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Does the eosinophil-to-monocyte ratio predict inflammation in patients with diabetic retinopathy?

Eozinofil/monosit oranı diyabetik retinopatili hastalarda inflamasyonu öngörüyor mu?

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Abstract

Background: Our purpose is to investigate the demographic, clinical, and haematological parameters of patients diagnosed with diabetic retinopathy (DRP) without coronary artery disease and control group.

Materials and Method: This study was retrospective and the information of all patients was retrospectively scanned and their anamnesis was noted from the medical record files. A total of 151 patients, 75 with DRP and 76 in the control group without diabetes and a history of coronary artery disease, were included in the study. For all statistics, a p-value below 0.05 was considered significant.

Results: There was no distinction between the DRP and the other group in terms of clinical and demographic features. The serum glucose (p<0.001), creatinine (p=0.029), and triglyceride (p=0.047) were higher in patients with the DRP group However, eosinophil level (p=0.009) and eosinophil-to-monocyte ratio (EMR) (p=0.003) values were lower in DRP patients. Multivariable linear regression analyses showed serum glucose (OR:1.241, 95% CI [1.087 – 1.418], p<0.001) and EMR (OR:0.966, 95% CI [0.440–2.117], p= 0.030) were potential risk factors for DRP.

Conclusion: In our research, we observed that the serum eosinophil level and EMR in patients with DRP were lower than in other patients and that this, together with the high glucose level, had an independent predictive value for DRP. Future large-scale studies will shed light on this topic.

Keywords: Diabetic retinopathy and Eosinophil-to-monocyte ratio, inflammation

ÖZ

Amaç: Amacımız, koroner arter hastalığı olmayan diyabetik retinopati (DRP) tanısı alan hastalar ile kontrol grubunun demografik, klinik ve hematolojik parametrelerini araştırmaktır. **Gereç ve Yöntem:** Bu çalışma retrospektif olduğundan tüm hastaların bilgileri retrospektif olarak tarandı ve tıbbi kayıt dosyalarından anamnezleri not edildi. Çalışmaya 75'i DRP'li, 76'sı diyabeti olmayan ve koroner arter hastalığı öyküsü olmayan kontrol grubundan olmak üzere toplam 151 hasta dahil edildi. Tüm istatistikler için 0.05'in altındaki bir p değeri anlamlı kabul edildi.

Bulgular: DRP ile diğer grup arasında klinik ve demografik özellikler açısından farklılık yoktu. Serum glukoz (p<0.001), kreatinin (p=0.029) ve trigliserit (p=0.047) DRP grubundaki hastalarda daha yüksekti. Ancak eozinofil düzeyi (p=0.009) ve eozinofil-monosit oranı (EMR) (p=0.003) değerleri DRP hastalarında daha düşüktü. Çok değişkenli doğrusal regresyon analizleri serum glukozunun (OR:1.241, %95 GA [1.087 – 1.418], p<0,001) ve EMR'nin (OR:0.966, %95 GA [0.440–2.117], p=0.030) DRP için potansiyel risk faktörleri olduğunu gösterdi.

Sonuç: Araştırmamızda DRP'li hastalarda serum eozinofil düzeyi ve EMR'nin diğer hastalara göre daha düşük olduğunu ve bunun yüksek glukoz düzeyiyle birlikte DRP için bağımsız bir prediktif değere sahip olduğunu gözlemledik. Gelecekte yapılacak geniş çaplı çalışmalar bu konulara ışık tutacaktır.

Anahtar Kelimeler: Diyabetik retinopati ve Eozinofil/monosit oranı, enflamasyon

Highlights

- Diabetic retinopathy, which develops in an inflammatory process, is a preventable cause of blindness worldwide.
- Eosinophils play an important role, especially in thrombosis formation and the vascular inflammation process.
- In recent years, the eosinophil-monocyte ratio has been associated with mortality in many disease, including coronary artery disease.

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Introduction

Diabetic retinopathy (DRP), a microvascular complication of diabetes, is one of the main occasions of preventable blindness worldwide (1). Unfortunately, damage to the retina vessels occurs in the presence of accompanying factors such as high glucose levels and hypertension. Neovascularization resulting from neural and retinal vascular dysfunction is the most important reason for the development of retinopathy. However, it is tough to know which patients will develop retinopathy and which will not (2).

Neutrophils, lymphocytes, and monocytes, which play a role in systemic inflammation, are thought to be related to the development and progression of atherosclerosis, plaque rupture, vascular dysfunction, and left ventricular restructuring in conditions such as coronary artery disease and cerebrovascular disease (3). In addition to these cells, in recent years it has been observed that eosinophils play an important role, especially in thrombosis formation and vascular inflammation process (4). Diabetic retinopathy, which develops in an inflammatory process, is a disease that can be prevented or its course can be slowed down with early diagnosis and treatment. The parameters that need to be studied to recognize these patients early are still being investigated. In this study, the clinical and laboratory findings of patients without any history of cardiac disease and diagnosed with DRP were compared with patients without diabetes and the relationship between them was examined.

Materials and Methods

Study design

151 patients with diabetes mellitus and non-diabetes mellitus were divided into the DRP group and those without the DRP group.

Patient population

The research was retrospective and the information of all patients was retrospectively scanned and their anamnesis were noted from the medical record files. A total of 151 patients, 75 with DRP and 76 in the control group without diabetes and a history of coronary artery disease, were included in the study.

All patient's demographic details such as age, sex, diabetes mellitus, hypertension, hyperlipidemia and smoking were recorded. Blood specimens were collected from all patients in the fasting situation and routine laboratory tests (absolute blood count, glucose, creatinine, lipid profile, and thyroid function tests) were studied. A standard protocol using auto-analyzer measures the level of glycosylated haemoglobin. Lymphocyte, monocyte, and eosinophil numbers were measured in haematological analyses using automatic devices and expressed as x10 3 cells/µ. EMR was expressed as the absolute eosinophil count/monocyte counts ratio.

When diagnosing diabetes, the American Diabetes Association (ADA) guidelines were taken into account (fasting blood sugar ≥126 mg/dL, 2-hour plasma glucose level in the oral glucose tolerance test ≥200 mg/dL). (5) Body mass index (BMI) was obtained by dividing kilograms by the square of height (weight, kg/height,m2). The logMAR scale was used to best corrected visual acuity (BCVA). Stereoscopic slit-lamp biomicroscopy and indirect ophthalmoscopy were used for All patients who underwent detailed fundoscopic examination using All patients underwent digital fundus photography and fluorescein angiography. The guidelines of the study group (ETDRS) for the early treatment of diabetic retinopathy in Type-2 DM were used for diagnosing and classifying patients with diabetic retinopathy (6). Patients with coronary artery disease, chronic liver or kidney diseases, and who received treatment for arrhythmias, and heart failure due to ischemic/valvular heart disease were excluded from the research. All patients go through cardiovascular examination and electrocardiographic and echocardiography measures were obtained. All patients were examined with a 12-lead ECG (Marquette Mac 1200, GE) in the supine situation after resting for at least 15-20 minutes Considering the advice of the American Society of Echocardiography, each of the patients go through a transthoracic echocardiographic scanning with a commercially accessible device utilized 4 MHz probes (Vivid 9 Pro, GE Vingmed, Milwaukee, Wisconsin, USA) in the left lateral decubitus position. Left ventricular ejection fraction (LVEF) was measured according to Simpson's method (7).

Statistical Analysis

Statistical analysis was implemented using SPSS 20.0 (USA, Armonk, NY, IBM Corporation) from the gathered data analysis, continuous factors are stated as mean ± standard deviation (SD), and categorical factors are stated as a percentage of the group total %. Kolmogorov Smirnov test was utilized to decide whether the factors demonstrated normal distribution Continuous factors with normal distribution were evaluated using Student's t-test. The Chi-Square test was utilized for categorical factors. Univariable and multivariable regression analyses were implemented for the relationship between DRP and creatinine, triglyceride, eosinophil, and EMR. For each of the statistics, a p-value under 0.05 was noted as significant.

Results

There was no dissimilarity between the DRP and the control group in terms of clinical and demographic features **(Table 1).** The average age of the DRP group was (58.8 ± 6.6) years, and the control group was (57.8 ± 9.5) years. The glucose level (210.9 ± 76.2 vs 96.3 ± 31.6 mg/dL, p<0.001), serum creatinine level (0.8 ± 0.2 vs 0.7 ± 2.1 mg/dL, p = 0.029) and serum triglyceride levels (196.8 ± 113.5 vs 162.9 ± 75.7mg/dL, p = 0.047) were higher in patients with DRP group **(Table 1).** The average HbA1c level was 10.1 ± 2.1 % with DRP group. However, eosinophil level (0.2 ± 0.1 vs 0.2 ± 0.2 x103/μL, p = 0.009) and EMR (0.38 ± 0.26 vs 0.52 ± 0.29, p = 0.003) values were lower in DRP patients **(Table 1), (Figure 1).**

Univariable linear regression analyses showed serum glucose level (OR:1.091 95% CI [1.050 – 1.133], p<0.001), serum creatinine level (OR:5.302, 95% CI [1.163 – 24.168], p = 0.031), eosinophil level (OR:0.041, 95% CI [0.003 – 0.506], p = 0.013) and EMR (OR:0.153, 95% CI [0.042 – 0.566], p = 0.005) were associated risk factors for DRP (Table 2).

Multivariable linear regression analyses showed serum glucose (OR:1.241, 95% CI [1.087 – 1.418], p<0.001) and EMR (OR:0.966, 95% CI [0.440 – 2.117], p = 0.030) were potential risk factors for DRP **(Table 2).**

Table 1. Demographic, clinical and hematologic features of patients with diabetic retinopathy and control group.

Variables	Diabetic retinopathy group (n=75)	Control group (n=76)	P-value
Age, years	58.8 ± 6.6	57.8 ± 9.5	0.447
Female gender, n, (%)	44 (58.6)	35 (46.1)	0.143
Body mass index, kg/m²	28.7 ± 5.3	27.4 ± 5.7	0.132
Systolic blood pressure, mmHg	132.4 ± 26.2	128.2 ± 22.76	0.287
Diastolic blood pressure, mmHg	81.4 ± 14.5	781 ± 12.4	0.145
Heart rate beat/min	81.3 ± 13.4	76.7 ± 10.9	0.104
Ejection fraction, %	58.5 ± 5.8	59.7 ± 6.2	0.214
Hypertension, n (%)	34 (45.3)	33 (43.4)	0.207
Current smoking, n (%)	18 (24.0)	16 (21.1)	0.786
Glucose, mg/dL	210.9 ± 76.2	96.3 ± 31.6	<0.001
HbA1c, %	10.1 ± 2.1		
Creatinine, mg/dL	0.8 ± 0.2	0.7 ± 2.1	0.029
Total cholesterol, mg/dL	200.1 ± 44.1	198.1 ± 34.9	0.768
LDL-C, mg/dL	111.3 ± 39.4	119.1 ± 3.5	0.224
HDL-C, mg/dL	49.8 ± 17.1	47.3 ± 8.7	0.298
Triglyceride, mg/dL	196.8 ± 113.5	62.9 ± 75.7	0.047
Vitamin B12, pg/mL	399.3 ± 206.2	382.7 ± 179.3	0.715
TSH, mlU/L	1.6 ± 1.1	1.7 ± 0.9	0.602
C-reactive protein, mg/dL	1.3 ± 2.3	1.5 ± 1.5	0.621
Neutrophil, 10^3/μL	5.8 ± 1.2	6.8 ± 3.8	0.550
Lymphocyte, 10^3/μL	4.8 ± 1.4	4.4 ± 0.9	0.062
Monocyte, 10^3/μL	0.5 ± 0.2	0.4 ± 0.4	0.089
Eozinofil, 10^3/μL	0.2 ± 0.1	0.2 ± 0.2	0.009
EMR	0.38 ± 0.26	0.52 ± 0.29	0.003

Abbreviations: EMR: Eosinophil to monocyte ratio, HDL: High-density lipoprotein, LDL: Low-density lipoprotein cholesterol, n: number of patients, TSH: Thyroid-stimulating hormone.

Table 2. The determination of independent risk factors for DRP with logistic regression analysis

Variables	Univariable		Multivariable	
	OR (95 % CI)	**P-value**	**OR (95 % CI)**	**P-value**
Glucose, mg/dL	1.091 (1.050-1.133)	<0.001	1.241 (1.087 - 1.418)	<0.001
Creatinine, mg/dL	5.302 (1.163-24.168)	0.031	1.175 (0.001 - 12.895)	0.601
Triglyceride, mg/dL	1.004 (1.000-1.008)	0.051	0.992 (0.979 - 1.005)	0.244
Eosinophil, 10^3/μL	0.041 (0.003-0.506)	0.013	177.781 (0.244 - 1.293)	0.066
EMR	0.153 (0.042-0.566)	0.005	0.966 (0.440 - 2.117)	0.030

Abbreviations: EMR: Eosinophil to monocyte ratio.

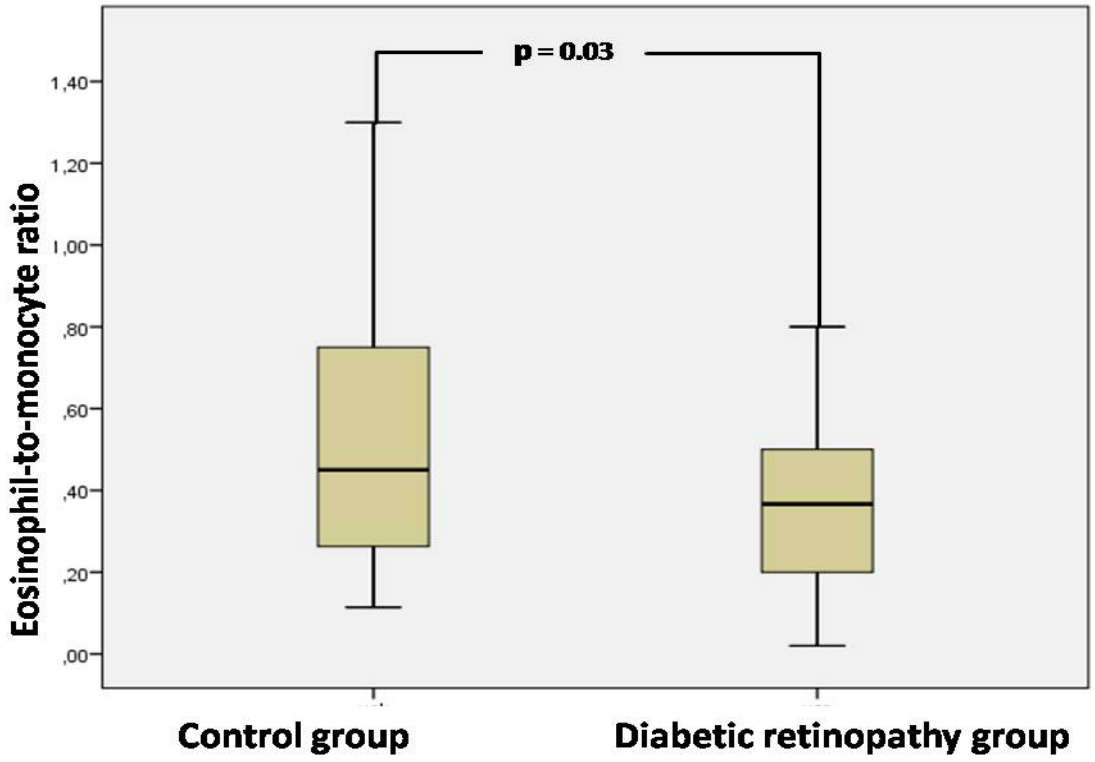

Figure 1. Demonstration of the relation between eosinophil-to-monocyte ratio with diabetic retinopathy and control group.

Discussion

In this study, we observed that the EMR in DRP patients without known coronary artery disease compared to the control group and that this was an independent risk factor in DRP patients.

DRP is an inflammatory process, and it is known that various cells migrate to areas of inflammation and certain cytokines are released (8,9). Eosinophils are increased in various allergic, parasitic and microbial diseases. They secrete immunosuppressive cytokines such as interleukin 10, 4 and 3. Eosinophils are thought to play a role in the secretion of endothelial growth factors, chemokines and some cytokines and promote angiogenesis (10). Eosinophilic activity has also been shown to contribute to fibroblast differentiation in damaged lung tissue and the release of proteases and cytokines, which are critical components of tissue remodeling (11).

Eosinophils also play a role in thrombus initiation, progression, and rupture. Eosinophils help platelets adhere to the beneficial vessel wall and cause the release of immunosuppressive cytokines such as IL-10, IL-4, and IL-13, which have been suggested to modulate the inflammatory response. Eosinophils assist platelets adhere to the injured vessel wall and cause the release of immunosuppressive cytokines such as IL-10, IL-4, and IL-13, which have been suggested to modulate the inflammatory response. Eosinophils infiltrate the myocardium in atherosclerotic plaque rupture, which is involved in the pathogenesis of acute coronary syndrome (10). In the study conducted by Deng et al., it was found that the EMR was lower in patients presenting with acute coronary syndrome and was associated with long-term mortality (12,13).

In our research, we observed that eosinophil count and EMR were lower in patients with DRP. There may be several reasons why the eosinophil rate was lower in our study than in the control group. DRP is an inflammatory process, and blood cell accumulation in the area triggers angiogenesis. Serum eosinophils also act with these inflammatory cells and gather in the inflamed area, which may explain the decrease in serum eosinophil levels (13,14,15).

Monocytes are pro-inflammatory cells, and where there is inflammation, they release cytokines and adhesion molecules such as interleukin 6, TNF alpha, and other cells into the environment through immune mediation (14). However, the number of eosinophils is normally less than in monocytes, so the decrease in eosinophils in the serum becomes more pronounced than in monocytes, causing the eosinophil-monocyte ratio to increase. During an

inflammatory process, reasons such as cellular destruction in peripheral tissue, suppression of mature eosinophil migration from the bone marrow, suppression of eosinophil production, and accumulation of eosinophils in inflammatory areas may cause a decrease in eosinophils. Also, under acute stress, adrenal glucocorticoid and epinephrine secretion may be related to eosinophil reduction (16,17)

In our study, the EMR was found to be 0.38 in patients with DRP, and since there is no other study similar to our study, a comparison could not be made. However, Kulahçıoğlu et al. In their study, they found that in patients with high-risk pulmonary embolism, the EMR was lower than 0.03 and was an independent predictor of all-cause mortality (4).

One of the inflammatory parameters investigated in diabetic patients is serum C peptide level. C-peptide is a molecule that co-excretes with insulin and is used to estimate the insulin reserves of diabetic patients. The role that C-peptide plays in the human body is not clearly known, but it varies depending on the target tissue, pathophysiological conditions, and interaction with bioactive molecules. Toprak et al. found a relationship between C-peptide level and acute coronary syndrome, coronary artery ectasias, contrast-associated nephropathy and no-reflow phenomenon (18,19,20,21)

Limitations

In this research, the number of patients was restricted and this study was a single-center. Patients were not followed up for adverse events Since it was a retrospective study. Since there has been no such study before, adequate comparisons with other studies could not be made. Since c-peptide kits were not available in our center, c-peptide levels could not be measured. Adding the c peptide level in the participants could have made the study more enriching.

Conclusion

In our study, we found that the serum eosinophil level and EMR in patients with DRP were lower than in other patients and that this, together with the high glucose level, had an independent predictive value for DRP. Eosinophils are one of the inflammatory cells, and while their serum level increases in infectious diseases, their level decreases in thrombus or non-infectious inflammations. It is thought that large-scale studies on this topic will help us understand the role and importance of eosinophils in inflammation.

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