

Original Article

Is there a relation between mean platelet volume and chronic kidney disease stages in diabetic patients?

Ezgi Coskun Yenigun¹, Cenk Aypak², Didem Turgut¹, Serhan Vahit Piskinpasa¹, Simal Koksal Cevher¹, Eyup Koc³, Fatih Dede¹

¹Department of Nephrology, Numune Education and Research Hospital, Ankara, Turkey; ²Department of Family Medicine, Diskapi Yildirim Beyazit Training and Research Hospital; ³Department of Nephrology, Kirikkale University, Kirikkale, Turkey

Received August 23, 2015; Accepted December 11, 2015; Epub January 15, 2016; Published January 30, 2016

Abstract: Objective: Chronic kidney disease (CKD) is a state of atherosclerotic and chronic inflammation and as the estimated glomerular filtration rate (GFR) declines, cardiovascular disease (CVD) risk and inflammation increase. Mean platelet volume (MPV) has shown to be influenced by cardiovascular risk factors. The aim of this study was to evaluate the relationship between MPV and CKD. Methods: This is prospective study of a total of 812 CKD patients. Patients with CKD were assigned to into the five groups depending on estimated GFR which were calculated by Modification of Diet in Renal Disease (MDRD). Patients demographics, comorbid disease were recorded, and laboratory variables were also evaluated. Results: The mean age of CKD patients was 62.6 ± 15.4 years. According to stages, 96 patients (11.8%) were classified as stage 1 (GFR >90 ml/min/1.73 m²), 77 patients (9.5%) as stage 2 (GFR 89-60 ml/min/1.73 m²), 306 patients (37.7%) as stage 3 (GFR 59-30 ml/min/1.73 m²), 198 (24.4%) patients as stage 4 (GFR 29-15 ml/min/1.73 m²) and 135 (16.6%) patients as stage 5 (GFR <15 ml/min/1.73 m², dialysis and non-dialysis). DM was found to be positive in 299 (152 female; 147 male) patients. The mean MPV was found to higher in diabetic patients compared to non-diabetic patients (9.5 ± 1.3 fL vs 9.3 ± 1.4 fL, p: 0.024). There was a positive correlation between CKD stage and MPV in diabetic male patients. Conclusion: The results of our study might suggest that diabetic male patients with CKD have higher MPV values support the idea that these groups have additional risks other than CKD and these patients should be followed closely in respect to its complications.

Keywords: Chronic kidney disease, mean platelet volume, diabetes mellitus

Introduction

Chronic kidney disease (CKD) a worldwide problem is an atherosclerotic state and patients with CKD have a high prevalence of cardiovascular complications [1]. Increased risk of cardiovascular disease (CVD) is present in all stages of CKD. Platelets have an important role in atherosclerotic lesion formation and its complications [2]. Large platelets have more dense granules and metabolically and enzymatically more active so their thrombotic potential is higher than small platelets [3]. Platelet size, measured as mean platelet volume (MPV), is a marker of platelet function and predictor for athero-thrombotic events such as unstable angina, myocardial infarction and stroke [4-6]. Furthermore, different studies showed that car-

diovascular risk factors such as hypertension (HT), diabetes mellitus (DM), dyslipidemia, insulin resistance, metabolic syndrome have higher MPV values [7-9]. Consequently, it has been accepted that MPV may be used in detection and evaluation of CVD [10-13].

Mean platelet volume is a routine examination in CKD patients by complete blood count (CBC) tests and it is fact that clinicians are not taken into consideration this simple laboratory test. MPV has been investigated in many conditions as an inflammatory/atherosclerotic biomarker but it is rarely analyzed in kidney diseases. There are some studies that have evaluated the association between CKD and platelet activation in patients with hemodialysis and glomerular pathology [14, 15]. In CKD, it is a known fact

Mean platelet volume and chronic kidney disease

Table 1. Clinical and laboratory characteristics of study population according to genders

	Female (n=408)			Male (n=404)		
	Non-diabetic (n=256)	Diabetic (n=152)	P	Non-diabetic (n=257)	Diabetic (n=147)	P
Age (years)	63.1±5.9	62.1±9.7	0.113	61.2±6.9	62.4±9.2	0.120
Hgb (g/dl)	11.8±1.6	11.6±1.6	0.158	12.8±2.2	12.9±2.1	0.805
RDW	14.7±1.5	14.9±1.4	0.113	14.7±2.3	14.4±1.4	0.164
Platelet (10 ³ /mL)	259.8±55.5	266.2±60.2	0.274	246.3±56.8	250.9±55.8	0.427
MPV (fL)	9.4±1.3	9.7±1.3	0.065	9.1±1.3	9.3±1.3	0.191
PDW (%)	16.2±1.0	16.3±1.4	0.305	16.4±1.2	16.4±1.5	0.570
Cre (mg/dl)	2.6±2.5	2.2±1.8	0.144	2.8±2.6	2.3±1.7	0.090
Urea (mg/dl)	69.2±38.1	76.7±40.1	0.062	70.6±42.2	76.4±45.9	0.197

Hgb, Hemoglobin; Hct, Hematocrit; RDW, Red cell distribution width; MPV, Mean platelet volume; PDW, Platelet distribution width; Cre, Creatinine.

Table 2. Correlation analyses between CKD stages and other variables

	Female (n=408)				Male (n=404)			
	Non-diabetic (n=256)		Diabetic (n=152)		Non-diabetic (n=257)		Diabetic (n=147)	
	r	P	r	P	r	P	r	P
Age	0.334	0.000	0.227	0.000	0.243	0.000	0.231	0.000
Hgb	-0.489	0.000	-0.419	0.000	-0.592	0.000	-0.496	0.000
RDW	0.078	0.216	0.107	0.191	0.104	0.195	0.013	0.873
Urea	0.772	0.000	0.677	0.000	0.751	0.000	0.645	0.000
Cre	0.715	0.000	0.745	0.000	0.743	0.000	0.776	0.000
Platelet	-0.116	0.065	-0.101	0.215	-0.114	0.068	0.083	0.319
MPV	-0.057	0.363	-0.048	0.558	-0.033	0.603	0.177	0.032
PDW	-0.116	0.065	-0.053	0.528	-0.019	0.763	0.143	0.083

CKD, Chronic kidney disease; Hgb, Hemoglobin; RDW, Red cell distribution width; MPV, Mean platelet volume; PDW, Platelet distribution width; Cre, Creatinine.

that decreases in glomerular filtration rate (GFR) related to progressive increase in atherothrombotic states. In this study we aimed to evaluate whether an association exists between CKD stages and MPV in diabetic and non-diabetic patients according to gender.

Patients and methods

Study population

This prospective study was carried out from January 2012 through January 2014 among patients (n=906) who had been admitted to nephrology unit of Balikesir Ataturk State Hospital in Turkey with different stages of CKD. The demographic characteristics of the patients, cause of CKD were recorded, and laboratory parameters including hemoglobin, hematocrit, platelet counts, MPV, serum creatinine and urea were evaluated. Subjects having

acute inflammatory disorders, hematological disorders, autoimmune diseases, cancer and chronic liver disease were excluded. In addition, patients having platelet counts of less than $150 \times 10^3/\text{mL}$ or more than $400 \times 10^3/\text{mL}$ were excluded.

Definitions

Chronic kidney disease was defined as kidney damage defined by structural or functional abnormalities or GFR $<60 \text{ mL}/\text{min}/1.73 \text{ m}^2$, for 3 months or more, irrespective of the cause [16]. GFR was calculated according to Modification of Diet in Renal Disease (MDRD) [17]. The patients were separated into 5 groups according to GFR according to KDOQI guideline [16]. Stage 1 defined as GFR $>90 \text{ mL}/\text{min}/1.73 \text{ m}^2$, stage 2 defined as GFR $89-60 \text{ mL}/\text{min}/1.73 \text{ m}^2$, stage 3 defined as GFR $59-30 \text{ mL}/\text{min}/1.73 \text{ m}^2$, stage 4 defined as GFR $29-15 \text{ mL}/\text{min}/1.73 \text{ m}^2$ and stage 5 defined as GFR $<15 \text{ mL}/\text{min}/1.73 \text{ m}^2$ with and without dialysis.

Diabetes mellitus (DM) was defined as fasting blood glucose $\geq 126 \text{ mg}/\text{dL}$ or taking antidiabetic medications [18]. Patients with no history of diabetes, but abnormal blood findings (blood glucose $100-126 \text{ mg}/\text{dL}$) were forwarded endocrinology for a definitive diagnosis. Patients were divided in two groups according to presence or absence of DM.

Mean platelet volume and chronic kidney disease

Table 3. Multivariate analyses with CKD stage as the dependent variable in diabetic male patients

CBC parameter	Beta	P
Hgb	-0.504	0.000
RDW	0.011	0.885
Platelet	-0.002	0.983
MPV	0.218	0.003
PDW	-0.041	0.582

CKD, Chronic kidney disease; CBC, Complete Blood Count; DM, Diabetes Mellitus; Hgb, Hemoglobin; RDW, Red cell distribution width; MPV, Mean platelet volume; PDW, Platelet distribution width.

Cardiovascular disease (CVD) status was defined as history of coronary artery disease, cerebral vascular disease, peripheral artery disease or heart failure. History of CVD was recorded from patients' histories and patients with the diagnosis of CVD (n=94) were excluded.

Biochemical Analysis

All laboratory analyses were performed in the hematology laboratory of our hospital. Complete blood count is measured by Beckman Coulter LH 780 Analyzer. CBC samples were measured with potassium-ethylenediaminetetraacetic acid (EDTA) and those samples were analyzed one hour after vein-puncture. Normal MPV value in the laboratory ranges between 7.0 and 11.1 fL. Creatinine and Urea were measured using an enzyme method with an auto-analyzer (Hitachi Modular Core).

All protocols were approved by the ethics committee of the institution (Ethics committee, Ankara Numune Education and Research Hospital, Turkey) before the initiation of the study.

Statistical analysis

Adequacy of all parameters to normal distribution was tested by using Shapiro-Wilk test. Data were expressed as mean \pm standard deviation (SD). Mean differences were compared with Student's *t*-test between groups according to gender. Pearson correlation coefficients were computed between CKD stages and laboratory results. Partial correlation analyses between CKD stages and MPV in DM (+) male patients were adjusted for age, and PLT. Multiple linear

analyses were used to explore independent associations between CKD stages with hematological parameters in diabetic male patients by enter method. CKD stages (from 1 upto 5) served as dependent variable and Hgb, RDW, Platelet, MPV and PDW were independent variables. Data were evaluated using the Statistical Package for Social Sciences (SPSS) 17.0 program for Windows (SPSS Inc., Chicago IL, USA). All *P*-values were 2-tailed, and statistical significance was set at *P*<0.05.

Results

A total of 812 (408 (50.2%) female and 404 (49.8%) male) CKD patients were enrolled in the study. The mean age of the study population was 62.6 \pm 15.4 years. According to CKD stages, 96 patients (11.8%) were classified as stage 1, 77 patients (9.5%) as stage 2, 306 patients (37.7%) as stage 3, 198 (24.4%) patients as stage 4 and 135 (16.6%) patients as stage 5. The primary renal diseases were diabetic nephropathy in 256 patients, hypertensive glomerulosclerosis in 135 patients, glomerulonephritis/nephrotic syndrome in 93 patients, tubulointerstitial nephritis in 86 patients, autosomal dominant polycystic kidney disease in 74 patients and unknown in 168 patients.

There is no difference between CKD stages with regard to MPV values (9.3 \pm 1.4 fL, 9.1 \pm 1.2 fL, 9.4 \pm 1.4 fL, 9.4 \pm 1.3 fL, and 9.2 \pm 1.3 fL in stage 1-5 CKD, respectively, *p*: 0.194).

DM was found to be positive in 299 (152 female; 147 male) patients. The mean MPV was found to higher in diabetic patients compared to non-diabetic group (9.5 \pm 1.3 fL vs 9.3 \pm 1.4 fL, *p*: 0.024). The comparison of clinical and laboratory features of diabetic and non-diabetic patients according to gender are presented in **Table 1**.

The correlation analyses revealed that there were significant positive correlations among CKD stage and patients' age, urea and creatinine levels in both diabetic and non-diabetic females and males whereas a significant negative correlation between CKD stage and Hgb. In addition there was a positive correlation between CKD stage and MPV in diabetic male patients (**Table 2**). Even after adjusting for age, and platelet, the correlation between CKD

Mean platelet volume and chronic kidney disease

stage and MPV in diabetic male patients was found to be persisted ($r: 0.201$; $p: 0.016$).

Multivariate analyses between hematological parameters and CKD stage have revealed that MPV was related to CKD stage in diabetic male patients (Table 3).

Discussion

We aimed to determine about association between MPV and CKD to discover novel biomarkers related to CKD. We hypothesized that all stages of CKD is a risk of atherosclerotic conditions and if MPV value is an indicator of atherosclerosis, it will progressively increases as the GFR decline. Although we didn't find any association between CKD stages and MPV values, we found that among CKD patients, MPV values were higher in patients with DM than in non-DM and there was also a positive correlation between CKD stage and MPV in diabetic male patients.

Datas concerning about the relationship between MPV and CKD are limited and conflicting. In a study that nondiabetic glomerular disease were assessed, the authors showed that MPV predicted the progression of the disease [19]. In a study that compare MPV in diabetics in different stages (noncomplicated, cases with microalbuminuria or overt nephropathy and stage 2-4 CKD), the highest MPV values were found in diabetic and stage 2-4 CKD [20]. They have found that MPV values increase as the level of nephropathy increases. In a recent study, it has been documented that as CKD stage proceeded, the MPV values also significantly increased so the authors claimed that MPV can predict the disease severity [21]. The study design was retrospective and this discrepancy from our study could be due to half of the patients were diabetic, but prevalence of DM was significantly different among the CKD stages. Also they showed that platelet counts were lower in the low GFR groups and they also didn't adjust MPV for platelet count. The relationship between platelet count and MPV is inversely correlated. In another study the authors showed higher MPV in the CKD group before transplant and at the end of the first posttransplant month, MPV levels decreased compared to pretransplant levels [22]. The authors claimed that decrease in MPV is mainly related to reducing chronic inflammatory state

after transplantation. In this aforementioned study, it was designed to identify MPV as a risk factor for the tendency to thrombotic complications after transplantation. In another study MPV values were investigated in hemodialysis, peritoneal dialysis, stage 3-4 CKD, and in transplanted patients and there were no difference among MPV between all groups [23]. A study has shown that MPV is associated with CVD in patients with hemodialysis [15]. In this study, the authors compared the patients with different quintile of MPV and they showed the number of patients with CVD was more in upper quintile.

Chronic kidney disease is a prothrombotic state that causes increased cardiovascular morbidity and mortality [24]. In CKD, cardiovascular problems are associated with traditional (e.g: DM, HT or age) and nontraditional risk factors such as albuminuria, oxidative stress or inflammation, mainly arising from CKD itself. Increased risk of cardiovascular and thromboembolic event is present in all stages of CKD. Ucar et al. [25] evaluated the association between GFR and MPV in patients with stable coronary artery disease and investigated that patients with higher SYNTAX score were mainly female and diabetic. And also these patients were with lower GFR but higher MPV level. They determined MPV was associated with GFR and diabetes in these patients. In NEPHRONA study [26], CKD related atherosclerotic risk factors were examined and it was documented that in every stage of CKD there were different risk factors. For example, male gender was a risk factor in all stages but DM was significant only in stage 3. It is known that MPV is increased in patients with DM. Herein we aimed to understand the fact in diabetic CKD patients and whether an association exists between MPV and CKD stages according to gender in this group. We demonstrated that, there were significant differences in MPV in CKD patients with diabetes compared to patients with non-diabetes. More importantly, there was a positive correlation between CKD stage and MPV in diabetic male patients. It is known that CVD risk increases significantly if DM and CKD present together. By this finding we claim that high MPV levels can be a marker in this patient group and may alert physicians. It is possible to suggest that MPV value can be important in CKD patients with DM.

Conclusion

In conclusion, this study demonstrated that MPV values in CKD patients correlated with CKD stage in diabetics. Although clinical significance of this finding is needed to be confirmed in clinical studies, we should evaluate the MPV values in CKD patients, and particularly, subject with diabetes. This is a simple, easy and economical method.

Disclosure of conflict of interest

None.

Address correspondence to: Ezgi Coskun Yenigun, Department of Nephrology, Ankara Numune Eğitim ve Araştırma Hastanesi, Nefroloji Kliniği, Ankara, Turkey. Tel: +90 312 508 4552; Fax: +90 312 310 4616; E-mail: drezgi_76@hotmail.com

References

- [1] Jones CA, McQuillan GM, Kusek JW, Eberhardt MS, Herman WH, Coresh J, Salive M, Jones CP, Agodoa LY. Serum creatinine levels in the US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 1998; 32: 992-999.
- [2] Massberg S, Schulz C, Gawaz M. Role of platelets in the pathophysiology of acute coronary syndrome. *Semin Vasc Med* 2003; 3: 147-162.
- [3] Thomson CB, Eaton K, Princiotta SM, Rushin CA, Valeri CR. Size dependent platelet subpopulations: relationship of platelet volume to ultrastructure, enzymatic activity, and function. *Br J Haematol* 1982; 50: 509-519.
- [4] Endler G, Klimesch A, Sunder-Plassmann H, Schillinger M, Exner M, Mannhalter C, Jordanova N, Christ G, Thalhammer R, Huber K, Sunder-Plassmann R. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. *Br J Haematol* 2002; 117: 399-404.
- [5] Ha SI, Choi DH, Ki YJ, Yang JS, Park G, Chung JW, Koh YY, Chang KS, Hong SP. Stroke prediction using mean platelet volume in patients with atrial fibrillation. *Platelets* 2011; 22: 408-414.
- [6] Choi CU, Seo HS, Kim YK, Na JO, Lim HE, Kim JW, Kim EJ, Rha SW, Park CG, Oh DJ. Can mean platelet volume predict coronary vasospasm? *Platelets* 2011; 22: 173-178.
- [7] Nadar S, Blann AD, Lip GY. Platelet morphology and plasma indices of platelet activation in essential hypertension: effects of amlodipine based antihypertensive therapy. *Ann Med* 2004; 36: 552-557.
- [8] Papanas N, Symeonidis G, Maltezos E, Mavridis G, Karavageli E, Vosnakidis T, Lakasas G. Mean platelet volume in patients with type 2 diabetes mellitus. *Platelets* 2004; 15: 475-478.
- [9] Gasparyan AY, Ayyavazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: A link between thrombosis and inflammation? *Curr Pharm* 2011; 17: 47-58.
- [10] Nebeck K, Gelaye B, Lemma S, Berhane Y, Bekele T, Khali A, Haddis Y, Williams MA. Hematological parameters and metabolic syndrome: Findings from an occupational cohort in Ethiopia. *Diabetes Metab Syndr* 2012; 6: 22-27.
- [11] Ellinger VC, Carlini LT, Moreira RO, Meirelles RM. Relation between insulin resistance and hematological parameters in a Brazilian sample. *Arq Bras Endocrinol Metabol* 2006; 50: 114-117.
- [12] Chen LK, Lin MH, Chen ZJ, Hwang SJ, Chiou ST. Association of insulin resistance and hematologic parameters: Study of a middle-aged and elderly Chinese population in Taiwan. *J Chin Med Assoc* 2006; 69: 248-253.
- [13] Kim DJ, Noh JH, Lee BW, Choi YH, Chung JH, Min YK, Lee MS, Lee MK, Kim KW. The associations of total and differential white blood cell counts with obesity, hypertension, dyslipidemia and glucose intolerance in a Korean population. *J Korean Med Sci* 2008; 23: 193-198.
- [14] Asanuma M, Seino K, Mizuno T, Nasu M, Yamachi F, Fujishima M. Plasma thrombopoietin level and platelet indices in hemodialysis patients receiving recombinant human erythropoietin. *Int J Lab Hematol* 2010; 32: 312-319.
- [15] Henning BF, Zidek W, Linder B, Tepel M. Mean platelet volume and coronary heart disease in hemodialysis patients. *Kidney Blood Press Res* 2002; 25: 103-108.
- [16] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Inter* 2013; 3: 1-150.
- [17] Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F. Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. *Clin Chem* 2007; 53: 766-772.
- [18] ADA Clinical Practice Recommendations. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2007; 30: 42-47.
- [19] Zdrojewski Z, Lizakowski S, Raszeja-Specht A, Skibowska A, Rutkowski B. Influence of spontaneous platelet aggregation on progression of glomerular disease. *Nephron* 2002; 92: 36-42.

Mean platelet volume and chronic kidney disease

- [20] Turgutalp K, Ozhan O, Akbay E, Tombak A, Tiftik N, Ozcan T, Yilmaz S, Helvaci I, Kiykim A. Mean platelet volume and related factors in patients at different stages of diabetic nephropathy: a preliminary study. *Clin Appl Thromb Hemost* 2014; 20: 190-195.
- [21] Ju HY, Kim JK, Hur SM, Woo SA, Park KA, Park MY, Choi SJ, Hwang SD. Could mean platelet volume be a promising biomarker of progression of chronic kidney disease? *Platelets* 2015; 26: 143-147.
- [22] Sakallı H, Baskın E, Bayrakçı US, Gülleroğlu KS, Moray G, Haberal M. Mean Platelet Volume as a Potential Predictor of Renovascular Thrombosis After Renal Transplant. *Exp Clin Transplant* 2013; 11: 27-31.
- [23] Bilen Y, Cankaya E, Keles M, Gulcan E, Uyanik A, Turkeli M, Albayrak B, Yildirim R. Does decreased mean platelet volume predict inflammation in chronic renal failure, dialysis, and transplanted patients? *Ren Fail* 2014; 36: 69-72.
- [24] Moody WE, Edwards NC, Chue CD, Ferro CJ, Townend JN. Arterial disease in chronic kidney disease. *Heart* 2013; 99: 365-372.
- [25] Uçar H, Gür M, Koyunsever NY, Şeker T, Türkoğlu C, Kaypaklı O, Sahin DY, Elbasan Z, Çaylı M. Mean platelet volume is independently associated with renal dysfunction in stable coronary artery disease. *Platelets* 2014; 25: 274-278.
- [26] Betriu A, Martinez-Alonso M, Arcidiacono MV, Cannata-Andia J, Pascual J, Valdivielso JM, Fernández E; Investigators from the NEFRONA Study. Prevalence of subclinical atheromatosis and associated risk factors in chronic kidney disease: the NEFRONA study. *Nephrol Dial Transplant* 2014; 29: 1415-1422.