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Spectral Domain Optical Coherence Tomography Based Alterations in Macular Thickness and Inner Segment Ellipsoidare Associated with Severity of Diabetic Retinopathy

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Abstract

Objective: To study the association of spectral domain optical coherence tomography (SD-OCT) based alterations in macular thickness and inner segment-ellipsoid band (ISel) with severity of retinopathy in cases of type 2 diabetes mellitus.

Method: Two hundred thirty eight consecutive cases and seventy nine healthy controls were included. Eyes of cases were divided into three groups according to ETDRS classification: diabetes without retinopathy (No DR) (n=79), non-proliferative diabetic retinopathy (NPDR) with macular edema (n=79), and proliferative diabetic retinopathy (PDR) with macular edema (n=80). Visual acuity was assessed using logMAR scale. Fasting and post prandial blood glucose and glycosylated hemoglobin were estimated as per standard protocol. All the study subjects were evaluated using SD-OCT using the macular cube 512×128 feature. Central subfield thickness (μm), cube average thickness (μm) and ISel disruption in foveal region were noted. The integrity of ISel was evaluated by two experienced observers masked to the status of diabetic retinopathy. Chi–square test, analysis of variance, unpaired t test and pearson correlation analysis were used to assess association between the study variables.

Results: Statistically significant decrease in visual acuity was found between the study groups ($p<0.0001$). Significant negative correlation of visual acuity was found with HbA1c, central sub field thickness and ISel disruption ($p<0.001$).Significant increase in central subfield thickness and cube average thickness were found between the study groups ($p<0.001$). ISel disruption increased with increase in severity of diabetic retinopathy [(NPDR, n=55) versus (PDR, n=68)] ($p<0.001$).Statistically significant difference in the mean central subfield thickness in the cases with intact and disrupted ISel was observed in NPDR and PDR groups respectively.

Conclusion: Diabetic macular edema as assessed by central subfield thickness, cube average thickness and ISel disruption, on SD-OCT, is associated with increased severity of diabetic retinopathy. For the first time, it has been demonstrated that with progression of retinopathy from non-proliferative to proliferative stage, increase in central subfield thickness is associated with ISel disruption.

Keywords

Diabetic retinopathy, Spectral domain optical coherence tomography, Photoreceptor, Inner segment ellipsoid, Central subfield thickness, Cube average thickness

Introduction

The prevalence of diabetes mellitus is attaining epidemic proportions worldwide [1,2]. It is estimated that 382 million people had diabetes mellitus in 2013. This number is expected to rise to 592 million by 2035 [3]. Macular edema is the most common cause of visual loss in diabetic retinopathy [4]. The Wisconsin Epidemiological Study of Diabetic Retinopathy reported a prevalence of diabetic macular edema, with duration of diabetes 20 years or more, as 29% in younger onset diabetics and 28% in older onset [5].

Optical Coherence Tomography (OCT) is a useful investigative tool for quantifying and classifying macular edema [6-8]. Optical coherence tomography allows us to quantify macular thickness in diabetic retinopathy with excellent reproducibility. Optical coherence tomography is able to detect sight-threatening macular edema with great reliability [9]. Diabetic retinopathy can result in structural changes in retina which correlate with severity of retinopathy. Photoreceptor dysfunction may be a significant predictor of visual acuity in such patients [10-13]. Inner segment-ellipsoid band disruption has been demonstrated to be an important predictor of visual acuity in diabetic macular edema [14].

Macular thickness parameters on SD-OCT have been correlated with severity of diabetic retinopathy.[9]In the present study, association of macular thickness and ISel disruption with severity of diabetic retinopathy was evaluated for the first time.

Materials and Method

Our study had institutional review board clearance and was performed in accordance to the tenets of the Helsinki declaration. In this tertiary care center based prospective cross sectional study, 238 consecutive cases and 79 healthy controls (presenting for refraction) were included after an informed voluntary consent. Cases were divided into three groups: patients with diabetes without retinopathy (No DR) (n=79), non-proliferative diabetic retinopathy (NPDR) with diabetic macular edema (n=79), and proliferative diabetic retinopathy (PDR) with diabetic macular edema (n=80) according

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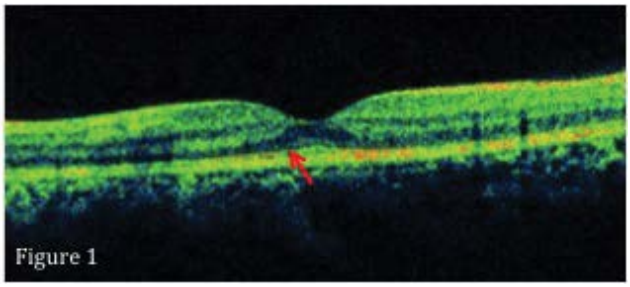

Figure 1: ISel disruption is seen in the foveal region (arrow).

to the ETDRS classification [15]. The morphological assessment of diabetic macular edema was done on the basis of presence or absence of clinically significant macular edema, which may be characterized as retinal thickening or adjacent hard exudate that involves or threatens the center of the macula16 [16].

The eye with a more severe form of diabetic retinopathy were included. Ocular diseases which could affect the retinal vascular pathology (hypertensive retinopathy, age-related macular degeneration), any previous ophthalmic surgical or laser interventions, uncontrolled diabetes based upon HbA1c levels (>9%), fluorescein angiography suggestive of ischemic maculopathy, cases with signal strength 5 or below on OCT examination and cases taking any mineral supplements or antioxidants were excluded. The best-corrected visual acuity was recorded on log MAR scale. Information regarding patient's age, gender, and disease duration, status of retinopathy and glycemic control was recorded. Slit lamp biomicroscopic and dilated ophthalmoscopic examination were performed. Fluorescein angiography was performed in cases with diabetic retinopathy. 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 512 × 128 feature. Central subfield thickness (μm) and cube average thickness (μm) were noted. Central subfield thickness was defined as thickness of the central circle in the circular map known as the ETDRS Grid. Cube average thickness was defined as an overall average thickness for the internal limiting membrane-retinal pigment epithelium tissue layer over the entire 6 x 6 mm square scanned area. Inner segment-ellipsoid band was defined as an outer highly reflective band next to retinal pigment epithelium located at the inner segment ellipsoids [17]. Inner segment-ellipsoid band disruption was defined as break in its continuity in the foveal region (Figure 1). 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.

Fasting and post prandial blood glucose and glycosylated haemoglobin was estimated as per standard protocol.

Data is presented as mean ± standard error (SD). The continuous variables (age, central subfield thickness, cube average thickness and visual acuity on logMAR scale) 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 Tukey's test. The discrete (categorical) variables (sex, ISel disruption) were compared by chi-square (χ^2) test. Interobserver correlation was computed using analysis of variance. Unpaired t test was used to test the significance of difference between two mean values. Pearson correlation analysis was used to assess association between the study variables. P<0.05 was considered statistically significant. All analyses were performed on STATISTICA (window version 6.0) software.

Results

There were 163 males and 154 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).

Table 1: Summary of glycosylated hemoglobin, visual acuity (logMAR), central subfield thickness, cube average thickness and inner segment ellipsoid band (ISel) disruption in the study groups.

Variable	Group			
	Controls	No DR	NPDR	PDR
Mean ± SD HbA1c (%)	6.181 ± 0.61	7.197 ± 1.13	8.064 ± 1.64	8.248 ± 1.48
Mean ± SD visual Acuity (logMAR)	0.15 ± 0.22	0.33 ± 0.18	0.52 ± 0.39	1.12 ± 0.61
Mean ± SD central subfield thickness (μm)	249.85 ± 12.62	233.15 ± 31.09	328.53 ± 90.30	421.36 ± 93.55
Mean ± SD cube average thickness (μm)	255.40 ± 12.6	265.20 ± 42.7	335.15 ± 74.6	495.61 ± 58.2
ISel disruption (n)	0	0	55	68

NODR: Patients of Diabetes with no Retinopathy; NPDR: Non Proliferative Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy.

Summary of glycosylated hemoglobin (HbA1c), visual acuity (logMAR), central subfield thickness, cube average thickness and ISel disruption have been shown in Table 1.

The central subfield thickness increased with increase in the severity of retinopathy. From the analysis of variance it was obtained that central subfield thickness was significantly different between study groups (p<0.001). From multiple comparisons amongst the study groups, it was obtained that the central subfield thickness was significantly different between controls and PDR group (p < 0.001), No DR and NPDR (p<0.001) and NPDR and PDR (p=0.001). For other pairs of group, no statistically significant difference was obtained.

The cube average thickness increased with increase in the severity of retinopathy. From the analysis of variance, it was obtained that cube average thickness was significantly different between study groups (p=0.001). From multiple comparisons amongst the study groups, it was obtained that cube average thickness was significantly different between controls and PDR (p<0.001) as well as No DR and PDR group (p=0.019). For other pairs of group, no statistically significant difference was obtained.

An interobserver correlation coefficient for disruption of ISel was 0.94 (95% confidence interval, 0.93 to 0.96). ISel disruption increased with increase in severity of diabetic retinopathy [(NPDR, n=55) versus (PDR, n=68)] (χ^2=5.368, p<0.05). Intact ISel was observed in all the cases of No DR and controls.

In the NPDR group, mean central subfield thickness in the cases with ISel disruption (n=55) and in the cases with intact ISel (n=24) was 328.53 ± 90.30μm and 278.6 ± 83.50μm respectively. Unpaired t test revealed a significant difference between the two mean values (p=0.02).

In the PDR group, mean central subfield thickness in the cases with ISel disruption (n=68) and in the cases with intact ISel (n=12) was 421.36 ± 93.55μm and 338.52 ± 90.32μm respectively. Unpaired t test revealed a significant difference between the two mean values (p=0.005).

Visual acuity decreased with increase in severity of retinopathy. On comparing visual acuity, ANOVA revealed significant difference amongst study groups (F=23.02, p<0.0001).Pearson correlation analysis revealed statistically significant correlation of visual acuity

(log MAR) with HbA1c (r=0.441; p<0.001), central sub field thickness (r=0.874; p<0.001) and ISel disruption(r=0.48; p<0.001).

Discussion

The present study evaluated the correlation of macular thickness and ISel disruption with severity of diabetic retinopathy.

Significant decrease in visual acuity was observed with increase in the severity of retinopathy, similar to studies concluded by Falkensteinet al. [18].

Severity of diabetic retinopathy has been reported to correlate with macular thickness parameters on SD-OCT. Mean macular thickness, retinal thickness, foveal thickness and central macular thickness have been shown to correlate with severity of diabetic retinopathy and visual acuity [19-24]. In the present study, statistically significant association of central subfield macular thickness and cube average thickness with severity of retinopathy was observed.

Importance of vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1 (ICAM-1) in the development of diabetic complications is well documented. . Our earlier study demonstrated that serum levels of VEGF and ICAM-1 increase significantly with severity of diabetic retinopathy. Increased levels of ICAM-1 cause vascular endothelial cell damage, retinal ischaemia and up regulation of VEGF [10]. Raised levels of VEGF and ICAM-1 lead to blood retinal barrier breakdown with resultant diabetic macular edema.

In the present study, significant increase in ISel disruption was observed with increase in the severity of diabetic retinopathy from non–proliferative to proliferative stage. Significant difference in the mean central subfield thickness in the cases with intact and disrupted ISel was observed in NPDR and PDR groups respectively. It was concluded that increase in central subfield thickness was associated with increase in ISel disruption in diabetic macular edema. This association has been established for the first time.

Ethical statement

Study had institutional review board clearance and was performed in accordance to the tenets of the Helsinki declaration.

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