study had institutional review board clearance and was performed in accordance to the tenets of the Helsinki declaration. A written informed voluntary consent was taken from all the study subjects. The study was a tertiary care center based prospective cross sectional study of 120 eyes of 120 consecutive patients with type 2 diabetes mellitus. Patients with ocular diseases which could affect the retinal pathology (for example hypertensive retinopathy, age related macular degeneration, polypoidal choroidal vasculopathy and central serous chorioretinopathy), any previous surgical or laser interventions, fluorescein angiography suggestive of ischemic maculopathy, vitreous hemorrhage, tractional retinal detachment and patients with signal strength 5 or below on SD-OCT examination (due to media opacity), were excluded from the study. The best-corrected visual acuity was recorded on logMAR scale. Information regarding patient's age, gender, disease duration, status of retinopathy and glycemic control were recorded. All the study subjects underwent detailed fundus evaluation using stereoscopic slit lamp biomicroscopy and indirect ophthalmoscopy. Digital fundus photography and fluorescein angiography were done using Zeiss fundus camera FF 450 Plus with pixel width of 0.0054 and image size 2588x1958. Fluorescein angiography was performed in cases with diabetic retinopathy. Cases were divided into three groups: patients of diabetes without retinopathy ($n = 40$), non- proliferative diabetic retinopathy ($n = 40$),

and proliferative diabetic retinopathy (n = 40) according to the ETDRS classification [9]. Diabetic macular edema was defined as per ETDRS classification and based on SD-OCT [10,11]. One eye per case was included. Eye with more severe form of diabetic retinopathy was included. Right eye of the cases without retinopathy was included.

Subsequently, all the study subjects were evaluated using SD-OCT [Cirrus High Definition OCT (Carl Zeiss Meditec Inc., CA, U.S.A)]. Every study subject underwent macular thickness analysis using macular cube 512x128 feature. Central subfoveal thickness (μm), cube average thickness (μm) and cube volume (mm^3) were noted. Inner segment-ellipsoid band was studied using horizontal and vertical SD-OCT scans passing through the fovea. The integrity of this layer was evaluated by two experienced observers masked to the status of diabetic retinopathy. ISeI disruption was graded into three categories- grade 0: intact ISeI; grade 1: focal disruption (subfoveal ISeI disruption) and grade 2: global disruption (ISeI disruption involving macular cube) (Figure 1).

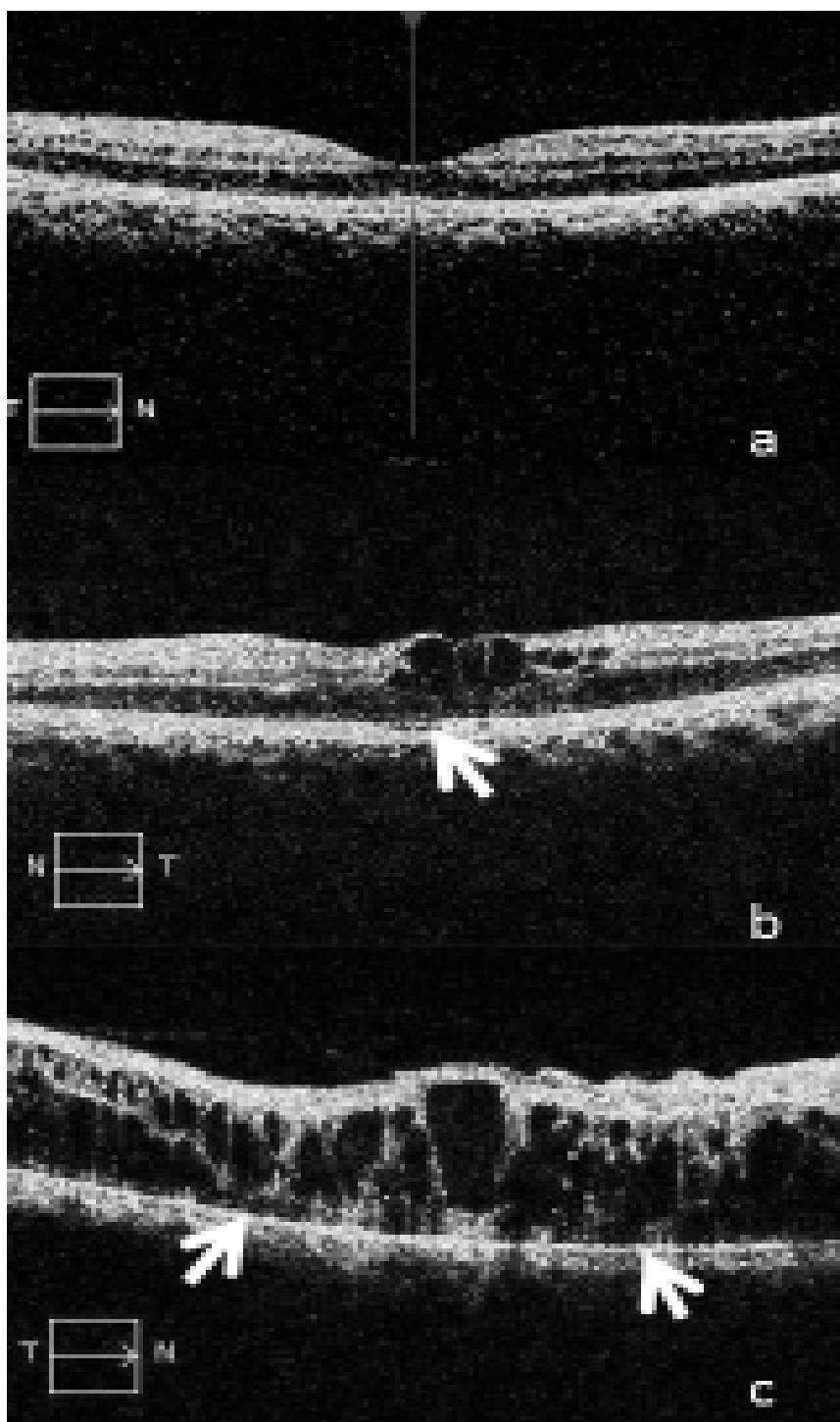


Figure 1: Spectral domain optical coherence tomography images through the fovea showing grades of inner segment-ellipsoid band (ISeI) disruption in patients with diabetic retinopathy. a) Grade 0: intact ISeI; b) Grade 1: Focal disruption (subfoveal ISeI disruption); c) Grade 2: Global disruption (ISeI) disruption involving macular cube. White arrow denotes the area of ISeI disruption.

Data is presented as mean \pm standard error (SE). The continuous variables (age, macular thickness and cube thickness) of the study groups - NPDR and PDR were compared by one factor analysis of variance (ANOVA) and the significance of mean difference between the groups was done by Newman-Keuls post hoc test. The categorical variables (sex and disruption of ISEL were compared by chi-square (χ^2) test. The logMAR vision score of two groups (NPDR and PDR) was compared by independent Student's t test and non-parametric Mann-Whitney U test. Pearson correlation analysis was used to assess association between the variables and intraclass correlation. Interobserver correlation was computed using analysis of variance. A $p < 0.05$ was considered statistically significant. All analyses were performed on STATISTICA (window version 6.0) software.

Results

One hundred and twenty eyes of 120 consecutive study subjects were included in the study. There were sixty eight males and fifty two females. The mean age of patients was 52.4 ± 4.36 years, 53.5 ± 3.68 years and 56.2 ± 4.12 years in patients of diabetes without retinopathy, NPDR and PDR groups respectively. No statistical difference was found among the age and sex of the three groups ($p > 0.05$). Mean logMAR visual acuity was 0.15 in patients with no diabetic retinopathy, 0.75 in NPDR and 1.3 in PDR. The mean macular thickness was 242.53 ± 4.09 μm in eyes without retinopathy, 321.45 ± 24.25 μm in eyes with NPDR and 319.03 ± 18.64 μm in eyes with PDR. Cube thickness was 253.83 ± 1.27 μm in eyes without retinopathy, 334.9 ± 10.47 μm in NPDR and 335.45 ± 7.46 μm in PDR groups. Cube volume was 11.28 ± 1.7 mm^3 in eyes without retinopathy, 12.29 ± 2.1 mm^3 in NPDR and 12.17 ± 2.8 mm^3 in PDR groups. In the NPDR group, 37/40 eyes had diabetic macular edema. All eyes (40/40) in the PDR group had diabetic macular edema.

Interobserver correlation for analysis of the ISEL on SD-OCT scan was computed as 0.72. An intraclass correlation coefficient for the grading of ISEL disruption was 0.93 (95% confidence interval, 0.93 to 0.96). Eyes without diabetic retinopathy had normal ISEL. Focal ISEL disruption was observed in 25 eyes (62.5%) with NPDR and 11 (27.5%) eyes with PDR. Global ISEL disruption was observed in 10 eyes (25%) with NPDR and 29 eyes (72.5%) with PDR. The χ^2 test revealed that focal disruption of ISEL in NPDR group was significantly higher as compared to PDR group. The χ^2 test revealed that global disruption of ISEL in PDR group was significantly higher as compared to NPDR group (Intact/Focal/Global: 5/25/10 (NPDR) vs. 0/11/29 (PDR), $\chi^2 = 19.70$; $p < 0.0001$).

Table 1 shows the correlation of the study variables. Our analysis revealed no significant association of central subfoveal macular thickness, cube average thickness and cube volume with severity of retinopathy and visual acuity. Increased severity of diabetic retinopathy was found to be associated with increase in disruption of ISEL from 'focal' to 'global' grade ($r = 0.49$, $p < 0.001$). Decrease in visual acuity was found to be associated with increase in grade of disruption of ISEL ($y = 0.5542x + 0.2315$; $r = 0.67$, $p < 0.001$). We also observed that there was marked decrease in visual acuity with global disruption as compared to the focal disruption (Figure 2).

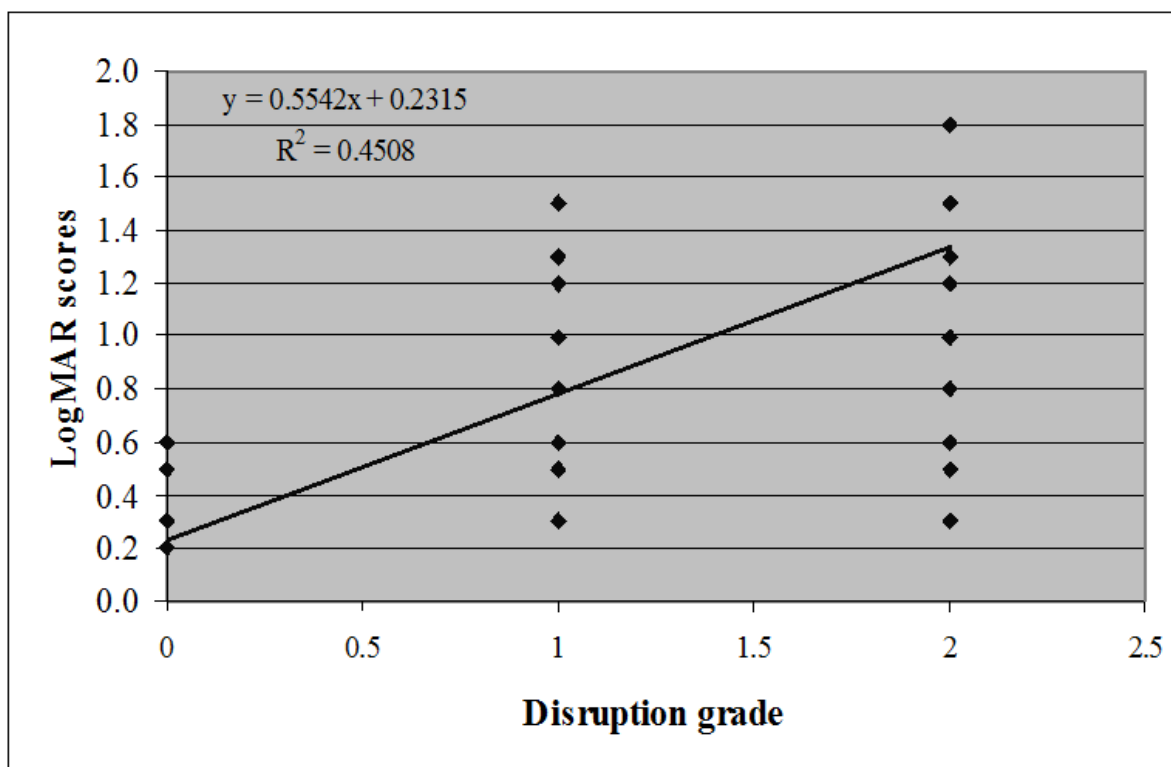


Figure 2: Relation of visual acuity with disruption of inner segment ellipsoid band (ISEL) – Intact (0), Focal (1) and Global (2) is shown above, reveals that as the disruption of ISEL increases there is decrease in visual acuity ($p < 0.001$).

Variables	Level of retinopathy	logMAR scale	ISel disruption	Cube average thickness	Central subfoveal macular thickness
Level of retinopathy	1.00				
LogMAR scale	0.54***	1.00			
ISel disruption	0.49***	0.67***	1.00		
Cube average thickness	0.00 ^{ns}	0.19 ^{ns}	0.28*	1.00	
Central subfoveal macular thickness	-0.01 ^{ns}	0.12 ^{ns}	0.18 ^{ns}	0.61***	1.00

ISel - inner segment ellipsoid band
^{ns} = p >0.05, * = p <0.05, ** = p <0.01, *** = p <0.001.

Table 1: Inter-correlation among variables of non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) groups (n=80).

Discussion

The present study evaluated the association between the grade of ISel disruption and change in visual acuity with severity of diabetic retinopathy. Several recent studies have highlighted the value of ISel integrity in various retinal diseases and found that its disruption correlated with poor visual acuity [12-16].

Photoreceptor dysfunction may be a significant predictor of visual acuity in patients with diabetic retinopathy [17,18]. The superior delineation of the photoreceptor ISel on SD-OCT images encouraged us to evaluate its structural integrity in vivo. Sandberg et al used ISel integrity to predict patients who were more likely to lose visual acuity as retinal thickness declined in retinitis pigmentosa [15]. Disruption of the ISel at the fovea was reported to be associated with a poor visual prognosis in resolved macular edema associated with branch retinal vein occlusion [12]. Many cross-sectional or longitudinal studies have shown the clinical relevance of the ISel in diabetic macular edema [19-25].

Maheshwary et al graded ISel disruption from grade 0–2. Grade 0: intact ISel, Grade 1: focal ISel disruption of 200 microns or less, and Grade 2: ISel disruption more than 200 microns. Grades from each patient's horizontal and vertical scan were added to yield a global disruption scale [25]. They demonstrated percentage disruption of photoreceptor ISel as an important predictor of visual acuity among diabetic macular edema patients. The transverse length of the disrupted or absent ISel has been related to visual impairment [24,26].

In the present study no significant association of central subfoveal macular thickness, cube average thickness and cube volume with severity of retinopathy and visual acuity was observed. This is in agreement with earlier findings of Browning et al [27]. Recently, taking ELM into consideration, we highlighted that the grade of subfoveal ELM and ISel disruption was associated with an increase in severity of diabetic retinopathy and decrease in visual acuity. In the present study, a simplified, comprehensive and physician friendly approach of grading ISel disruption was developed. ISel could be graded quickly on horizontal and vertical scans as 'focal' and 'global' and showed excellent reproducibility. ISel disruption was found to be significantly associated with the severity of retinopathy. 'Global' ISel disruption was associated with marked increase in severity and decrease in visual acuity of as compared to 'focal' disruption.

Conclusion

SD-OCT based grading of ISel disruption into 'focal' and 'global' scales reflect upon the structural and functional alterations associated with the disease progression. Appreciation of the grade of ISel disruption will improve our ability to elucidate the dynamic relationship between the structural alterations in retina and vision.

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