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ORIGINAL RESEARCH

Platelet Indices In Diabetes Mellitus And Its Association With Microvascular Complications

[1]Dr. Ashmita Joshi, [2]Dr. Sanjeev Kumar, [3]Dr. Kamna Chaudhary, [4]Dr. Samruddhi Mudgal

[1,2,3]Senior Resident, [4]Assistant Professor, Department of Pathology, MMCMSR, Haryana, India

Corresponding Author: Dr. Samruddhi Mudgal
Assistant Professor, Department of Pathology, MMCMSR, Haryana, India

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Abstract
Aim: To analyse the role of platelet indices in diabetes mellitus and its association with microvascular complications.
Material and Methods: The present cross sectional study was conducted among patients admitted in Medicine ward for a period of 1 year. During the study period; we were able to recruit 122 subjects. Patients were selected by convenience sampling technique till desired sample size was reached during the study period.All patients were completely evaluated clinically with special reference to any microvascular complications. Blood sample was taken under all aseptic conditions from ante cubital vein by a clean puncture avoiding any bubbles and froth. About 2 ml of blood sample each was collected in **Ethylene Diamine Tetra Acetic acid** (EDTA**)** vial (for complete hemogram and HbA1C) and **Fluoride bulb (**for Fasting Blood Sugar& Post Prandial Blood Sugar).The testing of blood was done within 2 hours of collection to avoid changing because of ageing of blood cells.
Results: Microvascular complications were present in 53.28% of the study subjects. Mean P-LCR was 45.19 in diabetic neuropathy subjects while 42.15 in non- diabetic neuropathy subjects with statistically significant difference. MPV (fL) and PDW (fL) was higher in nephropathy subjects as compared to non- diabetic neuropathy subjects with statistically significant difference. Mean MPV (fL), PDW (fL) and P-LCR was higher in retinopathy subjects as compared to non-diabetic retinopathy subjects with statistically significant difference.
Conclusion: The higher values of MPV, PDW, and P-LCR in participants with microvascular complications indicates that platelet indices can be used as better prognostic markers for early detection of diabetic complications and can be used as a simple and cost-effective parameter to monitor and predict the risk of microvascular complications and institute appropriate preventive measures in diabetes.
Keywords: MPV, PDW, P-LCR, Microvascular Complications

Introduction:

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycaemia, resulting from defects in insulin secretion, insulin action, or both. It is a leading cause of end-stage renal disease and adult-onset blindness etc. Hence Diabetes mellitus has been growing rapidly as a worldwide public health problem [1-2]. According to International Diabetes Federation (IDF) estimation, as of 2019, 463 million (8.8%) adults had DM worldwide. This global prevalence is estimated to be increased to 700 million (10.9%) by the end of 2045. It is estimated that the middle and low-income countries will bear the brunt of the diabetes epidemic to the extent of 80% of the global burden. In 2021, the global burden of diabetes was estimated to be 537 million persons (age group of 20–79 years old), and this number is predicted to increase to 643 million by 2030 and 783 million by 2045. The burden of diabetes in 2021 was estimated to be 90 million in South East Asia, and this figure is expected to reach 113 million by 2030 and 151 million by 2045 [3]. The prevalence of DM in India is showing increasing trend; it has risen from 7.1% in 2009 to 8.9% in 2019 [4].
Symptoms often include increased frequency of urination, thirst, and appetite. Untreated type 2 diabetes mellitus (T2DM) leads to a variety of complications [5-7]. Acute complications include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include macrovascular complications (cardiovascular disease, cerebrovascular accident, foot ulcers) and microvascular complications (damage to the nerves leading to diabetic neuropathy, damage to the eyes causing diabetic retinopathy, and renal involvement known as diabetic nephropathy) [8-9].Microvascular complications, such as retinal lesions, microalbuminuria, and proteinuria, have been described as factors predictive of cardiovascular and cerebrovascular morbidity and mortality among diabetic subjects [9].
The development of long-term complications has a close relationship with endothelial dysfunction mainly caused by poor glycemic control, and is the leading cause of death and poor quality of life in this group of individuals [10]. The search for assessment tools to establish an early diagnosis of these complications is a challenge, but in recent years, several studies have highlighted the participation of platelets as one of the coagulation system elements involved in the genesis of these events [11-14].

Diabetic patients exhibit increased platelet activity by encouraging the glycation of platelet proteins and associated hyperglycemia increases platelet reactivity [9]. Both insulin resistance and insulin deficiency increase platelet reactivity. Insulin prevents platelet activation. Therefore, an increase in platelet reactivity would result from an absolute or relative insulin deficiency [6-7].
Platelets play an important role in the integrity of normal homeostasis, and platelet indices act as an indicator for its function [15]. Larger platelets have a higher number of dense granules which make them more potent and thrombogenic. The number and size of granules in platelets do not change during the life span of the platelet. [16-18] Increased mean platelet volume (MPV) has been associated with metabolic syndrome, stroke, coronary artery disease and diabetes mellitus (DM) [19-20]. A few studies have shown that platelet indices are significantly increased in diabetics as compared to non-diabetic individuals. Platelet parameters have been available in the laboratory routine using blood cell counters for several years. These include MPV, Platelet distribution width (PDW), Plateletcrit (PCT) and Platelet-large cell ratio (P-LCR) [20,21].
The prothrombotic stage of platelet can be detected early with ease using the newer hematological analyzers through these platelet parameters. Hematology analyzers easily, simply and cost-effectively provide us various platelet indices which helps us to detect any change in platelet morphology thus helping in early detection of the prothrombotic states of platelets. Hence the present study was conducted to analyse the role of platelet indices in diabetes mellitus and its association with microvascular complications.

Material and Methods: The present cross sectional study was conducted among patients admitted in Medicine ward for a period of 1 year. During the study period; we were able to recruit 122 subjects. Patients were selected by convenience sampling technique till desired sample size was reached during the study period.

Inclusion Criteria:

- Patients suffering from type 2 diabetes mellitus admitted in the Medicine department who are willing to participate in the study aged >18 years.

Exclusion Criteria

- Abnormal platelet count (<100 and >400x10^3/microlitre).
- Using drugs affecting platelets functions (aspirin, heparin,warfarin etc.).
- Pregnant females.
- Patients suffering from any connective tissue or auto-immune disorders.
- Patients with malignancy.

Procedure:

a. All patients were completely evaluated clinically with special reference to any microvascular complications.
b. Blood sample was taken under all aseptic conditions from ante cubital vein by a clean puncture avoiding any bubbles and froth.
c. About 2 ml of blood sample each was collected in **Ethylene Diamine Tetra Acetic acid** (EDTA**)** vial (for complete hemogram and HbA1C) and **Fluoride bulb (**for Fasting Blood Sugar& Post Prandial Blood Sugar).
d. The testing of blood was done within 2 hours of collection to avoid changing because of ageing of blood cells.
e. Complete hemogram from EDTA vial included **Mean Platelet Volume** (standard reference range: **8-12** femtolitre), **Pateletcrit** (0.22-0.24%), **Platelet-Large Cell Ratio** (15% to 35%) and **Platelet Distribution Width** (standard reference range: **9-14**femtolitre) and **Platelet count** (1.5-4 lacs/ cubic millimeter). It was performed using automated blood counter **Transasia H560** from EDTA vial. Mean Platelet Volume (**MPV**) refers to the average size of platelets in blood whereas Platelet Distribution Width (**PDW**) measures the variation in size of platelets.
f. Plasma glucose was measured by **glucoseoxidase** method in auto-analyzer **Beckman Coulter AU480**.
g. **HbA1C** was recorded by **BIO-RADD-10** High Performance Liquid Chromatography machine. HbA1C is a measure of the average blood sugar level over past 3 months and is an indicator of glycemic control.
h. Additionally, diabetic patients were evaluated for microvascular complications like **diabetic retinopathy**, **neuropathy** and **nephropathy**.
i. The quantitative urine **albumin/creatinine ratio** (**ACR**) in the morning spot urine samples was used to diagnose **diabetic nephropathy**. Sample was collected in a sterile urine pot and should be evaluated within 20 minutes from collection. The semi-automated biochemistry analyzer machine **ERBA Mannheim Chem-5plusv2** was used for analysis. Patients with ACR<30 mg/g was categorized as

microalbuminuria negative whereas patients with ACR>30 mg/g was categorized as microalbuminuria positive.

j. **Diabeticretinopathy** was diagnosed by **indirect opthalmoscopy**/**slit-lamp** examination. Before that eyes of the patient had been dilated. Dilatation was done using an eye drop composed of a combination of Phenylephrine and Tropicamide which were applied in both eyes for 2-3 times at an interval of 15 minutes. After a wait time of 30 to 45 minutes eyes were examined under indirect opthalmoscope/slit-lamp examination. Then according to the findings in opthalmoscopy, based on **The International Classification of Diabetic Retinopathy** patients were grouped into five clinical categories:

- If no abnormalities detected: **No Apparent Retinopathy**.
- Microaneurysms only: **Mild Non-Proliferative Diabetic Retinopathy** (NPDR).
- More than microaneurysms only but less than severe NPDR: **ModerateNPDR**.
- Any of the following- More than 20 intraretinal hemorrhages in each of 4 retinal quadrants, Definite Venous Beading in 2 or more retinal quadrants, Prominent Intra-retinal Microvascular abnormalities in 1 or more retinal quadrants and no Proliferative Diabetic Retinopathy (PDR): **SevereNPDR**.
- One or more of retinal neo-vascularisation, vitreous hemorrhage or preretinal hemorrhage: **PDR**
- **Diabeticneuropathy** was diagnosed based on clinical findings. If there is weakness, wasting, impaired vibration, loss of position sense or loss of reflexes, it was categorized as **Large Fibre Neuropathy**. Whereas presence of superficial pain, electric shock, burning, allodynia, thermal imperception, normal strength and reflexes was categorized as **Small Fibre Neuropathy**[84]. The tools that were used to diagnose diabetic neuropathy at bedside were **128-HZ Tuning** Fork and **Semmes-Weinstein**
- **Monofilament (SWMF)**.

Data was collected and subjected to statistical analysis.

Statistical analysis: Data so collected was tabulated in an excel sheet.The means and standard deviations of the measurementsper group were used for statistical analysis (SPSS 25.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using t test and the level of significance was set at $p < 0.05$.

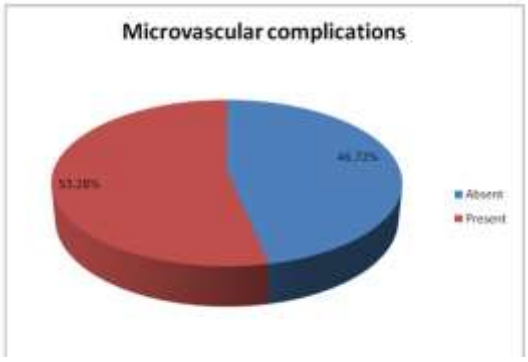
Results:

There was slightly more female (55.74%) than male (44.26%). Maximum subjects were from age group of 51-60 years (48.36%) followed by 60 years (33.61%) while minimum subjects were from 18-30 years followed by 31-40 years. Urban and rural residence was found in 58.20% and 41.80% of the subjects respectively. Mean fasting blood glucose (mg/dl) and HbA1c (%) was 149.56±7.23 and 8.2±1.64 respectively. Mean MPV (fL), PDW (fL), PCT (%) and P-LCR value was found to be 11.27±1.89, 15.98±2.32, 0.24±0.06 and 43.52±3.41 respectively (table 1).

Table 1: Descriptive analysis of Diabetic parameters and platelet indices among the study subjects

Variables	Mean	SD
Fasting blood glucose (mg/dl)	149.56	7.23
Post Prandial Blood Sugar(mg/dl)	206.19	28.95
HbA1c (%)	8.2	1.64
MPV (fL)	11.27	1.89
PDW (fL)	15.98	2.32
PCT (%)	0.24	0.06
P-LCR	43.52	3.41

Microvascular complications were present in 53.28% of the study subjects (graph 1).



Graph 1: Microvascular complications among the study subjects

Microvascular complications viz. diabetic neuropathy, nephropathy and retinopathy was reported among 27.05%, 11.48% and 4.10% of the subjects respectively. Combination of any 2 microvascular complications was revealed in 10.66% of the subjects (table 2).

Table 2: Distribution of microvascular complications among the study subjects

Microvascular complications	Number	Percentage
Diabetic Neuropathy	33	27.05
Diabetic Nephropathy	14	11.48
Diabetic Retinopathy	5	4.10
Combination of Any 2	13	10.66

PCT (%) was found to be slightly lower in diabetic neuropathy subjects as compared to non- diabetic neuropathy subjects though no significant difference was revealed. MPV (fL) and PDW (fL) was slightly higher in neuropathy subjects as compared to non- diabetic neuropathy subjects but no significant difference was found. Mean P-LCR was 45.19 in diabetic neuropathy subjects while 42.15 in non- diabetic neuropathy subjects. When mean P-LCR was compared statistically according to presence of diabetic neuropathy using t test, significant association was found as $p<0.05$ (table 3).

Table 3: Comparison of platelet indices according to Diabetic Neuropathy

Variables	Diabetic Neuropathy				p value
	Yes		No		
	Mean	SD	Mean	SD	
MPV (fL)	12.6	1.67	11.8	1.93	0.11
PDW (fL)	16.2	2.19	15.90	2.4	0.43
PCT (%)	0.21	0.05	0.26	0.07	0.10
P-LCR	45.19	3.12	42.15	3.48	0.042*

*: statistically significant

PCT (%) was found to be slightly lower in diabetic nephropathy subjects as compared to non- diabetic nephropathy subjects though no significant difference was revealed. MPV (fL) and PDW (fL) was higher in nephropathy subjects as compared to non- diabetic neuropathy subjects with statistically significant difference when compared using t test. Though mean P-LCR was higher in diabetic neuropathy subjects as compared to non- diabetic neuropathy subjects, but no significant difference was found (table 4).

Table 4: Comparison of platelet indices according to Diabetic Nephropathy

Variables	Diabetic Nephropathy				p value
	Yes		No		
	Mean	SD	Mean	SD	
MPV (fL)	13.1	1.7	11.4	1.82	0.045*
PDW (fL)	16.8	2.4	15.3	2.5	0.037*
PCT (%)	0.22	0.06	0.25	0.05	0.14
P-LCR	44.96	3.25	42.71	3.70	0.18

*: statistically significant

Mean MPV (fL), PDW (fL) and P-LCR was higher in retinopathy subjects as compared to non-diabetic retinopathy subjects with statistically significant difference when compared using t test. PCT (%) was found to be slightly lower in diabetic retinopathy subjects as compared to non-diabetic retinopathy subjects though no significant difference was revealed (table 5).

Table 5: Comparison of platelet indices according to Diabetic retinopathy

Variables	Diabetic Retinopathy				p value
	Yes		No		
	Mean	SD	Mean	SD	
MPV (fL)	13.9	1.6	11.2	1.9	0.008*
PDW (fL)	16.7	2.5	15.1	2.2	0.005*
PCT (%)	0.23	0.05	0.26	0.07	0.19
P-LCR	48.91	3.30	42.45	3.48	0.002*

*: statistically significant

According to Pearson correlation analysis; significant positive correlation was found between HbA1c and MPV (r=0.38, p=0.004), PDW (r=0.35, p=0.009) as well as P-LCR (r=0.34, p=0.016) i.e. with increase in HbA1c; these parameters also increase. Significant negative correlation was found between HbA1c and PCT (r=-0.23, p=0.032) as shown in (table 6).

Table 6: Pearson correlation for the association between platelet parameters and glycated haemoglobin (HbA1c) in diabetic patients

Variables	r value	p value
MPV (fL) and HbA1c	0.38	0.004*
PDW (fL) and HbA1c	0.35	0.009*
PCT (%) and HbA1c	-0.23	0.032*
P-LCR and HbA1c	0.34	0.016*

*: statistically significant

Discussion:

Diabetes mellitus is a metabolic disorder, associated with increased risk of macro- and microvascular complications. With easy availability of platelet indices, their utility as biomarkers for early detection of diabetes complications is being identified. Insulin resistance and hyperglycemia are considered imperative factors leading to increased platelet reactivity in diabetic patients. Platelet hyperreactivity is an important contributing factor for prothrombotic state in diabetic individuals by causing endothelial dysfunction, increased coagulation, and impaired fibrinolysis. Thus, these hyperreactive platelets have an important role in pathogenesis of thrombotic events leading to diabetic complications [22]. Hence the present study was conducted toanalyse platelet indices in patients with type 2 diabetes and its association with microvascular complications.

Out of 122 subjects; 44.26% were males and 55.74% were females. Hence there was slight female preponderance. Maximum subjects were from age group of 51-60 years (48.36%) followed by 60 years (33.61%) while minimum subjects were from 18-30 years followed by 31-40 years. In a study by Khanna P et al [23], the mean age of cases was 56.961±8.99 years and that of controls was 55.102±11.36 years. Among the 100 cases, there was a female preponderance, with 57% females and 43% males. This is in accordance to the present study. Kamilla R et al [24] in their study too revealed similar gender and age distribution. Psychosocial stress appears to have a greater impact on women rather than on men. Moreover, women have greater increases in cardiovascular risk, myocardial infarction, and stroke mortality than men [23].

Among the platelet indices, MPV is used to assess the platelet size, and it is an important potential biomarker of platelet reactivity. Literature also shows that larger platelets are more reactive than smaller ones. PDW is used to measure the variability in platelet size; therefore, high values of PDW suggest increase production of larger reticulated platelets [25].

In our study; mean MPV (fL), PDW (fL), PCT (%) and P-LCR value was found to be 11.27±1.89, 15.98±2.32, 0.24±0.06 and 43.52±3.41 respectively. Microvascular complications were present in 53.28% of the study subjects. Microvascular complications viz. diabetic neuropathy, nephropathy and retinopathy was reported among 27.05%, 11.48% and 4.10% of the subjects respectively. Combination of any 2 microvascular complications were present in 10.66% of the subjects.

In a study by Walinjkar et al [26], out of the total 125 individuals with T2DM, 66 had microvascular complications. Therewere 50 (40%) individuals with diabetic neuropathy. Kamilla R. Alhadas et al [24] in their study found that long-term complications of diabetes were present in 41% of patients with T2DM, and they are distributed as follows: retinopathy: 11%, nephropathy: 9%, both macrovascular and microvascular complications: 8%. In a study by Khanna P et al [23], the average mean platelet volume (MPV) in the diabetics was 12.089±1.450 fL, platelet distribution width (PDW) was 16.868±2.352 fL, and the mean P-LCR was 34.975±8.056%.

Plateletcrit (PCT:%) was found to be slightly lower in diabetic neuropathy subjects as compared to non- diabetic neuropathy subjects though no significant difference was revealed. Mean platelet volume (MPV: fL) and Platelet Distribution Width (PDW: fL) was slightly higher in neuropathy subjects as compared to non- diabetic neuropathy subjects but no significant difference was found. Mean Platelet-large cell ratio (P-LCR) among was 45.19 in diabetic neuropathy subjects while 42.15 in non- diabetic neuropathy subjects. Khanna P et al [23] in their study similarly revealed that the mean MPV, PDW, and P-LCR were significantly higher in patients with diabetic neuropathy than those without diabetic neuropathy as also seen in another study. It was observed that MPV, PDW, and P-LCR showed a positive correlation with diabetic neuropathy, which was significant (p = 0.0001, p = 0.023, p = 0.0001).

Mean MPV (fL), PDW (fL) and P-LCR was higher in retinopathy subjects as compared to non-diabetic retinopathy subjects with statistically significant difference when compared using t test. PCT (%) was found to

be slightly lower in diabetic retinopathy subjects as compared to non-diabetic retinopathy subjects though no significant difference was revealed. Khanna P et al [23] in their study similarly revealed that themean MPV, PDW, and P-LCR in the patients with diabetic retinopathy were 13.1051±1.34492 fL, 17.9682±2.52669 fL, and 35.373±8.0629%, respectively, which is higher than those without diabetic retinopathy with a p-value of 0.001, 0.012, and 0.020, respectively. This is in accordance with the results of studies, where similar conclusions were drawn (Kim JH et al [27], Brahmbhatt KJ et al [28] and Taderegew MM et al [29].In a study by Zuberi et al [19] (2008), MPV was significantly higher in diabetic patients with vascular complications than in diabetics without complications. However, Papanas et al found higher MPV values in diabetics with microvascular complications, and in the studies of Ates et al [30] and Tuzcu et al [31], the MPV was higher in patients with retinopathy.

Mean platelet volume was also positively correlating with the diabetic retinopathy and its grade, a similar finding was also seen in other studies like Atea et al [88], Jindal et al [61], Hekimsoy et al [13]. Mean platelet volume was also positively correlating with diabetic nephropathy, Unubol et al [32], showed a significant positive correlation with microalbuminuria and mean platelet volume.

Buch et al [33] had found that platelet distribution width varies significantly in diabetic and nondiabetic population and also it was significantly different in platelet with diabetic microvascular complications. In controversy to the previous study CHEN et al [60], had found that there is no significant difference in platelet distribution width among patients with diabetic microvascular complications and patients with no complications. Jindal et al [61], also supported this by saying mean platelet volume and platelet distribution width also relates to the occurrence of diabetic retinopathy. Various studies had found that platelet distribution width was relating positively with diabetic microvascular complications predominantly with diabetic retinopathy and nephropathy, duration of diabetes, HbA1C levels.

Prabhat A et al [34] in their study showed that there is statistically significant correlation of MPV with microvascular complications. According to Walinjgkar et al [70], platelet indices MPV, PDW, PCT, and P-LCR were significantly higher in diabetic persons than nondiabetic controls. The finding of no correlation between the plateletcrit and total platelet count with other microvascular complications may be due to the influence from other factors like infection, drugs causing thrombocytopenia even though most of these drugs were eliminated, and other systemic illness like dyslipedemia, hypertension and smoking which also can significantly alter the platelet count [35].

According to Pearson correlation analysis; significant positive correlation was found between HbA1c and MPV (r=0.38, p=0.004), PDW (r=0.35, p=0.009) as well as P-LCR (r=0.34, p=0.016) i.e. with increase in HbA1c; these parameters will also increase.Significant negative correlation was found between HbA1c and PCT (r=-0.23, p=0.032).

Various studies had found the positive correlation between the Mean platelet value and HbA1C, neuropathy and also in diabetic population when compared to nondiabetic population. Yilmaz et al [36], had found that Mean platelet volume is correlating directly with the stage of diabetic retinopathy. Mean platelet volume is also correlating with diabetic retinopathy, nephropathy and HbA1C levels. Mean platelet volume was also found to be related positively with the microalbuminuria and diabetic nephropathy. Kamilla R. Alhadas et al [24] in their study similarly reported a positive correlation with MPV ($p = 0.005$) and PDW ($p = 0.008$), indicating that patients with higher fasting blood glucose. levels tended to present higher values of MPV and PDW. Patients with higher A1C levels tend to have higher MPV, PCT, and PDW values.

The significant factors causing increased platelet reactivity in diabetics are hyperglycemia and insulin resistance. Increased coagulation, impaired fibrinolysis, and endothelial dysfunction cause prothrombotic state for which platelet hyper-reactivity is said to be an established contributing factor. Complications arise due to these hyperactive platelets which play a vital role in the pathophysiology of the thrombotic events [33].

Conclusion: MPV, PDW, and P-LCR have significantly increased in type 2 Diabetes Mellitus patients with complications as compared to those without complications. The higher values of MPV, PDW, and P-LCR in participants with microvascular complications indicates that platelet indices can be used as better prognostic markers for early detection of diabetic complications and can be used as a simple and cost-effective parameter to monitor and predict the risk of microvascular complications and institute appropriate preventive measures in diabetes.Therefore, it contributes to the early detection of these complications, as well as to a potential reduction in morbidity and mortality in this group of individuals.

We would also like to suggest that a follow-up study should be done to compare the association of platelet indices with progression and microvascular complications.

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