Original Article

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Evaluation of the Relationship Between Diabetic Nephropathy, Hemogram Parameters, and Uric Asid

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Abstract

Aim: Inflammation plays an important role in the development of diabetic nephropathy (DNP). In our study, we aimed to analyze the relationship between the mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), uric acid-lymphocyte ratio (UALR), and uric acid level with early diagnosis of DNP and DNP progression.

Methods: Our cross-sectional study, which is a type of observational study, included patients diagnosed with type 2 diabetes mellitus and followed in the internal medicine and nephrology clinics of our hospital. Patients were divided into four groups: Group 1: estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 and albuminuria <30 mcg/day; Group 2: eGFR >60 mL/min/1.73 m^2 and albuminuria: 30-300 mcg/day; Group 3: eGFR >60 mL/min/1.73 m^2 and albuminuria >300 mcg/day; and Group 4: eGFR <60 mL/min/1.73 m^2 and albuminuria >300 mcg/day. Thirty-six patients were included in group 1, 38 patients in group 2, 35 patients in group 3, and 40 patients in group 4. Mean platelet volume, NLR, PLR, UALR, and uric acid levels were compared among the groups.

Results: A total of 149 patients were included in the study; 57.7% were female, and the mean age was 55.2±9.2 years. Significant differences were found among the groups in terms of MPV, PLR, NLR, and UALR ($p<0.001$, $p=0.023$, $p\leq0.001$, $p<0.001$, respectively). There was a negative correlation between eGFR and MPV ($r=-0.218$, $p=0.008$). While there was no relationship between eGFR and platelet values, a relationship was obtained when platelets were compared with lymphocytes ($r=-0.263$, $p=0.002$). There was a weak relationship between eGFR and neutrophil levels ($r=-0.188$, $p=0.026$), but a stronger relationship was found when neutrophil and lymphocyte values were rationed ($r=-0.414$, $p<0.001$).

Conclusion: Mean platelet volume, PLR, NLR, UALR, and uric acid levels, especially MPV, can be used in the development and progression of DNP.

Keywords: Diabetic nephropathy, lymphocyte, neutrophil, mean platelet volume, platelet, uric acid

Introduction

Diabetic nephropathy (DNP) is the most common cause of end-stage kidney disease (ESKD) (1). Although DNP may appear as a late manifestation of diabetes, physiological, pathological, and clinical symptoms arise before the development of DNP. Early detection of DNP, which is a significant cause of mortality and morbidity in patients with diabetes mellitus (DM), can slow down the progression to ESKD with appropriate measures. Cytokines such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor play an important role in the development and progression of DNP (2). However, their use in daily practice is expensive and technically difficult. However, hematological parameters can be measured almost anywhere, are inexpensive, and can be adapted to daily practice (3,4).

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Diabetes mellitus is a prothrombotic condition associated with accelerated atherosclerosis and inflammation. Prothrombotic tendencies are associated with increased platelet reactivity. Increased platelet reactivity plays a crucial role in the pathogenesis of microvascular complications, such as DNP associated with DM (5). Previous studies have reported that the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are indicators of subclinical inflammation, along with the uric acid-lymphocyte ratio (UALR) and uric acid levels (6-12). In addition, mean platelet volume (MPV), a platelet index that reflects platelet stimulation and production rates, is associated with inflammation. These parameters have been shown to be strong inflammatory markers and can be easily measured, providing rapid results and inexpensive costs, which increases the interest in studies related to these parameters.

Our study aimed to investigate the potential correlation between easily quantifiable and cost-effective measures, such as PLR, MPV, NLR, UALR, and uric acid levels, as markers of inflammation in patients with DNP at various stages. We hypothesized that these parameters may be useful in predicting the early diagnosis and progression of DNP.

Materials and Methods

Compliance with Ethical Standards

Ethical approval was received by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval no.: 425, date: 05.04.2017).

Study Population

Our cross-sectional study, which is a type of observational study, included patients diagnosed with type 2 DM who were followed up in the internal medicine and nephrology clinics of our hospital between. The parameters used in the study were retrospectively obtained from hospital information management system records. Type 1 diabetic patients were not included in the study. People under 18 or over 70 years old, those with non-DNP renal disease, those with acute kidney injury, those with advanced heart, lung, or liver disease, those with an autoimmune disease, those with a cancer diagnosis, and those who had a history of systemic infectious or inflammatory events or acute ischemic vascular disease in the last three months were excluded from the study. Informed consent was obtained from all participants in the study.

Measurements and Definitions

The ADA criteria were used as the basis for the diagnosis of DM (13). Patients were divided into 4 groups based on estimated glomerular filtration rate (eGFR) and urine albumin concentration.

Group 1: Those with GFR >60 mL/min/1.73 m^2 and urine albumin <30 mcg/day,

Group 2: Those with GFR >60 mL/min/1.73 m^2 and urine albumin 30-300 mcg/day,

Group 3: Those with GFR >60 mL/min/1.73 m^2 and urine albumin >300 mcg/day,

Group 4: Those with GFR <60 mL/min/1.73 m^2 and urine albumin > Three hundred mcg/day.

Uric acid, C-reactive protein (CRP), urea, and creatinine levels were analyzed using the Architect c1600 device with spectrophotometric methods recommended by the manufacturer in our hospital's biochemistry laboratory. HbA1c levels were measured using high-performance liquid chromatography, and hematological parameters were measured using the HORIBO ABX petra dx 120 device. The eGFR was calculated using the chronic kidney disease (CKD) Epidemiology Collaboration formula (14). Proteinuria and microalbuminuria were calculated by dividing the corresponding values in the spot urine by the creatinine value. These measurements were considered significant if they were consistent with at least two measurements in the past three months.

Statistical Analysis

The SPSS program (15.0 for Windows) was used for statistical analysis. Descriptive statistics are given as mean, standard deviation, minimum, and maximum for numerical variables and as number and percentage for categorical variables. An one-way ANOVA test was used for numerical variables that met the normal distribution condition in more than two independent groups, whereas the Kruskal-Wallis test was used for numerical variables that met the normal distribution condition. Subgroup analyses were performed using the Tukey test for data that met the parametric conditions, and the Mann-Whitney U test was used for data that did not meet the parametric conditions and interpreted with Bonferroni correction. A comparison of proportional data between groups was performed using chi-square analysis. The relationships between numerical variables were examined using Spearman correlation analysis because the parametric test condition was not met. The statistical alpha significance level was set at $p<0.05$.

Results

A total of 149 patients were included in the study. The mean age of the patients was 55.2±9.2. Of the patients, 57.7% were female. Thirty-six patients were included in group 1, 38 patients in group 2, 35 patients in group 3, and 40 patients in group 4. The demographic characteristics and baseline laboratory data of the patients are presented

in Table 1. Neutrophil, hsCRP, and uric acid levels were correlated with the progression of DNP.

The differences between the groups in terms of MPV, NLR, and UALR levels and the parameters analyzed within the groups are shown in Table 2. While platelet and PLR toll-like receptor (TLR) did not differ between the groups, there were statistically significant differences in MPV, NLR, and UALR between the groups.

Correlations between eGFR and MPV, NLR, UALR, TLR, neutrophil, lymphocyte, and uric acid levels are shown in Figure 1.

Discussion

In this cross-sectional study, including patients at different stages of DNP, we analyzed the relationship between MPV, NLR, TLR, and UALR, which have previously been shown to be associated with inflammation and vascular complications in many studies, and eGFR in patients with DNP. We found no significant difference in terms of platelet count between the groups, but significant differences were observed in MPV, NLR, TLR, and UALR values. These differences were more pronounced in Group

Table 1. Baseline demographic and laboratory data of the patients

	Group 1	Group 2	Group 3	Group 4	p-value
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Age (years)	53.2±8.2	54.4±10.8	53.0±9.1	59.6±7.6[a, c]	0.004*
Gender, female n (%)	20 (55.6)	19 (50.0)	23 (65.7)	24 (60.0)	0.573**
Creatinine (mg/dL)	0.72±0.12	0.78±0.16	0.82±0.27	2.18±0.97[a, b, c]	<0.001*
eGFR (mL/min)	99.1±15.7[d]	95.7±15.9[d]	90.6±25.3[d]	33.1±14.5	<0.001*
Proteinuria (mg/day)	-	301.0±241.3	2451.5±1853.5[b]	3319.9±2790.3[b]	<0.001*
Microalbuminuria (mg/day)	10.7±9.7	87.3±63.1[a]	525.1±280.6[a, b]	1111.5±1497.7[a, b, c]	<0.001*
HbA1c (%)	8.1±2.5	8.5±2.0	9.1±2.0	8.9±1.7	0.120*
Leukocytes (/µL)	7.8±1.7	8.2±2.0	9.0±2.7	9.0±2.7	0.098*
Neutrophil (/µL)	4526.7±1470.8	4972.6±1907.3	5664.3±2195.6	5826.5±2363.6[a]	0.008*
Lymphocyte (/µL)	2538.1±672.7	2383.7±773.6	2497.1±761.0	2120.5±657.5	0.052*
hsCRP (mg/dL)	0.43±0.39	0.66±1.07	1.15±1.38	1.14±1.42[a]	0.003*
Uric acid (mg/dL)	4.9±1.5	4.8±1.1	5.3±1.8	6.2±1.3[a, b]	<0.001*

[a]: Group 1 vs. other group, [b]: Group 2 vs. other Group, [c]: Group 3 vs. other Group, [d]: Group 4 vs. other group
*Pearson chi-square test **One-Way ANOVA test
eGFR: Estimated glomerular filtration rate, hsCRP: High sensitive C-reactive protein, SD: Standard deviation

Table 2. Mean platelet volume, neutrophil-lymphocyte ratio, uric acid lymphocyte ratio values of the groups

	Group 1		Group 2		Group 3		Group 4	
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)
PLT*	275[a]±85	270 (218-314)	277[a]±50	270 (248-308)	285[a]±85	270 (233-333)	288[a]±91	268.5 (230-339)
OTH*	8.9[a]±1.0	8.85 (8.2-9.3)	9.5[b]±1.0	9.3 (8.6-10.4)	9.3[a, b]±1.1	9.3 (8.4-10.1)	8.9[a]±0.7	8.85 (8.4-9.3)
NLO*	1.9[a]±1	1.7 (1-2)	2.4[a, b]±2	2.0 (2-3)	2.5[a, b]±1	2.1 (2-3)	3.1[b]±2	2.5 (2-3)
UALO*	0.002[a]±0.001	0.001 (0.001-0.003)	0.002[a]±0.001	0.002 (0.002-0.002)	0.002[a]±0.001	0.002 (0.002-0.003)	0.003[b]±0.002	0.002 (0.002-0.004)
TLR*	0.12[a]±0.05	0.108 (0.08-0.13)	0.13[a]±0.05	0.1304 (0.09-0.16)	0.12[a]±0.05	0.109 (0.09-0.14)	0.16[a]±0.12	0.128 (0.10-0.16)
Uric acid* (mg/dL)	4.9[a]±1.5	4.8 (3.7-5.7)	4.8[a]±1.1	4.45 (4.0-5.7)	5.3[a]±1.8	5.1 (4.1-6.2)	6.2[b]±1.3	6 (5.5-7.1)
Neutrophil* (/µL)	4527[a]±1471	4285 (3545-5530)	4973[a, b]±1907	4870 (3720-5800)	5664[a, b]±2196	5000 (4400-7300)	5827[b]±2364	5600 (4415-6450)
Lymphocyte* (/µL)	2538[a]±673	2470 (2120-2800)	2384[a]±774	2145 (1800-2990)	2497[a]±761	2380 (1990-3100)	2121[a]±657	2160 (1800-2550)

*Kruskal-Wallis test
Note: Values in the same row and subtable not sharing the same subscript are significantly different at p<0.05 in the two-sided test of equality for column proportions.
PLT: Platelet, MPV: Mean platelet volume, NLR: Neutrophil lymphocyte ratio, UALO: Uric acid lymphocyte ratio, TLR: Platelet lymphocyte ratio, SD: Standard deviation, IQR: Interquartile range

4, which included patients with eGFR <60 mL/min/1.73 m^2 and albuminuria >300 mcg/g, compared with the other groups. On the other hand, a positive correlation was found between eGFR and MPV and lymphocyte levels, whereas a significant negative correlation was found between eGFR and NLR, UALR, TLR, neutrophil, and uric acid levels.

The NLR has been shown to be better than routine and conventional tests such as CRP, leukocyte count, and neutrophil count in the diagnosis of bacteremia (15,16). NLR has been found to be an effective parameter in the prognosis and follow-up of myocardial infarction, gangrenous appendicitis, and colorectal carcinoma in previous studies conducted on different patient groups (17,18). The presence of a low-grade inflammatory state in CKD has been shown in studies, and given that inflammation increases as GFR decreases, it is thought that NLR can provide predictive information for the progression of CKD (19-21). Khandare et al. (22) accepted NLR as a predictive and prognostic risk marker for DNP. On the other hand, Huang et al. (23) found that increasing NLR was associated with DNP and that NLR was a reliable predictor for early-stage DNP.

Large platelets have high adhesion capabilities. Mean platelet volume, an indicator of platelet function, is associated with various prothrombotic and proinflammatory diseases. Mean platelet volume is a prognostic biomarker of cardiovascular and cerebrovascular diseases. A meta-analysis reported that increased MPV values are associated with mortality after acute myocardial infarction and restenosis following coronary angiography (23). Other studies have also reported a relationship between increased MPV and sepsis severity, stroke, hypertension, venous thromboembolism, and DNP microvascular complications (24-29). Ju et al. (30) showed that MPV increases with CKD progression. In our study, we observed that MPV values increased relatively with decreasing GFR.

Platelet-lymphocyte ratio, an easy and inexpensive biomarker, has been shown to be a prognostic factor in cardiovascular mortality and some types of cancer in previous studies (30-34). There are also studies showing that TLR is related to inflammation and can predict

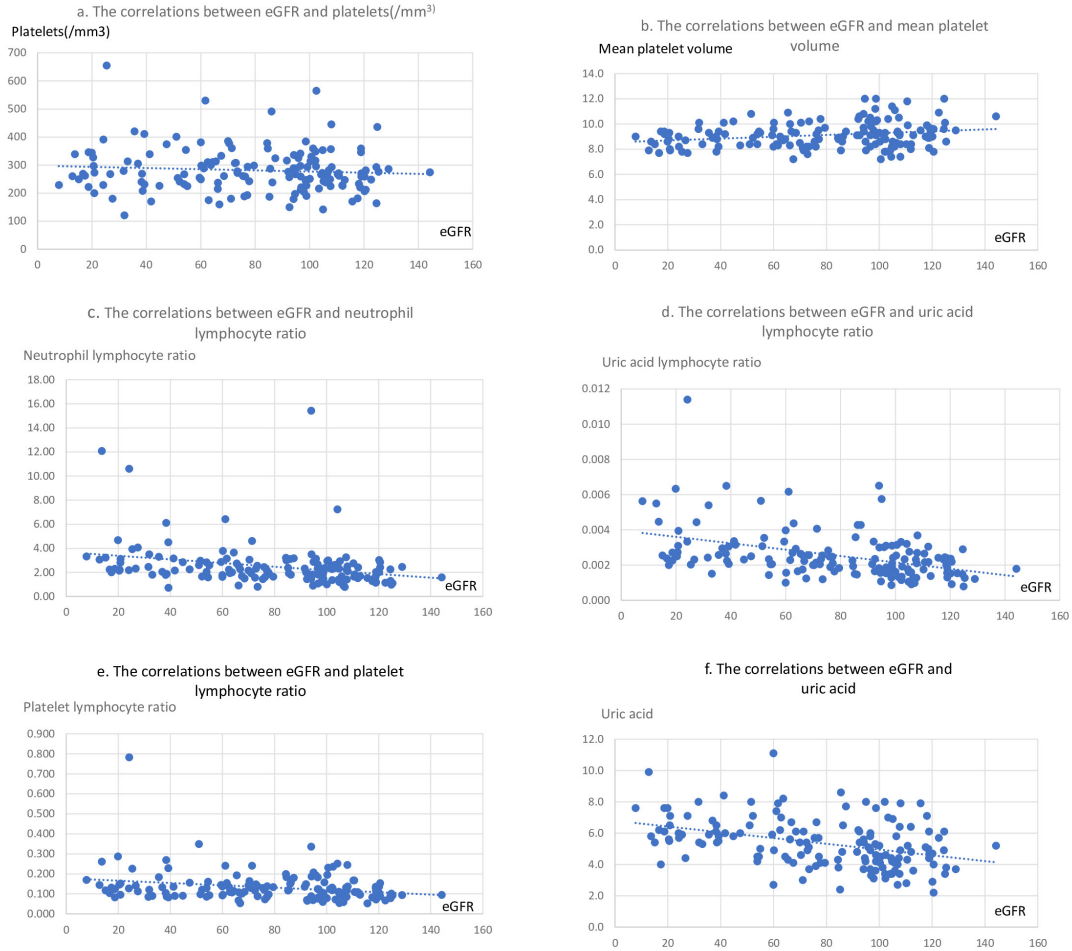

Figure 1. The correlations between eGFR and MPV, NLR, UALR, TLR, neutrophil, lymphocyte, and uric acid levels

mortality in hemodialysis patients (35,36). In our study, we did not find any relationship between platelet levels and GFR used in the classification of DNP, but we found a significant relationship between GFR and TLR obtained by rationing this parameter with lymphocyte levels. Similar to our results, Abdallah et al. (37) showed that NLR and TLR are important predictive and prognostic biomarkers for DNP.

Study Limitations

The main limitations of our study are that it is retrospective and cross-sectional. Due to the possible effects of neutrophil, lymphocyte, and platelet levels, gender, genetics, lifestyle, diet, seasonal factors, and existing diseases, the limited number of patients included in the study is another limitation. Despite these limitations, we believe that it is very valuable to use parameters such as PLR, MPV, NLR, UALR, and uric acid levels, which are easily accessible and can be used in daily clinical practice in the early diagnosis and prediction of progression in diabetics.

Conclusion

Mean platelet volume and TLR values, as well as NLR and UALR values, may have prognostic and predictive values for the development and monitoring of DM and complications such as DNP. It is cheap, easily integrated into daily practice, and reliable parameters reinforce their predictive value. However, more extensive and detailed studies are required on this topic.

Ethics

Ethics Committee Approval: Ethical approval was received by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval no.: 425, date: 05.04.2017).

Informed Consent: Informed consent was obtained from all participants in the study.

Authorship Contributions

Concept: T.E.S.O., Design: T.E.S.O., S.O., Data Collection or Processing: T.E.S.O., A.A., Analysis or Interpretation: S.Y., E.C., C.C., A.A., Literature Search: T.E.S.O., E.C., S.U., Writing: T.E.S.O., A.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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