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The relationship between neutrophil lymphocyte ratio and diabetes control in patients with type 2 diabetes mellitus

Tip 2 diabetes mellituslu hastalarda nötrofil lenfosit oranı ile diyabet kontrolü arasındaki ilişki

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ABSTRACT

Aim: The current study was purposed to examine the association between NLR and the control of glucose in patients with T2DM. We also aimed to reveal correlations between microalbuminuria, Mean Platelet Volume (MPV), Red Blood Cell Distribution (RDW), and glycosylated hemoglobin (HbA1c).

Materials and Methods: It was a retrospective study arranged in Ege University, in Endocrinology Department. We collected the fields of 198 patients having type 2 diabetes mellitus (T2DM), and they were categorized into two groups, patients with controlled T2DM (Hba1c≤7%) (n=82) and uncontrolled T2DM (Hba1c>7%) (n=116).

Results: There were no statistically significant differences between NLR, RDW and MPV in two groups (p=0.123, p=0.298, p=0.595 respectively). Duration of T2DM 5 years and below and after 5 years between two groups was statistically important (p=0.002). NLR was found higher in uncontrolled T2DM than controlled T2DM, but not statistically significant. Receiver operating characteristic curve of NLR, RDW, MPV, WBC were not found significant (p>0.05).

Conclusion: Our study revealed that duration of T2DM may predict microalbuminuria, and evaluated the relationship between RDW, MPV, NLR and Hba1c, microalbuminuria levels together in the patients with T2DM. According to NLR, RDW and MPV levels, we did not detect any statistically differences between uncontrolled T2DM than controlled T2DM.

Keywords: Neutrophil lymphocyte ratio, type 2 diabetes mellitus, white blood cell count, microalbuminuria.

ÖZ

Amaç: *Diyabetik hastalarda Nötrofil lenfosit oranı (NLR) ve glukoz kontrolü arasındaki ilişkiyi araştırmayı amaçladık. Ayrıca Ortalama Trombosit Hacmi (MPV), Kırmızı kan hücre dağılımı (RDW), mikroalbüminüri ve glikozile hemoglobin (HbA1c) arasındaki ilişkiyi saptamaya çalıştık.*

Gereç ve Yöntem: *Bu çalışma Ege Üniversitesi Tıp Fakültesi Endokrinoloji Bilim Dalı'nda gerçekleştirilen retrospektif bir çalışmadır. Tip 2 diabetes mellitus (T2DM) olan 198 hastanın tıbbi kayıtlarını aldık ve bu hastalar kontrollü T2DM li hastalar (Hba1c≤%7) (n=82) ve kontrolsüz T2DM li hastalar (Hba1c>%7) (n=116) olarak iki gruba ayrıldı.*

Bulgular: *NLR, RDW ve MPV'de iki grupta istatistiksel olarak fark yoktu (p=0,123, p=0,298, p=0,595). İki grup arasında 5 yıl ve altı ve 5 yıl üstü T2DM süresi istatistiksel olarak anlamlıydı (p=0,002). NLR, kontrolsüz T2DM'de kontrollü T2DM'den daha yüksek bulunsa da, istatistiksel olarak anlamlı fark yoktu. NLR, RDW, MPV ve WBC'nin ROC eğrisi analizi anlamlı değildi (p>0.05).*

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Sonuç: *Çalışmamız T2DM süresinin mikroalbüminüriyi öngörebileceğini ortaya çıkarmıştır ve T2DM'li hastalarda RDW, MPV, NLR ve Hba1c, mikroalbüminüri düzeyleri arasındaki ilişki de değerlendirilmiştir. NLR, RDW ve MPV düzeylerine göre kontrolsüz T2DM ile kontrollü T2DM arasında istatistiksel olarak herhangi bir farklılık tespit etmedik.*

Anahtar Sözcükler: *Nötrofil lenfosit oranı, tip 2 Diabetes Mellitus, Beyaz Kan Hücresi, Mikroalbüminüri*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disorder and it is a health problem in public at an important rate worldwide (1).T2DM is considered a serious disease and it may cause microvascular complications consisting of nephropathy, retinopathy, and neuropathy, besides macrovascular complications for instance, cerebrovascular disease, coronary artery disease and peripheral artery disease (2). In T2DM, hyperglycemia and insulin resistance are related with the stimulation of pro-inflammatory processes (3). Pro-inflammatory responses caused by various immune cells give rise to low-grade inflammation (4). Adiposity and obesity are usually contributory factors for T2DM risk, and inflammatory responses are related with the complications of T2DM and its progression (5).

Neutrophil lymphocyte ratio (NLR) is a significant indicator of systemic inflammation (6). Additionally, NLR is an indicative marker in various malignancies and in acute coronary syndrome (7-10). Moreover, NLR points out systemic inflammation in chronic kidney disease and diabetic nephropathy (11, 12). It could be calculated easily and it is relatively cost-effective (6). Moreover, NLR can increase in patients with T2DM and this increase may demonstrate the inflammatory burden of T2DM (13).

The current study was purposed to reveal the relationship between NLR and the control of glucose in patients with T2DM. We also aimed to reveal correlations between Mean Platelet Volume (MPV), glycosylated hemoglobin (HbA1c), Red blood cell distribution (RDW), and microalbuminuria. Patients with T2DM were grouped as patients with controlled T2DM (Hba1c≤7%) and uncontrolled T2DM (Hba1c>7%) (14).

MATERIALS and METHODS

This retrospective study was arranged in Ege University, in Endocrinology Department. We collected the data of 198 patients who applied to the outpatient polyclinic between January 2021 and June 2021, and they were classified into two groups; patients with controlled T2DM (Hba1c≤7%) (n=82) and patients with uncontrolled T2DM (Hba1c>7%) (n=116). The inclusion criteria were comprising patients with T2DM>40 years old with T2DM. Patients having acute infection such as diabetic foot infection, leukocytosis, anemia or leukopenia, having abnormal erythrocyte sedimentation rate and/or C-reactive protein levels, uncontrolled and secondary hypertension, cirrhosis, heart failure, kidney failure, patients taking steroids, and patients having malignancy or a history of malignancy were excluded.

We collected demographics, laboratory and clinical data of patients. Total cholesterol, low density lipoprotein (LDL), High density lipoprotein (HDL), triglycerides (TG), creatinine, HbA1c, fasting plasma glucose, Hemoglobin (Hb), White Blood Cell Count (WBC), RDW, platelet, MPV, Hematocrit (Htc), and microalbuminuria levels were obtained retrospectively. RDW and MPV levels were released from blood count of patients. NLR was estimated by dividing the absolute count of neutrophil by the absolute count of lymphocyte. All blood samples were obtained in the morning.

Ethics Committee of Ege University approved the protocol (21-11T/7). Informed consents were taken from all patients.

Statistical Analysis

Descriptive statistics of numerical variables were represented with median and interquartile range; frequencies were used for categorical variables. Normality assumptions were estimated by using the Shapiro-Wilk test. Because the data were not normally distributed, the correlations between variables were examined with the Spearman's correlation coefficient. The Wilcoxon rank-sum test was used to conclude the difference between two independent groups of controlled and uncontrolled T2DM. Receiver operating characteristic (ROC) curve was used for prediction of microalbuminuria (+/-) in NLR, WBC, RDW, MPV. Univariate logistic regression analysis was used to detect predictors for microalbuminuria (+/-). A p-value of less than 0.05 was evaluated statistically significant. IBM SPSS version 25.0 were performed in all statistical analyses (Chicago, IL, USA).

RESULTS

The demographic features of all patients were demonstrated in Table-1. Median age of the patients with uncontrolled T2DM was higher than the controlled T2DM. However, the difference was not significant (60 (14) vs. 56 (18), p=0.127). There were no differences in NLR, RDW and MPV between two groups (p=0.123, p=0.298, p=0.595; respectively). Duration of T2DM 5 years and below, and after 5 years between two groups was statistically significant (p=0.002).

Whereas the numbers of WBCs, PLT, Hb in the patients with uncontrolled T2DM were higher than those with controlled T2DM, but there was no statistically significant difference (p=0.107 vs. p=0.113, p=0.573). A weak positive correlation was displayed between HbA1c and WBC (r=0.146; p=0.040) (Figure-1)

NLR was found higher in uncontrolled DM than controlled DM, but not significant (p=0.123) (Figure-2). There was no statistically significant difference in terms of NLR levels between patients with taking insulin and patients without taking insulin (1.89 (0.94) vs. 1.68 (1.03); p=0.239). A Spearman's correlation test revealed that NLR was significantly correlated with fasting plasma glucose, age, creatinine, Hb, and RDW (r=0.197, p=0.005; r=0.177, p=0.013; r=0.202, p=0.004; r=-0.179, p=0.012; r=0.202, p=0.004; respectively). We found a significant weak correlation between WBC and NLR (r=0.264, p<0.001).

Results of ROC analysis for NLR, RDW, MPV, WBC were found not significant (p>0.05), displayed in Figure-3 and Table-2. Moreover, among diabetic patients 33 (16.5%) had microalbuminuria of various levels and 167 (83.5%) did not. The NLR of patients having microalbuminuria with controlled T2DM was higher than uncontrolled T2DM, however the difference was not significant (1.81 (0.97) vs. 1.71 (0.96); p=0.575).

Table-1. Demographic characteristics and laboratory parameters of the study population

Parameters[a]	Controlled Diabetes Mellitus (Hba1c≤7)(n=82)	Uncontrolled Diabetes Mellitus (Hba1c>7)(n=116)	p
Age (years)	56 (18)	60 (14)	0.127
Sex (Male/Female) (n %)	38 (46.3)/44 (53.7)	57 (49.1)/59 (50.9)	0.698
Duration of DM (month)	51 (140)	120 (149)	0.005*
Medical Treatment (n %)			
-OAD	34 (41.5)	25 (21.6)	
-Insulin	37 (45.1)	86 (74.1)	<0.001*
-None	11 (13.4)	5 (4.3)	
FBG (mg/dL)	119.00 (34)	171.50 (86)	<0.001*
HbA1c (%)	6.30 (0.8)	8.10 (2.28)	<0.001*
TC (mg/dL)	185.50 (59.00)	180.50 (69.00)	0.285
TG (mg/dL)	139.50 (109.00)	143.00 (108.00)	0.649
LDL (mg/dL)	103.00 (53.00)	112.50 (58.00)	0.103
HDL (mg/dL)	46.00 (17.00)	44.00 (15.00)	0.377
HB (g/dL)	13.65 (2.5)	14.00 (3.1)	0.573
WBC (10^3/µL)	7.08 (2.06)	7.57 (2.18)	0.107
PLT (10^3/µL)	247.50 (82.00)	268.00 (78.00)	0.113
RDW (%)	13.10 (1.53)	13.20 (1.40)	0.298
MPV (fL)	10.50 (1.22)	10.30 (0.90)	0.595
Serum creatinine (mg/dL)	0.84 (0.25)	0.80 (0.25)	0.211
Microalbumin/creatinine ratio (mg/day crea)	9.05 (18.35)	10.45 (15.30)	0.904
NLR	1.68 (0.77)	1.83 (0.99)	0.123

DM: diabetes mellitus; NLR: neutrophil/lymphocyte ratio; FBG: fasting plasma glucose;
TC: total cholesterol; TG: triglyceride; HB: hemoglobin; WBC: white blood cell; PLT: platelet; HbA1c: glycated hemoglobin; OAD: oral antidiabetic drugs.
[a]Median (IQR)

Table-2. Receiver operating characteristic (ROC) curve analysis for prediction of microalbuminuria using NLR, WBC, RDW, MPV.

Parameter	AUC	Standard Error	P-value	95% Confidence Interval (Lower Bound)	95% Confidence Interval (Upper Bound)
NLR	0.510	0.055	0.852	0.403	0.618
RDW	0.562	0.055	0.261	0.454	0.670
MPV	0.583	0.061	0.133	0.463	0.703
WBC	0.525	0.061	0.650	0.405	0.645

NLR: neutrophil/lymphocyte ratio; WBC: White Blood Cell Count, MPV: Mean Platelet Volume, RDW: Red blood cell distribution

Table-3. Univariate logistic regression analysis results of the possible predictors for microalbuminuria.

Parameters	Univariate	
	OR (95% CI)	p-Value
-Gender	1.520 (0.709-3.257)	0.282
-NLR	1.016 (0.658-1.569)	0.942
-RDW	1.072 (0.86-1.337)	0.535
-MPV	1.436 (0.937-2.203)	0.097
-Duration of DM	1.004 (1.001-1.007)	0.014 *
-Age	1.023 (0.983-1.064)	0.258
-FBG	0.997 (0.990-1.004)	0.439
-TC	0.998 (0.990-1.007)	0.695
-TG	1.000 (0.998-1.003)	0.791
-HDL	0.984 (0.958-1.011)	0.245
-LDL	1.000 (0.990-1.011)	0.937
-HbA1c	1.000 (0.835-1.198)	0.999
-creatinine	1.225 (0.162-9.245)	0.844
-WBC	1.079 (0.862-1.351)	0.506
-HB	0.779 (0.627-0.968)	0.024*
-PLT	1.002 (0.996-1.007)	0.601

DM: diabetes mellitus; NLR: neutrophil/lymphocyte ratio; FBG: fasting plasma glucose;
TC: total cholesterol; TG: triglyceride; HB: hemoglobin; WBC: white blood cell; PLT: platelet; HbA1c: glycated hemoglobin
OR: Hazard Ratio; CI: Confidence Interval

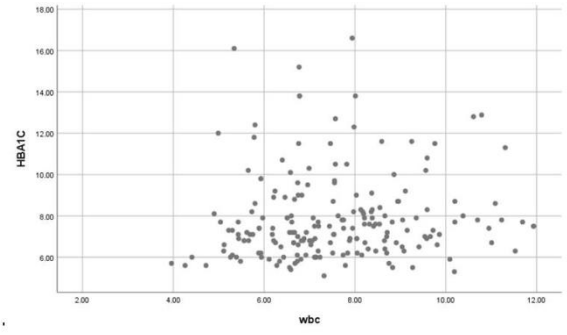

Figure-1. Scatter plot showing a positive weak correlation between HbA1c and WBC (r=0.146,p=0.040; Spearman's correlation coefficient)

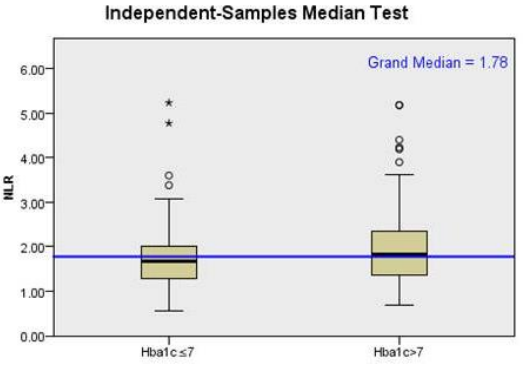

Figure-2. Box plot of NLR in the study groups. DM: Diabetes mellitus

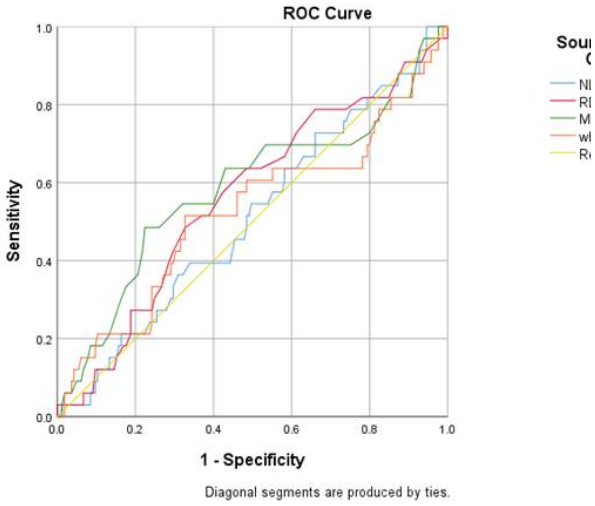

Figure-3. Receiver operating characteristic curve (ROC) analysis of NLR, RDW, MPV for microalbuminuria prediction.

DISCUSSION

Our study found that high levels of NLR had correlation with WBC. In addition, NLR was significantly correlated with fasting plasma glucose, creatinine, Hb, age, and RDW. Moreover, we demonstrated a significant correlation between WBC and HbA1c as well as NLR and WBC. Thus this study might suggest that WBC could be a new marker of control of diabetes mellitus.

Recently, many reports have revealed that chronic inflammation plays a significant role in the progress of T2DM (15). Chronic inflammation results in the pathogenesis and advancement of T2DM by means of immunologic inflammatory mechanisms (16, 17). Over secretion of some mediators and the injury of endothelium leads to complications of T2DM (18). The control of blood glucose is of great importance in preventing macrovascular and microvascular complications; and cut-off value of HbA1c is calculated as ≤7 % in T2DM (14).

Microalbuminuria is one of the microvascular complication of diabetes. T2DM with microalbuminuria usually proceed to diabetic nephropathy and proteinuria. It was found that both RDW and NLR had a positive predictive importance for microalbuminuria. Moreover, currently Jaaban et al (19) revealed that a positive correlation between albuminuria and NLR levels. Another study displayed that NLR could be a predictive indicator for early stage diabetic nephropathy (20). However, in our study, NLR, RDW, MPV did not have predictive value for microalbuminuria in T2DM.

WBC count is a pivotal marker of inflammation, and macro and microvascular complications of T2DM for example diabetic nephropathy (21). It may be related with various cytokines for instance transforming growth factor beta, IL-6, and tumor necrosis factor α released by activated leukocytes (22, 23). Vascular damage, atherosclerosis, endothelial dysfunction may occur due to cytokines and may cause the development of diabetic complications (24, 25). In addition, the study with Pima Indians suggested that high WBC predicted development of T2DM regardless of body fat (26). It was demonstrated that higher WBC count was detected in patients with impaired glucose tolerance than those with impaired fasting glucose (27). Moreover, Duman et al (13) indicated that WBC was higher in patients with T2DM than healthy controls. Furthermore, Sefil et al (28) revealed that NLR and WBC count were higher in patients with Hba1c >7% than patients with Hba1c ≤7%. In this present study, WBC and NLR in the patients with uncontrolled T2DM were higher than controlled T2DM, but they were not significant. Also, a weak and a positive correlation was displayed between WBC and HbA1c.

NLR is a non-invasive, easy and cost-effective indicator of systemic inflammation; it can be collected readily from complete blood count analysis. Previous studies reported that there was an association between NLR and T2DM (6, 29). In addition, NLR is related with coronary microvascular dysfunction in T2DM and positively correlated with cardiovascular diseases (30, 31). Ozturk et al (18) found that in geriatric patients, NLR was an independent predictor for microvascular complications. Hba1c levels demonstrate blood glucose regulation, and many studies revealed significant correlation between NLR and HbA1c (13, 28, 32-34). In contrast, NLR was found higher in uncontrolled DM than controlled DM in our study, but results were not statistically significant.

RDW levels may be increased due to inflammation via shortening the survival of red blood cell, inhibiting response to erythropoietin or decreasing the production of erythropoietin as well as impairing iron metabolism (35). In addition, RDW may predict cardiovascular diseases (36). Moreover, Atalay et al. revealed

that the effect of oxidative stress and inflammation on erythrocyte homeostasis provided the relationship between RDW and T2DM (37). Furthermore, Lippi et al. suggested that increased RDW level was related with HbA1c in elder patients (38). In contrast, in our study RDW level was found higher in uncontrolled DM than controlled DM, but not statistically significant.

MPV may indicate increased platelet activation (39). It was demonstrated that patients with T2DM have higher MPV levels than patients without diabetes (40). Papanas et al. reported that MPV was importantly higher in patients with T2DM than in patients without T2DM (41). Moreover, they displayed a significant relationship between higher MPV and microalbuminuria. In contrast, MPV was not related with HbA1c and the duration of diabetes. Similarly, in patients with T2DM, Unubol et al. revealed a crucial relationship between MPV and microalbuminuria (42). Nevertheless, we and Assulyn et al. did not report any association between microalbuminuria and MPV (34).

Our study had some limitations. First, smoking status and body mass index of the patients which might affect NLR did not exist in the dataset because the study design was retrospective. Second, as results were obtained from single measurements, laboratory measurement error possibility could not be excluded. Third, given the fact that this study was carried out in a single center, yielding a relatively limited span, the results obtained may hardly be generalized. Lastly, hyperglycemia may be affected by treatment. In our study, 62.6 % patients were taking insulin, 29.2 % were taking only oral antidiabetic drugs. Thus, the evaluation of NLR and WBC between the two groups might be influenced by the use of insulin or antidiabetic drugs.

In conclusion, elevations of WBC levels may be related with diabetes control. Duration of T2DM may predict microalbuminuria. Our study revealed that duration of T2DM may predict microalbuminuria, and evaluated the relationship between RDW, MPV, NLR and Hba1c, microalbuminuria levels together in the patients with T2DM. According to NLR, RDW and MPV levels, we did not detect any statistically differences between uncontrolled T2DM than controlled T2DM.

Conflict of interest: The authors declare no conflict of interest.

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