Original Research Article

Correlation of serum lipid profile and diabetic retinopathy: a prospective study

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ABSTRACT

Background: To correlate serum lipid levels and presence of Diabetic Macular edema in diabetic retinopathy patients. To compare the serum lipid profile of patients with and without Diabetic Macular edema. To compare and analyze the present study with reference to other studies on serum lipid profile in diabetic retinopathy. To emphasize the importance of doing serum lipid profile as routine investigation in patients with diabetic retinopathy and to initiate treatment for those appropriate.
Methods: A prospective cross-sectional study conducted at Tertiary Eye Care Centre, Salem, TamilNadu with petients presenting to Retina clinic for 6 months with a sample size of 186.
Results: The data analysis was performed using statistical software package SPSS version 22.0. Both the descriptive and inferential statistics were used. The continuous variables were summarized as mean with standard deviation. The categorical variables were summarized as frequencies and proportions.
The comparison of continuous variables was done using unpaired 't' test and comparison of categorical variables were done using Chi square test or Fisher's exact test depending on distribution. P value of less than 0.05 was considered significant.
Conclusions: The present study gives good evidence of a significant correlation between higher levels of total cholesterol, LDL-C, HbA1C and lower levels of HDL-C with the presence of Diabetic Macular edema. Hence along with diabetes control drugs, lipid lowering drugs should be started for diabetic patients having dyslipidemia.

Keywords: Hyperlipidemia, Diabetes, Diabetic macular edema

INTRODUCTION

Diabetes mellitus (DM) is a global epidemic. The World Health Organization (WHO) estimates revealed that the global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014.[1] The ninth edition of Diabetes Atlas by International Diabetes Federation released in 2019 estimates that there are 463 million persons with diabetes in the world and this figure will go up to 700 million by the year 2045.[2]

Risk factors

Race/ethinicity

In four population-based studies,retinopathy was more prevalent in blacks than in whites (nearly all with type 2 diabetes).

In addition, there were no statistically significant interactions of race with diabetes severity.

Genetic factor

Data from studies that examined familial clustering suggest that genetic factors may be involved more strongly in susceptibility to diabetic retinopathy than previously thought.[38,39]

Sex

There were no significant differences in the prevalence or 10-year incidence of retinopathy or rates of progression to proliferative retinopathy between the sexes.

Duration of diabetics

The most consistent relationships of risk factors for complications of diabetes are found between duration of diabetes and the prevalence and severity of diabetic retinopathy and macular edema.

Exogenous Insulin

In the WESDR41, there was no association between amount or type of exogenous insulin used and the presence, severity, incidence or progression of retinopathy in the older-onset group using insulin whose C-peptide was 0.3 nM or greater.

Blood Pressure

A 10 mmHg rise in diastolic blood pressure was found to be associated with a 210% increased risk in those with type 2 diabetes.

Smoking

In the WESDR41, cigarette smoking was not associated with the 4- or 10-year incidence or progression of diabetic retinopathy nor macular edema.

Alcohol

Moderate alcohol consumption is associated with decreased platelet aggregation and adhesiveness, improved glycemic control and reduction of inflammation.

One might anticipate a possible protective effect in reducing the incidence and progression of retinopathy.

Physical activity

Decreased sedentary times and the inclusion of more physical activity have been linked to the delayed onset and progression of diabetic retinopathy and less severe forms of said condition.

Physical activity provides both protective and anti-inflammatory effects on the retina.

Hormone and reproductive exposures in women

Pregnant women were compared with nonpregnant diabetic women of similar age and duration of diabetes, the pregnant women were more likely to develop retinopathy.

Comorbidity and mortality

Risk of developing a heart attack, stroke, diabetic nephropathy and amputation was higher in those with proliferative diabetic retinopathy compared to those with no or minimal no proliferative retinopathy at baseline.

According to WHO, there were nearly 102.26 million cases of diabetes in India in 2016 with a prevalence of 7.8% (7.9% in males and 7.5% in females).[6] Nationwide study funded by the National program for control of blindness and visual impairment, India shows that the prevalence of DR in population aged 50 years and above was 16.9%.

Higher prevalence of DR among the urban population than in the rural population (20.7% vs. 15.5%). The prevalence of sight threatening DR was 3.6%.[7]

Prevalence of diabetic retinopathy in relation to duration of diabetes mellitus, <6 months,6months-5 years and >5 years was 9.23%,15.12% and 35.12% respectively.[8]

Sight-threatening diabetic retinopathy (STDR) comprises severe NPDR, PDR (including advanced diabetic disease), or diabetic macular edema.[9]

Prevalence of any DME among patients with diabetics to be 8.9% and that of referable DME as 2.4%. Recent estimates suggest that there are 77 million patients with DM in India. Considering conservative estimate of 2% patients with DM having DME, likely magnitude of treatable DME is 15,40,000 persons.[10]

Prevalence of DME in the total diabetic population was 5.0%, whereas among the known diabetic subjects it was 6.3% and among the newly detected diabetic subjects, 1.1%. The prevalence of diabetic macular edema was 2.4%.[11]

To correlate lipid profile in development of diabetic macular edema in DR patients. To assess vision loss in patients with DR and deranged lipid profile and their impact of final visual acuity.

METHODS

Study design

6 months of prospective cross-sectional study.

Study type

A prospective cross-sectional study.

Study place

The study was conducted at Tertiary Care Centre, Salem, Tamil Nadu.

Selection of study subjects

Patients presenting to retina clinic, AEH Salem with diabetic retinopathy fulfilling the inclusion criteria were studied.

Sample size

186 patients divided in to two groups of 93 each. Group A: Patients with diabetic retinopathy with Diabetic macular oedema. Group B: Patients with diabetic retinopathy without Diabetic macular oedema.

Sample size = (Z-score)2 * (StdDev)/ (d)2
Taking SD for LDL as 26.4 according to previous studies
=2.58*.(26.4)2/52
=6.65*696.96)/52 =46.39.244/25
=185.56
186

Inclusion criteria

Patients aged more than 40 years having type 2 diabetes mellitus with retinopathy, in euglycemic status during the time of study, attending Ophthalmology outpatient department and are willing to participate in the study and have given consent to undergo blood tests for serum lipid levels and renal parameters, were included in the study.

Exclusion criteria

Patients with type 1 diabetes mellitus. Patients with any pre-existing retinal manifestations of systemic diseases, other than DR. Patients who have had treatment for diabetic retinopathy. Patients on treatment for dyslipidaemias.

Patients with macular dystrophies and degenerations. Patients with ocular anomalies. Patients with ocular trauma. Patients, with history of retinal surgeries. All grades of diabetic retinopathy except Advanced diabetic eye disease and High-risk PDR.

Data collection procedure

All patients with Type 2 DM were subjected to complete ocular examination by assessing visual acuity with Snellen's chart, slit lamp examination, intraocular pressure with rebound tonometry. Fundus examination done with slit lamp biomicroscopy using +90 D lens. After fundus examination, patients having diabetic retinopathy with and without diabetic macular edema were grouped into 2 and were recruited for further study. OCT (Optical Coherence Tomography-SPECTRALIS) was done in some patients to quantify and find out the type of macular edema. FFA (Fundus Fluorescein Angiography) was done in few patients to plan the treatment. In all these study subjects, aseptically collected venous blood was used for estimating fasting lipid profile, fasting blood glucose and post prandial blood glucose. Further, lipid profile values were correlated with the occurrence/incidence of diabetic macular edema in these patients.

RESULTS

The results suggested that in diabetic retinopathy age was not significantly associated with macular edema but males predominated in the group associated with Macular edema (Table 1) Males predominated in the group (Table 2) with duration of 6-10 years of DM, Males predominated with higher prevalence in non-insulin usage group (Table 3) with equal prevalence of DR in right and left eye (Table 4). Patients with high total cholesterol and (Table 5) triglyceride levels in our study were observed to be higher in patients in both the groups, and lower levels of HDL-C was found to be associated with the development of Macular edema with higher levels of mean LDL-C were found in the group with diabetic macular edema (Table 6).
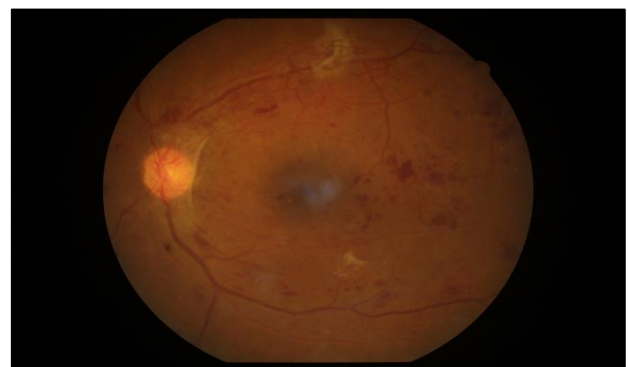
Figure 1: Proliferative diabetic retinopathy without CSME.

Figure 2: Moderate NPDR with CSME with diffuse leakage.

Table 1: Distribution of cases according to age and sex.

		Age level (in years)				Total	Sex		Total	X^2	P value
		40-50	51-60	61-70	71-80		Male	Female			
Group	Group A-Count	11	34	42	6	93	48	33	81	2.75	0.253
	%	11.8	36.6	45.2	6.5	100.0	59.3	40.7	100		
	Group B-Count	15	42	30	6	93	47	46	93		
	%	16.1	45.2	32.3	6.5	100.0	51	49	100		
Total	Count	26	76	72	12	186	94	80	174		
	%	14	40.9	38.7	6.5	100	54.6	45.4	100		

Table 2: Distribution of cases according to duration of DM.

		Duration of DM (in years)					Total	X^2	P value
		Newly detected	1-2	2-5	6-10	11-15			
Group	Group A-Count	10	22	31	26	4	93	48.242	0.000
	%	10.8	23.7	33.3	28	4.3	100		
	Group B-Count	12	15	65	1	0	93		
	%	12.9	16.1	69.9	1.1	0	100		
Total	Count	22	37	96	27	4	186		
	%	11.8	19.9	51.6	14.5	2.2	100		

Table 3: Distribution of cases according to Insulin usage.

		Insulin usage		Total	X^2	P value
		Yes	No			
Group	Group A-Count	5	88	93	52.55	0.000
	%	5.4	94.6	100		
	Group B-Count	47	46	93		
	%	50.5	49.5	100		
Total	Count	52	134	186		
	%	28	72	100		

Table 4: Severity of diabetic retinopathy in both eyes.

		DR stage								Total	X^2		P value	
		Mild NPDR		Moderate NPDR		Severe NPDR		PDR			RE	LE	RE	LE
		RE	LE	RE	LE	RE	LE	RE	LE					
Group	Group A-Count	5	8	46	38	38	43	4	4	93	21.74	18.58	0.000	0.001
	%	5.4	8.6	49.5	40.9	40.9	46.2	4.3	4.3	100				
	Group B-Count	24	23	31	42	27	20	11	7	93				
	%	25.8	24.7	33.3	45.2	29	21.5	11.8	7.5	100				
Total	Count	29	31	77	80	65	63	15	11	186				
	%	15.6	16.7	41.4	43	34.9	33.9	8.1	5.9	100				

Table 5: Total cholesterol, triglycerides and diabetic macular edema.

		Level of TC			Level of TG		Total	X^2		P value	
		<200	>200	Total	<150	>150		TC	TG	TC	TG
Group	Group A-Count	43	50	93	32	61	93	3.662	0.024	0.056	0.878
	%	46.2	53.8	100	34.4	65.6	100				
	Group B-Count	56	37	93	33	60	93				
	%	60.2	39.8	100	35.5	64.5	100				
Total	Count	99	87	186	65	121	186				
	%	53.2	46.8	100	34.9	65.1	100				

Table 6: HDL and diabetic macular edema.

Group		Level of HDL <40	Level of HDL >40	Total	Level of LDL <130	Level of LDL >130	Total	X^2 HDL	X^2 LDL	P value HDL	P value LDL
Group	Group A-Count	52	41	93	51	42	93	35.52	14.473	0.000	0.000
	%	55.9	44.1	100	54.8	45.2	100				
	Group B-Count	14	79	93	75	18	93				
	%	15.1	84.9	100	80.6	19.4	100				
Total	Count	66	120	186	126	60	186				
	%	35.5	64.5	100	67.7	32.3	100				
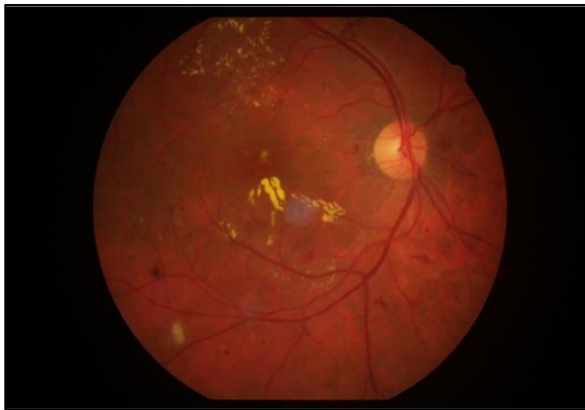
Figure 3: Moderate NPDR with Macular edema.
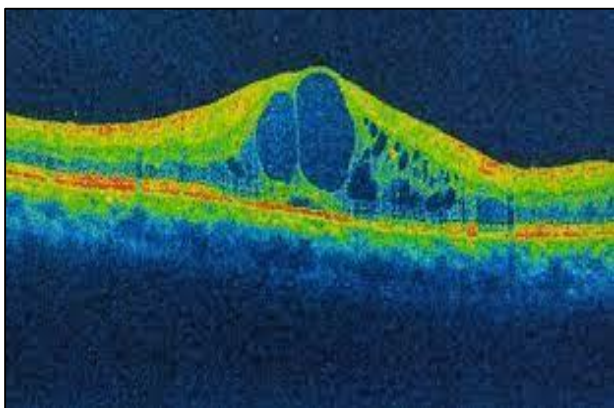
Figure 4: Diabetic macular edema.

DISCUSSION

Diabetes mellitus is an important health problem affecting the whole world. Its impact is on the increase for the past many years. Diabetic macular edema forms the leading cause of blindness among the patients with diabetic retinopathy. There have been many studies correlating the severity of diabetic retinopathy and the various risk factors, including level of serum lipids. Studies also have been reported regarding the efficiency of hypolipidemic drugs in decreasing the severity of retinopathy, maculopathy and vision loss. This study was done in our setting to observe how much the lipid level varies in those with Diabetic Macular Edema and those without in our region and to stress the importance of lipid lowering as a part of diabetic retinopathy management.

Most of the results obtained in this study correlated with the available literature, both in the global scenario and the Indian set up. Acan et al, stated duration of diabetes was significantly longer in those patients with DME, particularly in those diagnosed between 10 and 20 years. In our study we found that among the patients with duration of DM 6-10 years were 27 patients, 26 of them has diabetic macular edema and only 1 patient did not have diabetic macular edema. And 4 patients with duration 11-14 years of DM, all of them had diabetic macular edema and it was statistically significant.

Ferris et al, stated that a high percentage of visual loss can be prevented through laser, pharmacological or surgical treatment places great importance on the proper detection and classification of patients with DR especially those with severe NPDR who are at great risk for developing visual loss due to macular oedema. In our study we found that most of the patients with diabetic macular edema which causes visual impairment belong to moderate NPDR stage (49.5%) in right eye and sever NPDR stage (46.2%) in left eye signifies the importance of staging of diabetic retinopathy to initiate appropriate treatment protocol at that stage.

Sagolsem et al, stated that, severity of diabetic retinopathy was strongly associated with duration of type 2 DM. In our study we found that 80% eyes had moderate NPDR stage, because 51.6% patients had duration of DM 2-5 years and 13 % eyes only had PDR because only 4 % patients had duration of DM >10 years.

Based on Zander et al, stated that, diabetic patients with long standing diabetes have a high risk for the development of diabetic maculopathy. In our study we found that, among 6-10 years duration group, 26% had NPDR with diabetic macular edema and only 1% had NPDR without diabetic macular edema signifying that as duration of DM increases the incidence of diabetic macular edema which was clinically significant (p=0.0000).

By Aurthur et al, stated that, diabetic males had thicker retinas than females, exacerbated by Diabetic Macular edema. Even in our study we found that, males had more

incidence of diabetic macular edema than females but it was not statistically significant (p=0.253).

As per Varma et al, there were no clear differences in DME prevalence by age group. In this study, most of the patients with diabetic retinopathy who seek treatment were in 4th-6th decade with almost equal distributions of Diabetic Macular Edema and without Diabetic Macular Edema group but results were not statistically significant (p=0.325).

The Wisconsin epidemiologic study of diabetic retinopathy. XVI 41 stated that, there was no relationship between higher levels of C-peptide at baseline and lower 6-year incidence or progression of retinopathy. Data suggest that glycaemic control and not C-peptide, is related to the incidence and progression of diabetic retinopathy, whereas in our study we found that, those on insulin and having diabetic macular edema was found to be 5 in number(5.4%),while those on insulin and did not develop diabetic macular edema made 57 in number accounting for 50.5% with p value 0.00, signifying its protective effect, which probably attributes to the good glycemic control in patients on insulin.

Das R et al, stated that, evidence from the cohort studies and meta-analysis of the case-control studies suggesting a strong relationship between lipid levels and DME, this was not confirmed by the meta-analysis that included only prospective RCTs. In our study we found out that, not all lipid profile but higher level of total cholesterol, LDL-C and lower level of HDL-C had strong relationship with Diabetic Macular Edema with p value<0.05.

Chung et al, stated that, the levels of HbA1c, triglycerides, total cholesterol and HDL cholesterol correlated with central retinal thickness. Specifically, the levels of triglycerides at 6 months prior to diabetic macular edema, HbA1c at the onset and 3 months prior to diabetic macular edema and total cholesterol at the onset and 1 month prior to diabetic macular correlated positively with central retinal thickness; the HDL cholesterol level at 3 months prior to Diabetic Macular edema had a negative correlation with central retinal thickness.

Although we did not measure the central retinal thickness to correlate with lipid profile of the patient, it was observed in our study that those with diabetic macular edema had significantly increased levels of total cholesterol with an average value of 216.12 mg/dl. Those without macular edema were found to have high values of total cholesterol but were less than that of those with diabetic macular edema with a mean value of 197.80 mg/dl. The difference between the two groups was statistically significant (p=0.056).

But triglyceride levels in our study were observed to be higher in patients in both the groups with mean values of 187.7 mg/dl and 163.8 mg/dl but was not statistically significant (p=0.878). This is similar to the study observed with UKPDS, where triglyceride levels and low-density lipoprotein cholesterol levels did not appear to be related to the severity of retinopathy.

Only 32.2 % patients had higher level of LDL-C, among those 42 patients had NPDR with diabetic macular edema and 18 patients had NPDR without diabetic macular edema. Higher levels of mean LDL-C (135.6 mg/dl) were found in the group with diabetic macular edema when compared with the non-diabetic macular edema group (108.7 mg/dl) and was found to be statistically significant (p=0.0000).

Similar findings were observed in the CHS study which states that the prevalence of diabetic retinopathy after controlling for age, sex and blood glucose, retinopathy was more in those with higher plasma low density lipoprotein (LDL) cholesterol. In the Indian scenario also, the CURES study done in South of India and a study by Sachdevn et al, from North India also showed similar results. In another study done in the South Indian population, SN-DREAMS, no correlation was observed between the levels of LDL-C and diabetic macular edema.

From our study clinical significance was for total cholesterol and LDL-C level for development of diabetic macular edema but total cholesterol was elevated in both the group, so LDL-C is a major risk factor among lipid profile for development of diabetic macular edema.

According to Ozer et al, no correlation was found between serum lipid levels and macular edema severity, but the duration of diabetes was demonstrated as a significant factor in the progression of macular edema. In our study lower levels of HDL-C was found to be associated with the development of macular edema and was statistically significant (p=0.0000) which is in contrast to above study.

The study has a minimal sample size of 186 with short term (6 months). Other parameters like Nephropathy, Neuropathy needs to be assessed for patients with deranged lipid profile to prevent morbidity and mortality.

CONCLUSION

The present study gives good evidence of a significant correlation between higher levels of total cholesterol, LDL-C, HbA1C and lower levels of HDL-C with the presence of Diabetic Macular edema. Hence, along with diabetes control drugs, lipid lowering drugs should be started for diabetic patients having dyslipidemia.

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