An Observational Study on the Association between Diabetic Retinopathy and Serum Lipid Levels in a Tertiary Centre in Thiruvananthapuram

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ABSTRACT

BACKGROUND

Dyslipidaemia has been proposed as a possible risk factor for diabetic retinopathy (DR) but results from previous studies are inconsistent. We designed this study to find the association of abnormal serum lipid levels with diabetic retinopathy and diabetic macular oedema (DME).

METHODS

This was a single centre observational study conducted at a tertiary care hospital, where patients with type 2 diabetes of more than five years duration were enrolled. A comprehensive ophthalmic evaluation was performed on all study subjects. Detailed fundoscopy was done after obtaining the best possible mydriasis with 1 % tropicamide and 5 % phenylephrine eye drops using direct ophthalmoscopy, indirect ophthalmoscopy with + 20 D lens and stereoscopic slit lamp biomicroscopy of the disc and macula using + 78 D Volk lens. Fundus photographs were taken in patients with any grade of diabetic retinopathy by Topcon fundus camera. DR and DME were diagnosed and classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system. Fasting blood sugar (FBS), fasting lipid profile and glycated haemoglobin (HbA1c) was assessed for each patient.

RESULTS

A total of two hundred and twelve participants was enrolled. Mean age of the study group was 63.93 ± 9.52 and the mean duration of diabetes was 13.54 ± 6.07. DR was present in 164 (78.1 %) of whom 71 (43.3 %) had mild non proliferative diabetic retinopathy (NPDR), 42 (25.6 %) had moderate NPDR, 31 (18.9 %) had severe NPDR, and 20 (12.2 %) had proliferative diabetic retinopathy (PDR). Of those with DR, 59 (36 %) had DME. Duration of diabetes (14.62 ± 6.18 vs 9.72 ± 3.68 years, P < 0.001), higher fasting blood glucose (176.79 ± 59.13 vs 138.46 ± 49.44 mg / dL, P < 0.001), higher HbA1c (8.21 ± 1.38 vs. 7.48 ± 1.25 %, P = 0.002), higher total cholesterol (215.04 ± 49.78 vs 184.37 ± 30.84 mg / dL, P < 0.001), higher triglyceride levels (155.23 ± 59.06 vs 125.13 ± 37.3 mg / dL, P = 0.001) and higher low density lipoprotein (LDL) cholesterol levels (139.28 ± 37.38 vs 120.85 ± 22.75 mg / dL, P = 0.002) were significantly associated with the severity of DR. Higher total cholesterol, higher triglyceride levels and higher LDL cholesterol levels were also associated with DME.

CONCLUSIONS

There is a significant association of abnormal serum lipid levels and hyperglycaemia with the presence and severity of DR and presence of DME. Early identification and intervention to control these modifiable risk factors, hyperglycaemia and dyslipidaemia may delay the development and progression of DR in diabetic patients. These observations also support the current management strategies for diabetes, which include control of dyslipidaemia in addition to hyperglycaemia.

KEYWORDS

Diabetic Retinopathy, Diabetic Macular Oedema, Dyslipidaemia

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BACKGROUND

Diabetic retinopathy is one of the leading causes of visual disability and blindness worldwide.[1] More than 360 million people worldwide are estimated to be affected by diabetes mellitus by the year 2030 and approximately 34.6 % of these individuals will develop diabetic retinopathy and 10.2 % will develop vision-threatening DR.[2] Therefore, it is important to investigate and control the risk factors associated with diabetic retinopathy. Various population based epidemiological studies have identified hyperglycaemia, duration of diabetes, hypertension, high body-mass index, smoking, nephropathy, genetic susceptibility and ethnicity as risk factors for development and progression of DR.[3] Dyslipidaemia has also been proposed as a possible risk factor for DR.[4]

High lipid levels can cause endothelial dysfunction due to a reduced bioavailability of nitric oxide (NO). This endothelial dysfunction results in the breakdown of blood retinal barrier leading to exudation of serum lipids and lipoproteins into the retinal intercellular space resulting in formation of retinal exudates. High lipid levels also cause endothelial dysfunction through a local inflammatory response with subsequent release of cytokines, hypoxia and increase in LDL oxidation.[5] Results from various studies investigating the association between serum lipid levels and severity of DR have been inconsistent and still remains controversial. The objective of this study was to evaluate the association of various components of serum lipids including total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C) with the presence and severity of diabetic retinopathy and diabetic macular edema status in type-2 diabetic patients.

METHODS

This was a single centre cross sectional observational study conducted in the Department of Ophthalmology, SUT Medical College Hospital, a tertiary care teaching hospital in South India from October 2019 to March 2020. The study was approved by the hospital ethics committee and was conducted in accordance with declaration of Helsinki. A total number of 212 patients with type 2 diabetes mellitus of more than 5 years duration were enrolled in the study. Patients with type 1 diabetes mellitus, opaque or hazy media which may interfere with fundus examination, other retinal disorders such as retinal vein or artery occlusions, previous laser therapy or intravitreal injection and patients on lipid lowering medications were excluded from the study. All consecutive patients coming to the ophthalmology clinic of the hospital for diabetic retinopathy screening who provided consent for the study were enrolled.

Information including age, sex, duration of diabetes, height, body weight, smoking status, blood pressure, any associated illness and concomitant medication were recorded in a standard questionnaire. A comprehensive ophthalmic evaluation was performed on all study subjects which included best corrected visual acuity (BCVA), slit lamp examination of anterior segment and intraocular pressure (IOP) measurement. Detailed fundoscopy was done after obtaining the best possible mydriasis with 1 % tropicamide and 5 % phenylephrine eye drops using direct ophthalmoscopy, indirect ophthalmoscopy with + 20 D lens and stereoscopic slit lamp biomicroscopy of the disc and macula using + 78 D Volk lens. Fundus photographs were taken in patients with any grade of diabetic retinopathy by Topcon fundus camera. DR and DME was diagnosed and classified according to the Early Treatment Diabetic Retinopathy Study grading system.[6] DR severity was categorised as mild NPDR, moderate NPDR, severe NPDR and PDR based on the severity in the worse eye. DME was defined as retinal thickening at or within one-disc diameter of the centre of the macula or the presence of definite hard exudates and was categorised as absent or present. Fasting blood sugar, glycated haemoglobin, fasting total cholesterol, low density lipoprotein, triglyceride and high-density lipoprotein was assessed for each patient and the values were compared between the groups. Classification of lipid abnormalities was done according to the Adult Treatment Panel III (ATP III) Guidelines.[7]

Statistical Methods

Continuous data is expressed as mean ± SD along with median with interquartile range. Kolmogorov–Smirnov test was used to test normality of the sample size. Categorical variables are expressed as number and proportion. Means of two groups of continuous variables with normal distribution was compared by independent sample t test and those with non-normal distribution by Mann-Whitney U test. Means of different categories of DR with normal distribution were compared using analysis of variance (ANOVA) and those with non-normal distribution by Kruskal Wallis test. Comparison of categorical variables was done using chi Square test. All analysis was performed using SPSS version 20.0.

RESULTS

The demographic and clinical characteristics of the 212 patients enrolled in the study are detailed in Table 1. The mean age of the study group was 63.93 ± 9.52 (ranging from 42 to 91 years). The study group included 108 (51.4 %) males and 102 (48.6) females. The duration since diagnosis of diabetes ranged from 5 to 29 years (mean 13.54 ± 6.07). Among the 212 participants, DR was present in 164 (78.1 %) individuals compared to 46 (21.9 %) who had no signs of DR. In those with DR, 71 (43.3 %) had mild NPDR, 42 (25.6 %) had moderate NPDR, 31 (18.9 %) had severe NPDR, and 20 (12.2 %) had PDR. Of those with DR, 59 (36 %) had diabetic macular oedema.

Table 2 shows the clinical and biochemical characteristics of the study groups with and without retinopathy. Participants with DR had a significantly longer mean duration of diabetes as compared to those without retinopathy (14.62 ± 6.18 vs 9.72 ± 3.68 years, $P < 0.001$). Higher fasting blood glucose (176.79 ± 59.13 vs 138.46 ± 49.44 mg / dL, $P < 0.001$), higher HbA1c (8.21 ± 1.38 vs 7.48 ± 1.25 %, P

= 0.002), higher total cholesterol (215.04 ± 49.78 vs 184.37 ± 30.84 mg / dL, P < 0.001), higher triglyceride levels (155.23 ± 59.06 vs 125.13 ± 37.3 mg / dL, P = 0.001), lower HDL levels (43.52 ± 10.04 vs. 45.59 ± 7.43, P = 0.033) and higher LDL cholesterol levels (139.28 ± 37.38 vs 120.85 ± 22.75 mg / dL, P = 0.002) were significantly associated with DR.

Age-Years	Mean Median	63.93 ± 9.52 64 (57 - 71)
Gender-no (%)	Male Female	108 (51.4) 102 (48.6)
Duration of diabetes mellitus-years	Mean Median	13.54 ± 6.07 13.5 (8 - 17)
FBS-mg / dL	Mean Median	168.4 ± 59.21 156 (128 - 206)
HbA1c - %	Mean Median	8.05 ± 1.38 7.8 (7.1 - 8.9)
Retinopathy-no (%)	Present Absent	164 (78.1) 46 (21.9)
Stage of retinopathy-no (%) N = 164	Mild NPDR Moderate NPDR Severe NPDR PDR	71 (43.3) 42 (25.6) 31 (18.9) 20 (12.2)
DME-no (%) N = 164	Present Absent	59 (36) 105 (64)
Total cholesterol-mg / dL	Mean Median	208.32 ± 47.95 204 (172.5 - 239)
Triglycerides-mg / dL	Mean Median	148.64 ± 56.36 142.5 (102 - 182.5)
HDL-mg / dL	Mean Median	43.97 ± 9.55 44 (38 - 49)
LDL-mg / dL	Mean Median	135.24 ± 35.49 128.5 (107.75 - 156.5)

Table 1. Characteristics of Study Population

Factors	Retinopathy Present (N = 164)	Retinopathy Absent (N = 46)	Test Value	P Value
Gender - No (%)				
Male Female	86 (79.6) 78 (76.5)	22 (20.4) 24 (23.5)	0.30@	0.580
Age - Years				
Mean	64.2 ± 9.13	62.96 ± 10.85	0.78#	0.435
Duration of Diabetes Mellitus - Years				
Mean	14.62 ± 6.18	9.72 ± 3.68	- 5.07$	< 0.001*
FBS - mg / dL				
Mean	176.79 ± 59.13	138.46 ± 49.44	- 4.45$	< 0.001*
HbA1c - %				
Mean	8.21 ± 1.38	7.48 ± 1.25	- 3.59$	< 0.001*
Total Cholesterol - mg / dL				
Mean	215.04 ± 49.78	184.37 ± 30.84	- 3.72$	< 0.001*
Triglycerides - mg / dL				
Mean	155.23 ± 59.06	125.13 ± 37.3	- 3.24$	0.001*
HDL Cholesterol - mg / dL				
Mean	43.52 ± 10.04	45.59 ± 7.43	- 2.12$	0.033*
LDL Cholesterol - mg / dL				
Mean	139.28 ± 37.38	120.85 ± 22.75	- 3.01$	0.003*

Table 2. Factors Associated with Retinopathy

*p value less than 0.05 was considered as significant
@Chi square test
independent sample t test
$ Mann Whitney U test

Factors	Retinopathy Mild NPDR (N=71)	Moderate NPDR (N=42)	Severe NPDR (N=31)	PDR (N=20)	Test Value	P Value
FBS - mg / dL						
Mean	149.08 ± 48.01	190.67 ± 56.97	203.35 ± 59.85	204.85 ± 59.73	30.13£	< 0.001*
HbA1c - %						
Mean	7.60 ± 1.17	8.45 ± 1.32	8.83 ± 1.45	8.87 ± 1.28	31.45£	< 0.001*

Table 3. Association between Glycaemic Control and Severity of Retinopathy

*p value less than 0.05 was considered as significant £ Kruskal Wallis test

A statistically significant association of severity of DR with fasting blood glucose, HbA1c, total cholesterol, triglyceride and LDL cholesterol levels was documented (Table 3 and 4).

Factors	Retinopathy Mild NPDR (N=71)	Moderate NPDR (N=42)	Severe NPDR (N=31)	PDR (N=20)	Test value	P Value
Total Cholesterol – No. (%)						
Mean	193.13 ± 43.52	210.71 ± 42.41	253.81 ± 42.53	241.8 ± 50.02	16.57b	< 0.001*
Triglycerides – No. (%)						
Mean	127.20 ± 41.61	149.43 ± 41.78	206.74 ± 76.05	187.1 ± 47.34	43.32£	< 0.001*
HDL Cholesterol – No. (%)						
Mean	46.06 ± 8.64	43.4 ± 11.71	40.1 ± 9.18	40.05 ± 10.26	14.11£	0.003*
LDL Cholesterol – No. (%)						
Mean	122.41 ± 32.18	136.43 ± 32.55	164.52 ± 30.12	166.05 ± 39.72	45.12£	< 0.001*

Table 4. Association between Serum Lipids and Severity of Retinopathy

*p value less than 0.05 was considered as significant
b ANOVA
£ Kruskal Wallis test

Table 5 shows the correlation of serum lipid levels with DME status. Serum total cholesterol, triglycerides and LDL cholesterol levels were significantly higher in participants with DME compared to those without.

Factors	DME Present (N = 59)	DME Absent (N = 105)	Test Value	P Value
Total Cholesterol – No. (%)				
Mean	231.27 ± 52.47	205.91 ± 45.99	- 3.11$	0.002*
Triglycerides – No. (%)				
Mean	176.03 ± 67.36	143.54 ± 50.54	- 3.23$	0.001*
HDL Cholesterol – No. (%)				
Mean	44.12 ± 11.81	43.18 ± 8.94	- .009$	0.993
LDL Cholesterol – No. (%)				
Mean	152.03 ± 40.67	132.11 ± 33.51	- 3.26$	0.001*

Table 5. Association of Serum Lipid Levels with DME Status

*p value less than 0.05 was considered as significant
$ Mann Whitney U test

Total cholesterol, triglycerides and LDL cholesterol levels had significant positive correlation with FBS and HbA1c, while HDL had significant negative correlation with FBS in patients with DR

Retinopathy		TC	TG	HDL	LDL
Yes	FBS	.432*	.426*	- .219*	.384*
	HbA1c	.398*	.337*	-.121	.333*
No	FBS	.181	.052	- .397*	.282
	HbA1c	.378*	.175	- .363*	.181

Table 6. Correlation between FBS, HbA1c and Lipid Profile in Patients with and without Retinopathy

DISCUSSION

We have demonstrated a statistically significant association of abnormal lipid parameters with presence and severity of DR and DME. Though the association of serum lipids with DR was first reported by Keiding et al in 1952,[8] results from various studies investigating the association between serum

lipid levels and severity of DR have been inconsistent. The association of serum lipid profile with severity of DR in this study is comparable with data from Chennai Urban Rural Epidemiology Study (CURES) which demonstrated that mean cholesterol, triglyceride, and non-HDL levels were higher in patients with DR compared to those without DR.[9] The results are also consistent with Early Treatment Diabetic Retinopathy Study, which reported an association between high total cholesterol and LDL levels with the onset and severity of retinal hard exudates.[10] Early Treatment Diabetic Retinopathy Study suggest that lipid lowering may also decrease the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy. Diabetes Control and Complications Trial (DCCT) reported that severity of retinopathy is positively associated with serum triglycerides (TG) and negatively associated with HDL-C in type 1 diabetes.[11] However, Singapore Malay Eye Study reported that higher TC levels have a protective effect on DR.[12] There are also contradictory studies like the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) which did not find significant association of serum lipid levels with the severity of DR.[13] Multi-Ethnic Study of Atherosclerosis (MESA) also showed no association of serum lipid levels with DR.[14] The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab) also found no difference in the prevalence of DR among patients with varying lipid levels.[15] Main reasons for these inconsistent reports could be the variability of the lipid levels in relation to short term changes in diet and life style. Differences in the methodologies used to diagnose DR and the grading protocols, differences in socioeconomic factors, racial differences in the effect of DR risk factors and genetic susceptibility may possibly explain some of these disparities.

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study reported that treatment with fenofibrate, a lipid-lowering drug, resulted in a significant reduction in the progression of DR and in the rate of laser treatment for diabetic macular oedema and proliferative diabetic retinopathy.[16] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study also reported the benefits of fenofibrate in slowing the progression of DR.[17] In our study, we also found a statistically significant positive association of the presence and severity of DR with the mean blood glucose level and HbA1c. Studies have consistently established poor glycaemic control as a risk factor for development and progression of DR and that intensive glycaemic control can substantially delay the onset and progression of DR.[18] The UK Prospective Diabetes Study (UKPDS)[19] and Diabetes Control and Complications Trial (DCCT) have demonstrated that patients with intensive glycaemic control in the initial years developed less microvascular complications on long-term follow-up. This data supports the need for preventive strategies to prevent or limit the onset and progression of DR, which include regular screening for DR risk factors and pharmacological intervention to optimise glycaemic control and dyslipidaemia.

We also observed that participants with DR had a significantly longer mean duration of diabetes as compared to those diabetics without retinopathy. The correlation between duration of DM and DR was first reported by WESDR (13)) Another interesting observation in our study was, more than three fourth of diabetic patients with duration of diabetes more than five years had evidence of diabetic retinopathy on screening. It was observed that Indians with type 2 diabetes mellitus develop microvascular complications much faster, when compared to the Western population.[20] One reason that can be postulated for this rapid progression is delayed diagnosis of diabetes as screening programmes are not popular in India. The lack of strict glycaemic control due to factors like irregular treatment and alternative systems of medicine, a lack of incorporation of HbA1c testing in the routine diabetic care and late initiation of insulin therapy are factors responsible for faster progression to microvascular complications.[21]

CONCLUSIONS

This study confirms the association of three risk factors with the presence and severity of DR and presence of DME- duration of diabetes, hyperglycaemia and dyslipidaemia. This data supports the need for effective screening and timely intervention to control DR risk factors as it may prevent or limit the development and progression of DR in these patients. These observations also support the current management strategies for diabetes, which include control of dyslipidaemia in addition to hyperglycaemia. This is all the more relevant with regard to efforts to prevent visual complications of diabetic retinopathy.

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