Platelet Indices: A Neglected Tool in Predicting Diabetic Ulcer Formtion in Type 2 Dibetes

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Abstract
BACKGROUND:

Diabetes Mellitus is a group of metabolic disease with increasing incidence every year with severe complications. The occurrence of ulcers in diabetic patients is the most common, attributed to the presence of thrombosis due to increased platelet function. Platelet volume indices (PVI) such as mean platelet volume (MPV), platelet distribution width (PDW), and platelet-large cell ratio (P-LCR) are the indicators of increased platelet activity and can be considered as potential biomarkers for diabetic complications.
AIM
To study PVI in Type 2 diabetics with and without diabetic ulcer in comparison to non diabetic patients.
MATERIALS AND METHODS:

A cross sectional and observational study was conducted on 68 Type 2 diabetics and 22 nondiabetics. Detailed clinical history regarding duration, hypertension, and complications was taken. PVI was obtained using automated cell counter, Fasting blood glucose and hemoglobin A1c were also obtained. Diabetics were further categorized into patients with ulcers and without ulcers. Participants were divided into three groups according to their HbA1c levels:
☐ *Group 1, HbA1c<6% (control group)*
☐ *Group 2, HbA1c between 6% to8% (poor control/unregulated diabetes) and*
☐ *Group 3,HbA1c>8.5%(worst control).*
RESULTS:

Platelet count was significantly increased in diabetics. MPV was significantly increased in diabetic patients with complications as compared to diabetics without complications and non diabetic group (P < 0.0001). PDW showed statistically significant difference between diabetics with and without complications and nondiabetics (P < 0.0001). However, no statistically significant difference was observed in platelet-large cell ratio (P-LCR) among all the three study groups. We found statistically significant correlation of MPV with diabetic foot (P = 0.048). Platelet indices were found to increase in diabetic patients with diabetic foot ulcers indicating more reactive and aggregatable platelet function.
CONCLUSION:

MPV and PDW are predictive biomarkers of diabetic vascular complications. They are more significant in microvascular complications than macrovascular complications.
Keywords: *Diabetes, mean platelet volume, platelet distribution width and platelet large cell ratio, platelet volume indices*

I.   Introduction

Diabetes mellitus (diabetic) is a group of metabolic disease with increasing incidence steadily every year, from 366 million patients in 2011 to 552 million in 2030.[1] Diabetic complications are mainly due to hyperglycemia. Fasting blood glucose, postprandial blood glucose, and hemoglobin A1c (HbA1c) are widely used to monitor glycometabolic control in patients with DM. HbA1c is a more useful marker to determine mean blood glucose levels over a long time period.[5] DM is considered as a "prothrombotic state" owing to sustained hyperglycemia. Altered platelet morphology and function has been observed in diabetes in the form of enhanced platelet activity which may contribute to this "prothrombotic state".[6] Larger platelets that contain denser granules are metabolically and enzymatically more active than smaller ones and have higher thrombotic potential. Hence, increased mean platelet volume (MPV) and platelet distribution width (PDW) might be linked with increased thrombotic potential.[7] Until now, diabetic foot ulcers is still one of the complications of diabetics with a high mortality rate (16%), and amputation rate reaches 25%, even 3-year mortality rate after amputation reaches 37%.[2] . Platelet indices, consisting of platelet count, mean platelet volume (MPV), platelet distribution width (PDW), Plateletcrit (PCT) has become part of the current routine hematological examination. There is a change of morphology and platelet function in diabetic patients resulting in changes in

platelet indices.[3] MPV describes the size of platelets associated with the risk of thrombosis. PDW illustrates variation in size and PCT measure total platelet mass in which the increase can also describe the presence of atherosclerosis and thrombosis.[4] MPV and PDW were known to increase in patients with diabetes [2], but there have not been many studies about these parameters in patients with diabetic foot ulcers. The newer hematological analyzers are giving variety of platelet parameters which helps in easy detection of change in platelet structure, which may help in early detection of prothrombotic state of the platelets. These can act as an alarm for diagnosing initiation/progression of diabetic complications. Therefore, this study aims to see if there were differences in platelet indices in diabetic patients with and without diabetic foot ulcers. It becomes a prediction that diabetic patient will have a diabetic foot ulcers complication in order to prevent this complication as early as possible.

II.   Material And Method

A cross sectional and observational study was conducted on 68 Type 2 diabetics and 22 non diabetics. Detailed clinical history regarding duration, hypertension, and complications was taken. PVI was obtained using automated cell counter, Fasting blood glucose and HBA1c were also obtained. Diabetics were further categorized into patients with ulcers and without ulcers. Participants were divided into three groups according to their HbA1c levels:

 Group 1, HbA1c<6% (control) The control group was obtained from individuals without DM, as obtained from their medical records

 Group 2, HbA1c between 6% to8% (poor control/unregulated diabetes) and

 Group 3,HbA1c>8.5%(worst control).

 Verbal informed consent was obtained from all patients. Statistical analysis was performed by Statistical Package for the Social Sciences Version 17 . Categorical data were in numbers and percentages. Numerical data with normal distribution were in mean standard deviation, . The level of significance was set at 0.05. Platelets indices were examined and looked for differences in diabetic patients with and without diabetic foot ulcer.

INCLUSION CRITERIA

Diabetic patients with diabetic foot ulcers regardless of other comorbidities.

EXCLUSION CRITERIA

Females with Hb <10 g% and males Hb <12 g%, nondiabetic subjects with CAD, pregnant women, patients on antiplatelet drugs such as aspirin and clopidogrel and subjects with any diagnosed malignancy were excluded from the study.

METHOD OF COLLECTION OF DATA

 After an overnight fast, venous blood samples (2ml) were collected into

haemogram tubes containing di-potassium ethylenediaminetetra-acetic

acid(EDTA) (1.5– 2.2mg/ml).

 Samples were maintained at room temperature and tested within 1h of collection,

to minimize variations due to sample ageing.

 Platelet indices were determined using an automated blood cell counter.(Sysmex XS 800i)

 HbA1c levels were measured using automated ion exchange high performance

liquid chromatography.

 Serum glucose levels were measured using a hexokinase enzymatic method

III.   Observation And Result

TABLE 1: CHARACTERISTICS OF SUBJECTS

	DIABETIC ULCER(+)	DIABETIC ULCER(-)	CONTROL GROUP
No. of patients (n)	35	33	21
Males	21	13	12
Females	14	20	9
Mean Age(yrs)	55	57	54

TABLE 2: COMPARING THE MEAN VALUES OF PLATELET INDICES

	Platelets(in lakhs)	PDW	MPV	P-LCR	PCT
Control group(HBA1c<6%)	263	10.5	9.4	19.3	0.21
Diabetic Ulcer(-)	280	11.33	10.0	19.8	0.30
Diabetic Ulcer(+)	298	12.8	12.2	19.6	0.36

TABLE 3: COMPARING THE MEAN VALUES

	RANDOM BLOOD SUGAR	HBA1c(%)
Controls(HBA1c<6%)	120	5.08
Diabetics without ulcer(HBA1c 6-8%)	162	6.7
Diabetics with ulcer(HBA1c>8%)	290	9.8

- A total of 68 diabetic patients (34 males, 34 females) and 22 controls (12 males, 9 females) were selected for the study .
- Out of 68 diabetics,35 patients had diabetic ulcer, having worse control over the sugar levels with HBA1c >8%.
- There was no significant difference regarding age, though diabetic males were more than females with foot ulcer.(TABLE 1 &3)
- From the platelet indices, the number of platelets, PDW and PCT had p values of 0.041; 0.027; 0.007, which are statistically significant.
- The number of platelets, PDW,MPV And PCT were found to be increased more in patients with diabetes, having diabetic ulcers as compared to the control group and diabetics without ulcer.
- Also, there was no significant difference in the values of P-LCR, in all the three groups.
- The study reinforced the fact that poor glycemic control and raised FBS causes increased the risk of diabetic complications.

IV.   Discussion

Diabetes is a growing health problem associated with increased risk of micro- and macro-vascular complications.[12] With the easy availability of various blood tests such as platelet volume indices (PVI), efforts are made to identify and prove their utility to act as biomarkers for early detection of diabetic complications.

In this study, platelet counts were higher in the diabetic foot ulcers group. Other studies –show different results regarding the number of Platelets in patients with adiabetic.

Swaminnatthan et al.found higher mean platelet count in diabetic group than non-diabetic although not significantly different.[8] The other study by **Demirtunc et al** showed a significant difference in platelet count between patients with and without diabetic.[9]The elevated MPV levels in diabetic patients with foot ulcers have been reported **by Gunes et al.[10]**

High MPV values can be an interpretation of large platelet size. Large platelets become more hyperreactive resulting in a prothrombotic factor. This platelet has more alpha granules, expressing increased adhesion molecules, producing more thromboxane A2 and showing greater thrombogenic potential when compared with small platelets.[8,11]

Hyperglycemia is said to be the important factors causing increased platelet reactivity in diabetic patients. Platelet hyper reactivity is a well-known contributing factor to the prothrombotic state in diabetics.

MPV is a parameter used to assess platelet size, and it is a potential biomarker of platelet reactivity. It has been shown that larger platelets are more reactive than smaller ones.[13] PDW can directly measure the variability in platelet size, and its high values suggest increased production of larger reticulated platelets.[14]

In this study, we found differences in PDW and PCT values which are significantly higher in diabetic foot ulcers patients. In a study by **Aldahas et al**, diabetic patients with complications showed an increase in MPV, PDW,and PCT versus uncomplicated diabetic patients. MPV and PDW often associated with macrovascular complications whereas MPV and platelet count associated with microvascular complications. Elevation in MPV and PDW level indicating more reactive and aggregatable platelets that can explain the incidence of complications of diabetes. The **Swaminathun et al.** study showed that MPV level in diabetic patients associated with poor glycemic control and duration of a diabetic.[6] Also, no other comorbid matching experienced by the patient in which comorbidity may also affect the platelet indices such as infection.

Our study suggests that increased MPV is associated with poor glycometabolic control and it is also reflected diabetic foot

Several studies indicated positive correlation of FBS and HbA1c with platelet indices.[15,16] However, some studies have not shown any relation of FBS and HbA1c with platelet indices.[17,18] It has been proposed that increase in MPV could be because of raised blood sugar leading to osmotic swelling and shorter life span of platelets in diabetic patients. Alternatively, this may suggest that platelet activation is related to glycemic control.[19]

There were not much data on these newer biomarkers in the literature search. However, further prospective studies with larger sample size are required for identifying the utility of these markers to predict the diabetic disease burden, keeping all the compounding risk factors in mind, especially to predict the impact of PVI on diabetic complications.

V.   Conclusion

We all are aware of the risk factors for diabetic complications such as duration, glycemic control, blood pressure, and dyslipidemia. We found increase in MPV and PDW in all these high risk groups. This implies that raised MPV and PDW can be considered as biomarkers for early detection of impending complication. We found that these platelet indices were more statistically significant in microvascular complications as compared to macrovascular complications. P-LCR did not have much statistical significance in predicting diabetic complications.

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