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Association of diabetic retinopathy with dyslipidemia: a multicenter study

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ABSTRACT

Introduction: Diabetic Retinopathy (DR) is a retinal vascular disorder that occurs as a complication of diabetes mellitus and is one of the leading causes of blindness in working age adults**.**

Objectives: To measure the lipid profile (total cholesterol, HDL, LDL, triglycerides) in diabetic retinopathy patients and compare and contrast lipid profile among the groups and with controls.

Materials & Methods: This was a cross sectional study conducted from June to October 2010 in three main hospitals of Peshawar and the Al-Shifa Eye Trust hospital Rawalpindi, in which a total of 338 confirmed diabetic patients with or without retinopathy were enrolled. Positive and negative controls were diabetic non-retinopathic (DNR, n = 38) and normal healthy subjects (NS, n = 39) respectively. The study was conducted in. A fasting blood sample was taken to measure lipid profile and other blood parameters. Data was analyzed in SPSS version 17. Student's T test and one-way ANOVA was used to compare the differences of means between different groups. A $p \leq 0.05$ was taken as significant.

Results: Diabetic patients with or without retinopathy had no significant difference in plasma cholesterol concentration as compared to normal subjects (p=0.969). High density lipoprotein concentration was found significantly lower in DNR, Non Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR) patients as compared to normal subjects ($p<0.001$). Low density lipoprotein and serum triglyceride concentration was significantly elevated in DNR, NPDR and PDR patients as compared to normal subjects ($p< 0.001$).

Conclusion: Serum Low-density lipoproteins, TC/HDL ratio, and LDL/HDL ratio were higher in diabetic retinopathy patients as compared to diabetics without retinopathy and normal subjects, findings that may or may not indicate disease association.

Keywords: Diabetic Retinopathy; Cholesterol; High Density Lipoprotein; Low Density Lipoprotein; Triglyceride.

The authors declared no conflict of interest. All authors contributed substantially to the planning of research, data collection, data analysis, and write-up of the article, and agreed to be accountable for all aspects of the work.

INTRODUCTION

Diabetic retinopathy (DR) is the primary reason for visual disorders in the working age population of the Western world.[1] Among other microvascular complications associated with Diabetes Mellitus (DM), DR is the most typical. The prevalence of DR for all adults aged forty and older with polygenic disease is 28.5% within the USA (4.2 million people) and 34.6% worldwide (93 million people).[2,3] The rising prevalence of polygenic disease is expected to increase the prevalence of DR within USA to six million persons by the year 2020, with 1.34 million persons having vision-threatening disease.[4] The substantial worldwide public health burden of DR highlights the importance of constantly checking out new approaches beyond the current standards of Diabetic disease care.[5]

Diabetic retinopathy is characterized by ophthalmoscopically visible tube-shaped structure (and closely associated) lesions. It is staged into a non-proliferative stage (NPR), characterized by tube-shaped structure torsion, retinal hemorrhages, microaneurysms, and lipoid exudates; and a proliferative stage (PR), where fragile new aberrant retinal vessels develop. A very important further categorization in DR is Diabetic Macular Edema (DME), fluid accumulation into the neural tissue layer that ends in abnormal retinal thickening and infrequently cystoid edema of the macula. DME might occur across all DR severity levels of NPDR and PDR and represents the foremost common reason for vision loss in DR. As one of the foremost common microvascular complications of Diabetes Mellitus, DR was the foremost reason for visual problems within the working age cluster.[6] Apart from damaging effects on vision, presence of DR conjointly multiplied the danger of vessel diseases.[7,8] With the increasing morbidity of DM, the worldwide prevalence of DR is expected to extend to 5.4% by 2025. Hyperglycemia is a classical risk factor for DR, though higher glucose level management had disappointing impact on preventing the event of DR.[9] Additionally, the Diabetes Control and Complications Trial[10] reported that only 11% of the overall risk for DR might be explained by glycemic exposure, the remaining 89% could be generated by alternative potential factors.

Therefore, exploring the potential risk factors and also the potential treatments for DR would be imperative.

Early in 1952, Keiding et al[11] foremost proved the involvement of serum lipids in progression of DR. Since then, increasing studies investigating the link between serum lipids and DR progression have been conducted. However, the results remained disputable. In Early Treatment Diabetic Retinopathy Study (ETDRS),[12] elevated serum lipids levels were associated with retinal arduous exudates. The Chennai Urban Rural Epidemiology Study[13] verified the higher serum lipids levels in DR cases. However, the Australian Diabetes, Obesity and Lifestyle study,[14] involving 11,247 adults from 42 areas of Australia, did not show a major association between serum lipids and DR. Similarly, another study[15] found no obvious variations in DR prevalence among patients with completely different total cholesterol (TC) levels. Unexpectedly, higher TC levels showed protecting impact on DR in the Singapore Malay Eye Study.[16] Since most of the previous studies could not ascertain the association of serum lipids with diabetic retinopathy, this study was conducted to outline the association between triglycerides (TG), TC, High density lipoprotein cholesterol (HDL-C), and beta-lipoprotein cholesterol (LDL-C), and to compare the findings across groups.

MATERIALS & METHODS

This was a cross sectional study in which a total of 338 patients with confirmed diabetes and with or without retinopathy were selected. Retinopathy groups were designated as diabetic non-proliferative retinopathy (NPDR) and diabetic proliferative retinopathy (PDR). Positive and negative controls were diabetic but non-retinopathy (DNR, n = 38) and normal healthy subjects (NS, n = 39) respectively. The study was carried out from June to October 2010 in the Outpatients Departments of four main hospitals, including Khyber Teaching Hospital, Hayatabad Medical Complex, Lady Reading Hospital, located in Peshawar city and Al-Shifa Eye Trust Hospital located in Rawalpindi city.

Written informed consents were obtained from all patients presented for complaints of diabetes or diabetes related visual impairment. Ethical approval was given by Pakistan Medical Research Council (PMRC) and National Institute of Health (NIH), Islamabad.

A structured questionnaire was designed to record anthropomorphic and clinical case histories such as age, weight, height etc. Exclusion criteria were systemic diseases, kidney or heart disease, liver malfunctioning, respiratory and gastrointestinal disorders. Inclusion criteria were marked diabetes, adult onset of the disease and visual symptoms.

Patients were advised to have an overnight fast for serum preparation. Blood samples collected from normal healthy subjects, diabetic non-retinopathy and retinopathy patients were processed for serum preparation through standard procedures. Serum collected after centrifugation was stored at -20˚C until analyzed for related serum parameters.

Clinical laboratory examination included determination of the random blood sugar (RBS); fasting blood glucose / sugar (FBS); glycated hemoglobin (HbA1c); serum total cholesterol (TC); triglycerides (TG); high density lipoprotein (HDL); low density lipoprotein (LDL). HbA1c was measured with immunoturbidimetric method. Total cholesterol was measured using the commercial kit (Ecoline, Germany) on Autoanalyzer II (Technicon) by the Liebermann Burchard Reaction using un-extracted sample. High density lipoprotein (HDL) cholesterol was measured in the supernatant obtained by precipitate of low-density lipoprotein (LDL) with heparin and manganese chloride according to the previously described method of Burstein et al. (1970).[17] Serum with triglyceride contents >1000 mg/L tends to produce turbid supernatants or HDL cholesterol was measured in the supernatant obtained after precipitation of VLDL by sodium dodecyl sulphate while the LDL cholesterol was obtained by difference.

Triglycerides were measured by enzymatic hydrolysis using a commercial kit (Boehringer Mannheim Corporation, Germany) on an automated spectrophotometer. Reference Values were: Total cholesterol: 120 – 200 mg/dl; HDL cholesterol: >60 mg/dl; LDL cholesterol: <100 mg/dl.

Data were analyzed by SPSS version 17. Mean and standard deviation were determined for various numerical variables of lipid profile. Student's T test was used to compare the differences of mean between different groups. A p-value of ≤0.05 was taken as significant.

RESULTS

Plasma cholesterol concentration of diabetic and diabetic retinopathy patients did not differ significantly than normal subjects (p=0.969). PDR patients had however highest upper limit of 275 mg/dl (Table 1).

Table 1: Comparison of Total Cholesterol and Serum Lipids between normal subjects and patients (n=338).

#	Biochemical Values	Categories	Mean & SD	p value
1	Cholesterol (mg/dl)	Normal DNR NPDR PDR	165.74 ± 25.62 169.18 ± 38.47 168.32 ± 35.24 168.36 ± 32.54	0.969
2	HDL (mg/dl)	Normal DNR NPDR PDR	51.59 ± 08.65 30.52 ± 06.71* 36.34 ± 10.48* 39.19 ± 09.59*	<0.001
3	LDL (mg/dl)	Normal DNR NPDR PDR	71.30 ± 15.83 70.86 ± 41.66 95.32 ± 28.43* 91.73 ± 28.76*	<0.001
4	TG (mg/dl)	Normal DNR NPDR PDR	116.46 ± 48.54 197.39 ± 46.95* 170.04 ± 68.30* 181.72 ± 82.12*	<0.001

HDL * p<0.001 vs normal; LDL * p<0.001 vs normal; TG * p<0.001 vs normal

High density lipoprotein concentration was found significantly lower in DNR, NPDR and PDR patients as compared to normal subjects (p<0.001). Lowest concentration was found in DNR patients with a median value of 31 mg/dl and differed significantly from levels in NPDR and PDR patients. Low density lipoprotein concentration was significantly elevated in NPDR and PDR patients when compared with DNR patients and normal subjects (p<0.001). Serum triglyceride

concentration was significantly elevated in DNR, NPDR and PDR patients as compared to normal subjects (p<0.001). Intergroup comparison showed significantly greater mean TG concentration in DNR patients as compared to NPDR and PDR patients (p=0.008).

TC/HDL ratio was significantly greater in DNR, NPDR and PDR patients than the normal subjects (p<0.001) as seen in Table 2.

LDL/HDL ratio was significantly greater in DNR, NPDR and PDR patients than normal subjects (p<0.001). LDL/HDL ratio was comparatively lower in diabetic but non-retinopathy patients as compared to diabetic retinopathy patients.

Table 2: Comparison of Total cholesterol, HDL and LDL ratios between normal subjects and patients (n=338).

#	Biochemical Values	Categories	Mean & SD	p value
1	TC/HDL ratio	Normal DNR NPDR PDR	3.32 ± 0.87 0.74 ± 0.51* 5.13 ± 2.20* 4.62 ± 1.71*	<0.001
2	LDL/HDL ratio	Normal DNR NPDR PDR	1.43 ± 0.47 2.32 ± 1.07* 2.88 ± 1.36* 2.51 ± 1.00*	<0.001

TC/HDL ratio * p<0.001 vs normal; LDL/HDL ratio * p<0.001 vs normal

DISCUSSION

A strong association exists between diabetes and dyslipidemia. Patients with elevated cholesterol, triglycerides, and LDL levels have double the possibility of developing diabetic retinopathy and studies show that 30-40% diabetics have further impaired macromolecular metabolism owing to associated renal disorder. On the other hand, some studies have shown no modification in total cholesterol, triglycerides, and HDL-cholesterol concentration in PDR, NPDR, and no diabetic retinopathy groups.[18] Groups of diabetics with associated nephropathy showed higher levels of serum triglycerides and serum cholesterol associated with the duration and severity of diabetic retinopathy.[19]

The Wisconsin Study of Diabetic Retinopathy,[20] conducted in 1979 to 2014, involving 903 diabetic patients, finally found very little effect of TG or HDL-C on the prevalence of proliferative DR. Another global case-control study[21] conducted in 24 sites in 13 countries involving 1202 DR patients demonstrated a rather higher risk of DR in patients with higher TG or lower HDL-C levels. However, after adjustment for hypertension and glycated hemoglobin (HbA1c), no vital results were conferred. Above studies suggested that the consequences of serum lipids were exaggerated by alternative confounders, i.e. HbA1c and hypertension.

Nevertheless, our results were somewhat different from a previous meta-analysis[22] within which higher TG, TC, and LDL-C levels were found in patients with diabetic macular edema (DME). Though, DME was invariably an associated degree indicator of severe stages of DR, we tend to think the role of hyperlipidemia concerned in DR and DME can be totally different to some extent. As previously reported for DME, it is the inflammatory process or ischemia[23] that results in breakdown of the blood-retinal barrier and consequently leakage of serum lipids[24] into the intercellular areas. Whereas for DR, it had been the lipid-induced arteriosclerotic changes[25] that dominantly accounting for the pathology.

Till now, the role of dyslipidemia in DR progression has been comparatively undiscovered. Two prospective studies[26,27] with 5-year follow-ups recorded no vital variations in serum lipid levels between DR progressors and controls. Recently, another longitudinal follow-up study,[28] named Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS II), involving 890 diabetic patients, discovered a three times higher risk of PDR in patients with higher TG levels. Perhaps the following three reasons may partly account for the varied results. First, totally different definitions of DR progression in articles would possibly confound the results. For instance, recent studies[26,27] outlined the progression as a rise of DR severity regardless of DR absence or presence at baseline. Thus, the progressors conjointly enclosed the new-onset ones. In contrast, the SN-DREAMS II outlined people who were diagnosed with pre-existing DR at baseline and deteriorated on follow-up as progressors. Second, the sample size of some studies was too less to attain applied statistical significance. Third, treatment of dyslipidemia throughout the follow-up may conjointly have an effect on the ultimate results. Thus, a lot of large-scale prospective studies are needed to confirm the results.

Although the connection between serum lipids and DR progression remained inconclusive, Fenofibrate was confirmed to benefit the DR cases.[29] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[30] revealed that Fenofibrate may stop the progression of DR while not considerably changing the serum lipids levels, and therefore, the authors have seen that intraretinal lipid transport instead of serum lipids concentrations can be vital for DR progression. As another randomized trial, the Action to Control Cardiac Risk in Diabetes (ACCORD) Eye study[29] discovered comparable effects of dominant DR progression between Fenofibrate treatment, and therefore, the intensive treatment of glycemia. Thus, the Fenofibrate treatment ought to be strongly suggested for the DR cases, and therefore, the actual mechanisms of Fenofibrate still need to be investigated.

CONCLUSION

Though the dyslipidemia of diabetes observed in the study can account for the higher values of important serum lipids of diabetics and normal subjects, differences between the diabetics with retinopathy and those without retinopathy may indicate additional disturbances of lipid metabolism in these patients, in line with previous studies. Nevertheless, any causative role cannot be attributed on the basis of the present study.

RECOMMENDATION

Further in-depth studies with larger sample sizes, stricter classifications of diabetics and retinopathy groups, are likely to provide a more decisive answer to the role of diabetic dyslipidemia in the causation of diabetic retinopathy.

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