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Serum Lipid Levels in Patients with Diabetic Retinopathy

Diyabetik Retinopatili Hastalarda Serum Lipid Seviyeleri

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ABSTRACT

Aim: Diabetic retinopathy is one of the most common microvascular complications of diabetes mellitus. This study aimed to investigate the association between DR and dyslipidemia.

Methods: This retrospectively designed study included 1363 individuals: 352 patients with type 2 diabetes and retinopathy, 553 patients with type 2 diabetes without retinopathy, and 457 healthy individuals. There were 202 and 150 patients with non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), respectively. The groups were compared according to their demographic properties, high-density lipoprotein (HDL), triglyceride (TG), low-density lipoprotein (LDL), glycosylated hemoglobin (HbA1c) and serum fasting glucose levels. MedCalc 15.8 (MedCalc Belgium) was used for the statistical analysis.

Results: The groups were similar in terms of age and sex (p>0.05). Serum HDL levels were lower in patients with DR than in those without retinopathy (p<0.001). Patients with PDR had lower HDL levels than those with NPDR (p=0.011). There was an association between low HDL level and PDR (Odds Ratio: 2.1, %95 CI: 1.4 3.1, p=0.003).

Conclusion: In this study, we observed low serum HDL levels in patients with PDR. Low serum HDL levels are associated with atherosclerosis and other vascular disorders. Patients with diabetes with low serum HDL levels may be more predisposed to retinopathy. Patients with diabetes should be examined for dyslipidemia to delay the development of vascular complications.

Key Words: Diabetic Retinopathy, Dyslipidemia, High-Density Lipoprotein, Proliferative Diabetic Retinopathy.

ÖZ

Amaç: Diyabetik retinopati, diyabetes mellitusun en sık görülen komplikasyonlarından biridir. Bu çalışmanın amacı, diyabetik retinopati ve dislipidemi arasındaki ilişkiyi incelemektir.

Yöntem: Retrospektif olarak planlanan çalışmaya toplam 1363 birey dahil edildi: Tip 2 diyabet ve retinopatisi olan 352 hasta, retinopatisi olmayan 553 tip 2 diyabetli hasta ve 457 sağlıklı birey. Non proliferatif diyabetik retinopati (NPDR) ve proliferatif diyabetik retinopati (PDR) gruplarında sırayla 202 ve 150 hasta vardı. Gruplar, demografik veriler, yüksek yoğunluklu lipoprotein (HDL), trigliserid (TG), düşük yoğunluklu lipoprotein (LDL), glikolize hemoglobin (HbA1c) ve açlık kan şekeri düzeyleri açısından karşılaştırıldı. İstatiksel olarak verilerin değerlendirilmesinde MedCalc 15.2.2 (MedCalc Belgium) istatistik paket programı kullanıldı.

Bulgular: Gruplar yaş ve cinsiyet açısından benzer bulundu (her biri için p>0.05). Serum HDL düzeyleri diyabetik retinopatisi olan hastalarda retinopatisi olmayanlara göre daha düşüktü (p<0.001). PDR olan hastalarda Serum HDL düzeyi NPDR olan hastalara göre daha düşüktü (p=0.011). Retinopatisi olan hastalarda düşük HDL düzeyi PDR ile ilişkili bulundu (OR:2.1, %95 CI: 1.4-3.1, p=0.003).

Sonuç: Bu çalışmada, PDR'si olan hastalarda HDL düzeylerini düşük bulduk. Düşük HDL ateroskleroz ve diğer vasküler problemlerle ilişkilidir. Düşük HDL düzeyi diyabetik hastalarda retinopatiye yatkınlık oluşturabilir. Vasküler komplikasyonların gelişimini geciktirmek için diyabetik hastalar dislipidemi açısından incelenmelidir.

Anahtar Sözcükler: Diyabetik Retinopati, Dislipidemi, Yüksek Yoğunluklu Lipoprotein, Proliferatif Diyabetik Retinopati.

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Introduction

The prevalence of diabetes mellitus (DM) is increasing in our country as well as all over the world [1]. According to the atlas published by the International Diabetes Federation (IDF), there are 382 million persons worldwide afflicted with the disease and these figures are estimated to reach 592 million individuals by the year 2035 [2]. According to the results of the Turkish Diabetes Epidemiology Study (TURDEP-2) conducted on adults over the age of 20 in our country, its prevalence is 13.7% [3].

Diabetes is one of the leading causes of mortality and morbidity in the world, as a result of macrovascular and microvascular complications [4]. Diabetic retinopathy (DR), one of the most important complications of diabetes, is found in 25% of diabetic patients and the condition is also one of the most significant preventable and/or treatable causes of blindness [5].

It has been reported that the frequency of dyslipidemia is approximately twice as high in patients with diabetes [6]. It is one of the most important cardiovascular risk factors that increase the chance of developing atherosclerotic disease [7]. The relationship between dyslipidemia and microvascular complications of diabetes has not been yet fully clarified [8]. In the present study, the association between DR and dyslipidemia was investigated.

Patients And Methods

This study was designed as a retrospective study. The study was launched on 11/03/2015 after receiving the approval of a tertiary hospital Scientific Ethics Committee, numbered 127. The data of the study were collected between April 1 and June 30, 2015. A total of 1363 participants, 905 type 2 DM patients and 457 healthy individuals, who applied to the Internal Medicine and Endocrinology Polyclinics of a tertiary hospital, were included in the study. The study group included 352 patients with DR, 553 diabetic patients without retinopathy in the active control group and 457 healthy individuals in the passive control group. Of the 352 patients with DR, 202 were included in the non-proliferative diabetic retinopathy (NPDR) and 150 in the proliferative diabetic retinopathy (PDR) group. Patients with gestational diabetes, chronic kidney failure, chronic liver disease, malignancies, secondary diabetes, nephrotic syndrome, hypothyroidism, those who use drugs to cause transient dyslipidemia as well as alcohol-dependent patients, were excluded from the study.

The reference values used in the present study were as follows: fasting blood glucose (FBG) 74-106 mg/dL, glycosylated hemoglobin (HbA1c): 4.8-6.1 %, insulin: 2.6-24.9 µIU/mL, alanine aminotransferase (ALT): 0-41 U/L, aspartate aminotransferase (AST): 0-40 U/L, creatinine: 0.70-1.20 mg/dL, high-density lipoprotein (HDL): 35-55 mg/dL, low-density lipoprotein (LDL): 0-100 mg/dL, Thyroid Stimulating Hormone (TSH): 0.27-4.2 µU/ml, total cholesterol: 0-200 mg/dL.

Diabetes Mellitus was diagnosed according to the fasting blood glucose and HbA1c. Diabetes duration, medications, additional diseases, height, waist circumference and patient weight were recorded. The body mass index of all individuals was calculated using the following formula: weight (kg)/height (m)2. Serum urea, creatinine, glucose, ALT, AST, total cholesterol, HDL, LDL, triglyceride (TG) and HbA1c levels of individuals, were screened retrospectively and the results were recorded. In terms of DR, the records of the patients in the ophthalmology clinic were examined. FBG, lipid, ALT, AST and creatinine levels were measured using a Beckman Coulter Synchron LX 20 (Massachusetts, USA). The percentage of HbA1c was analyzed using high-performance liquid chromatography. Patients who were examined by the same physician in the ophthalmology clinic for the diagnosis of DR were included. A fundus camera (Inomi Ophthalmic Instruments, Japan) was used for retinal imaging during the ophthalmological examinations of the patients. The MedCalc 15.8 (MedCalc Belgium) statistical package program was used for the statistical evaluation. The Chi-square test was used to compare demographic data and frequencies between groups. The Kolmogorov-Smirnov test was used for the distribution of data within groups and the t-test or Mann-Whitney U test was used according to distribution patterns to compare the data in both groups. The Odds ratio was calculated to determine the degree of the

relationship between low HDL and proliferative diabetic retinopathy. The results were evaluated at 95% confidence intervals (CIs).

Results

The study and control groups were comparable according to the sex and age (p=0.09 and 0.071, respectively). HDL was found to be lower in the diabetic group than in the control group, while LDL and TG were found to be significantly higher in the diabetic group than in the control group (p<0.001) (Figure 1-3).

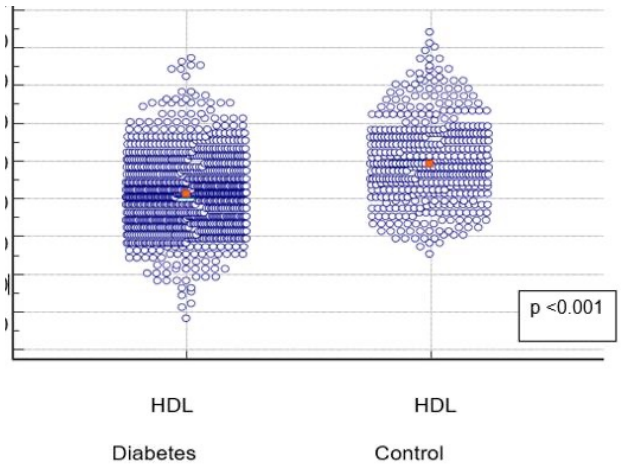

Figure 1. Distribution of serum high-density lipoprotein (HDL) levels in diabetic and control groups (Student t test, p < 0.001).

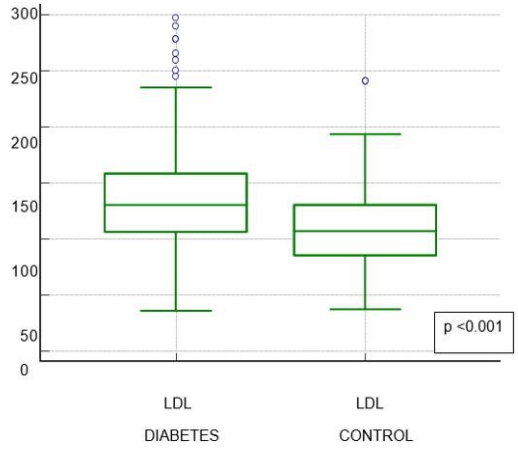

Figure 2. Distribution of serum low-density lipoprotein (LDL) levels in diabetic and control groups (Student t test, p < 0.001).

The systolic and diastolic blood pressure values of the groups were found to be higher in the diabetic group than in the control group (p<0.001). AST levels were significantly lower in the diabetic group (19 ± 8.8) than in the control group (21.2 ± 7.5) (p<0.001). ALT was higher in the diabetic group (21.9±12.7) than in the control group (19.7±9.5) and this value was found to be statistically significant (p=0.037). Creatinine was found to be higher in the diabetic group (0.75±0.25), compared to the control group (0.70±0.15) and was found to be statistically significant (p=0.018, Table 1).

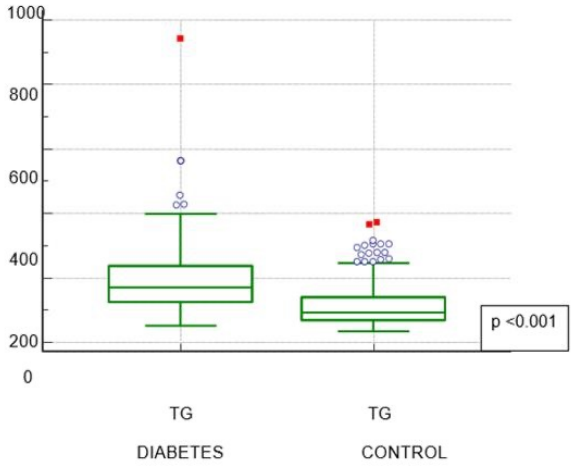

Figure 3. Distribution of serum triglyceride (TG) levels in diabetic and control groups (Student t test, p < 0.001).

When diabetic patients with and without DR were compared, they were found to be similar in terms of sex distribution (p=0.900). The mean age of both groups was 55.8±8.7 and 54.5±10.7 respectively, and no statistically significant difference was found (p=0.05). Patients in both groups were found to be obese and statistically similar (p=0.159). No statistically significant differences were found between systolic and diastolic blood pressures (p=0.084, p=0.133). FBG and HbA1c levels were found to be statistically similar in both groups (p=0.062 and p=0.076, respectively). Fasting insulin levels were found to be lower in patients with DR than in those without retinopathy, and the difference was statistically significant (p<0.001). Diabetes duration of the patients was 10.9±6.4 and 10.1±6.3 in diabetics patients with and without retinopathy. There was no statistically significant difference (p=0.064).

HDL was found to be lower in the group with DR (39.3±10.5) than in the group without DR (42.4±10.4) and low HDL was found to be

Table 1. Clinical Characteristics and Laboratory Values of Diabetes Mellitus and Control Group Patients

	DM	CONTROL	p
	Mean ± SD	Mean ± SD	
Age	55.0±10.0	53.9±13.0	**0.071***
BMI (kg/m²)	32.1±6.3	31.4±6.7	**0.069***
FBG (mg/dl)	187.3±76.0	91.5±10.7	**<0.001***
HbA1c (%)	8.5±1.8	5.4±0.4	**<0.001***
Insulin (µIU/mL)	14.5±17.7	11.0±7.9	**<0.001****
HDL (mg/dl)	41.2±10.5	49.7±11.0	**<0.001***
LDL (mg/dl)	133.0±38.6	108.2±32.6	**<0.001***
TG (mg/dl)	184.3±81.3	109.1±60.0	**<0.001***
Systolic blood pressure (mmHg)	131.8±18.1	112.8±14.4	**<0.001***
Diastolic blood pressure (mmHg)	77.9±10.9	69.6±10.6	**<0.001***
AST (U/L)	19.0±8.8	21.2±7.5	**<0.001***
ALT (U/L)	21.9±12.7	19.7±9.5	**0.037***
Creatinine (mg/dl)	0.75±0.25	0.7±0.15	**0.018***

*Student t test

**Mann-Whitneu U test

Values with p < 0.05 are highlighted in bold.

SD: Standart deviation, DM: Diabetes Mellitus, ALT: Alanine aminotransferase, AST: Aspartate amino transfer, BMI: Body mass index, FBG: Fasting blood glucose, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride.

Table 2. Clinical Characteristics and Laboratory Values of Diabetes Patients with and Without Diabetic Retinopathy

	PDR	NPDR	p
	N (%)	N (%)	
Male	148 (%42)	224 (%40.5)	0.900*
Female	204 (%58)	329 (%59.5)	
	Mean ± SD	Mean ± SD	
Age	55.8±8.7	54.5±10.7	0.052**
BMI (kg/ m²)	31.7±6.2	32.3±6.3	0.159**
FBG (mg/dl)	193.2±77.4	183.5±74.9	0.062**
HbA1c (%)	8.6±1.5	8.5±1.9	0.076**
Insulin (µIU/mL)	13.6±21.6	15.1±14.6	**<0.001*****
HDL (mg/dl)	39.3±10.5	42.4±10.4	**<0.001****
LDL (mg/dl)	131.5±40.5	134.0±37.3	0.230**
TG (mg/dl)	183.8±76.5	184.6±84.2	0.890**
Systolic blood pressure (mmHg)	133.0±18.2	131.0±18.1	0.084**
Diastolic blood pressure (mmHg)	77.2±11.7	78.3±10.3	0.133**
AST (U/L)	18.4±9.3	19.0±7.7	**0.017****
ALT (U/L)	19.4±11.2	23.4±13.3	**<0.001*****
Creatinine (mg/dl)	0.77±0.22	0.73±0.25	0.068**
DM duration (year)	10.9±6.4	10.1±6.3	0.064**

*Chi square test

**Student t test

***Mann-Whitney U testi

Values with p < 0.05 are highlighted in bold.

SD: Standart deviation,DM: Diabetes Mellitus,DRP:Diabetik Retinopati, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, FBG: Fasting blood glucose, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride.

associated with DR (p<0.001). When LDL and TG values were examined, no statistically significant difference was found between the two groups (p=0.230 and p=0.890, respectively).

The groups with non-proliferative DR and PDR were found to be similar in terms of sex distribution (p=0.391). The mean ages of the NPDR and PDR groups were 55.9±8.6 and 55.8±8.7, respectively and were statistically similar (p=0.967).

The body mass index of the patients were found to be statistically similar (p=0.092). There was no statistically significant difference between the FPG and HbA1c values (p=0.430, p=0.802). Fasting insulin levels were similar in both the groups (p=0.721). There was no statistically significant difference between the ALT, AST and creatinine levels (p=0.150, p=0.129 and p=0.094, respectively).

HDL levels were found to be significantly lower in the PDR group than in the NPDR group (p=0.011). PDR was found to be associated with low HDL levels (OR=2.4, 95% CI: 1.5-3.9, p=0.002). There was no statistically significant difference between LDL and TG levels (p=0.795, p =0.736) (Table 3).

Table 3. Clinical Characteristics and Laboratory Values of Patients with Non-Proliferative Diabetic Retinopathy and Patients with Proliferative Retinopathy

	PDR	NPDR	p
	N (%)	N (%)	
Male	67 (%44.7)	81 (%40.1)	0.391*
Female	83 (%55.3)	121 (%59.9)	
	Mean ± Sd	**Mean ± Sd**	
Age	55.9±8.6	55.8±8.7	0.967**
BMI (kg/ m²)	31.1±6.2	32.1±6.7	0.092**
FBG (mg/dl)	197.8±81.3	189.8±74.6	0.430**
HbA1c (%)	8.5±1.4	8.6±1.6	0.802**
Insulin (µIU/mL)	13.7±17.9	13.6±24.2	0.721***
HDL (mg/dl)	37.6±9.3	40.5±11.1	**0.011****
LDL (mg/dl)	132.0±38.1	131.1±42.3	0.795**
TG (mg/dl)	186.0±78.2	182.6±75.2	0.736**
Systolic blood pressure (mmHg)	133.7±18.0	132.5±18.4	0.546**
Diastolic blood pressure (mmHg)	77.0±11.4	77.2±11.8	0.882**
DM duration (year)	11.5±6.2	10.6±6.5	0.182**

*Chi square test

**Student t test

***Mann-Whitney U testi

Values with p < 0.05 are highlighted in bold.

SD: Standart deviation, PDR: Proliferatif Diyabetik Retinopati NPDR: Non Proliferatif Diyabetik Retinopati

BMI: Body mass index, DM: Diabetes Mellitus, FBG: Fasting blood glucose, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride.

Discussion

The serum lipid levels in patients with DR were investigated in this study. HDL levels were found to be lower in patients with DR than in those without retinopathy. Pathophysiological pathways of DR include retinal capillary damage, retinal haemorrhage, retinal exudate, neovascularization and intraretinal microvascular abnormalities [9]. Low levels of HDL cholesterol has also been found to be an effective biomarker for a variety of diabetic complications and coronary heart disease [10]. It is associated with many vascular pathologic mechanisms, notably in the vascular cell migration and proliferation [11].

Anti-inflammatory and anti-oxidant effects of HDL may decrease retinal microvascular damage and according to these hypothesis, the lowest HDL levels may be associated with more progressive retinopathy [12]. In an observational study conducted by Toth et al. with some 72267 newly diagnosed diabetes patients, all lipid fractions were independently associated with microangiopathy and the highest HDL associated with decreased microangiopathy [13]. Sacks et al. reported an association between low HDL and DR in their study [14]. In a study conducted by Agroiya et al., a negative correlation was found between HDL levels and the development of DR [15]. Recent meta-analyses have further confirmed that reduced HDL levels are strongly associated with higher odds of DR, independent of glycemic control, supporting its protective vascular role [16]. Interestingly, Xu et al. (2024) reported an inverted U-shaped relationship between HDL and DR, suggesting that not only low but also excessively high HDL levels may be associated with increased risk, indicating a more complex relationship than previously assumed [17].

Unsurprisingly, serum LDL levels were found to be higher in patients with diabetes in this study. Insulin resistance is one of the most important causes of type 2 diabetes. Insulin resistance at the adipocyte also plays a central role in the pathogenesis of diabetic dyslipidemia, characterized by an increase in LDL particles [18]. Then again, no association has been confirmed between LDL levels and DR. In an epidemiological study conducted on 996 patients with type 1 DM,

no relationship was found between serum oxidized LDL levels, macular edema and DR progression [19]. Benarous et al. analysed 500 patient with DR and reported that LDL cholesterol is not an independent and strong risk factor, for DR [20]. However, a recent meta-analysis by Li et al. reported significantly higher TG and LDL levels among DR cases, underscoring the heterogeneity of findings and the need for standardized lipid assessment in future studies [16].

In the present study, no relationship was found between DR and TG levels. Some studies have shown that elevated TG levels may be associated with hard exudates, increased retinal vascular permeability and macular edema. However, hypertriglyceridemia is not considered an independent and strong risk factor for DR [20]. Likewise, in a prevalence study conducted with 3173 patients in China, no relationship was found between TG levels and DR [21]. Nevertheless, Li et al. (2023) reported in a cross-sectional study that higher TG levels were associated with increased risk of diabetic microvascular complications, including retinopathy, suggesting that TG may still play a contributory role in certain patient populations [22].

In addition to lipid parameters, our study also revealed that insulin levels were significantly lower in patients with DR, while ALT levels were elevated and AST levels decreased in diabetic individuals. These findings may reflect hepatic metabolic alterations or insulin resistance associated with microvascular complications. Li et al. (2024) reported that increased AST/ALT ratio was associated with a higher risk of DR [23]. Similarly, Mantovani et al. (2018) demonstrated that liver enzyme changes were linked to metabolic dysfunction and type 2 diabetes development [24].

Limitation of the study

The main limitation of this study is its retrospective design. The relatively small sample size and the fact that this was not a multicenter study were also limiting factors. In addition, although non-HDL cholesterol could have been calculated, the scope of this study was limited to HDL, LDL, and TG levels. This may also be considered one of the limitations of the study. The evaluation of patients based on one-time lipid results may be deficient and a yearly average would be preferable. In addition, it would have been more suitable to compare the parameters of high blood pressure and smoking, which may have affected patients' lipid profiles. Another limitation is that the study focused only on a microvascular complication without evaluating macrovascular complications such as coronary artery disease, cerebrovascular disease, or peripheral artery disease, which may also be related to lipid metabolism. Although a strong association between DR and lipid levels has been proven in meta-analyses of case-controlled and cohort studies, this has not been confirmed in meta-analyses involving prospective randomized controlled trials. Therefore, further prospective studies on this subject are required.

Conclusion

In this study, it was observed that serum HDL levels were lower in patients with DR, particularly in those with proliferative DR. No significant association was found between DR and LDL or TG levels, in either group. Despite this, the assessment of serum lipid profiles remains significant in patients with DR. Furthermore, the management of dyslipidemia should be considered as part of the overall care strategy in these individuals.

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literature review, supervised the study.

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