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A COMPARATIVE STUDY OF LIPID PROFILE IN DIABETES MELLITUS PATIENTS WITH AND WITHOUT DIABETIC RETINOPATHY

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ABSTRACT **PURPOSE**: 1. To study the relationship between the severity of diabetic retinopathy and serum lipid levels. 2. To evaluate the relationship between serum lipid levels, diabetic retinopathy changes including CSME.

METHODS: 100 diabetic patients without retinopathy (group A), 100 diabetic patients with retinopathy (group B), 100 nondiabetic patients with no retinopathy as control (group C) according to ETDRS chart were studied. Total cholesterol(TC), triglycerides(TG), high-density lipoprotein(HDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) and Fasting plasma glucose (FPG), 2hr Plasma Glucose (2hr PG), HbA1C (glycosylated hemoglobin) levels were compared among the groups.

RESULTS: The groups were age and gender matched (P= 0.474 and P= 0.84 respectively, one-way ANNOVA test). The mean duration of diabetes was higher in Group A than Group B (P= <0.0001; P= >0.0001 respectively). The Body Mass Index is higher in both Group A and Group B than Group C (P= <0.0001; P= <0.0001 ; P= >0.0001 respectively). The mean FBS, PPBS, and HbA1C were higher for Group A and B than the control group C (P= <0.0001; P= <0.0001;P= >0.0001 respectively). The mean TG and VLDL are higher in Group A and B than Group C (P= 0.043; P= 0.044 respectively). The mean HDL was lower in Group A than the other two (P=0.674).

Out of 56 cases of CSME among diabetic patients, 44(78.5%) had CSME in both eyes which were significantly higher (Z=6.87;p<0.0001). No CSME was found among Group B and C.

CONCLUSION: Serum Lipid levels were significantly associated with the severity of DR and the existence of CSME in those patients.

KEYWORDS :

INTRODUCTION

Diabetes Mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on the etiology of the Diabetes Mellitus, factors contributing to hyperglycemia include reduced insulin secretion, inefficient insulin action or decreased glucose utilization and increased glucose production.

Diabetic retinopathy (DR) a major microvascular complication of Diabetes remains a leading cause of visual disability and blindness frequently accompanied by lipid exudation[1] followed by dyslipidemia leading to the development of hard exudates and Clinically Significant Macular Edema (CSME)[2].

Patients with Diabetic Retinopathy are 25 times more likely to become blind than non-diabetics. In diabetes mellitus, there is an alteration in carbohydrate, lipid and protein metabolism due to the development of microvascular and macrovascular complications which have a significant impact on the quality of life and result in a substantial increase in morbidity and mortality.

MATERIALS AND METHODS

METHODS

1. STUDY AREA: Regional Institute of Ophthalmology, Kolkata and Department of Medicine, Medical College, Kolkata.
2. STUDY POPULATION: Patients attending RIO and Department of Medicine, Medical College, Kolkata.
3. STUDY PERIOD: One and half years (January 2017 - July 2018)
4. SAMPLE SIZE: 300
5. CASES: 100 Diabetic patients with different stages of Retinopathy (Mild NPDR, Moderate NPDR, Severe NPDR, Very Severe NPDR, PDR) 100 Diabetic patients with No Retinopathy
6. CONTROLS: 100 age and sex-matched healthy patients.

7. PARAMETERS TO BE STUDIED :

a) Age
b) Sex
c) Best-corrected visual acuity (BCVA) of each eye using Snellen's chart and ETDRS chart
d) Slit-lamp Biomicroscopic examination of Anterior Segment
e) Dilated Fundus evaluation using Direct Ophthalmoscopy / Indirect Ophthalmoscopy with +20 D lens
f) Slit Lamp Biomicroscopy using +78 D / + 90 D
g) Optical Coherence Tomography, wherever indicated.
h) Fasting blood sugar level, Postprandial blood sugar level, and HbA1C
i) Fasting serum lipid level

8. TYPE OF STUDY: Observational Study
9. INCLUSION CRITERIA : Type - II Diabetes Mellitus cases (on antidiabetic medications) as defined by American Diabetes Association 2011.

10. EXCLUSION CRITERIA :

- Those in whom dilatation of pupils is contraindicated such as Angle Closure Glaucoma, small pupil due to posterior synechiae.
- Patients with hazy media which impairs visualization of the fundus due to Uveitis.
- Patients who have been treated earlier with either LASER or Intravitreal anti-VEGF injections.
- Patients on hypolipidemic drugs.

MATERIALS :

1) Snellen's chart and ETDRS chart
2) Slit-lamp Biomicroscopy
3) Direct Ophthalmoscopy
4) Indirect Ophthalmoscopy
5) +20 D Lens6) +90 D Lens
7) Optical Coherence Tomography

RESULTS AND ANALYSIS STATISTICAL ANALYSIS

Statistical Analysis was performed with the help of Epi Info (TM) 7.2.2.2 which is a trademark of the Centers for Disease Control and Prevention (CDC).

Table-1: Comparison of demographic parameters of the patients of the three groups

Also, One Way Analysis of variance (ANOVA) followed by post hoc Tukey's test was performed with the help of Critical Difference (CD) or Least Significant Difference (LSD) at 5% and 1% level of significance to compare the mean values. $p<0.05$ was taken to be statistically significant.

Chi-square (x^2) test showed that there was no significant difference in gender and the patients of the three groups ($p=0.84$)

ANOVA-test showed that there was no significant difference in the mean ages of the patients of the three groups ($p=0.474$).

Thus the patients of the three groups were matched for their ages and gender.

t-test showed the mean duration of diabetes of Group-A was significantly higher than that of Group-B.

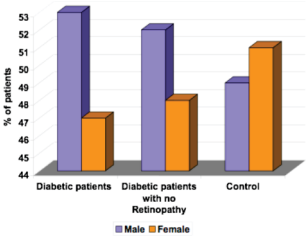

Table-2: Comparison of parameters related to the level of blood sugar of the patients of the three groups

ANOVA-test showed that there were significant differences in mean FBS, PPBS, and HbA1c of the patients of the three groups ($p<0.0001$). As per Tukey's Critical Difference (CD), the mean FBS, PPBS, and HbA1c of the patients of Group-A and Group-B were significantly higher than that of the control group ($p<0.0001$).

Also, the mean FBS, PPBS, and HbA1c of the patients of Group-A were significantly higher than that of Group-B ($p<0.0001$).

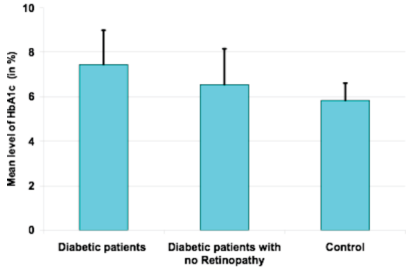

Table-3: Comparison of the lipid profile of the patients of the three groups

ANOVA-test showed that there were significant differences in mean TG and VLDL of the patients of the three groups ($p<0.0001$). As per the Tukey's Critical Difference (CD), the mean TG and VLDL of the patients of Group-A were significantly higher than that of Group-B and control group ($p<0.0001$).

ANOVA-test showed that there were no significant differences in mean TCH, LDL, and HDL of the patients of the three groups ($p>0.05$). But the mean of these parameters except HDL was higher in Group-A. Mean HDL was lower in GroupA.

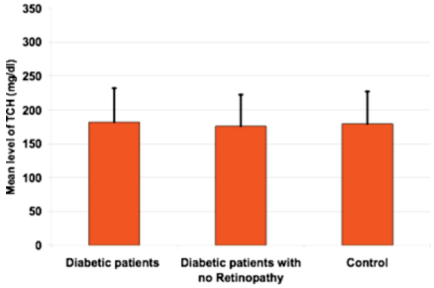

Table-4: Distribution of fundus finding and status of CSME of the diabetic patients

Corrected Chi-square (x^2) test showed that there was a significant association between fundus finding and status of CSME of the patients ($p=0.0001$).

The presence of CSME significantly increased with the severity of NPDR.

Fundus finding	CSME		TOTAL
	Present	Absent	
Mild NPDR	1	27	28
Row %	3.6	96.4	100.0
Col %	1.8	11.1	9.3
Moderate NPDR	23	14	37
Row %	62.2	37.8	100.0
Col %	41.1	5.7	12.3
Severe NPDR	15	1	16
Row % Col %	93.8	6.3	100.0
	26.8	0.4	5.3
Very Severe	4	0	4
NPDR	100.0	0.0	100.0
Row% Col %	7.1	0.0	1.3
PDR	13	2	15
Row %	86.7	13.3	100.0
Col %	23.2	0.8	5.0
Normal	0	200	200
Row %	0.0	100.0	100.0
Col %	0.0	82.0	66.7
TOTAL	56	244	300
Row %	18.7	81.3	100.0
Col %	100.0	100.0	100.0

DISCUSSION

The present study was conducted in a tertiary care teaching institute. This was an observational study done to identify the different stages of diabetic retinopathy in correlation with serum lipid levels.

It is believed that the Indian population generally has an unusually efficient glucose metabolism. Paralleling the high prevalence of diabetes is a concern that the complications of diabetes, mainly diabetic retinopathy are increasing.

Hyperglycemia and dyslipidemia are two major metabolic disorders seen in patients with diabetes mellitus. Diabetes mellitus is justifiably known as 'devil' or silent killer affecting almost every tissue and cell in the human body. Ocular complications like retinopathy which are microvascular complications are innocuous in onset progressively destructive in their course and are remediable only to a point. Over the years, voluminous information has accumulated on the pathogenesis of diabetes complications like retinopathy. Many clinical trials and researches have yielded fruitful results.

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, 200 patients having type 2 diabetes mellitus were studied. 100 age and gender matched controls were also studied. The patients were categorized with respect to the presence or absence of diabetic retinopathy. In the group having retinopathy, patients were subcategorized depending on the severity/grade of retinopathy and the presence or absence of CSME.

The present study had a near equal gender distribution. The male to female ratio [M: F] was 53:47. In a clinical cohort in Chennai diabetic retinopathy appeared to be prevalent more in the males compared to the females (sex ratio 2:1). Similar male preponderance was also seen in the CURES Eye study, UKPDS study Gupta et al and the Andhra Pradesh Eye Disease Study (APEDS). However, the difference with respect to gender distribution was not significant statistically in the current study ($p=0.84$).

The mean age in each group was 57.04±10.27; 56.32±9.89; 58.10±10.89 years. The relationship of retinopathy with age was in concordance to that found in many other studies. Like several other epidemiologic studies, this study also showed an increased prevalence of DR with increasing age. APED Study, CURES Eye Study, Dondana, et al also found a significant correlation between the patient's age and diabetic retinopathy.

In the present study, the duration since diagnosis of diabetes (diabetic age) ranged from 5 - 25 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 a lack of symptoms and the insidious onset of type 2 diabetes. The mean duration of diabetes in group A and group B were 11.12±6.27 and 9.46±5.51 respectively.

The association of longer duration with a higher risk of diabetic retinopathy was in accordance with previously published reports (DCCT; WESDR/Klein et al; UKPDS; Larsson et al; Wong et al; Varma). It is obvious that patients with retinopathy significantly had a longer mean duration of diabetes. Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) also found that the risk of retinopathy is directly related to the duration of diabetes. In India, virtually all studies have shown an increased prevalence of DR as the duration of diabetes increased (Gupta et al; APEDS Study; Agarwal et al). The CURES Eye study has found that for every five-year increase in the duration of diabetes, the risk of DR increased by 1.89 times.

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 DR. In the present study most of the subjects in group 1 had poor glycemic control suggested by raised FBS and PPBS levels. The mean values of FBS and PPBS were higher in group A than group B, reinforcing the fact that the development and progression of DR are influenced by the level of hyperglycemia. Intensive glycemic control was effective in substantially reducing the incidence and progression of retinopathy in the Diabetes Control and Complications Trial (DCCT) group.[4] The UKPDS (UK Prospective Diabetes Study) also showed that intensive glucose control reduced the risk of a two-step change in retinopathy by 21% at 12 years follow up.[4] Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) also found that the risk of retinopathy is related to the control of blood glucose levels.[5] The CURES Eye Study observed a linear trend between the prevalence of DR and poor glycemic control.[6] HbA1c which is a better indicator of glycemic control was also found to be significantly higher in group A and group B than the control group. A study conducted by Prof K. Goswami et al found there was a significant correlation of HbA1c levels and improvement in diabetes management.

The present study showed a statistically significant correlation between diabetic retinopathy and raised triglyceride (p=0.043). Increased triglyceride level was significantly associated with the occurrence of all grades of retinopathy. The mean value of triglyceride in group A, group B, group C were 177.21±69.4;155.36±57.0; 161.22±64 mg/dl respectively. The mean value of total cholesterol was higher in group A than group B and group C. However this value was statistically not significant.

Al-Bdour et al, while investigating the risk factors associated with diabetic retinopathy among diabetic patients, found a positive relationship between diabetic retinopathy and hypercholesterolemia (p=0.04). This finding is in accordance with the findings of the present study.[8] Larsson et al, also found a significant correlation between higher levels of serum total cholesterol and retinopathy.[9]

Rema et al (CURES Eye Study) studied the association of serum lipids with diabetic retinopathy in urban South Indians. The serum triglyceride (p=0.001) levels and total cholesterol (p=0.014) were higher in patients with diabetic retinopathy as compared to patients without diabetic retinopathy.[10] The association was maintained even after adjusting for age, as age by itself is a significant risk factor for hyperlipidemia. Similar results were obtained by Haddad et al.[11] In the present study ANOVA-test showed that there were significant differences in mean TG and VLDL of the patients of the three groups (p<0.0001). The mean TG and VLDL of the patients of Group-A were significantly higher than that of Group-B and control group (p<0.0001).

The Hoorn study, a large population-based study to determine the potential risk factors for retinopathy in diabetic and nondiabetic individuals showed that retinopathy, and hard exudates in retinopathy, in particular, are related to elevated serum total and LDL cholesterol levels.[12] Agarwal et al[5] and Sachdev et al[13] also observed raised the level of total and LDL cholesterol and reduced the level of HDL/LDL cholesterol ratio in patients with diabetic retinopathy. The hypertriglyceridemia was found to be a risk factor for retinopathy in the current study.

Klein et al, while assessing the serum lipid levels in the subjects who participated in the Wisconsin Epidemiologic Study of Diabetic Retinopathy found a significant trend for increasing severity of diabetic retinopathy and of retinal hard exudate with increasing cholesterol.[14] In the present study although there was an overallassociation of DR with total triglyceride, it did not correlate with the severity of DR.

In contrast to the present study, the EURODIAB Complications Study found that the triglyceride level was related to all levels of retinopathy.[15] Lyons et al studied serum lipoprotein subclass profiles in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) cohort and found that severity of retinopathy was positively associated with triglycerides and negatively associated with HDL cholesterol.[16]

Different observations were made by Gupta et al who demonstrated that diabetics with raised LDL levels showed a higher prevalence of Diabetic Retinopathy (38%) compared to others (28.3%) (p=0.05).[17]

In the present study, all lipid parameters were higher in subjects with severe NPDR, very severe NPDR and PDR compared with subjects without DR. Elevated triglyceride was found to be a significant risk factor for severe NPDR and PDR even after age adjustment, duration of diabetes, HbA1c, and albumin excretion rate in EURODIAB study.[16] In CURES Eye study serum cholesterol concentrations were higher in subjects with moderate NPDR compared with subjects without DR (p<0.05). Triglyceride concentrations were higher in those with mild NPDR compared with those without DR (p<0.05).[6]

The present study found a significant association with the increasing presence of CSME with increased severity of DR. Out of 56 cases of CSME among the diabetic patients 44 (78.5%) had CSME in both eyes which were significantly higher (Z=6.87; p<0.0001). This was in accordance with the study by Al-Bdour et al who found a significant association between the development of diabetic maculopathy and hypercholesterolemia.[18] Higher total cholesterol level was positively associated with the presence of CSME, in a cross-sectional analysis of participants with diabetes in the WESDR Study. CURES Eye Study also showed an association of Diabetic Macular Edema in type 2 diabetic subjects with increased cholesterol.

The present study showed that there was an increase in the severity of diabetic retinopathy with increasing levels of different serum lipid sub-fractions. Larsson et al showed a linear relationship of serum cholesterol levels with severity of diabetic retinopathy.[9] WESDR Study also found that there was a significant trend for increasing severity of diabetic retinopathy with increasing cholesterol.[6]

The present study did not find any correlation between serum lipid levels and visual acuity. This may be because of the fact that most of the patients included in the group for the study had various types and grades of cataract and correction for the same could not be done during statistical analysis. CURES Eye study showed that visual acuity decreases with an increase in severity of retinopathy.[6] ETDRS Study has found that elevated serum cholesterol at baseline increases the risk of visual loss by 50% compared to lower serum cholesterol levels.[7] These findings have been supported by examination of a subgroup of the WESDR cohort.[14] Miljanovic et al did not observe any relationship between lipids and vision loss.[20]

Most of the diabetics in the present study had poor glycemic control. Hyperglycemia is also associated with dyslipidemia, specifically increased levels of total cholesterol and triglycerides, a slight elevation of LDL, but generally little if any change in HDL. Consequently, hyperglycemia may be an important confounding factor in the study with respect to both diabetic retinopathy and hypertriglyceridemia. HbA1c levels were increased with increasing severity of diabetic retinopathy.

CONCLUSION

The number of adults with diabetes in the world is estimated to increase by 122% (135 million in 1995 to 300% in 2025). This increase is expected to be 42% in the developed world and 170% in the developing countries. India stands first with 195% (18 million in 1995 to 54 million in 2025)

Numerous studies have shown an association of lipid fractions with

macrovascular complications of diabetes, while relatively few looked at the association of serum lipids with microvascular complications such as diabetic retinopathy and the available results are conflicting.[6]

The present study demonstrated a statistically significant correlation between diabetic retinopathy and hypertriglyceridemia. Increased triglyceride level was significantly associated with the occurrence of all grades of retinopathy, especially severe NPDR, very severe NPDR and PDR. It showed a statistically significant correlation between FBS, PPBS and HbA1c with the development of CSME in diabetic retinopathy. It showed no correlation with CSME and visual acuity in diabetic patients with no retinopathy and controls.

Further studies are required to establish a causal relationship between dyslipidemia and diabetic retinopathy. If established, these data can lend additional support to current treatment guidelines recommending the aggressive lowering of elevated lipids among diabetic patients. Rigorous lipid control, in addition to its known health benefits in preventing cardiovascular disease, may also lessen ocular morbidity and associated health care costs, thereby potentially improving the quality of life and vision among people with type 2 diabetes.

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