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PDW: An Unexplored Marker of Diabetes Related Angiopathies

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Abstract

Objectives: The aim is to determine and compare Platelet distribution width (PDW) with glycaemic levels and duration of diabetes and to assess utility of PDW in early identification of vascular complications especially in developing countries like India. Methods: A two year prospective analytical case control study with total 930 individuals segregated into three groups on basis of HbA1c:- (a) Subjects with Diabetes (b) Subjects with Impaired fasting glucose (IFG) (c) Subjects without Diabetes. Further, diabetic group was divided into two groups on the basis of known diabetes related vascular complications. Samples for HbA1c and PDW were obtained and processed on SYSMEX-X-800i autoanalyser. Results: The study revealed significant positive correlation between PDW with glycaemic levels and duration of diabetes across the groups (PDW-HbA1c r = 0.875). PDW of diabetics, IFG and non diabetics was 19.17 ± 1.48, 15.49 ± 0.67 and 10.59 ± 0.67 respectively with a significant p value 0.00. PDW was higher in diabetic group with complications (20.09 ± 0.98 fl) as compared to the diabetic group without complications (17.5 1± 0.39 fl) with a significant p value (0.000).Conclusion:The current study demonstrates raised PDW in association with rising glycaemic levels and in those with diabetes related vascular complications. PDW should be researched and explored further as surrogate marker to develop a clinical tool for early recognition of diabetic vascular changes.

Keywords: PDW, IFG, HBA1c, Diabetes

INTRODUCTION

In Diabetes mellitus, there is an increased risk for vascular complications due to imbalance amongst various systems responsible for maintaining the integrity of endothelium of the blood vessels. This causes disturbances in the normal homeostasis initiating a vicious cycle of events in the vascular wall which includes platelet hyperactivity and dysfunction, increased inflammation, altered coagulation and endothelial dysfunction. These complications are attributed to platelet activation recognised by an increase in Platelet Volume Indices (PVI) which include Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW). The metabolic state in DM alters platelet and endothelial function in early stages of diabetes.[1]

Pathophysiologically platelets may cause vascular injury and tissue damage by three principal mechanisms: triggering of acute arterial thrombosis, microembolisation of the capillaries and enhancing the local progression of vascular lesions.[2] It has been reported that predominantly large platelets which are more reactive, circulate in patients with DM and this has been considered to reflect an activated megakaryocyte-platelet system.[3] PDW is an indication of variation in platelet size which can be a sign of active platelet release. PDW is more specific and authentic in knowing the activation and dysfunction of platelets as it is not affected by osmotic swelling due to raised blood glucose and shorter life span of platelets.[4,5]

Among all indices, the PDW has been receiving attention due to its usefulness for distinguishing between reactive thrombocytosis and thrombocytosis associated with other vascular disorders. Determination of the PDW reference range is fundamental, and the association of this parameter with the platelet number and mean platelet volume may be used for the diagnosis and differentiation of several vascular pathologies.

This is the first study of its kind in India which has included a large number of subjects to evaluate PDW in diabetics, non diabetics and patients with IFG. This study represents a pioneering effort in India on account of the fact that both platelet indices as well as platelet count have been evaluated together for the first time in Diabetics, non diabetics and patients with IFG and also in the diabetic patients with vascular complications. Moreover the large sample volume of the study has made it statistically significant.

MATERIALS AND METHODS

This study was conducted in the Department of Pathology, Index Medical College and associated Hospital, Indore for a 2 years period from June 2012 to June 2014. The study protocol was implemented after obtaining approval and due clearances from the Ethical Committee of the institute. This is a prospective analytical case control study.The cases and controls were those attending the Out Patient Department (OPD) and admitted in the hospital. A total of 1100 individuals were selected based on the laboratory investigations and all cases were subjected to clinical examination and diagnoses were reviewed. All patients for whom HbA1c level and FPG was requested by the clinician were included and segregated into 3 groups according to the ADA criteria[6] :- the patients with HbA1c < 5.7% were considered as controls and put into non-diabetic (ND) group, those with HbA1c between 5.7% to 6.4% were considered as pre-diabetic and put into IFG (I) group and patients with HbA1c 6.5% were considered as diabetics and put into the diabetic (D) group.

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

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antiplatelet drug therapy were excluded. Pregnant women were also excluded from the study.

Samples for the platelet count and indices were collected using K3 EDTA (ethylene diamine tetra acetic acid) as an anticoagulant and were processed on SYSMEX-XS-800i autoanalyser. Platelet volume indices were determined by this instrument according to the Hydro Dynamic Focusing (DC Detection) and flow cytometry method (using a semi conductor laser). MPV and PDW were calculated as:-

PDW (Platelet Distribution Width)

With the peak height assumed to be 100%, the distribution width at the 20% frequency level is PDW.The reference range for PDW was taken as :- 9.0 – 17.0 fl

Blood sampling was performed after an overnight fast. The samples for FPG were collected in plain tube and for HbA1c were collected in the EDTA tube. Samples for glycosylated haemoglobin were processed on the fully automatic autoanalyser "ERBA EM 360."

The obtained data was tabulated using MS Excel to create a master chart. "Analysis of Variance (ANOVA)" was done to calculate the F value to compare the difference of mean of three study groups together. "Post Hoc Tukey's test" was also applied for comparison of difference of mean in two study groups. The p value was calculated for each parameter and p value <0.05 was considered to be significant. 95% CI and t value were also calculated. The power of study was kept at 99% and level of significance (α) at 5%. Statistical analysis was carried out with Statistical Package for Social Sciences (SPSS) version 20.0 for windows.

RESULTS

Out of the patients attending the hospital (both OPD & IPD), a total of 1100 patients were enrolled for study. Out of these 930 individuals were found fulfilling inclusion criteria and eligible for data analysis.

A total of 330 individuals were enrolled in the diabetic group (D) of which 194 (58 %) were males and 136 (42 %) were females. A total of 300 individuals were grouped under 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 glycaemic levels, platelet volume indices (PVI) and platelet counts of all patients were analyzed and compared as per their groups.

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 0.000).

The mean HbA1c 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 HbA1c between all the three groups was analyzed and it was statistically significant (p 0.000).

The mean platelet counts were 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 0.000).

The Mean Platelet Volume (MPV) was significantly higher 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 0.000).

The Platelet Distribution Width (PDW) was highest in the diabetic group (19.17fl) with a SD of 1.48 followed by IFG group (15.49 fl) with a SD of 0.67 and lowest in the non diabetic group (10.59 fl) with a SD of 0.67. The difference of means of MPV between all the three groups was analyzed and it was statistically significant (p value 0.000). (Table 1)

On correlation coefficient r, a positive correlation between PDW and FPG, PDW and HbA1c and PDW and duration of diabetes was found. (Table 2)

On correlation analysis, a statistically significant positive association of PDW with FPG (r 0.462, p value 0.000), HbA1c (r 0.875, p value 0.000) and duration of diabetes (r 0.630, p value 0.000) was found. (Figure 1 a, b, c)

This shows that PDW is directly proportional to the glycaemic levels and duration of diabetes and with increase in the glycaemic levels and duration of diabetes, PDW also increases.

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 duration of diabetes was compared in the two diabetic groups with and without diabetic complications. 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)

Comparison of total number of complicated cases of diabetes showed that out of total 330 diabetic cases, 80 cases (24.24%) suffered from coronary artery disease, 40 cases (12.12%) from peripheral arterial diseases, 36 cases (10.90%) from peripheral neuropathy, 33 cases (10%) from diabetic neuropathy and 24 cases (7.27%) suffered from diabetic retinopathy.

Table 1. Comparison of the demographic, glycaemic characteristics (FPG & HbA1c), platelet counts and platelet volume indices (MPV & PDW) using ANOVA

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**

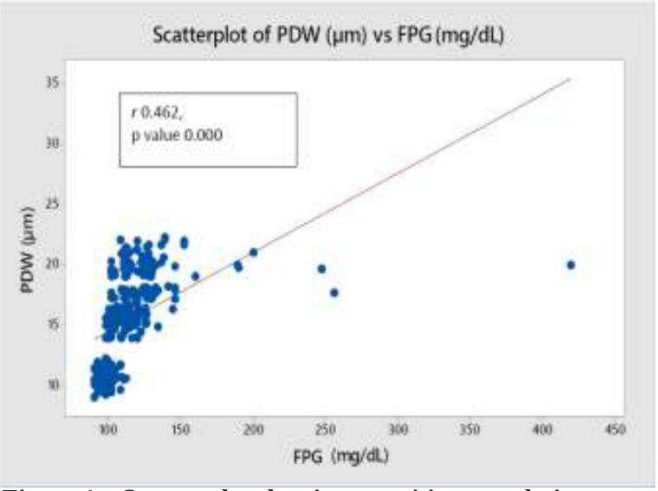

Figure 1a. Scatter plot showing a positive correlation between PDW and FPG

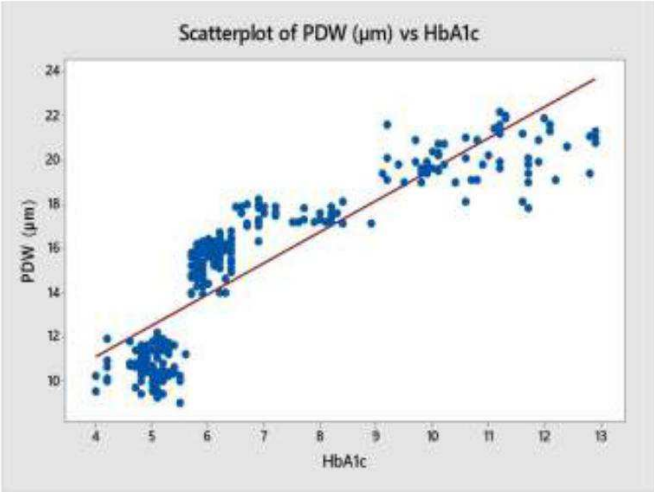

Figure 1b. Scatter plot showing a positive correlation between PDW and HbA1c

Comparison of glycaemic characteristics of diabetic patients with complications and patients without complications was done. 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)

HbA1c 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)

Comparison of PDW of diabetic patients with complications and patients without diabetes related complications was done. 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). (Table 3)

DISCUSSION

Diabetes cause 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 like India. Any marker that can be useful in predicting the onset of

Table 2. Correlation coefficient (r) between PDW and Various Parameters

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

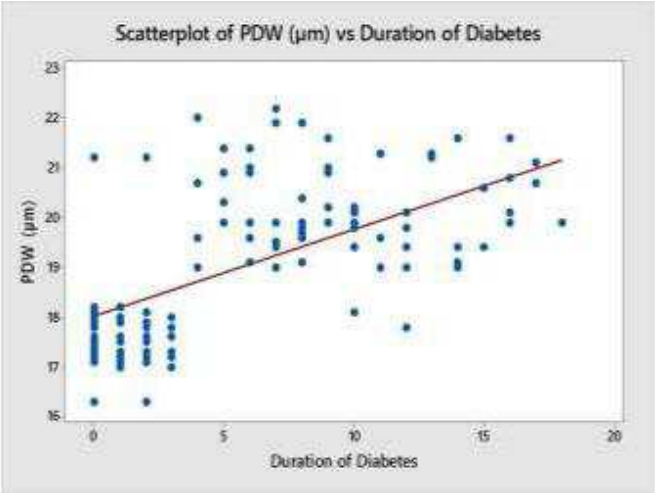

Figure 1c. Scatter plot showing a positive correlation between PDW and duration of diabetes

Table 3. Comparison of demographic, glycaemic characteristics (FPG & HbA1c), platelet counts and platelet volume indices (MPV & PDW) in 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

complications in DM will be a boon for the patient in particular and India in general. Only very few studies from all over the world are available that have evaluated PDW in patients according to their glyacemic status.

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.

In literature no study has ever evaluated and compared PDW in three glycaemic groups viz. diabetics, non diabetics and patients with IFG. Though, few workers have compared this parameter between diabetics and non diabetics. In our study we have added the third dimension of IFG as a better predictable factor.

Jabeen F et al (2013),[7] and Kir Young Kim et al (1986),[8] evaluated and compared PDW in diabetics and non diabetics and showed an increase in PDW in diabetics as compared to the non diabetics. However, the present study found a significantly higher PDW in diabetics and the IFG group as compared to the non diabetics and confirmed a direct relationship of PDW with the glycaemic levels revealed by significant p value.

The present study also evaluated and compared PDW 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 PDW were significantly higher in diabetic cases with vascular complications as compared to diabetic cases without complications.

It is postulated that generalized platelet activation occurs before an acute coronary event. The increase in platelet consumption at the site of coronary atherosclerotic plaque causes larger platelets to be released by bone marrow. It has been emphasized that the high PVI even persists after the acute event is over. This extrapolates to the fact that PVI are indicators of the damage already done and these markers maintain their strength and predictive value for a long time.[9]

Vagdatli et al (2010).[5] and Kir Young Kim et al (1986),[8] compared 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 PDW was found to be significantly increased in patients with vascular complications of diabetes.

CONCLUSION

The current study demonstrates raised PDW in association with rising glycaemic levels across the various study groups. PDW can be used as cost effective markers to predict and prevent the angiopathic complications of diabetes. It 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 all the more useful in developing countries like India.

ABBREVIATIONS

ADA:	American Diabetes Association
D:	Diabetic
DM:	Diabetes Mellitus
FBS:	Fasting Blood Glucose
FPG:	Fasting Plasma Glucose
HbA1c:	Glycosylated Haemoglobin
IFG:	Impaired Fasting Glucose
MPV:	Mean Platelet Volume
ND:	Non Diabetic
PDW:	Platelet Distribution Width

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