

Platelet indices in type 2 diabetes mellitus and their association with microvascular complications

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Abstract

The platelets play a vital role in the pathological changes in diabetes leading to micro-vascular complications. Platelet indices being indicators of platelet activity, may be useful predictive markers of these complications. The aim of this study was to evaluate the platelet indices in diabetic patients and correlate them with micro-vascular complications of the disease. We included 60 patients of Type 2 diabetes and 60 non-diabetics in this case-control study. Detailed clinical history including duration of diabetes and presence of micro-vascular complications was noted. Platelet indices - (Platelet count-PLT, Mean platelet volume-MPV, Platelet distribution width-PDW and Plateletcrit-PCT) were obtained using automated cell counter. Fasting blood glucose and HbA1c were also obtained. Diabetics were further categorized into patients with complications and without complications. Statistical analysis was performed by EPI INFO software version 7, Student's t-test and ANOVA test. The study showed that MPV was significantly higher in Diabetics than non-diabetic controls ($p < 0.05$). HbA1c ($p < 0.05$) and duration of diabetes ($p < 0.05$) were statistically significantly higher in diabetics with microvascular complications as compared to diabetics without microvascular complications. MPV showed statistically significant difference between diabetics with and without complications and nondiabetics ($P < 0.05$). PDW and MPV were positively correlated with duration of diabetes. Duration of diabetes was significantly higher in diabetics with retinopathy (< 0.05) and neuropathy ($p < 0.05$). Diabetics have higher MPV. MPV and PDW are predictive biomarkers of diabetic micro-vascular complications.

Keywords: Diabetes, Platelet indices, Platelet count, Mean platelet volume, Platelet distribution width, Plateletcrit.

Introduction

Diabetes Mellitus (DM) has become a global health crisis with 422 million people suffering from it and its incidence is rapidly rising in middle- and low-income countries.¹ Over 80% of cases of DM are type 2 diabetes, which is characterised by either deficiency of insulin or resistance to action of insulin or both.² Diabetes is a complex disease with chronic hyperglycemia, metabolic abnormalities, and long-term macro- and micro-vascular complications involving the blood vessels, eyes, kidneys, and nerves.³ Diabetes and uncontrolled hyperglycemia contribute to increased morbidity and mortality including development of cardiovascular disease.⁴ Microvascular complications are predictors of coronary heart events.⁵ The hyperglycemia, dyslipidemia, and insulin resistance in diabetes causes endothelial and pericyte injury, making it a prothrombotic state. Platelets are known to play a vital role in thrombosis. Platelets with altered morphology are found in diabetics.⁶ They are larger with denser granules which are enzymatically and functionally hyperactive and contribute to this prothrombotic state.

Mean platelet volume (MPV) is a blood parameter used for measuring platelet size.⁷ Larger platelets have higher MPV. Hence increased mean platelet volume (MPV) and platelet distribution width (PDW) might be associated with increased thrombotic potential.⁸ Diabetic patients have shown significantly higher MPV than the nondiabetic subjects.⁹ Larger Platelets with altered morphology could be associated with increased risk of vascular complications in diabetes.¹⁰ In recent years, there has been renewed interest in hematological parameters such as white blood count (WBC), mean platelet volume (MPV), platelet distribution

width (PDW), plateletcrit (PCT), platelet count, platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) and they are designated as predictors of endothelial dysfunction and inflammation. The newer hematological analyzers can give us various platelet parameters which help in easy detection of change in platelet structure, which may help in early detection of prothrombotic state of the platelets. Platelet indices may serve as useful tools, being simple, quick, effective and routinely available at a relatively low cost, to detect early vascular complications in patient with DM, aiding in better patient care.¹¹⁻¹³ Thus they can act as an alarm for diagnosis, initiation or progression of diabetic complications. Hence, in view of this, we aimed to study platelet parameters in type 2 diabetes and its association with the microvascular complications of diabetes.

Materials and Methods

Patient Population and Study Design

This cross-sectional analytical study was conducted in a tertiary care hospital and research centre catering services to central India. The study included 60 diabetic patients and 60 nondiabetics as controls without CAD. All cases of Diabetes type 2 were recruited from the inpatient department of medicine and the non-diabetic controls from the inpatient department of Eye over a period of 2 years from June 2015 to May 2017. Institutional Ethical Committee clearance was obtained before the start of study. Informed and written consent of all the subjects was taken.

We included diabetic patients who were already on treatment either oral and / or insulin injection for previously diagnosed DM or newly diagnosed in accordance with the

American Diabetes Association.¹⁴ The control group was obtained from individuals without DM, as obtained from their medical records. Females with Hb <10gm% and males Hb <12 gm%, nondiabetic subjects with CAD, pregnant women, patients on antiplatelet drugs such as aspirin or clopidogrel and subjects with any diagnosed malignancy were excluded from the study. Also patients with hematologic diseases, hepatic or renal or cardiac failure, acute illness, chronic diseases like chronic infections, alcohol abuse, that are on medication altering the platelet function, and atherosclerotic diseases except for arterial hypertension were not included in the study.

Evaluation of Demographical and Clinical Specifications

All the diabetic and nondiabetic subjects had a complete clinical examination including details of medical history and medications. Blood pressure, height and weight measurements, waist and Hip circumference were recorded and body mass index (BMI) was calculated by using Quetlet index with weight in Kgs / height in Mt² formula and waist circumference and Waist/hip ratio was calculated by the readings obtained. Diabetics were evaluated for presence of microvascular complications i.e. retinopathy, nephropathy, and neuropathy. Retinopathy diagnosis was made based on the findings of proliferative or non-proliferative changes in the fundus examination by a trained ophthalmologist. Nephropathy was diagnosed by doing urine analysis by dipsticks method. Diabetic neuropathy symptom and signs, such as hypoaesthesia or anaesthesia or absent ankle jerks, were used to determine the presence of diabetic peripheral neuropathy.

Biochemical and Hematologic Evaluation

The blood investigations performed were - complete blood count including platelet indices i.e. Platelet count (PLT), Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and Plateletcrit (PCT); Fasting (FBS) and postmeal (PMBS) blood sugar and HbA1c in diabetic subjects and random blood glucose in non-diabetic controls. Blood sample was taken under all aseptic precautions from the antecubital vein by a clean puncture avoiding bubbles and

froth. About 2 ml of blood sample each was collected in EDTA, fluoride bulb, and 4ml in plain bulb. The testing of the blood samples was done within 2 hours of collection of blood to avoid changes due to aging of the blood sample. Complete hemogram was performed by using automated Haematology cell counter ABX Micros 60 from EDTA bulb. Hb, platelet count, MPV, PDW, and PCT were also recorded. Plasma glucose levels were measured by the glucose oxidase method. HbA1c level was analyzed by immunoturbidometric inhibition method.

Statistical Analysis

Statistical analysis was performed by EPI INFO software version 7. Student's t-test was used to find the significant difference of FBS, HbA1c, PLT, MPV, PDW, PCT according to complications. Diabetics were subdivided in 2 groups depending on presence or absence of microvascular complication/s and ANOVA test was used to find the significance of platelet indices between these two groups and the controls. Correlations of platelet indices with individual microvascular complications were obtained using Pearson's formula. Data were expressed as mean ± standard deviation. A P < 0.05 was considered statistically significant.

Results

In this study total 124 subjects were evaluated, out of which 63 were cases of diabetes and 61 were non-diabetic controls. 3 cases and 1 control were excluded due to haemoglobin less than 10 gm%. In both the groups males were 33 and females were 27 in number respectively. The average age of diabetes subjects was 57.05±9.39 years (males 57±9.0; females 56.6±8.94) while that of control group 56.75±8.59 9 years (males 57±9.1; females 56.56±8.13). There was no significant difference in age and gender distribution. However diabetic group showed significantly higher BMI, waist circumference, systolic (SBP) and diastolic blood pressure (DBP), and MPV than the controls. But the PLT, PCT and PDW were not significantly different between the two groups (Table 1).

Table 1: Demographic and biochemical parameters in diabetic subjects vs controls

S. No.	Parameter	Diabetes Group (n = 60)	Control Group (n = 60)	'P' Value
1	Age (years)	57.05±9.39	56.75±8.59	0.896
2	Gender F/M	27/33	27/33	----
3	BMI (Kg/M ²)	23.40±2.88	21.75±3.52	<0.001*
5	Waist Circumference (cms)	90.67 ± 6.18	76.68 ± 9.52	<0.001*
5	SBP (mm of Hg)	135.53±14.35	127.87±13.69	0.004*
6	DBP (mm of Hg)	83.43±8.58	79.60±7.16	0.009
7	PLT (x10 ³ /uL)	2.93±1.00	3.05±0.76	0.469
8	MPV (fL)	8.07±1.00	7.70±0.61	0.016*
9	PCT(%)	0.23±0.08	0.24±0.09	0.393
10	PDW (fL)	13.82±1.80	13.49±1.64	0.303

*Significant P value

The duration of diabetes was 4.0 ± 3.23 years. The fasting blood glucose in diabetes group was 171 ± 65.17 and post meal blood glucose was 264.15 ± 81.53 mg% while HbA1c was $8.63 \pm 1.42\%$. Out of 60 subjects of diabetes, 30 (50%) had one or more of the 3 microvascular complications, namely retinopathy, neuropathy and nephropathy, while 30 subjects were without complications. Among the microvascular complications, retinopathy was seen in 11(18.33%) subjects, neuropathy in 13(21.67%) and nephropathy in 18(30%) subjects respectively. 21 subjects had at least 1 microvascular complication while 6 had 2

complications and 3 subjects had all the 3 complications. 20 subjects in Diabetic group also had hypertension and 1 had ischemic heart disease. The platelet indices, FBS, HbA1c, and duration of diabetes in diabetic subjects with microvascular complications when compared with that of diabetic subjects without complications, showed that there was no significant difference in platelet indices, FBS and PMBS between the two groups but the HbA1c and the duration of diabetes were found to be significantly higher in diabetics with complications than in diabetics without complications. (Table 2).

Table 2: Platelet indices, control and duration of diabetes in diabetics with microvascular complications vs. diabetics without complications

Parameters	Diabetics with microvascular complications (n = 30)	Diabetics without microvascular complications (n = 30)	P value
PLT	2.99 ± 0.87	2.87 ± 1.12	0.666
MPV	8.19 ± 1.17	7.95 ± 0.79	0.357
PCT	0.23 ± 0.07	0.23 ± 0.09	0.964
PDW	13.98 ± 1.60	13.56 ± 1.97	0.372
FBS	175.30 ± 67.08	167.87 ± 64.13	0.662
HBA1C	9.02 ± 1.64	8.24 ± 1.05	0.031*
Duration of DM	4.83 ± 3.17	3.24 ± 2.60	0.045*

*Significant P value

We divided the subjects in 3 groups namely DM with microvascular complications, DM without complications and normal controls and analysed through one way ANOVA to find the significance of platelet indices between the 3 groups. It showed significant value with respect to MPV and not with other platelet parameters. (Table 3)

Table 3: Comparison of platelet indices in diabetics with complications, without complications and non-diabetic controls

Group	N	PLT		MPV		PCT		PDW	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
DM with Complication	30	2.99	0.87	8.19	1.17	0.23	0.07	13.98	1.60
DM without complication	30	2.87	1.12	7.95	0.79	0.23	0.09	13.56	1.97
Controls	60	3.05	0.76	7.70	0.61	0.24	0.09	13.49	1.64
P Value		0.68		0.03*		0.69		0.43	

*Significant P value

Table 4: Comparison of platelet count (PLT) and mean platelet volume (MPV) according to the complications in Diabetic group

Complication	Yes / No	N	PLT ($\times 10^3/\mu\text{L}$)		MPV (fL)	
			Mean \pm S.D.	'P'	Mean \pm S.D	'P'
Retinopathy	Yes	11	2.66 ± 0.66	0.33	8.37 ± 0.93	0.28
	No	49	2.99 ± 1.05		8.01 ± 1.01	
Neuropathy	Yes	13	2.94 ± 1.02	0.98	8.54 ± 1.08	0.06
	No	47	2.93 ± 1.00		7.95 ± 0.95	
Nephropathy	Yes	18	3.08 ± 0.82	0.45	8.13 ± 1.32	0.76
	No	42	2.86 ± 1.07		8.05 ± 0.84	

Platelet count was found to be decreased in diabetic subjects with retinopathy as compared to those without retinopathy whereas it was more in those with neuropathy and nephropathy groups but these differences were not statistically significant. MPV, although was found to be higher in all the 3 complications but was insignificant (Table 4). Similarly, PDW and HbA1c although were found to be higher in all the 3 complications but failed to achieve significant level (Table 5 and 6).

Table 5: Comparison of plateletcrit (PCT) and platelet distribution width (PDW) according to the complications in diabetic group

Complication	Yes / No	N	PCT (%)		PDW (%)	
			Mean ± S.D.	'P'	Mean ± S.D	'P'
Retinopathy	Yes	11	0.21 ± 0.04	0.26	14.58 ± 1.18	0.10
	No	49	0.24 ± 0.08		13.60 ± 1.88	
Neuropathy	Yes	13	0.22 ± 0.07	0.70	13.85 ± 2.10	0.87
	No	47	0.07 ± 0.08		13.76 ± 1.74	
Nephropathy	Yes	18	0.24 ± 0.06	0.53	14.02 ± 1.15	0.52
	No	42	0.23 ± 0.08		13.68 ± 2.02	

Table 6: Comparison of fasting blood sugar (FBS), HbA1c and duration of diabetes according to the complications in diabetic group

Complication	Yes / No	N	FBS		HbA1c		Duration of DM	
			Mean ± S.D.	'P'	Mean ± S.D	'P'	Mean ± S.D	'P'
Retinopathy	Yes	11	192.82 ± 89.29	0.235	8.76 ± 1.83	0.73	6.27 ± 4.54	0.01*
	No	49	166.82 ± 58.591		8.60 ± 1.34		3.49 ± 2.66	
Neuropathy	Yes	13	161.31 ± 75.40	0.53	8.93 ± 1.60	0.39	5.77 ± 3.86	0.02*
	No	47	174.43 ± 62.66		8.55 ± 1.38		3.51 ± 2.90	
Nephropathy	Yes	18	183.00 ± 69.06	0.38	9.02 ± 1.62	0.17	3.35 ± 0.79	0.44
	No	42	166.69 ± 63.66		8.46 ± 1.32		3.20 ± 0.49	

*Significant P value

There was no significant difference of FBS between the two groups in all the 3 microvascular complications. Higher duration of diabetes was associated significantly with presence of retinopathy and neuropathy but not with nephropathy (Table 7).

Table 7: Pearson's correlation of platelet indices with duration of DM, FBS and HbA1c

Platelet Indices →	PLT		MPV		PCT		PDW	
Other Parameters ↓	r'	P	r'	P	r'	P	r'	P
DM –Duration	-0.23	0.08	0.34	0.01*	-0.22	0.65	0.43	0.00*
FBS	-0.19	0.15	-0.06	0.65	-0.26	0.04*	0.03	0.82
HBA1C	-0.03	0.82	-0.06	0.65	-0.06	0.65	-0.10	0.45

* Significant P value

On correlation analysis MPV and PDW were found to be positively correlated with the duration of diabetes while plateletcrit showed significant negative correlation with FBS.

Discussion

Diabetes mellitus is a chronic and complex metabolic syndrome with hyperglycemia and various complications such as microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (Coronary heart disease, cerebrovascular episodes, Peripheral vascular disease etc.³ The microvascular complications occur due to increased prothrombotic and atherosclerotic potential in diabetes especially when it is prolonged and / or poorly controlled.⁵ These complications are predictive markers of macrovascular complications, notably cardiovascular disease, that are responsible for increased morbidity and mortality in Diabetes.¹⁵ Diabetes and its complications result into a heavy burden on our health services and economy.¹⁶ Survey by Nanditha et al revealed increased prevalence of Diabetes in rural India.¹⁷ Previous studies have suggested that platelet indices may be useful to predict the microvascular complications in diabetes.¹⁸ Good control of DM type 2 has shown to decrease the severity and prolong the onset of vascular complications and hence

decrease the morbidity and mortality.^{19,20} Platelet indices that we studied included – Platelet count, MPV, PDW, and PCT which are quickly available at affordable costs in routinely done peripheral blood counts and can be monitored repeatedly. Previous studies have mostly studied MPV in various conditions including diabetes but very few of them have included other of these parameters.²¹⁻²³ Hence in this study we aimed to find out the platelet indices in type 2 DM and their association with the presence of microvascular complications, and with the regulation and duration of hyperglycemia in patients predominantly from periurban villages and rural population in central India. In our study amongst the platelet indices we found that MPV was significantly higher in diabetics than controls. PDW though also higher yet was not statistically significant. PLT and PCT were found to be decreased but were not significant. Considering the microvascular complications, in our study none of the platelet indices showed significant difference between diabetics with and without complications. However, the duration of diabetes and the HbA1c were significantly higher in diabetics with

microvascular complications than in diabetics without complications. The study reinforced the fact that poor glycemic control and longer duration may increase the risk of diabetic complications. Previous studies have shown altered platelet indices in diabetic patients and its complications^{9,21,22,24,25}. Most of the previous studies have shown that diabetics have higher PLT^{9,21,24,25} while our study revealed lower PLT in DM group as compared to non diabetic controls which is similar to that observed by Hekimsoy et al and Buch A. et al. It was postulated that this may be because of various factors such as high production and turnover rate in T2DM with diminished mean platelet survival.

The platelet function and its size are said to be related to each other. Larger platelets are highly active and have more dense granules, secrete more prothrombotic factors e.g. thromboxane A₂, thromboxane B₂, platelet factor 4, serotonin, and platelet-derived growth factor than smaller sized platelets and hence cause increased tendency to thrombotic events.²⁶⁻³⁰ Platelet hyperactivity in DM is also attributed to hyperglycemia as it is postulated that large sized platelets may form because of persistent and unregulated blood sugar levels.²⁶ This seems to occur through certain mechanisms such as nonenzymatic protein glycation of these platelets and also osmotic effect of glucose and protein kinase C activation.²⁶ Our study revealed that the MPV was significantly higher in diabetics than non diabetics which is similar to the observation of most of the previous other studies^{9,18,21,27,28} which indicates that larger and hence hyperactive platelets are due to the chronic hyperglycemia but this was not seen in the study by Akinbami Akinsegun et al.²⁹ Some authors obtained significantly higher MPV in DM with vascular complications than without complications.^{22,31,32} Our study although found higher MPV in DM with complications as compared to DM without complications but the difference was not statistically significant which was similar to Kodiatte TA et al. Our study revealed that there is significant positive correlation of MPV with the duration of diabetes, but there was no such observation in regards to FBS, and HbA1c. Hekimsoy Z, also did not find a significant correlation in MPV vs FBS.

We found that MPV was not correlated with FBS and HbA1c. Hekimsoy Z, et al also did not find a significant correlation in MPV vs FBS. Some studies have reported positive association of MPV with elevated FBS and HbA1c levels.^{9,21,24,27} However, it is proposed that FSG is not directly associated with increased cardiovascular events in patients with type 2 DM.³³ In our study PDW also showed significant positive correlation with the duration of DM similar to K L, Sushma et al. PDW is a measure of the platelet size variability, and it increases when there is increased production of larger reticulated platelets.²² The platelets which are activated are different in size than non-activated ones because of pseudopodia formation and change in shape from discoid to spherical giving rise to increased PDW.³⁴

On analysing PDW in diabetics we found that although it was higher in diabetics than controls and also in diabetics with complications than diabetics without complications yet the differences were not significant statistically. Other authors have shown PDW to be significantly higher in diabetics.^{21,35} Study by Alhadas KR et al showed higher PDW in diabetics with complications and found a positive correlation between FBS and PDW in diabetics; between HbA1c and PDW as well as MPV and PCT. These changes were attributed to the osmotic effect due to hyperglycemia and some of its metabolites in blood.³⁵

However present study showed no significant difference of PDW between diabetics with complications, diabetics without complications and nondiabetic groups. This was similar to that of Buch A. et al, while K L, Sushma et al have reported positive correlation between PDW with FBS and HbA1c level which is discordant to our study. Many other factors like platelet number and reactivity along with the cardiovascular comorbidities such as hypertension; dyslipidemia, obesity, cigarette smoking, albuminuria contribute to the progression of diabetes and its effect on platelet indices which may account for the thrombotic potential of diabetics with time.²² Regarding PCT few studies are available in the literature. In the present study no significant difference of PCT levels was seen between the diabetics and the controls and there was no significant correlation of PCT with the microvascular complications. However PCT was negatively correlated to increase in FBS. To maintain constant platelet mass or PCT, the platelet count tends to decrease as the platelet volume increases. However Alhadas KR, et al obtained higher PCT in diabetics and also in diabetics with chronic complications. It is explained by the observation that in diabetic patients the platelets is larger and more reactive, due to which the platelet mass increases, thus increasing the PCT.

Conclusion

Among the platelet indices mean platelet volume (MPV) and platelet distribution width (PDW) are associated with diabetes and its microvascular complications and hence they may be considered as markers of platelet activation. However, the increased MPV as the cause or the result of vascular complications needs to be further explored. But being cost effective, simple to obtain, and easily available in peripheral blood counts can be used to monitor the progression and control of DM and its cardio-vascular complications.

Limitations

In this study because of the cross-sectional design, we cannot establish a causal relationship between platelet indices and microvascular complications of diabetes. Another limitation is that qualitative platelet disorders could not be assessed.

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