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Correlation of Retinal Nerve Fibre Layer Thinning and Central Subfield Thickness with Type 2 Diabetic Retinopathy on Spectral Domain Optical Coherence Tomography

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Abstract

Purpose: To study the correlation of retinal nerve fibre layer (RNFL) thinning and central subfield thickness (CST) with severity of type 2 diabetic retinopathy (DR) on spectral domain optical coherence tomography (SD-OCT). *Methods:* Sixty consecutive cases of type 2 diabetes mellitus were divided into three groups: diabetes without retinopathy (NO DR; n=20), non-proliferative diabetic retinopathy (NPDR; n=20), and proliferative diabetic retinopathy (PDR; n=20). Twenty healthy controls were included. Visual acuity (VA) was assessed on logMAR scale. Glycosylated hemoglobin (HbA_{1c}) was assessed using standard protocol. Average RNFL thickness and CST were measured using SD-OCT. Data was analyzed statistically. *Results:* Significant decrease in RNFL thickness was observed with increase in severity of DR ($F=21.92$, $p<0.001$). Significant increase in CST and logMAR VA with increase in severity of DR was also observed ($F=33.18$; $F=47.19$ respectively, $p<0.001$). On Pearson correlation, significant negative correlation of RNFL thickness with VA, CST and HbA_{1c} ($r= -0.62$; $r= -0.575$; $r= -0.357$, $p<0.001$) was observed whereas significant positive correlation between logMAR VA and CST ($r= 0.35$; $p<0.05$) was also observed. Multiple regression analysis revealed CST to be the sole predictor of impaired visual acuity (OR=3.07, 95% CI=1.16–8.16, $p<0.05$). *Conclusion:* RNFL thinning is associated with progression of diabetic retinopathy, poor glycemic control and increase in CST. RNFL thinning does not contribute significantly to visual impairment in type 2 diabetic retinopathy.

Keywords

Retinopathy, Diabetes Mellitus, Retinal Nerve Fibre Layer, Central Subfield Thickness, Spectral Domain Optical Coherence Tomography

1. Introduction

Diabetic retinopathy (DR) is the leading cause of visual impairment in the working age population. The prevalence of diabetes mellitus is attaining epidemic proportion worldwide with number expected to rise to 592 million by 2035 [1]. Diabetic retinopathy characterized by retinal microangiopathy in the past, is now deemed to be preceded by retinal neurodegeneration [2]. Numerous studies have evidenced that alteration of different metabolic pathways in diabetes induces functional deficits and loss of different types of retinal cells including ganglion cells, bipolar cells and eventually photoreceptors [3].

In the retina, glia and neurons closely interact with retinal vasculature to maintain the homeostasis necessary for normal retinal function [4]. Diabetes causes a chronic loss of retinal neurons by increasing the frequency of apoptosis and the activation of glial cells. Both retinal glia and neurons are compromised early in the disease progression and display altered metabolic functions and deregulated neurotrophic support. Several clinical tools indicate functional deficits in

the neuronal component of retina during the early stages of diabetes [5], [6], [7]. Recent studies have demonstrated the presence of neurodegeneration even before the clinical manifestation of DR [8]. High reproducibility and reliable quantitative measurement realized with spectral domain optical coherence tomography (SD-OCT) has improved the assessment of average retinal nerve fibre layer (RNFL) thickness.

In the present study, we evaluated the correlation between thinning of RNFL layer and central subfield thickness (CST) with severity of type 2 DR on SD-OCT.

2. Material and Methods

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, 60 consecutive cases of type 2 diabetes mellitus were divided into three groups: patients of diabetes without retinopathy (No DR; n = 20); non-proliferative diabetic retinopathy (NPDR; n = 20) and proliferative diabetic retinopathy (PDR; n = 20) on the basis of ETDRS classification. Twenty healthy controls were included. Subjects with ocular or systemic diseases like Alzheimer's disease, peripheral neuropathy, glaucoma, age related macular degeneration, end stage renal disease were excluded. Also excluded were subjects with previous ophthalmic surgical or laser interventions; receiving drug/vitamin/antioxidant supplementation and signal strength 5 or below on SD-OCT.

All the study subjects were evaluated by means of SD-OCT [Cirrus High Definition OCT (Carl Zeiss Meditec Inc., CA, U.S.A)]. Average RNFL thickness was analyzed for each subject using optic disc cube 200x200 feature. The 'optic disc cube' scan protocol was used to image the optic disc and the RNFL over the 6x6mm^2 parapapillary region. The RNFL thickness within a circular scan of 3.45mm diameter, centered at the optic disc, was measured. Subsequently, all the study subjects underwent macular thickness analyses. Macular cube 512x128 feature was used and central subfield thickness (CST) (μm) was documented. CST was defined as thickness of the central circle in the circular map known as the ETDRS Grid.

Five millilitres of blood sample was drawn and analyzed for glycosylated haemoglobin (HbA_{1c}), serum levels of urea, creatinine, cholesterol (CHO), triglycerides (TG), high density lipoprotein(HDL) following the standard protocol. Very low density lipoprotein (VLDL) and low density lipoprotein (LDL) were calculated using the above values [VLDL= TG/5, LDL= (VLDL+HDL) - CHO].

Data has been summarized and presented as Mean ± SE. The continuous variables of the study groups were compared by one factor analysis of variance (ANOVA). The discrete (categorical) variables were compared by chi-square ($\chi 2$) test. Pearson correlation analysis and logistic regression analysis were also performed. P value less than 0.05 was considered statistically significant. All analyses were performed using STATISTICA 6.0 software package (StatSoft, 2001).

3. Results

The mean age (in years) of the four groups was controls: 50.32±9.44; No DR: 53.1±5.0; NPDR: 55.0±6.30; PDR: 65.10±7.2. No statistically significant difference in age was observed (F=1.30, p=0.2). Similarly, $\chi 2$ test revealed comparable sex proportion among all the four groups (male/female: 12/8 vs. 11/9 vs. 13/7 vs. 10/10, $\chi 2$=1.052; p=0.34).

The mean duration of diabetes mellitus (in years) was No DR: 3.88±5.96; NPDR: 13.7±6.22; PDR: 15.7±3.35. A significant difference was observed among the three groups (F=24.95, p<0.001).

Table 1 summarizes the mean values of logMAR VA, HbA_{1c}, serum levels of urea, creatinine, CHO, TG, LDL, VLDL, HDL along with RNFL thickness and CST in the study groups. ANOVA revealed a significant increase in logMAR VA and HbA1c with severity of DR (F=47.2; F=8.9; respectively, p<0.001). Figure 1 demonstrates decrease in RNFL thickness with severity of DR (F=21.9, p<0.001). Figure 2 illustrates increase in CST with severity of DR (F=33.2, p<0.001).

Table 1. *Summary of various parameters (Mean±SD) between study groups.*

	GROUPS			
Variables (Mean ± SE)	**Controls**	**No DR**	**NPDR**	**PDR**
Vision (logMAR)	0.081±0.09	0.262 ±0.25	0.649±0.36	1.278±0.51
Glycosylated hemoglobin	6.21±1.02	6.39±0.41	8.35±2.53	7.95±1.69
Serum urea (mg/dl)	29.90±4.95	32.49±7.70	38.20±10.68	54.19±18.67
Serum creatinine (mg/dl)	0.58±0.07	0.83±0.28	1.05±0.48	1.89±0.87
Serum Cholesterol (mg/dl)	140.11±22.39	169.74±42.69	175.47±40.0	203.46±53.50
S.Triglyceride (mg/dl)	95.68±26.92	166.45±98.84	208.22±141.88	220.94±110.93
S. High density lipoprotein (mg/dl)	43.54±6.2	40.95±9.18	46.80±12.92	41.49±13.50
S. Low density lipoprotein (mg/dl)	73.16±16.55	104.64±43.79	108.54±33.16	125.86±54.96
S. Very low density lipoprotein (mg/dl)	24.53±7.44	26.10±9.81	26.57±10.79	30.25±13.65
Mean of average RNFL thickness (μm)	96.75±10.3	93.15±9.86	86.95±14.14	65.90±115.98
Central subfield thickness (μm)	249.85±12.62	233.15±31.09	330.10±90.02	421.60±93.55

Pearson revealed a significant positive correlation between logMAR VA and CST (r= 0.35; p<0.05) (figure 3). Table 2 summarizes Pearson correlation of average RNFL thickness with VA, HbA_{1c} and CST. Pearson correlation revealed negative correlation of RNFL thickness with VA (r= -0.62; p<0.001) and CST (r= -0.58; p<0.001) (figure 4, 5 respectively). $HbA_{1c}$was found to be negatively correlated with RNFL thickness (r= -0.36; p=0.001).

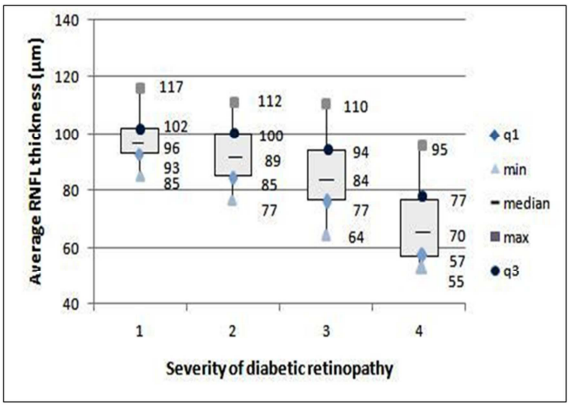

Figure 1. *Box and whisker plot between average retinal nerve fibre layer thickness and severity of diabetic retinopathy. 1: Controls; 2: No DR; 3: NPDR; 4: PDR.*

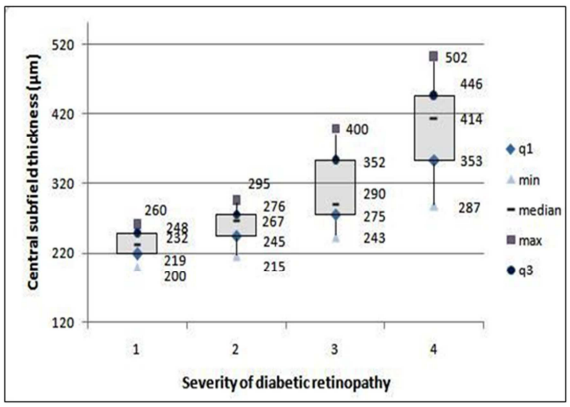

Figure 2. *Box and whisker plot between central subfield thickness and severity of diabetic retinopathy. 1: Controls; 2: No DR; 3: NPDR; 4: PDR.*

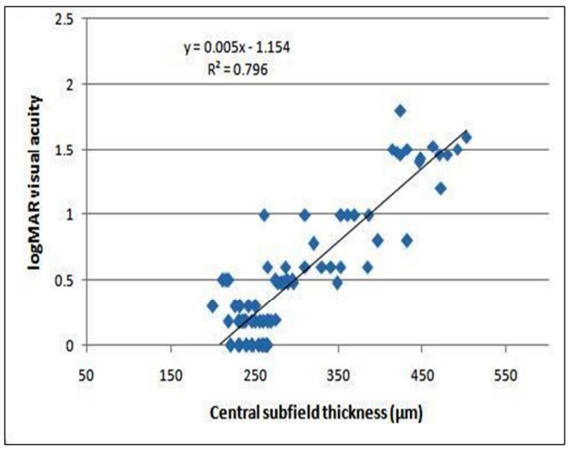

Figure 3. *Scatter plot between logMAR visual acuity and central subfield thickness.*

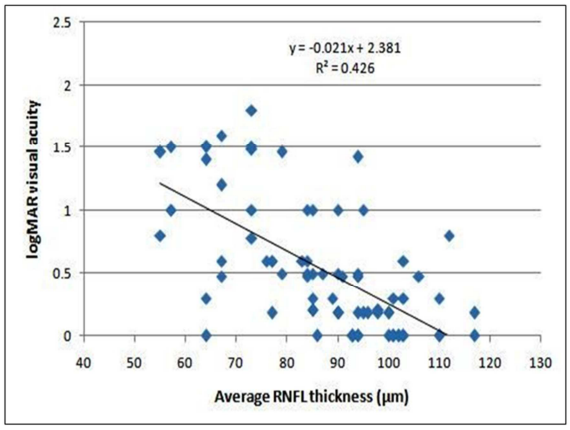

Figure 4. *Scatter plot between logMAR visual acuity and average retinal nerve fibre layer thickness.*

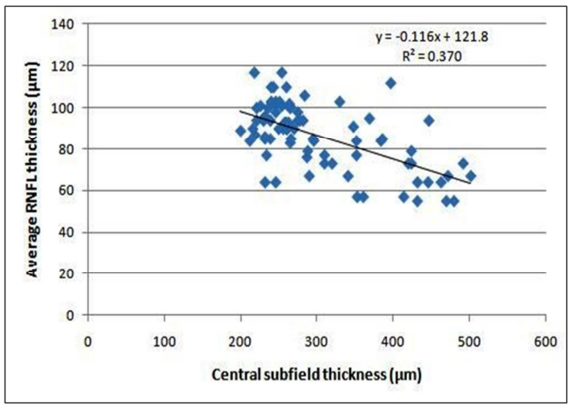

Figure 5. *Scatter plot between average retinal nerve fibre layer thicknes and central subfield thickness.*

Table 2. *Pearson correlation of average retinal nerve fibre layer thickness with logMAR visual acuity, glycosylated hemoglobin and central subfield thickness.*

Variables	Correlation	p-value
Vision (logMAR)	-0.62	<0.001
Glycosylated hemoglobin	-0.36	0.001
Central sub-field thickness	-0.58	<0.001

On multiple regression analysis, association of CST and average RNFL thickness with logMAR VA was analyzed using HbA_{1c} as confounding variable. A significant association was found between logMAR VA and CST (OR=3.07, 95% CI=1.16–8.16, p<0.05) but not between logMAR VA and average RNFL thickness (OR=2.25, 95% CI=0.84–5.98, p=0.1).

4. Discussion

RNFL thinning has been ascertained to precede vasculopathy in DR [9]-[13]. Several authors have studied the neuronal loss in early diabetic retinopathy. Takahashi et al found significant decrease in peripapillary RNFL thickness with increase in severity of DR on scanning laser polarimetry [14]. Our finding is an adjunct to this study.

Vujosevic et al studied the average RNFL thickness in

macula as well as peripapillary area of subjects with No DR and early DR [15]. Reduction in RNFL thickness in macula of diabetics as compared to healthy controls was statistically significant. However, no significant difference between RNFL thickness in diabetics with No DR and with early DR was observed. The difference in the results can be attributed to better metabolic control of the patients at early stages of DR. Furthermore, the difference in peripapillary RNFL thickness was not statistically significant. Dense arrangement of peripapillary retinal nerve fibresis probably accountable for variation in the result [15].

Ozdek et al demonstrated the decrease in RNFL thickness with impairment of glucose regulation on scanning laser polarimetry [16]. Significant negative correlation of RNFL thickness with HbA1c, observed in our study, supplements the findings of this study.

Ma et al studied the structure-function relationship between the optic RNFL thickness and visual function in cases with NO DR and NPDR [17]. Optic RNFL thickness of the nasal and inferior quadrant was reduced in patients with NPDR and was significantly correlated with the impairment of visual function. Significant negative correlation of RNFL thickness with VA, observed in our study, is an adjunct to the above study.

Severity of DR has been reported to correlate with CST on SD-OCT [18]-[21]. In our previous study, statistically significant association of CST with severity of retinopathy was observed. Statistically significant positive correlation of log MAR VA with CST was also observed [22]. Our findings are in corroboration with these studies.

In the present study, significant negative correlation between RNFL thickness and CST has been established for the first time. On multiple regression analysis central subfield thickness was found to be the sole predictor for visual impairment in type 2 diabetic retinopathy.

5. Conclusion

RNFL thinning is associated with progression of diabetic retinopathy, poor glycemic control and increase in central subfield thickness. However, RNFL thinning does not contribute significantly to visual impairment in type 2 diabetic retinopathy.

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