

# Association of Lipid Profile with the Severity of Diabetic Retinopathy: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Diabetic Retinopathy (DR) is a microvascular complication of diabetes that damages the retina and is the primary cause of irreversible vision loss among young adults of working age worldwide. It is important to understand the risk factors, such as dyslipidemia, as they have been linked to the pathogenesis and progression of this microvascular disease.

**Aim:** To assess the association of lipid profiles with the severity of DR.

**Materials and Methods:** This cross-sectional study included 150 participants of both genders with type 2 diabetes, aged 35-80 years, attending the Retina Clinic at the Outpatient Department (OPD) of Ophthalmology, Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India, between December 2021 and December 2022. The Early Treatment Diabetic Retinopathy Scale (ETDRS) was used to grade the severity of DR.

**Results:** The mean age of diabetic patients with Non Proliferative Diabetic Retinopathy (NPDR) was 53.28±8.56 years, while the

mean age of those without DR was 54.35±7.79 years, with  $p=0.3$ . The mean Fasting Blood Sugar (FBS) was significantly higher in patients with NPDR than in those without DR ( $199.76\pm65.47$  vs.  $177.69\pm62.75$ ,  $p<0.031^*$ ). Similarly, the mean HbA1c level was higher in patients with DR compared to those without ( $9.77\pm2.27$  vs.  $8.71\pm1.97$ ,  $p=0.002^*$ ). A statistically significant association was found between the level of Low-density Lipoprotein (LDL) cholesterol and severe NPDR ( $p=0.03^*$ ), but no correlation was found between Fasting Blood Sugar (FBS) and Glycated Haemoglobin (HbA1c) with the lipid profile among type 2 diabetes patients with NPDR and those without DR.

**Conclusion:** A significant association was found between blood glucose, HbA1c, and the duration of diabetes in patients with NPDR and those without DR. Additionally, when NPDR is subcategorised as mild, moderate, and severe, a statistical increase in LDL cholesterol in severe NPDR was observed.

**Keywords:** Dyslipidemia, Hyperglycaemia, Low-density lipoproteins

## INTRODUCTION

One of the most common consequences of diabetes is DR, which damages the microvasculature of the retina and is the primary cause of irreversible vision loss among young adults of working age worldwide [1]. It progresses from various grades of NPDR to Proliferative Diabetic Retinopathy (PDR) if not adequately managed, which can lead to irreversible effects such as vision loss. The SMART India study found that among Indians aged 40 years or older, the prevalence of DR was 12.5%, and the prevalence of vision-threatening DR/PDR was 4% (3.4 to 8.8%) [2]. Hypertension, dyslipidemia, and chronic hyperglycaemia are the main risk factors for DR, as they have been linked to the pathogenesis and progression of this microvascular disease. Other modifiable risk factors include the duration of diabetes, age, and inadequate glycaemic control [3]. Additionally, lipid oxidation in DR mediates oxidative stress and various inflammatory mediators that regulate inflammatory cytokines like Vascular Endothelial Growth Factor (VEGF). The mitochondrial damage caused by this may accelerate the death of retinal neurons, aggravating microvascular damage and retinal degeneration in diabetes [4,5]. If left untreated, dyslipidemia can lead to other conditions, including cardiovascular disease and stroke [6].

While there is sufficient evidence that dyslipidemia contributes to the risk of diabetes [7,8], there is insufficient confirmation that it also plays an independent role in the diabetic retina. Thus, the objectives of present study were to assess the glycaemic and lipid profile status among diabetic patients with NPDR and those without DR, study the association of the lipid profile with the severity of DR, and examine the correlation between glycaemic status and lipid profile in diabetic patients with NPDR and those without DR.

## MATERIALS AND METHODS

This cross-sectional study included participants with Type 2 Diabetes Mellitus (T2DM) attending the retina clinic at the Outpatient Department of Ophthalmology, Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India, between December 2021 and December 2022. It was approved by the Institutional Ethics Committee (NI/21/AUG/79/104) and adhered to the guiding principles of the Declaration of Helsinki 1975. Informed consent was obtained from the study participants before enrollment in the study, and confidentiality was maintained throughout the research.

**Inclusion and Exclusion criteria:** Patients with T2DM attending the retina clinic at the outpatient department, who were diagnosed by a consultant ophthalmologist as having DR and were aged 35-80 years of both genders, were included. The exclusion criteria were as follows: subjects with any history or active treatment of cancer, pregnant women, individuals with psychological disorders, those not under treatment for diabetic nephropathy, hypertensive retinopathy, PDR, and other ocular conditions such as uveitis, glaucoma, autoimmune diseases, and communicable diseases.

**Sample size calculation:** The sample size was determined to detect a medium effect size ( $d$ ) of 0.5 with an alpha of 0.05 and 80% power. Using OpenEpi version 3, the estimated sample size was 150.

## Study Procedure

Every participant underwent a comprehensive ophthalmological examination, which included an assessment of visual acuity using a Snellen chart, refraction with an auto-refractometer, a slit-lamp examination, and a dilated stereoscopic fundus examination with an indirect ophthalmoscope to determine the grades of retinopathy.

According to the ETDRS, patients were classified as mild, moderate, or severe NPDR depending on the severity of the disease. Optical Coherence Tomography (OCT) of the macula was performed to determine macular thickness by a consultant ophthalmologist who was blinded to the study [9].

Based on fundus findings, authors divided the participants into two groups:

- Group 1: 75 participants with a history of T2DM but no signs of DR;
- Group 2: 75 participants with Type 2 DM and signs of NPDR.

**Biochemical parameters:** Anthropometric measurements (weight and height) were collected for Body Mass Index (BMI) calculation. The American Diabetes Association’s criteria [10] were used to diagnose diabetes, and the lipid levels were assessed according to the Adult Treatment Panel III (ATP III) guidelines [11]. Clinical data regarding past medical history and the duration of diabetes were acquired through a standardised inquiry. A blood sample was drawn from each participant, and the serum was separated from the BD vacutainer tube for lipid profile analysis, which was then stored at -20°C for batch testing. The following laboratory parameters were measured using methods and reagents supplied by the Beckman Coulter AU5800 clinical chemistry analyser (Beckman Coulter Inc., Brea, CA, USA): Total Cholesterol (TC) was measured using the cholesterol oxidase and peroxidase method; Triglycerides (TGL) were measured using the enzymatic method; High-density Lipoprotein cholesterol (HDL-c) was measured using the polymer-polyanion method; Low-density Lipoprotein cholesterol (LDL-c) was measured using the LDL direct method; FBS was measured using the hexokinase method; and HbA1c was measured using High Performance Liquid Chromatography (HPLC).

STATISTICAL ANALYSIS

The data obtained were entered into a Microsoft Excel spreadsheet and subjected to statistical analysis. All analyses were carried out using the Statistical Package for Social Sciences (version 26, IBM, Chicago, USA). Continuous variables were expressed as mean±Standard Deviation (SD), and categorical variables were expressed as n and %. The normal distribution of the data was checked using the Shapiro-Wilk test. As the data followed a normal distribution, parametric tests of significance were used. The level of significance was set at 5%. An Independent sample t-test was used for intergroup comparisons of continuous variables, while the Chi-square test was used for categorical variables.

RESULTS

Of the 150 patients, 48 were females (32%) and 102 were males (68%), resulting in a male-to-female ratio of 2.1:1. The average age of the patients was 53.81±8.17 years, and the mean BMI was 24.90±4.26 kg/m². In present study, among the 75 patients with T2DM and DR, 35 (46.66%) had mild DR, 1 (1.33%) patient had mild DR with Clinically Significant Macular Oedema (CSME), 19 (25.33%) had moderate DR, 8 (10.66%) had moderate DR, 8 (10.66%) had severe DR, and 4 (5.33%) had severe DR with CSME.

**Association of risk factors and biochemical measurements among two groups:** The mean ages of the patients in the control group and the NPDR group were 53.28±8.56 years and 54.35±7.79 years, respectively (p=0.3). In the control group, there were 70.66% males and 29.33% females, while the NPDR group comprised 65.33% males and 34.66% females. [Table/Fig-1] shows the demographic baseline characteristics of the patients included in the study. The study groups were matched in terms of age and gender (p=0.3, p=0.5, respectively). The mean Systolic Blood Pressure (SBP) was 124.81±13.68 mmHg, and the mean Diastolic Blood Pressure (DBP) was 76.39±8.19 mmHg; however, no significant association was found in mean SBP or mean DBP between the control group and NPDR group (p=0.7, p=0.5). The mean duration

of diabetes was significantly higher in patients with DR (11.45±6.71 years) compared to patients without DR (6.43±5.48 years) (p<0.001). Among these patients, 69.33% of those with NPDR and 29.33% without DR had been diagnosed with T2DM for more than 10 years. The mean fasting blood glucose level was significantly higher in patients with DR (199.76±65.47 mg/dL) compared to patients without DR (177.69±62.75 mg/dL) (p<0.031). Similarly, the mean HbA1c level in the NPDR group (9.77±2.27) was higher than in the control group (8.71±1.97) (p=0.002). However, there was no statistically significant association between the lipid profiles of these groups.

Characteristics	T2DM without DR (n=75)	Non proliferative DR, (n=75)	p-value
Age (years)	53.28±8.56	54.35±7.79	0.3
Gender n (%)			
Female	22 (29.33%)	26 (34.66%)	-- 0.48
Male	53 (70.66%)	49 (65.33%)	
BMI (kg/m²)	25.08±4.37	24.72±4.16	0.5
Blood pressure (mmHg)			
SBP	124.08±11.83	125.55±15.35	0.7
DBP	76.96±7.07	75.81±9.20	0.5
Diabetes duration (years)	6.43±5.48	11.45±6.71	<0.001*
<10 years	53 (70.66%)	23 (30.66%)	
>10 years	22 (29.33%)	52 (69.33%)	
FBS (mg/dL)	177.69±62.75	199.76±65.47	0.031*
70-110 (mg/dL)	10 (13.33%)	7 (9.33%)	0.2
110-200 (mg/dL)	42 (56%)	34 (45.33%)	
>200 (mg/dL)	23 (30.66%)	34 (45.33%)	
HbA1c (%)	8.71±1.97	9.77±2.27	0.002**
Normal: <5.6	1 (1.33%)	2 (2.66%)	0.2
Pre: 5.7-6.4	7 (9.33%)	2 (2.66%)	
Diab >6.5	67 (89.33%)	71 (94.66%)	
Total cholesterol (mg/dL)	193.52±51.91	181.83±52.93	0.2
Desirable ≤200 (mg/dL)	44 (58.6%)	48 (64%)	0.7
Borderline high 201-240 (mg/dL)	15 (20%)	15 (20%)	
Very high >240 (mg/dL)	16 (21.33%)	12 (16%)	
TGL (mg/dL)	176.85±87.07	162.39±84.84	0.2
Desirable ≤150 (mg/dL)	32 (42.66%)	44 (58.66%)	0.09
Borderline high 150-199 (mg/dL)	16 (21.33%)	15 (20%)	
High 200-499 (mg/dL)	27 (36%)	16 (21.33%)	
HDL-c (mg/dL)	42.87±17.30	39.96±12.23	0.2
Low ≤40 (mg/dL)	36 (48%)	41 (54.66%)	0.5
Normal 40-60 (mg/dL)	35 (46.66%)	29 (38.66%)	
High >60 (mg/dL)	4 (5.33%)	5 (6.66%)	
LDL-c (mg/dL)	124.98±34.61	120.24±46.59	0.3
Optimal ≤100 (mg/dL)	21 (28%)	28 (37.33%)	0.6
Near-optimal 100-129 mg/dL	23 (30.66%)	21 (28%)	
Borderline high 130-159 (mg/dL)	16 (21.33%)	13 (17.33%)	
High >160 (mg/dL)	15 (20%)	13 (17.33%)	
Chol/HDL ratio	4.72/1.14	4.766/1.47	0.7

[Table/Fig-1]: Baseline characteristics of the study participants. Values presented as mean±SD. \*p<0.05, \*\*p<0.01, BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; TGL: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein

The association of lipid profiles with different degrees of NPDR is shown in [Table/Fig-2]. Among the patients with NPDR, 36% had high TC levels (>200 mg/dL), 34% had high LDL cholesterol levels (≥130 mg/dL), 41% had high triglyceride levels (>150 mg/dL), and only 8% had high HDL cholesterol levels (≥60 mg/dL). The association between serum LDL cholesterol levels and the severity

of DR was statistically significant, with a p-value of 0.03. The LDL increases the chances of severe NPDR by 1.01 times; however, this was not statistically significant [Table/Fig-3]. No significant correlation was observed between FBS, HbA1c, and lipid profile among the type 2 diabetes patients with NPDR and without DR (p>0.05) [Table/Fig-4a,b].

Lipid profile	Mild NPDR 36%	Moderate NPDR 27%	Severe NPDR 12%	p- value
Total cholesterol (mg/dL)				
Desirable: ≤200 (mg/dL)	21 (58.33%)	19 (70.37%)	8 (66.66%)	0.5
Borderline high: 200-239 (mg/dL)	10 (27.77%)	4 (14.81%)	1 (83.33%)	
Very high: ≥240 (mg/dL)	5 (13.88%)	4 (14.81%)	3 (25%)	
LDL cholesterol (mg/dL)				
Optimal: ≤100 (mg/dL)	8 (22.22%)	16 (59.25%)	4 (33.33%)	0.03*
Near-optimal: 100-129 (mg/dL)	14 (38.88%)	3 (11.11%)	4 (33.33%)	
Borderline high: 130-159 (mg/dL)	9 (25%)	3 (11.11%)	1 (83.33%)	
High: ≥160 (mg/dL)	5 (13.88%)	5 (18.51%)	3 (25%)	
HDL cholesterol (mg/dL)				
Low: ≤40 (mg/dL)	22 (61.11%)	13 (48.14%)	6 (50%)	0.5
Normal: 40-60 (mg/dL)	12 (33.33%)	12 (44.44%)	4 (33.33%)	
High: ≥60 (mg/dL)	2 (5.55%)	2 (74.0%)	2 (16.66%)	
Triglyceride (mg/dL)				
Desirable: ≤150 (mg/dL)	17 (47.22%)	18 (66.66%)	9 (75%)	0.4
Borderline high: 150-199 (mg/dL)	9 (25%)	5 (18.51%)	1 (83.33%)	
High: 200-499 (mg/dL)	10 (27.77%)	4 (14.81%)	2 (16.66%)	

[Table/Fig-2]: Association of lipid profiles in different degrees of NPDR. \*p<0.05, \*\*p<0.01, LDL: Low density lipoprotein; HDL: High density lipoprotein; NPDR: Non-proliferative diabetic retinopathy

Variable	β	S.E	Adjusted OR 95% CI	p-value
LDL	0.015	0.016	1.01 (0.78-1.32)	0.35

[Table/Fig-3]: Binary logistic regression for independent predictors LDL on severity of NPDR.

Variables	T2DM without DR		NPDR	
	R-value	p-value	R-value	p-value
Total cholesterol (mg/dL)	0.065	0.579	-0.097	0.407
Triglyceride (mg/dL)	0.098	0.402	-0.034	0.772
HDL cholesterol (mg/dL)	-0.071	0.544	-0.027	0.818
LDL cholesterol (mg/dL)	0.119	0.309	-0.044	0.707

[Table/Fig-4a]: Correlation of HbA1C with lipid profile among type 2 diabetes patients with and without DR.

Variables	T2DM without DR		NPDR	
	R-value	p-value	R-value	p-value
Total cholesterol (mg/dL)	-0.027	0.818	0.067	0.567
Triglyceride (mg/dL)	0.186	0.110	0.142	0.224
HDL cholesterol (mg/dL)	-0.145	0.214	-0.002	0.986
LDL cholesterol (mg/dL)	0.0040	0.972	0.122	0.297

[Table/Fig-4b]: Correlation of FBS with lipid profile among type 2 diabetes patients with and without DR.

DISCUSSION

In present study, FBS, HbA1c, and the duration of T2DM were significantly higher in diabetic patients with NPDR compared to those without DR. There was a significant association between LDL-C and severe NPDR. Hyperlipidemia in severe DR leads to endothelial dysfunction, resulting in the collapse of the blood-retinal barrier and causing lipids to leak from injured retinal capillaries.

This contributes to retinal oedema and the accumulation of hard exudates in the retina [12]. Although the association between DR and serum lipids was assessed globally, there was a disparity in the relationship between the different stages of retinopathy.

According to the results of Ezhilvendhan K et al., the duration of diabetes with DR was significant (7.9 vs. 6.2 years; p<0.001), and there was a strong correlation between serum cholesterol and DR in unadjusted analysis, but not when glycaemic control, age, gender, and the duration of diabetes were taken into consideration [13]. Similar findings were also reported in a single-centre observational study by Seema KS et al., where there was a statistically significant association between serum lipid levels and hyperglycaemia across the severity of DR, which increased from mild to severe NPDR and PDR [14]. In contrast, the current investigation did not show an upward trend in the lipid levels of those with and without DR; however, LDL-C levels were higher in severe NPDR than in mild and moderate NPDR, with a statistically significant p-value of 0.03. This may be because the majority of patients in both the NPDR and control groups in present study had normal TC and HDL cholesterol levels.

When comparing the different stages of NPDR, 25% of patients with severe NPDR had high LDL cholesterol (≥160 mg/dL). The specific observation of the association of dyslipidemia (elevated LDL-C) with severe NPDR may indicate that dyslipidemia develops concomitantly with an increase in the severity of DR. Furthermore, a systematic review and meta-analysis by Zhou Y et al., found no differences in TG, TC, and HDL-C levels, but slightly higher LDL-C levels were observed in DR cases, similar to the results of this study [15]. In a cross-sectional study, Zhang X et al., observed that TC and LDL-C showed a statistically significant association, but TG and HDL did not show any association among different stages of DR [16]. Similarly, in another study by Alattas K et al., the mean LDL levels of patients with severe NPDR were considerably higher than those of patients with other DR phases (p=0.005). Nevertheless, there was no significant association between HDL and the DR stage (p=0.534) [17].

As the results of studies regarding the relationship between lipid profile and retinopathy were inconsistent, it is suggested that more research on lipidemia-induced regulation of circulating biomarkers associated with the degree of DR is needed to predict dyslipidemia at its early stage. The primary advantage of this research is that it covers different stages of NPDR.

Limitation(s)

Small sample size and exclusion of patient medication information.

CONCLUSION(S)

A statistically significant association was found between blood glucose, HbA1c, and the duration of diabetes with DR, and there was also a significant association between LDL cholesterol and the severity of NPDR. These results demonstrate the importance of monitoring lipid levels at each stage of retinopathy, which would enable effective treatment and help avoid further complications of dyslipidemia in patients with retinopathy.

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**Authors’ contribution:** TS, AS, and RA: conception and design, TK: proof read, LC: supervised the whole research. All the authors read and approved the final manuscript.

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