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Diabetic Retinopathy and its Relation with Serum Lipid and Serum Homocysteine Levels

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Abstract: ***Purpose: To study the relation of serum lipid levels and serum homocysteine levels with diabetic retinopathy. Method: Cross sectional study involving 82 type 2 diabetic patients with retinopathy evaluated between May 2017 to September 2018. 56 were males and 26 were females. Diabetic retinopathy was graded according to ETDRS classification. 50 patients had Non proliferative diabetic retinopathy and 32 patients had Proliferative diabetic retinopathy. Serum lipid and serum homocysteine was assessed for all. Glycemic control was assessed by FBS and HbA1c. Results: Analysis showed statistically significant correlation of serum cholesterol and serum triglyceride with NPDR,PDR and macular edema. Serum homocysteine was elevated in 28% of NPDR and 60% of PDR patients, with statistically significant relation seen with NPDR, PDR and CSME. Conclusion: Significant relation between serum cholesterol, triglyceride and homocysteine was seen in type 2 diabetics with retinopathy which implicates that these risk factors may contribute a role in progression of diabetic retinopathy.***

Keywords: NPDR, Non proliferative diabteic retinopathy, PDR proliferative diabteic retinopathy CSME clinically significant macular edema

1. Introduction

Diabetic retinopathy is the most frequent microvascular complication of diabetes mellitus and the most common cause of blindness in the working-age population.

As per the ICMR-INDIAB, the prevalence of diabetes mellitus in India ranges from 10.9% to 14.2% in urban areas and 3% to 8.3% in rural areas[1].

It is estimated that in 2002 diabetic retinopathy accounted for about 5% of world blindness, representing almost 5 million blind[2]. Strongest predictors for diabetic retinopathy are age of the patient and duration of diabetes. Dyslipidaemia and hyper homocysteinemia are some of the factors whose role as predictors of diabetic retinopathy is not well established. Lipid abnormalities seen in Type 2 diabetic patients are increased serum TG, LDL , VLDL ,cholesterol and low level of HDL.

ETDRS showed that patients of diabetic retinopathy with elevated levels of total cholesterol and LDL cholesterol were twice as likely to have hard exudates as compared to those with normal levels[3] .In Chennai Urban Rural Poor Study (CURPS), total cholesterol, triglycerides and HDL cholesterol were higher in cases of diabetic retinopathy as compared to those without retinopathy[4]. Multi Ethnic Study of Atherosclerosis (MESA) showed no associations of serum lipids with diabetic retinopathy[5]. Lipid lowering therapy was shown to have some beneficial effects on DR. It was reported that intensive glycemic control and combination treatment of dyslipidemia reduced the rate of progression of DR and treatment with fenofibrate reduced the need for laser treatment for DR [6].

Hyperhomocysteinemia in diabetic patients may contribute to the development of chronic vascular complications, increased risk for occlusive vascular disease, thrombosis, and stroke by causing endothelial dysfunction. In spite of many research works on homocysteine in diabetic patients, the association between these two is not totally clear[7-10].

The present study was undertaken to evaluate the association of homocysteine and lipid profile with diabetic retinopathy as elevated levels of both has been linked with wide range of health disorders such as cardiovascular disease, stroke etc.

2. Materials and Methods

This was a clinic-based observational study. We consecutively recruited 82 subjects aged between 40-80 years, attending diabetic clinic, from March 2017-October 2018. Type 2 diabetic patients with signs of retinopathy were included in the study. Consent was taken from all subjects and details of procedure were explained to them in the local language.

Participants were excluded if they had severe hypertension, acute infections, known cardiovascular and renal diseases, liver dysfunction, severe anemia and thyroid disorders, history of glaucoma, had undergone previous vitreal surgery, seriously ill patients whose sensorium and higher functions are altered, prolong supplementation of B-complex vitamins specially Vitamin B6,Vitamin B12 and folic acid, pregnancy.

Diagnosis of type 2 DM was made according to WHO criteria[11]. Diabetic retinopathy was graded according to the modified Airlie House Classification system[12]. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined Diabetic Macular Edema (DME) as retinal thickening or presence of hard exudates within 1 disc diameter of the center of the macula[13]. Macular edema is clinically significant if one of the following conditions is present: retinal thickening at or within 500 micron of the center of the macula; and/or hard exudates at or within 500 micron of the center of the macula if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disc area in size, at least part of which is within 1 disc diameter of the macular center. Optical coherence tomography (OCT) was used for macular oedema. An individual's diabetic retinopathy level was based on the diabetic retinopathy level of the worse eye.

All participants underwent a standardized clinical examination and detailed questionnaire to obtain information including past medical history, current cigarette smoking status, and the use of antihypertensive medications, lipid-lowering medications, and oral hypoglycemic agents. Hypertension was defined as systolic blood pressure (SBP) >140 mmHg, diastolic blood pressure (DBP) >90 mmHg, or current use of antihypertensive medications. After overnight fasting and 2 hours after meals, fasting and postprandial blood samples were obtained from all the subjects. Fasting Blood Sugar (FBS) and Postprandial Blood Sugar (PPBS) were estimated by Glucose oxidase-peroxidase method. The samples were analysed for serum homocysteine, and serum lipid profile including serum cholesterol, triglyceride, high density lipoprotein (HDL), LDL and VLDL. The diabetic retinopathy group was further categorised based on homocysteine levels as normal and hyperhomocysteinemic. The data obtained for each analyze were presented as mean ±SD. The data were analyzed using t test. P<0.05 and P<0.001 was considered to be significant and highly significant respectively.

3. Results

Of the 82 patients included in the study, 56 were males and 26 were females. 50 (60%) cases had NPDR and 32(40%) cases had PDR grade retinopathy. Highest percentage (36%) of subjects included in the sample belong to the age group of 51-60 years and the lowest percentage belong to the age group <45 years and >70 years (Table no.1).

It was observed that PDR patients had higher mean HbA1c levels and post prandial blood sugar levels showing poor glycemic control in PDR patients (Table no.2).

Lipid profile variables were compared and analysed (Table no.3). Mean serum cholesterol concentration was 178.33±56.30 in NPDR group, whereas in PDR group mean serum cholesterol was significantly higher (p=0.0035), value being 211.44±32.66 mg/dl. Serum triglyceride levels were also significantly raised in PDR group as compared to NPDR group (p=0.0032). Mean value of LDL was slightly raised in PDR group but was not statistically significant. A significant variation was not observed with mean values of both VLDL and HDL. Upon supplementary analyses of NPDR , PDR and CSME we found that triglycerides and cholesterol maintained their association with even severe forms of diabetic retinopathy and CSME (Table no. 4).

A serum homocysteine value >15micromol/l is termed hyperhomocysteinemia. 14 patients of NPDR and 20 patients of PDR had homocysteine value >15µmol/l respectively.

Mean value of serum homocysteine was higher in patients of PDR and in patients with macular edema, with homocysteine showing statistically significant association with NPDR, PDR and CSME (Table no. 5)

Table 1: Age distribution

Age of patient	PDR		NPDR	
	No.	%	No.	%
41-50	8	25	10	20.00
51-60	12	37.50	24	48.00
61-70	10	31.25	14	28.00
>70 yrs	2	6.25	2	4.00
Total	32	100.00	50	100.00

*PDR-proilferative diabetic retinopathy, NPDR-non proliferative
Diabetic retinopathy

Table 2: Baseline characteristics of participants

	NPDR	PDR	P-value
No.	50	32	
HbA1c	6.67±1.18	8.19±1.476	<0.0001
Fasting blood sugar	139.44±52.57	150.29±34.62	0.3052
Post prandial blood sugar	198.10±80.87	241.93±62.22	0.0108*

Table 3: Serum Lipids with Diabetic retinopathy

Diagnosis	VLDL (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	S.cholesterol (mg/dl)	S. triglyceride (mg/dl)
PDR	37.45± 14.59	96.05± 29.95	46.09± 9.92	211.44± 32.66	198.73± 78.16
NDPR	36.41± 16.01	85.22± 35.12	46.82± 8.02	178.33± 56.30	150.77± 63.88
t-value	-0.297	-1.440	0.366	-3.014	-3.037
p-value	0.7673	0.1537	0.7152	0.0035*	0.0032*

Table 4: Serum lipids with diabetic retinopathy severity

	NPDR	CSME	PDR	P-value
LDL	85.22±35.12	118.50±13.75	96.05±29.95	0.059
HDL	46.82±8.02	44.08±0.50	46.09±9.92	0.244
S.Triglyceride	150.7±63.88	211.66±0.44	198.73±78.16	0.029*
S.Cholesterol	178.33±56.30	242.50±3.73	211.44±32.66	0.037*

CSME- clinically significant macular edema

Table 5: Serum homocysteine with diabetic retinopathy and macular edema

	s. homocysteine (<15)		S. homocysteine (>15)		t-value	p-value
	No.	mean ±SD	No.	mean ±SD		
NPDR (n=50)	36	11.0±1.71	14	16.94±0.97	-12.2065	<0.0001
PDR (n=32)	12	11.55±1.55	20	23.84±4.98	-8.26395	<0.0001
CSME(n=32)	14	11.88±1.37	18	21.05±5.64	-5.9288	<0.0001

4. Discussion

Diabetes mellitus represents an increasing problem for patients and health care systems worldwide with diabetic retinopathy been a potentially blinding complication. There are multiple risk factors which have been associated with the development and progression of diabetic retinopathy, strongest predictors been age of the patient and duration of diabetes. Dyslipidaemia, microalbuminuria, hyper homocysteinemia are some of the factors whose role as predictors of diabetic retinopathy is not well established.

The present study depicts the association between NPDR and PDR with lipid and serum homocysteine. A significant

association of TG and cholesterol was observed (p<.05)in both non proliferative and proliferative retinopathy patients. This is in accordance to the CURES eye study[14] which found that both serum triglyceride levels and total cholesterol were higher in patients with diabetic retinopathy.

However different studies have depicted varying results in the past. Alpana Mathur, Rishi Mathur [15] observed that TG levels were significantly raised in those with DR, but LDL and cholesterol were not found to be significantly raised. Some other studies, by Hove et al[16], Miljanovic et al, Larsson reported no significant association between diabetic retinopathy, triglycerides, HDL and total cholesterol in diabetic population.

High lipid levels are known to cause endothelial dysfunction due to a reduced bioavailability of nitric oxide leading to endothelial dysfunction which plays a role in retinal exudate formation and might contribute to retinopathy and macular edema[22].There may also be incorporation of triglycerides into the cell membrane leading to changes in membrane fluidity and leakage of plasma constituents into the retina. This results in haemorrhage and oedema in the retina[23].

Our study showed that LDL, total cholesterol and TG was significantly associated with macular edema, which is similar to results of ETDRS report, where Chew et al stated that patients with high total cholesterol and LDL levels were more likely to have retinal hard exudates compared to patients with normal lipid profile. Other studies also showed that retinal exudates or macular edema was associated either with LDL or total cholesterol, or both[14,17,18,19]. In another study, it was reported that lipid profile was not associated with retinal thickness, but only clinically significant macular edema[20]. On the contrary, Ozer et al[21] could not show a correlation between serum lipid levels and macular edema in diabetic patients.

Diabetes is a microvascular occlusive disease, an adjuvant risk factor contributing to a hypercoagulability state, such as increased levels of plasma homocysteine, may accelerate or aggravate the development or progression of diabetic retinopathy. Mild to moderate elevation of homocysteine may explain the role of vascular dysregulation and endothelial dysfunction in patients with diabetic retinopathy resulting in macular edema. Oxidative stress is thought to be increased in diabetes; this makes them more susceptible to hyperhomocysteinemia induced oxidative damage

5. Conclusion

Our study suggests that type 2 diabetic patients are at risk of developing dyslipidemia and hyperhomocysteinemia. Proper identification of various risk factors can aid in management of retinopathy and thus help in preventing further ocular complications and morbidity. As a good percentage of type 2 diabetic patients present with retinopathy, measurement of homocysteine may open a new window for determining the additive risk factor in the development of retinopathy in type 2 diabetic patients from the very beginning.

It is necessary that plasma homocysteine should be assessed routinely in all diabetic patients and any existing hyperhomocysteinemia should be treated to reduce the toxic effect of homocysteine.

With the advent of systemic lipid lowering therapy , there may be potential for medical therapy along with laser treatment . As some studies have shown the effect of lipid lowering agents in reducing hard exudates.

Rigorous lipid control by adoption of a healthy lifestyle in addition to its known health benefits in preventing cardiovascular disease, may also lessen ocular morbidity and associated health care costs, thereby potentially improving quality of life and vision among people with type 2 diabetes.

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