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ORIGINAL ARTICLE

A Study of Platelet Indices in Type 2 Diabetes Mellitus Patients

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Abstract Altered platelets have been reported in patients with diabetes mellitus and has been considered as a 'pro-thrombotic state' with enhanced platelet reactivity. They have been associated with increased risk of vascular complications in these patients. Platelet indices correlate with functional status of platelets and is an emerging risk factor of vascular complications in diabetes. The study was undertaken to know the efficacy of platelet analysis in assessing the prognosis of diabetes mellitus. A prospective hospital based study of platelet parameters MPV, PDW and P-LCR was carried out on 280 cases diagnosed with Type 2 diabetes Mellitus and 280 controls with normal blood glucose levels. The blood glucose levels and HbA1c level were also measured. Statistical evaluation was performed by using Student's unpaired *t* test and Pearson correlation test. The average age of presentation with type 2 diabetes mellitus was 53 ± 5.7 years. The mean duration of diabetes was 4.7 ± 2.5 years. MPV, PDW and P-LCR were significantly higher in diabetics compared to non diabetics (11.3 ± 1.0 vs. 9.0 ± 0.6, 14.2 ± 2.5 vs. 10.7 ± 0.7 fl, 35.0 ± 8.1 vs. 23.0 ± 2.4%). Among the diabetics, MPV, PDW and P-LCR were higher in those with complications as compared to those without complications, which was not statistically significant. The higher values of MPV, PDW and P-LCR indicates that they serve as better risk indicator of initial vascular complications in diabetes mellitus patients and can be used as a simple and cost effective tool to assess vascular events.

Keywords Mean platelet volume · Platelet distribution width · Platelet-large cell ratio · Diabetes mellitus

Introduction

Definition

World Health Organization (WHO) defines diabetes mellitus (DM) as a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Diabetes Mellitus currently affects more than 171 million people worldwide and will affect an estimated 366 million by 2030. India will be the country with the maximum number of diabetics in the world by 2030. In 2014, 40.9 million people were affected with diabetes in India and the projected estimate for the year 2030 is 80 million [1].

People with diabetes, exhibit increased platelet reactivity. Hyperglycemia contributes to greater platelet reactivity through direct effects and by promoting glycation of platelet proteins. Both insulin resistance and insulin deficiency increase platelet reactivity. Insulin inhibits activation of platelets. Therefore, relative or absolute deficiency of insulin would increase platelet reactivity [2].

Mean platelet volume (MPV) is an indicator of average size and activity of the platelets and is reported to be high in diabetes mellitus and is considered as a risk factor for heart disease. Similarly platelet distribution width (PDW) is an indicator of variation in platelet size which may be a

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sign of active platelet release. Platelet large cell ratio (P-LCR) is directly related to PDW and MPV [3].

Although several measurements of platelet activity have emerged as potential contributors to atherothrombosis, many of them are time consuming, expensive and use a high sample volume. Alternatively, MPV, PDW and P-LCR can be easily determined on routine automated hemograms available at low cost. Patients with larger platelets can easily be identified during routine haematological analysis and timely treatment could be undertaken.

Materials and Methods

Ethics Approval was Granted by the Institution

A cross sectional hospital based study was carried out on 280 diagnosed cases of Type 2 DM from November 2013 to June 2015 fulfilling the inclusion and exclusion criteria attending either outpatient or inpatient department and compared with 280 controls with normal blood glucose levels. The prevalence rate of diabetes mellitus in India was taken as 9.3% [4]. At 95% confidence interval and ±5% margin of error, the required sample size was calculated using the statistical formula

$$n = \frac{(Z\alpha)^2 p \times q}{d^2}$$

$Z\alpha = 1.96$ for α value; Where p: prevalence rate, $q = 100 - p$; d: margin of error.

Cut off values of platelet indices have been derived by calculating the minimum value of these indices in the diabetic cases. All the diabetic and nondiabetic subjects were interviewed as per the prepared proforma and underwent a complete clinical evaluation with specific reference to any associated macro-or microvascular complications as well as any drugs taken. Relevant investigations like blood glucose levels and HbA1c level was performed for confirmation of the diagnosis. The instrument used for HbA1c and other glucose parameters was Roche Hitachi Cobas c311 (Hitachi Ltd, Tokyo, Japan). The blood samples of the patients were drawn from the antecubital vein using a 5 ml syringe and immediately mixed in EDTA vacuutainers. The sample was run within 2 h of venepuncture using the five part differentiated automated Hematology analyzer Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) and complete blood count analysis of the sample was made including the platelet indices (MPV, PDW and P-LCR). Statistical tests used for handling the data was unpaired t test for mean and comparison and also Pearson correlation coefficient to correlate various platelet indices with biochemical parameters. The statistical software used for the study was SPSS Version 24 [International Business Machines Corporation (IBM), United States].

Exclusion Criteria

Male patients with hemoglobin below 13 gm% and female patients with Hb below 12 gm%. Subjects on antiplatelet drugs such as aspirin and clopidogrel and with any diagnosed malignancy were also excluded from the study. After baseline evaluation, diabetic patients were divided into two groups according to their HbA1c levels: group A consisted of patients with HbA1c levels <6.5% and group B consisted of patients with HbA1c levels ≥6.5%. The latest HbA1c cut-off for diabetic range was considered according to American Diabetic Association 2016 criteria.

Results

280 Type 2 diabetic cases and 280 controls with normal blood glucose parameters were included in the present study. In the present study, the age ranged from 45 to 70 years. The mean age of diabetic patients in our study was 53 ± 5.7 years and that of the control group was 54.1 ± 5.2 years. Majority of the patients diagnosed with Type 2 DM belonged to 5th decade of life. The mean duration of diabetes was 4.7 ± 2.5 years. In the present study total number of males including both cases and controls were 315 (56.25%) and total number of females were 245 (43.75%). The number of males in the diabetic group were 144 (51.43%) compared to 171 (64.57%) in non-diabetic group. The numbers of females in diabetics were 136 (48.57%) compared to 109 in non diabetics.

Out of 280 patients in the present study, 117 (41.79%) patients had complications such as diabetic foot, hypertension, coronary artery disease, diabetic retinopathy, diabetic nephropathy, autonomic neuropathy, peripheral neuropathy, peripheral vascular disease, hypercholesterolemia and hypertriglyceridemia and 163 (58.21%) cases did not present with complications. Sixty-nine of the 144 males and forty-eight of the 136 females had diabetic complications.

The blood glucose parameters (FBS, RBS, PPBS and HbA1c) were statistically significantly higher in diabetics compared to the non-diabetics (p value <0.001). The MPV, PDW and P-LCR were evaluated in diabetic and non diabetic population. The mean MPV in diabetic cases were 11.3 ± 1.0 fl compared to 9 ± 0.6 fl in non diabetics with p value 0.004. Mean PDW and P-LCR in diabetic patients were 14.2 ± 2.5 fl and 35.0 ± 8.1% compared to non diabetics where it was 10.7 ± 0.7 fl and 23.0 ± 2.4% respectively. Our study observed p value of MPV, PDW

and P-LCR to be highly significant in diabetic patients ($p < 0.05$) (Table 1).

Among the diabetic subjects, a positive statistical Pearson correlation was observed between MPV, PDW and P-LCR with HbA1c, FBS, RBS, PPBS, and complications. However, no statistical correlation was seen between MPV, PDW and P-LCR and the duration of DM in the diabetic group (Table 2).

Diabetic patients were also divided into two groups after baseline evaluation according to their HbA1c level. Out of 280 Type 2 DM cases, there were 60 patients (21.43%) in group A (mean HbA1c <6.5%) and 220 patients (78.57%) in group B. The mean MPV in group B (11.7 ± 1.0 fl) was significantly higher in group A (11.1 ± 1.2 fl). Significantly higher mean PDW in group B (14.3 ± 2.4 fl) was observed in our study compared to group A (13.5 ± 2.7 fl). Our study also observed stastistical significant difference between mean P-LCR in group B (35.6 ± 7.7%) than group A (32.7 ± 9.1%). Duration of diabetes was not statistically significant between groups A&B (p value 0.746) (Table 3).

Platelet indices were also compared between diabetic patients with and without complications. Although the mean of MPV, PDW and P-LCR was higher in diabetics with complications (11.5 ± 1.4, 14.4 ± 2.7 fl and 35.9 ± 8.3%) than without complications (11.3 ± 1.0, 13.9 ± 2.1 fl and 34.4 ± 7.8%) it was not statistically significant (p value of MPV = 0.105, PDW = 0.098 and P-LCR = 0.104; Table 4).

Discussion

Diabetes mellitus is not a single disease entity but rather a group of metabolic disorders sharing the common underlying feature of hyperglycemia. The chronic hyperglycemia and metabolic dysregulation may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes and blood vessels [5].

Diabetes mellitus is a major global health problem [6]. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". It is one of the major causes of morbidity and mortality affecting youth and middle aged people in India [5]. The mean age of onset is 42.5 years. The estimated prevalence of Impaired Glucose Tolerance (IGT) is thought to be around 8.7 and 7.9% in urban and rural areas. It is thought that around 35% of IGT sufferers go on to develop type 2 diabetes so India is genuinely facing a healthcare crisis [7].

Therefore, preventing vascular complications and monitoring of DM are the need of the hour. Type 2 DM

Table 1 Comparison of mean of blood sugar and platelet indices among diabetic cases and non-diabetic controls

Parameters	Diabetic (n = 280) Mean ± SD	Non-diabetic (n = 280) Mean ± SD	t test p value (2 tailed)
HbA1c (%)	7.3 ± 1.1	3.3 ± 0.4	0.004
FBS (mg/dl)	158.1 ± 33.7	81.7 ± 5.1	0.002
RBS (mg/dl)	214.2 ± 42.1	118.3 ± 20.6	0.002
PPBS (mg/dl)	235.6 ± 38.5	145.8 ± 9.2	0.005
MPV (fl)	11.3 ± 1.0	9.0 ± 0.6	0.004
PDW (fl)	14.2 ± 2.5	10.7 ± 0.7	0.003
P-LCR (%)	35.0 ± 8.1	23.0 ± 2.4	0.002

Table 2 Correlation of MPV, PDW and P-LCR with various parameters studied among diabetic cases

Characteristics	MPV (fl)		PDW (fl)		P-LCR (%)	
	Correlation coefficient (r value)	p value	Correlation coefficient (r value)	p value	Correlation coefficient (r value)	p value
HbA1c (%)	0.148	<0.001	0.171	<0.001	0.164	<0.001
FBS (mg/dl)	0.055	<0.01	0.098	<0.001	0.091	<0.001
RBS (mg/dl)	0.011	<0.001	0.049	<0.05	0.021	<0.02
PPBS (mg/dl)	0.029	<0.05	0.075	<0.02	0.052	<0.05
Duration of diabetes (years)	0.126	0.538	0.161	0.553	0.140	0.148
Complications	0.097	<0.05	0.099	<0.02	0.097	<0.001

Table 3 Comparison of diabetic cases in group A and group B

Parameters	Group A Hba1c < 6.5% (n = 60) Mean ± SD	Group B Hba1c ≥ 6.5% (n = 220) Mean ± SD	*t* test *p* value (2-tailed)
Age (years)	50.2 ± 5.6	53.8 ± 5.5	0.001
MPV (fl)	11.1 ± 1.2	11.7 ± 1.0	0.024
PDW (fl)	13.5 ± 2.7	14.3 ± 2.4	0.022
P-LCR (%)	32.7 ± 9.1	35.6 ± 7.7	0.013
FBS (mg/dl)	137.9 ± 12.4	163.7 ± 35.5	0.002
RBS (mg/dl)	183.5 ± 17.6	222.6 ± 42.9	0.004
PPBS (mg/dl)	212.1 ± 24.7	242.1 ± 39.1	0.001
Duration of diabetes (Years)	3.4 ± 1.6	3.6 ± 1.7	0.746

Table 4 Comparison of selected parameters among diabetic patients with and without complications

Parameters	Complications absent (n = 163) Mean ± SD	Complications present (n = 117) Mean ± SD	*t* test *p* value (2-tailed)
MPV (fl)	11.3 ± 1.0	11.5 ± 1.4	0.105
PDW (fl)	13.9 ± 2.1	14.4 ± 2.7	0.098
P-LCR (%)	34.4 ± 7.8	35.9 ± 8.3	0.104
HbA1c (%)	7.0 ± 1.0	7.8 ± 1.1	0.005
FBS (mg/dl)	149.6 ± 24.2	168.9 ± 36.3	0.004
RBS (mg/dl)	200.9 ± 30.6	227.9 ± 43.1	0.007
PPBS (mg/dl)	225.3 ± 26.9	266.8 ± 43.0	0.002
Duration of diabetes (Years)	3.3 ± 1.3	6.7 ± 2.3	0.025

accounts for 90–95% of all DM cases. They exhibit insulin resistance and consequent hyperinsulinemia for 10–20 years before manifesting diabetes. Deficient insulin action is the cardinal factor for development of DM and clearly contributes to platelet dysfunction [8].

Platelets from patients with type 2 diabetes mellitus have increased reactivity and baseline activation which are likely to play a key role in development and sustainment of vascular complications [9]. Sustained hyperglycemia leads to a series of interrelated alterations that can cause evident endothelial dysfunction and vascular complications. Moreover, hyperglycaemia-induced up-regulation of glycoproteins (Ib and IIb/IIIa), and P2Y12 signalling which are key events underlying atherothrombotic risk in T1DM and T2DM [10]. Formation of advanced glycation end products, activation of protein kinase C and disturbances in polyol pathways are the possible mechanisms by which increased glucose induces vascular abnormalities [11].

Human platelets are anucleate discoid cells that circulate in the bloodstream and participate in hemostasis. In response to stimuli generated by the endothelium of blood vessels, platelets change shape, adhere to subendothelial surfaces, secrete the contents of intracellular organelles, and aggregate to form a thrombus [12]. Higher MPV in diabetic patients indicates larger platelet size suggesting stimulated thrombopoiesis and augmented platelet activation [13]. Platelet hyperactivity is accompanied by an increased production of thromboxaneA2, serotonine, thromboglobulin or a decreased synthesis of prostacycline. One possible mechanism of increased MPV in DM is osmotic swelling due to raised blood glucose and perhaps due to a shorter life span of platelets in diabetic patients [14].

In our study, the MPV was significantly higher in the diabetic group than the nondiabetic controls which was similar to the studies done by other researchers (Table 5). In an earlier study by Akinsegun et al. [18] showed lower MPV in diabetic cases compared to the controls with no statistical significant difference.

In addition, other platelet indice PDW was also significantly higher in diabetic subjects compared to controls (p 0.003 respectively). Similar results were noted in other studies done by Demirtas et al. [22], Jabeen et al. [23] and Dalamaga et al. [24] with significantly higher PDW levels among diabetic cases (Table 6).

The P-LCR is not often quoted in literature, probably because it is relatively a new platelet volume parameter. It is generated by only a few machines, with the Sysmex analyser being one of them. Our study concluded that P-LCR was significantly higher (p value 0.002) in diabetic

Table 5 Comparison of MPV with other studies

Publication	Cell counter	Cases	MPV (fl)	Controls	MPV (fl)	*p* value
Kodiatte et al. [11]	Beckman coulter Act5Diff	300	8.29	300	7.47	<0.001
Jindal et al. [15]	Sysmex SF 3000	75	12.08	50	11.42	<0.05
Zuberi et al. [16]	Sysmex autoanalyzer	204	9.34	204	8.63	0.000
Demirtunc et al. [17]	Cell Dyn 3500	70	8.7	40	8.2	0.002
Akinsegun et al. [18]	Sysmex KN-21 N	100	8.69	100	8.91	0.593
Ozder and Eker [19]	Sysmex 1800t	201	10.66	201	10.04	<0.001
Ulutas et al. [20]	Abbott cell dyn 3200	65	8.3	40	7.1	<0.001
Papanas et al. [21]	Sysmex SF-3000	265	14.2	151	7.1	0.01
Present study	Sysmex XN-1000	280	11.3	280	9	<0.05

Table 6 Comparison of PDW with other studies

Publication	Cases	PDW (fl)	Controls	PDW (fl)	*p* value
Demirtas et al. [22]	307	16.4	187	15.4	<0.001
Jabeen et al. [23]	170	15.02	92	14.12	0.003
Dalamaga et al. [24]	30	16.4	30	13.0	<0.001
Present study	280	14.2	280	10.7	0.003

cases. This is in agreement with the studies done by Jindal et al. [15] and Ashraf et al. [25] which concluded significantly higher P-LCR in diabetes compared to non diabetics.

In agreement with studies done by Kodiate et al. [11] and Mowafy et al. [10], our study showed non statistically significant higher MPV in diabetic patients with micro and macrovascular complications than nondiabetic controls. However Papanas et al. [21] and Demirtas et al. [22] concluded significantly higher MPV in diabetics with complications than without complications in their study. This suggested a role for the increased platelet activity in the pathogenesis of vascular complications.

Furthermore, non significant higher levels of PDW and P-LCR were also observed in diabetics with complications in our study. Similar finding was observed in study done by Mowafy et al. [10]. However, in contrast to our study, Jindal et al. [15] observed a statistically significant higher PDW and P-LCR in diabetics with complications than without complications.

In our study, MPV, PDW and P-LCR were significantly higher in diabetics with HbA1c levels ≥6.5% than in diabetics with HbA1c levels <6.5%. This is in agreement with the studies conducted by Kodiatte et al. [11], Ozder and Eker [19], Ulutas et al. [20] and Demirtas et al. [22].

There were higher number of diabetics with HbA1c levels ≥6.5% which is similar to the observation in the study done by Kodiatte et al. [11] This might have been due to poor dietary practices and lack of knowledge regarding the diet and exercise regimens that ought to be followed in diabetes. Ozder and Eker [19] also concluded that as glycemic control improves, HbA1c and MPV tends to decrease. Therefore, it may be concluded that glycemic control improves platelet activity and function and may delay possible diabetic vascular complications.

Limitations of the Study

Follow up of the cases was not possible to determine the prognostic significance of our findings. Platelet function tests could not be conducted on the sample to substantiate our findings further. Patients with qualitative disorders and reactive causes for raised platelets were not assessed that constitute a minor role.

Conclusion

Our study suggest that increased platelet volume indices and larger platelets contributes to the prothrombotic state in diabetes mellitus. Because larger platelets are hemostatically more active, therefore its presence probably is a risk factor for developing diabetic vascular complications. Platelets with larger platelets can be easily identified during routine hematological analysis as MPV, PDW and P-LCR are generated as by product of the automated blood counts. Hence, MPV, PDW and P-LCR would be a useful prognostic marker of vascular complications in diabetes. Therefore, the derived cut off values of platelet indices MPV, PDW and P-LCR studied for vascular complications to warn the diabetes patients compared to non-diabetics were 9.6, 12.2 fl and 18.4%. However, the increased MPV, PDW and P-LCR as the cause or the end result of vascular complications needs to be further explored. Thus, platelet volume indices MPV, PDW and P-LCR provides an

important, simple, effortless and cost effective tool which can be useful in predicting an impending thrombotic state and vascular complications of diabetes.

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Compliance with Ethical Standards

Conflict of interest Author Dr. Kumari Shilpi declares that she has no conflict of interest. Author Dr. R. M. Potekar declares that he has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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