

Case Series: Lipid profile in diabetic retinopathy: A North Indian study

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Abstract**Objective:** To study the role of serum lipids in diabetic retinopathy.**Materials and Method:** Cross-sectional study of 48 consecutive patients of diabetic clinic. Diabetic retinopathy (DR) was graded according to modified Airlie House Classification system. Serum lipids (total, LDL, and HDL cholesterol and triglycerides) were assessed.**Results:** Triglyceride was associated with an increase likelihood of having more severe diabetic retinopathy levels ($P < 0.05$). Also HDL showed significant association ($P < 0.05$). Association of total ($P > 0.05$) and LDL cholesterol ($P > 0.05$) with diabetic retinopathy was insignificant.**Conclusions:** The significant association of triglycerides and HDL with DR shown by this study indicates, along with glycemic control, correction of hyperlipidemia is important in preventing the development of DR.**Keywords:** Diabetic Retinopathy, HDL, Total Cholesterol, LDL, Triglycerides

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Introduction

Diabetic retinopathy (DR) is a major cause of blindness among the working age group.^[1-4] According to a report of World Health Organization, India will become one of the major hubs of diabetic population during the next 2 decades; the number of cases of adult-onset diabetes mellitus will grow to nearly 80 million in 2030 from 18 million in 1995.^[3] Duration of Diabetes and hyperglycemia are known risk factors for diabetic retinopathy, but current understanding of other risk factors remains poor.^[5,6]

There is controversy regarding the role of lipids in the pathogenesis of diabetic retinopathy.^[7,8,9] The diabetes complications study demonstrated that high triglycerides and high Low Density Lipoprotein Cholesterol (LDL-C) levels at baseline are associated with subsequent progression of retinopathy over 2 years.^[10] In ETDRS report, high total cholesterol and LDL levels were associated with retinal hard exudates. And Chennai Urban Rural Epidemiology Study (CURES) showed that total cholesterol is an independent risk factor of DR.^[11,12]

On the other hand, these findings were not confirmed by other large studies. Multi Ethnic Study of Atherosclerosis (MESA) showed no associations of serum lipids with diabetic retinopathy.^[13] A large randomized

controlled trial in type 2 diabetes, the FIELD Study, showed that fenofibrate use over 5 years reduced the need for laser treatment for diabetic retinopathy and macular edema, although it did not affect diabetic retinopathy incidence.^[14] Furthermore, in Singapore Malay Eye study, it was reported that higher cholesterol levels were protective of any retinopathy.^[15]

Therefore, we conducted a study to investigate the role of serum lipids in Diabetic Retinopathy.

Materials and Methods

This was a clinic-based observational study. We consecutively recruited 48 subjects aged 30-70 years, attending diabetic clinic, from April 2014 to April 2015. Type 2 DM patients with and without signs of DR were included in the study. Consent was taken from all subjects and details of procedure were explained to them in the local language. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Participants were excluded if they had severe hypertension, acute infections, known cardiovascular and renal diseases, liver dysfunction, severe anemia and thyroid disorders, history of glaucoma, had undergone previous vitreal surgery, and/or had a dense cataract on examination. Participants had a standardized clinical examination and retinal photography.

Diagnosis of type 2 DM was made according to WHO criteria.^[16] Diabetic retinopathy was graded according to the modified Airlie House Classification system.^[13] The Early Treatment Diabetic Retinopathy Study (ETDRS) defined Diabetic Macular Edema

(DME) as retinal thickening or presence of hard exudates within 1 disc diameter of the center of the macula. This definition has been used consistently in most of the diabetes related research studies.^[17,18,19] To characterize the severity of macular edema and for treatment guidelines, the term clinically significant macular edema (CSME) is used. Macular edema is clinically significant if one of the following conditions is present: retinal thickening at or within 500 micron of the center of the macula; and/or hard exudates at or within 500 micron of the center of the macula if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disc area in size, at least part of which is within 1 disc diameter of the macular center.^[17,18]

Vision-threatening diabetic retinopathy (VTDR) was defined to include severe NPDR, PDR, and CSME. An individual's diabetic retinopathy level was based on the diabetic retinopathy level of the worse eye.

All participants underwent a standardized clinical examination and interview using a detailed questionnaire to obtain information including past medical history, current cigarette smoking status, and the use of antihypertensive medications, lipid-lowering medications, and oral hypoglycemic agents. Hypertension was defined as systolic blood pressure (SBP) >140 mmHg, diastolic blood pressure (DBP) >90 mmHg, or current use of antihypertensive medications.

After overnight fasting and 2 hours after meals, fasting and postprandial blood samples were obtained from all the subjects. Fasting Blood Sugar (FBS) and Postprandial Blood Sugar (PPBS) were estimated by Glucose oxidase-peroxidase method. Serum lipids were measured in the fasting blood sample. Serum triglycerides (TG) and cholesterol were measured by enzymatic methods, Glycerol 3 phosphate oxidase N-ethyl sulphopropyl anisidine and cholesterol oxidase-peroxidase end point methods respectively. Serum high density lipoprotein (HDL) was estimated by precipitation method Polyethylene glycol precipitation method. Serum low density lipoprotein (LDL) was calculated using Friedwald's formula ($LDL = TC - HDL - TG/5$).

Data analysis was performed using SPSS statistical software (version 22, SPSS, Inc, Chicago, Illinois, USA). $P < 0.05$ was considered statistically significant, while $P < 0.001$ considered highly significant.

Results

Of 48 participants, 16.66% (4) had mild NPDR, 33.32% (8) had moderate NPDR, 49.98% (12) had VTDR. It was observed that DR patients had longer diabetes duration and higher HbA1c value. The results are summarized in table 1.

Mean levels of triglycerides and HDL were significantly different between participants with and without DR. While others did not show significant association with DR. The results are summarized in table 2.

Table 3 shows associations of serum lipids with diabetic retinopathy severity. HDL was associated with a reduced likelihood of having more severe diabetic retinopathy levels ($P = 0.02$). While triglyceride showed significant positive association with DR severity ($P = 0.05$). Total cholesterol ($P = 0.40$) and LDL ($P = 0.11$) were not significantly associated with DR severity.

In supplementary analyses we stratified VTDR into severe NPDR ($n = 6$), PDR ($n = 4$), and CSME ($n = 2$) and found that triglycerides and HDL maintained their association with even severe forms of diabetic retinopathy and CSME. The results are summarized in table 4.

Table 1: Baseline characteristics of participants

	Retinopathy		P-value
	Yes	No	
No. of Subjects	24	24	
Male sex	66.66	45.83	0.244
Current Cigarette Smoker	58.33	37.50	0.247
BMI(kg/m ²)	29.5±5.6	31.1±6.6	0.07
Diabetes duration	11±1.8	9±2.5	0.04*
HBA1c	9.4±0.50	8.6±0.20	“<0.001”†
Fasting blood sugar	130.37±38.58	133.08±42.28	0.81
Post-prandial (blood sugar)	210.37±72.20	201.48±60.78	0.64

Data are %, mean±SD. P values were obtained using χ^2 test (categorical), a t test (continuous and normally distributed), comparing diabetic participants with and without retinopathy. Significant* (P<0.05), Highly Significant† (P<0.001).

Table 2: Association of serum Lipids with DR

	Mean±SD		P-value
	Subjects with signs of DR	Subjects without signs of DR	
Triglyceride	148.54±23.70	135.08±20.47	0.04*
Total Cholesterol	205.19±30.11	200.48±29.13	0.58
HDL	43.50±6.78	48.75±9.63	0.03*
LDL	129.86±23.77	126.90±28.59	0.69

P-values were obtained using unpaired t-test. Significant* (P<0.05)

Table 3: Association of Serum lipids with DR severity

	Mean±SD			P-value
	Mild NPDR	Moderate NPDR	VTDR	
Triglyceride	130±0	136±16.47	163.08±23.06	0.04*
Cholesterol	191.40±9.93	200.25±41.57	213.08±24.78	0.409
LDL	119.90±13.97	119.90±28.59	139.83±19.78	0.119
HDL	45.50±4.04	47.75±6.60	40±6.00	0.027*

P-Values are calculated using ANOVA test. Significant* (p<0.05)

Table 4: Stratifying VTDR to see association of Serum Lipids with DR severity

	Mean±SD			p-value
	Severe NPDR	PDR	CSME	
Triglycerides	157±10.97	159.38±14.57	186.66±0.44	0.037*
Total Cholesterol	163.33±46.54	210.50±5.19	232.50±3.53	0.059
LDL	130.59±10.79	140.50±20.09	148.50±13.75	0.244
HDL	48.57±4.04	41.50±6.50	38.08±0.50	0.04

P-Values are calculated using ANOVA test. Significant* (p<0.05)

Discussion

The aim of our study was to find out the association of serum lipids with DR and this study showed statistically significant association of Triglycerides and HDL with DR. But there was no statistically significant association of Total Cholesterol and LDL with DR. These results are consistent with several other studies.

High lipid levels are known to cause endothelial dysfunction due to a reduced bioavailability of nitric oxide

and dysfunction of the vascular endothelium is regarded as an important factor in the pathogenesis of diabetic vascular complications. It was also 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 also chemical modification of vascular proteins by advanced lipoxidation end products which affect both the structure and function of the vas-

cular wall.^[20] Consequently, it was proposed that, hyperlipidemia might contribute to DR and Macular Edema (ME) by endothelial dysfunction and breakdown of the blood retinal barrier leading to exudation of serum lipids and lipoproteins.^[21]

There are conflicting reports in the literature regarding the effect of lipid profile on retinopathy or maculopathy. In ETDRS report, Chew et al^[11] stated that patients with high total cholesterol and LDL levels were more likely to have retinal hard exudates compared to patients with normal lipid profile. Moreover, patients with elevated serum total cholesterol, LDL, or triglyceride levels that did not have retinal hard exudate initially, were at increased risk of developing retinal hard exudate during follow up. Other studies showed that retinal exudates or ME was associated either with LDL or total cholesterol, or both.^{[9],[12],[22],[23],[24]} In another study, it was reported that lipid profile was not associated with retinal thickness, mild or moderate DME but only clinically significant ME.^[21] On the contrary, Ozer et al^[25] could not show a correlation between serum lipid levels and macular edema in diabetic patients.

Hove et al^[26] reported no significant association between DR, triglycerides, HDL and total cholesterol in diabetic population in Denmark. Miljanovic et al^[9] reported no lipid profile association with progression of DR or with PDR. In another study, there was no association between DR and lipid profile, however, clinically significant ME was found to be associated with serum lipids.^[21]

On the contrary, in the Chennai Urban Rural Epidemiology Study, Rema et al^[12] showed that mean cholesterol, triglyceride and non HDL levels were higher in patients with DR compared to those without DR. However, only triglycerides were independently associated with.^[12] Cause of discrepancy might be ethnicity.

Significant differences in the prevalence of DR and DME between different ethnic groups was reported.^[13] Although all ethnic groups are susceptible to the established risk factors of DR such as duration the disease, severity of hyperglycemia and hypertension, ethnicity specific risk factors also may have an effect. Such risk factors may include differential susceptibility to conventional risk factors, insulin resistance, truncal obesity and genetic susceptibility.^[27] It may be hypothesized that serum lipid levels may also affect such different populations at a different level, however, this should be supported by further studies.

In conclusion, we found a significant correlation of DR with triglycerides and HDL however, there was no significant association with total cholesterol and LDL. Large multi centric prospective studies are needed about this subject, especially to clarify the reasons of discrepancies between the findings of studies.

Conflicts of Interest: None

Source of Support: Nil

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