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STUDY OF ASSOCIATION OF DIABETIC RETINOPATHY WITH DYSLIPIDEMIA IN TYPE II DIABETES MELLITUS

Pasumarthi Pavani Yelamanchili, Madhuri Kurakula, Puwala Sai Kiranmayi, Kalluru Viswanath

Diabetic retinopathy is the leading cause of visual disability in the working-age population of industrialized countries. It is considered the hallmark of generalized microangiopathy occurring in a diabetic patient.
***The aim**: association of Diabetic Retinopathy and CSME with mean values of lipids and Association of the pattern of hard exudates in the fundus in patients with Diabetic retinopathy with or without CSME with mean values of lipids.*
***Materials and methods:** 320 eyes of 160 urban diabetic patients who were seen at the OPD, at Pushpagiri Eye Institute, Secunderabad having diabetic retinopathy were included in the study. Detailed history was taken to note the duration of diabetes, hypertension, history of CAD, CVA, CKD. Patients with duration of diabetes >=5 years were enrolled. Thorough work up was done with slit lamp and indirect ophthalmoscope and posterior segment was examined to evaluate the stage of diabetic retinopathy and presence or absence of CSME. Patients with DR were investigated for Fasting Lipid Profile and HbA1c.*
***Results:** a total of 320 eyes of 160 patients were included in the study. In patients with CSME, mean values of Total Cholesterol, Triglycerides, LDL, HDL, VLDL were higher in the plaque pattern of hard exudates in the macula compared to Discrete and Circinate. There was a statistically significant difference between the mean values of total cholesterol (p=0.00), triglycerides (p =0.035), ldl(p=0.00) in discrete and plaque patterns. There was slightly higher prevalence of PDR among hypertensives compared to non-hypertensives. There was no significant association between DR stage and hypertension(p=0.628). The correlation between CSME and BCVA could not be determined accurately due to the presence of cataract in most of the patients.*
***Conclusion**: this study demonstrated that, diabetic retinopathy is not associated with lipid profile whereas there is statistically significant correlation between mean values of total cholesterol, triglycerides, LDL, VLDL and clinically significant macular edema (CSME)*
***Keywords:** diabetic retinopathy, total cholesterol, triglycerides, hypertensives, low-density lipoprotein, high density lipoprotein, cataract, Uncorrected Visual Acuity (UCVA), Best Corrected Visual Acuity (BCVA)*

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1. Introduction

Diabetes mellitus is a major cause of avoidable blindness in both the developing and the developed countries. According to a WHO fact sheet reviewed in October 2013, 347 million people worldwide have diabetes, and the number is set to increase to 438 million by the year 2030. The major proportion of this increase will occur in developing countries of the world where the disorder predominantly affects younger adults in the economically productive age group. A study published in WHO states that India was the global leader in 2000 with a total of 31.7 million people suffering from Diabetes and will remain the leader with a total of 79.4 million diabetics in 2030. Majority of the patients have non-insulin-dependent diabetes mellitus (NIDDM) or Type 2 diabetes, prevalence accounting to 85-90 % of diabetic population [1, 2].

Diabetes clusters with multiple comorbid conditions, including hypertension and dyslipidemia, which often complicate the management of diabetes and increase the risk for vascular complications of diabetes. A targeted approach to treatment, which includes combined control of glycemia, hypertension and dyslipidemia, may prove most beneficial in both patient and health service terms and can dramatically delay or prevent the micro and macrovascular complications of diabetes including diabetic retinopathy.

The multisystem effects of diabetes such as retinopathy, nephropathy, neuropathy, and cardiovascular & cerebrovascular diseases are considered important impinging on public health. Diabetic retinopathy involves damage to the microvasculature of the retina because of prolonged exposure to the metabolic changes induced by diabetes.

Prevalence of DR in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) [9] was 50.1 %. In the Diabetes control and complications trial (DCCT) the prevalence of IDDM was 54.2 % and in the United Kingdom Prospective Diabetes Study (UKPDS) for NIDDM it was 35-39 %. Zooming in to Indian figures, in the Andhra Pradesh Eye Disease Study (APEDS) of self-reported diabetics, the prevalence of DR was 22.4 % [3].

Diabetic retinopathy is the leading cause of visual disability in the working-age population of industrialized countries. According to WHO, it is responsible for 3–7 % of total blindness in Asia. It is considered the hallmark of generalized microangiopathy occurring in a diabetic patient. It occurs in both Type 1 and Type 2 Diabetes Mellitus. Changes in lifestyle have increased the risk of diabetes as well as blindness in many developing countries and it is important that organised efforts are undertaken to address eye complications of diabetes.

While there are multiple risk factors that have been associated with the development and progression of diabetic retinopathy, the duration of disease and the age of the patient are said to be the strongest predictors. Other risk factors like hyperglycemia, hypertension, presence of nephropathy (microalbuminuria) are shown to have strong association. Dyslipidemia, BMI, and smoking are some of the factors whose role as predictors of diabetic retinopathy is not well established.

Diabetic retinopathy is frequently accompanied by lipid exudation. Elevated serum lipid levels are associated with an increased risk of retinal hard exudates in persons with diabetic retinopathy. Although retinal hard exudates usually accompany diabetic macular edema, increasing amounts of exudates appear to be independently associated with increased risk of visual impairment. The elevated lipid levels are also associated with endothelial dysfunction, due to a reduced bioavailability of nitric oxide which appears to play an important role in pathogenesis of diabetic retinopathy particularly in retinal exudate formation, and in relation to breakdown of blood-retina barrier.

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 vascular wall. 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 [4].

Technological advances have improved the diagnostic accuracy of screening methods and access of the diabetic patients to the specialist care. In the last three decades, the treatment strategies have been revised to include good glycemic control and control of associated comorbidities to arrest the development and progression of DR and decrease the visual loss. Besides pharmacotherapies, laser photocoagulation and early surgical interventions help reduce the incidence of blindness.

2. Materials and methods

320 eyes of 160 patients > 40 years of both genders with Type 2 Diabetes Mellitus of >=5 years duration with Diabetic Retinopathy who attended the outpatient department (OPD) at Pushpagiri Eye Institute, Secunderabad were recruited between 1st January 2014 and 30th November 2014 in this study. Informed consent was obtained from all the patients who agreed to participate in the study. Ethical clearance number is obtained and numbered as Reg No: 226A12135A132A108442 dated June 2013.

The following criteria were used to guide patient enrolment:

Inclusion criteria: Self-reported Type 2 Diabetes Mellitus patients with history of >=5 years and diagnosed with Diabetic retinopathy in either of the eyes were included in the study.

Exclusion criteria: pregnant women with diabetes mellitus, patients with significant hazy media due to dense cataract or any other pathology which impairs visualisation of fundus.

Data was collected using a piloted proforma meeting the objectives of the study after informed consent was taken. A detailed systemic history for each patient regarding age, duration of diabetes, history and duration of hypertension, anti-diabetic treatment, coronary artery disease, chronic kidney disease, cerebrovascular accidents, and ocular history regarding previous consultation, previous treatment for diabetic retinopathy like laser therapy, intravitreal injections was taken.

Among diabetic patients with history of duration >=5 years the following parameters were evaluated as Uncorrected Visual Acuity (UCVA) and Best Corrected Visual Acuity (BCVA) using Snellen's chart at 6 meters was recorded. A meticulous ocular examination was done including detailed slit lamp examination of anterior and posterior segment with 90 or 78D lens and dilated fundus examination with an indirect ophthalmoscope. All cases were examined to evaluate the stage of diabetic retinopathy, presence or absence of CSME and anterior segment pathology.

Cases with fundus showing features of Diabetic retinopathy were graded into the following classes according to ETDRS classification:

- Mild NPDR;
- Moderate NPDR;
- Severe NPDR;
- PDR.

Severe grade of retinopathy between the two eyes was considered for scoring and analysis. Based on Macula status, patients were again divided into those with CSME present and CSME absent (including No CSME, obscured macula, Comorbidities). All patients diagnosed to have diabetic retinopathy and willing to participate in the study were investigated for fasting lipid profile estimation total cholesterol by cholesterol oxidase-PAP method, HDL Cholesterol by PEG-CHOD-PAP, End Point Assay with Lipid Clearing Factor (LCF), triglycerides by GPO-PAP, End Point Assay on calorimeter, LDL cholestrol by Friedewald equation and HbA1C by HPLC method in D10 instrument. Reference range of lipid profile according to NCEP ATP III guidelines.

Patterns of hard exudates in the retina were graded as Absent, Sparse, Discrete, Circinate, Plaque from less severe to more severe. Higher grade of pattern of hard exudates in the same eye was taken for scoring and common score was given for higher grade between the two eyes for correlating with mean values of lipids. Discrete, Circinate & Plaque patterns of Hard exudates at or within 500 μ from the centre of the macula in patients with CSME were again correlated with mean values of lipids in patients with CSME. Age and sex distribution of DR stages and correlation with diabetes mellitus duration, hypertension, mean values of lipids, HbA1c were done. Diabetic retinopathy was diagnosed and classified based on ETDRS classification mentioned earlier: The following stages were considered in the study:

- Mild NPDR
- Moderate NPDR
- Severe NPDR
- PDR

Retinal thickening within 500 μm of the centre of the macula. Exudates within 500 μm of the centre of the macula, if associated with retinal thickening (which may be outside the 500 μm.) Retinal thickening one disc area (1500 μm) or larger, any part of which is within one disc diameter of the centre of the macula.

Pattern of hard exudates: all over posterior pole.

- Absent- No hard exudates
- Sparse- Very minimal hard exudates
- Discrete-Well demarcated hard exudates more than Sparse
- Circinate – Hard exudates forming a whorl
- Plaque- Confluent hard exudates

Reference range of lipid profile according to NCEP ATP III guidelines [84]

HbA1C (glycosylated hemoglobin) was used as a measure of glycemic control as it gives us the picture of blood sugars (average blood glucose) over the past 3 months. The method for estimation of HbA1C was HPLC (High Performance Liquid Chromatography).

Statistical analysis.

SPSS version 19 was used for analysis of the data. Data was recorded on a predesigned proforma and managed on an Excel spreadsheet. All the entries were checked for any possible keyboard error. Descriptive and inferential statistical analysis has been carried out. Results on continuous measurements are presented using descriptive statistics like Mean +/- SD (Min- Max) and results on categorical measurements are presented in number (%).

Significance is assessed at 5 % (0.05) level of significance. Significant figures:

+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value:0.01<P 0.05)
** Strongly significant (P value: P<0.01)

3. Results.

In the sample, age of the patients ranged from 40 years to 88 years. Mean age was 56.87± 8.09 years (Table 1). Out of 160 patients, males were 111 (69 %), females were 49 (31 %) (Table 2).

All the diabetic subjects aged <=40 years, progressed to PDR.

Table 1

Distribution of Diabetic retinopathy stages among various age groups

Age group	Mild NPDR		Moderate NPDR		Severe NPDR		PDR		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
<=40	0	0.0 %	0	0.0 %	0	0.0 %	5	100.0 %	5	3 %
41–50	2	6.5 %	5	16.1 %	5	16.1 %	19	61.3 %	31	19 %
51–60	5	6.7 %	18	24.0 %	17	22.7 %	35	46.7 %	75	47 %
61–70	2	4.5 %	14	31.8 %	8	18.2 %	20	45.5 %	44	28 %
>70	0	0.0 %	2	40.0 %	0	0.0 %	3	60.0 %	5	3 %

Table 2

Distribution of diabetic retinopathy stages among various gender groups

Gender	Mild NPDR		Moderate NPDR		Severe NPDR		PDR		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Males	4	3.6 %	18	16.2 %	21	18.9 %	68	61.3 %	111	69 %
Females	5	10.2 %	21	42.9 %	9	18.4 %	14	28.6 %	49	31 %
Total	9	5.6 %	39	24.4 %	30	18.8 %	82	51.2 %	160	100 %

Only one eye is selected. Higher grade of retinopathy between the two eyes is considered for analysis. Mild and Moderate NPDR was mostly seen in females whereas Severe NPDR and PDR was mostly seen in males. Only one eye was selected. Higher grade of retinopathy between the two eyes was considered for analysis. PDR contributed to most of the sample (51 %) (Fig. 1).

PDR with Sub hyaloid hemorrhage PDR with Preretinal and vitreous hemorrhage + FVP

Among 160 patients, 116 had a similar DR stage in both the eyes whereas 44 had dissimilar stages (Table 3).

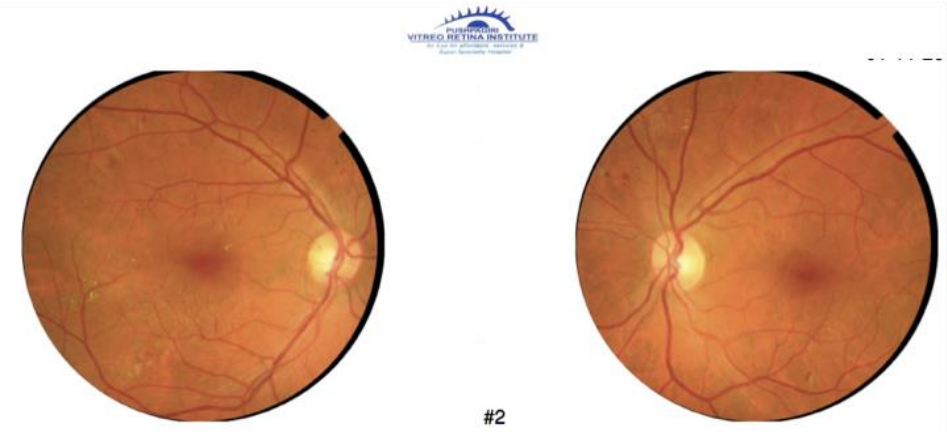

Fig. 1. Fundus picture of moderate NPDR

Table 3

Distribution of macula status in both the eyes

RE			LE		
Macula status	Number	Percentage	Macula status	Number	Percentage
CSME present	60	43.13 %	CSME Present	60	43.75 %
No CSME	69	16.88 %	No CSME	70	18.13 %
Obscured macula	27	37.50 %	Obscured macula	29	37.50 %
CME(CRVO)	3	1.88 %	CME(CRVO)	0	0.00 %
Scar	1	0.63 %	Scar	1	0.63 %

There was no significant association of Diabetic retinopathy severity with duration of Diabetes Mellitus (P=0.712).

Presence of CSME in any stage of DR was analysed in different groups of DM duration. Overall, there were more patients in 7–8 group and more severe NPDR and PDR patients in the 8–9 group. There is significant association of HbA1C with severity of Diabetic Retinopathy (P=0.024) (Table 4).

There was no significant association of DR +CSME with duration of Diabetes Mellitus as CSME was noticed in 62.6 % (62) of DR patients with duration of 5-10 years which signifies CSME is independent of duration of Diabetes. There was no significant association of HbA1C with CSME (P=0.764) (Table 5).

Mean values of all the lipids were similar across DR stages. There is no statistically significant association of lipids with Severity of Diabetic Retinopathy (Table 6).

The mean values of Total Cholesterol, triglycerides, LDL, VLDL were higher and HDL were lower in patients with CSME compared to patients with no CSME and obscured macula (Table 7).

There was a statistically significant association of mean values of Total Cholesterol, triglycerides and VLDL with CSME. Only one eye with a higher grade of hard exudates pattern was taken for analysis. For 9 patients with advanced stage – PDR with High Risk Characteristics, pattern of hard exudates could not be determined.

Table 4

DR stages distribution was analysed in different groups of DM duration

Duration of diabetes (years)	Mild NPDR		Moderate NPDR		Severe NPDR		PDR		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
5–10	6	6 %	24	24 %	21	21 %	48	49 %	99	62 %
11–15	2	8 %	6	23 %	4	15 %	14	54 %	26	16 %
16–20	1	5 %	7	32 %	1	5 %	13	59 %	22	14 %
21–25	0	0 %	1	10 %	4	40 %	5	50 %	10	6 %
>25	0	0 %	1	33 %	0	0 %	2	67 %	3	2 %
Total	9	5.6 %	39	24.4 %	30	18.8 %	82	51.2 %	160	100 %
DR stages with HbA1c										
<7.0	5	19 %	9	33 %	6	22 %	7	26 %	27	16.9 %
7.0–8.0	3	7 %	9	20 %	11	25 %	21	48 %	44	27.5 %
8.0–9.0	0	0 %	6	15 %	8	21 %	25	64 %	39	24.4 %
9.0–10.0	1	4 %	7	30 %	2	9 %	13	57 %	23	14.4 %
>=10	0	0 %	8	30 %	3	11 %	16	59 %	27	16.9 %
Total	9	5.6 %	39	24.4 %	30	18.8 %	82	51.2 %	160	100 %

Table 5

CSME vs Duration of Diabetes and HbA1C

Duration of diabetes (years)	CSME present		CSME absent		Total	%
	No.	%	No.	%	No.	%
5–10	62	62.6 %	37	37.4 %	99	62 %
11–15	7	26.9 %	19	73.1 %	26	16 %
16–20	6	27.3 %	16	72.7 %	22	14 %
21–25	2	20.0 %	8	80 %	10	6 %
>25	1	33.3 %	2	66.7 %	3	2 %
Total	78	48.75 %	82	51.25 %	160	100 %
CSME vs HbA1c						
<=7	12	44 %	15	56 %	27	16.9 %
7.0–8.0	22	50 %	22	50 %	44	27.5 %
8.0–9.0	18	46 %	21	54 %	39	24.4 %
9.0–10.0	10	43 %	13	57 %	23	14.4 %
>=10.0	16	59 %	11	41 %	27	16.9 %
Total	78	49 %	82	51 %	160	100 %

CSME Absent – Includes No CSME, obscured macula, comorbidities

Table 6

DR Stages vs mean values of lipids (mg/dl)

Mean Lipid Values	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Total Cholesterol	171.00 mg/dl+19.4	182.30 mg/dl±42.7	187.23 mg/dl±50.4	182.88 mg/dl±39.6
Triglycerides	141.56 mg/dl ±33.7	157.26 mg/dl±66.4	166.10 mg/dl±82.4	172.46 mg/dl±88.3
LDL	101.58 mg/dl±24.1	109.28 mg/dl±38.6	114.82 mg/dl±41.5	104.13 mg/dl±32.6
HDL	41.22 mg/dl±4.6	42.33 mg/dl±10.2	41.93 mg/dl±12.8	41.48 mg/dl±10.5
VLDL	28.09 mg/dl±6.4	30.86 mg/dl±13.6	30.55 mg/dl±13.8	34.88 mg/dl±17.3

Table 7

Comparison of mean values of lipids (mg/dl) in CSME vs No CSME group

Mean Values of Lipids	CSME Present	CSME Absent	P value
Total Cholesterol	190.86±41.27	175.30±40.68	0.021
Triglycerides	182.68±82.23	149.79±74.77	0.011
LDL	113.61±41.04	98.88±32.74	0.31
HDL	40.46±10.49	43.00±10.61	0.123
VLDL	35.55±14.99	29.36±16.29	0.031

Note: CSME Absent – Includes No CSME, obscured macula, comorbidities

Mean values of Total Cholesterol, Triglycerides, LDL, were significantly higher in Plaque followed by Circinate patterns of hard exudates compared to Sparse, Discrete patterns (Table 8).

According to Post Hoc test, the difference in the mean values of total cholesterol, were significantly different in those with no or sparse exudates compared to circinate and plaque (p=0.00, p=0.02 between no exudates vs plaque, circinate patterns respectively and p=0.00, p=0.012 between sparse vs plaque, circinate patterns respectively.

The difference in the mean values of triglycerides were significantly higher in circinate (p=0.032) and plaque (p=0.002) compared to those with no hard exudates.

The difference in the mean values of LDL was significantly higher in circinate (p=0.012) and plaque (p=0.00) in comparison to sparse hard exudates.

Table 8

Pattern of hard exudates in retina vs mean values of lipid (mg/dl)

Mean Value of lipid	Absent	Sparse	Discrete	Circinate	Plaque	P value
Total cholesterol	152.50±30.1	I38.00±41.28	171.35±32.5	190.30±27.98	221.35±44.3	0.00
Triglycerides	116.25±50.7	173.50±150.834	151.51±70.8	192.17±87.79	209.69±82.45	0.01
LDL	86.25±26.8	66.05±11.8	98.81±27.93	112.58±21.86	137.26±43.69	0.00
HDL	43.00±8.07	37.50±4.79	41.18±11.46	39.42±3.6	43.11±10.9	0.722
VLDL	23.10±9.6	34.65±30.17	30.75±15.3	38.30±17.62	39.21±12.57	0.16

Mean values of total cholesterol, triglycerides, LDL, HDL, VLDL were higher in the plaque pattern of hard exudates in the macula compared to discrete and circinate (Table 9). P values mentioned were according

to the ANOVA test. According to the Post Hoc test, there was a statistically significant difference between the mean values of total cholesterol (p=0.00), triglycerides (p=0.035), ldl (p=0.00) in discrete and plaque patterns.

Table 9

Pattern of Hard Exudates in the macula in CSME vs mean values of lipids (mg/dl)

Mean value of lipids	Discrete	Circinate	Plaque	P value
Total Cholesterol	168.49±30.35	182.20±29.10	219.58±38.16	0.00
Triglycerides	165.89±82.84	163.13±48.45	207.50±83.64	0.083
LDL	96.01±29.40	111.25±24.34	136.53±37.52	0.00
HDL	39.07±10.76	38.50±2.39	42.59±11.22	0.32
VLDL	33.98±16.015	32.42±9.89	38.37±12.12	0.36

a *b*

Fig. 2. Hard Exudates: *a* – discrete pattern; *b* – circinate pattern

There was slightly higher prevalence of PDR among hypertensives compared to non-hypertensives. There was no significant association between DR stage and Hypertension (p=0.628). The correlation between lens status and stage of DR could not be made out as most of the eyes were phakic (Table 10).

Table 10

Correlation of diabetic retinopathy stages with – "Phakic" vs Pseudophakic (IOL) status in both eyes separately

Left Lens status	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Total
Phakic	6	34	28	51	125
Pseudophakic	2	11	7	14	35
Right lens status					
Phakic	9	33	27	58	129
Pseudophakic	2	5	10	14	31

Majority of patients with CSME had BCVA 6/9-6/12. The correlation of CSME with BCVA could not be accurately determined due to various grades of cataract (Table 11).

Table 11

Correlation of CSME with BCVA in both eyes

BCVA	RE	LE
6/6	0	0
6/9-6/12	36	39
6/18-6/36	21	18
<=6/60	3	3

4. Discussion

The various risk factors for diabetic retinopathy and its spectrum are still poorly understood in the Indian population. Of the traditional risk factors for DR, longer duration of diabetes, hyperglycemia and hypertension are clearly involved in the pathogenesis of DR and DME. The control of hyperglycemia and hypertension has been shown in landmark randomized trials to delay the onset of DR in eyes without DR, to reduce the rate of progression of DR when it is already present and to prevent visual loss [5].

Hyperglycemia and dyslipidemia are two major metabolic disorders in patients with Diabetes Mellitus. Despite considerable progress in understanding of hyperglycemia induced disease over the past decade, the link between diabetic metabolic disorders and retinopathy still eludes us. The role of diabetic dyslipidemia in the development of microvascular complications has received much less attention. This study aimed to determine the relationship between serum lipid profile and the severity

of Diabetic Retinopathy in Type 2 Diabetes patients. In the present study, 160 patients having Type II diabetes mellitus >=40 years age and Diabetic retinopathy in at least one eye and with or without CSME were recruited.

The mean age of the sample was 56.87± ±8.09 years. Occurence of PDR at age 40years with 5 years duration, majority of patients in 41–50 years age group suggests that these patients were younger onset diabetics diagnosed late. This finding is comparable to results of WESDR [9]. They should have been started on Insulin, to prevent progression of Diabetic retinopathy. In the current sample, the majority were PDR (82 patients, 51 %), because PDR is a sight threatening disease and they reported to the Hospital. CSME was found mostly in the age group of 51–60 years [3].

The present study had male preponderance, M: F=2:1 like other clinical cohorts in Chennai- CURES and study done by Rema et al APEDS and also UKPDS [10]. Like our study in the WESDR, higher frequencies of proliferative retinopathy were present in younger-onset men compared to women [6].

In the present study, the duration of Diabetes ranged from 5-30years.Mean duration of Diabetes in the sample was 11.54±6.03 years. There may be some bias in estimating the real duration of diabetes in these patients, as the discovery of diabetes could have been delayed due to lack of symptoms and insidious onset of Type 2 diabetes. However, there was no statistically significant correlation between severity of diabetic retinopathy and duration of diabetes (p=0.712). The association of longer duration of diabetes with high risk of retinopathy was shown in previously published reports like DCCT, WESDR, UKPDS, Wong et al [7]. In India, studies have shown an increased prevalence of Diabetic retinopathy as the duration of diabetes increased [8, 9].

There is strong evidence to suggest that long term glycemic control plays an important role in delaying the onset and slowing down the progression of Diabetic retinopathy according to various well conducted observational studies and randomised clinical trials [10]. In our study, most of the patients were in the 7-8 range suggesting poor glycemic control. 84 % (133 patients) of the sample had HbA1C values >7. At higher levels of HbA1C,majority had PDR suggesting that PDR is associated with high hyperglycemia.70 % patients had Severe NPDR and PDR above HbA1C value of 7. CSME was also seen mostly in patients with HbA1C in the 7–8 range. Higher chances of Diabetic retinopathy above HbA1C 7 was also reported in Indian studies like CURES and SN- DREAMS. [10] Ours being a cross-sectional observational study and knowing the fact that HbA1C detects average blood glucose in the last 3 months before the test, lower grades of retinopathy at higher HbA1C and higher grades at lower HbA1c are understood. Landmark Clinical trials like DCCT and UKPDS proved that intensive glycemic control significantly reduces the progression of DR [11]. UKPDS found that decreasing HbA1C from 7.9 to 7.0 % with intensive therapy was associated with a 25 % decrease in microvascular complications. The data from these trials provided further support for the ADA guidelines of a target goal of HbA1c level of 7.0 % for persons with diabetes, and suggest that this level of control, when achieved earlier after diagnosis of diabetes, may have greater long-term benefit in terms of reducing the incidence and progression of retinopathy. However, data from the NHANES III and the WESDR suggest that few persons with diabetes reach this targeted level of glycemic control [12].

Individually, CSME was mostly seen in eyes with Severe NPDR followed by Moderate NPDR suggesting no association between CSME and severity of Diabetic Retinopathy.

There was no statistically significant correlation of Diabetic Retinopathy severity with dyslipidemia (p>0.05 for all the lipids) in our study similar to results of Australian Diabetes, Obesity and Lifestyle Study (AusDiab) which reported that cholesterol was not associated with DR. Similarly, Rehab Benarous et al, [13] concluded that serum lipid levels were not related to DR or DME, but in multivariate models adjusting for traditional risk factors and lipid medications, persons with higher total, LDL, and non-HDL-Cholesterol were more likely to have CSME. In Diabetes Control and Complications Trial (DCCT) also, the relationship of lipids with progression of DR and development of PDR were not significant. Similarly, Klein et al in Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) also showed that serum total cholesterol was not a significant factor in the severity of retinopathy but was significantly associated with the presence (odds ratio (OR) 1.65) and severity of hard exudates in subjects with young -onset DM. In older-onset DM, however, serum cholesterol was not related to either DR severity or the severity of hard exudates. The WESDR did not, however, evaluate TG levels or differentiate between LDL and HDL levels. [14] In contrast to present study, studies like CURES in India by Rema et al on random urban south indian population of Chennai showed that mean serum cholesterol, serum triglycerides and non-high-density lipoprotein (HDL)-cholesterol were higher in subjects with DR compared with those without DR. According to Zhang et al also Among Chinese type 2 diabetic patients, hyperlipidemia, higher VLDLC, and higher triglyceride were independently associated with increased risk of DR, suggesting that control of serum lipids may decrease the risk of DR [15].

In the present study, there was statistically significant association between severity of hard exudates in retina, specifically macula (in patients with CSME) and dysipidemia (Higher mean values of Total cholesterol, triglycerides, LDL). Mean values of Total Cholesterol, Triglycerides, LDL, were significantly higher in plaque followed by circinate patterns of hard exudates compared to sparse, discrete patterns. The difference in the mean values of total cholesterol, were significantly lower in those with no or sparse exudates compared to circinate and plaque. The difference in the mean values of Triglycerides was significantly higher in Circinate and Plaque compared to those with no hard exudates. The difference in the mean values of LDL was significantly higher in circinate (p=0.012) and plaque (p=0.00) in comparison to sparse hard exudates. in landmark trials like early Treatment of Diabetic Retinopathy Study (ETDRS) where serum lipids were associated with the presence and severity of hard exudates. Elevated serum total

cholesterol (‡ 6.21 mmol/ l) was associated with a two-fold increased risk of retinal hard exudates in subjects with type 2 diabetes, and subjects with higher LDL levels were also more likely to have hard exudates (OR-1.79). Elevated total cholesterol, LDL and TG were also risk factors for the development of hard exudates over 5 years of follow-up. In other studies like the Hoorn Study, [16] plasma total and LDL cholesterol levels showed positive associations with retinal hard exudates. In the Atherosclerosis Risk In Communities (ARIC) study, the presence of retinal hard exudates was associated with higher plasma low-density lipoprotein cholesterol (or per 10 mg/dl 1.18) and plasma Lp(a) (OR per 10 mg/dl 1 .02). Zooming in to an Indian study by Sachdev et al, [17] results were like our study. On univariate analysis they found that retinal hard exudates were significantly associated with total cholesterol ($p<0.001$), LDL($p=0.008$) and TG($p=0.013$) however, on linear regression analysis, total cholesterol and LDL cholesterol were independent risk factors affecting density of hard exudates.

In our study CSME was significantly associated with Total cholesterol ($p=0.021$), Triglycerides ($p=0.011$) and LDL ($p=0.031$). The Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS) also evaluated the association between lipids and CSME.

High serum LDL (OR 2.72), high serum non-HDL cholesterol (OR 1.99) and high cholesterol ratio (OR 3.08) were associated with non-CSME DME, and high serum total cholesterol (OR 9.09) with CSME [18]. Benarous et al found that higher total, LDL, and non-HDL-C were more likely to have CSME [13].

Association between cataract surgery and diabetic retinopathy could not be determined as majority of the sample were phakic. According to literature, cataract surgery is known to worsen diabetic retinopathy. Association of CSME with BCVA could not be made out accurately due to presence of cataract.

Limitations of our study: Most of the diabetics in the present study had poor glycemic control. Hyperglycemia is also associated with dyslipidemia, increased levels of total cholesterol and triglycerides, slight elevation of LDL but trivial change in HDL. Age and sex, duration of diabetes, hyperglycemia, duration of hypertension, genetic factors may be important confounding factors in the study with respect to both diabetic retinopathy and hypercholesterolemia. Accurate relationship between lipids and diabetic retinopathy can be made out with logistic regression analysis.

Detection and documentation of macular edema was done by clinical examination using sit lamp biomicroscopy using 78D /90 D and not the sensitive method of assessing retinal thickening like OCT. Grading of retinal hard exudates was not done using standard photographs and Modified Airlie House Classification. It was done based on clinical examination and use of fundus photographs and noting down the pattern.

Prospects for further research. Further studies are required to establish the causal relationship between dyslipidemia and diabetic retinopathy. Lipid lowering therapy should be added to antidiabetic therapy to prevent vision threatening CSME and severe hard exudates in the macula.

5. Conclusion

This study demonstrated that, Diabetic retinopathy is not associated with lipid profile but there is statistically significant correlation between mean values of Total cholesterol, Triglycerides, LDL, VLDL and clinically significant macular edema (CSME). It also showed that high mean values of total cholesterol, triglycerides, LDL were found in patients with severe pattern of hard exudation (plaque, circinate pattern) vs no hard exudation, discrete pattern. The correlation between CSME and Visual acuity could not be determined accurately as most of the patients had some form of lenticular opacity. There was no significant association of Diabetic Retinopathy severity and CSME with duration of Diabetes Mellitus as CSME was noticed in 62.6 % of DR patients with duration of 5–10 years which signifies CSME is independent of duration of Diabetes. All the diabetic subjects aged less than 40 years showed Proliferative Diabetic Retinopathy demonstrating positive correlation between early onset of diabetes and severity of Diabetic Retinopathy. There was also no significant association between HbA1C and CSME. Though there was slightly higher prevalence of PDR among hypertensives compared to non-hypertensives, there was no significant association between DR stage and Hypertension.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Pasumarthi Pavani Yelamanchili*, Assistant Professor, Department of Ophthalmology, Maheshwara Medical College and Hospital, Near, Chitkul, X Roads, Isnapur, Patancheruvu, Telangana, India, 502307

Madhuri Kurakula, Assistant Professor, Department of Ophthalmology, Malla reddy Medical College for Women, Jeedimetla, Suraram, X Road, Quthbullapur, Hyderabad, Telangana, India, 500055

Puwala Sai Kiranmayi, Retina Senior consultant, Department of Ophthalmology, Pushpagiri Vitreo Retina Institute, Plot No 241, Uma Plaza, 9, Marredpally Rd, Secunderabad, Telangana, India, 500026

Kalluru Viswanath, Uvea Senior Consultant, Department of Ophthalmology, Pushpagiri Vitreo Retina Institute, Plot No 241, Uma Plaza, 9, Marredpally Rd, Secunderabad, Telangana, India, 500026

****Corresponding author:** Pasumarthi Pavani Yelamanchili, e-mail: pasumarthipavaniyelamanchili@gmail.com*