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Platelet indices as surrogate markers of complications in T2DM patients

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Abstract
Background and Objective: Type 2 diabetes mellitus (T2DM) is a prothrombotic state induced by multiple mechanisms, and increased platelet activity being one of the important mechanisms among them. The aim of this study was to evaluate platelet indices in T2DM patients with and without overt complications and to assess their usefulness as markers of vascular complications in patients with T2DM.
Material and Methods: A total 100 T2DM patients (50 with overt complications and 50 without any overt complication) were enrolled. Venous samples from the subjects were collected in EDTA tubes and analyzed with in 2 hours using the same automated cell counter (Mindray, Model BC-5800). Student t-test and Chi-square test were used to analyze the data.
Results: MPV (Mean Platelet volume), PDW (Platelet Distribution Width), P-LCC (Platelet Large Cell Count) and P-LCR (Platelet Large Cell Ratio), were higher in T2DM patients with overt complications as compared to T2DM patients without overt complications, but the difference was statistically significant only for PDW (p = 0.305 for MPV; p = 0.01 for PDW; p = 0.653 for P-LCC; p=0.189 for P-LCR). MPV, PDW, P-LCC and P-LCR, were higher in T2DM patients with overt macrovascular complications (n = 41), versus T2DM patients without overt complications (n = 50), and the difference was statistically significant for MPV, PDW, and P-LCR (p =0.05 for MPV; p = 0.004 for PDW; p = 0.399 for P-LCC, p = 0.02 for P-LCR). No significant difference was noted in Plateletcrit (PCT) between different groups.
Conclusion: MPV, PDW and P-LCR, tend to be higher in T2DM patients with overt macrovascular complications, as compared to T2DM patients without overt complications.

Keywords: diabetes mellitus, myocardial infarction, platelets, P-LCR, stroke

Introduction

Type 2 diabetes mellitus (T2DM) has emerged as a big epidemic in 21st century, and along with its complications, it is taking large share in healthcare expenditure in most parts of the world including India. T2DM has a gradual onset and quite often it is diagnosed due to the presence of macrovascular complications like myocardial infarction (MI), stroke, peripheral arterial disease and/or microvascular complications (neuropathy, nephropathy, retinopathy) [1, 2]. There seems to be a need to find tools to diagnose or predict these complications at an early stage. It has been shown that there is increased thrombotic tendency in Diabetes Mellitus, and the increased platelet activity has an important role in the genesis of these complications, especially the thrombotic events (myocardial infarction and stroke) [3, 5].

Further, platelet size is emerging as a measure of its function. Larger platelets carry higher number of dense granules and are more reactive and aggregable as compared to platelets of smaller size. Thus, large platelets are more active and thrombogenic than smaller platelets [6, 8].

Nowadays, the platelet indices are easily available at most medical centers, delivered by automated cell counters. Platelet indices are measured by same techniques that are used to size erythrocytes. *Mean platelet volume* (MPV) is a measure of the average size of platelets. *Platelet distribution width* (PDW) is a measure of platelet anisocytosis. *Plateletcrit* (PCT) is a measure of platelet mass, the product of MPV and platelet count, by analogy with hematocrit. *Platelet large cell count* (P-LCC) is the number of platelets with size threshold more than 12 fl. The *platelet-large cell ratio* (P-LCR) is the percentage of platelets with a size above the 12 fl threshold. (P-LCR=P-LCC/PLT). PLT is the absolute platelet count [9, 11].

In recent years, platelet indices especially MPV and PDW have been revealed to be higher in diabetic patients as compared to the healthy subjects. Increase in MPV has also been reported in myocardial infarction, stroke, and proliferative diabetic retinopathy. Thus, MPV being taken a representative of platelet function, is emerging as a risk factor for atherothrombosis. These findings give a clue, that in diabetic patients, the changed morphology of platelets may be associated with the increased risk of vascular complications [12, 16].

The present study aimed to evaluate the platelet indices, namely MPV, PDW, P-LCC, P-LCR, and PCT in T2DM patients with overt complications versus T2DM patients without overt complications.

Material and Methods

This is a cross-sectional, observation study, which was conducted in Department of General Medicine, in a tertiary care institute in Haryana (India) after obtaining institute's ethical committee clearance. Patients were enrolled from outpatient department (OPD), and from the admitted patients. A total of 100 T2DM patients (50 with overt complications and 50 without any overt complication) were enrolled between January 2017 and May 2018.

Patients who had any evidence of one or more of the vascular complications of T2DM overtly expressed by symptoms or revealed by physical examination or by relevant

investigations, were included in the complicated group. Three macrovascular complications (coronary artery disease, cerebrovascular disease and peripheral artery disease) and three microvascular complications were specifically considered. Patients who have had acute coronary syndrome (Unstable angina, STEMI, or NSTEMI) in past were considered to have coronary artery disease, in addition to those who have been diagnosed based on coronary angiography. Patients who have been clinically diagnosed stroke, were considered to have cerebrovascular disease, irrespective of whether ischemic or hemorrhagic. Peripheral arterial disease was diagnosed based on CT or MR angiography. Retinopathy was diagnosed based on fundoscopic examination. Nephropathy was diagnosed on basis of microalbuminuria and/or azotemia. Neuropathy was diagnosed based on clinical history and examination. Patients who had no evidence of any of these vascular complications of T2DM, were included in the uncomplicated group.

At the time of enrollment, after taking informed consent each patient was interviewed in detail, especially information was recorded regarding symptoms, duration of disease, and presence or absence of any overt complications of diabetes. Specific history of exertional angina/breathlessness, weakness/numbness and claudication was asked to rule out coronary artery disease, cerebrovascular disease and peripheral artery disease (PAD), respectively. Other relevant history was taken, and other comorbid conditions were recorded. Height, weight and body mass index (BMI) were noted in all patients. Vitals were recorded including the systolic and diastolic blood pressure (SBP and DBP). Detailed physical examination was done, especially to look for signs of complications related to diabetes. Nervous system examination was done, especially to rule out any evidence of central nervous system (CNS) deficit or peripheral neuropathy. Fundus examination was done in all the patients to look for any evidence of diabetes related retinopathy.

All the patients were tested for Blood glucose levels (Fasting and Postprandial), and Glycated Hemoglobin (HbA1c) levels, to check the status of glycemic control. ECG was done in all patients to rule out any evidence of ischemic heart disease. Renal function tests and urine analysis were done in all patients to look for any evidence of microalbuminuria or azotemia. Liver function tests, Ultrasound abdomen and Chest X-ray postero-anterior (CXR-PA) view were done in all patients, to look for any obvious pathology, especially malignancy. Other specific investigations were recorded in relevant cases, e.g. CPK-MB (in MI patients), and CT Head / MRI Brain (in stroke patients).

Age below 25 years and above 75 years with pre-existing psychiatric illness, morbid patients, patients not giving consent, neither speak English, nor Hindi language and any condition which precluded the patients from participating in this study like pregnancy, malignancy, and drug abuse were excluded.

Venous samples from the subjects were taken and collected in EDTA tubes. Samples were analyzed for complete blood count, within 2 hours of collection, using the same automated cell counter (Mindray, Model BC-5800) installed in the Department of Pathology, Pt. B.D. Sharma PGIMS, Rohtak. Complete Blood Count report included, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Plateletcrit (PCT), Platelet-Large Cell Count (P-LCC), and Platelet-Large Cell Ratio (P-LCR) in addition to Total leucocyte count, Absolute neutrophil count, Absolute Lymphocyte count, Absolute monocyte count, Absolute eosinophils count, Absolute basophils count, Neutrophils %, Lymphocyte %, Monocyte %, Eosinophils %, Basophils %, RBC count, Hemoglobin (Hb), Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), RBC distribution width (RDW) – CV, RBC distribution width (RDW) – SD, and Platelet Count (PLT).

Statistical analysis

At the end of the study, the data was collected, compiled and analyzed by using Student t-test and Chi-square test. Data and results were expressed as mean ± SD (Standard Deviation). Pearson's coefficient of correlation was used for correlation of various indices (r value). A p value of < 0.05 was considered significant.

Results

T2DM patients with overt complications were comparatively elder as compared to the T2DM patients without overt complication ($p = 0.01$). In both groups, maximum number of patients were in the 5th and 6th decades of their life. The mean duration of disease was more in T2DM patients with overt complications as compared to T2DM patients without overt complications ($p = 0.02$). The RBC count was slightly low in T2DM patients with overt complications as compared to the T2DM patients without overt complications ($p = 0.009$), although the hematocrit and hemoglobin levels were comparable in the two groups. Both the groups were statistically comparable in terms of sex distribution, family history of T2DM, weight, height, BMI, systolic and diastolic blood pressure, fasting and post prandial blood glucose levels, HbA1c levels, leucocyte counts, hematocrit (HCT), platelet count (PLT), and plateletcrit (PCT). The baseline characteristics of the study population are depicted in table 1. MPV, PDW, P-LCC and P-LCR were higher in T2DM patients with overt complications as compared to the T2DM patients without overt complications, but the difference was statistically significant only for the PDW. ($p = 0.305$ for MPV; $p = 0.01$ for PDW; $p = 0.653$ for P-LCC; $p=0.189$ for P-LCR). No significant difference was noted in the PCT between the two groups ($p = 0.856$). Various platelet indices observed in the two groups are shown in table 2.

Out of the 50 patients of T2DM with overt complications, 41 patients were having overt macrovascular complications. Out of these 41 patients, 7 patients were also having microvascular complications, in addition to the macrovascular complications. Among these 41 T2DM patients with macrovascular complications, 29 patients were having coronary artery disease, 9 patients were having cerebrovascular disease, 2 patients were having both coronary artery disease as well as cerebrovascular disease, 1 patient was having peripheral arterial disease. The other 9 patients out of the 50 patients of T2DM with overt complications, were having overt microvascular complications only. Out of these 9 patients, 3 patients were having diabetic neuropathy, 3 patients were having diabetic nephropathy, 1 patient was having diabetic retinopathy, 1 patient was having retinopathy and neuropathy, and 1 patient was having diabetic triopathy.

Table 3 and figure 1 depicts the values of platelet indices in T2DM patients with overt macrovascular complications

versus T2DM patients without overt complications. MPV, PDW, P-LCC and P-LCR, were higher in T2DM patients with overt macrovascular complications (n = 41), versus T2DM patients without overt complications (n = 50), and the difference was statistically significant for MPV, PDW, and P-LCR (p =0.05 for MPV; p = 0.004 for PDW; p = 0.399 for P-LCC, p = 0.02 for P-LCR). No significant difference was noted in PCT between the two groups.

Table 4 depicts the values of platelet indices in T2DM patients with overt microvascular complications versus T2DM patients without overt complications. MPV and PLCR were low in T2DM patients with microvascular complications as compared to T2DM patients without overt complications (p value = 0.01 and 0.05 respectively). No significant difference was noted in PDW, PCT P-LCC between the two groups.

There was no correlation noted between HbA1c and any of the platelet indices (p > 0.05). There was no correlation noted between duration of disease and any of the platelet indices (p > 0.05). PDW and PLCR were found to be positively correlated with MPV which was statistically significant with p value of < 0.01. PCT and PLT were found to be negatively correlated with MPV which was statistically significant (p < 0.01). Table 5 shows correlation of MPV with various indices of total study population irrespective of their complication status.

Table 1: Baseline characteristics of the patients.

Characteristic	T2DM with overt complication (n= 50)	T2DM without overt complication (n = 50)	P value
Mean Age – years	60.3±8.64	55.14±11.80	0.01
Male sex – no. (%)	28 (56%)	27 (54%)	0.840
Family history of T2DM – no. (%)	22 (44%)	14 (28%)	0.09
Duration of disease – years	7.0±6.21	4.57±4.48	0.02
Weight – kg	64.14±11.86	65.06±10.71	0.685
Height – ft	5.42±0.30	5.42±0.26	1
BMI - Kg/m2	21.79±3.72	22.08±3.20	0.680
Systolic BP – mmHg	129.02±16.68	130±16.55	0.770
Diastolic BP – mmHg	81.51±11.11	80.72±12.03	0.735
Fasting blood sugar - mg/dl	180.72±50.63	167.42±46.03	0.172
Postprandial blood sugar - mg/dl	215.3±52.38	211.58±49.06	0.714
HbA1c - %	8.52±0.97	8.36±1.032	0.351
Total leucocyte count - 10^9/l	9.14±3.65	9.62±3.52	0.502
RBC count - 10^{12}/l	4.17±0.82	4.56±0.66	0.009
Hematocrit (Hct) - %	37.73±6.62	39.83±5.89	0.09
Platelet count (PLT) - 10^9/l	229.84±138.41	235.94±85.28	0.791
* Plus–minus values are means ±SD (standard deviation).			

Table 2: Platelet indices in T2DM patients with overt complications vs T2DM patients without overt complications

Parameters	T2DM patients with overt complications (n = 50)	T2DM patients without overt complications (n = 50)	P value
MPV (fl)	10.12 ± 1.71	9.79 ± 1.43	0.305
PDW (fl)	16.83 ± 0.75	16.47 ± 0.62	0.01
PCT (%)	0.22 ± 0.11	0.22 ± 0.06	0.856
P-LCC (10^9/L)	85.88 ± 47.92	82.44 ± 25.05	0.653
P-LCR (%)	41.08 ± 14.33	37.57 ± 12.18	0.189
Note: Plus, minus values are mean + SD (standard deviation); n – sample size.			

Table 3: Platelet indices in T2DM patients with overt macrovascular complications vs T2DM patients without overt complications

Parameters	T2DM patients with overt macrovascular complications (n = 41)	T2DM patients without overt complications (n = 50)	P value
MPV (fl)	10.43±1.68	9.79±1.43	0.05
PDW (fl)	16.90±0.78	16.47±0.62	0.004
PCT (%)	0.222±0.119	0.22±0.06	1
P-LCC (10^9/L)	89.39±51.13	82.44±25.05	0.399
P-LCR (%)	43.75±13.99	37.57±12.18	0.02
Note: Plus, minus values are mean + SD (standard deviation); n – sample size.			

Table 4: Platelet indices in T2DM patients with overt microvascular complications vs T2DM patients without overt complications.

Parameters	T2DM patients with overt microvascular complications (n=9)	T2DM patients without overt complications (n-50)	P value
MPV (fl)	8.7±1.03	9.79±1.43	0.03
PDW (fl)	16.47±0.486	16.47±0.62	1
PCT (%)	0.213±0.055	0.22±0.06	0.639
P-LCC (10^9/L)	69.88±25.31	82.44±25.05	0.172
P-LCR (%)	28.9±8.74	37.57±12.18	0.04
Note: Plus, minus values are mean + SD (standard deviation); n – sample size.			

Table 5: Correlation of MPV with various indices of total study population.

Parameters	Pearson's coefficient of correlation (r value)	P value
PDW (fl)	0.512	0.000
PCT (%)	-0.2464	0.013
P-LCC (10^9/L)	0.1795	0.074
P-LCR (%)	0.985	0.000
PLT (10^9/L)	-0.530	0.000

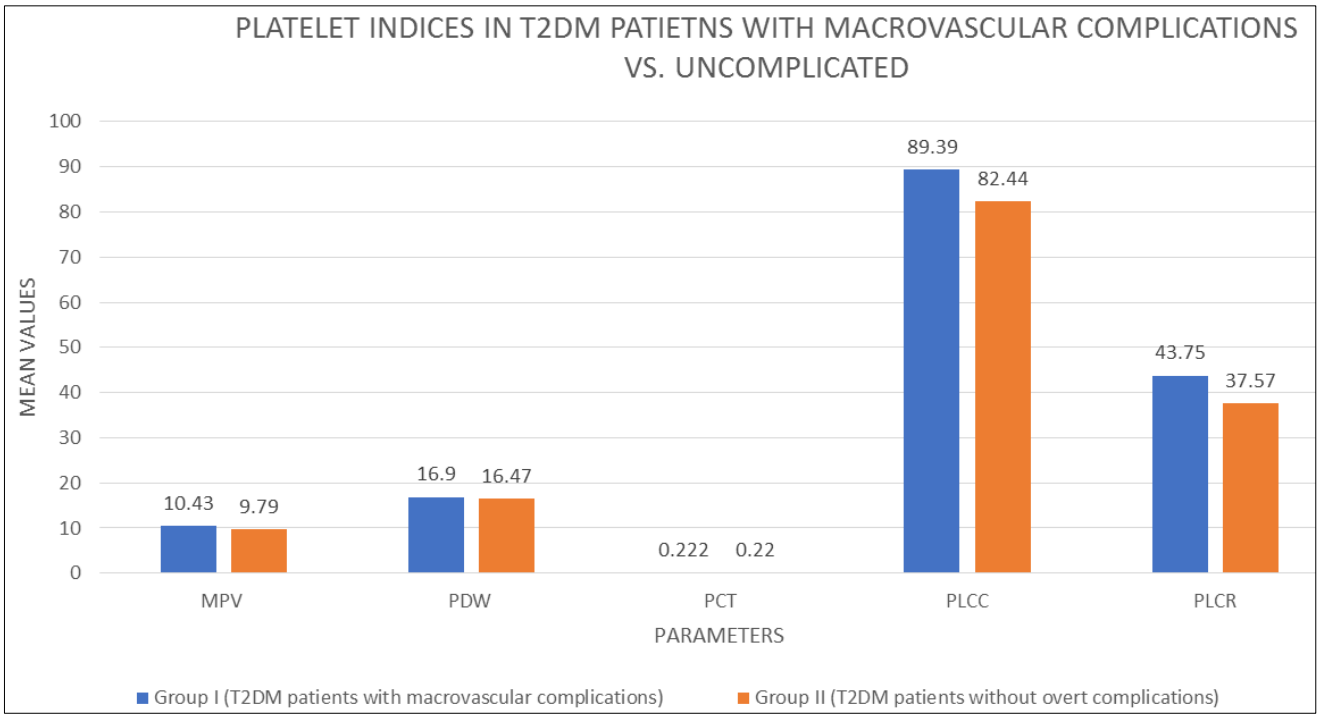

Fig 1: Platelet indices in T2DM patients with macrovascular complications vs T2DM patients without overt complications.

Discussion

In this study we observed that only PDW was significantly high in T2DM patients with overt complications as compared to T2DM patients without overt complications (p = 0.01). This is similar to findings of Jindal *et al* who reported significantly high PDW in diabetic patients with complications in comparison to diabetic patients without complications [6].

On subgroup analysis, we noted that MPV, PDW, and PLCR, were high in T2DM patients with overt macrovascular complications (n = 41), when compared to T2DM patients without complications (n = 50) (p =0.05 for MPV; p = 0.004 for PDW; p = 0.02 for P-LCR). Majority of patients in this group were having coronary artery disease and/or cerebrovascular disease, and have had suffered MI or stroke in past.

Khandekar *et al* have observed in their study that mean platelet volume (MPV) and platelet large cell ratio (P-LCR) were higher in patients with stable coronary artery disease (CAD) as compared to healthy persons [17]. Similarly, among acute coronary syndrome (ACS) patients, the platelet volume indices were shown to be higher in cases of myocardial infarction than in unstable coronary artery disease (CAD) [18]. A recent study has also suggested that high MPV and PLCR values may be used as prognostic markers in coronary artery disease and myocardial infarction [19] Rechcinski *et al* in their study found that MPV, PDW and P-LCR are strong indicators of unfavorable prognosis in post MI patients who had undergone primary percutaneous coronary intervention. They asserted that PDW and P-LCR are even more stronger indicators of prognosis than MPV. They found that PDW is an independent risk factor for recurrent MI and mortality.[11]

There are reports published in literature, which suggests that larger platelets are found in circulation in post MI patients [12, 20, 21]. It has been reasoned that it is because of stimulation of bone marrow for increased thrombocytopoiesis, in response to consumption of platelets in the thrombotic event in coronaries [22].

Bath *et al* found in their prospective analysis, That higher MPV correlates with higher risk of stroke in patients who have had an ischemic stroke or transient ischemic attack [5].

In our study, we observed that T2DM patients with macrovascular complications were on antiplatelet therapy, even then the platelet indices were high in these patients as compared to T2DM patients without complications. This is in concordance with the studies which have reported high platelet aspirin resistance in diabetic patients, and therefore have suggested higher aspirin doses in diabetic patients to overcome this resistance [23].

On the other hand, we didn't observe any increase in MPV, PDW, P-LCC, and P-LCR in T2DM patients with microvascular complications (n= 9), as compared to T2DM patients without overt complications (n=50). Rather, MPV and PLCR were found to be low in T2DM patients with microvascular complications as compared to patients without any complications (p value = 0.01 and 0.05 respectively). As the sample size was too small to make an inference, our findings are not able to verify or refute the findings of Jindal *et al* [16] and Buch *et al* [24] who observed high MPV and PDW in diabetes mellitus patients with microvascular

complications when compared with diabetes mellitus patients without complications. Papanas *et al* [25] have also noted higher MPV in diabetic patients with microvascular complications including retinopathy.

In contrast to these studies, Giovanetti *et al* [26] have reported no significant variations in platelet indices in patients of hypertension or diabetes mellitus as compared to healthy subjects. They also reported no difference in platelet indices in relation to hyperglycemia, use of aggregation inhibitors, anticoagulants, antihypertensive agents or hypoglycemic medications.

We also observed that MPV was not associated with duration of diabetes and HbA1c. These findings are consistent with the findings of Yenigun *et al* [27] who observed no association between MPV and HbA1c and duration of diabetes mellitus. In contrast to these findings, a statistically significant correlation between MPV and duration of disease, has been observed by Kodiatte *et al* [28].

In our study, the platelet count in the two groups was comparable, hence the effect of platelet count on platelet indices may be ruled out. This finding is consistent with the findings of Hasan *et al* [29]. An inverse relationship was noted between MPV and platelet count ($p < 0.01$) which corroborates with the results of Giovaneti *et al* and Jackson *et al* [26, 30]. A positive correlation was noted between MPV and PDW ($p < 0.01$). A positive correlation was also noted between MPV and PLCR (p value < 0.01).

We observed that the values of P-LCR were persistently high in T2DM patients with macrovascular complications, including coronary artery disease and cerebrovascular disease. The values are statistically significant, and a clear difference can be noted as compared to the values of P-LCR in the T2DM patients without overt complications. Hence, P-LCR appears to be the most promising platelet parameter which may be taken as a surrogate marker of macrovascular complications in T2DM patients, especially those related to thrombotic events.

The small sample size was a limitation, especially, we are not able to make a comment on the platelet indices in T2DM patients with microvascular complications. This is a cross-sectional study, and we are not able to determine, what was the actual status of the platelet indices in T2DM patients, before the occurrence of the complications. Therefore, the contradictory plausibility of the increase in the values of platelet indices, as a result of the complications themselves, remains to be ruled out affirmatively. Thus, a large prospective study is required to further examine the association of platelet indices with the thrombotic events in T2DM patients, and to assess the usefulness of raised platelet indices as markers of impending macrovascular complications, such as myocardial infarction and ischemic stroke.

Conclusion

It may be concluded from the study that the MPV, PDW and P-LCR, tend to be higher in T2DM patients with overt macrovascular complications, as compared to T2DM patients without overt complications. Among these P-LCR appears to be the most promising platelet parameter, which may be taken as a surrogate marker of macrovascular complications in T2DM patients. A large prospective study is required to draw an inference about the utility of platelet indices as markers of impending thrombotic events in T2DM patients.

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