Original Article

Platelet Volume Indices: Silver Linings for Vascular Complications in Diabetes Mellitus

Mitakshara Sharma[1]*, Sanjeev Narang[2] and Maj. (Gen.) S.K. Nema[2]

[1]Dept. of Pathology, All India Institute of Medical Sciences, Rishikesh, India
[2]Dept. of Pathology, Index Medical College & Research Centre, Indore, India

Keywords: *Platelet Volume Indices, Mean Platelet Volume, Platelet Distribution Width, IFG, HBA1c, Diabetes*

ABSTRACT

Background: Morbidity and mortality in diabetes owing to micro and macro angiopathic complications is well known. Platelet indices are potentially useful surrogate markers for early diagnosis of diabetic complications attributed to platelet activation and recognized by increase in Platelet Volume Indices (PVI) including Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW). The aim is to determine and compare MPV and PDW in known cases of diabetics with and without diabetes related complications. To document changes in platelet indices with duration of diabetes and to assess utility of platelet indices in early identification of vascular complications especially in developing countries like India.

Methods: A two year cross sectional study with total 330 individuals segregated into two groups:- (a) Diabetic subjects with diabetes related complications (b) Diabetic subjects without diabetes related complications. Samples for HbA_{1c} and platelet indices were obtained and processed on SYSMEX-X-800i autoanalyser.

Result: The study revealed significant positive correlation between PVI and duration of diabetes across the groups (MPV-HbA1c $r = 0.951$; PDW-HbA1c $r = 0.875$). MPV & PDW of subjects with and without diabetes related complications were (15.14 ± 1.04) fl & (17.51±0.39) fl and (18.96 ± 0.83) fl & (20.09 ± 0.98) fl respectively with a significant p value 0.00.

Conclusion: The current study demonstrates raised platelet indices in association with rising glycaemic levels and diabetes related vascular complications. This is the first study of its kind in India which is comprehensive with an adequately powered study design. PVI should be researched and explored further as surrogate marker to develop a clinical tool for early recognition of diabetic vascular changes.

***Corresponding author:**
Dr. Mitakshara Sharma, AIIMS, Rishikesh (UK)- 249203
Phone: +91 9993795966
Email: mitakshara.sharma@yahoo.com

Introduction

Diabetes mellitus (DM) is a metabolic disorder prevalent in pandemic proportions, incurring significant morbidity and mortality due to associated complications chiefly arising out of micro and macro angiopathic changes. Platelet related thrombogenesis plays a key role in the pathogenesis of these complications. These complications are attributed to platelet activation which can be recognized by an increase in Platelet Volume Indices (PVI) which includes Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW). Therefore, it is postulated that Platelet Indices can potentially be useful surrogate markers for the early detection of thromboembolic and cardiovascular complications in diabetes.

Patients with Diabetes Mellitus have a higher risk of vascular complications and burden of atheromatous plaque and recurrent thrombotic events which worsens the prognosis of vascular angiopathies as compared to non diabetic patients. [1] The vascular complications caused in diabetes include Coronary Artery Disease (CAD), atherosclerosis, medial calcification, retinopathy, nephropathy, neuropathy and peripheral arterial disease (PAD). [2] Data suggests that there is a 2-4 fold increase in CAD and PAD and also a 3 fold increased risk for stroke as compared to non diabetics.

Deaths due to diabetes are increasing and there is a need to prevent these deaths by early diagnosis of impending complications. A large proportion of patients with Type 2 DM suffer from preventable vascular angiopathies and so there is a need to develop risk factor modifications and interventions to reduce the impact of such complications. Thrombogenic platelets are large, active and dysfunctional and these patients of DM with larger platelets can easily be identified during routine haematological analysis and could possibly benefit by early preventive measures. The introduction of automated cell counters has facilitated the availability of PVI (MPV and PDW) as routine parameters.

Platelet Volume Indices as a group constitute an important, simple, effortless and cost effective tool that should be extensively explored and used as a marker for early diagnosis of diabetic complications, especially in developing countries with limited financial resources for predicting the possibility of impending vascular events in patients with Diabetes mellitus.

Materials and Methods

The present study was conducted in the Department of Pathology, Index Medical College and associated Hospital, Nemawar Road, Indore between June 2012 and May 2014. The study protocol was implemented after obtaining approval and due clearances from the Ethical Committee of the institute.The current study is a prospective analytical case control study conducted over 2 years.

The cases and controls were those attending the Out Patient Department (OPD) and admitted in the hospital.

As per the American Diabetes Association (ADA) criteria, [3] the subjects were segregated into 3 groups. The patients with $HbA_{1c} < 5.7\%$ were considered as controls and put into non-diabetic (ND) group, those with HbA_{1c} between 5.7% and 6.4% were considered as pre-diabetics and put into IFG (I) group and patients with $HbA_{1c} \geq 6.5\%$ were considered as diabetics and put into the diabetic (D) group. Further, the diabetic group was divided into two groups on the basis of history of diabetes related vascular complications

Patients suffering from idiopathic thrombocytopenic purpura, acute post streptococcal glomerulonephritis, renal failure, iron deficiency anaemia, cyanotic congenital heart diseases, hypertension, aplastic anaemia and patients on antiplatelet drug therapy were excluded. Pregnant women were also excluded from the study.

Informed prior consent was taken from the patients and clinical details were recorded in a predesigned proforma. All the investigations were done in the central laboratory (pathology and clinical biochemistry) of INDEX Hospital, Indore.

Since platelets are extremely easily activated; therefore, in order to avoid artefactual results, the sampling procedure was standardized and clean venipunctures were performed. All subjects were made to abstain from tobacco and caffeine-containing beverages on the day of sampling.

In every case 2.0-5.0 ml blood was collected under aseptic precautions in the respective blood collection tube. All the samples were processed within 2 hours of collection.

Samples for Platelet Indices and Platelet Count

Sample of the blood was drawn from the antecubital veins of the patients that allowed technically good sampling for platelet function testing and the blood sample was, with few exceptions, collected by a single laboratory technician/nurse in each study. Venipunctures were always performed without stasis with the subjects in a semi-recumbent position. They were collected using K3 EDTA (ethylene diamine tetra acetic acid) as an anticoagulant and were processed on SYSMEX-XS-800i autoanalyser.

Samples for FPG and HbA_{1c}

Blood sampling was performed after an overnight fast. The samples for blood glucose and HbA_{1c} were drawn from the antecubital vein. The samples for FPG were collected in plain tube and for HbA_1c were collected in the EDTA tube and were processed on ERBA EM 360 autoanalyser.

Statistical Analysis

The p value was calculated for each parameter and p value <0.05 was considered to be significant. The power of study was kept at 99% and level of significance (α) at 5%. "Correlation Coefficient *(r)"* was also done to find the correlation between glycaemic levels (HbA_{1c} & FPG) and PVI & PVI and duration of diabetes. Statistical analysis was done by the Statistical Package for Social Sciences (SPSS) version 16 for windows.

Result

A total of 1100 individuals were selected based on the laboratory investigations and all cases were subjected to clinical examination and diagnoses were reviewed, out of which 930 individuals fulfilled the selection criteria.

A total of 330 individuals were enrolled in the diabetic group (D) of which 194 (58 %) were male and 136 (42 %) were females. A total of 300 individuals were enrolled in impaired fasting glucose (I) group of which 176 (58.6 %) were males and 124 (41.4 %) were females. Non diabetic (ND) group also had a total of 300 patients of which 134 were males (44.6%) and rest were females (43.4 %).

The mean age in the diabetic group was 64.82 with a SD of 8.16. The youngest patient in this group was 45 years and the eldest patient was 99 years. The mean age in the IFG group was 60.50 with a SD of 7.34. The youngest patient in this group was 46 years and the eldest patient was 75 years. The mean age in the non diabetic group was 59.80 with a SD of 10.09. The youngest patient in this group was 37 years and the eldest patient was 82 years.

The mean fasting plasma glucose (FPG) was highest in the diabetic group (128.12 mg/dl) with a SD of 37.26, followed by the IFG group (109.36mg/dl) with a SD of 7.81 and lowest in the non diabetic group (98.90 mg/dl) with a SD of 4.26. The difference of mean of FPG between all the three groups was analyzed and it was statistically significant (p value <0.001). The mean HbA_{1c} was highest in the diabetic group (9.55%) with a SD of 1.80 followed by the IFG group (6.01%) with a SD of 0.21 and the non diabetic group (4.97%) with a SD of 0.32. The difference of mean for HbA_{1c} between all the three groups was analyzed and it was statistically significant (p <0.001).

The mean platelet count was recorded for various study groups. The mean platelet count was highest in the non diabetic group (2.97 lacs) with a SD of 0.82 followed by IFG group (2.55 lacs) with a SD of 0.71 and lowest in the diabetic group (2.51 lacs) with a SD of 0.69. The difference of mean of platelet count between all the three groups was analyzed and it was statistically significant (p value <0.001). The mean platelet volume (MPV) was highest in the diabetic group (17.60 fl) with a SD of 2.04 followed by IFG group (11.76 fl) with a SD of 0.73 and lowest in the non diabetic group 9.93 with a SD of 0.64. The difference of means of MPV between all the three groups was analyzed and it was statistically significant (p value <0.001).

The platelet distribution width (PDW) was highest in the diabetic group (19.17µm) with a SD of 1.48 followed by IFG group (15.49 µm) with a SD of 0.67 and lowest in the non diabetic groups was analyzed and it was statistically significant (p value <0.001). (Table 1, Figure 1) On correlation coefficient *r*, a positive correlation was found between PVI (MPV & PDW) and FPG, HbA_1c & duration of diabetes. (Table 2, Figure 2a, 2b, 2c, 2d, 2e, 2f). In the diabetic group, based on the presence or absence of diabetes related vascular complications two groups were formed.

Out of 330 diabetic patients, 213 patients (64.55%) suffered from diabetic complications and 117 patients (35.45%) were diabetic patients without diabetes related complications. There were 67 males & 50 females in the diabetic group without complications and 127 males & 86 females in the diabetic group with complications. The sex distribution was more equitable in the group of diabetics without complications. The mean age in the diabetic group with complication was (65.93) with a SD of 8.22 and the mean age in the diabetic group without complications was (62.80) with a SD of 7.71.

The mean duration of diabetes among those with diabetic complications was found to be 9.82 years with a SD of 3.86 and only 0.85 years with a SD of 0.93 in those without complications. (p value <0.001) The mean FPG was higher in the diabetic group with complications (129.64 mg/dL) with a SD of 42.84 as compared to the group without diabetic complications (125.37mg/dL) with a SD of 23.95. (p value 0.246) HbA_1c was also higher (10.70%) with the SD of 1.04 in the group with diabetic complications as compared to the group without complications (7.46%) with a SD of 0.65. (p value 0.001)

In diabetic patients with complications MPV was higher (18.96fl) with a SD of 0.83 as compared to the other group with MPV (15.14fl) with a SD of 1.04. (p value 0.000) Also, in diabetic patients with complications PDW was higher (20.09 fl) with a SD of 0.98 as compared to the diabetic group without complications PDW (17.51 fl) with a SD of 0.39. (p value 0.000) The platelet count was slightly decreased in diabetic group with complications (2.46 lacs) with a SD of 0.77 as compared to those without complications (2.54 lacs) with a SD of 0.53. (p value 2.340) (Table 3, Figure 3)

Table 1: Comparison of the demographics, glycaemic characteristics (FPG & HbA_{1c}), platelet counts and platelet volume indices (MPV & PDW) among different groups using ANOVA (analysis of variance).

Parameter	Diabetic Group (D) (N=330)	IFG Group (I) (N=300)	Non-Diabetic Group (N) (N=300)	F value	P value	Remark
Total No.	330	300	300	-	-	-
Male (No.)	194	176	134	-	-	-
Female (No.)	136	124	166	-	-	-
FPG (mean ± SD) (fl)	128.12 ± 37.26	109.36 ± 7.81	98.09 ± 4.26	139.23	<0.001	S
HbA_{1c} (mean ± SD) (%)	9.55 ± 1.80	6.01 ± 0.21	4.97 ± 0.32	1521.09	<0.001	S
TotalPlatelet count (mean ± SD) (lacs)	2.51 ± 0.69	2.55 ± 0.71	2.97 ± 0.82	34.56	<0.001	S
MPV (mean ± SD) (fl)	17.60 ± 2.04	11.76 ± 0.73	9.93 ± 0.64	2832.89	<0.001	S
PDW (mean ± SD) (µm)	19.17 ± 1.48	15.49 ± 0.67	10.59 ± 0.67	5345.21	<0.001	S

Table 2: Correlation coefficient (*r*) between PVI and Various Parameters

Parameter	PDW *r* value	MPV *r* value	p value	Remark
FPG	0.462 (positive correlation)	0.460 (positive correlation)	0.000	S
HbA_{1c}	0.875 (positive correlation)	0.951 (positive correlation)	0.000	S
Duration of diabetes	0.630 (positive correlation)	0.714 (positive correlation)	0.000	S

Table 3: Comparison of demographics, glycaemic characteristics (FPG & HbA_{1c}), platelet counts and platelet volume indices (MPV & PDW) between diabetic patients with complications and diabetic patients without complications.

Parameters	With diabetic complications	Without diabetic complications	z value	p value	Remark
Total (No.)	117 (35.45%)	213 (64.55%)	-	-	-
Male (No.)	67	127	-	-	-
Female (No.)	50	86	-	-	-
Age (mean ± SD)	62.80 ± 7.71	65.93 ± 8.22	-	-	-
Duration of diabetes (mean ± SD)	0.85 ± 0.93	9.82 ± 3.86	-32.25	<0.001	S
FPG (mean ± SD) (mg/dL)	129.64 ±42.84	125.37 ± 23.95	-1.16	0.246	NS
HbA_1c (mean ± SD) (%)	10.70 ± 1.04	7.46 ± 0.65	-34.76	0.001	S
MPV (mean ± SD) (fl)	15.14 ± 1.04	18.96 ± 0.83	-34.20	0.000	S
PDW (mean ± SD) (fl)	17.51 ± 0.39	20.09 ± 0.98	-33.85	0.000	S
Total Platelet count (mean ± SD) (lacs)	2.54 ± 0.53	2.46 ± 0.77	-1.11	0.267	NS

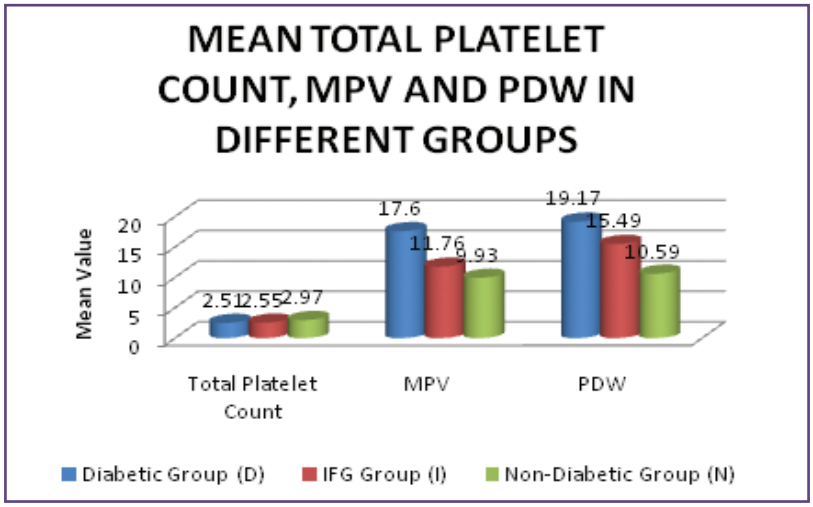

Fig. 1: Comparison of the platelet counts and platelet volume indices (MPV & PDW) of study participants in diabetics, impaired fasting group (I) and the non diabetic (D).

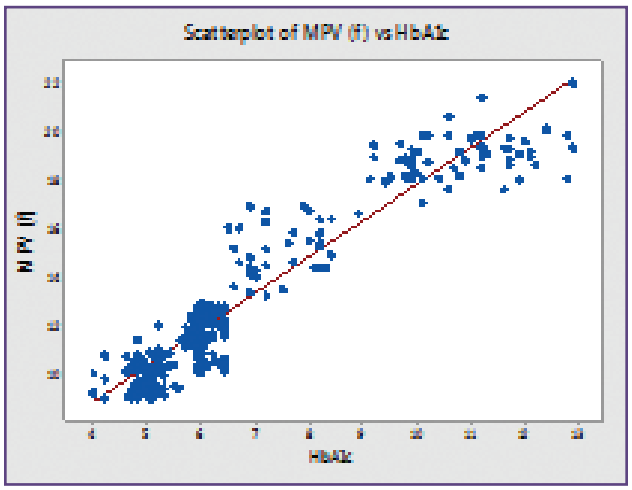

Fig. 2a: Scatter plot showing a positive correlation between MPV and HbA1c.

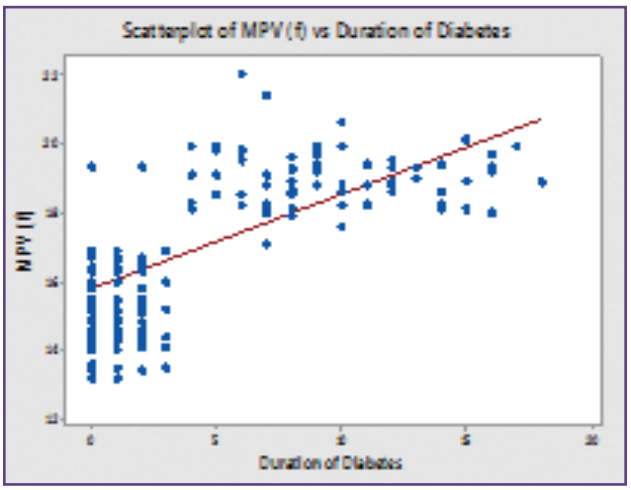

Fig. 2b: Scatter plot showing a positive correlation between MPV and duration of diabetes.

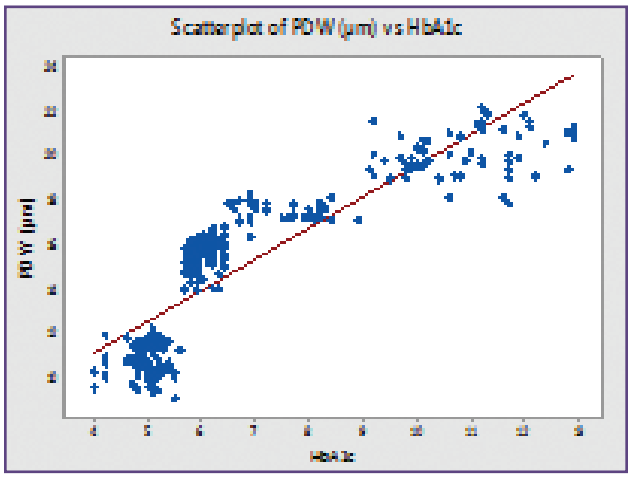

Fig. 2c: Scatter plot showing a positive correlation between PDW and HbA1c.

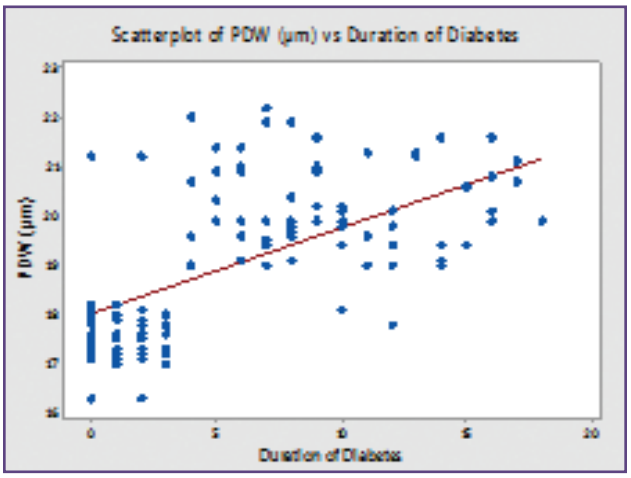

Fig. 2d: Scatter plot showing a positive correlation between PDW and duration of diabetes.

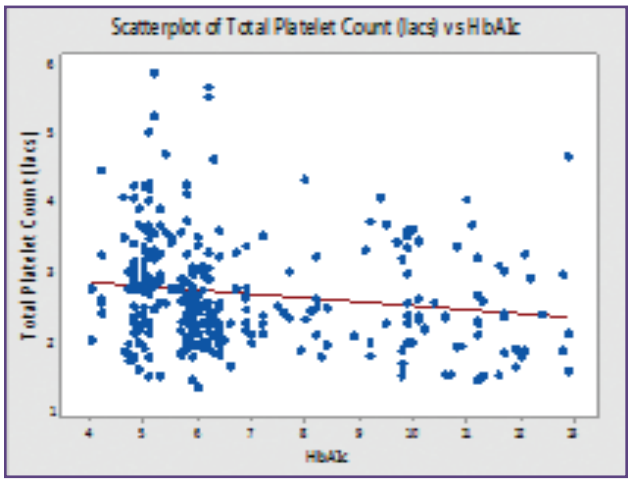

Fig. 2e: Scatter plot showing a positive correlation between Total Platelet Count and HbA1c0.

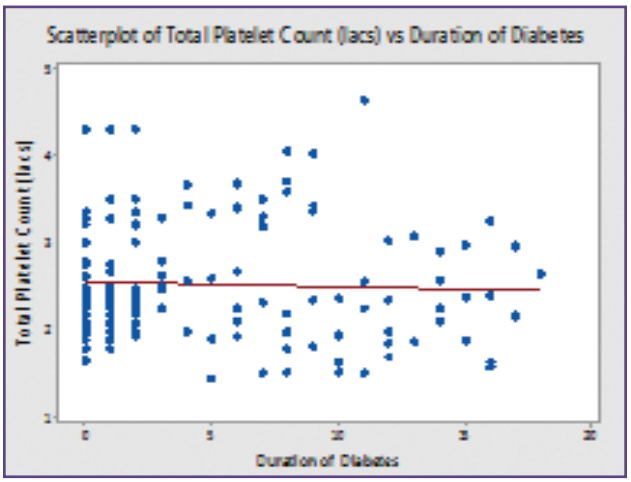

FiG. 2f: Scatter plot showing a positive correlation between Total Platelet Count and duration of diabetes.

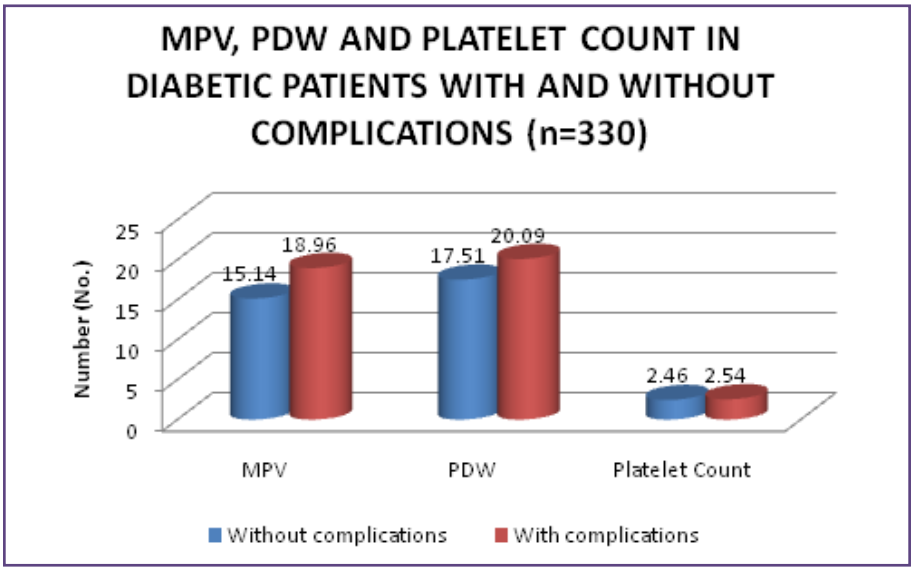

Fig. 3: Comparison of platelet counts and platelet volume indices (MPV & PDW) of study participants in diabetics with complications and diabetics without complications.

Discussion

Diabetes is increasing in leaps and bounds and so are its complications. This pandemic disorder is the cause for large scale morbidity and mortality owing to micro and macro angiopathic complications and is proving to be a big economic burden especially in poor countries with scarcity of resources.

Any marker that can be useful in predicting the onset of complications in DM will be a boon for the patient in particular and country in general. In keeping with this line of thinking, this study was undertaken

Studies have shown that there is a constant association of increased MPV with atherosclerotic diseases like coronary ischemic disease, myocardial infarction and cerebral infarct as well as with diabetes and hypertension.[4] MPV is a new emerging risk factor for atherothrombosis. In our study, MPV as a parameter was studied and evaluated across different glycaemic groups. A direct relationship was found between MPV and glycaemic status. The poorer the glycaemic control the higher was the MPV. It was found to be significantly higher in the diabetic group, followed by the IFG group. Normal MPV was found in all the non diabetic individuals. It was very conspicuously obvious that MPV increased with the duration of diabetes and it was found to be significantly higher in those with longer duration and high glucose level as compared to patients with short duration of diabetes (Figure 2 a & b). Zuberi et al (2008) [5] evaluated MPV in three different glycaemic categories (diabetics, IFG and non diabetics). The results of the present study are in agreement with this study which also reported a stepwise increase in MPV from non diabetic group to IFG group to diabetic group. Authors viz. Papanas et al (2004),[6] Demirtunc et al (2009),[7] Jindal et al (2011) [8] have compared MPV values only in diabetics and non diabetics and have found an increased MPV in diabetics as compared to the non diabetics.

The present study was compared with that of Bhayana et al (2013).[9] They documented no significant changes in MPV found in diabetic and non diabetic group (MPV in non-diabetics and diabetics was 8.04 fl). This was in contrast to our study where significantly higher MPV was found in diabetics (17.60±2.04)fl as compared to the non diabetics (9.93±0.64)fl with a significant p value. All other workers have reported results similar to the present study.

In this study, PDW as an isolated parameter was also studied and evaluated in different glycaemic groups. PDW was corroborated as being directly proportional to the glycaemic status and duration of diabetes. The patients with poor glycaemic control revealed higher values of PDW. It was found to be significantly higher in the diabetic group, followed by the IFG group whereas normal PDW was found in the non diabetic group. It was also seen that values of PDW were also affected by the duration of diabetes and were significantly higher in those with longer duration of diabetes (Figure 3 a & b). Farah Jabeen et al (2013) [10] and Kir Young Kim et al (1986) [11] evaluated and compared PDW in diabetics and non diabetics and showed an increase in PDW in diabetics as compared to the non diabetics.

Hence it can be stated that Platelet Volume Indices (PVI) increase during platelet activation. In the present

study, PVI were evaluated and compared across different groups based on glycaemic status. Stepwise increase in the PVI from non-diabetics to IFG to diabetics was observed and MPV & PDW were found in increasing order from: - Non-diabetics IFG Diabetics. They were found to have a significant linear positive correlation and a direct relationship with glycaemic control and duration of diabetes. With rising glycaemic levels, it was found that PVI levels also increased correspondingly. Similar relation was found with duration of diabetes. The longer the duration, the higher are the PVI.

The present study also evaluated and compared PVI (MPV and PDW) and platelet count amongst diabetic cases with and without vascular complications such as acute and after recovery Coronary artery disease (CAD), Diabetic retinopathy (DR), Peripheral neuropathy (PN), Peripheral vascular disease (PVD) and Diabetic nephropathy (DN).

In our analysis it was found that PVI (MPV & PDW) were significantly higher in diabetic cases with vascular complications as compared to diabetic cases without complications.

Kir Young Kim et al (1986) [11] compared MPV and PDW in patients with known platelet activation with the controls and have concluded that PVI (MPV in particular) are increased in patients with known platelet activation as seen in the vascular diseases like myocardial infarction (MI), Coronary artery disease (CAD) and Ischaemic heart disease (IHD) as compared to the healthy individuals. The findings of our study were in accordance with the results of these studies and the PVI were found to be significantly increased in patients with vascular complications of diabetes.

The present study also reported significantly higher PDW in patients suffering from Ischaemic heart disease (IHD). This was similar to the findings of Khanderkar et al (2006). [12]

Conclusion

This is the first study of its kind in India representing a pioneering effort including a large number of subjects and adequately powered to evaluate both platelet indices viz. MPV and PDW in diabetics, non diabetics and patients with IFG.

PVI are a useful means for identifying larger & active platelets which play an important role in the development of micro and macro angiopathic complications of diabetes leading to mortality and morbidity. Simultaneous and serial measurements of platelet indices is easy and therefore might serve as a valuable predictor of impending vascular complications, predict a poor outcome in patients with vascular disease and also prevent the worse outcome of these angiopathies. Due to the introduction of automated cell counters, PVI (MPV & PDW) are routinely available in almost all clinical laboratories with ease, speed and accuracy.

The prevalence of DM and its vascular burdens are increasing day by day and it's the need of the hour to prevent and monitor them. Thus, PVI should be researched and explored further as surrogate markers to develop a clinical tool for early recognition of diabetic vascular changes and thereby help prevent them. They can prove to be more useful in developing countries with limited financial resources. Patients with larger platelets can easily be identified during routine haematological analysis because PVI are generated as a by product of automated blood counts.[13]

Acknowledgements

Nil

Funding

Nil

Competing Interests

Nil

Reference

1. Mahdavi et al. The effect of seeing a family physician on the level of glycosylated hemoglobin (HbA1c) in type 2 Diabetes Mellitus patients. Journal of Diabetes & Metabolic Disorders 2013;12:2.
2. Ferroni P, Basili S. Platelet activation in type 2 diabetes mellitus. J Thromb Haemost 2004;2:1282–1291.
3. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes care 2013;36(Supplement 1):S11-S66.
4. Khemka, R., Kulkarni, K. Study of relationship between Platelet Volume Indices and Hyperlipidemia. Annals Of Pathology And Laboratory Medicine, 2014;1(1), 8-14.
5. Zuberi BF. Comparison of mean platelet volume in patients with diabetes mellitus, impaired fasting glucose and non-diabetic subjects. Singapore Medical Journal 2008;49(2):114-6.
6. Papanas N, Symeonidis G, Maltezos E. Mean platelet volume in patients with type 2 diabetes mellitus. Platelets 2004;15:475-8.

7. Demirtunc R. The relationship between glycemic control and platelet activity in type 2 diabetes mellitus. J Diabetes Complications 2009;23(2):89-94.
8. Jindal S. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. Hematology 2011;16(2):86-9.
9. Bhayana A. Is large platelet size a risk factor for acute coronary syndrome: A retrospective case-control study. J MGIMS, 2009 Sep;14(ii):52-55.
10. Farah Jabeen. Role of platelet indices, glycemic control and hs-CRP in pathogenesis of vascular complications in type-2 diabetic patients. Pak J Med Sci 2013;29(1):152-156.
11. Kim KY. Mean platelet volume in the normal state and in various clinical disorders. Yonsei Medical Journal 1986;27(3).
12. Khandekar MM, Khurana AS. Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: an Indian scenario. J Clin Pathol 2006;59:146–149.
13. Manchanda, J, Potekar R, Badiger S, Tiwari, A. The study of platelet indices in acute coronary syndromes. Annals Of Pathology And Laboratory Medicine, 2015;2(1), A30-A35.