Ophthalmology and Allied Sciences
Volume 1 Number 1, July - December 2015

Original Article

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

Sandeep Saxena[1], Shivani Sinha[1], Khushboo Srivastav[1], Vinod Kumar B. M.[1]

Authors Affiliation: [1]Retina Service, Department of Ophthalmology, King George's Medical University, Lucknow, India.

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 2diabetes 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=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.

Reprint Request: Prof. Sandeep Saxena
Department of Ophthalmology, King George's Medical University, Lucknow, India. 226003.
E-mail: sandeepsaxena2020@yahoo.com

Method

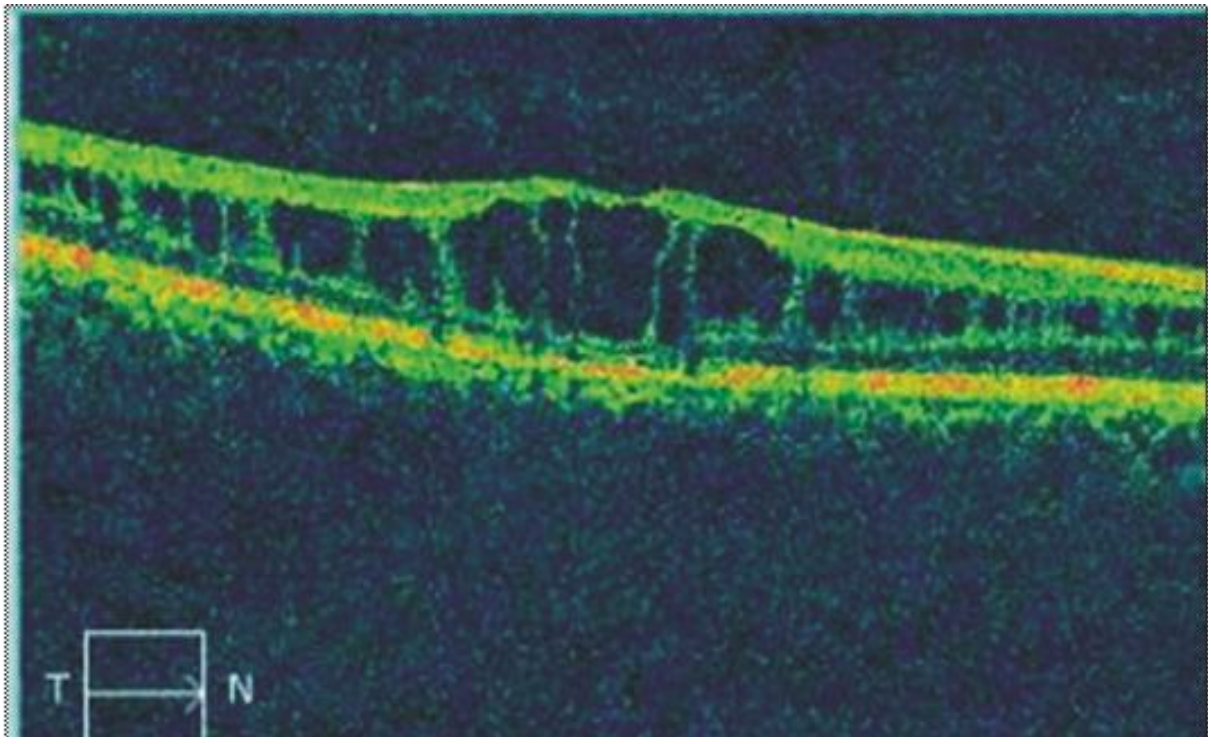
The study was conducted according to the tenets of the Declaration of Helsinki after approval from the institutional review board. An informed voluntary consent was obtained from all the study subjects. This was a tertiary care centre based cross sectional study. Sixty consecutive cases of type 2 DM 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 flourescein angiography was done using Zeiss fundus camera FF 450 Plus with pixel width of 0.0054 and image size 2588 × 1958.

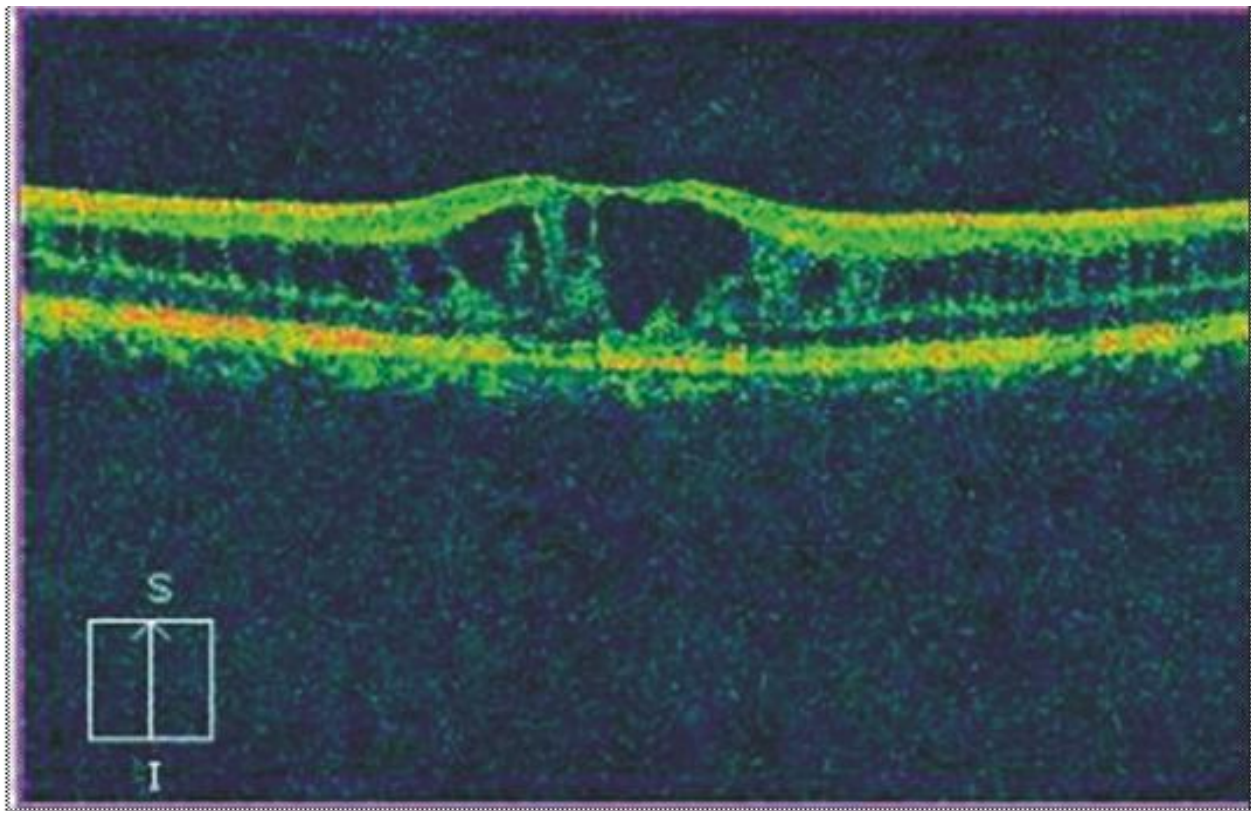
All study subjects underwent macular thickness analysis using three dimensional spectral domain optical coherence tomography (SD-OCT) (Carl Zeiss Meditec Inc.,CA, U.S.A). Macular cube analysis 512 × 128 protocol was used figure 1. Blood samples were collected from all the study subjects by aseptic venepuncture.

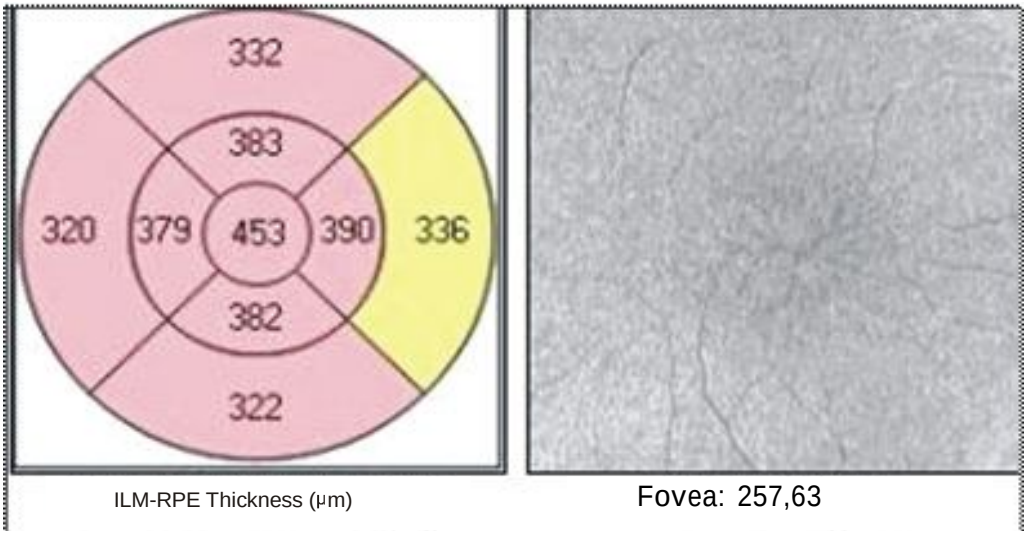
Total cholesterol (CHO) and triglycerides (TGs) were measured by enzymatic method. High density lipoprotein (HDL) was analysed using phosphate tungsten method. All tests were performed using standard protocol. Very low density lipoprotein (VLDL) and LDL were calculated using the above values [VLDL= TG/5, 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 (÷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 X^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, X^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, C9T 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 ± SD) of central subfield thickness and cube average thickness in study group

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

Table 2: showing various biochemical parameters amongst different groups

	Groups			
	Controls	No DR	NPDR	PDR
S. cholesterol (mg/dl)	141.36±23.64	171.18±41.59	176.15±36.11	205.51±61.67
S. triglyceride (mg/dl)	90.90±10.99	127.1±46.78	1 128.19±51.19	1 157.24±38.11
S. high density lipoprotein (mg/dl)	45.23±7.89	44.44±14.93	43.41±15.69	39.07±10.88
S. low density lipoprotein (mg/dl)	72.21±15.39	93.71±42.90	102.29±33.81	127.17±55.17
S. very low density lipoprotein (mg/dl)	24.57±7.71	27.46±15.99	26.25±9.32	31.09±9.17

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

	CST(µm)		CAT (µm)		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 ie., 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.

References

1. Cheung N, Wong TY: Diabetic retinopathy and systemic complications. In Diabetic Retinopathy. Duh EJ, Ed: Totowa, NJ, Humana Press. 2009: 465–482.
2. Raman R, Rani PK, Reddi RS, Gnanamoorthy P, Uthra S, Kumaramanickavel G, Sharma T. Prevalence of diabetic retinopathy in India: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study report 2. Ophthalmology. 2009; 116: 311-318.
3. West KM, Erdreich LJ, Stober JA. A detailed study of risk factors for retinopathy and nephropathy in diabetes. Diabetes.1980; 29: 501-508.

4. Haddad OAWE, Saad MK. Prevalence and risk factors for diabetic retinopathy among Omani diabetics. Br J Ophthalmol. 1998; 82: 901-906.

5. Ashakiran S, Krishnamurthy N, Navin S, Patil S. Behaviour of serum uric acid and lipid profile in relation to glycemic status in proliferative and non-proliferative diabetic retinopathy. Current Neurobiology. 2010; 2: 57-61.

6. Bloomgarden ZT. Screening for and managing diabetic retinopathy: current approaches. American Journal of health-system pharmacy.2007; 64: S8-S14.

7. Emily CY, Michael KL, Frederick L. Association of Elevated Serum Lipid Levels With Retinal Hard Exudate in Diabetic RetinopathyEarly Treatment Diabetic Retinopathy Study (ETDRS) Report 22. Arch Ophthalmol. 1996; 114: 1079-1084.

8. Yu JY, Lyons TJ: Modified Lipoproteins in Diabetic Retinopathy: A Local Action in the Retina. J Clin Exp Ophthalmol. 2013; 18: 314.

9. Omri S, Omri B, Savoldelli M, Jonet L, Thillaye-Goldenberg B, Thuret G, Gain P, Jeanny JC, Behar-Cohen F. The outer limiting membrane (OLM) revisited: clinical implications. Clin Ophthalmol. 2010; 4: 183–95.

10. Saxena S, Srivastava K, CM Chui, Cheung G, L Timothy. Photoreceptor inner segment ellipsoid band integrity on spectral domain optical coherence tomography. Clin Ophthalmol. 2014;8:2507–2522.

11. Sasaki M, Kawashima M, Kawasaki R, Uchida A, Koto T, Shinoda H, Kazuo T, Wang JJ, Ozawa Y. Association of Serum Lipids With Macular Thickness and Volume in Type 2 Diabetes Without Diabetic Macular Edema. Investigative ophthalmology and visual science. 2014.

12. Corrêa ZMS, Freitas AM, Marcon IM. Risk factors related to the severity of diabetic retinopathy. Arq Bras Oftalmol. 2003; 66: 739-43.

13. Maheshwary AS, Oster SF, Yuson RMS, Cheng L, Mojana F, Freeman WR. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. AmJophthalmol. 2010; 150: 63–67.

14. Browning DJ, Glassman AR, Aiello LP, Beck RW, Brown DM, Fong DS, Bressler NM, Danis RP, Kinyoun JL, Nguyen QD, Bhavsar AR, Gottlieb J, Pieramici DJ, Rauser ME, Apte RS, Lim JI, Miskala PH. Relationship between Optical Coherence Tomography–Measured Central Retinal Thickness and Visual Acuity in Diabetic Macular Edema. Ophthalmology. 2007; 114: 525-536.

15. Sharma S, Saxena S, Srivastav K, Shukla R, Mishra N, Meyer CH, Kruzliak P, Khanna VK. Nitric oxide and oxidative stress is associated with severity of diabetic retinopathy and retinal structural alterations.Clin Experiment Ophthalmol. 2015; 12.

16. Jain A, Saxena S, Khanna VK, Shukla R, Meyer CH. Status of serum VEGF and ICAM-1 and its association with external limiting membrane and inner segment-outer segment junction disruption in type 2 diabetes mellitus. Mol Vis. 2013; 19: 1760–1768.

17. Saxena S, Mishra N, Khanna V, Jain A, Shukla R, Meyer CH. Increased Serum N-CML, VEGF and ICAM-1 is Associated with Photoreceptor Inner Segment Ellipsoid Disruption in Diabetic Retinopathy. JSM Biotechnol Bioeng 2: 1039

18. Sharma SR , Saxena S, Mishra N,Akduman L, Meyer CH. The Association of Grades of Photoreceptor Inner Segment-Ellipsoid Band Disruption with Severity of Retinopathy in Type 2 Diabetes Mellitus. Journal of Case Reports and Studies. 2014: 10.

19. Falkenstein I, Cochran D, Azen S. Comparison ‘of visual acuity in macular degeneration patients measured with Snellen and early treatment diabetic retinopathy study charts. Ophthal mology. 2008; 115: 319-323.

20. Otani T, Yamaguchi Y, Kishi S. Correlation between visual acuity and foveal microstructural changes in diabetic macular edema. Retina.2010; 30: 774-780.

21. Hishan A, Dustan K, Ahmed AM. The correlation between optical coherence tomographic features and severity of retinopathy, macular thickness and visual acuity in diabetic macular edema. International Ophthalmology. 2005; 26: 93-99.

22. Wu M, Chen Y, Wilson K, Chirindel A, Michael AI, Yu Y, Boulton ME, Szweda LI, Ma JX, Lyons TJ. Intraretinal Leakage and Oxidation of LDL in Diabetic Retinopathy. Invest. Ophthalmol. Vis. Sci. 2008; 49 (6): 2679-2685.

23. Fu D1, Yu JY, Wu M, Du M, Chen Y, Abdelsamine SA, Li Y, Chen J, Boulton ME, Ma JX, Lopes FM, Virella G, Lyons JT . Immune complex formation in human diabetic retina enhances toxicity of oxidized LDL towards retinal capillary pericytes. J Lipid Res. 2014; 55: 860-9.

24. Li J, Wang JJ, Chen D. Systemic administration of HMG-CoA reductase inhibitor protects the blood–retinal barrier and ameliorates retinal inflammation in type 2 diabetes. Experimental eye research.2009; 89: 71-78.

25. Idiculla J, Nithyanandam S, Mohan VA, Vasu U, Sadiq M. Serum lipids and diabetic retinopathy: A cross-sectional study. Indian J Endocrinol Metab. 2012; 16: S492–S494.

26. Franks SM, Michel HP, Fioretto P, Valensi P, Davis T, Horton, Wanner C. Association Between Plasma Triglycerides and High-Density Lipoprotein Cholesterol and Microvascular Kidney Disease and Retinopathy in Type 2 Diabetes Mellitus A Global Case–Control Study in 13 Countries. Circulation. 2014; 129: 999-1008.

27. Chowdhury TA, Hopkins D, Dodson PM, Vafidis GC.The role of serum lipids in exudative diabetic maculopathy: is there a place for lipid lowering therapy?. Eye. 2002; 16: 689-693.

28. Rema M, Srivastava BK Anitha B, Deepa R, Mohan V. Association of serum lipids with diabetic retinopathy in urban South Indians: the Chennai Urban Rural Epidemiology Study (CURES) Eye Study–2. Diabet Med. 2006; 23:1029–1036.

29. Jain A, Saxena S, Ruia S, Srivastav K, Natu MS. Altered lipid profile is associated with external limiting membrane and inner segment ellipsoid band disruption in type 2 diabetes mellitus: A preliminary study. Open Science Journal of Clinical Medicine. 2015; 3: 37-41

30. Rahman MR, Arslan MI, Hoque MM. Serum Lipids and Diabetic Retinopathy in Newly Diagnosed Type 2 Diabetic Subjects. J Enam Med Col. 2011;1: 63-66.

31. Lyons JT, Jenkins AJ, Zheng D, Lackland DT, McGee D, Garvey WT, Klein RL. The DCCT/EDIC Research Group. Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. Invest Ophthalmol Vis Sci. 2004; 45: 910–918.

32. Kissebah AH, Kohner EM, Lewis B, Siddiq YK, Lowy C, Fraser TR: Plasma lipids and glucose/insulin relationship in non-insulin-requiring diabetics with and without retinopathy. Lancet 1975; 305: 1104-1108.

33. Yu Y., Lyons T.J. A lethal tetrad in diabetes: hyperglycemia, dyslipidemia, oxidative stress, and endothelial dysfunction. The American journal of the medical sciences. 2005; 330: 227-232.

34. Guyer D, Yannuzzi L, Chang S. Diabetic Retinopathy. Retina. 2007; 1: 316-344.