Original Article

Platelet Indices as a Predictor of Microvascular Complications in Type 2 Diabetes

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Abstract

Background: Type 2 diabetes mellitus (T2DM) patients have a higher risk of developing micro- and macrovascular complications, which lead to decrease in the quality of life and increase in morbidity. Platelet indices have been available in the laboratory routine using blood cell counters for several years. These indices could alert us regarding endothelial dysfunction and in turn regarding the microvascular complications. Hence, this study was done to prove the correlation between platelet indices and microvascular complications in T2DM. **Materials and Methods:** In total, 125 diabetic patients attending diabetes OPD and admitted in medicine department along with age and sex-matched non-diabetic controls were studied. A detailed history was taken regarding duration of diabetes, medication, past history of stroke, IHD, and hypertension. Patients with T2DM were specially evaluated for microvascular complications. Platelet indices, fasting blood glucose, Post prandial blood glucose, HbA1C, and Sr. Creatinine were obtained from venous blood samples. All parameters were then subjected to statistical analysis using SPSS 17.0. **Results:** Platelet indices, namely MPV, PCT, PDW, and P/LCR were significantly higher in diabetic individuals than those in age and gender-matched controls. Moreover, the increase in MPV, PDW, and P/LCR was more significant in diabetic subjects with microvascular complications when compared with those without microvascular complications. Platelet dysfunction also showed a positive association with HbA1C, retinopathy, nephropathy, and neuropathy individually. **Conclusions:** Changes in platelet indices were found to be statistically associated with diabetes and its complications.

Keywords: Diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, microvascular complications, platelet indices, type 2 diabetes mellitus

Introduction

In the modern world, diabetes mellitus (DM) has become a global health problem.[1] The global burden of diabetes worldwide in 2017 was estimated to be 425 million and 82 million in South East Asia. This is expected to rise to 629 million worldwide and 151 million in South East Asia by 2045.[2] It is estimated that the developing countries will bear the brunt of diabetes epidemic to the extent of 77% of the global burden, in the 21st century.[3] At present, the prevalence of diabetes in Indian adults is 8.8%.[2]

Hyperglycemia is a characteristic of diabetes which causes an array of long-term systemic complications. They have a considerable impact on the patient as well as society, as the disease typically affects individuals in their most productive years.[4] Generally, the injurious effects of hyperglycemia are separated into macrovascular complications (Coronary Artery Disease, Peripheral Arterial Disease, Stroke) and micro-vascular complications (Diabetic Retinopathy, Diabetic Nephropathy, Diabetic Neuropathy).[5]

Diabetic patients have an increased risk of developing micro- and macrovascular disease, and platelets may be involved as a causative agent with respect to altered platelet morphology and function.[6] DM is characterized by the prothrombotic state of platelets which owes to the persistent hyperglycemia and insulin resistance, causing injury to pericytes and endothelium. The increased platelet activity is believed to play a vital role in the development of vascular complications of this metabolic disease.[7]

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Microvascular complications, retinal lesions, microalbuminuria, and proteinuria have been described as factors that are predictive of cardiovascular and cerebrovascular morbidity and mortality among diabetic subjects.[8] Hence, if detected early, microvascular complications would alert us regarding the increased risk of cardiovascular and cerebrovascular complications. Thus, microvascular complications were chosen to be studied in this study.

Platelets play an important role in the integrity of normal homeostasis, and platelet indices act as an indicator for its function.[9] Larger platelets have a higher number of dense granules which makes them more potent and thrombogenic. The number and size of granules in platelets do not change during the life span of the platelet.[10-12] Increased mean platelet volume (MPV) has been associated with metabolic syndrome, stroke, coronary artery disease and diabetes mellitus (DM).[13,14] A few studies have shown that platelet indices are significantly increased in diabetics as compared to non-diabetic individuals.[6,13,15]

Platelet parameters have been available in the laboratory routine using blood cell counters for several years.[16] These include MPV, Platelet distribution width (PDW), Plateletcrit (PCT), and platelet-large cell ratio (P-LCR). The prothrombotic stage of platelet can be detected early with ease using the newer hematological analyzers through these platelet parameters.[7]

The aim of this study was to evaluate platelet indices in patients with type 2 diabetes mellitus (T2DM), to compare them with nondiabetic individuals and to correlate platelet indices with microvascular complications. This study also enabled us to check if platelet indices can effectively predict the occurrence of microvascular complications in patients with type 2 diabetes.

Materials and Methods

This case-control study was conducted at a tertiary care hospital in a rural area of Central India over a period of two years after ethical clearance from the institutional ethical committee. A total of 153 individuals were enrolled for the study who were either newly diagnosed diabetics as per the WHO criteria or individuals already on treatment with either OHA or parenteral insulin. Of these, 28 individuals were excluded as per the exclusion criteria which consisted individuals with anemia, myeloproliferative disorders, malignancies, history of blood transfusion in last 14 days, drugs causing bone marrow suppression, thrombocytopenia, pregnancy, individuals consuming high protein diet, and individuals with UTI. Age and sex-matched 125 non-diabetic individuals were taken as controls. The study design is summarized in Figure 1. All the study subjects were evaluated according to a standardized study proforma. A detailed history was taken regarding duration of diabetes, medication, past history of stroke, IHD, and hypertension. The subjects underwent a complete clinical evaluation. Diabetic individuals were evaluated with specific reference to microvascular complications. Neuropathy was evaluated by testing sensory perceptions of light touch using a 10-g monofilament, pain sensation using pinprick, vibration sense using a tuning fork of 128 Hz and a biothesiometer from Genesis medical systems, temperature sense, and ankle jerk. The neuropathy disability score (NDS)[17] was calculated to assess the severity of neuropathy [Table 1].

Fundus was visualized by direct ophthalmoscopy and was checked for diabetic retinopathy. The blood sugar levels were tested twice, once after at least 8 h of fasting and second 2 h after meal using semi-automated analyzer RX Imola from Randox Biosciences which uses the colorimetric method. HbA1C and serum creatinine were also tested in the same machine. An automated cell counter ABX Pentra XLR from Horiba Medical Diagnostic systems was used, which provided with the hemoglobin (Hb) values along with the platelet count and platelet indices PCT, PDW, and MPV. The same samples were also processed in Sysmex – automated hematology analyzer KX-21N which provided with the P-LCR. Urinary microalbuminuria was tested using Micral-Test (cobas) urine test strips from Roche Diagnostics for micro-albuminuria.

Observations and Results

In this stuy, 125 individuals with T2DM and 125 nondiabetic controls were included. Both groups were age and gender matched. The majority of the individuals were between the age group of

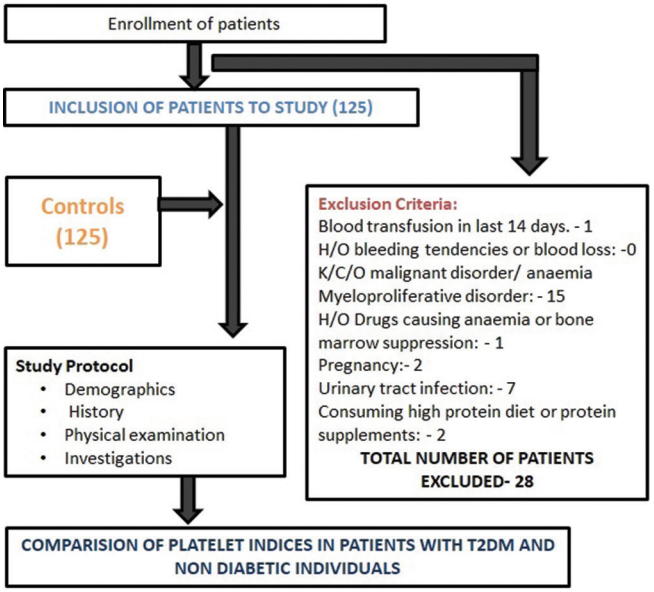

Figure 1: Flowchart of the study protocol

Table 1: Revised Neuropathy Disability Score (NDS)[17]

NDS Items	Description and scoring (Each Side)
Vibration sensation (128-Hz tuning fork)	0=present, 1=reduced/absent
Temperature sensation (cold tuning fork)	0=present, 1=reduced/absent
Pin Prick	0=present, 1=reduced/absent
Ankle	0=present, 1=present with reinforcement, 2=absent per side

31-60 yrs. Out of these, 60% of the individuals were males. It was observed that BMI in the diabetic group (26.20 ± 3.90) was significantly higher than that in control group (22.40 ± 3.05). There was a much higher incidence of abdominal obesity in T2DM cases (61.60%) than that in nondiabetic control subjects (19.20%). There was no statistically significant difference in the platelet counts in the two groups. The baseline characteristics of the two groups are shown in Table 2. Out of the total 125 individuals with T2DM, 66 had microvascular complications, the distribution of which is shown in Figure 2.

In our study, out of 125 cases, there were 50 (40%) individuals with diabetic neuropathy . Out of 50 individuals, 47 individuals (94%) had a history of neuropathic pain or tingling numbness in at least one of the limbs. Also, 40% had impaired ankle jerk, 66% had impaired pain sensation, 42% had impaired temperature sensation, and 64% had impaired fine touch. In total, 44 (%) individuals had impaired vibration sense when tested using a tuning fork of 128 Hz, whereas 36 (%) individuals had impaired vibration sense when tested using a digital biothesiometer.

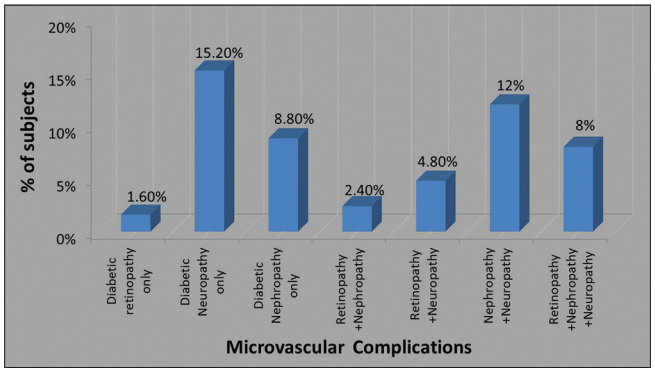

Figure 2: Distribution of diabetic subjects according to the presence of microvascular complications

Student's (unpaired) *t*-test was used to study if there was a significant change in the platelet indices of diabetic and non-diabetic individuals. The mean of MPV, PDW, PCT, and P-LCR of cases was 11.32fL, 15.57fL, 0.241%, 43.15 and that in controls was 8.56fL, 11.69fL, 0.22%, and 34.6,8 respectively [Table 3]. These values of MPV, PDW, PCT, and P-LCR were significantly higher in individuals with T2DM as compared to controls.

It was also observed that the MPV, PDW, and P-LCR were significantly higher in diabetic individuals with microvascular complications as compared to those without complications [Table 4].

Platelet indices were also compared to the severity of neuropathy using the NDS, and it was found that MPV, PDW, and P-LCR had a positive correlation with the NDS [Table 5].

MPV, PDW, P-LCR were seen to be higher in individuals with increased HbA1C levels and the correlation was found to be statistically significant [Table 6].

Discussion

Diabetes is a metabolic disorder characterized by hyperglycemia and metabolic dysregulation leading to secondary micro- and

Table 2: Baseline characteristics of study population

Baseline characteristics	(Mean±SD)/(%)		*t*	*P*
	Cases (*n*=125)	Controls (*n*=125)		
Age (years)	50.46±15.71	50.54±15.85	1.63	0.1, NS
Gender-Male (%)	75 (60.0%)	75 (60%)	-	
Gender-Female (%)	50 (40%)	50 (40%)	-	
H/O IHD	63 (50.4%)	23 (18.4%)	22.82	0.0001, S
H/O HTN	45 (36%)	21 (16.8%)	9.26	0.0023, S
H/O Stroke	14 (11.2%)	6 (4.8%)	2.44	0.11, NS
Smoking	27 (21.6%)	14 (11.2%)	4.39	0.036, S
Alcoholism	13 (10.4%)	14 (11.2%)	0.05	0.81, NS
Duration of diabetes	4.33±2.66		-	
BMI	26.20±3.90	22.40±3.05	3.35	0.001, S
W/H Ratio	0.91±0.14	0.85±0.02	3.96	0.0001, S
PMBS	185.38±34.60	151.12±15.72	10.07	0.0001, S
FBS	140.48±28.05	96.02±9.40	16.80	0.0001, S
Platelet Count $\times 10^3$	268.92±92.22	271.73±92.58	0.24	0.81, NS
MPV (fL)	11.32±1.72	8.56±1.71	13.47	0.0001, S
PDW (fL)	15.57±3.23	11.69±2.28	10.92	0.0001, S
PCT (%)	0.240±0.046	0.220±0.026	4.09	0.0001, S
P-LCR	43.15±10.60	34.68±11.73	5.98	0.0001, S
HbA1C (%)	7.45±1.48		-	
Sr. Creatinine (mg/dl)	0.82±0.23		-	
eGFR (ml/min/1.73 m^2)	111.35±41.03		-	

Table 3: Comparison of Platelet indices in two study groups

Platelet index	Normal range	Group	Mean	Std. deviation	Std. error mean	*t*	*P*
MPV (fL)	8.6-15.5 fL	Cases	11.32	1.72	0.15	13.47	0.0001, S
		Controls	8.56	1.51	0.13		
PDW (fL)	9.0-14 fL	Cases	15.57	3.23	0.28	10.92	0.0001, S
		Controls	11.69	2.28	0.20		
PCT (%)	0.22-0.24%	Cases	0.241	0.045	0.004	4.24	0.0001, S
		Controls	0.220	0.022	0.002		
P-LCR		Cases	43.15	10.60	0.94	5.98	0.0001, S
		Controls	34.68	11.73	1.049		

Table 4: Comparison of platelet indices in cases with and without microvascular complications

Platelet indices	Microvascular complications	*n*	Mean	Std. deviation	Std. error mean	*t*	*P*
MPV (fL)	Present	66	12.35	1.50	0.18	9.03	0.0001, S
	Absent	59	10.17	1.12	0.14		
PDW (fL)	Present	66	16.66	3.01	0.37	4.25	0.0001, S
	Absent	59	14.34	3.05	0.39		
PCT (%)	Present	66	0.244	0.047	0.005	1.01	0.31, NS
	Absent	59	0.235	0.043	0.005		
P-LCR	Present	66	47.40	9.79	1.20	5.21	0.0001, S
	Absent	59	38.39	9.46	1.23		

Table 5: Comparison of platelet indices with Neuropathy Disability Score (NDS)

NDS	MPV (fL)	PDW (fL)	PCT (%)	P-LCR
<6	10.98±1.57	15.24±3.34	0.238±0.046	41.31±10.22
≥6	12.69±1.63	16.88±2.38	0.244±0.044	50.48±8.95
t	4.83	2.30	0.55	4.10
P	0.0001, S	0.023, S	0.58, NS	0.0001, S

Table 6: Comparison of platelet indices with HbA1C levels

HbA1C (%)	MPV (fL)	PDW (fL)	PCT (%)	P-LCR
<7.5	10.49±1.35	14.78±3.21	0.234±0.042	38.97±9.34
7.5 to 10	12.25±1.58	16.26±3.02	0.249±0.049	48.14±10.03
>10	12.56±1.93	18.28±2.88	0.218±0.033	46.45±10.18
t	22.79	5.64	2.24	13.51
P	0.0001, S	0.005, S	0.110, NS	0.0001, S

macrovascular complications.[18] Efforts are being made to identify and prove the utility of platelet indices in early detection of diabetic complications. This would be of immense benefit with the easy availability of these indices.

The significant factors causing increased platelet reactivity in diabetics are hyperglycemia and insulin resistance. Increased coagulation, impaired fibrinolysis, and endothelial dysfunction cause prothrombotic state for which platelet hyper-reactivity is said to be an established contributing factor. Complications arise due to these hyperactive platelets which play a vital role in the pathophysiology of the thrombotic events.[7] Platelet indices are also affected by anticoagulant drugs. However, in this study, no subject was taking anticoagulant drugs.

In this study, we found that biothesiometer is more sensitive in the detection of impaired vibration sense as compared to a tuning fork. Moreover, a biothesiometer provides with quantification of the severity of impairment and, hence, enable us to study the progression of the disease. In contrast, the tuning fork is a much cheaper, portable, and commonly available modality of testing.

The platelet indices, namely MPV, PDW, PCT, and P-LCR were significantly higher in individuals with diabetes as compared to non-diabetic controls.

It was observed that MPV, PDW, and P-LCR were deranged in diabetic individuals with complications as compared those without complications. However, PCT did not show any such correlation. This can be attributed to the dependence of PCT on platelet count.[19] Platelet count being unaffected in this study, PCT does not show significant derangement in diabetic individuals with and without microvascular complications.

The severity of Diabetic neuropathy was assessed using the NDS as per the standardized protocol according to the Cochrane Systematic Review from the Cochrane Database.[17] It was observed that MPV, PDW, and P-LCR showed a positive correlation which was significant ($P = 0.0001$, $P = 0.023$, $P = 0.0001$), whereas PCT did not show a significant correlation ($P = 0.58$) with the severity of neuropathy.

Limitations of the Study

The platelet indices are also affected by thyroid and rheumatic diseases which were not considered in this study.

All patients with ischemic heart disease were consuming statins which are shown to alter platelet indices.

The follow up of the cases was not possible to determine the prognostic significance of our findings. This would have enabled us to compare its association with the progress of the microvascular complications. Moreover, it could have been possible to correlate and check the reversibility of platelet dysfunction with glycaemic control over a period of time.

Conclusions

Changes in platelet indices are seen to be statistically associated with diabetes and its complications. They are easily available, simple, convenient, noninvasive, and easy to interpret method to determine platelet dysfunction and in turn predict the presence of microvascular complications.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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