·Clinical Research·

Association of serum lipid levels with diabetic retinopathy

Ebru Nevin Cetin[1], Yunus Bulgu[1], Seyfullah Ozdemir[1], Senay Topsakal[2], Fulya Akın[2], Hulya Aybek[3], Cem Yıldırım[1]

[1]Department of Ophthalmology, Faculty of Medicine, Pamukkale University, Denizli, Turkey
[2]Department of Endocrinology, Faculty of Medicine, Pamukkale University, Denizli, Turkey
[3]Department of Biochemistry, Faculty of Medicine, Pamukkale University, Denizli, Turkey
Correspondence to: Ebru Nevin Cetin. Department of Ophthalmology, Faculty of Medicine, Pamukkale University, Denizli, Turkey. cetin.ebru@gmail.com, ecetin@pau.edu.tr
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Abstract

• AIM: To assess the association between serum lipids and diabetic retinopathy (DR).

• METHODS: Sixty –one diabetic patients without retinopathy (NDR), 55 diabetic patients with non – proliferative retinopathy (NPDR) and 75 diabetic patients with proliferative retinopathy (PDR) according to ETDRS grading scale were enrolled in this study. Total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and triglyceride values were compared between the groups.

• RESULTS: The groups were well–balanced in terms of age and gender (P=0.071, P=0.265 respectively). The mean HbA1c values were significantly lower in NDR group than the NPDR and PDR groups(P=0.004, P=0.009 respectively). Mean total cholesterol, triglyceride, LDL, HDL and VLDL levels were not significantly different between the groups (P=0.693, P=0.774, P=0.644, P= 0.910 and P=0.967 respectively, one way ANOVA). Mean total cholesterol, triglyceride, LDL, HDL and VLDL levels were not significantly different between the patients with ME and patients without ME(P=0.622, P=0.113, P=0.955, P=0.735 and P=0.490 respectively, t–test). The mean blood glucose significantly correlated with total cholesterol (r=0.173, P=0.017) and LDL (r=0.190, P= 0.008). The mean HbA1c significantly correlated with total cholesterol (r=0.158, P=0.030) and triglyceride (r=0.148, P=0.042).

• CONCLUSION: Serum lipid levels were not significantly associated with the severity of DR or existence of ME despite the significant correlation between the mean blood glucose, HbA1c and total cholesterol.

• **KEYWORDS:** cholesterol; diabetes mellitus; diabetic retinopathy; high density lipoprotein; low density lipoprotein; macular edema; triglyceride
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INTRODUCTION

Diabetic retinopathy (DR) is a major cause of blindness worldwide. Previous studies have shown that intensive control of risk factors such as high blood sugar and blood pressure can be helpful in reducing the onset and progression of DR [1]. High serum lipid levels have also been proposed as a risk factor for DR. High lipid levels are known to cause endothelial dysfunction due to a reduced bioavailability of nitric oxide and this endothelial dysfunction was suggested to play a role in retinal exudate formation in DR [2]. However large clinical studies showed a discrepancy about the association of serum lipids with the severity of DR or diabetic macular edema (DME). In ETDRS report, high total cholesterol and LDL levels were associated with retinal hard exudates; in the Chennai Urban Rural Epidemiology Study, serum lipids were higher in patients with DR than those without DR [3,4]. On the other hand, those findings were not confirmed by other large studies such as Multi-Ethnic Study of Atherosclerosis and the Australian Diabetes, Obesity, and Lifestyle Study [5,6]. Furthermore, in Singapore Malay Eye study, it was reported that higher cholesterol levels were protective of any retinopathy [7]. Therefore, in this study, we aimed to investigate whether serum lipids have an effect on the severity of DR or DME.

SUBJECTS AND METHODS

Subjects In this retrospective study, the charts of diabetic patients who were seen in the Departments of Ophthalmology and Endocrinology at Pamukkale University were reviewed following institutional review board approval. The patients were divided into three groups according to the retinopathy status based on ETDRS scale [8]. The first group consisted of the patients without retinopathy (NDR), the second group consisted of the patients with non-proliferative retinopathy

(NPDR) and the third group consisted of the patients with proliferative retinopathy (PDR). DME was defined as thickening of retina within one disc diameter of the center of macula or the presence of obvious hard exudates in this region[9].

Methods Blood glucose, HbA1c, triglyceride, total cholesterol, high density cholesterol (HDL), low density cholesterol (LDL) and very low density cholesterol (VLDL) measurements (Cobas 6000 system, Roche-Hitachi Diagnostics, Japan) were recorded for all patients.

Statistical Analysis The difference and the correlation of the parameters between the groups were analyzed by SPSS software program. A P value <0.05 was considered significant.

RESULTS

A total of 191 diabetic patients were included in this study. Table 1 shows age, gender, comorbid pathologies and the number of patients per group.

The groups were well-balanced in terms of age and gender (P=0.071 and P=0.265 respectively). Systemic hypertension was associated in 36.3% (73) of the patients. Thirty-five percent (68) of the patients had DME.

The mean HbA1c values were significantly lower in NDR group than the NPDR and PDR groups (P=0.004 and P= 0.009 respectively). There was no significant difference in total cholesterol, triglyceride, HDL, LDL and VLDL levels between the groups (One way ANOVA, Figure 1).

The mean HbA1c was significantly higher in the patients with DME (8.6±1.6) compared to patients without DME (7.9±1.7, P=0.008). The level of total cholesterol, triglyceride, HDL, LDL and VLDL did not differ significantly according to the existence of DME although higher values were measured in the group with DME (Independent samples test, Figure 2).

DME was not significantly associated with high triglyceride levels (P=0.161), high total cholesterol (P=0.269) or high LDL levels (P=0.875) when lipid profile was stratified according to ETDRS (for triglyceride <204, 205-398, >399mg/dL, for total cholesterol<200, 201-239 and >240mg/dL and for LDL <130, 131-159, >160mg/dL) [3]. DR stages were also not significantly associated with high LDL (P=0.654), total cholesterol (P=0. 421) or triglyceride (P= 0.953) levels.

The mean blood glucose correlated significantly with total cholesterol (r=0.173, P=0.017) and LDL (r=0.190, P= 0.008). The mean HbA1c correlated significantly with total cholesterol (r=0.158, P=0.030) and triglyceride (r=0.148, P=0.042).

DISCUSSION

Dysfunction of the vascular endothelium is regarded as an important factor in the pathogenesis of diabetic vascular complications and has been shown to originate from hyperglycaemia.Hyperglycaemia and its biochemical sequelae either alter endothelial function directly or influence endothelial cell functioning indirectly by affecting the pathways of growth factors, cytokines and vasoactive agents[10]. Endothelial dysfunction is also a well-known finding in

Table 1 Age, gender and coexisting pathologies of the diabetic patients

Parameters	NDR[1] (n=61)	NPDR[2](n=55)	PDR[3] (n=75)
Age (a)	56.2±8.1	58.3±5.3	58.6±5.6
Gender			
Female	26(57.4%)	34(61.8%)	36(48%)
Male	35(42.6%)	21(38.2%)	39(52%)
Systemic hypertension	16(26.2%)	25(45.5%)	29(38.7%)

[1]No diabetic retinopathy; [2]Non-proliferative diabetic retinopathy; [3]Proliferative diabetic retinopathy.

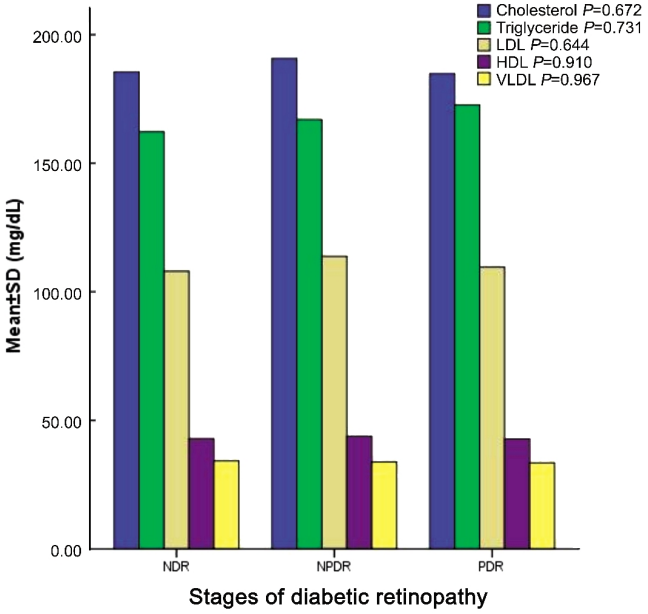

Figure 1 Graph shows the association of serum lipid levels and the stages of diabetic retinopathy (NDR: No diabetic retinopathy, NPDR: Non -proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, one way ANOVA).

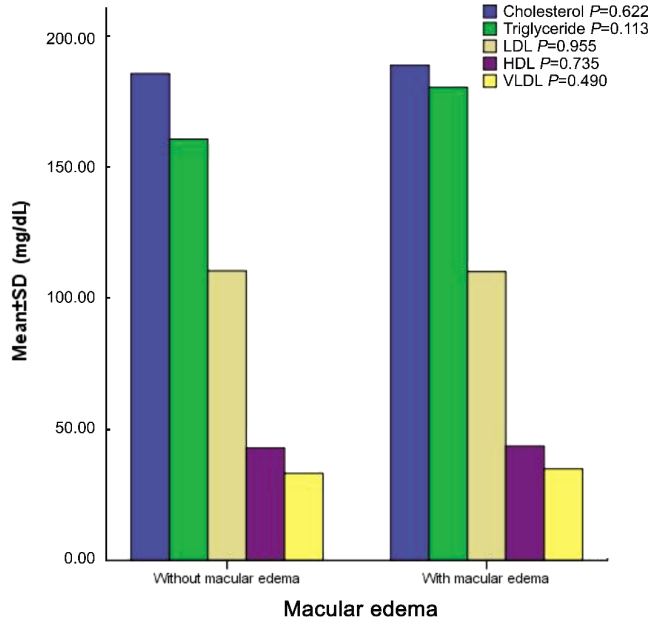

Figure 2 Graph shows the association of serum lipid levels and diabetic macular edema (independent samples test).

hypercholesterolemic patients and it is believed that multiple factors contribute to this, including increased inactivation of nitric oxide by radicals and inhibition of nitric oxide formation by different mechanisms[2]. It was laso reported that the peroxidation of lipids in lipoproteins in the vascular wall leads to local production of reactive carbonyl species that mediate recruitment of macrophages, cellular activation and proliferation, and also chemical modification of vascular proteins by advanced lipoxidation end-products which affect both the structure and function of the vascular wall [11]. Consequently, it was proposed that, hyperlipidemia might contribute to DR and ME by endothelial dysfunction and breakdown of the blood retinal barrier leading to exudation of serum lipids and lipoproteins[12].

There are conflicting reports in the literature regarding the effect of lipid profile on retinopathy or maculopathy. In ETDRS report, Chew *et al* [3] 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. Moreover, patients with elevated serum total cholesterol, LDLC, or triglyceride levels that did not have retinal hard exudate initially, were at increased risk of developing retinal hard exudate during follow-up. Other studies showed that retinal exudates or ME was associated either with LDL or total cholesterol, or both [4, 13-16]. In another study, it was reported that lipid profile was not associated with retinal thickness, mild or moderate DME but only clinically significant ME [12]. On the contrary, similar to our study, Ozer *et al* [17] could not show a correlation between serum lipid levels and macular edema in diabetic patients.

In our study, we found a significant correlation between HbA1c and total cholesterol, but there was no association between serum lipids and DR. The lack of association of lipid profile with severity of DR in this study is compatible with previous data from the Multi-Ethnic Study of Atherosclerosis, which show no association between serum lipids and and DR and the Australian Diabetes, Obesity, and Lifestyle Study [5,6,12]. Similarly, Hove *et al* [18] reported no significant association between DR, triglycerides, HDL and total cholesterol in diabetic population in Denmark. Miljanovic *et al* [15] reported no lipid profile association with progression of DR or with PDR. In another study, there was no association between DR and lipid profile, however, clinically significant ME was found to be associated with serum lipids [12]. Moreover, Singapore Malay Eye study showed that higher cholesterol levels were protective of any retinopathy[7].

On the contrary, in the Chennai Urban Rural Epidemiology Study, Rema *et al* [4] showed that mean cholesterol, triglyceride and non-HDL levels were higher in patients with DR compared to those without DR. However, only triglycerides were independently associated with[4]. Similarly, Ebeling and Koivisto [19] reported that duration, age, and triglyceride level explained nearly half of the variation in the severity of retinopathy [19]. Significant associations between DR and total cholesterol was found in patients in Sweden[20].

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 DM reduced the need for laser treatment for DR [21]. The mechanism, however, seemed to be related to intraretinal lipid transportation rather than serum lipid levels.

It was speculated that serum lipids may have a strong influence only in the severe forms of diabetic microvascular disease. They may not cause direct injury to the endothelium but are rather involved in the pathogenesis of DME only *via* exudation of lipids through damaged retinal vasculature, which occurs at a later stage. Thus, it was suggested that serum lipids are involved in the later, more severe stages than in earlier stages; as an explanation to the discrepancies among the findings of the studies[12].

Another cause of discrepancy might be ethnicity-at least in part. Significant differences in the prevalance of DR and DME between different ethnic groups was reported [22]. Although all ethnic groups are susceptible to the established risk factors of DR such as duration the disease, severity of hyperglycemia and hypertension, ethnicity specific risk factors also may have an effect. Such risk factors may include differential susceptibility to conventional risk factors, insulin resistance, truncal obesity and genetic susceptibility[23]. It may be hypothesized that serum lipid levels may also affect such different populations at a different level, however, this should be supported by further studies.

In conclusion, we found a significant correlation between the mean blood glucose, HbA1c and total cholesterol, however, there was no significant association between serum lipids and the severity of DR. Large multi-centric prospective studies are needed about this subject, especially to clarify the reasons of discrepancies between the findings of studies.

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