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Retinal Nerve Fibre Layer Thinning is Independent of Deranged Serum Lipoprotein Levels in Diabetic Retinopathy

Khushboo Srivastav[1], Sandeep Saxena[1], Surabhi Ruia[1], Abbas A. Mahdi[2], Vinay Khanna[3]

[1]Retina Service, Department of Ophthalmology, King George's Medical University, Lucknow, India
[2]Department of Biochemistry, King George's Medical University, Lucknow, India
[3]Indian Institute of Toxicology and Research, Lucknow, India

Email address

sandeepsaxena2020@yahoo.com (S. Saxena)

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Abstract

Purpose: To correlate retinal nerve fibre layer (RNFL) thinning on spectral domain optical coherence tomography (SD-OCT) with altered levels of serum lipoproteins in diabetic retinopathy. *Methods:* In a cross sectional observational study, 60 consecutive cases of type 2 diabetes mellitus between the age group of 40-65 years were included. Cases were divided into three groups according to ETDRS classification: 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. Serum lipid profile was measured using standard protocol. Average RNFL thickness was measured using SD-OCT. Data was analyzed statistically. *Results:* Significant increase in serum cholesterol ($p<0.001$), triglycerides ($p=0.001$) and low density lipoprotein ($p<0.001$) was found between the study groups. Significant decrease in average RNFL thickness was also observed ($p<0.001$) between the study groups. However, no significant correlation was found between RNFL thinning and increase in serum levels of cholesterol ($r= 0.09$; $p= 0.4$), low density lipoprotein ($r= 0.05$; $p= 0.6$) and triglycerides ($r= 0.00$; $p= 1.0$). *Conclusion:* Increase in serum levels of lipoproteins is associated with progression of diabetic retinopathy, however, RNFL thinning occurs independent of deranged levels of lipoproteins. Serum lipoprotein levels cannot be considered as a surrogate marker for RNFL damage.

Keywords

Retinopathy, Diabetes Mellitus, Lipid Profile, Retinal Nerve Fibre Layer, Dyslipidemia, Oxidized LDL, Lipoprotein

1. Introduction

Diabetic retinopathy (DR), characterized by retinal microangiopathy is a major cause of blindness. It is a manifestation of dysfunctioning group of metabolic, endocrine and haematological systems. Incidence of type 2 diabetes mellitus (T2DM) continues to grow worldwide. It is estimated that number of people with diabetes mellitus is expected to rise to 592 million by 2035.[1]

Diabetic retinopathy considered solely a vascular disease in the past is now recognized as a neuro-vascular disease.[2] Retinal neurodegeneration by increased frequency of apoptosis and the activation of glial cells has been shown to precede early microvascular changes in DR including the breakdown of the blood-retinal barrier (BRB).[3,4] Diabetes-induced metabolic dysregulation causes increased oxidative stress, which damages these retinal ganglion cells.

Studies have revealed significant correlation between dyslipoproteinemia and DR.[5,6,7] Lipoproteins play an indirect role in pathogenesis of DR with impairment of BRB being a crucial initiator of events.[8] With impaired BRB, extravasation of serum lipoprotein and their subsequent modification to oxidized and glycated lipoproteins, contribute to retinal neurovascular injuries.

With the advent of spectral domain optical coherence tomography (SD-OCT), retinal nerve fibre layer (RNFL) thickness can be measured quantitatively in vivo with high reproducibility.

In the present study, we evaluated the correlation between deranged levels of serum lipoproteins and thinning of retinal nerve fibre layer 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); non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) (n = 20; n=20; n=20), on the basis of ETDRS classification. Twenty healthy controls were included. We excluded subjects with ocular or systemic diseases affecting the retinal vasculature (hypertensive retinopathy); systemic illnesses like Alzheimer's disease, peripheral neuropathy, glaucoma, age related macular degeneration, end stage renal disease; previous ophthalmic surgical or laser interventions; drug/vitamin/antioxidant supplementation; 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.

Five millilitres of blood sample was drawn and subjected to autoanalyser for measurement of serum cholesterol (CHO), triglycerides (TGs), low density lipoprotein (LDL), and high density lipoprotein (HDL). Total (CHO) and TGs were measured by enzymatic method. High density lipoprotein was analysed using phosphate tungsten method. Very low density lipoprotein (VLDL) and LDL were calculated using the above values [VLDL= TG/5, LDL= (VLDL+HDL) - cholesterol].

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 was used to assess association between the variables. A $p<0.05$ 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 Control:53.22±9.74; No DR:55.1±7.0; NPDR:53.0±6.70; PDR:50.10±7.2. No statistically significant difference in the age was observed ($F=1.303$, $p=0.25$). The $\chi 2$ test revealed similar ($p>0.05$) sex proportion among all the four groups (Male/Female: 14/6 vs. 13/7 vs. 11/9 vs. 10/10, $\chi 2=1.052$; $p=0.344$).

The mean duration of diabetes mellitus (in years) of the four groups was Control: 0.0±0.0; No DR: 4.98±6.96; NPDR: 12.7±6.82; PDR: 13.7±6.35. A significant difference was observed ($F=24.95$, $p<0.001$).

Table 1 summarizes the mean serum CHO, TGs, LDL, VLDL, HDL in the study groups. ANOVA revealed a significant increase in serum levels of CHO, TGs and LDL among the study groups. No significant difference was found between HDL and VLDL between the study groups.

Table 1. *Summary (Mean ± SD) of serum cholestrol, triglycerides, high density lipoprotein, low density lipoprotein and very low density lipoprotein in the study groups.*

Variable	Group					
	Controls	No DR	NPDR	PDR	Ratio	P value
Serum Cholesterol (mg/dl)	140.11±22.39	169.74±42.69	175.47±40.00	203.46±53.50	7.95	p<0.001
Triglyceride (mg/dl)	95.68±26.92	166.45±98.84	208.22±141.88	220.94±110.93		P=0.001
High density lipoprotein (mg/dl)	43.54±6.20	40.95±9.18	46.80±12.92	41.49±13.50	1.19	p=0.320
Low density lipoprotein (mg/dl)	73.16±16.55	104.64±43.79	108.54±33.16	125.86±54.96	6.11	p=0.001
Very low density lipoprotein (mg/dl)	24.53±7.44	26.10±9.81	26.57±10.79	30.25±13.65		

Mean average RNFL thickness in control, No DR, NPDR and PDR was 95.80±10.30 µm, 93.12±9.90 µm, 87.10±14.14 µm and 66.12±15.02 µm respectively. Difference in average RNFL thickness levels was significant between the study groups ($p<0.001$).

Table 2 summarizes Pearson correlation of average RNFL thickness with serum levels of CHO, TGs, and LDL. No significant correlation was obtained between average RNFL thickness and increased serum levels of CHO, TGs and LDL .

Table 2. *Pearson correlation of average retinal nerve fibre layer thickness with serum levels of cholesterol, triglycerides and low density lipoproteins in study groups.*

Variable1	Variable2	Correlation(r)	P-Value
Average RNFL thickness	Serum cholesterol	0.094	0.407
Average RNFL thickness	Serum LDL	0.054	0.635
Average RNFL thickness	Serum triglycerides	0.004	0.969

4. Discussion

In the present study, the correlation of deranged levels of serum lipoproteins with RNFL thinning on SD-OCT was explored.

Significant association of duration of diabetes with increase in severity of diabetic retinopathy has been previously demonstrated by Correa et al.[9] Our findings are in agreement with this study. Several studies have explored the relationship between serum levels of CHO, TGs and LDL and the severity of DR.[10,11] Our recent study, demonstrated a significant association of increase in serum levels of CHO, TGs and LDL with severity of retinopathy.[12]

Previous studies have documented RNFL defects in diabetic retinopathy.[13-17] Several mechanisms have been put forward to explain neurodegeneration followed by retinal hemodynamic response in diabetic retinopathy.[18] Retinal ganglion cell death by apoptosis with increase in the

expression of Bax (Bcl-2 associated X protein), a pro-apoptotic protein, has been found in diabetic retinas.[19,20] Our finding, increase in retinal nerve fibre layer thinning with increase in severity of retinopathy is in corroboration with the previous studies.

Nor-Sharina et al, studied serum oxidized LDL in cases of NPDR. They demonstrated significant correlation between RNFL thinning and increased level of oxidized LDL in early NPDR .[21] However, in the present study, No DR, NPDR and PDR cases were included. A significant correlation of altered levels of serum cholesterol, triglycerides, low density lipoproteins with retinal nerve fibre layer thinning was not observed (p>0.05).

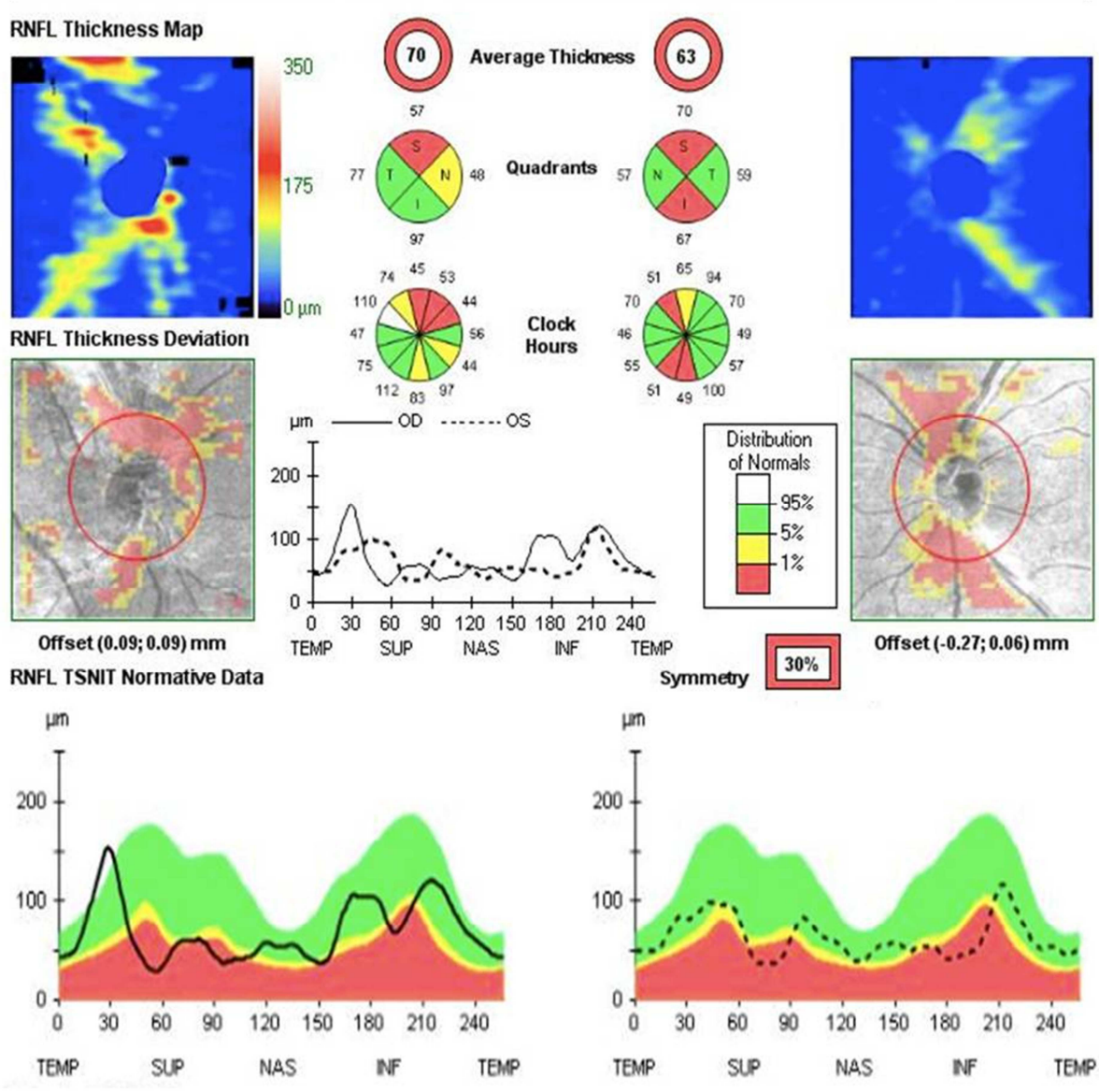

Figure 1. *Average retinal nerve fibre layer (RNFL) thickness analysis using optic disc cube 200x200 feature showing decreased average RNFL thickness in both the eyes. Quadrant map of right eye shows thinness in the superior quadrant and of left eye shows thinness in the superior and inferior quadrant. RNFL Thickness maps, RNFL deviation maps, RNFL TSNIT normative data and RNFL TSNIT graph of both the eyes also demonstrate thinness in the corresponding quadrants.*

The difference in the results of the present study can be explained with the insight into the difference of proportion and role of oxidized LDL in serum and retina. Oxidized LDL have a non-uniform distribution with concentrations at points of retinal vascular leakage in DR, much higher than in plasma.[22] Serum lipoproteins have no role in the development of DR in cases with intact BRB. Impaired BRB causes extravasation of serum lipoproteins in the retinal layers which become modified by oxidation and glycation, subsequently contributing to prolonged, widespread retinal neurovascular injuries. This has been substantiated with studies by Wu et al, who demonstrated that oxidized LDL was expressed throughout all layers of the retina, mainly in the ganglion cell layer adjacent to retinal blood vessels.[23] Another study demonstrated extravasated LDL via distribution of apoB-100 and oxidized LDL staining in human diabetic retina.[24] The injurious effects of oxidized LDL are likely to affect the neural retina, retinal pericytes, blood vessels, and pigment epithelial

cells consistent with recent concepts of a general retinal injury in DR.[25,26] The retinal pathology caused by the extravasated oxidized LDL in the retina is largely an isolated phenomena from serum lipoproteins.[27] ACCORD (Action to Control Cardiovascular Disease in Diabetes) and FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study suggested that fenofibrate was found to reduce the progression of DR by pleiotropic effects on intra-retinal oxidized LDL and not through effects on plasma lipoproteins.[28,29]

The evidence put forward by the above mentioned research, support the postulatation of the present study that RNFL thinning in diabetic retinopathy occurs independent of deranged levels of lipoprotein in serum. Serum lipoprotein levels cannot be considered as a surrogate marker for RNFL damage in diabetic retinopathy.

5. Conclusion

Increase in serum lipoproteins is associated with progression from no diabetic retinopathy to proliferative diabetic retinopathy. Retinal nerve fibre layer thinning is associated with severity of retinopathy and is independent of deranged serum lipoproteins levels.

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