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PLATELET VOLUME INDICES IN CHRONIC KIDNEY DISEASE

Dr. Varsha Kumar*	M.D., Assistant Professor, Department of Pathology, M.L.N. Medical College, Allahabad. *Corresponding Author
Dr. Parul Sachan	M.D., Resident, Department of Pathology, M.L.N. Medical College, Allahabad.
Dr. Mudita Bhargava	M.D., Resident, Department of Pathology, M.L.N. Medical College, Allahabad.
Dr. Arvind Gupta	M.D., D.N.B. , Professor, Department of Medicine, M.L.N. Medical College, Allahabad.
Dr. Vatsala Misra	M.D., F.I.C. Path, M.A.M.S., M.N.A.Sc., Professor and Head, Department of Pathology, M.L.N. Medical College, Allahabad.

ABSTRACT **Purpose:** Chronic kidney disease is defined as decreased kidney function shown by GFR of less than 60 mL/min per 1.73 m2 or markers of kidney damage, or both, of at least 3 months duration, regardless of underlying cause. The best indicator of overall kidney function is estimated glomerular filtration rate (eGFR) evaluated using the MDRD formula.

Method: A cross sectional study was done wherein 142 cases of Chronic Kidney disease and 28 age matched healthy controls were enrolled. Cases were divided into 4 groups according to the estimated eGFR: Group – 1: 60-89 ml/ min/1.73m^2 ; Group– 2: 30-59 ml/ min/1.73m^2; Group - 3: 15-29 ml/ min/1.73m^2 and Group - 4 : < 15 ml/ min/1.73 m^2. Complete blood count including platelet volume indices and laboratory parameters were estimated. Parameters were also compared by dividing cases in to 2 groups: eGFR low group= eGFR< 60 ml/minute/1.73m2 and GFR high group = GFR > 60 ml/min per 1.73m^2

Results: Mean ages of CKD patients in males was 51.5±18.3 years and in females were 44.9±16.9 years with a male to female ratio as 1.84:1. Platelet count, Mean platelet volume, Plateletcrit and Platelet distribution width showed significant difference between eGFR low and high group.

Conclusion: MPV and PDW were significantly higher in eGFR low group compared to eGFR high group which may explain the increase in atherothrombotic risk in patients with slightly impaired renal function. Greater care is necessary during treatment of patients with higher MPVs, however further studies are required to establish the relationship between platelet indices and progression of CKD.

KEYWORDS : Platelet indices, eGFR, CKD

INTRODUCTION

Chronic Kidney Disease (CKD) is a worldwide public health problem that affects millions of people, Diabetes Mellitus being its leading cause [1]. The diagnosis of CKD rests on establishing a chronic reduction in kidney function and structural kidney damage. The best indicator of overall kidney function is glomerular filtration rate (GFR). The GFR can be estimated from serum creatinine concentration, demographic and clinical variables, such as age, sex, ethnicity, and body size. The normal mean value for GFR in healthy young men and women is approximately 130 mL/min per 1.73 m^2 and 120 mL/min per 1.73 m^2 respectively and declines by approximately 1 mL/min per 1.73 m^2 per year after 40 years of age. Estimation of GFR can be done using various methods such as equations derived from the Modification of Diet in Renal Disease (MDRD) Study [2].

CKD patients have an increased risk of atherothrombotic cardiovascular complications leading to morbidity and early mortality. Platelets are small (2-3mm), anucleated, disc-shaped cells that originate from the cytoplasm of bone marrow megakaryocytes and play a key role in thrombus formation. Mean platelet volume (MPV) is a marker of their function [3]. Larger platelets contain more dense granules and produce more thromboxane A2. Increased MPV has been associated with greater aggregation in response to ADP and collagen. Elevated MPV levels have been identified as an independent risk factor for various conditions associated with metabolic syndromes, vascular risk factors and pre eclampcia [4]. PDW is a measure of platelet heterogeneity which may be due to platelet aging or heterogenous demarcation of megakaryocytes [5]. Plateletcrit (PCT) was recently accepted as an indicator of platelet activation, and it reportedly increases in cardiovascular diseases [6].

MATERIAL AND METHODS:

A cross sectional study was conducted in the Department of Pathology with enrolment of 142 cases of Chronic Kidney disease and 28 age matched healthy controls. Blood samples were collected in Ethylene diamine tetra acetic acid (EDTA) and Plain vacutainers and processed within 30 minutes of collection. Complete blood count including all haematological parameters and platelet volume indices i.e. platelet count, mean platelet volume, plateletcrit and platelet distribution width (PDW) were obtained by automated analyser, Medonic M series. Serum Creatinine, serm urea, blood glucose levels were estimated using the automated analyser selectra Pro M ELITech Group. Adequate controls were run before evaluating the samples. Estimation of eGFR was done using the MDRD formula:

eGFR = 186.3 x (s. Cr) - 1.154 x age - 0.203 x (0.742 if female) x (1.21 if black).(8)

Cases were divided into 4 groups according to the estimated eGFR value : Group – 1: 60-89 ml/ min/1.73m^2 ; Group – 2: 30-59 ml/ min/1.73m^2, Group -3: 15-29 ml/ min/1.73m^2 and Group - 4 : < 15 ml/ min/1.73m^2. The parameters were also compared by dividing cases into eGFR low groups = eGFR< 60 ml/minute/1.73m^2 and GFR high group = GFR > 60 ml/min per 1.73m^2.

Subjects having acute inflammatory disorder, haematological disorder, autoimmune diseases, cancer, chronic liver diseases and taking drugs affecting platelet membrane and function were excluded from the study.

STATISTICAL ANALYSIS

Unpaired t- test and one way ANOVA test were used for statistical evaluation. p value ≤ 0.05 was taken as critical level of significance.

RESULTS

Mean age of presentation in males was 51.5±18.3 years and in females were 44.9±16.9 years with a Male to female ratio of 1.84:1.

On comparing the haematological parameters between the cases and controls, mean platelet count in control and chronic kidney disease patients were 2.32± 1.31 Lac/mm3 and 1.76 ±0.8 Lac/mm3 respectively. The difference was statistically significant. Mean value of MPV in control and chronic kidney disease patients were 10.6±1.3fl and 11.43 ± 1.6fl and mean PDW in control and chronic kidney disease

patients were 12.46± 2.34fl and 14.4± 2.4fl respectively. A statistically significant difference was observed. Comparison of the mean value of Plateletcrit between cases and controls yielded no significant difference. (Table 1)

Table 1- Comparison of platelet indices in cases and control.

Parameter	Case	Control	P value
	N=142	N=28	
Platelet count (Lac/mm3)	1.76± 0.8	2.32±1.31	0.0031
Mean platelet volume (fl)	11.43±1.6	10.64 ±1.3	0.00151
Plateletcrit (%)	0.19±0.08	0.20±0.05	0.5
Platelet Distribution Width (%)	14.4±2.4	12.46±2.34	0.0001

Platelet indices were compared amongst different groups of CKD divided on the basis of eGFR. Platelet count and MPV did not yield statistically significant results however PCT and PDW in different stages of CKD were found to be statistically significant (p value<0.0001) (Table 2).

Table 2- Comparison of platelet indices according to GFR in different stages of CKD.

Parameter	Group I	Group II	Group III	Group IV	p – value
	N=30	N=58	N=25	N=29	
Platelet count (lac/mm3)	1.94±0.295	1.7±0.9	1.7±0.7	1.6±0.8	0.59
Mean Platelet Volume (fl)	11±0.59	11.35±2.2	11.22±1.5	11.82±1.8	0.30
Plateletcrit (%)	0.26±.04	0.16±0.09	0.18±0.07	0.17±0.09	0.00001
Platelet Distribution Width(%)	11.9±0.7	15.2±2.4	14.9±2.1	14.9±1.9	0.00001

Various platelet indices were compared in the GFR high and GFR low groups taking a cut off 60 ml/min/1.73m^2. Mean age of presentation in GFR low group was 52.25±18.71 years and it was significantly higher than the mean age in the GFR high group. Likewise, mean values of fasting blood sugar in GFR low group was 127± 71.86 mg / dl and in GFR high group was 99.5± 13.0 mg /dl, difference being statistically significant. Similarly, mean of eGFR in low GFR group was 29.36±15.7 ml/min/1.73m2 compared to eGFR high group of 86.65±32.92 ml/min/1.73m2. Mean platelet count in GFR high group and GFR low group were 1.97 ±0.52 Lac/mm3 and 1.7 ±0.9 Lac/mm3 and mean MPV in high GFR and low GFR groups were 10.78±1.02fl and 11.46 ±2.03 fl respectively. Comparison of mean values of MPV, PCT and PDW in were statistically significant on taking cut off GFR= 60ml/min/1.73m2)(p value <0.0001) (Table 3)

Table 3- Comparison of platelet indices in low group GFR and high group GFR.

	GFR high group >60ml/min/1.73m2	GFR low group <60ml/min/1.73m2	P value
Age	40.36+13.25	52.25+18.71	0.0001
Sex (male)	30	76	-
Urea (mg/dl)	30.36±9.2	82.33±61.36	0.0001
Creatinine (mg/dl)	0.99±0.20	3.54±3.16	0.0001
Platelet Count (lac cell/mm3)	1.97±0.52	1.7±0.89	0.036
Mean Platelet Volume (fl)	10.78±1.02	11.46±2.03	0.0176
Plateletcrit (%)	0.234±.05	0.17±0.08	0.0001
Platelet Distribution Width (%)	12.1±1.65	15.07±2.28	0.0001
Fasting plasma glucose (mg/dl)	99.5±13.0	127±71.86	0.0044
eGFR* (ml/min/1.73m2)	86.65.5±32.92	29.36±15.7	0.0001
*eGFR- estimated glomerular filtration rate			

DISCUSSION

MPV has been investigated in many conditions as an inflammatory atherosclerotic biomarker but has been rarely analyzed in kidney disease [7]. It has been established in previous studies that decrease in GFR relates to progressive increase in atherothrombotic states in CKD patients. MPV is a part of routine examination in CKD patients but despite its clinical significance, it is not taken into consideration by physicians. In this study we determined whether an association exists between CKD stages and various platelet parameters.

Mean value of platelet counts in cases of CKD were lower than in control and the difference was statistically significant. This finding was in concordance with the study by Gafter et al. [8] who demonstrated that platelet counts were lower in patients with end stage renal disease on maintenance haemodialysis and chronic renal failure before haemodialysis compared to control. Similar findings were demonstrated in the studies by Lokesh et al. [9] wherein platelet count was lower in end stage renal disease patients compared to healthy control. In the present study, mean platelet count decreased with decrease in eGFR in progressive stages of CKD but the intergroup difference was not statistically significant. On taking a cut-off of eGFR of 60 ml/min/1.73m2, significantly lower values of platelet count were observed in low eGFR group when compared with high eGFR group. This finding was consistent with Young et al. [10] who showed similar results in their study.

Mean platelet volume (MPV) is an indicator of the average size and activity of platelets [3]. The platelet volume is found to be associated with cytokines (thrombopoietin, interleukin-6 and interleukin-6 and interleukin-3) that regulate megakaryocyte ploidy, number and result in the production of platelets [11-13]. When platelet production is decreased, young platelets become bigger and more active and MPV levels increase. Increased MPV indicates increased platelet diameter, which can be used as a marker of production rate and platelet activation. During activation, platelets shapes change from biconcave discs to spherical, and a pronounced pseudopod formation occurs that leads to increased MPV.

In our study mean value of MPV was significantly higher in cases of CKD compared to healthy controls ($p<0.05$). Mean values of MPV increased with progressive decline in the eGFR but the inter group difference was not statistically significant. Concordant findings by Yenigun et al. [14] demonstrated no difference between CKD stages with regard to MPV values.

On the contrary Young et al. [10] showed statistically significant intergroup differences in MPV with progressive stages of CKD. Bilen et al (2013) [15] investigated MPV in renal transplant, haemodialysis , peritoneal dialysis and chronic renal failure stages 3-4 patients and did not detect a significant difference in MPV among the four groups. Comparison of mean values of MPV between the low eGFR and high eGFR group yielded a significant difference. Ucar et al. [16] demonstrated similar results in patients with stable coronary disease wherein a poorer prognosis was noted in patients with low GFR but higher MPV.

Mean value of PCT in cases was lower than control and the difference was not statistically significant. Koroglu et al. [17] demonstrated that the plateletcrit levels of chronic renal disease group were significantly higher than the controls and dialysis group. Lokesh et al. [9] demonstrated that the mean value of plateletcrit among cases of CKD receiving hemodialysis for more than 6 months was lower than healthy control and the findings were statistically significant. In our study PCT showed a decreasing trend from stage1 to stage 2 of CKD. The decrease in PCT with declining eGFR was statistically significant. Our findings were contradictory to the results of Young et al. [10] wherein no statistically significant difference among the groups of CKD with respect to plateletcrit was observed. On taking a cut off of eGFR of 60 ml/min/1.73m2, significantly lower values of plateletcrit were observed in eGFR< 60ml/min/1.73m2 when compared with eGFR> 60ml/min/1.73m2.

Platelet distribution width (PDW) directly measures variability in platelet size, changes with platelet activation, and reflects the heterogeneity in platelet morphology. In our study mean PDW was higher in CKD patients than control and the difference was statistically significant. Lokesh et al. [9] demonstrated significantly lower levels of PDW among cases of ESRD receiving haemodialysis for 6 months compared to healthy control. Koroglu et al. [17] in their study found no significant variation in PDW values between CKD patients and other groups comprising of controls and dialysis group. Mean value of PDW increased significantly in group II compared to group I. Intergroup difference of PDW was statistically significant .Our finding was consistent with Young et al. [10] who demonstrated that mean PDW increased with decrease in the eGFR from stage 1 to 4 of CKD.

Previous studies have shown that athero-thrombotic risk progressively increases as the renal function decreases. The present study further lays emphasis on the role of platelet parameters especially MPV and PDW in assessing the risk of thrombosis in patients with renal dysfunction. Since platelet indices can be easily assessed in most primary health centers in resource poor settings, it can be used as a prognostic marker for follow up and an adequate management in patients with end stage renal disease thereby reducing morbidity.

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