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The Effect of Systemic Inflammatory Biomarkers and Dyslipidemia on the Prognosis of Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus: Retrospective Research

Tip 2 Diabetes Mellituslu Hastalarda Sistemik İnflamatuar Biyobelirteçlerin ve Dislipideminin Diyabetik Retinopati Şiddetine Etkisi: Retrospektif Araştırma

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ABSTRACT Objective: To evaluate the levels of serum lipid and inflammatory biomarkers in patients with Type 2 diabetes mellitus (T2DM) and to determine the effects of these biomarkers on the presence and severity of diabetic retinopathy (DR). **Material and Methods:** This retrospective study included 544 patients with T2DM divided into three groups: those without diabetic retinopathy, those with non-proliferative diabetic retinopathy (NPDR), and those with proliferative diabetic retinopathy (PDR). A control group of 154 healthy individuals was also included. The study examined inflammatory indices and lipid parameters in these patients. The changes in parameters in the presence of diabetes and how they vary according to the severity of DR were also investigated. **Results:** The T2DM group consisted of 291 females (53.5%) and 253 males (46.5%), while the control group comprised 81 females (52.5%) and 73 males (47.5%). T2DM patients exhibited significantly higher triglycerides and total cholesterol ($p<0.001$), with further significant elevations observed in patients with NPDR and PDR compared to the NPDR group ($p<0.001$). C-reactive protein, systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), were all significantly elevated in the T2DM group ($p<0.05$). Notably, PDR patients displayed significantly higher SII, SIRI, NLR, and PLR values compared to both patients with NPDR and those without DR ($p<0.05$). **Conclusion:** Inflammation and dyslipidemia may play an important role in the development, course, and treatment of DR. Consideration of these factors during follow-up and treatment may improve clinical care. Prospective studies involving large populations are needed to better observe all these effects and to increase their reliability.

Keywords: Diabetic retinopathy; risk factors; inflammation biomarkers; triglyceride; cholesterol

ÖZET Amaç: Bu çalışmanın amacı, Tip 2 diabetes mellituslu (T2DM) hastalarda serum lipid ve inflamatuar biyobelirteçlerin düzeylerini incelemek ve bu biyobelirteçlerin diyabetik retinopati (DR) varlığı ve şiddeti üzerindeki etkilerini belirlemektir. **Gereç ve Yöntemler:** Bu retrospektif çalışmaya 544 T2DM hastası ve 154 sağlıklı kontrol grubu dâhil edildi. T2DM hastaları kendi içerisinde diyabetik retinopatisi olmayan, non-proliferatif diyabetik retinopatisi (NPDR) olanlar ve proliferatif diyabetik retinopatisi [proliferative diabetic retinopathy (PDR)] olanlar olarak 3 ayrı gruba ayrıldılar. Bu katılımcılarda kan hücreleri ilintili inflamasyon belirteçleri ve serum lipid düzeyleri incelendi. Bu parametrelerin ayrıca diyabet varlığında ve DR şiddetindeki artışla gerçekleşen değişimleri incelendi. **Bulgular:** T2DM'li hastaların 291'i (%53,5) kadın 253'ü (%46,5) erkek iken, kontrol grubunda 81 (%52,5) kadın ve 73 (%47,5) erkek bulunmaktaydı. Trigliserid ve total kolesterol seviyeleri T2DM hastalarında kontrol grubuna göre anlamlı olarak daha yüksekti ($p<0,001$). Trigliserid ve total kolesterol seviyeleri ayrıca NPDR ve PDR hastalarında diyabetik retinopatisi olmayan hastalara göre daha yüksekti ($p<0,001$). C-reaktif proteini, sistemik immün-inflamasyon indeksi, sistemik inflamasyon yanıt indeksi, nötrofil/lenfosit oranı, platelet/lenfosit oranı seviyeleri de T2DM hastalarında daha yüksekti ve bu parametreler PDR'li hastalarda NPDR'li hastalara göre anlamlı şekilde daha yüksekti ($p<0,05$, tüm karşılaştırmalar için). **Sonuç:** Sonuç olarak, inflamasyon ve dislipidemi diyabetik retinopati gelişimi, seyri ve tedaviye yanıtında önemli roller oynayabilecek parametreler olabilirler. Takip ve tedavi sırasında bu faktörlerin göz önünde bulundurulması klinik bakımı iyileştirebilir. Tüm bu etkilerin daha iyi gözlemlenebilmesi ve güvenilirliklerinin artırılabilmesi için geniş popülasyonları içeren prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Diyabetik retinopati; risk faktörleri; inflamasyon biyobelirteçleri; trigliserid; kolesterol

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Diabetes mellitus (DM) is a multifactorial, chronic, systemic metabolic syndrome.[1] Uncontrolled or poorly managed diabetes poses a significant threat to various organ systems, leading to both microvascular and macrovascular complications. Among the microvascular complications, diabetic retinopathy (DR) stands out as a particularly devastating consequence, with its potential to cause irreversible vision loss and even complete blindness disproportionately impacting the working-age demographic on a global scale. This highlights the crucial importance of effective diabetes management to prevent the onset and progression of DR, preserving sight and quality of life for millions of individuals.[1,2] Projections indicate a substantial rise in the prevalence of DR in the coming years, reaching 130 million in 2030 and 161 million in 2045.[3]

DR manifests through a series of characteristic pathological features, including increased vascular permeability, capillary non-perfusion, fibrotic tissue deposition, and neovascularization.[3] Notably, the early stage, known as non-proliferative diabetic retinopathy (NPDR), primarily exhibits pericyte loss in retinal capillaries alongside heightened vascular permeability. In contrast, the advanced stage, proliferative diabetic retinopathy (PDR), is defined by the emergence of new blood vessels within the retina, culminating in the formation of a fibrovascular epiretinal membrane, vitreous hemorrhage, and potentially retinal detachment.[4,5]

DR exhibits a well-defined risk factor profile categorized as either modifiable or non-modifiable. Within the modifiable domain, hyperglycemia, hypertension, hyperlipidemia, and obesity emerge as the most prominent contributors to DR pathogenesis.[4,5] As for the non-modifiable risk factors, the most important are DM duration and age of onset, puberty, and pregnancy.[6,7] Hyperglycemia, a hallmark of diabetes, triggers a cascade of detrimental events in the retina, leading to microvascular complications, inflammation, and neurodegeneration. Disruption of the blood-retina barrier within retinal vascular endothelial cells initiates this pathological process. The pivotal role of inflammatory pathways and abnormal angiogenesis in driving the structural and molecular alterations characteristic of DR has attracted considerable research interest, becoming a central focus of numerous investigations.[8]

The final visual outcome after DR treatment is influenced by multiple factors. With the widespread clinical use of optical coherence tomography (OCT), DR and its complications have become more diagnosable. Anti-vascular endothelial growth factor (anti-VEGF) treatment has significantly changed treatment success.[9,10] Therefore, with early diagnosis and improvements in treatment, the use of biomarkers that can reveal risk factors in patients appears to have become even more important. This study aimed to evaluate the levels of serum lipid and inflammatory biomarkers in Type 2 DM (T2DM) and to determine the effects of these biomarkers on the severity of DR.

MATERIAL AND METHODS

This study employed a retrospective design, analyzing data of the participants who attended the ophthalmology clinic, between August 2022-April 2023. Patient data was obtained from the electronic medical record system of the hospital. The study protocol received approval from the Mersin University Clinical Research Ethics Committee (date: December 29, 2021; number: 2021/798), and all procedures adhered to the ethical principles outlined in the Declaration of Helsinki. Blood test results obtained during a morning fasting state and outpatient clinic summaries for internal medicine consultations, retrieved from the electronic medical records database, were assessed for a two-month window surrounding the date of each ophthalmic examination (i.e., 30 days before or 30 days after). This analysis included only participants with complete laboratory data available within the specified timeframe. T2DM was defined as an eight-hour fasting serum glucose level ≥126 mg/dL or a serum glucose level ≥200 mg/dL at two hours after oral glucose intake or an hemoglobin A1C (HbA1c) level ≥6.5%.

Any ocular disease other than DR that may affect the retinal vasculature (glaucoma, systemic arterial hypertension, hyperviscosity syndromes, oral contraceptive drug users), younger than 35 years of age, cataract surgery after diagnosis of DM, 6.00

Dioptres (D) myopia, 3.00 D hyperopia and 3.00 D astigmatism, axial length shorten than 20 mm and longer than 25 mm, optical media haze that may affect retinal imaging (corneal haze, cataract or vitreous opacity), cholesterol-lowering medication use, and rheumatic disease were excluded. A total of 544 participants with T2DM and 154 age-matched healthy controls were recruited from the internal medicine and ophthalmology outpatient clinics during the study period. All participants presented for routine check-ups within the same timeframe. The participants were divided into 4 groups: healthy participants (control group), T2DM patients without DR (non-DR), T2DM patients with NPDR, T2DM patients with PDR.

Duration of diabetes if any, and body mass index (BMI, kg/m^2) values of all participants were noted. Complete blood count (lymphocyte, neutrophil, platelet, and monocyte counts), glycated haemoglobin (HbA1c), C-reactive protein (CRP), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides (TG) and total cholesterol were measured from the peripheral venous blood. Duration of diabetes was confirmed by review of medical records. Blood cell-associated inflammation parameters, including platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammatory index (SII, neutrophil × platelet/lymphocyte counts) and systemic inflammatory response index (SIRI, monocyte × neutrophil/lymphocyte counts) were calculated with parameters obtained from complete blood count. In addition, monocyte count to HDL cholesterol ratio (MHR) was calculated.

All study subjects' examination records, including a detailed fundus examination using stereoscopic slit-lamp, colour fundus photographs, macular OCT pictures and fundus fluorescein angiography results (HRA+OCT; Heidelberg Engineering) were evaluated. The best corrected distance visual acuity (BCDVA) was measured using the logarithm of the minimum angle of resolution (logMAR) scale. The number of intravitreal anti-VEGF injections administered to T2DM patients for diabetic macular oedema was recorded. Central retinal thickness change (ΔCRT, μm) during intravitreal injection treatment was measured. Two trained masked ophthalmologists (ÖÖ, LD) independently evaluated the T2DM patients based on the examination records, colour fundus photographs, and fundus fluorescein angiography. Using the International Clinical Disease Severity Scale for Diabetic retinopathy classification based on the findings of the Early Treatment of Diabetic Retinopathy Study, T2DM patients were divided into 3 groups those without DR (n=206), NPDR (n=173), and PDR (n=165). In instances of asymmetric retinopathy, patients were categorized according to the eye exhibiting the more severe manifestation on the retinopathy scale.[9]

STATISTICAL ANALYSIS

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Mean and standard deviation values were used to define continuous variables. Two independent variables conforming to normal distribution were analysed by Student t-test and more than two independent variables were analysed by one-way analysis of variance. The relationship between two numerical variables was evaluated with Pearson correlation coefficient. Receiver operating characteristic (ROC) curve was used for continuous variables. Area under the curve (AUC), standard error and 95% confidence interval values were recorded. The relationship between categorical variables was analysed by chi-square or Yates continuity correction where appropriate. Statistical significance level was accepted as $p<0.05$. Analyses were performed using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium).

RESULTS

Of the 544 T2DM patients included in the study, 291 (53.5%) were female and 253 (46.5%) were male. There were 154 healthy participants, including 81 (52.5%) females and 73 (47.5%) men. The mean age was 54.4±7.9 and 53.8±7.1 in T2DM patients and healthy participants, respectively. The T2DM and control groups exhibited no significant differences in gender and age distribution ($p=0.243$ and $p=0.112$, respectively). The lowest mean BMI value was ob-

served in the control group, while the highest BMI value was observed in T2DM patients with PDR (p<0.001). The duration of diabetes was 12.8±4.2 years in patients with PDR, and this value was significantly higher than the other T2DM patients (p<0.001). The demographic characteristics of the participants were presented in Table 1.

HbA1C levels were highest in patients with PDR, however, did not show a significant difference between diabetic patients (p>0.05, post hoc tests). TG and total cholesterol levels were significantly higher in T2DM patients compared to the control group (p<0.001 for two comparisons), and these values were significantly higher in patients with NPDR and PDR than in non-diabetic retinopathy (NDR) patients (p<0.001, for two comparisons). HDL levels did not differ between the control group and T2DM patients, nor between NDR, NPDR, and PDR patients (p>0.05 for all comparisons). The serum biochemical parameters were summarized in Table 2.

The inflammatory indexes, including CRP, SII, SIRI, NLR, and PLR were significantly higher in patients with T2DM (p<0.05, for all comparisons), while LMR and MHR values were not significantly different between the diabetic and healthy participants (p=0.378 and p=898, respectively). In PDR patients, SII, SIRI, NLR, and PLR values were significantly higher than the T2DM patients with

TABLE 1: Demographic data of the different groups.

	NDR (n=206) ($\bar{X}$±SD)	NPDR (n=173) ($\bar{X}$±SD)	PDR(n=165) ($\bar{X}$±SD)	Healthy participants (n=154) ($\bar{X}$±SD)	p value
Age (years)	53.1±6.9	54.3±7.1	55.7±5.9	53.8±7.4	0.112
Gender (M/F)	93/113	82/91	78/87	73/81	0.243
BMI (kg/m^2)	24.6±2.1	25.0±2.4	25.9±1.9	22.7±1.8	**<0.001***
Duration of DM (years)	8.61±4.22	10.8±3.13	12.8±4.38		**<0.001***
BCDVA (logMAR)	0.11±0.24	0.39±0.43	0.57±0.55	0.0±0.0	**<0.001***

*Analysis of variance test; NDR: Non-diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; SD: Standard deviation; BMI: Body mass index; DM: Diabetes mellitus; BCDVA: Best corrected distance visual acuity; logMAR: Logarithm of the minimum angle of resolution.

TABLE 2: Serum biochemical and blood count results of the participants.

	NDR (n=206) ($\bar{X}$±SD)	NPDR (n=173) ($\bar{X}$±SD)	PDR (n=165) ($\bar{X}$±SD)	Healthy participants (n=154) ($\bar{X}$±SD)	p value
HbA1c (%)	6.09±2.99	7.17±2.63	7.65±3.79	5.03±0.86	**0.001**
Total cholesterol (mg/dL)	204.9±26.8	241.8±26.8	269.4±31.3	157.4±22.5	**<0.001***
Triglyceride (mg/dL)	184.5±39.5	199.5±39.5	239.7±63.9	126.1±17.3	**<0.001***
HDL (mg/dL)	55.6±13.9	54.5±12.2	57.3±23.6	55.8±18.1	0.159
LDL (mg/dL)	107.9±31.7	119.9±33.1	131.4±38.2	87±12.6	**<0.001***
CRP (mg/dL)	0.54±0.38	0.64±0.29	0.86±0.31	0.32±0.21	**<0.001***
Neutrophils (10^3/µL)	4.8±0.8	5.1±1.1	5.6±1.7	4.1±0.9	**0.022***
Monocytes (10^3/µL)	0.55±0.26	0.57±0.22	0.56±0.18	0.53±0.22	0.342
Platelets (10^3/µL)	378.9±112.8	391.9±102.1	441.9±135.9	342.5±91.0	**<0.001***
Lymphocytes (10^3/µL)	2.49±0.66	2.51±0.54	2.68±0.79	2.6±0.76	0.583
NLR	2.08±0.67	2.18±0.72	2.22±1.09	1.53±0.24	**<0.001***
PLR	161.05±59.6	172.15±68.1	182.7±89.9	126.8±29.3	**<0.001***
LMR	5.92±3.12	5.81±3.29	5.53±3.73	4.78±1.51	0.378
SII (10^3/µL)	769.7±298.4	861.7±388.1	970.6±551.7	532.6±238.8	**<0.001***
SIRI (10^3/µL)	1.16±0.63	1.19±0.72	1.25±0.77	0.82±0.33	**0.009***
MHR [(10^{3}x mg)/(dL x µL)]	0.011±0.008	0.010±0.008	0.011±0.006	0.009±0.003	0.898

*Analysis of variance test; Bold values are statically significant; NDR: Non-diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; SD: Standard deviation; HbA1c: Hemoglobin A1C; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; MHR: Monocyte to HDL ratio.

NDR and NPDR (p<0.05, post hoc tests). The relationship among the control group, NDR, NPDR, and PDR patients in terms of the inflammatory indexes is shown in Table 3.

The relationship between the blood cell-associated inflammation parameters of the patients with T2DM and the treatment criteria is summarized in Table 4. Accordingly, a positive correlation was observed between the number of intravitreal injections and platelet count., NLR, PLR, SII and SIRI, and a negative correlation with lymphocyte count and LMR (p<0.001). Moreover, BCDVA (logMAR) was positively correlated with platelet count, NLR, PLR, SII, and SIRI (r=0.361) and negatively correlated with lymphocyte count and LMR (p<0.001). In the ROC analysis, HbA1c (AUC=0.602), total cholesterol (AUC=0.857), TG (AUC=0.844), CRP levels (AUC=0.897), PLR (AUC=0.562, p=0.013), SII (AUC=0.599), and SIRI (AUC=0.603) are statistically useful in predicting the development of DR (p<0.001) (Table 5).

DISCUSSION

DR poses a significant threat to public health affecting many people worldwide. The main risk factors for DR have been investigated in many epidemiologic studies and clinical trials. However, there is considerable disagreement about the consistency and strength of these reported risk factors and their impact on treatment response. Therefore, identifying all possible risk factors and assessing their impact is an important research topic.

TABLE 3: Pairwise comparisons of participants.

	P*							
	CRP	**SII**	**SIRI**	**NLR**	**PLR**	**TG**	**HDL**	**LDL**
Controls-T2DM patients	**0.041**	**0.012**	**0.021**	**0.044**	**0.039**	**<0.001**	**0.043**	**<0.001**
Controls-NDR	0.059	0.065	0.098	0.432	0.521	0.032	0.798	**0.041**
Controls-NPDR	**0.037**	**0.041**	**0.037**	0.102	0.147	**0.003**	0.337	**<0.001**
Controls-PDR	**<0.001**	**<0.001**	**<0.001**	**0.012**	**<0.001**	**0.024**	0.543	**<0.001**
NDR-NPDR	0.132	0.078	0.201	0.543	0.104	**<0.001**	0.365	**0.023**
NDR-PDR	**0.009**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.056	**0.003**
NPDR-PDR	**0.011**	**0.024**	**0.013**	**0.024**	**0.002**	0.306	0.236	0.101
NDR -(NPDR-PDR)	0.211	**0.038**	**0.041**	0.101	0.077	**<0.001**	0.187	**0.012**

Bold values are statically significant; *Post-hoc tests; CRP: C-reactive protein; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NDR: Non-diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; LMR: Lymphocyte to Monocyte ratio; MHR: Monocyte to HDL ratio.

TABLE 4: Relationship between the study parameters and treatment criteria.

	Number of IV injections		**BCDVA (logMAR)**		**Δ CRT**	
	r value	**p value**	**r value**	**p value**	**r value**	**p value**
Platelets (10^3/μL)	0.705	**<0.001***	0.719	**<0.001***	0.045	0.503
Lymphocytes (10^3/μL)	-0.685	**<0.001***	-0.641	**<0.001***	0.015	0.826
NLR	0.440	**<0.001***	0.407	**<0.001***	-0.065	0.330
PLR	0.941	**<0.001***	0.847	**<0.001***	0.028	0.083
LMR	-0.253	**<0.001***	-0.218	**0.001***	0.078	0.244
SII (10^3/μL)	0.748	**<0.001***	0.712	**<0.001***	-0.031	0.640
SIRI (10^3/μL)	0.364	**<0.001***	0.361	**<0.001***	-0.115	0.083

*Pearson correlation, the bolds are significant correlations; IV: Intravitreal injection; BCDVA: Best-corrected distance visual acuity; logMAR: Logarithm of the minimum angle of resolution; ΔCRT: Central retinal thickness change; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index.

TABLE 5: Results of ROC analysis in diabetic patients.

	AUC	SE	95% CI		p value
HbA1c (%)	0.602	0.024	0.552	0.648	<0.001
Total cholesterol (mg/dL)	0.857	0.016	0.825	0.889	<0.001
Triglyceride (mg/dL)	0.844	0.018	0.808	0.880	<0.001
HDL (mg/dL)	0.527	0.027	0.475	0.579	0.276
LDL (mg/dL)	0.453	0.025	0.403	0.503	0.062
C-reactive protein (mg/dL)	0.897	0.017	0.865	0.930	<0.001
Neutrophils (10^3/μL)	0.604	0.027	0.551	0.656	<0.001
Monocytes (10^3/μL)	0.518	0.025	0.470	0.567	0.464
Platelets (10^3/μL)	0.649	0.024	0.602	0.697	<0.001
Lymphocytes (10^3/μL)	0.568	0.025	0.518	0.618	0.007
NLR	0.502	0.026	0.451	0.554	0.925
PLR	0.562	0.026	0.512	0.612	0.013
LMR	0.504	0.025	0.456	0.552	0.875
SII (10^3/μL)	0.599	0.026	0.549	0.650	<0.001
SIRI (10^3/μL)	0.603	0.025	0.487	0.585	<0.001
MHR	0.523	0.025	0.474	0.572	0.353

ROC: Receiver operating characteristic; AUC: Area the under curve; SE: Standard error; CI: Confidence interval; HbA1c: Hemoglobin A1C; HDL: High density lipoprotein; LDL: Low density lipoprotein; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index; MHR: Monocyte to HDL ratio.

Several studies have explored the relationship between the dyslipidemia and the severity of DR. The WESDR XIII study found a significant association between elevated total cholesterol and the severity of DR, particularly retinal hard exudate, in insulin-dependent individuals.[11] Similarly, the ETDRS Report 22 initially reported an association between high total and LDL cholesterol levels with increased prevalence of retinal hard exudate.[12] The UKPDS observed an association of higher HDL cholesterol levels with more severe DR.[13] Additionally, the Hoorn Study demonstrated a positive correlation between DR prevalence and high BMI, total cholesterol, and TG levels. Furthermore, they found high total and LDL cholesterol to be associated with the presence of retinal hard exudate.[14] Similar findings were reported in the CURES study, where individuals with DR exhibited significantly higher mean levels of total cholesterol, TG, and HDL cholesterol compared to those without DR, and Uçgun et al. demonstrated significantly higher total and LDL cholesterol levels in patients with exudative diabetic macular edema, a complication of DR.[15,16] These findings suggest a complex interplay between cholesterol and TG levels and the development and progression of DR. In line with the literature, the present study showed that TG and cholesterol values were significantly higher in patients with DR.

The adverse effect of dyslipidemia on the retina has been demonstrated in animals without DM. In one study, amyloid-beta (Aβ) levels were increased in retinal photoreceptors and ganglion cell layers in animals fed on a high-cholesterol diet.[17] The underlying cause is thought to be disruption of the blood-retinal barrier. Hypoxia due to excess Aβ causes structural changes in retina cells. Reactive oxygen species (ROS) production increases due to high levels of Aβ peptide in the retina. High levels of ROS have detrimental effects on ganglion cells. These changes accelerate apoptosis of retinal cells. In addition, dyslipidemia significantly contributes to the promotion of inducible nitric oxide synthase-mediated damage by elevating intracellular calcium concentrations. Calretinin concentrations, a predictor for intracellular calcium content, are increased in retinal neurons of animal models with dyslipidemia.[17] Dyslipidemia is considered an important risk factor for early progression of DR. However, this risk factor is often overlooked in the development of DR. Therefore, dyslipidemia is an independent factor that can help

prevent diabetic complications if the patient is given appropriate treatment.[18]

In a study conducted in China, duration of diabetes was reported as a significant risk factor in patients who developed DR compared to the NDR group.[19] A hospital-based study showed a significant association between DR and LDL cholesterol. Patients with DR had high LDL cholesterol and TG and low HDL cholesterol. Duration of diabetes was longer in patients with DR (7.9 vs. 6.2 years; p<0.001). DR severity is only associated with HDL cholesterol level.[20] In one study in the literature, the prevalence of DR increased with longer disease duration and higher HbA1c. Similar associations are evident in the prevalence patterns of PDR and diabetic macular oedema.[1] In a randomized trial, higher BMI was estimated to be causally associated with a genetically increased risk of DR.[21]

In a study of risk factors, HbA1c was reported as the variable with the strongest effect on DR progression, and this was followed by total cholesterol.[22] In a study reported from Nepal, duration of diabetes (p=0.001), systemic arterial hypertension (p=0.04), abdominal obesity (p=0.015), high LDL cholesterol (p=0.011) and low HDL cholesterol (p=0.012) were associated with DR.[23] In a population-based cross-sectional study, 1,008 patients with DM were evaluated. In this study, BMI, duration of diabetes, total cholesterol, TG and HbA1c concentrations were found to be higher in DR compared to patients NDR.[24] In a study conducted in Jordan, DR was found to be significantly more prevalent in participants who had diabetes for more than 10 years, used insulin, and had a BMI >30 kg/m^2.[25]

In our study, BMI and duration of diabetes were higher in patients with DR compared to NDR and healthy participants. In addition, mean total cholesterol, TG and CRP levels were higher in patients with DR. In the ROC analysis, total cholesterol, TG and CRP levels were statistically significant in predicting DR. However, their associations with post-treatment BCDVA (logMAR) and ΔCRT were not statistically significant. The results of our study and the literature data show that dyslipidemia is a metabolic problem that should be considered in patients with DR. Prevention and treatment of this problem can prevent the development of DR in patients who have not developed DR and prolong life without complications. In addition, treatment of dyslipidemia may also control high BMI, which is another risk factor for DR progression.

The inflammatory response in the retinal vasculature can be triggered by several factors including hyperglycemia, growth factors (VEGF) and advanced glycation end products (HbA1c). Leukocyte adhesion to retinal capillaries (leukostasis) leads to the release of free radicals and proinflammatory cytokines. This increases vascular permeability and leads to loss of capillary pericytes. Therefore, inflammatory processes are critical in the development of DR, especially in the early stages.[26]

In a published study, DR patients had a longer duration of diabetes compared to NDR patients (15.8 years versus 8.9 years), and PLR was found to be higher in DR patients compared to NDR and controls.[27] In another study conducted in patients with DM, neutrophil count and NLR levels were found to be significantly higher in patients with PDR, and SII levels were found to be significantly higher in both PDR and severe NPDR patients.[28] According to Dascalu et al., NLR, MLR, and SII were significantly higher in the PDR group compared to NDR and NPDR, and this study showed that PDR was correlated with NLR [odds ratio (OR): 1.65] and duration of diabetes (OR: 1.3).[29] Additionally, Sasongko et al. found a positive association between increased CRP levels and the presence of vision-threatening DR.[30]

The SII and SIRI are emerging markers gaining traction in the investigation of DR. These indices, calculated from readily available blood parameters, offer a comprehensive assessment of low-grade systemic inflammation, a suspected driver of DR pathogenesis. Studies have demonstrated significant associations between elevated SII and SIRI levels and the presence and severity of DR, suggesting their potential as not only diagnostic aids but also independent risk factors for the development of this vision-threatening condition.[31,32] Furthermore, the combined use of SII and SIRI has shown promise in improving diagnostic accuracy, highlighting their potential as

valuable tools in the clinical management of DR.[33,34] However, further research is warranted to elucidate the specific mechanisms underlying the link between these inflammatory markers and DR, paving the way for potential therapeutic interventions targeting the underlying inflammatory processes. Additionally, two readily available blood markers, the PLR and the NLR, have emerged as potential indicators of this underlying inflammatory state. Elevated PLR and NLR have been associated with an increased risk and severity of DR in several studies.[31-34] These ratios reflect the interplay between pro-inflammatory cells (platelets and neutrophils) and anti-inflammatory lymphocytes, offering a simple and non-invasive assessment of systemic inflammation. While the exact mechanisms remain under investigation, the potential of PLR and NLR as cost-effective screening tools and prognostic markers for DR is attracting significant interest. Our study demonstrated a significant increase in SII, SIRI, NLR, and PLR values not only in individuals with diabetes but also with increasing severity of diabetic retinopathy. T2DM patients with PDR had significantly higher values in terms of these indicators than the other patient groups and the control group. Moreover, in the present study, neutrophil count, platelet count, NLR, PLR and SII were found to be higher in patients with DR. In the ROC analysis for the development of DR in the patient group; Neutrophil (AUC=0.604), platelets (AUC=0.649), lymphocyte counts (AUC=0.568, p=0.007), PLR (AUC=0.562, p=0.013), SII (AUC=0.599), and SIRI (AUC=0.603) were statistically useful in predicting the development of DR. In addition, there was a positive correlation between the number of intravitreal injections and platelet count (r=0.705), NLR (r=0.440), PLR (r=0.941), SII (r=0.748) and SIRI (r=0.364) and a negative correlation with lymphocyte count (r=-0.685) and LMR (r=-0.253) (p<0.001). On the other hand, BCDVA (logMAR) was positively correlated with platelet count (r=0.719), NLR (r=0.407), PLR (r=0.847), SII (r=0.712) and SIRI (r=0.361) and negatively correlated with lymphocyte count (r=-0.641) and LMR (r=-0.218, p=0.001) (p<0.001).

In patients with T2DM, SII, SIRI, NLR, and PLR were positively correlated with the number of anti-VEGF injections applied and negatively correlated with visual acuity. This study suggests that blood cell-related inflammatory markers are associated with the presence and severity of diabetes and DR, and that these markers are elevated in patients who have received more intravitreal injections and have lower visual acuity. Notably, a correlation between anti-VEGF injection-induced macular thickness alterations and blood cell-associated inflammation markers was not established. This lack of association might be attributed to the potential confounding effect of pre-injection macular thickness on the observed macular thickness changes.

According to our results, inflammation plays an essential and critical role in the development of DR. Close monitoring of inflammatory parameters may be a warning for the development of DR. Similarly, it can be a guide when assessing a patient's risk of DR development. Control and treatment of inflammation may slow the development of DR, reduce the need for treatment and improve post-treatment success.

Limitations of the study include the time to onset of DR and the rate of need for treatment could not be assessed due to its retrospective and cross-sectional design. Serum lipid and inflammatory biomarkers were not evaluated according to DR severity, only presence of proliferation was considered. In addition, the effects of anti-diabetic treatments used by the patients were also a confounding factor. Since the study parameters were related to dietary intake, dietary intake was another confounding factor.

CONCLUSION

In conclusion, inflammation, and dyslipidemia can play an important role in the development, course, and treatment response of DR. Consideration of these factors during follow-up and treatment may improve clinical care. Prospective studies involving large populations are needed to better observe all these effects and to increase their reliability in clinic practice.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Levent Doğan, Ömer Özer, Emin Güçlü;* ***Design:*** *Levent Doğan, Ömer Özer;* ***Control/Supervision:*** *Levent Doğan;* ***Data Collection and/or Processing:*** *Ömer Özer;* ***Analysis and/or Interpretation:*** *Ömer Özer, Emin Güçlü;* ***Literature Review:*** *Levent Doğan;* ***Writing the Article:*** *Levent Doğan;* ***Critical Review:*** *Levent Doğan;* ***References and Fundings:*** *Ömer Özer;* ***Materials:*** *Levent Doğan, Ömer Özer, Emin Güçlü.*

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