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ADMA, neutrophil to lymphocyte, platelet to lymphocyte ratios and phase angle: effects on inflammation and nutrition in hemodialysis patients

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ABSTRACT

Objectives: Neutrophil/lymphocyte ration (NLR) and platelet/lymphocyte ratio (PLR) levels can be used as systemic infallamotory parameters. Asymmetric dimethyl arginine (ADMA) inhibits endothelial nitric oxide synthase. Phase Angle (PhA) is a potential paremeter to screen for inflammatory abnormalities. In present study we aimed to determine the relations between NLR, PLR, ADMA, and PhA in terms of early markers for nutritonal status in addition to their well-known role in inflammation.

Methods: A total of 89 patients undergoing maintenance hemodialysis 3 days a week at least 6 months were enrolled. To assess nutritional status, we performed the dietary questionnaire and mini nutritional assessment score (MNAS). ADMA was measured by ELISA. NLR and PLR are calculated from monthly complete blood count tests. Patients were divided into 2 groups accordng to NLR levels as group 1 (NLR≥4.6; n=48) ve and group 2 (NLR<4.6, n=41).

Results: The mean ADMA level was 0.03±0.01 µmol/L, the mean PhA was 7.2±1.1°. In subgroup analysis, MNAS, albumin levels and phase angle of patients in group 1 were lower and CRP, PLR, ADMA levels were higher when compared to group 2. In correlation analysis, NLO was positively correlated with PLR, CRP and ADMA however negatively correlated with albumin and PhA levels. In regression analysis, NLR, PLR and ADMA were detected as independent predictors of MNAS.

Conclusion: In conclusion our study suggests that NLR, PLR and ADMA are independent predictors for nutritional status and inflammation in patients ongoing hemodialysis.

Keywords: ADMA neutrophil, lymphocyte, platelet, phase angle, inflammation, nutrition, hemodialysis

Maintenance hemodialysis (MHD) is the most applied treatment option for end stage kidney disease [1]. Previous studies have shown that inflammation could be resulted as malnutrition in this population [2]. Several factors as inadequate food intake, uremic toxins, comorbid diseases, the dialysis procedure, inflammatory conditions are all involved in the development of malnutrition [3]. The prevalence of malnutrition varies up to 76% in MHD patients and considered significantly important for morbidity and mortality of this population [4].

Neutrophil to lymphocyte ratio (NLR) is an inflammatory parameter that shows the presence of systemic inflammation [5]. Previous reports have shown

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that NLR plays a significant role in the development of arteriosclerosis [6, 7]. Besides studies also reported that NLR in MHD patients was related to malnutrition [8]. Platelet to lymphocyte ratio (PLR) is another parameter that is associated with inflammation in patients on MHD [9].

Asymmetric dimethyl arginine (ADMA) is competitive inhibitor of endothelial nitric oxide synthase [10]. Phase angle (PhA) by bioimpedance analysis is an alternative approach for inflammation [11].

In present study we aimed to determine the relations between NLR, PLR, ADMA and PhA in terms of early markers for nutritonal status in addition to their well-known role in inflammation.

METHODS

This is a cross-sectional, observational, single-center study aimed to analyze the relationship between inflammation, malnutrition, ADMA, neutrophil to lymphocyte, platelet to lymphocyte ratios and phase angle in MHD patients. Among 130 MHD patients, 89 patients were selected according to following exclusion criteria: (1) lack of regular follow-up, (2) history of chronic inflammatory disease of unknown origin, (3) Kt/V<1.4, (4) active systemic infection or hospitalization in last 3 months, (5) active gastrointestinal disorders, (6) history of peripheral artery disease, (7) active smoking, and (8) history of malignancy. The study was approved by Baskent University Institutional Review Board and Ethics Committee (KA13/245, 12/02/2013). All patients gave informed consent for this study.

Biochemical Assays

All patients' demographical, clinical, and biochemical parameters were analyzed. Venous blood samples were taken after an overnight fast. All blood samples were collected pre dialysis [8]. Lipid profile was measured every 6 months, glycosylated hemoglobin (HbA1C; by high-performance liquid chromatography) levels were measured every 3 months and serum fasting plasma glucose (FPG), uric acid, creatinine, C-reactive protein (CRP), calcium, phosphorus, albumin levels, and complete blood count were measured in monthly periods. NLR and PLR levels were calculated from montly complete blood count parameters.

Serum ADMA levels were measured by ELISA method by using an Immunodiagnostic human ADMA kit.

Nutritional Status Assessment

The dietary survey was performed with 3-day dietary histories recorded in a self-completing food diary. The Mini Nutritional Assessment Score (MNAS) includes 18 questions [12].

Phase Angle (PhA) Measurement

After measurement of body weight and height, body composition was measured using the Tanita. Four electrodes were placed on the right hand and foot on the side c ontralateral to the arteriovenous fistula (if present) of the supine patient. Two electrodes were dorsally placed on the hand: inthemetacarpophalangeal articulations and in the corpus, 5cm apart. The pair on the foot were located in the metatarsophalangeal and in the articulation, 6 cm apart. The following were determined: extracellular water (ECW), intracellular water (ICW), and PhA.

Patients were divided into 2 groups according to mean NLR cut-off level as group 1 (NLR≥4.6; n=48) ve and group 2 (NLR<4.6, n=41).
All patients were anuric without any residual urine output which is the most important mortality indicator in this population.

Statistical Analysis

Statistical Package for Social Sciences (version 14.0; SPSS) was used. Kolmogorov-Smirnov test is used for distribution analysis. Normal distributions were expressed as mean (standard deviation). Related data were compared with paired samples t test. Categorical data were compared by χ^2 test, and $P<0.05$ was considered statistically significant.

RESULTS

This study evaluated 89 patients ongoing MHD. The etiology of CKD in MHD patients was as following: Type 2 DM 38%, hypertension 26%, glomerulonephritis 12%, ADPKD 8 %, and unknown 16 %.

Demographic data of MHD patients were as follows: Patients were 57 (47.8 %) males with mean of age of 58.1±4.8 years. The mean of BMI is 20.4±4.8 kg/m2. Duration of dialysis in MHD patients was 12.2±3.6 years. The mean NLR was 4.6±0,7, the mean PLR was 148.4±28.6, the mean CRP was 29.4±2.4 mg/L, the mean albumin level was 3.4±0.2 g/dL, the mean ADMA level was 0.4±0.01 µmol/L, the mean PhA was 7.2±1.1º.

According to MNAS of MHD patients, 18.4 % of patients had malnutrition, 42% of patients had risk of malnutrition and 39.6% of patients had normal nutritional status.

In subgroup analysis of study population, demographic data as age, gender, duration of dialysis BMI and ECW/ICW ratio were similar in 2 groups. The MNAS, albumin levels and PhA of patients in group 1 were significantly lower and CRP, PLR, ADMA levels were significantly higher when compared to group 2 (Table 1).

In correlation analysis, NLR was positively correlated with PLR, CRP and ADMA (r: 0.747, P=0.001, r: 0.534, P =0.003, and r: 0.342, P=0.001, respectively), however negatively correlated with albumin and PhA levels (r: -1.8, P=0.016, r: -1.4, P=0.014, respectively).

In regression analysis, NLR, PLR and ADMA were detected as independent predictors of MNAS (P=0.001, P=0.01, and P=0.02, respectively).

DISCUSSION

Inflammation plays an essential role in the development and progression of malnutrition in patiens ongoing hemodialysis. The peripheral blood cell analysis is preferred for prediction of inflammation and nutritional status [13]. Besides, ADMA is the most potent endogenous inhibitor of nitric oxide synthase and have an important role in inflammation [14]. PhA by is another parameter for inflammatory abnormalities especially in MHD patients.

In present study, we detected ADMA, NLR and PLR are important early markers for nutritional status in addition to their well-known role in inflammation in MHD patients. The incidence of malnutriton in MHD patients reaches up to 60 % in previous studies [15]. Inflammatory parameters as CRP are the most used marker for predicting malnutriton [16]. The negative correlation between inflammation parameters and serum albumin levels are also well known [17]. Recent studies have shown that NLR was also related

Table 1. Subgroup analysis of study population

	Group 1 (n=48)	Group 2 (n=41)	P value
Age (years)	57.4±3.8	59.2±4.4	0.05<
Gender			
Male (n)	31	26	0.05<
Body mass index (kg/m^2)	21.4±2.6	22.1±3.2	0.05<
CRP (mg/dL)	17.8±2.9	5.7±0.7	**0.01**
Albumin (g/dL)	3.1±0.8	3. ±0.4	**0.03**
NLR	4.9±0.2	4.1 ± 0.5	**0.01**
PLR	154.6±16.6	144.6±21.2	**0.03**
ADMA (µm/L)	0.4±0.01	0.28±0.03	**0.01**
MNAS	18. ±0.4	25.7±0.4	**0.01**
ECW/ICW	0.41±0.2	0.43±0.1	0.05<
PhA (º)	6.8±1.0	7.7±1.2	**0.02**

Data are shown as mean ±standard deviation or number (frequency). ADMA=Asymmetric Dimethylarginine, BMI=Body mass index, CRP=C-Reactive Protein, ECW=Extracellular water, ICW=Intracellular water, NLR=Neutrophil Lymphocyte Ratio, PLR=Platelet Lymphocyte Ratio, MNAS=Mini Nutritional Assessment Score, PhA=Phase Angle

to protein energy wasting. In present study, patients with higher NLR had lower albumin levels and nutritional status and higher inflammation levels as like previous studies. We agree with Malhotra et. al. [18] as leukocytes acts as principal effectors cell in the acute inflammation. Martinez et.al. [19] reported that NLR were significantly associated with nutritional status and inflammation. A recent study suggested that serum albumin was significantly decreased in MHD patients with malnutrition, and NLR was an independent risk factor for malnutriton [20]. In addition, they also demonstrated that NLR was negatively correlated with albumin levels as like present study. They identified these results with the increased NLR might reduce albumin levels, resulting in malnutriton. Our findings are consistent with the previous studies that albumin acts as a negative acute phase parameter in MHD patients.

An elevated PLR level is a novel inflammation marker in chronic kidney disease. In present study, we detected patients with lower nutritional status had higher values of PLR in addition to higher NLR and CRP. A recent study found that patients with poor nutritional status had higher levels of PLR than healthy population [21, 22]. Another study on non-dialysis patients with end stage renal disease detected that either NLR or PLR was positively correlated with CRP. Moreover, they concluded NLR can be an alternative parameter to predict inflammation than PLR in this population [23]. Okyay *et al*. [24] also detected significantly higher NLR in CKD patients than healthy population. Moreover, they showed the presence of higher NLR ratio in both pre-dialysis and dialysis patients, and significantly higher NLR was correlated with higher PLR in CKD patients [24] as like present study. Another study in CKD patients, couldn't detected a statistically significant correlation between SGA score and NLR, PLR, or CRP in patients' group. They showed both ratios of PLR and NLR were positively correlated to high CRP in CKD group when compared to healthy subjects. [25].

ADMA is shown to be a strong predictor of CV disease and mortality in MHD patients [26]. Previous studies reported both malnutrition and inflammation may affect serum ADMA levels especially in chronic kidney disease patients [27].

Moreover, phase angle (PhA) is a simple non-invasive technique that predicts nutritional status [28]. Generally, a low PhA shows a disrupted ability of store energy [29]. However, PhA may be affected by fluid status especially in MHD patients. In present study ECW/ICW ratios were similar in two groups thus we could regard as PhA as an indicator for nutritional status. In present study, patients with higher NLR and PLR had higher levels of ADMA and lower levels of PhA had worse nutritional status that demonstares ADMA and PhA may be used as early predictors of nutritional status in MHD patients.

Limitations

The limitations of present study include, firstly, the quite weak statistical power in relation to the small number of patients; secondly, other anthropometric measurements should be added to incease the power of study.

CONCLUSION

In conclusion our study suggests that NLR, PLR and ADMA are independent predictors for nutritional status and inflammation in patients ongoing hemodialysis. Thus, these parameters via complete blood count can be used as an early marker for detecting nutritional status in MHD patients.

Authors' Contribution

Study Conception: BGD; Study Design: BGD; Supervision: MŞK; Funding: BGD; Materials: BGD; Data Collection and/or Processing: BGD; Statistical Analysis and/or Data Interpretation: MŞK; Literature Review: BGD; Manuscript Preparation: BGD and Critical Review: MŞK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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