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"Association of Lipid Profile with Diabetic Retinopathy in Patients Attending a Tertiary Care Centre"

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Abstract
***Background:** Diabetes mellitus results in considerable morbidity and mortality, affecting about 180 million people worldwide.[1] Diabetes is a multisystem disease, having many manifestations in the eye, of which cataracts and Diabetic Retinopathy(DR) are the most significant cause of visual impairment and blindness, and people with diabetes are 25 times more likely than the general population to become blind.[11] In developed countries, diabetic eye disease represents the leading cause of blindness in adults under 75 years.[12] The current study is undertaken to determine the association of serum lipid profile with diabetic retinopathy and its severity.*
***MaterialsandMethods:** This was aHospital based cross-sectional study conducted in the Department of Ophthalmology and Diabetes Clinic, AGMC & GBP Hospital for a duration of 2 years.*
***Results:** Of the 100 Type 2 diabetic patients included in this study, diabetic retinopathy was detected in 55%. Mean LDL levels in diabetics without diabetic retinopathy was113.13,116.04 in NPDR and 99.33 in PDR. there was no significant association between serum HDL levels and diabetic retinopathy severity (p- value 0.19). 39 of 55 (70.9%) retinopathy patients had low HDL levels and only 2 (3.6%) had high HDL levels which is desirable.*
***Conclusion:** In our study, 45% had no signs of diabetic retinopathy, 46% had non- proliferative retinopathy and 9% had proliferative retinopathy.*
No significance was found with total serum cholesterol levels and severity of diabetic retinopathy. 36.3% of patients with retinopathy had elevated serum total cholesterol levels. There was no significant association between serum LDL levels and severity of diabetic retinopathy .60% of retinopathy cases had elevated LDL levels.
***Keywords:** Diabetic Retinopathy, Diabetes mellitus, Hard exudates, Lipid profile.*

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I. Introduction

Diabetes mellitus results in considerable morbidity and mortality, affecting about 180 million people worldwide.[1] The disease is classified according to three distinct groups of patients:a) type I diabetes (previously known as 'insulin dependent' or 'juvenile onset') is characterized by destruction of the insulin secretory pancreatic β-cells of the islets of Langerhans caused by an autoimmune process, usually leading to absolute insulin deficiency);b) type II diabetes (noninsulin dependent, adult-onset) is characterized by insulin resistance in peripheral tissues and an insulin secretory defect of the β-cell and c) Gestational diabetes.[2] Between 70 and 90% of diabetic patients have type II diabetes.[3] However, current statistics suggest that an estimated 50% of diabetes sufferers remain undiagnosed.[4, 5, 6]

Diabetes is a multisystem disease, having many manifestations in the eye, of which cataracts and Diabetic Retinopathy(DR) are the most significant cause of visual impairment and blindness, and people with diabetes are 25 times more likely than the general population to become blind.[11]In developed countries, diabetic eye disease represents the leading cause of blindness in adults under 75 years.[12] DR is the most common complication in type I diabetes and nearly all patients will have some degree of retinopathy 15–20 years after onset.[13, 14, 15, 16] Similarly, more than 60% of type II diabetes sufferers will have evidence of DR during this period.[14, 12] Visual impairment as a result of DR has a significant impact on patients' quality of life,[11] thus compromising their ability to manage their disease successfully, which can in turn have an impact on the incidence of diabetic complications and overall life expectancy.

DR is a progressive disease predominantly affecting the integrity of the microcirculation of the retina. DR can be broadly divided into three clinical stages: a)nonproliferative(NPDR),b)proliferative diabetic retinopathy (PDR) and c)diabetic maculopathy. During nonproliferative DR, the earliest visible sign of retinal

damage results from abnormal permeability and/or nonperfusion of capillaries, leading to the formation of microaneurysms.[16]Abnormal capillary permeability results in the leakage of fluid and solutes into the surrounding retinal tissue, which collects around the macula, causing macular oedema which in turn threatens visual acuity. PDR develops following the occlusion of retinal capillaries leading to retinal ischaemia, promoting the release of VEGF, resulting in neovascularization(a process by which new blood vessels proliferate on the surface of the retina). However, these vessels are fragile and rupture easily. The resulting accumulation of blood in the vitreous cavity from these haemorrhaging vessels seriously impairs vision. This may be permanent due to further complications such as tractional retinal detachment leading to blindness. It has been estimated that without treatment for PDR, 50% of all patients will become blind within 5 years following diagnosis.[13]

Diabetic retinopathy is characterised by gradually progressive alterations in retinal microvasculature, leading to areas of retinal non-perfusion, increased vasopermeability, and pathologic intraocular proliferation of retinal vessels.

All patients with type 1 diabetes and more than 60% of patients with type 2 diabetes develop some degree of retinopathy after 20 years. In patients with type 2 diabetes, approximately 20% have retinopathy at the time of diabetes diagnosis &approximately 25% of patients with type 1 diabetes have retinopathy after 5 years, with this figure increasing to 60% and 80% after 10 and 15years, respectively.[12]

The association between serum lipid levels and diabetic retinopathy has been investigated in few studies. Lipid profile or lipid panel is a panel of blood tests that serves as an initial broad medical screening tool for abnormalities in lipids, such as cholesterol and triglycerides. A lipid profile usually includes the levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and the calculated low-density lipoprotein (LDL) 'cholesterol. Some studies show a positive relationship between serum cholesterol and low-density lipoprotein levels and retinal hard exudation. Other studies show serum triglyceride levels as being important
in the progression of retinopathy. Certain other studies show no relationship between serum lipid levels and diabetic retinopathy.

The current study was undertaken to determine the association of serum lipid profile with diabetic retinopathy and its severity. The inconclusive reports in the literature regarding the association between serum lipid levels and diabetic retinopathy and the lack of studies relating to the existing case load prompted us to undertake this study. If the correlation of lipid profile with diabetic retinopathy is established the study can lend additional support to the current treatment guidelines of recommending aggressive lowering of elevated serum lipids among diabetic patients.

II. Aim and Objectives

Aim- To study the association of diabetic retinopathy with serum lipid levels.

Objectives -

1. Toassesstheproportionofpatientswithdyslipidemiaamongpatientswithdiabetic retinopathy attending AGMC and GBP Hospital,Agartala.
2. To assess association between various types of lipoproteins with diabeticretinopathy.

III. Materials and Methods

STUDY DESIGN- Hospital based cross-sectional study.

SETTING - Department of Ophthalmology and Diabetes Clinic, AGMC & GBP Hospital.

STUDY DURATION- 2 years.

STUDY POPULATION- All Diabetic patients attending the Diabetes clinic, Retina clinic and Ophthalmology OPD at Agartala Govt. Medical College and GBP Hospital, Agartala during the study period.

SAMPLE SIZE: $\mathbf{n= \frac{Z^2\alpha/2 \times P \times (1-P)}{d^2}}$ where $Z\alpha/2$= normal deviate at 5% level of significance,

P= Prevalence of Diabetic Retinopathy (21.7%) and d= absolute precision(10%). Thus, n= (4 x 0.217 x 0.783) / $(0.1)^2$ = 0.6796/0.01 = 70 (approx.)

The final sample size was taken as 100 patients by Systematic Random Sampling.

SAMPLING METHOD: Systematic Random Sampling- On average 2 Diabetic patients attended the Retina clinic and Ophthalmology OPD. Thus during two years there was 936 study population (approx.), from which 100 sample population were selected by Systematic Random Sampling.

INCLUSION CRITERIA: All diabetic patients attending Diabetes clinic, Ophthalmology OPD and Retina clinic at AGMC & GBP Hospital who were screened for diabetic retinopathy.

EXCLUSION CRITERIA:

- Patients who were not willing to participate in thestudy.
- Any other ocular disease causing diminution ofvision.
- Those in whom dilatation of pupils was contraindicated such as angle closureglaucoma.
- Patients with hazy media which impaired visualization of the fundus.

STUDY TOOLS- 1) Snellen's chart. 2) Near Vision test type book. 3) Slit lamp examination with +90D lens. 4) Direct ophthalmoscope. 5) Indirect ophthalmoscope 6) Funduscamera. A detailed history of each patient was obtained regarding the age, duration of diabetes, the anti- diabetic treatment they were on and any associated illness. Diabetic retinopathy was classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system.

DATA COLLECTION-All patients were informed in detail about the purpose of the study and procedures to be followed and consent was obtained for participation in the study. Each patient was subjected to detailed history taking followed by ocular and Adnexal examination as per a predesigned proforma. To obtain the uniocular and binocular visual acuity a Snellen's chart and near vision test type book was used. Best corrected visual acuity was recorded. Intraocular pressure was measured by applanation tonometer and non-contact tonometer. Pupil was dilated with a combination of 0.8% tropicamide and 5% phenylephrine eye drop.

Fundus examination after mydriasis using direct ophthalmoscope and Indirectophthalmoscopy and slitlamp examination of the fundus using +90 D lens wasdone.Fundus photograph was taken for documentation.

SPECIMEN COLLECTION: 3ml of 12 hrs fasting blood sample was used to assess lipid profile and blood sugar level. Serum triglyceride, HDL cholesterol, LDL cholesterol, total cholesterol, blood sugar level, heamoglobin and Glycosylated Haemoglobin(HbA_{1c}) was estimated in the Dept. of Biochemistry.

DATA ANALYSIS- Data was recorded, entered and analysed with computer using SPSS version 15.0[17] and Epi-info-version-7[17]. Descriptive statistics and other statistical tests like Chi square test, binary logistic regression analysis etc was used as per applicability. P value of less than 0.05 as considered as statisticallysignificant.

ETHICAL ISSUE- Informed written consent was obtained from each and every participant as per modified ICMR template. Confidentiality was ensured while collecting and analysingthe dataandwasusedforresearchpurposeonly.ApplicationwasplacedbeforetheInstitutional Ethics Committee of Agartala Government Medical College for approval which was given as per request.

IV. Results

	DM WITHOUT RETINOPATHY	DM WITH RETINOPATHY
NO. OF CASES	45	55
PERCENTAGE	45%	55%

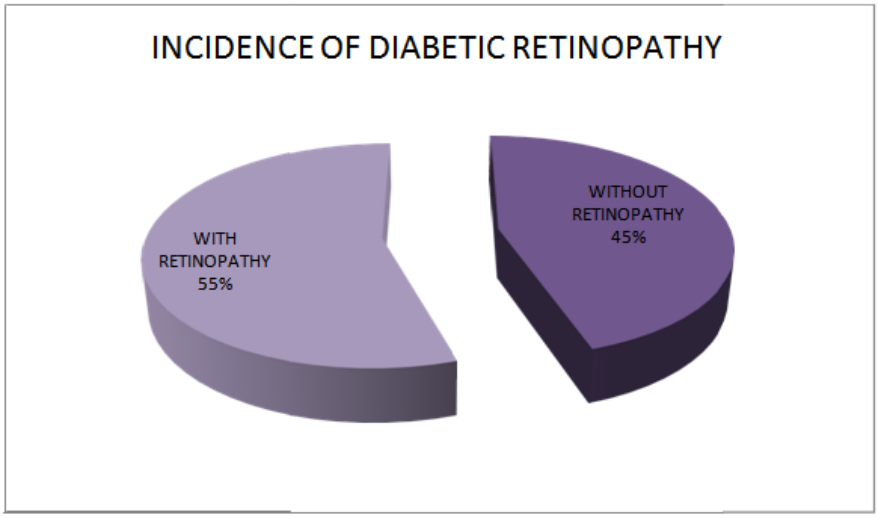

Chart 1: Showing Incidence of Diabetic Retinopathy amongst Diabetic Patients

TOTAL CHOLESTEROL

	No DR	NPDR	PDR
MEAN	177.22	186.86	159.33
STANDARD DEVIATION	41.15	52.12	47.74
P VALUE	0.24		

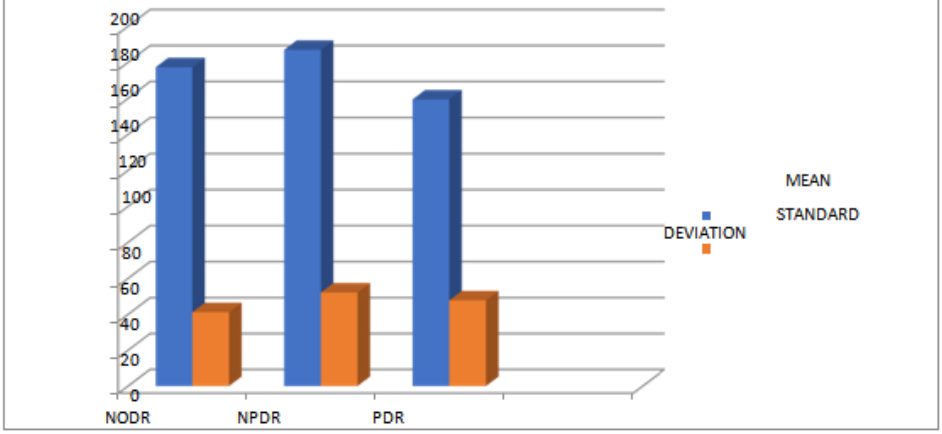

Chart 5: Total Cholesterol levels in Diabetic Retinopathy patients.

According to our study, the mean total cholesterol levels are 177.22 in diabetics without retinopathy, 186.86 in NPDR and 159.33 in PDR. However since the p value is 0.24, there was no significant association found with serum cholesterol levels and severity of diabetic retinopathy.

TRIGLYCERIDES

	No DR	NPDR	PDR
MEAN	141.97	163.13	195.00
STANDARD DEVIATION	68.87	86.05	192.50
P VALUE	0.243		

The mean triglyceride levels were calculated as 141.97 in diabetics without diabetic retinopathy, 163.13 in NPDR and 195.00 in PDR patients. There was no significant association between serum triglyceride levels and severity of diabetic retinopathy with p value being0.24.

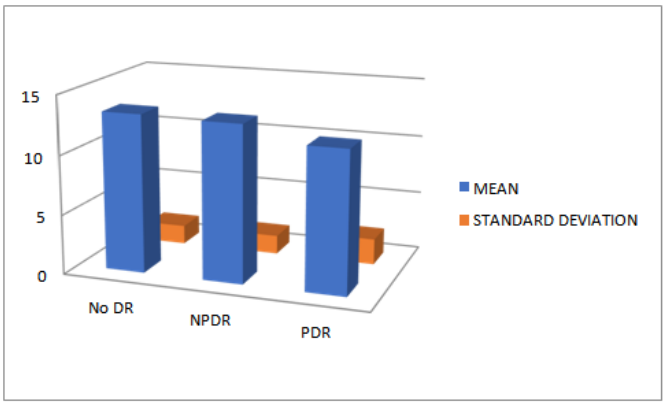

Chart 7: Triglyceride levels in Diabetic Retinopathy patients

HDL LEVELS IN RETINOPATHY PATIENTS

	No DR	NPDR	PDR
MEAN	**39.73**	**36.80**	**31.66**
STANDARD DEVIATION	**15.01**	**10.32**	**12.43**
P VALUE	**0.19**		

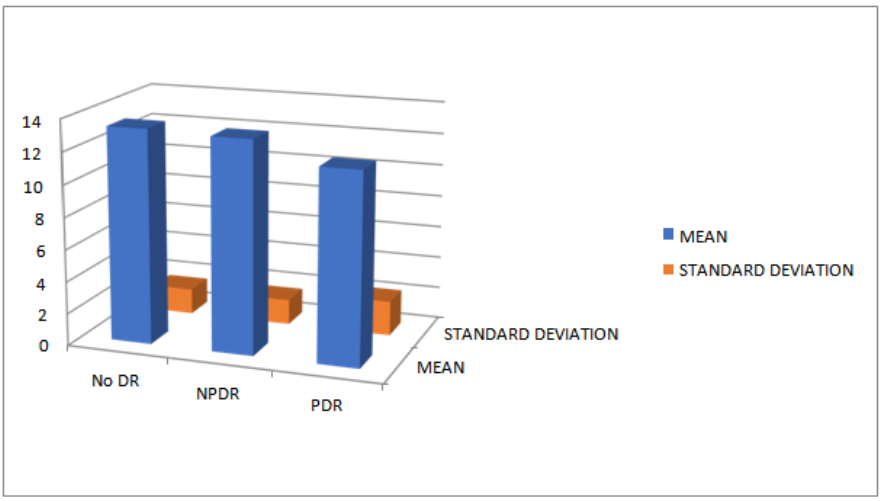

Chart 8: HDL levels in Diabetic Retinopathy patients

LDL LEVELS IN RETINOPATHY PATIENTS
LDL

	No DR	NPDR	PDR
MEAN	**113.13**	**116.04**	**99.33**
STANDARD DEVIATION	**40.10**	**47.87**	**42.24**
P VALUE	**0.58**		

Mean LDL levels in diabetics without diabetic retinopathy was 113.13, 116.04 in NPDR and 99.33 in PDR. There was no significant correlation between serum LDL levels and severity of diabetic retinopathy (p-value0.58).

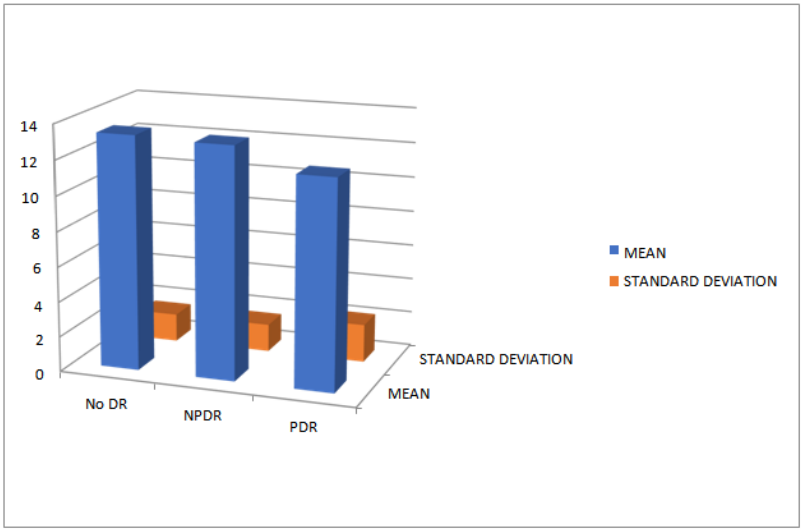

Chart 10: LDL levels in Diabetic Retinopathypatients

V. Discussion

Of the 100 Type 2 diabetic patients included in this study, diabetic retinopathy was detected in 55%.The results are consistent with the Wisconsin Epidemiological Study for Diabetic Retinopathy conducted in the USA among 1313 subjects where 50.3% had diabetic retinopathy. However WESDR study was conducted among type I diabetics.[10]

In the Chennai Urban Rural Epidemiological Study I (CURES I) which is an ongoing study conducted in India the prevalence of diabetic retinopathy in the 1715 subjects was 17.6% which is considerably lower than the above studies conducted in Western countries.[13]

In this study mean age in the no diabetic retinopathy group was 54.02,in NPDR group it was 57.56 and in the PDR group it was 55.55.There was no significant association between increasing age and diabetic retinopathy status according to this study (p-value 0.195).

According to our study, the mean total cholesterol levels are 177.22 in diabetics without retinopathy, 186.86 in NPDR and 159.33 in PDR. However since the p-value is 0.24, there was no significant association found between serum lipid levels and severity of diabetic retinopathy. 20 of the 55 patients with retinopathy (36.3%) had elevated serum total cholesterol levels and 63.6% of retinopathy patients had desirable cholesterollevels.

The mean triglyceride levels were calculated as 141.97 in diabetics without diabetic retinopathy, 163.13 in NPDR and 195.00 in PDR patients. There was no significant association between serum triglyceride levels and severity of diabetic retinopathy with p value being 0.24.

The mean HDL values were 39.73 in diabetics without diabetic retinopathy, 36.80 in NPDR and 31.66 in PDR. Again there was no significant association between serum HDL levels and diabetic retinopathy severity (p- value 0.19). 39 of 55 (70.9%) retinopathy patients had low HDL levels and only 2 (3.6%) had high HDL levels which is desirable.

Mean LDL levels in diabetics without diabetic retinopathy was113.13,116.04 in NPDR and 99.33 in PDR. There wasno significant association between serum LDL levels and severity of diabetic retinopathy (p-value 0.58). 22 of 55 retinopathy cases (40%)had optimal levels of LDL. Very high levels were seen only in NPDR cases in ourstudy. ETDRS report 22 states that those diabetics with increased total cholesterol, LDL or Triglyceride levels are more likely to have or develop retinal hard exudates, which can be associated with risk of vision loss, independent of the extent of macular edema. They also stated that the risk was twofold in cases with elevated serum LDL-c and total cholesterol levels[17].

Klein et al inferred that this relationship was not applicable to type 2 diabetics that did not use insulin, and was seen in type 1 diabetics only[18]. This is consistent with our study which was conducted on type 2 diabetics.

Mohan R, Mohan V et al concluded that the mean serum total cholesterol and LDL levels and also the mean total/HDL cholesterol and mean LDL/HDL cholesterol ratios were significantly increased in diabetic maculopathy group as compared to the no retinopathy group. It was also reported that the mean serum HDL and VLDL cholesterol and the triglyceride levels were similar in both groups.Rema et al in 2005 showed association of diabetic retinopathy with total cholesterol and serum triglycerides and also that diabetic macular edema showedacorrelation with high LDL levels.[20]The CURES[6] and WESDR[10] all report that the level of hyperglycemia influences the development and progression of diabetic retinopathy. The WESDR and DCCT[6] studies in type 1 and UKPDSstudy in type 2 showed protective role of glycemic control in prevention and non-progression of diabetic retinopathy. In the CURES Eye Study, for every 2% elevation of HbA1c level, the risk of diabetic retinopathy increased by a factor of 1.7 and in the UKPDS study, for every 1% reduction of HbA1c, the risk reduction in eye complications was 19%.

VI. Conclusion

Diabetic retinopathy was detected in 55%. In our study, 45% had no signs of diabetic retinopathy, 46% had non- proliferative retinopathy and 9% had proliferative retinopathy. No significant association between increasing age and diabetic retinopathy status is seen.

Of the 100 diabetic patients included in the study,65 were males and 35 were females. In all 3 groups males predominated in this study with a decreased male : female ratio in the PDRgroup.

No significance was found with total serum cholesterol levels and severity of diabetic retinopathy.

36.3% of patients with retinopathy had elevated serum total cholesterol levels.

There was no significant association between serum triglyceride levels and severity of diabetic retinopathy. Again there was no significant association between serum HDL levels and diabetic retinopathy severity.70.9% of retinopathy patients had low HDL.

There was no significant association between serum LDL levels and severity of diabetic retinopathy .60% of retinopathy cases had elevated LDL levels. There was significant association between glycosylated haemoglobin levels and staging of diabetic retinopathy. There was no significant association found between fasting blood glucose levels and severity of diabetic retinopathy. There was significant negative association with haemoglobin levels and severity of diabetic retinopathy.

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