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Original Article

Association of epicardial adipose tissue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy

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Abstract: Background: The relationship between diabetic nephropathy, visceral adipose tissue (VAT), and inflammation has been shown. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are simple, inexpensive, and useful markers to determine inflammation. However, to date, in the literature, there have been no studies demonstrating the relationship between epicardial adipose tissue (EAT), inflammation, and albuminuria. Aims: We aimed to investigate the association between diabetic nephropathy, NLR, and PLR as inflammatory markers and EAT thickness. Methods: This was a cross-sectional study involving 200 diabetic patients. The patients were separated into three groups according to their albuminuria levels. The NLR and PLR were calculated from a complete blood count. EAT was measured by transthoracic echocardiography. The estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in renal disease (MDRD) equation. Results: Disease duration, EAT, creatinine, NLR, PLR, absolute neutrophil, lymphocyte, and platelet count tended to increase with increasing albuminuria while the eGFR decreased. When patients were separated into two groups according to NLR and PLR medians, albuminuria levels increased with an increase of the NLR ($p = 0.003$) and PLR ($p = 0.009$). A correlation analysis showed that albuminuria was significantly correlated with EAT, disease duration, creatinine, eGFR, PLR, and NLR levels. Additionally, in a binary logistic regression analysis, EAT, NLR, and PLR were found to be independently associated with albuminuria. Conclusions: Determining various inflammatory cytokines and measuring abdominal VAT in diabetic patients is complex and expensive. Simply measuring EAT and calculating NLR and PLR can predict inflammation and albuminuria in patients with diabetes.

Keywords: Epicardial adipose tissue, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, diabetic nephropathy

Introduction

Patients with diabetes, compared to non-diabetic patients, are at an increased risk for coronary artery disease [1]. The association between micro- and macrovascular disease in diabetes mellitus (DM) and the importance of early detection of microangiopathy for vascular risk assessment in DM has been determined [2]. Moreover; the association between diabetic nephropathy (DN), inflammation, and coronary artery disease has been defined [3-7].

DN is the leading cause of end-stage renal failure worldwide [8]. It is a chronic disease that contributes to patient morbidity and mortality, and increases nations' health care costs. The pathogenesis of DN is still not fully elucidated, and induction of inflammation and oxidative stress by the metabolism of hyperglycemia and dyslipidemia may play a significant role in developing vascular complications including DN [3-5, 9-12].

Many patients with DN have increased serum levels of inflammatory mediators including C-reactive protein (CRP), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interferon-γ (IF-γ), and Tumor Necrosis Factor-α (TNF-α) [3-5]. The white blood cell (WBC) count and its subtypes are classic markers of inflammation [13-16]. In recent years, the neutrophil-to-lymphocyte ratio

Table 1. Demographic, clinic and laboratory features of the study groups

Parameters	Normoalbuminuric patients (n = 132)	Microalbuminuric patients (n = 34)	Macroalbuminuric patients (n = 34)	*P* value
Age (years)*	56.03±10.54	60.35±11.40	59.03±9.61	0.061
Female/Male**	69/63	16/18	18/16	0.849
BMI (kg/m^2)***	30.50 (19.50-49.80)	29.65 (21.40-46.50)	31.25 (21.10-41.40)	0.662
Waist Circumference (cm)***	104 (75-142)	102.5 (76-127)	102 (78-128)	0.571
EAT (mm)***	4.21 (1.76-9.77)	4.45 (2.00-9.00)	5.30 (4.44-9.00)	<0.001
Disease Duration (Months)***	60 (0-324)	108 (0-360)	102 (12-348)	0.002
SBP (mmHg)***	140 (80-220)	137.5 (100-210)	130 (90-190)	0.504
DBP (mmHg) ***	80 (40-140)	77.5 (60-90)	80 (40-110)	0.233
HbA1c (%)***	8.25 (4.10-15.60)	9.15 (6.00-14.50)	9.00 (6.20-13.10)	0.168
eGFR (mL/min)*	102.69±28.76	94.06±29.35	64.29±44.26	<0.001
Albuminuria (mg/g Cr)***	9.79 (0.30-27.50)	74.87 (33.40-293.80)	716.35 (312.50-1985.00)	<0.001
Creatinine (mg/dL)***	0.75 (0.37-1.87)	0.75 (0.48-1.96)	1.43 (0.44-3.45)	<0.001
WBC(10^3/mm^3)***	7.30 (3.30-13.20)	7.05 (4.90-11.10)	7.90 (4.20-11.40)	0.486
Absolute neutrophil count (10^3/mm^3)***	4.22 (1.49-9.11)	4.27 (1.33-6.83)	4.58 (2.12-7.76)	0.041
Absolute lymphocyte count (10^3/mm^3)***	2.51 (1.40-5.99)	2.28 (0.96-4.31)	2.23 (0.75-3.90)	0.019
Absolute platelet count (10^6/mm^3)***	238 (95-451)	236 (150-393)	271 (183-458)	0.037
NLR***	1.56 (0.76-4.14)	1.96 (0.81-3.71)	2.03 (0.85-6.91)	0.001
PLR***	95.70 (31.33-181.31)	115.22 (50.51-276.04)	118.45 (57.73-361.33)	<0.001

*Oneway ANOVA Test (mean ± standard deviation), **Chi-Square Test, ***Kruskal Wallis Test [median(min-max)]. BMI: Body Mass Index, EAT: Epicardial adipose tissue, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, eGFR: Estimated Glumerular Filtration Rate, WBC; White Blood Cell, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio.

(NLR) and platelet-to-lymphocyte ratio (PLR) were introduced as potential markers to determine inflammation in cardiac and non-cardiac disorders [13, 14, 17-21]. Additionally, an association between NLR and worsening renal function in diabetic patients has been determined [22].

Epicardial adipose tissue (EAT) has been proposed as a novel cardiovascular risk in the general population [23-25] and in end-stage renal disease patients [26-28]. Additionally, it has been demonstrated that EAT acts as an extremely active organ that produces several bioactive adipokines, proinflammatory and proatherogenic cytokines [23, 29-34].

However, to date, the data about EAT, the simple inflammatory markers of the NLR and PLR, and their association with DN are scant in the literature. Therefore, we aimed to define the relationship between EAT, the novel inflammatory markers of the NLR and PLR, and the association between DN in type 2 DM patients.

Study population and methods

Patients

This was a cross-sectional study involving 200 type 2 diabetic patients (103 females, 97 males; mean age = 57.28±10.64; known diabetes duration = 93.69±78.74). The study protocol was approved by the Medical Ethics Committee of Erzincan University (School of Medicine, Erzincan, Turkey). Written informed consent was obtained from all subjects included in the study. Patients aged 18-80 years who were willing to participate were screened. A review of their medical records (including information on age, sex, weight, height, disease duration, medications, and history of other diseases) was undertaken. Exclusion criteria were infection, autoimmune disease, and acute diabetic complications.

Two hundred and sixteen patients were evaluated and 16 patients were excluded from the study. Of these 16 patients, 15 patients had an active infection, and one patient had diabetic ketoacidosis. The remaining 200 diabetic patients fulfilled the above criteria and were enrolled in the study. Of these 200 patients, 44 patients were taking insulin and oral antidiabetics, 95 patients were taking only oral antidiabetics, 27 patients were taking only insulin, and 34 patients were not taking any antidiabetic medication.

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings were measured

Table 2. Bivariate correlation results between albuminuria and other significant parameters in diabetic patients

Parameters	r_s	*P* value
EAT (mm)	0.318	<0.001
Disease Duration (Months)	0.202	0.004
Creatinine (mg/dL)	0.261	<0.001
eGFR (mL/min)	-0.264	<0.001
NLR	0.259	<0.001
PLR	0.252	<0.001

EAT: Epicardial adipose tissue, eGFR: Estimated Glumerular Filtration Rate, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio.

using an Erka sphygmomanometer (PMS Instruments Limited, Berkshire, UK) with an appropriate cuff size in the upright sitting position after more than five minutes of rest. Two readings were recorded for each individual and the mean value of the two readings was used for analysis. Patients who were already on antihypertensive treatment (n = 99) or with a SBP and DBP >140 mmHg and 90 mmHg (24 patients not on any antihypertensive treatment), respectively, were assumed to be hypertensive.

Weight and height was measured with the lightest clothing possible and without shoes.

Biochemical analyses, data collection, and procedures

Venous blood samples for biochemical analyses were drawn after at least 10 hours of fasting and before taking any medication. All biochemical analyses were undertaken in the Central Biochemistry Laboratory of the Erzincan University School of Medicine, Mengücek Gazi Training and Research Hospital.

The quantitative urine albumin/creatinine (Cr) ratio in morning spot urine samples were used for standard microalbuminuria determination. Normoalbuminuria was defined as ≤ 30 mg/g Cr and increased albuminuria was defined as >30 mg/g Cr (microalbuminuria: 30-299 mg/g Cr and macroalbuminuria: >300 mg/g Cr). Serum and urine creatinine and albumin were measured with spectrophotometric analysis (Beckman Coulter Inc. kits and LH 2000 analyzer, Lismeehan, O'Callaghan's Mills, Ireland). Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography (Adams A1c HA-8160, Arkray). Estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in renal disease (MDRD) equation.

Definition of PLR and NLR

Complete blood counts with automated differential counts, which included total WBCs, neutrophils, and lymphocytes, were obtained. The NLR and PLR were calculated as the ratio of the neutrophils and platelets to lymphocytes, respectively, with both obtained from the same automated blood sample at the onset of the study.

Definition of EAT

All participants underwent transthoracic echocardiography imaging using an echocardiograph equipped with a broadband transducer (Vivid S4, GE Medical Systems, USA). Echocardiograms were recorded on videotapes. EAT appears as an echo-free space in the pericardial layers on a 2-D echocardiography. EAT thickness was measured on the free wall of the right ventricle at the end-diastole from the parasternal long- and short-axis views by two cardiologists (E.M.B and H.H) blinded to clinical data. Measurements from the parasternal long- and short-axis were averaged.

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences for Windows version 15.0 (SPSS, Chicago, IL, USA). Descriptive statistics for each variable were determined. Normally distributed data were expressed as mean ± standard deviation. Median and minimum-maximum values were used for variables without a normal distribution. Data with a normal distribution were compared by Student's t test and ANOVA test. Comparisons of continuous variables with an asymmetric distribution were made by using the Mann-Whitney U test and Kruskal-Wallis test. Associations between the variables were explored using the Pearson correlation and Spearman's rho (for data that were not normally distributed). Binary logistic regression analysis was also performed to define variables associated with albuminuria. Receiver-operating characteristic (ROC) analyses was used to

Table 3. Binary logistic regression of Albuminuria

Parameters	Odds Ratio	95% C.I.		*P* value
		Lower	Upper	
BMI (kg/m^2)	0.956	0.896	0.183	0.183
EAT (mm)	1.320	1.050	0.017	0.017
Disease Duration (Months)	1.006	1.002	0.006	0.006
HbA1c (%)	1.193	1.014	0.033	0.033
NLR	1.823	1.038	0.037	0.037
PLR	1.012	1.000	0.041	0.041
eGFR (mL/min)	0.983	0.973	0.002	0.002

BMI: Body Mass Index, EAT: Epicardial adipose tissue, eGFR: Estimated Glumerular Filtration Rate, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio.

compare the performance and prognostic power of the EAT, NLR, and PLR for albuminuria. The predictive validities were quantified as the area under the ROC curves (c statistics), and the comparisons of c statistics were performed by MedCalc statistic software (version 11.3.8.0, Mariakerke, Belgium). A *P* value less than 0.05 was considered significant.

Results

The baseline characteristics of 200 DM patients enrolled in the study are shown in **Table 1**. There were no differences with respect to the following variables between normoalbuminuric, microalbuminuric, and macroalbuminuric patients: age, gender, body mass index (BMI), waist circumference, SBP, DBP, HbA1c, and WBC. Disease duration, EAT, creatinine, NLR, PLR absolute neutrophil, lymphocyte, and platelet count tended to increase with increasing albuminuria while eGFR decreased.

When the patients were separated into two groups according to the NLR median [group 1; NLR < 1.68 (n = 100) and group 2; NLR ≥ 1.68 (n = 100)], albuminuria [12.88 (0.30-1079.90) vs 19.09 (0.90-1985.00); *P* = 0.003], and creatinine [0.76 (0.37-3.43) vs 0.85 (0.44-3.45); p = 0.015], the levels increased with an increase of the NLR while the eGFR [102.07±30.96 vs 87.32±37.00; *P* = 0.003] decreased and other parameters of the patients were not statistically different.

When the patients were separated into two groups according to the PLR median [group 1; PLR < 101.45 (n = 100) and group 2; PLR ≥ 101.45 (n = 100)], albuminuria [12.88 (0.30-1079.90) vs 19.09 (0.90-1985.00); *P* = 0.009], the levels increased with an increase of the PLR while other parameters of the patients were not statistically different.

The correlation between albuminuria and several other parameters was tested using bivariate correlation analysis. As shown in **Table 2**, albuminuria was significantly correlated with EAT, disease duration, creatinine, eGFR, PLR, and NLR levels.

Binary logistic regression analysis was also performed to define variables associated with albuminuria (**Table 3**). Disease duration, BMI, EAT, HbA1c, NLR, PLR, and eGFR levels were included in this model. Disease duration, EAT, HbA1c, NLR, PLR, and eGFR levels were found to be independently associated with albuminuria.

The cut-off values of EAT, NLR, and PLR for albuminuria were 4.5 mm with a sensitivity of 70.6% and a specificity of 67.4% (AUC, 0.678; 95% CI, 0.608-0.742; *P*<0.0001), 1.7 with a sensitivity of 61.8% and a specificity of 70.5% (AUC, 0.660; 95% CI, 0.590-0.725; *P* = 0.0001), and 135.2 with a sensitivity of 36.8% and a specificity of 91.7% (AUC, 0.654; 95% CI, 0.583-0.719; *P* = 0.0004), respectively, in the ROC curve analysis (**Figure 1**). However, AUC comparison of these parameters did not reach statistical significance (*P*>0.05).

Discussion

There were four main findings of the present study. First, inflammation markers, including the PLR and NLR, were significantly elevated in patients with increased albuminuria. Second, EAT was found to be greater in the albuminuric group compared to the normoalbuminuric group. Third, albuminuria was positively correlated with the PLR, NLR, EAT, and disease duration, and creatinine was negatively correlated with the eGFR. Fourth, the PLR, NLR, and EAT were found to be independent predictors of increased albuminuria with disease duration, HbA1c, and the eGFR in diabetic patients. Finally, we demonstrated threshold values for EAT, the NLR, and the PLR (4.5 mm, 1.7, and 135.2, respectively) to determine high risk for albuminuria.

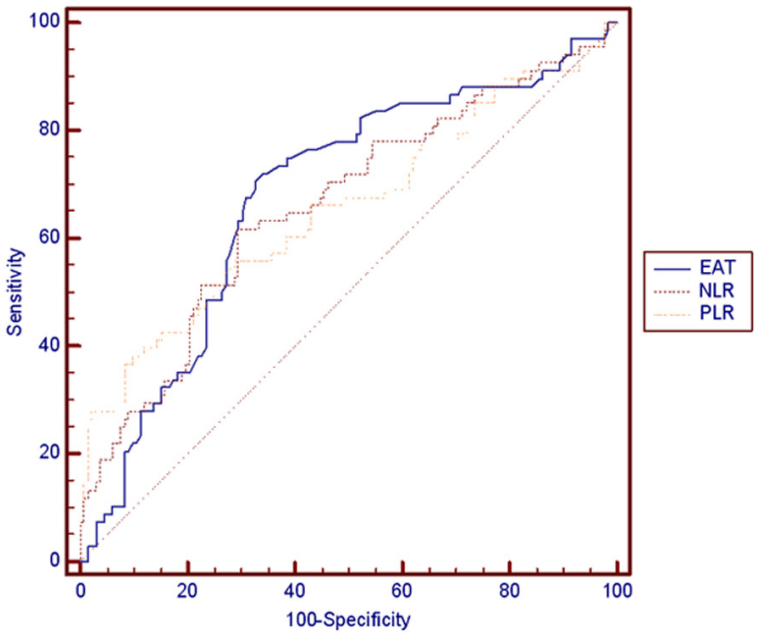

Figure 1. Comparison of receiver-operating characteristics (ROC) analysis of Epicardial adipose tissue (EAT), Neutrophil-to-Lymphocyte (NLR), and Platelet-to-Lymphocyte Ratio (PLR) for predicting albuminuria.

Developments in recent decades have revealed that inflammation, endothelial dysfunction, and procoagulant imbalance play a significant role in the development of diabetes, insulin resistance, and diabetes-related complications [3-5]. Increased inflammatory markers such as C-reactive protein, IL-1, IL-6, and TNF, and especially interstitial cellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin are associated with nephropathy, retinopathy, and cardiovascular disease in DM [3-5, 9-11]. Although metabolic and hemodynamic factors are the main causes of DN, inflammation and inflammatory molecules are believed to effect glomerular functions by alternations in vascular permeability, vasodilatatory and vasoconstrictor mechanisms, extracellular matrix dynamics, and the proliferation of mesangial, endothelial, and vascular smooth muscle cells, and the induction of cytotoxicity, apoptosis, and necrosis [4, 9, 11]. The NLR and PLR have emerged as simple, inexpensive and useful markers of inflammation related to various inflammatory, cardiovascular, and neoplastic diseases [13, 14, 17-20, 35]. An association between the WBC and DN and an association between the NLR and worsening renal function in diabetic patients has been determined [22, 36-38]. In the present study, we found that albuminuric patients had higher EAT, PLR, and NLR levels than normoalbuminuric patients. Patients with NLR values greater than 1.7 were found to be associated with albuminuria with a higher sensitivity but lower specificity when compared to patients with PLR values greater than 135.2 (61.8% vs 36.8% and 70.5% vs 91.7%, respectively). Moreover, patients with higher NLR and PLR had higher albuminuria; and NLR, PLR were found to be predictors of albuminuria in diabetic patients. This relationship might be attributed to increased inflammation and impaired endothelial dysfunction in this population.

Visceral fat deposition has been recognized as an important risk factor for cardiovascular disease, insulin resistance, and pathogenesis of diabetes. Hence, determining the amount of visceral fat is a helpful and practical tool for clinicians whose aim is to manage patients at high risk for cardiovascular disease [39]. Additionally, studies suggest that increased visceral adipose tissue (VAT), but not subcutaneous fat, is associated with microalbuminuria in patients with diabetes [40, 41]. In clinical practice, visceral fat is typically measured by surrogate markers, such as waist circumference or other anthropometric measurements. Direct measurements of visceral fat, including magnetic resonance imaging (MRI), computerized tomography (CT), or dual energy X-ray absorptiometry are more definitive, but the implementation is difficult and expensive for clinical practice. VAT has a strong correlation with EAT [39]. EAT is a metabolically active tissue that produces proatherogenic, proinflammatory bioactive adipokines, including TNF-α, IL-6, resistin, visfatin, omentin, leptin, plasminogen activator inhibitor-1 (PAI-1), and angiotensinogen [23, 33, 34, 42].

In the present study, we found that albuminuric patients had higher levels of EAT. We also demonstrated that diabetic patients with EAT values greater than 4.5 mm were found to be

associated with albuminuria with a sensitivity of 70.6% and a specificity of 67.4%. Moreover, EAT was found to be a predictor of albuminuria with disease duration, HbA1c, and eGFR. The authors believe that increased albuminuria at higher EAT levels may be explained with advanced endothelial dysfunction caused by proatherogenic, proinflammatory, and bioactive molecules secreted from epicardial fat tissue. Thus, VAT, inflammation, and EAT are closely related. Additionally, measuring EAT with echocardiography is more sensitive than VAT assessments with anthropometric measurements such as waist circumference, and more practical than CT and MRI. From this perspective, EAT might be a useful tool for evaluating patients with a higher degree of albuminuria and risk determination in normoalbuminuric diabetic patients.

Our study had two main limitations. First, this was a cross-sectional analysis. Second, the sample size was relatively small. This was not a prospective controlled study; therefore, we cannot draw cause-and-effect relationships from our findings.

In conclusion, determining various inflammatory cytokines and measuring abdominal VAT in diabetic patients is extremely complex and expensive. However, simply measuring EAT and calculating the NLR and PLR can predict inflammation in this population. Further randomized and controlled studies evaluating the relationship between EAT, PLR, NLR, and DN are needed.

Disclosure of conflict of interest

None.

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