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Platelet indices in controlled and uncontrolled type 2 diabetes mellitus: A cross sectional study

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ABSTRACT

Background: Diabetes is an emerging health problem across the world. Underlying prothrombotic state leads to cardiovascular complications in diabetics especially those with poor glycemic control. Though multiple mechanisms are responsible, platelet activation plays a major role in the pathogenesis of prothrobotic state. Platelet activation causes increase in their size which is represented by Mean Platelet Volume (MPV) whereas variation in their size associated with release reaction is reflected by Platelet Distribution Width (PDW). So MPV and PDW together may help to detect emergence of prothrombotic state at an earlier stage.

Aims: To find out whether any significant difference exists in platelet count, MPV and PDW in controlled and uncontrolled Type 2 diabetics.

Materials and Methods: It was a hospital based cross sectional study where total 277 patients of Type 2 Diabetes Mellitus were included following predetermined inclusion and exclusion criteria and categorized into controlled (193 subjects) and uncontrolled (84 subjects) groups with HbA1c level ≤ 7% and >7% respectively. Blood from all the participants were analyzed for MPV, PDW and platelet count. Unpaired t-test was done to compare the platelet count and platelet indices among two groups.

Results: MPV and PDW were found to be significantly higher ($p < 0.0001$) among uncontrolled group compared to controlled group with Mean MPV 13.47±0.56 fl vs 10.25±1.32 fl and Mean PDW 23.37±2.47% vs 15.57±2.69% respectively. But there was no significant difference in platelet count among two groups.

Conclusion: The higher value of MPV and PDW in uncontrolled diabetics indicates that they can be utilized as an inexpensive yet useful method for early detection of thrombotic complication in these patients.

1. Introduction

Diabetes mellitus (DM) is an emerging global health problem affecting the population of both developed and developing countries of the world. The prevalence rate of diabetes mellitus in India is 9.3%.[1] It is estimated that more than 171 million people is currently suffering from diabetes in the world and it will affect approximately 366 million people by the year 2030. It is predicted that by 2030, 79.4 million individuals may be afflicted by the disease in India.[2] Diabetes is a complex metabolic disorder resulting in both macrovascular and microvascular complications. Macrovascular disease causes accelerated atherosclerosis among diabetics, resulting in an increased risk of developing myocardial infarction, stroke, and lower extremity ischemia. The effects of microvascular disease are most profound in the retina, kidneys, and peripheral nerves, resulting in diabetic retinopathy, nephropathy, and

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neuropathy, respectively. Underlying prothrombotic state is mostly responsible for the above complications. However multiple mechanisms identified, among them, platelet activation is considered to play an important role in the pathogenesis of thrombotic complications in patients with DM.[3,4] It is found that activation of platelet causes an increase in their size.[5] The size of the platelets can be determined by estimating Mean platelet volume (MPV).It can be measured by automated blood cell counters which is an easy and inexpensive method. Thus MPV can be used as a useful parameter for detecting platelet activation. Previous studies found high MPV in patients with diabetes mellitus and it is considered as a risk factor for heart disease. Similarly, another platelet indices namely Platelet distribution width (PDW) represents the variation in platelet size which may be an indicator of active platelet release.[6] So the measurement of these platelet indices can be useful to determine the platelet activation and thus to predict the underlying vascular complications in patients with diabetes mellitus. Thus this inexpensive and simple test can help to reduce the mortality arising from vascular complications in these patients. Again according to American Diabetic Association Criteria (2013) patients of type 2 diabetes mellitus can be divided into two categories based on their HbA1c level in blood. Patients with HbA1c $\leq$ 7% are considered as having controlled diabetes whereas those with HbA1c > 7% are categorized as having uncontrolled diabetes.[7] Previous studies were mostly confined to compare the MPV value between diabetic and non-diabetic individuals. So there is paucity of data to compare the platelet indices among controlled and uncontrolled group of these patients. Furthermore there is limited data available regarding the effect of glycemic control over PDW and there is discrepancy in the data available also. It necessitates further study in this topic for better understanding of the effect of glycemic control on platelet activation. With this background of knowledge, the present study was carried out to find out whether there is any significant difference exists in platelet count, MPV and PDW in controlled and uncontrolled group of patients with diabetes mellitus. So we tried to find out the effects of glycemic control on platelet count and platelet indices which are the known indicator of underlying platelet activation and thus predictor of vascular complications in diabetic patients.

2. Materials and Methods

This study was a hospital based cross sectional study carried out in a tertiary care hospital of West Bengal over a period of 4 months. It was done after obtaining Institutional Ethical Clearance and proper consent from all the participants. All the diagnosed patients of type 2 diabetes mellitus $\geq$ 25 years of age attending Diabetic Clinic of this hospital during this study period were first evaluated for detailed clinical history. Patients suffering from hematological disorders like malignancy or any bone marrow disorders, chronic systemic inflammatory disorders, patients with renal failure, smokers, patients suffering from thyroid-related disorders, having any infectious diseases, AIDS, sepsis, pregnant women, patients on anti-platelet drugs and cancer chemotherapy were excluded from the study due to their anticipated effect on MPV.[8,9] Then venous blood samples were collected in EDTA anti coagulant from all the participants maintaining appropriate aseptic precautions. All the blood samples were analyzed for HbA1c level by automated clinical biochemistry analyzer Konelab 600i Prime using immunological methods. Based on the HbA1c level, the participants were divided into two categories as per ADA criteria 2013.[7] Patients with HbA1c $\leq$ 7% were considered as having controlled diabetes whereas those with HbA1c > 7% were categorized as having uncontrolled diabetes. All the blood samples were also analyzed by Sysmex 6-part automated hematology analyzer for platelet count, Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) in the central laboratory of the hospital within 3 hours of blood collection. Platelet count and size were correlated by peripheral blood smear study on Leishman stained slide by binocular light microscope. Results were tabulated and data were analyzed using Statistical packages for social sciences (SPSS) software version 11. Unpaired t-test was done to compare the platelet count and platelet indices among the patients of controlled and uncontrolled Type 2 diabetes mellitus to find out whether there is any significant differences exists in the aforesaid parameters between two groups.

3. Results

Out of total 277 patients included in the study as per inclusion and exclusion criteria, 193 (69.7%) patients have HbA1c value $\leq$7% designated as controlled group while rest 84 (30.3%) patients having HbA1c value >7% designated as uncontrolled group. In the controlled group, the mean and Standard deviation (SD) of HbA1c value (%) was 5.81 and 0.64 respectively with range of 4.4 to 7 while in the uncontrolled group the values were 9.3 and 1.8 respectively with range of 7.1 to 14.4. In the controlled group, numbers of male and female patients were 98 and 95 respectively while in the uncontrolled group, the numbers were 41 and 43 respectively for male and female. Regarding age distribution, mean age (year) for controlled and uncontrolled group was 54 (range 26 to 87) and 53.6 (range 27 to 81) respectively (Table 1). Table 2 shows the data regarding study parameters like MPV, PDW and Platelet count comparing between the two groups. Mean values of MPV, PDW and platelet count were 10.24 fl, 15.57% and $176X10^3$/cumm for controlled group respectively while they were 13.47 fl, 23.37% and $177X10^3$/cumm for uncontrolled group respectively. Unpaired t test results revealed that MPV and PDW is

significantly higher (p<0.0001) in uncontrolled group in comparison to controlled group but there is no significant difference in platelet count among the two groups.

Table 1: Characteristics of study participants (n= 277)

Characteristics	Controlled group	Uncontrolled group
No. of cases (%)	193 (69.7%)	84(30.3%)
Age in years (Mean±SD)	54±15.63	53.6±14.33
Male (%)	98(50.78%)	41(48.8%)
Female (%)	95(49.22%)	43(51.19%)
HbA1c (Mean ± SD)%	5.81±0.64	9.3±1.8

Table 2: MPV, PDW and platelet count in controlled and uncontrolled diabetic group

Platelet parameter	Controlled (n=193)	Uncontrolled (n= 84)	P value
MPV(fl) [Mean±SD]	10.24±0.56	13.47± 1.32	<0.0001
PDW(%)[Mean±SD]	15.57±2.69	23.37±2.47	<0.0001
Platelet count ($X10^3$/mm) [Mean±SD]	176±55	177±73	0.985

4. Discussion

Diabetes is a chronic health problem affecting large number of individuals throughout the world. Changing lifestyle and food habit further increases the burden of the disease among the population of developing countries in recent years. These patients are prone to suffer from both macrovascular and microvascular complications owing to underlying prothrombotic state in these individuals and it is a leading cause of morbidity and mortality among diabetics. Though a single mechanism cannot explain the pathohenesis of prothrombotic state in diabetics, but the role of platelet activation has been proposed by many studies in the past.[3,4] Platelet activation causes increase in their size which is followed by platelet release reaction. Platelet activation is enhanced by increased expression of surface glycoproteins Ib and IIb-IIIa combined with increased production of Thromboxane A2 and reactive oxygen species in patients with diabetes. The prothrombotic state is further aggravated by reduced production of platelet inhibitors like nitric oxide.[10–12] Platelet activation alongwith endothelial dysfunction play significant role in the pathogenesis of thrombotic complications in diabetic individuals. Size of the platelet is determined by MPV. The variation in the sizes of platelets is represented by PDW which reflects platelet release reaction. Thus both of these platelet indices may indicate the underlying platelet activation and associated prothrombotic state. So the regular measurement of these platelet indices may help to detect the prothrombotic state at an early stage and thus it can reduce the morbidity and mortality of these patients.

In the present study controlled and uncontrolled diabetes was found among 30.3% and 69.7% of the total study participants respectively and there was no gender predilection in either of the two groups. Mean age of the uncontrolled group was found to be slightly higher than that of the controlled group in our study (54±15.63years vs 53.6±14.33 years respectively). This finding is in concordance with the study done by Jaman S, et al. They also found similar age and sex distribution among controlled and uncontrolled diabetics in their study. The mean age of the uncontrolled group was 55 years which was slightly higher than that of the controlled group with a mean age of 48 years in their study.[13] The mean HbA1c among controlled and uncontrolled group was 5.81±0.64% and 9.3±1.8% respectively in this study (Table 1). Previous study found mean HbA1c level among controlled and uncontrolled diabetics as 9.86±1.91% and 6.08±0.49% respectively.[13] In the current study MPV (13.47±0.56 fl vs 10.25±1.32 fl) and PDW(23.37±2.47% vs 15.57±2.69%) was significantly higher (p<0.0001) in uncontrolled group compared to controlled group (Figure 1). In the year 2015, Lippi G et al also found a positive association between MPV and HbA1c in diabetics.[14] Kodiatte, et al. recorded significantly higher(p <0.003) value of MPV among patients with HbA1C >6.5% compared to those with HbA1c <6.5%(8.35±0.724 vs 7.95±0.72 fl).[15] Our study was also in concordance with the findings of Buch A, et al. who found a significantly higher value (p<0.0001) of MPV among patients with complicated diabetes compared to those without complication (11.31 vs 9.91 fl respectively). A positive correlation between HbA1c and MPV and a higher value of MPV among patients with uncontrolled diabetes was also supported in the study done by Demirtunc et al. (Mean MPV 8.7 vs 8.2 fl with p value 0.002), Jindal et al. (Mean MPV 12.08 vs 11.42fl with p value <0.05), Papanas et al., (Mean MPV 14.2 vs 7.1 fl p=0.01) and Ozder et al. (Mean MPV 10.66 vs 10.04 fl with p value <0.001).[16–19] However this association was not supported by Kim et al. and Akinsegun et al. in their study.[20,21] Mean PDW among controlled and uncontrolled group was found to be 23.37±2.47% and 15.57±2.69% respectively in the present study and the difference was statistically significant with a p value of <0.0001(Table 2). Demirtas et al., Jabeen et al. and Dalamaga et al. found significantly higher value of PDW among diabetics (Mean PDW 16.4%, 15.02% and 16.4% respectively) compared to non-diabetics (Mean PDW 15.4%, 14.12% and 13.0% respectively) with p value <0.001, <0.01 and <0.001 respectively.[22–24] There was only limited data available to compare the PDW between controlled and uncontrolled group of diabetics. Non-significant higher value of PDW among diabetics with

complications compared to those without complication was observed by Mowafy et al. and Shilpi K et al in their study.[25,26] Our finding is in concordance with the study done by Jindal et al. who also found a statistically significant higher value of PDW among patients with uncontrolled diabetes.[17] We found no statistical significant correlation between the glycemic control and platelet count in this study (p value 0.985)(Table 2) which was corroborative with the study done by Jabeen F et al. They compared the platelet count among diabetic and healthy individuals and the p value was found to be 0.737 which was not statistically significant.[27] Similar study done by Demirtas L et al to compare the platelet count among controlled and uncontrolled group of diabetics also found no effect of glycemic control on platelet count with a p value >0.05.[22]

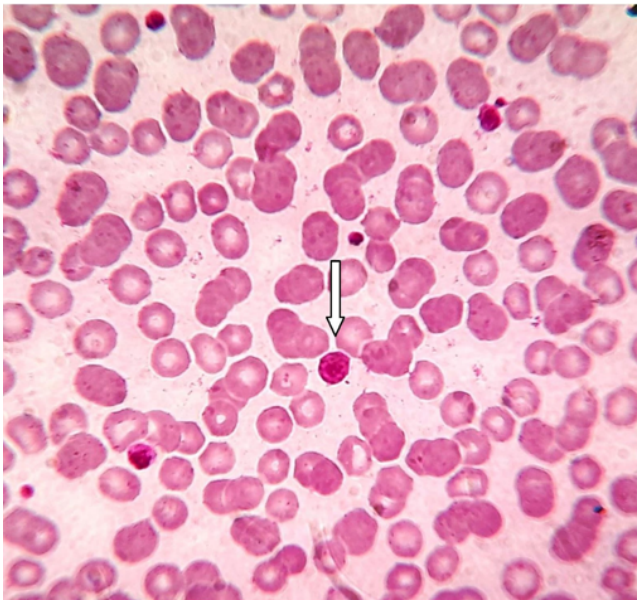

Fig. 1: Peripheral blood smear shows large platelet (arrow) in a case of uncontrolled diabetes patient with HbA1C 9.1% (leishman stain, oil immersion)

5. Conclusion

In the present study, we found a positive association between MPV, PDW and glycemic status of the diabetics. Both microvascular and macrovascular complications are more common in patients with poor glycemic control. As uncontrolled group showed significantly higher MPV and PDW, we concluded that these platelet indices can be utilized as a useful parameter for early detection of platelet activation which is a major cause of thrombotic complications in patients with diabetes. Thus these inexpensive yet useful tests can reduce the morbidity and mortality of these patients.

6. Limitations of the Study

We could not include Platelet large cell ratio (P-LCR) which is a relatively new platelet volume parameter in our study as it was not generated by the machine we used. This may also represent the underlying platelet activation as mentioned by Shilpi K et al. in their study.[26] Further, a community based prospective study with larger sample size along with follow up can generate better insight regarding correlation of platelet indices, glycemic status and complications of diabetes in the future.

7. Source of Funding

None.

8. Conflict of Interest

None.

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