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Original Research Article

Association of platelet parameters with chronic complications in type 2 diabetes mellitus

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ABSTRACT

Aim and Objective: To determine the association of platelet parameters with chronic complications in patients with type 2 diabetes mellitus.

Background: Platelets play an important role in the integrity of normal homeostasis. Altered platelet morphology and platelet hyperactivity is associated with an increased prothrombotic state. In diabetes mellitus, there is increased platelet activity which eventually play a role in the development of vascular complications which are responsible for its morbidity and mortality.

Material and Methods: A hospital based prospective cohort study was performed to study the level of platelet parameters in patients with type 2 diabetes mellitus. Platelet parameters such as platelet count, MPV (Mean Platelet Volume), PDW (Platelet Distribution Width), PCT (plateletcrit) and P-LCR (Platelet-Large Cell Ratio) were assessed using Mind ray BC-5150 Auto Haematology Analyser. The data were entered into SPSS (IBM) version 21 and descriptive statistical methods like mean, standard deviation, percentages, etc. were applied. T-test was applied to find out the association of platelet parameters in patients with type 2 diabetes mellitus at baseline and after 6 months of follow-up.

Results: The age of the study population ranged from (30-60) years. From the total of 110 participants that were followed - up, 98(89.1%) presented with micro vascular complications. On the other hand, 32(29.1%) had at least one macro vascular complication. Platelet parameters – MPV, PDW, PCT and P-LCR were found to be significantly higher in type 2 DM with micro vascular as well as macro vascular complications as compared to those without complications.

Conclusion: Higher values of MPV, PDW, PCT and P-LCR indicates that platelet parameters can be used as better prognostic markers for early detection of diabetic complications and therefore can be used as a simple and cost-effective tool to monitor and predict the risk of micro vascular and macro vascular complications in diabetes.

1. Introduction

Diabetes mellitus is a metabolic disorder. Its characteristic feature is hyperglycemia. Hyperglycemia in diabetes mellitus is due to deficiency of insulin release from pancreas or defect in insulin action or both.[1]

As per the American Diabetes Association, the criteria for diagnosis of diabetes are - (1) Fasting blood glucose ≥ 126 mg/dL, (2) Random plasma glucose ≥ 200 mg/dL, (3) 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test and (4) Glycated hemoglobin (HbA1C) level ≥ 6.5%.[2]

Diabetes mellitus is subdivided into 2 categories- type 1 diabetes (T1DM) and type 2 diabetes (T2DM). T1DM is caused by autoimmune destruction of pancreatic β cell

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destruction causing absolute deficiency of insulin. T2DM is characterized by inadequate release of insulin by the pancreatic β cells as well as peripheral resistance to its action. T2DM is more common accounting for 90% to 95% of diabetes.[1]

Diabetes persisting for a long period is associated with chronic complications. These complications may be either (i) macrovascular which is due to damage of large and medium-sized muscular arteries or (ii) microvascular due to damage of small vessels. In diabetic patients, there is an accelerated rate of atherosclerosis resulting from macrovascular complications which in turn increases the risk of myocardial infarction, stroke and ischemia of lower extremities. On the other hand, microvascular complications are most marked in the kidneys (diabetic nephropathy), retina (retinopathy) and peripheral nerves (neuropathy).[1]

Platelets play a pivotal role in the maintenance of normal homeostasis. Platelet parameters are indices which correlate with platelets' function. These indices include plateletcrit (PCT), platelet distribution width (PDW), mean platelet volume (MPV) and platelet large cell ratio (PLCR).[3]

MPV defines the average size of platelets. PDW indicates variation in size of platelets which is suggestive of active platelet release. PLCR is directly related to PDW and MPV.[4]

DM is a "prothrombotic state". Sustained hyperglycemia, dyslipidemia, and insulin resistance contribute to this state by causing endothelial injury. Altered platelet morphology and platelet hyperactivity play a crucial role in the development of complications in Diabetes mellitus.[5–7] Larger platelets generate more thromboxane. Increased thromboxane synthesis is associated with thrombotic complications because platelets can aggregate better.[8,9]

The aim of the present study was to assess the level of platelet parameters in T2DM and to determine its association with chronic complications first at baseline and after 6 months.

2. Materials and Methods

A prospective cohort study was conducted in Pathology Department, RIMS Imphal in coordination with the Medicine Department, RIMS Imphal for a duration of two years from September 2019 to December 2021 in patients with T2DM excluding thrombocytopenic patients, patients on antiplatelet medications (aspirin, clopidogrel), pregnant ladies and those with alcoholic liver disease.

The following statistical formula was used to calculate the sample size of 130:

$$N = \frac{\sigma^2(Z_{1-\beta}+Z_{1-\alpha/2})^2}{(\mu_0-\mu_1)^2}$$

Note, N = Sample size

μo= population mean = 8.4[7]

μ1 = mean of study population = 8.69[7]

σ = variance of study population = 1

α = probability of type I error = 0.05

β = probability of type I error = 0.2

z = critical Z value for a given α or β

Attrition Rate = 10% of N

= 10% of 93

= 9.3

Corrected sample size = 93 + 9.3 = 102.3 = 102.

Independent variables: Glycosylated haemoglobin (HbA1c), complete blood count, kidney function test, weight, waist circumference.

Dependant variables: Platelet Parameters – platelet count, PCT, PDW, MPV and PLCR.

The study was conducted by using a proforma that had detailed history of the patient as regard to the age, sex, address and the development of signs and symptoms of complications in diabetes, treatment history of the patient. Follow-up was done for patients with T2DM after 6 months from his or her initial visit.

The blood sample of the patients was collected in vial containing K3 EDTA (ethylene diamine tetra acetic acid). Samples were collected according to the guidelines of criteria for inclusion and exclusion. The weight and waist-circumference of the subjects were recorded. Routine physical examination was performed. The following tests were undertaken: estimation of the serum blood glucose levels and glycosylated haemoglobin (HbA1c), creatinine, LFT. Patients were made to either sit or lie down in a comfortable position and blood was drawn from the anti-cubital fossa under strict aseptic precautions.

Estimation of platelet parameters was done using Mindray BC-5150 Auto Hematology Analyzer manufactured by Shenzen Mindray Bio-Medical Electronics Co., Ltd., Shenzen, China in 2013. HbA1C was estimated by ADAMSTMA1C HA-818OT based on HPLC (High Performance Liquid Chromatography) by ARKRAY Inc, UK. Blood Sugar level was estimated by photometric assay using Latex enhanced reagent by RANDOX RX IMOLA, 2007 manufactured by Randox Lab., UK. KFT values were obtained by RANDOX RX IMOLA, 2007 manufactured by Randox Lab., UK.

2.1. Patient consent

The purpose and aims of the study were explained to the participants and written consent was obtained. Privacy and confidentiality of the patients were maintained throughout the study.

2.2. Statistical analysis

Data were collected and entries were made into SPSS (IBM) version 21.0 for statistical analysis. Descriptive statistical methods like mean, cross tabulations, standard deviation and frequency charts were used to analyse the data collected. For the continuous variables, mean +

standard deviation was used to express the data and for categorical variables frequency and percentage were used. t-test and chi-square test were used to find the association of platelet parameters in patients with type 2 diabetes mellitus at the baseline and after 6 months with the presence or absence of complications respectively. Binary logistic regression was also used to see the association of microvascular complications with platelet parameters. Independent variables with a P value <0.25 were used to identify the predictors that were independently associated with microvascular complications. All inferences were considered statistically significant at P<0.05.

3. Results

A total of 110 cases were included in the study. The male: female ratio was 1.03:1. 51 years was the mean age of the study participants. The weight and the waist circumference were found to be increased after 6 months but was statistically insignificant whereas the value of HbA1c was significantly increased. From the total of 110 participants, 98(89.1%) showed at least one of diabetes related microvascular complications (Table 1) – DR, DN and nephropathy. On the other hand, 32(29.1%) has at least one macrovascular complication (Table 2). Diabetic patients showed significantly higher MPV, PCT and PLCR at start and after 6 months of follow up. (Table 3).

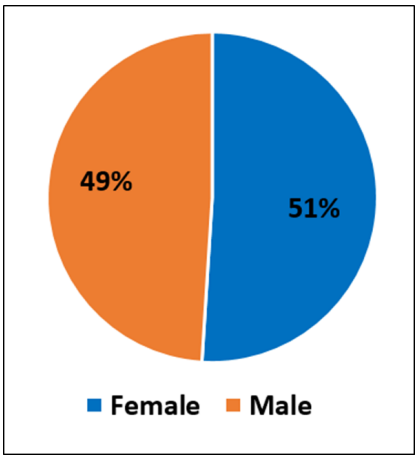

Figure 1: Showing the gender-wise distribution of study population

Figure 1 shows the gender-wise distribution of study population. Out of the total 110 cases, 51% (56) were female and 49% (54) were male.

More than half 69% (76) of the study participants were suffering from diabetes for >5 years. The duration of diabetes ranged from 1 to 12 years as depicted in the Figure 2.

Significantly higher MPV, PDW and PLCR were seen in diabetic patients with microvascular complications than those without microvascular complications (P<0.05) but showed similar values of PCT (P>0.05) (Table 4).

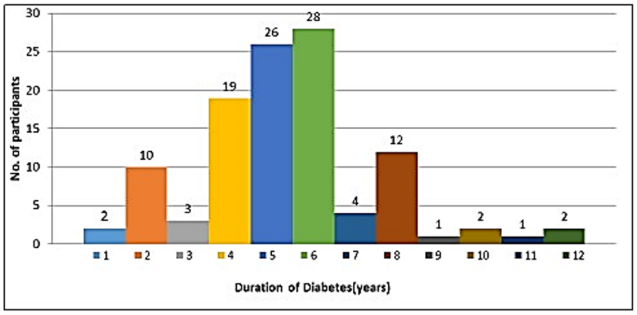

Figure 2: Representing duration of diabetes

Table 1: Frequency of microvascular complications

Microvascular complications	Present	Absent
Frequency	98	12
Percentage	89.1	10.9

Table 2: Frequency of macrovascular complications

Macrovascular complications	Present	Absent
Frequency	32	78
Percentage	29.1	70.9

The platelet parameters MPV, PDW, and PLCR were seen to be higher in diabetic retinopathy (Table 5). MPV and PCT were found to be elevated in diabetic neuropathy (P<0.05) and (P<0.05) respectively (Table 6).

It was found that MPV, PDW, and PLCR were significantly increased in diabetic nephropathy (Table 7). MPV, PDW and PLCR were higher in diabetic patients with macrovascular complications than patients without macrovascular complications. They also showed higher platelet count and PCT as compared to patients without macrovascular complications, but these differences were statistically insignificant(P>0.05) (Table 8).

4. Discussion

Longstanding diabetes is directly related to higher levels of microvascular and macrovascular complications.[8] Attempts are made to recognise and establish the utility of platelet parameters in early diagnosis of diabetic complications.

In this prospective cohort study, the study of association of platelet parameters with microvascular complications among type 2 DM patients at Regional Institute of Medical Sciences, Imphal has been done. Significantly higher values of MPV, PDW, and P-LCR were found in T2DM patients with microvascular complications as compared to those without complications.

The increase in MPV, PDW and P-LCR levels in microvascular complications agreed with studies conducted

Table 3: Comparison of platelet parameters at start and after 6 months

Platelet parameters	Mean value at start	Mean Value after 6 months	t test (p value)
Platelet count (10^9/L)	231.39+26	220.55+42	0.002
Mean Platelet Volume (MPV) (fL)	10.69+2.0	11.12+1.1	0.001
Platelet Distribution Width (PDW)	14.36+1.2	13.97+1.2	0.06
Plateletcrit (PCT) (%)	0.202+0.03	0.219+0.11	0.04
Platelet Large Cell Ratio PLCR (%)	32.78+1..6	42.11+2.4	0.002

Table 4: Comparison of platelet parameters among patients with or without microvascular complications (after 6 months)

Platelet parameters after 6 months	Mean Value with microvascular complications	Mean Value without microvascular complications	t test (p value)
Platelet count (10^9/L)	217.33+60	233.11+28	0.001
MPV (fL)	11.25+2.52	10.09+1.01	0.001
PDW	13.89+1.80	10.63+1.2	0.001
Plateletcrit (%)	0.219+0.050	0.219+0.052	0.134
Platelet LCR (%)	43.20+1..61	33.17+2.00	0.001

Table 5: Comparison of platelet parameters among patients with or without retinopathy (after 6 months)

Platelet parameters	Mean Value with retinopathy	Mean Value without retinopathy	t test (p value)
Platelet count (10^9/L)	218.30+56	234.30+40	0.015
MPV (fL)	11.24+1.01	10.57+1.02	0.010
PDW	14.01+1.01	13.78+1.2	0.008
Plateletcrit (%)	0.224+0.03	0.184+0.061	0.040
Platelet LCR (%)	43.78+1..61	34.6+1.82	0.006

Table 6: Comparison of platelet parameters among patients with or without neuropathy (after 6 months)

Platelet parameters	Mean Value with neuropathy	Mean Value without neuropathy	t test (p value)
Platelet count (10^9/L)	226.55+26	246.26+20	0.001
MPV (fL)	11.18+2.00	11.10+1.02	0.008
PDW	13.25+1.42	14.20+1.21	0.011
Plateletcrit (%)	0.242+0.030	0.210+0.011	0.020
Platelet LCR (%)	37.44+1.61	43.62+2.10	0.010

Table 7: Comparison of platelet parameters among patients with or without nephropathy (after 6 months)

Platelet parameters	Mean Value with nephropathy	Mean Value without nephropathy	t test (p value)
Platelet count (10^9/L)	230.75+56	237.80+20	0.011
MPV (fL)	12.10+1.01	11.02+1.00	0.005
PDW	12.38+1.012	10.13+1.24	0.001
Plateletcrit (%)	0.194+0.031	0.221+0.016	0.020
Platelet LCR (%)	41.40+1.61	36.18+2.01	0.006

Table 8: Comparison of platelet parameters among patients with or without macrovascular complications (after 6 months)

Platelet parameters after 6 months	Mean Value with macrovascular complications	Mean Value without macrovascular complications	t test (p value)
Platelet count (10^9/L)	220.36+26	258.28+20	0.054
MPV (fL)	11.28+2.0	11.06+1.0	0.001
PDW	14.34+1.4	13.82+1.2	0.001
Plateletcrit (%)	0.218+0.03	0.219+0.01	0.190
Platelet LCR (%)	42.53+1..6	40.76+2.0	0.001

by Jindal et al,[10] Buch et al.,[6] Alhadas et al[11] in which MPV and PDW values were found to be higher in diabetics with diabetic retinopathy (DR). Dubey I et al[7] also found that both higher value of MPV and PDW were associated with DR.

Kodiatte et al,[12] Papanas et al,[13] Hekimsoy et al.,[14] Citrik et al[15] and Gungor et al[16] also found significant association between MPV and DR. There was no significant association between PDW and DR in study by Demirtunc et al,[17] Citrik et al.[15]

In our study an increase in the platelet parameters was observed in T2DM with macrovascular complications as compared to those without macrovascular complications. It was in concordance with a study conducted by Inoue et al.[18] Our study showed a significantly increased MPV in diabetics with both microvascular and macrovascular complications than those without these complications in agreement with studies done by Demirtas et al,[19] Shilpi et al[3] and Papanas et al[13] while this was in contrast to the study Kodiatte et al,[12] Demitunc et al,[17] Zuberi et al,[5] Mowafy et al[20] and Hekimsoy et al.[21]

Significantly increased MPV, PDW, and PLCR were in diabetics with HbA1c levels >7.5% were seen in our studies than in diabetics with HbA1c levels <7.5%. This was in accordance with the studies conducted by Kodiatte et al,[12] Demirtas et al,[19] Ozder et al[22] and Dubey I et al.[7] A significant association was also found between HbA1c and MPV which were seen in study done by Demirtunc et al.[17] In studies conducted by Kodiatte et al,[12] Akinsegun et al[23] and Ulutas et al.[24] similar findings were seen.

This study found that increased MPV correlates with poor glycemic control. This coincides with the results of studies conducted by Kodiatte et al,[12] Ozder et al,[22] Zuberi et al,[5] Demirtunc et al,[17] Buch et al,[6] Jindal et al,[10] Hekimsoy et al,[21] Papanas et al,[13] but was in contrast with the results of Unobol et al[25] and Alhadas et al.[11]

Diabetes is a hyperglycaemic state. High blood glucose level in diabetes leads to non-enzymatic glycation of glycoproteins on the platelet surface. Glycated platelets are hyperactive and have decreased membrane fluidity.[26] There is an enhanced production of thromboxane (TXA2) due to increased glucose concentration by directly activating the arachidonic acid pathway. TXA2 is a strong platelet activator and causes platelet hyperactivity in diabetic patients.[26]

Hyperactive platelets which are large platelets release more granular contents which enhances coagulation, impairs fibrinolysis and causes endothelial dysfunction. In addition, hyperactive platelets develop multiple pseudopodia on their surface increasing their adhesive capacity to the vessel wall.[26] All these factors contribute to the development of vascular complications.

In diabetics, the increased level of blood glucose and other glucose derivatives lead to osmotic swelling and shortening of its life span. There is a rapid release of young platelets from bone marrow hence young platelets are large. These large platelets have increased propensity to cause complications due to their hyperactivity and increased ability to cause thrombosis.[26]

Like study done by Buch et al,[6] our study also found that platelet count was lower in patients with microvascular complications than patients without complications, but it was statistically insignificant. A probable reason for the decreased platelet counts in participants with microvascular complications is the rapid utilization of activated platelets in thrombosis leading to complications.[12] Another possible reason is the rapid destruction of the platelets due to oxidative stress caused by an imbalance between antioxidant mechanism and production of reactive oxygen species.[26]

5. Conclusion

We have tried to assess the level of multiple platelet parameters in patients of type 2 diabetes mellitus and see its association with the development of complications. There is paucity of similar prospective studies in the region. According to our study, MPV, PDW, PCT and P-LCR have statistically significant increased values in T2DM patients with microvascular as well as macrovascular complications as compared to those without complications. The higher values of these parameters in diabetics with microvascular and macrovascular complications implies that platelet parameters can be used as an easy and cheap tool to prognosticate and predict the risk of development of complications in T2DM. However, there lies a close relationship between the development of complications and duration of diabetes mellitus. The incidence of complications increases with duration of the disease. Hence, a follow – up for only 6 months may not be enough for the complete understanding of various microvascular and macrovascular complications of diabetes mellitus. Further, studies and follow – up needs to be done.

6. Ethical Approval

The study was performed in agreement with the ethical standard of Research Ethics Board (REB), RIMS. Ethical approval number A/206/REB-Comm (SP)/RIMS /2015/582/60/2019.

7. Source of Funding

None.

8. Conflict of Interest

None.

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