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Association of serum lipids and random plasma glucose levels with severity of diabetic retinopathy

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ABSTRACT

Diabetic retinopathy is the most common vision-threatening chronic microvascular, microangiopathy complication of diabetes militias.

We have designed this cross sectional observational study to understand the role of serum lipids and random plasma glucose level with severity of diabetic retinopathy (DR). This study was accomplished with 210 patients that came to us in the diabetic clinic. There were two groups: Group A - All DM patients with no apparent sign of diabetic retinopathy (Grade I) and Group B - All DM Patients with any signs of diabetic retinopathy (Grade II - V). Diabetic retinopathy (DR) was graded according to The International Clinical Diabetic Retinopathy Disease Severity Scale on dilated fundus examination and fundus phtotograpgy. Serum lipids (Total, LDL, and HDL cholesterol and triglycerides) were then assessed according to NCEP ATP III guidlines. The correlation of the severity DR was then assessed with serum lipids and random plasm glucose.

We found that total cholesterol and triglycerides played a detrimental role in the severity of diabetic retinopathy and the likelihood of developing a more severe form of diabetic retinopathy was dependent on their levels (P<0.05). The Association of HDL and LDL with different grades of diabetic retinopathy was also found significant (P<0.05). However, the association of VLDL (P>0.05) was found insignificant. Similarly, the values of total cholesterol, triglycerides and HDL showed a significant rise with severity of diabetic macular edema (DME)

In this present study, the significant association of total cholesterol, triglycerides and HDL with DR thus concludes that along with strict glycemic monitoring and control, the of control of hyperlipidemia is also noteworthy to prevent the progression of DR and DME.

1. Introduction

Diabetic retinopathy (DR) is the most common chronic microvascular, microangiopathy complication of diabetes militias (DM).[1] It is a well-characterized, vision-threatening disease that in due course burdens virtually all patients with this chronic disease. Diabetic retinopathy is set apart by unspectacularly increasing variations in the retinal vasculature, leading to areas of retinal hypoxia and non-perfusion, escalating capillary permeability, retinal micro-aneurysms at the posterior pole and pathologic intraocular angiogenesis and neovascularization.

The prevalence of DR is said to be more than 90 million worldwide and it's the most common cause of blindness in the working class. In India, DR has a prevalence of 5.5% among general population and 21.8% in the diabetic population. It is more common in males as seen in advance

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DR in type 2 diabetes.[2,3]

The correlation of chronic hyperglycaemia and progression of diabetic retinopathy was confirmed by 2 most successful trials- the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS).[4,5] DR and Diabetic Macular Edema (DME) both have certain disruptions in the vascular channels in the form of permeability, failure to perfuse, and flow abnormalities. Changes occurring in the structural and functional configuration of blood vessels and capillaries constitute as the hallmark of DR.[6] Blood retinal barrier (BRB) damage causes damage to endothelial cells, vascular permeability disruptions and damage to permeability of blood vessels. Breakdown of BRB is seen with the damage to the inner cells which causes extracellular fluid to collect in the macula.[7] Certain pathways are responsible for causing diabetic retinopathy. Increase in Polyol pathway flux, vascular endothelial growth factor and insulin like growth factor along with some vascular haemodynamic changes, renin angiotensin aldosterone system activation among many others are potential risks. In DM, increased retinal leukostasis causes damage to the endothelia, reducing the blood supply of retina and causes growth of new blood vessels.[8]

A study by Miyamoto K et al showed that diabetic vascular leakage and lack of perfusion are temporally associated with retinal leukostasis in diabetic rats.[9] Clinically, in diabetic patients, on examination there is impaired visual field, contrast vision and color vision along with dark adaptation.[10] During hormonal changes like pregnancy and adolescence it is seen that diabetic retinopathy further deliberates. This further confirms the association of hormones with DR.

Dyslipidemia has been proposed by earlier studies that its escalating level is a crucial component for DR because high levels of lipid are well known for creating an endothelial dysfunction because of the decreased availability of nitric acid and this is also known for having a part during formation of retinal exudates in diabetic retinopathy. Resources have also concluded that the per-oxidation of the lipids emits proteins inside the vascular walls that are responsible for the local production of the reactive carbonyl species which are responsible for the following activities:

1. Mediating recruitment of the macrophages
2. Cellular proliferation
3. Cellular activation,[11]

Dyslipidemia acts like a multi systemic disorder involving the mechanisms which are central as well as organ specific and previous studies have shown higher levels of LDL cholesterol in comparison to non-diabetics, passing through the retinal blood barrier in the diabetic retinal vessels.[12]

The National Cholesterol Education Program Adult Treatment Panel III has been used for defining and classifying Dyslipidemia as the following:[13]

1. VLDL cholesterol is < 30 mg/dl
2. HDL cholesterol is < 40 mg/dl
3. LDL cholesterol is ≥ 100 mg/dl
4. Triglycerides is ≥ 150 mg/dl
5. Total cholesterol is ≥ 200 mg/dl8

Previous literature studies have reported the effect of lipids to retinopathy or maculopathy can be considered to be an intraepithelial dysfunction which is a very frequent occurrence in the hypercholesterolemic patients. Additionally it was also stated that hyperlipidemia can be responsible for adding DR or DME in regard to endothelial dysfunction and blood retinal barrier failure that has led to the exudation of proteins as well as serum lipids.[13,14]

This study has been conducted to focus on determining the relationship between the plasma lipids and random blood glucose levels with progression of diabetic retinopathy among the type II diabetic patients for the results of this study will be helpful in not only early diagnosis of DR and DME but also can lend additional support to current treatment guidelines recommending aggressive lowering of elevated lipids among diabetic patients.

2. Materials and Methods

The present cross sectional observational study was carried out in the Department of Ophthalmology, Teerthankar Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh for all diabetic patients above the age of 18 years that came to us in the diabetic clinic between the period of January 2021 to June 2022. A total of 210 patients were enrolled and equally divided into two groups on the basis of inclusion and exclusion criteria. Group A (All DM patients with no apparent sign of diabetic retinopathy-Grade I) and Group B (All DM Patients with any signs of diabetic retinopathy-Grade II – V). Both females (n=106) and males (n=104) of variable ages in both groups were considered in the study. All subjects were of Indian ethnicity from western and central Uttar Pradesh. The study was approved by the Institutional Medical Ethical Committee No.TMU/IEC/20-21/113. All subjects were informed about the study and their consents were taken prior to the start of the study.

2.1. Study design

For all patients in group A & B who were included in this study, demographic data was recorded by performing a systematic clinical and ocular examination and using a detailed Performa to acquire patient information. History of past medical and drug history including antihypertensive, oral or IV hypoglycemic drugs and lipid lowering drugs was taken. History of any tobacco, cigarette smoking or alcohol consumption was taken. Blood pressure was recorded. Systemic Hypertension was defined as Systolic

BP >140mmHg and Diastolic BP >90 mmHg. They underwent an initial work-up and following parameters were recorded:

1. Best Corrected Visual Acuity (BCVA
2. Anterior segment examination on Slit Lamp
3. IOP Measurement
4. Dilated fundus examination using 90 diopter lenses at slit lamp and 20 D with Indirect Ophthalmoscope to visualize peripheral retina.
5. Fundus picture was taken using Zeiss fundus camera and grading of DR was done on the basis of the International Clinical Diabetic Retinopathy Disease Severity Scale.
   For each group, the presence or absence of clinically significant macular oedema was also noted.
6. Laboratory procedures:
   (a) Serum Lipid levels
   Serum Triglyceride (TG), Total Cholesterol (TC), High density Cholesterol (HDL), Low density cholesterol (LDL) and Very low density cholesterol (VLDL) measurements, were sent to hospital laboratory.
   (b) Random Plasma Glucose (RBS
   Only those patients who fulfilled our inclusion and exclusion criteria were enrolled in this study and informed consent was taken. Participants with cataracts and corneal opacity were excluded because their fundus photography was unclear and difficult to assess.

All the patients' were then graded according to the International Clinical Diabetic Retinopathy Disease Severity Scale: [12]

1. Grade I: Diabetes with no apparent retinopathy (NDR)
2. Grade II: Diabetes with mild non-proliferative Diabetic Retinopathy (Mild NPDR)
3. Grade III: Diabetes with moderate non-proliferative Diabetic Retinopathy (Moderate NPDR)
4. Grade IV: Diabetes with severe non-proliferative Diabetic Retinopathy (Severe NPDR)
5. Grade V: Diabetes with Proliferative Diabetic Retinopathy. (PDR)

Mild NPDR was graded according to the presence of micro-aneurysms only, Moderate was defined as presence of more than just micro-aneurysms but less than Severe NPDR, Severe NPDR was graded by presence of > 20 intra-retinal haemorrhages in each of 4 quadrants, definite venous bleeding in 2+ quadrants, prominent intraretinal microvascular abnormalities (IRMA) in 1+ quadrant and no signs of proliferative disease. PDR was graded by all the findings of Severe NPDR along with one or more of - Neovascularization or Vitreous/Pre-retinal haemorrhages.

DME was classified as the following: [12]

1. Macular Edema apparently absent (no apparent retinal thickening or hard exudates (HE) in posterior pole) and
2. Macular Edema apparently present (some apparent retinal thickening or HE in posterior pole)
3. And if present it can be graded as:
4. Mild DME (some retinal thickening or HE in posterior pole but distant from centre of the macula),
5. Moderate DME (retinal thickening or HE approaching the centre of the macula but not involving the centre) or
6. Severe DME (retinal thickening or HE involving the centre of the macula).

The patients were divided into 2 groups -

Group A: All DM patients with no apparent sign of diabetic retinopathy (Grade I)

Group B: All DM Patients with any signs of diabetic retinopathy (Grade II - V).

Group A had 105 patients (male=46; female=59) and similarly Group B had 105 patients (male=58; female=47). (Table 1)

2.2. Statistical analysis

Comparison of Mean values of different parameters between Group A and Group B, we used Independent t-Test. To find the Association of Lipid Profile with Diabetic Retinopathy, we used Fixer Exact Test. Association of Lipid Profile with Diabetic Macular Edema, we used Fixer Exact Test. Test is statistically Significant if $P<0.05$.

3. Results

Of the 210 patients, Group A had 105 patients out of which 43.8% (46) were male and 56.2% (59) were female and the average age of this group was 55.06. Similarly, Group B had 105 patients out of which 55.2% (58) were male and 44.8% (47) were female and the average age of this group was 54.67 as seen in Table 1 and Figure 1.

Table 1: Characteristics of the subjects (n=210)

Characteristics		Group A (Diabetic without any DR)	Group B (Diabetic with any sign of DR)
No of Subject		105	105
Age (Average)		55.06	54.67
Sex	Male	46(43.8%)	58(55.2%)
	Female	59(56.2%)	47(44.8%)
RBS (Average)		219.07	292.53
Duration of DM	1-5 Year	58(55.2%)	21(20%)
	6-10 Year	35(33.3%)	43(41%)
	>10Year	12(11.4%)	41(39%)
Systemic Hypertension		43(41%)	61(58.1%)

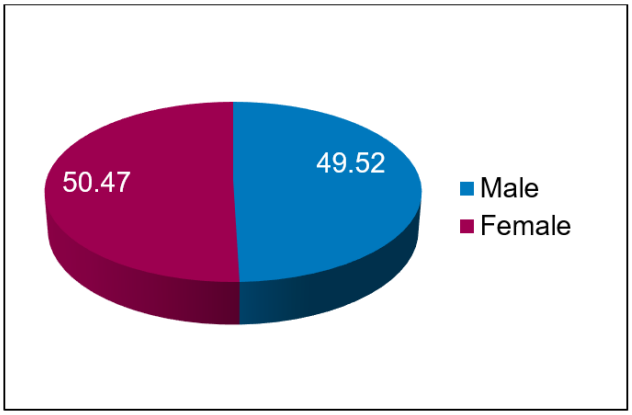

Fig. 1: Diagram showing sex distribution

The mean values of RBS, Triglycerides, Total Cholesterol, High density Cholesterol, Low density cholesterol and Very low density cholesterol between both groups with or without DR showed significant difference as summarized in Table 2.

In Table 3, the association of lipid profile with different grades of diabetic retinopathy was compared and results showed that Total Cholesterol and Triglycerides both showed high significant association with diabetic retinopathy (p=0.001) with mean values of Triglycerides increasing with advancement in disease. Similarly, HDL (p=0.006) showed less probability of progressing to advance disease and LDL (p= 0.019) showed some significance with different grades of retinopathy. However, no such correlation was found with VLDL.

Table 2: Mean values of different parameters between Group A and Group B

Parameters	Group A Mean ± SD	Group B Mean ± SD	P-value
RBS	219.07±64.28	292.53±125.9	0.001
TG	122.32±30.18	255.92±105.96	0.001
TC	164.59±24.18	243.89±76.6	0.001
HDL	58.14±21.15	73.3±28.5	0.001
LDL	80.63±34.62	100.78±38.92	0.001
VLDL	29.68±15.6	42.84±23.52	0.001

Comparison of Mean values of different parameters between both groups, we used Independent t-Test. Significant (P<0.05)

In Table 4, the results show the association of serum lipids with different grades of diabetic macular edema. TC and TG showed high likelihood of developing severe DME (p=0.001) with mean values of TG (338.8±83.5) and TC (299.4±80.6) increasing with advancing macular edema. The results are summarized below.

4. Discussion

Dyslipidemia acts like a multi systemic disorder involving the mechanisms which are central as well as organ specific and previous studies have shown higher levels of LDL cholesterol passing through the retinal blood barrier in the diabetic retinal vessels as compared with the condition of non-diabetic patients.[12] Additionally it was also stated that hyperlipidemia can be responsible for adding DR or DME in regard to endothelial dysfunction and blood retinal barrier failure that has led to the exudation of proteins as well as serum lipids.[11]

This current study is therefore, an effort at early detection of retinopathy at an early stage with the help of Fundus examination and the relationship of serum lipid and RBS to the severity of DR and DME. The aim of our study was to find association of Serum Lipids & RBS with severity of DR.

In our study, when the association of serum lipid with grades of DR was analysed between the patients of Diabetic retinopathy in the group B, it was observed that serum lipid levels were found increased in the grade 5 patients(statistically significant) which indicates the higher risk of developing the retinopathy with the severity of the disease.

Similar to our study, in the study by Cetin et al,[15] it was reported that patients with increased serum total cholesterol and systemic hypertensionwere at increased risk of developing retinal hard exudates and have a correlation between both. In another study reported by Idiculla et al,[16] in 2012 reported that the elevated LDL cholesterol and presence of dyslipidaemia showed association with DME and retinal hard exudates.

On the contrary, Cetin et al,[15] also explained a significant correlation between DM and cholesterol but no relation between serum lipids and DR, which is contradictory to our results.

When we looked into the grade of DME in both the groups 62.9% cases were without Macular Edema, 11.4% with mild DME, 13.8% with moderate DME and 11.9 with severe DME respectively. On comparing the grade of DME between Group A and Group B, 27.6% were suffering with moderate DME, 23.8% were suffering with severe DME and no case was found in group A, which was statistically significant.

In contrast to ours, the study reported by Ozer et al in 2009,[17] postulated that there was no correlation between serum lipid levels and macular edema severity.

In our study, measuring the hemodynamic parameters such as SBP, DBP, RBS, TG, TC, HDL, LDL and VLDL of the patients between both the groups (A &B) were statistically significant.

But the study conducted by Schocket et al,[18] reported that no significant correlations were observed between SBP, DBP and any of the circulatory parameters in diabetic

Table 3: Associations of lipid profile with different grades of diabetic retinopathy

Lipid Profile	Grade 1 NDR	Grade 2 Mild NPDR	Grade 3 Moderate NPDR	Grade 4 Severe NPDR	Grade 5 PDR	P-value
TG	122.3±30.2	171.96±79.36	232.79±93.04	283.17±95.26	318.44±94.47	0.001*
TC	164.6±24.2	188±66.71	236.21±61.51	279.92±63.3	266.28±79.83	0.001*
HDL	58.1±21.2 (p=0.001)	60.76±20.5	67.04±23.79	76.46±23.03	85.44±35.63	0.006*
LDL	80.6±34.6 (p=0.001)	81.4±35.52	113.5±37.28	99.38±38.1	107.44±39.02	0.019*
VLDL	29.7±15.6 (p=0.001)	34.96±20.73	47.92±28.7	40.46±20.24	46.97±22.74	0.160

To find the Association of Lipid Profile with Diabetic Retinopathy, we used Fixer Exact Test. Significant* (P<0.05)

Table 4: Associations of lipid profile with diabetic macular edema

Lipid Profile	Grade0 Macular Edema apparently absent	Grade 1 Mild DME	Grade 2 Moderate DME	Grade 3 Severe DME	P-value
TG	187.6±103.9	243.7±89.6	258.2±91.3	338.8±83.5	0.001*
TC	179.3±63.4	251.7±58.6	249.7±52.9	299.4±80.6	0.001*
HDL	52.9±18	76.3±19.4	72.6±20.3	93.4±37.8	0.001*
LDL	81.9±37.1	111.6±33.1	99.8±41.3	112±37.2	0.014*
VLDL	32.1±18.7	43.5±23.7	43.2±24.2	53.3±23.5	0.012*

Association of Lipid Profile with Diabetic Macular Oedema, we used Fixer Exact Test. Significant* (P<0.05)

patients or control subjects. In diabetics, no statistically significant correlations were found, which is contradictory with our study.

On comparing the serum lipids with DME and the severity of Diabetic Retinopathy in Group B, serum lipids were found to be significantly high with the progression of the disease in Grade 4 NPDR and Grade 5 PDR which is contradictory with many of the past studies, as Schocket et al.,[18] said that independent correlation of lipid was noticed with CSME, however no such correlation was seen with NPDR but in contrast, we found strong associations with severity in PDR as well as DME.

We found a statistically significant correlation of TC, TG and HDL with grades of DR. However, not much association was found with LDL and VLDL. In our study, TC and TG showed high likelihood of developing severe DME.

5. Conclusion

In conclusion, it was noted that there is a statistically significant correlation of TC, TG and HDL and Diabetic Retinopathy especially in grade 4 Severe NPDR and grade 5 PDR along with significant correlation between the mean blood glucose and total cholesterol with the severity of the disease. However, this is a small study with small sample size due to which the data of patients enrolled was also limited. With a larger sample size we can correlate data for a bigger population as India is the diabetic capital of the world. Also, the patients in our study were from a similar geographic area and did not account for areas further away.

6. Conflicts of Interest

None

7. Ethical Clearance

The study was approved by the Institutional Medical Ethical Committee No.TMU/IEC/20-21/113. All subjects were informed about the study and their consents were taken prior to the inception of the study. No animals were violated in this study.

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