

Correlation between Altered Serum Lipid Profile and Spectral Domain Optical Coherence Tomography based Macular Thickness Parameters in Diabetic Retinopathy

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Abstract

Aim: To study the correlation between altered serum lipid profile and spectral domain optical coherence tomography (SD-OCT) based macular thickness parameters in diabetic retinopathy. **Method:** Study subjects included 60 cases of type 2 diabetes mellitus (DM): no diabetic retinopathy (No DR, n=20); non proliferative DR (NPDR, n=20); proliferative DR (PDR, n=20) and 20 healthy controls. Best corrected visual acuity (BCVA) was measured on logMAR scale. Cube average thickness (CAT) and central subfield thickness (CST) was assessed using SD-OCT. Serum lipid profile was analyzed using standard protocol. Data was analyzed statistically. **Result:** Decrease in BCVA positively correlated with increased CAT ($r=0.25$, $p=0.028$), increased CST ($r=0.28$, $p=0.04$), increased serum cholesterol ($r=0.292$, $p=0.01$) and decreased high density lipoprotein ($r=-0.714$, $p=0.01$). Statistically significant positive correlation was found between increase in CAT with increase in serum cholesterol ($r=0.403$, $p=0.00$) and also with increase in low density lipoprotein ($r=0.343$, $p=0.02$). **Conclusion:** Deranged lipid profile correlates with the progression of diabetic retinopathy. Further, this study demonstrates the correlation of deranged lipid profile and decreased visual acuity with increased CAT.

Keywords: Diabetic Retinopathy; Lipid Profile; Spectral Domain Optical Coherence Tomography; Cube Average Thickness; Central Subfield Thickness.

Introduction

Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus (DM) and is a leading cause of morbidity in people with DM [1]. The prevalence of DR is 18% in urban population older than 40 years with DM [2]. Although the pathogenesis of DR is not completely understood, several risk factors have been established. These include poor glycemic control, hypertension, increasing age, dyslipidemia, serum urea, serum creatinine and duration of DM [3, 4, 5, 6, 7].

Lipoproteins play an indirect role in DR by affecting the integrity of the blood retina barrier (BRB). In retina with an intact BRB, plasma lipoproteins may be largely irrelevant but when BRB is impaired in diabetes, it leads to lipoprotein extravasation and subsequent modification, hence causes toxicity to the neighbouring retinal cells [8]. The external limiting membrane (ELM) is a part of the retinal barrier that is disrupted by pathological conditions contributing to fluid accumulation in the macula, hence affecting the macular thickness [9,10].

In a previous study it was found that high low density lipoprotein (LDL) was found to be associated with increased central subfield macular thickness (CSMT) and central subfield macular volume (CSMV) in diabetic patients without diabetic macular edema (DME) [11]. The present study was undertaken to explore the association of deranged lipid profile with central subfield thickness (CST) and cube average thickness (CAT) in DR.

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Method

The study was conducted according to the tenets of the Declaration of Helsinki after approval from the institutional review board. An informed voluntary consent was obtained from all the study subjects. This was a tertiary care centre based cross sectional study. Sixty consecutive cases of type 2 DM and twenty healthy controls, between age group 45-70 years, were included. Based on the fundus photography and fluorescein angiography, cases 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) according to the ETDRS classification. Cases with ocular or systemic diseases affecting the retinal vascular pathology, end stage renal disease, cases with history of any previous intravitreal injection(s), ophthalmic surgical or laser interventions and cases with media haze at any level giving signal strength of less than 5 on OCT were excluded. Cases on lipid lowering medications were also excluded. Best corrected visual acuity (BCVA) was documented on logMAR scale. All the study subjects underwent detailed fundus evaluation using stereoscopic slit lamp bio-microscopy and indirect ophthalmoscopy. Digital fundus photography and fluorescein angiography was done using Zeiss fundus camera

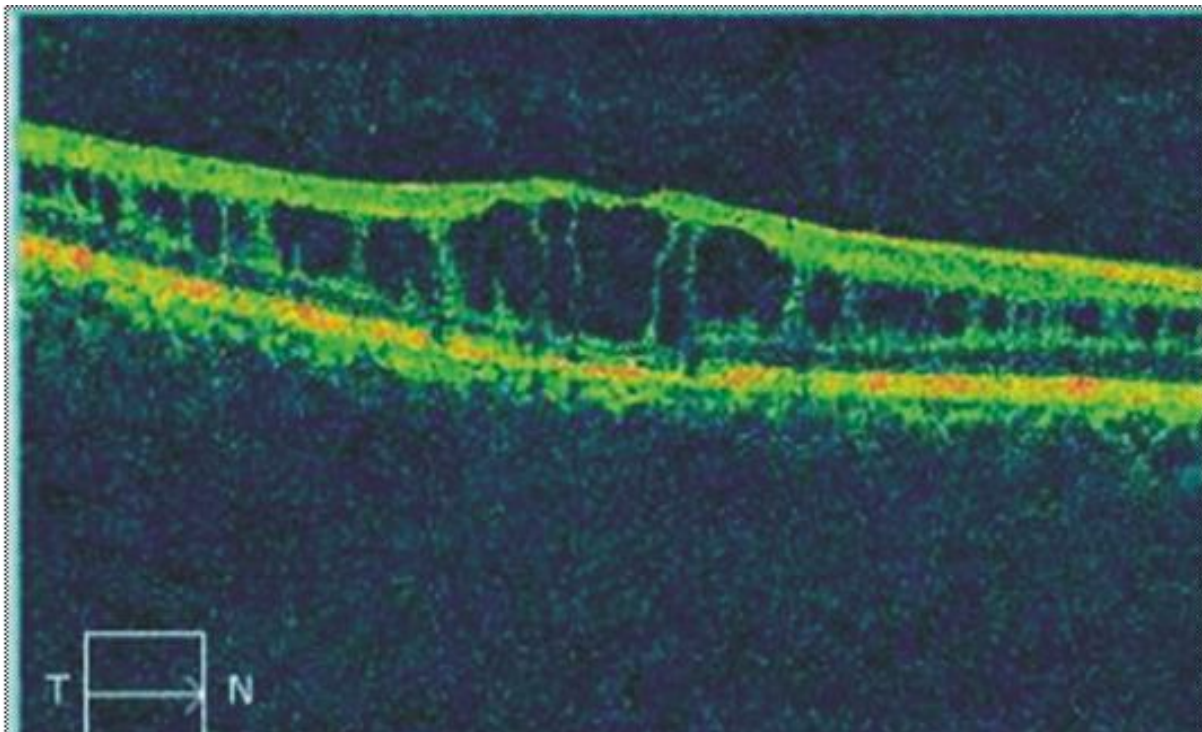
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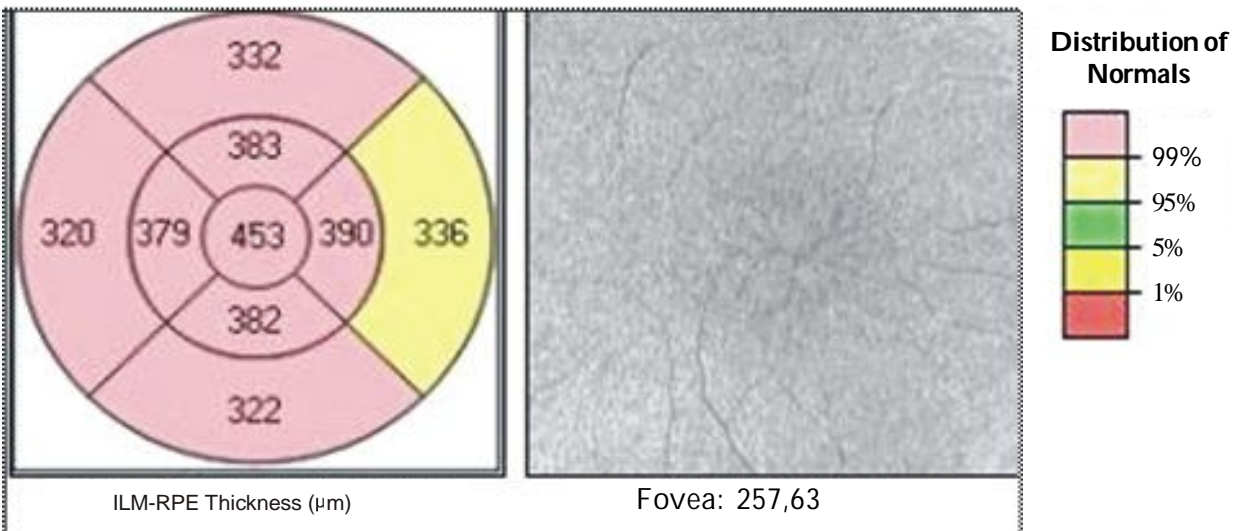
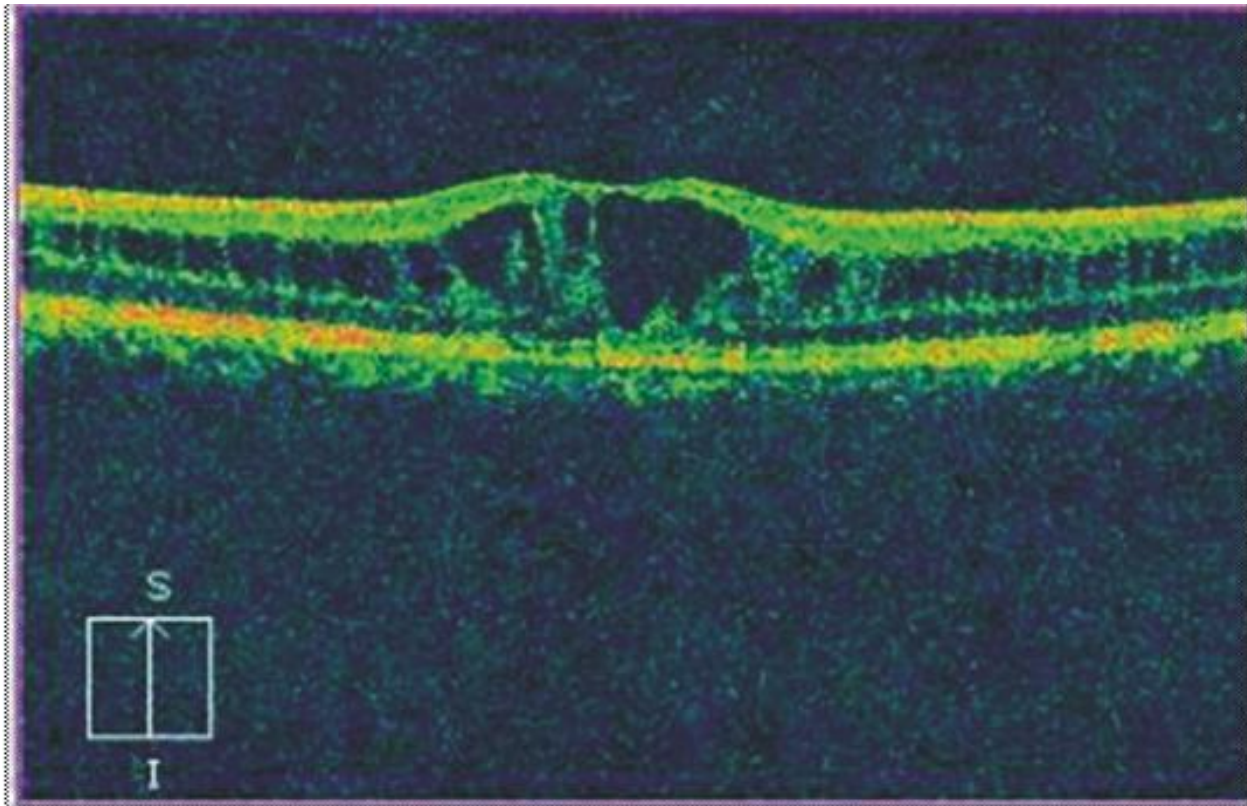
All study subjects underwent macular thickness analysis using three dimensional spectral domain optical coherence tomography (SD-OCT) (Carl Zeiss Meditec Inc.,CA, U.S.A). Macular cube analysis 512 × 128 protocol was used figure 1. Blood samples were collected from all the study subjects by aseptic venepuncture.

Total cholesterol (CHO) and triglycerides (TGs) were measured by enzymatic method. High density lipoprotein (HDL) was analysed using phosphate tungsten method. All tests were performed using standard protocol. Very low density lipoprotein (VLDL) and LDL were calculated using the above values [VLDL= TG/5, LDL=(VLDL+HDL) -cholesterol].

Data has been summarized 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 (X^2) test. For pair wise comparison between the groups, Tukey's test for multiple comparisons was used. The logMAR vision score of two groups (NPDR and PDR) was compared by independent Student's t test. Pearson correlation analysis was used to assess association between the variables. A $p < 0.05$ was considered statistically significant. All analyses were performed STATISTICA 6.0 software package (StatSoft, 2001).

Fig. 1: Spectral domain optical coherence tomography showing macular thickness analysis on a macular cube using 512 × 128 protocol in diabetic macular edema.





	Central Subfield Thickness (μm)	Cube Volume (mm^3)	Cube Average Thickness (μm)
ILM-RPE	453	12.2	340

Results

Mean age (in years) of the four groups was 53.6 ± 8.06 in controls, 54.00 ± 6.05 in No DR, 57.6 ± 4.64 in NPDR and 55.3 ± 8.14 in PDR groups. No significant

difference in the age was observed among the groups ($F=2.46$, $p=0.06$).

The χ^2 test revealed similar ($p>0.05$) sex proportion among all the four groups (Male/Female: 6/14 vs. 13/7 vs. 14/6 vs. 15/5, $\chi^2=7.2$, $p=0.080$).

Mean duration of diabetes mellitus in years was 7.14 ± 5.22 in No DR, 10.38 ± 5.91 in NPDR and 12.18 ± 4.66 in PDR groups. Significant association of severity of diabetic retinopathy with increase in the duration of the disease was documented ($F=17.62$, $p<0.0001$).

Mean glycated hemoglobin (%) was 6.08 ± 1.22 , 6.36 ± 0.61 , 7.28 ± 1.48 and 7.71 ± 1.91 in controls, NODR, NPDR and PDR respectively. No significant difference was found between glycated hemoglobin among the groups on analysis of variance (ANOVA).

Mean logMAR BCVA was 0.04 ± 0.09 in control, 0.3 ± 0.36 in No DR, 0.5 ± 0.39 in NPDR and 1.4 ± 0.40 in PDR groups. On ANOVA, significant difference in visual acuity was found among the group ($F=42.68$, $p<0.0001$).

Table 1 summarizes the central subfield thickness (CST) and cube average thickness (CAT) in study group. Decrease in BCVA was significantly associated with increase in CST ($r=0.28$, $p=0.04$) and CAT ($r=0.262$, $p=0.018$).

Mean values of the serum levels of CHO, HDL, LDL and VLDL has been shown in Table 2. While analyzing the lipid profile using ANOVA, difference in serum CHO ($F=6.617$, $p<0.001$), serum HDL ($F=4.436$, $p<0.001$), serum LDL ($F=6.274$, $p<0.001$), serum VLDL ($F=6.17$, $p<0.001$) was found between the study groups.

Table 3 shows correlations between various biochemical parameters with CAT, CST and BCVA. On pearsons correlation analysis, CST was not significantly correlated with serum CHO ($r=0.172$, $p=0.135$), HDL ($r=-0.120$, $p=0.297$), LDL ($p=0.192$, $p=0.095$) and VLDL ($r=0.63$, $p=0.585$). CAT was found to be correlated with CHO ($r=0.403$, $p=0.00$), HDL ($r=-0.42$, $p=0.714$), LDL ($p=0.343$, $p=0.02$) and VLDL ($r=0.159$, $p=0.167$) on applying pearsons correlation. Increased logMAR BCVA was significantly associated with increased serum cholesterol ($p=0.01$) and decreased HDL ($p=0.01$). There was no significant association between BCVA with LDL ($r=0.312$, $p=0.06$) and VLDL ($r=0.041$, $p=0.723$).

Table 1: Summary (Mean \pm SD) of central subfield thickness and cube average thickness in study group

Variable	Groups			
	Controls	No DR	NPDR	PDR
Mean of central subfield thickness(μ m)	249.90 \pm 11.52	234.73 \pm 31.63	313.35 \pm 120.05	367.1 \pm 119.9
Mean of cube average thickness(μ m)	244.31 \pm 12.41	264.52 \pm 16.10	303.58 \pm 52.42	319.6 \pm 73.56

Table 2: showing various biochemical parameters amongst different groups

	Groups			
	Controls	No DR	NPDR	PDR
S. cholesterol (mg/dl)	141.36 \pm 23.64	171.18 \pm 41.59	176.15 \pm 36.11	205.51 \pm 61.67
S. triglyceride (mg/dl)	90.90 \pm 10.99	127.1 \pm 46.78	128.19 \pm 51.19	157.24 \pm 38.11
S. high density lipoprotein (mg/dl)	45.23 \pm 7.89	44.44 \pm 14.93	43.41 \pm 15.69	39.07 \pm 10.88
S. low density lipoprotein (mg/dl)	72.21 \pm 15.39	93.71 \pm 42.90	102.29 \pm 33.81	127.17 \pm 55.17
S. very low density lipoprotein (mg/dl)	24.57 \pm 7.71	27.46 \pm 15.99	26.25 \pm 9.32	31.09 \pm 9.17

Table 3: Correlation of various bio-chemical parameters with CST, CAT and visual acuity

	CST (μ m)		CAT (μ m)		logMAR visual acuity	
	Correlation(r)	P value	Correlation (r)	P value	Correlation(r)	P value
S. cholesterol (mg/dl)	0.172	0.135	0.403	0.00	0.292	0.010
S. high density lipoprotein (mg/dl)	-0.120	0.297	-0.42	0.714	-0.148	0.010
S. low density lipoprotein (mg/dl)	0.192	0.095	0.343	0.02	0.312	0.06
S. very low density lipoprotein (mg/dl)	0.63	0.585	0.159	0.167	0.041	0.723
Visual acuity	0.28	0.04	0.262	0.018	1.00	1.00

Discussion

Our present study was aimed at establishing a correlation of deranged lipid profile and BCVA with CAT and found that deranged lipid profile is significantly correlated with decreased BCVA and with increased CAT. It also shows that increased CST and increased CAT are positively correlated with decreased BCVA.

Severity of diabetic retinopathy was found to be significantly associated with duration of disease in accordance with a study by Correa et al [12].

Various studies have found decreased visual acuity to be significantly associated with increase in grade of ELM and inner segment ellipsoid band (ISel) disruption in DM [13, 14]. The grades of disruption increases with increase in severity of diabetic retinopathy. Our previous studies involving nitric oxide, oxidative stress, advanced glycation end products, VEGF and ICAM in DR have been associated with in vivo structural changes in inner segment ellipsoid and retinal pigment epithelium [15, 16, 17]. Another recent study of ours has found a significant association between increase in central subfield thickness and grade of inner segment ellipsoid band (ISel) disruption on SD-OCT with progression of diabetic retinopathy [18].

Our current study has correlated significantly the decrease in visual acuity with increase in the severity of retinopathy, similar to studies concluded by Falkenstein et al [19]. We found in our study that decrease in BCVA was significantly correlated with increased CST and CAT and was in accordance with the study conducted by Sasaki et al [10]. But in a study by Otani et al, CST was found to be weakly and negatively correlated with BCVA [20]. Significant correlation has been found between OCT patterns of clinically significant diabetic macular edema and severity of retinopathy, central macular thickness (CMT) and BCVA [21].

The study by Wu et al demonstrated that heavily oxidized-glycated LDL induced the activation of caspase, mitochondrial dysfunction and apoptosis in human retinal capillary pericytes suggesting potentially important role of extravasated, modified LDL in promoting DR by promoting apoptotic pericyte loss [22]. Recently it has also been shown that levels of circulating oxidized LDL immune complexes (ox-LDL-ICs) predict the development of DR [23]. In retinal sections from people with type 2 diabetes mellitus, ox-LDL and IgG was present proportionate to DR severity. Ox-LDL-IC exhibited greater cytotoxicity than ox-LDL toward retinal

pericytes. Another study elaborated the role of lipids in diabetic retinopathy by studying the effect of cholesterol lowering agents i.e., statins on BRB in DR. Statins normalize the expression of pro-inflammatory factors which are drastically up-regulated in diabetic retina [24]. This further supports the role of lipids in pathogenesis of DME.

The study by Sasaki et al associated high LDL with increased CSMT and CSMV in diabetic patients without DME [10]. High serum cholesterol, LDL and low HDL levels were also found to be associated with retinal hard exudate formation, CSME, decreased BCVA and with DME in patients of type 2 DM [25, 26, 27, 28].

Our recent study highlighted, significant correlation of deranged lipid profile with ELM and ISel disruption [29]. Deranged lipid profile was found to have a significant correlation with progression of diabetic retinopathy in our present study which is in harmony of previous studies where high TGs and low HDL were found to be associated with increased severity of DR [30, 31, 32, 33, 34]. This present study significantly positively correlated increased serum levels of CHO and LDL levels with increased CAT but not with increased CST.

In our study increased serum CHO and decreased HDL was found to be significantly correlated with decrease in BCVA.

Conclusion

Deranged lipid profile is significantly correlated with decreased BCVA and with increased CAT. Increased CST and increased CAT were positively correlated with decreased BCVA.

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