ORIGINAL ARTICLE

Study of Platelet Indices as Markers of Retinopathy in Patients with Diabetes Mellitus

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Abstract

Background: Diabetes mellitus poses a substantial global health burden, with diabetic retinopathy (DR) being a prevalent and potentially devastating microvascular complication. Platelet activation has been implicated in the pathogenesis of DR, suggesting platelet indices such as mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR), and plateletcrit (PCT) as potential noninvasive markers for predicting its onset.

Materials and Methods: We conducted a cross-sectional study involving 300 patients diagnosed with type 2 diabetes mellitus (T2DM) attending a tertiary care center. Demographic data, duration of diabetes, and HbA1c levels were recorded. Platelet indices were measured using complete blood counts, and DR was diagnosed based on fundus examination findings.

Results: Among the study participants, group B (n = 140) comprising patients with DR had significantly higher levels of MPV (13.28 ± 2.14 fL), PDW (14.56 ± 2.37), P-LCR (29.59 ± 6.018%), and PCT (0.29 ± 0.06) compared to group A (n = 160) without DR (MPV: 9.99 ± 1.64 fL, PDW: 12.81 ± 2.28, P-LCR: 27.64 ± 8.36%, PCT: 0.26 ± 0.09) (p < 0.001 for all comparisons). Subgroup analysis within poorly controlled diabetics (HbA1c > 7%) also showed significantly higher platelet indices in those with DR compared to those without.

Conclusion: Our findings underscore a significant association between elevated platelet indices and the presence of DR in patients with T2DM, independent of glycemic control status. These indices could serve as valuable surrogate markers for identifying individuals at risk of developing DR, facilitating early intervention strategies in clinical practice.

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Introduction

Diabetes mellitus is a complex disease that is considered to be a global pandemic. Due to its expanding population, India is on the way to becoming the diabetes capital of the world. At present, India has the world's second-largest population with diabetes. In the tenth edition of the diabetes atlas, the global prevalence of diabetes is estimated as 537 million (10.5%), which is expected to rise to 783 million by 2045. In India, there are approximately 74.2 million people with diabetes, and the number is expected to cross 124.87 million by 2045.[1]

Diabetic retinopathy is a prevalent and potentially severe complication in the natural history of diabetes mellitus. The onset of diabetic retinopathy serves as a critical warning for treating physicians, as it is often one of the earliest indicators of microvascular damage and signals the need for a more intensive approach to achieving optimal glycemic control. Therefore, early identification of diabetic retinopathy is crucial for physicians to address and manage this condition effectively.

Abnormally increased platelet activation is thought to be the central dogma in the pathophysiology of diabetic retinopathy.[2] Platelet activation can be noninvasively studied by analyzing the platelet indices, which include mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR), and plateletcrit (PCT). These may be used as predictors of the onset of diabetic retinopathy.

Distorted platelet morphology and their abnormal functions are reported in patients with uncontrolled diabetes,[3] and the association between platelet indices and diabetes was most obvious in those with poorly controlled diabetes.[4] The effect of hyperglycemia on platelet indices has been studied less. Also, the relationship between platelet indices and diabetic retinopathy remains to be clarified.

The present study aimed to evaluate the relationship between HbA1c, which is a parameter used to define uncontrolled diabetes, and platelet indices, and to evaluate the relationship between these variables and diabetic retinopathy.

Materials and Methods

Study Design

This was an observational, descriptive, cross-sectional study conducted at the Department of Medicine, Jawahar Lal Nehru Medical College and Associated Hospitals, Ajmer, Rajasthan. The study duration spanned over 1 year and included both inpatients and outpatients diagnosed with type 2 diabetes mellitus.

Ethical Considerations

The study was initiated only after obtaining ethical clearance from the Institutional Ethics Committee (IEC). Written informed consent was obtained from all the participants prior to inclusion in the study.

Study Population and Sampling

The sample size was calculated using the formula for comparing two proportions, assuming a power of 80%, alpha of 5%, and an expected difference of 20% in abnormal platelet indices between patients with and without diabetic retinopathy. Based on prior literature, the estimated proportions were 30% in nonretinopathy group and 50% in the retinopathy groups. The minimum required sample size was 91 patients per group (~182 total). Adjusting for a 10% nonresponse rate, the sample size was revised to ~200–210. We included 300 participants in our study to enhance the robustness and validity of results. Patients with type 2 diabetes mellitus (T2DM) on treatment with oral hypoglycemic agents and/or insulin therapy were included using consecutive sampling over the study

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period. These patients were enrolled from medical wards and outpatient services.

Inclusion Criteria

- Patients with a confirmed diagnosis of type 2 diabetes mellitus.
- Patients on treatment with oral hypoglycemic agents and/or insulin.
- Patients are willing to give informed consent.

Exclusion Criteria

- Patients with type 1 diabetes mellitus.
- Patients on antiplatelet drugs (e.g., aspirin, clopidogrel).
- Patients with severe anemia (Hb < 6 gm/dL).
- Patients with recent febrile or viral illnesses.
- Patients with hematologic disorders affecting bone marrow (e.g., aplastic anemia, leukemia).
- Patients with preexisting nondiabetic retinal disorders.

Data Collection

Participants were interviewed to obtain detailed demographic and clinical data, including age, sex, duration of diabetes, treatment history, and family history. Anthropometric measurements and blood pressure were recorded.

Laboratory Investigations

Complete blood count and platelet indices: Blood samples were collected in EDTA vials and analyzed using the SYSMEX XP-100 hematology analyzer based on flow cytometry and electrical impedance.

Platelet indices measured included:

- Mean platelet volume (MPV).
- Platelet distribution width (PDW).
- Plateletcrit (PCT).
- Platelet-large cell ratio (P-LCR).
- Glycated hemoglobin (HbA1c): Estimated using a latex agglutination inhibition assay with reagents provided by the institutional central laboratory. HbA1c values were categorized as:
  - Good glycemic control: HbA1c ≤7%.
  - Poor glycemic control: HbA1c >7%.

Ophthalmologic Evaluation

The initial fundoscopic examination was performed by the primary investigator. All findings were subsequently reviewed and confirmed by a senior ophthalmologist with over a decade of clinical experience in diagnosing diabetic retinopathy. This two-step approach was implemented to ensure diagnostic accuracy and consistency across all study participants.

Diabetic retinopathy was diagnosed based on presence of at least two microaneurysms and/or retinal hemorrhages, exudates, and other retinal lesions consistent with DR.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics v24.0. Continuous variables were expressed as mean ± standard deviation, and categorical variables as percentages. Comparisons between groups were performed using unpaired *t*-tests or chi-square tests as appropriate. A *p*-value <0.05 was considered statistically significant.

Results

A total of 300 patients ($N = 300$) were included in study, considering the inclusion and exclusion criteria. After the baseline investigations, the study participants were categorized according to presence of diabetic retinopathy.

Group A ($n = 160$) comprised of patients without diabetic retinopathy, and group B ($n = 140$) comprised of patients with diabetic retinopathy. In group A, 71 patients had HbA1c ≤7 (labeled as group A1) and 89 patients had HbA1c >7 (labeled as group A2), while in group B, only 10 patients (labeled as group B1) had good control of diabetes and 130 patients had HbA1c > 7 (labeled as group B2) ($p < 0.001$). Platelet indices were calculated and compared among these groups.

The data analysis revealed that group B contained older-aged (61.84 ± 11.07 years) patients as compared to group A (53.64 ± 9.67 years), having a *p*-value of 0.03, which was significant. Females outnumbered males in both study groups, but this was not statistically significant ($p = 0.15$).

Group B patients had a longer duration of diabetes (10.66 ± 5.04 years) as compared to group A (6.44 ± 3.69 years), and this difference was statistically significant($p = 0.03$).

Comparison of HbA1c Among Study Groups (Table 1)

The mean HbA1C of study participants in group B was more (9.08 ± 1.74 gm%) when compared with group A (7.405 ± 1.87 gm%), having a *p*-value <0.001, which is statistically significant.

The mean HbA1C of group A2(study population without retinopathy and HbA1C >7) was 8.15 ± 2.05, and mean HbA1C of group B2 (patients with retinopathy and HbA1C >7) was 9.26 ± 1.67. The difference observed was significant ($p < 0.001$) (Table 2).

Comparison of Platelet Indices Among Study Groups

- All the studied platelet indices, viz PDW, MPV, P-LCR and PCT, were higher in group B patients as compared to group A patients (Table 3).

Table 1: HbA1C values in the study groups A and B

Groups	*Mean HbA1c*	*Std deviation*	*p-value*
Group A	7.405	1.87	<0.001 (S)
Group B	9.08	1.74	

Table 2: HbA1C values in the study groups A2 and B2

Groups	*Mean HbA1c*	*Std deviation*	*p-value*
Group A2	8.15	2.05	<0.001 (S)
Group B2	9.26	1.67	

Table 3: Comparison of platelet indices between study groups

Index	*Group A (without retinopathy)*	*Group B (with retinopathy)*	*p-value*
PDW	12.81 ± 2.28	14.56 ± 2.37	<0.001 (S)
MPV	9.99 ± 1.64	13.28 ± 2.14	<0.001 (S)
P-LCR	27.64 ± 8.36	29.59 ± 6.018	0.02 (S)
PCT	0.26 ± 0.09	0.29 ± 0.06	0.002 (S)

Table 4: Comparison of Platelet indices between Group A2 and Group B2

	Group A2 [without retinopathy (n = 89)]	*Group B2 [with retinopathy (n = 130)]*	*p-value*
PDW	12.8 ± 2.25	14.56 ± 2.37	<0.01
MPV	10.05 ± 1.67	13.28 ± 2.14	<0.01
LPCR	27.62 ± 8.12	29.59 ± 6.01	0.01
PCT	0.26 ± 0.08	0.29 ± 0.06	0.003

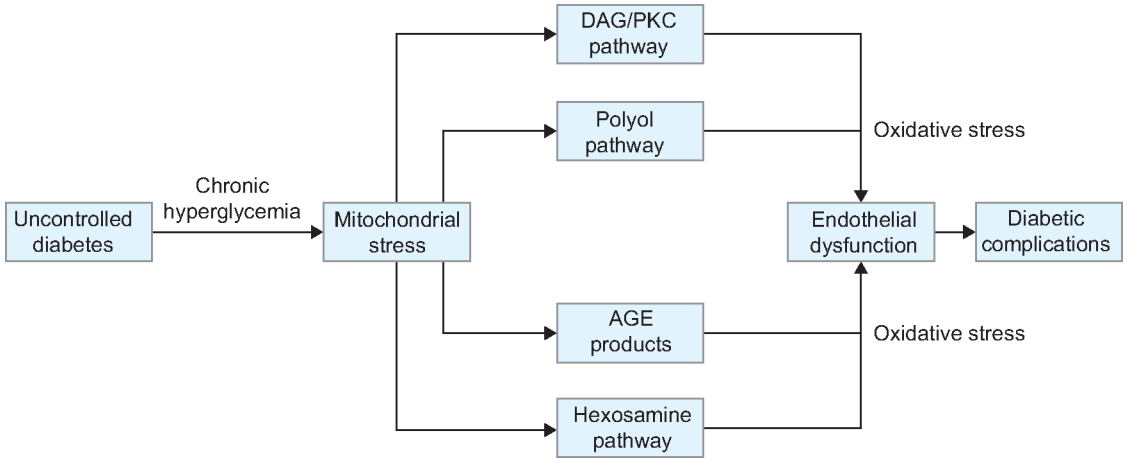

Fig. 1: Endothelial dysfunction in diabetes mellitus

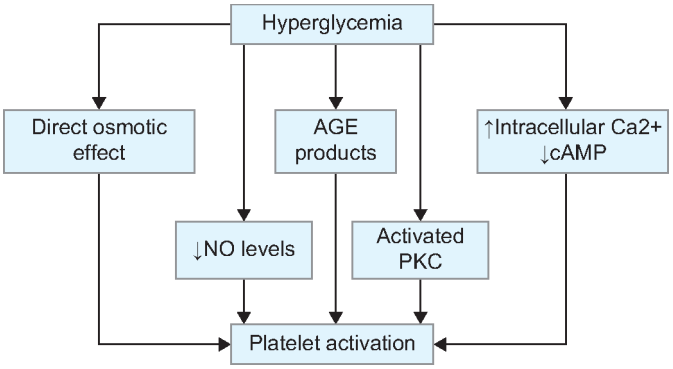

Fig. 2: Effect of hyperglycemia on platelets

- Comparison of platelet indices between uncontrolled diabetics (HbA1 C >7) without retinopathy (group A2) and with retinopathy (group B2) (Table 4).
- This showed that, although in both groups HbA1C was >7, PDW, MPV, L-PCR, and PCT were elevated in patients with retinopathy, and this difference was significant, as shown in the table.

Discussion

Diabetes mellitus encompasses a range of prevalent metabolic disorders characterized by chronically elevated blood glucose levels. A shared characteristic among the long-term complications of diabetes is damage to the vascular system, including both microvascular and macrovascular issues. These events are marked by the progressive narrowing of blood vessel lumens and abnormal protein permeability.[5] Platelets are instrumental in the development of diabetic complications, with various abnormalities in platelet function observed both *in vitro* and *in vivo*.[6]

Chronic hyperglycemia can lead to several complications, broadly categorized into:

- Microvascular complications: These include diabetic retinopathy, neuropathy, and nephropathy.
- Macrovascular complications: These encompass coronary artery disease (CAD), cerebrovascular stroke, and peripheral artery disease (PAD).

While chronic hyperglycemia is a significant contributor to the development of these complications, genetic factors may also predispose individuals to specific issues. Extensive randomized clinical trials, which included type-1 and type-2 diabetes patients, have shown that reducing chronic hyperglycemia can delay or prevent nephropathy, neuropathy, and retinopathy. Endothelial dysfunction is identified as a key mechanism driving both microvascular and macrovascular complications of diabetes mellitus. Endothelial dysfunction results from Chronic hyperglycemia, leading to mitochondrial stress (Fig. 1).

Effects of Hyperglycemia on Platelet Function (Fig. 2)

Both acute and chronic hyperglycemia cause the activation of protein kinase C (PKC), which plays an important role in mediating several proaggregatory platelet signals.[7] Persistent and recurrent hyperglycemia induces nonenzymatic glycation reactions between reducing sugars and the primary amino branches of proteins, resulting in the production of advanced glycation end products (AGEs).[8] These AGEs promote the externalization of phosphatidylserine on the thrombocyte membrane, which activates surface clotting factors and directly increases the prothrombotic state.[9]

Chronic hyperglycemia also causes the release of large-sized platelets with reduced levels of cyclic adenosine monophosphate (cAMP). In patients with chronic diabetes, platelets exhibit elevated intracellular calcium levels. The combination of higher calcium levels and decreased cAMP makes these platelets more prone to activation and aggregation even at lower stimuli.

The interaction between glucose and lipids results in the formation of glycated

low-density lipoprotein, which adversely affects nitric oxide (NO) formation. A low nitric oxide level leads to increased platelet activity.

In our study, platelet indices, namely MPV, PDW, P-LCR, and PCT were compared between patients with diabetic retinopathy and without retinopathy. Mean platelet volume serves as an indicator of function as well as activation of platelets. Similarly, PDW reflects the variation in size of platelets and is also considered another marker of platelet activation.

Mean Platelet Volume

In the present study, the mean platelet volume values were elevated in patients with diabetic retinopathy (13.28 ± 2.14 fL) when compared to those without diabetic retinopathy (9.99 ± 1.64 fL), with $p < 0.001$. Also, the MPV values were elevated in patients with poorly controlled diabetes (12.09 ± 2.52 fL) when compared to patients with good control of diabetes (10.124 ± 1.76 fL), and this was statistically significant ($p = 0.002$). Comparable findings were observed in the studies conducted by Bhattacharjee et al.[10] and Dermitas et al.[11] Additionally, Kodiatte et al.[12] concluded that MPV is significantly increased in diabetic patients with microvascular complications.

Platelet Distribution Width

Platelet distribution width was elevated in diabetic patients with retinopathy (14.56 ± 2.37) when compared to those patients without retinopathy (12.81 ± 2.28), and this difference was statistically significant ($p < 0.001$). Also, the platelet distribution width values were elevated in patients with poorly controlled diabetes (13.88 ± 2.505) as compared to patients with well-controlled diabetes (12.92 ± 2.22), which was statistically significant ($p = 0.003$). These results were comparable to the results of studies published by Dermitas et al.,[11] Bhattacharjee et al.[10]

Buch et al.[13] conducted a study to evaluate platelet volume indices as predictive biomarkers for complications in patients with type 2 diabetes mellitus. A study showed that platelet volume markers (MPV and PDW) are predictive biomarkers for diabetic microvascular complications.

Platelet-large Cell Ratio

Platelet-large cell ratio was higher in diabetic patients with retinopathy (29.59 ± 6.018) when compared to those patients without retinopathy (27.64 ± 8.36) and this difference was statistically significant ($p < 0.001$).

Also, the P-LCR values were elevated in patients with poorly controlled diabetes (29.16 ± 7.42) as compared to patients with well controlled diabetes (27.80 ± 7.21), which was statistically not significant ($p = 0.15$). This might be explained by the fact that there was large difference between number of patients with poorly controlled diabetes ($n = 219$) and number of patients with good control of diabetes ($n = 81$).

Plateletcrit

Plateletcrit levels were higher in diabetic patients with retinopathy (0.29 ± 0.06) when compared to those without retinopathy (0.26 ± 0.08). This difference was statistically significant ($p < 0.001$).

Also, the plateletcrit values were higher in patients with poorly controlled diabetes (0.28 ± 0.077) as compared to patients with a good control of diabetes (0.27 ± 0.092), which was statistically not significant ($p = 0.14$). This might be due to large difference between number of patients with poorly controlled diabetes ($n = 219$) and number of patients with good control of diabetes ($n = 81$).

Dermitas et al.[11] conducted a study to evaluate the association between hematological indices and diabetes, impaired glucose regulation, and microvascular complications of diabetes. They concluded that platelet indices were inexpensive and easily accessible markers of inflammation and tendency of coagulation, and microvascular complications.

In our study, when platelet indices were compared between uncontrolled diabetics without retinopathy and those with retinopathy, all the indices were significantly higher among those with retinopathy, showing that the presence of retinopathy had a significant effect on the platelet indices, irrespective of HbA1c levels.

Conclusion

Our findings reveal that elevated platelet indices are associated with higher HbA1C levels, suggesting that poor glycemic control significantly impacts platelet activation. Additionally, our study also demonstrated that platelet indices were notably elevated in patients with diabetic retinopathy compared to those without, with this difference reaching statistical significance.

These results underscore the potential of using platelet indices as surrogate markers for the onset of retinopathy in diabetic patients, highlighting their importance in monitoring and managing diabetic complications.

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