



STUDY OF ASSOCIATION OF SERUM LIPID PROFILE WITH DIABETIC RETINOPATHY

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ABSTRACT Diabetic retinopathy is a very common, potentially preventable, long-term, microvascular complication of Diabetes Mellitus and a leading cause of visual disability and blindness. (1) Elevated serum lipid levels are associated with an increased risk of retinal hard exudate in persons with diabetic retinopathy. **Materials and methods:** A study with 120 patients, 40 diabetics with retinopathy, 40 diabetics without retinopathy and 40 nondiabetics as controls, was conducted at tertiary eye care centre. Along with complete routine ophthalmological examination, dilated fundus examination was done using slit lamp examination and indirect ophthalmoscope. Complete lipid profile was done for each subject. **Results:** Serum cholesterol and VLDL were significantly greater ($p < 0.05$) in diabetics with retinopathy than in those without. There was also a significant difference in both values in diabetics with retinopathy as compared to non-diabetics. The values were greater in diabetics without retinopathy than in controls but not statistically significant ($p > 0.05$). There was no statistical significance in the difference in the Triglycerides and HDL values among any of the three groups, however their values were found to be higher in diabetics with retinopathy. There was a significant difference between LDL values in diabetics with retinopathy as compared to controls but no significant difference between that in diabetics with retinopathy compared to diabetics without retinopathy or between diabetics without retinopathy and controls.

KEYWORDS : Lipid profile, Diabetic retinopathy, Diabetes mellitus, Fundus changes.

INTRODUCTION

Diabetic retinopathy is a very common, potentially preventable, long-term, microvascular complication of Diabetes Mellitus and a leading cause of visual disability and blindness. (1)

Diabetic retinopathy is frequently accompanied by lipid exudation. (2) Elevated serum lipid levels are associated with an increased risk of retinal hard exudate in persons with diabetic retinopathy. Although retinal hard exudate usually accompanies diabetic macular oedema, increasing amounts of exudate appear to be independently associated with an increased risk of visual impairment. (3)

The elevated lipid levels are also associated with endothelial dysfunction, which appears to play an important role in the pathogenesis of diabetic retinopathy, particularly in relation to the breakdown of blood-retinal barrier. The association between serum lipid levels and diabetic retinopathy has been investigated in few studies. Some studies show a positive relationship between serum cholesterol and low-density lipoprotein levels and retinal hard exudation. Other studies show serum triglyceride levels as being important in the progression of retinopathy. Certain other studies show no relationship between serum lipid levels and diabetic retinopathy. (4) This study aimed to determine the relationship between plasma lipid profile and the severity of diabetic retinopathy in type 2 diabetes patients.

MATERIALS AND METHODS

The study was conducted in The Ophthalmology Outpatient Department (OPD) and In Patient Department (IPD), Smt. Kashibai Navale Medical College and General Hospital, Narhe, Pune, after obtaining ethical clearance. A written consent was taken from all subjects and the details of the procedure were explained to them. The study was conducted on 120 people, 40 diabetics with varying grade of retinopathy (group 1), 40 diabetics with no retinopathy (group 2) and 40 healthy individuals as controls (group 3).

Criteria for inclusion were patients with Type 2 Diabetes Mellitus, aged between 40-80 years, duration of diabetes more than 5 years with a clear view of the retina.

Patients with ocular conditions causing hazy fundus view (cataract; cloudy media), those with previous history of laser or vitreo retinal surgery and those on anti-hyperlipidemic drugs were excluded from the study.

Considering, the inclusion and exclusion criteria, the subjects were selected for the study. After taking Written informed consent, the demographic details and detailed history were taken. Then the visual acuity as well as refractive error in both eyes were assessed using Snellen's visual acuity chart and Autorefractometer respectively. Detailed ocular examination was done on slit lamp biomicroscope and recorded. After that, the Intraocular pressure was measured by non-contact tonometry. Dilated fundus examination using Indirect ophthalmoscope was done and OCT scanning was done whenever needed. Fasting blood sample were collected under asepsis from the anterior cubital vein using disposable syringe to assess lipid profile and blood sugar level.

Lipid profile of patients was tabulated under the following headings: Serum cholesterol, Serum triglycerides, Serum HDL, LDL, VLDL. Dyslipidemia was defined using NCEP ATP III guidelines as:

Total cholesterol ≥ 200 mg/dl
Triglycerides ≥ 150 mg/dl
HDL cholesterol < 40 mg/dl
LDL cholesterol ≥ 100 mg/dl
VLDL ≥ 30 mg/dl

The data obtained was compared statistically on the openepi software by applying the one-way ANOVA test.

RESULTS:

Subjects were divided into 3 groups:

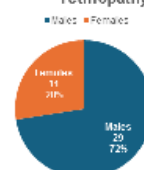
Group 1: diabetics with diabetic retinopathy.

Group 2: diabetics without retinopathy

Group 3: nondiabetics

Mean age in each group was 63.43 ± 10.2 , 63 ± 7.79 and 63 ± 9.3 years.

Sex distribution in patients with diabetic retinopathy



The sex distribution in patients with diabetic retinopathy is shown above. Out of 40 patients present in this group, 29 were males and 11 females.

VARAIBLE	GROUP 1	GROUP 2	GROUP 3
Total cholesterol	225.33 ± 42.57	192.12 ± 32.74	172.09 ± 47.56
Triglycerides	177.9 ± 81.77	140.39 ± 56.19	138.76 ± 86.85
HDL	39.8 ± 10.64	38.96 ± 14.60	39.53 ± 11.74
LDL	115.98 ± 39.32	98.33 ± 34.90	90.88 ± 37.70
VLDL	38.43 ± 23.53	28.34 ± 17.51	26.23 ± 14.08

	Group 1	Group 2	P value
Total cholesterol	225.33 ± 42.57	192.12 ± 32.74	0.0014
triglycerides	177.9 ± 81.77	140.39 ± 56.19	0.3863
HDL	39.8 ± 10.64	38.96 ± 14.60	0.9948
LDL	115.98 ± 39.32	98.33 ± 34.90	0.0915
VLDL	38.43 ± 23.53	28.34 ± 17.51	0.0466

	Group 2	Group 3	P value
Total cholesterol	192.12 ± 32.74	172.09 ± 47.56	0.0820
Triglycerides	140.39 ± 56.19	138.76 ± 86.85	0.9948
HDL	38.96 ± 14.60	39.53 ± 11.74	0.9873
LDL	98.33 ± 34.90	90.88 ± 37.70	0.6464
VLDL	28.34 ± 17.51	26.23 ± 14.08	0.8703

	Group 1	Group 3	P value
Total cholesterol	225.33 ± 42.57	172.09 ± 47.56	0.0000
Triglycerides	177.9 ± 81.77	138.76 ± 86.85	0.4406
HDL	39.8 ± 10.64	39.53 ± 11.74	0.9948
LDL	115.98 ± 39.32	90.88 ± 37.70	0.0090
VLDL	38.43 ± 23.53	26.23 ± 14.08	0.0121

Serum cholesterol and VLDL were significantly greater ($p < 0.05$) in diabetics with retinopathy than in those without. There was also a significant difference in both values in diabetics with retinopathy as compared to non-diabetics. The values were greater in diabetics without retinopathy than in controls but not statistically significant ($p > 0.05$).

There was no statistical significance in the difference in the Triglycerides and HDL values among any of the three groups, however their values were found to be higher in diabetics with retinopathy.

There was a significant difference between LDL values in diabetics with retinopathy as compared to controls but no significant difference between that in diabetics with retinopathy compared to diabetics without retinopathy or between diabetics without retinopathy and controls.

Thus, concluding that Serum cholesterol and VLDL were found to be significantly higher in diabetics with retinopathy.

DISCUSSION

Hyperglycemia and dyslipidemia are two major metabolic disorders seen in patients with diabetes mellitus. The role of diabetic dyslipidemia in the development of microvascular complications has received much less attention.⁽⁵⁾

Out of 40 patients present in this group, 29 (72%) were male and 11 (28%) females. Similar male preponderance was also seen in the CURES Eye study,⁽¹³⁾ UKPDS study⁽¹⁴⁾ Gupta et al⁽¹⁵⁾ and the Andhra Pradesh Eye Disease study (APEDS).⁽¹⁶⁾

The present study showed statistically significant correlation between diabetic retinopathy and raised total cholesterol level. The mean total cholesterol was higher in group 1 as compared to group 2 and group 3. Increased cholesterol level was associated with all grades of retinopathy. Al-Bdour et al⁽⁹⁾ also found significant correlation between higher levels of serum total cholesterol and retinopathy. However, Larsson et al (1999)⁽¹⁰⁾ and Hove et al (2004) found no association between total cholesterol with diabetic retinopathy.⁽¹⁷⁾ Kulshreshtha et al (1979) observed raised levels of cholesterol in patients of Diabetic Retinopathy.⁽¹⁸⁾ The significantly raised serum cholesterol in diabetics with and without retinopathy can be attributed to increased flow of glucose and fatty acids to liver due to lack of insulin.

The present study showed statistically significant correlation between diabetic retinopathy and raised VLDL level. The mean VLDL was higher in group 1 as compared to group 2 and group 3. In contrast, in a

study done by E.N. Cetin et al. there was no significant difference VLDL in diabetics with retinopathy and those without.⁽²⁶⁾

The mean triglyceride level was also higher in group 1 as compared to group 2 and group 3. However, this correlation was not statistically significant. The raised Triglyceride level is due to increased blood viscosity and altered fibrinolytic activity which leads to formation of hard exudates. Also, triglycerides incorporate into cell membrane altering its fluidity and permeability which leads to haemorrhage and oedema.⁽¹²⁾ Rema et al (CURES eye study)⁽¹³⁾ and Haddad et al⁽²⁰⁾ found that both serum triglyceride ($p = 0.001$) levels and total cholesterol ($P = 0.014$) were higher in patients with diabetic retinopathy as compared to those without diabetic retinopathy.

The HDL level in all three groups was nearly similar. Similarly, Larsson et al (1999) and Hove et al (2004) showed no association of HDL with diabetic retinopathy.⁽¹⁷⁾

The mean serum LDL level was clinically significant in group 1 as compared to group 3, and was higher but not clinically significant when compared with group 2. Gupta et al⁽¹⁵⁾ demonstrated that diabetics with raised LDL levels showed higher prevalence of Diabetic retinopathy (38%) compared to others (28.3%). Dornan et al (1982) first showed an association of LDL cholesterol with diabetic retinopathy. Sachdev & Sahni (2010) proved that cholesterol and LDL are risk factors for retinal hard exudates in Type II DM in North Indian population.⁽¹⁹⁾

Hyperglycaemia and its biochemical sequelae either alter endothelial function directly or influence endothelial cell functioning indirectly by affecting the pathways of growth factors, cytokines and vasoactive agents⁽²³⁾. Endothelial dysfunction is also a well-known finding in hypercholesterolemic patients, and it is believed that multiple factors contribute to this, including increased inactivation of nitric oxide by radicals and inhibition of nitric oxide formation by different mechanisms⁽²³⁾. It was reported that the peroxidation of lipids in lipoproteins in the vascular wall leads to local production of reactive carbonyl species that mediate recruitment of macrophages, cellular activation and proliferation, and chemical modification of vascular proteins by advanced lipoxidation end-products which affect both the structure and function of the vascular wall⁽²⁴⁾. Consequently, it was proposed that, hyperlipidemia might contribute to diabetic retinopathy and macular oedema by endothelial dysfunction and breakdown of the blood retinal barrier leading to exudation of serum lipids and lipoproteins⁽²⁵⁾.

CONCLUSION

The present study demonstrated statistically significant correlation between diabetic retinopathy and hypercholesterolemia. With the advent of systemic lipid lowering therapy over the last decade, there may be potential for medical therapy also.⁽²¹⁾ Keech et al (2007) showed that lipid lowering agents like fenofibrate decreases the progression of diabetic retinopathy. There is some anecdotal evidence of the effect of lipid lowering agents in reducing hard exudates. Further studies are required to establish the causal relationship between dyslipidemia and diabetic retinopathy. If established, these data can lend additional support to current treatment guidelines recommending aggressive lowering of elevated lipids among diabetic patients. Rigorous lipid control, in addition to its known health benefits in preventing cardiovascular disease, may also lessen ocular morbidity and associated health care costs, thereby potentially improving quality of life and vision among people with type 2 diabetes.

REFERENCES

- Miljanovic B, Glynn RJ, David M, Nathan, Joann E, Manson, Debra A et al. Prospective Study of Serum Lipids and Risk of Diabetic Macular Edema in Type 1 Diabetes. *Diabetes* 2003 Nov; 53: 2883-2902.
- Chowdhury TA, Hopkins D, Dodson PM, Vafidis DF. The role of serum lipids in exudative diabetic maculopathy: is there a place for lipid lowering therapy? *Eye* 2002 (16): 689-693.
- Reanita, Bardosono S, Victor AA. Relationship between plasma lipid profile and the severity of diabetic retinopathy in type 2 diabetes patients. *Med J Indones* 2008; 17: 221-225.
- D H W Su, K T Yeo. Diabetic Retinopathy and Serum Lipids. *Singapore Med J* 2000; 41(6): 295-297.
- Weigin Chen, Donald B. Jump, Maria B. Grant, Walter J. Esselman, and Julia V. Busik. Dyslipidemia, but Not Hyperglycemia, Induces Inflammatory Adhesion Molecules in Human Retinal Vascular Endothelial Cells. *IOVS*, 2003 Nov; 44(11): 5016-5022.
- Sunil Gupta, Ajay Ambade. Prevalence of Diabetic Retinopathy and Influencing Factors amongst type 2 Diabetics from Central India. *International Journal of Diabetes in Developing Countries*, 2004; 24: 75-78
- Lyons TJ, Jenkins AJ, Zheng D, Lackland DT, McGee D, Garvey WT et al. and The DCCT/EDIC Research Group. Diabetic Retinopathy and Serum Lipoprotein Subclasses

- in the DCCT/EDIC Cohort Investigative Ophthalmology & Visual Science, March 2004; 45: 910-918. 20. Klein BEK, Moss SE
8. Ning Cheung, Paul Mitchell, Tien Yin Wong. Diabetic retinopathy. *The Lancet* 2010 July; 376(9735): 124–136
 9. Muawyah D Al-Bdour, Maha I Al-Till, Khawla M Abu Samra. Risk factors for diabetic retinopathy among Jordanian diabetics. *Middle East African Journal of Ophthalmology* 2008; 15: 77-80.
 10. Lill-Inger Larsson, Albert Alm, Folke Lithner, Gosta Dahlen, Reinhold Bergstrom The association of hyperlipidemia with retinopathy in diabetic patients aged 15-50 years in the county of Umea. *Acta Ophthalmol. Scand.* 1999; 77: 585-591.
 11. Hegde SS, Vekategowda HT. Association of lipid profile with diabetic retinopathy - a comparative study. *Int J Health Sci Res.* 2016; 6(7):74-81.
 12. Study of Association of Serum Lipids with Diabetic Retinopathy in Type 2 Diabetes Mellitus Alpana Mathur, *Rishi Mathur Department of Physiology, *Department of Ophthalmology, Government Medical College, Surat.
 13. 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. *Diabetic Medicine* 2006; 23: 1029-1036.
 14. Rema M, Ponnaiya M, Mohan V. Prevalence of retinopathy in non insulin dependent diabetes mellitus at a diabetes centre in southern India. *Diabetes Res Clin Pract* 1996; 34: 29-36
 15. Sunil Gupta, Ajay Ambade. Prevalence of Diabetic Retinopathy and Influencing Factors amongst type 2 Diabetics from Central India. *International Journal of Diabetes in Developing Countries*, 2004; 24: 75-78
 16. Paromita K, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol.* 1999 November; 48(5): 643-648.
 17. Hove MN, Kristensen JK, Lauritzen T, Bek T: The prevalence of retinopathy in an unselected population of type 2 diabetes patients from Arhus County, Denmark. *Acta ophthalmologica Scandinavica* 2004; 82(4):443-448.
 18. Kulshreshtha OP, Nayar SK, Sharma DP: Role of serum lipids in diabetic retinopathy. *Indian Journal of Ophthalmology*, 1979; 27(4):116-118.
 19. Sachdev N, Sahni A: Association of systemic risk factors with the severity of retinal hard exudates in a north Indian population with type 2 diabetes. *Journal of Postgraduate Medicine*, 2010; 56(1):3-6.
 20. Haddad E, Ossama A W, Mohammed Kamal Saad. Prevalence and risk factors for diabetic retinopathy among Omani diabetics. *Br J Ophthalmol* 1998; 82: 901-90.
 21. Chowdhury TA, Hopkins D, Dodson PM, Vafidis DF. The role of serum lipids in exudative diabetic maculopathy: is there a place for lipid lowering therapy? *Eye* 2002 (16): 689- 693.
 22. Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. *Clin Sci (Lond)* 2005; 109(2):143–159. [PubMed] [Google Scholar]
 23. Landmesser U, Hornig B, Drexler H. Endothelial dysfunction in hypercholesterolemia: mechanisms, pathophysiological importance, and therapeutic interventions. *Semin Thromb Hemost.* 2000; 26(5):529–537. [PubMed] [Google Scholar]
 24. Baynes JW, Thorpe SR. Glycoxidation and lipoxidation in atherogenesis. *Free Radic Biol Med.* 2000; 28(12):1708–1016. [PubMed] [Google Scholar]
 25. Benarous R, Sasongko MB, Qureshi S, Fenwick E, Dirani M, Wong TY, Lamoureux EL. Differential association of serum lipids with diabetic retinopathy and diabetic macular edema. *Invest Ophthalmol Vis Sci.* 2011; 52(10):7464–7469. [PubMed] [Google Scholar]
 26. Cetin EN, Bulgu Y, Ozdemir S, Topsakal S, Akın F, Aybek H, Yıldırım C. Association of serum lipid levels with diabetic retinopathy. *Int J Ophthalmol.* 2013 Jun 18; 6(3):346-9. doi: 10.3980/j.issn.2222-3959.2013.03.17. PMID: 23826531; PMCID: PMC3693018.