Original Article

Platelet indices as an accouterment for monitoring short-term glycemic levels and as an economical alternative to HbA1c

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Abstract

Background: India is facing a galloping diabetes epidemic with an estimated 62 million patients and is projected to explode beyond 85 million by the year 2030. There is platelet dysfunction with platelet hyper-reactivity in diabetes mellitus. **Aim:** To assess for any correlation between HbA1c levels with various platelet indices like mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR). **Material and Methods:** Applying inclusion and exclusion criteria, diabetes mellitus patients have undergone detailed history, clinical examination, and laboratory investigations. Data is statistically analyzed for levels of HbA1c and their correlation to platelet indices. **Results:** 58.7% study population is with HbA1c levels of more than 8%. In patients with normal range HbA1c levels between 4-6%, the MPV, PDW, and P-LCR are found to be 9.9 ± 0.97 fl, 10.84 ± 2.08 fl, and 23.75 ± 7.99%, respectively. In patients with HbA1c levels of 6.1 to 7%, the MPV, PDW, and P-LCR are found to be 10.22 ± 1.04 fl, 11.79 ± 1.8 fl, and 26.36 ± 7.05%, respectively. In patients with HbA1c levels of 7.1 to 8%, the MPV, PDW, and P-LCR values are found to be 10.21 ± 1.06 fl, 12.03 ± 2.52 fl, and 26.65 ± 8.05%, respectively. In patients with poor glycemic control with HbA1c levels more than 8%, the MPV, PDW, and P-LCR are found to be 10.64 ± 1.1 fl, 12.81 ± 2.61 fl, and 30.26 ± 8.24%, respectively. **Conclusion:** In type 2 diabetes mellitus patients, HbA1c is positively correlated with platelet indices.

Keywords: HbA1c levels, mean platelet volume (MPV), platelet distribution width (PDW), platelet indices, platelet-large cell ratio (P-LCR), type 2 diabetes mellitus (T2DM)

Introduction

With the increasing prevalence of diabetes globally, India is faced with a galloping diabetes epidemic that is progressing at speed, with an estimated 62 million patients with diabetes in India, and this number is projected to explode beyond 85 million by the year 2030 and more than 3 million patients die from the disease on annual basis with some Indian urban societies, one out of every five adults has diabetes.[1] Type 2 diabetes mellitus accounts for 90% of cases of total diabetes cases globally. From 2000 to 2025, it is projected that there will be a 150% increase in type 2 diabetes in South Asia. "International Diabetes Federation (IDF) projects that global prevalence will increase from an estimated 150 million in 2000 and 415 million in 2015 to nearly 600 million by 2035."[2]

According to American Diabetic Association, annual per capita healthcare expenditure is 2.3 times higher for people with diabetes compared with those without diabetes with major portion of

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medical expenditure is associated with diabetes associated micro and macrovascular complications.[3]

The increased platelet activity is to play a role in the development of vascular complications in type 2 diabetes mellitus.[4] Diabetic patients have an increased risk of developing micro- and macro-vascular disease, and platelets may be involved as a causative agent concerning altered platelet morphology and function.[5] Platelet function is of path physiological importance in atherosclerotic disease and there is strong support for platelet dysfunction with platelet hyper-reactivity in both type 1 and type 2 DM.[6,7] The metabolic state that accompanies DM may alter platelet and endothelial function already in the early stages of diabetic disease. However, it is debatable whether anti-diabetic treatment and improved metabolic control can restore the observed platelet hyperactivity in DM. In addition, studies of the effect of acute hyperglycemia on platelet function in patients with DM are sparse.[8] Large platelets are hemostatically more active and are a risk factor for developing coronary thrombosis, leading to myocardial infarction.[9]

In a study conducted in Serbia, based on the correlation of various platelet parameters with glycemic control it was concluded that to assess glycemic control various complete blood picture parameters can be used.[10] MPV, PDW, and PLCR are quantitative measures of the variability in platelet size. MPV reflects the average platelet size, PDW indicates the volume variability in platelet size, and PLCR indicates the percentage of large platelets in the blood. Larger platelets are metabolically more active with faster rates of aggregation and release of TxA2 and ADP. MPV, PDW, and PLCR are suggested as markers of subclinical platelet activation and platelet health. PLCR is significantly higher in dyslipidemia and T2DM compared to healthy children. Twomey *et al.* have hypothesized that PLCR has the potential to be a prognostic biomarker.[11]

With the advent of technology, automated cell counters are available even in the peripheries which can provide cell counts and various cell parameters which could have potential use in diagnosis and assessing metabolic disorders like type 2 diabetes mellitus. In this study, we aimed to assess the correlation between glycemic control and various platelet parameters using HbA1c and mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR). To assess short-term glycemic levels over a period of two to three weeks, glycated albumin and serum fructosamine levels are generally proposed but not widely used in clinical practice either because of non-availability or cost of the tests with inherent limitations of being influenced by presence of other endocrine and renal disorders in the patients. This study has attempted to look at platelet parameters as a surrogate marker for short-term glycemic levels assessment, which could be at large scale, reduce the economic burden of investigations for patients and assist clinicians in remote areas of practice for assessing treatment response of glycemic levels over period of two to three weeks.

Material and Methods

Study design and subjects

This cross-sectional observational study is conducted on 150 type 2 diabetes mellitus patients[12] who have attended outpatient departments and satisfied inclusion and exclusion criteria. Patients who have new-onset type 2 diabetes mellitus and who are already on treatment are included in the study. Pregnant females, patients who are on long-term proton pump inhibitors, patients with renal disease, patients on loop and thiazide diuretics, patients on multivitamin and trace element supplementation, patients taking antibiotics like aminoglycosides, amphotericin, pentamidine, patients with Acute Diarrheal disease, steatorrhea, Crohn's disease, Ulcerative colitis, Whipple's disease and celiac sprue, patients on drugs; Digitalis, Adrenergics, Cisplatin, Cyclosporine, Mycophenolate mofetil, patients of Acute myocardial infarction, Malabsorption, Acute pancreatitis, and massive blood transfusion are excluded from the study. Data collection: With Institutional Ethical committee clearance on 17-11-2018 with approval number 286/18 and with consent, data is collected with prepared pro forma and complete physical examination, and blood parameters like complete blood picture with platelet parameters, renal function test, and liver function tests are obtained.

Groups and definitions cut-off values

For assessing glycemic control, HbA1c levels are obtained from Bio-rad d10 automated analyzer with 2 ml blood sample collected in EDTA tube, and patients are grouped into normal, good, fair, and poor control groups with HbA1c levels of 4-6, 6.1-7, 7.1-8, more than 8, respectively. Platelet parameters like mean MPV, PDW, and P-LCR are obtained by an automated cell counter analyzer.

Statistical analysis

All characteristics were summarized descriptively. The summary statistics of mean ± standard deviation (SD) were used for continuous variables. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square ($\chi 2$) test was used for an association between two categorical variables. The difference in the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance. If the P value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v. 23 (IBM Statistics, Chicago, USA) and Microsoft office 2007.

Results

Out of 150 patients, 60 were aged over 60 years and 73 were aged between 41 to 60 years [Table 1, Figure 1]. 88.7% of study population were over 60 years, and females were 51 (34%) and males were 99 (66%) [Table 1, Figure 2]. In this study population, 58.7% of patients have HbA1c levels more than 8% indicative

of poor glycemic controls, 12.7% of patients have HbA1c levels between 7.1 to 8%, and 16.7% of patients have HbA1c levels between 6.1 to 7% [Table 1, Figure 3]. Results as depicted [Table 2 and Figure 4] are as follows: Patients with normal range HbA1c levels between 4-6%, the MPV, PDW, and P-LCR are found to be 9.9 ± 0.97 fl, 10.84 ± 2.08 fl, and 23.75 ± 7.99%, respectively.

Table 1: Distribution of study population by Age, Gender, and HbA1c Levels

	Number	Percentage
Age (in Years)		
≤40	17	11.3
41-60	73	48.7
>60	60	40
Gender		
Male	99	66
Female	51	34
HbA1c Levels		
Normal (<6.1)	18	12
Good Control (6.1-7)	25	16.7
Fair Control (7.1-8)	19	12.7
Poor Control (>8)	88	58.7

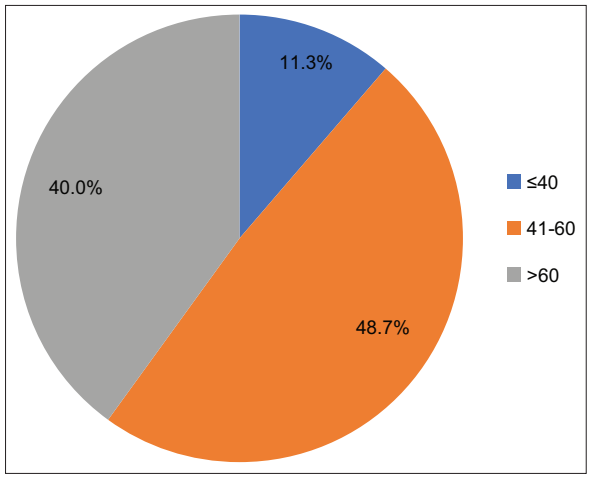

Figure 1: Distribution cases by age

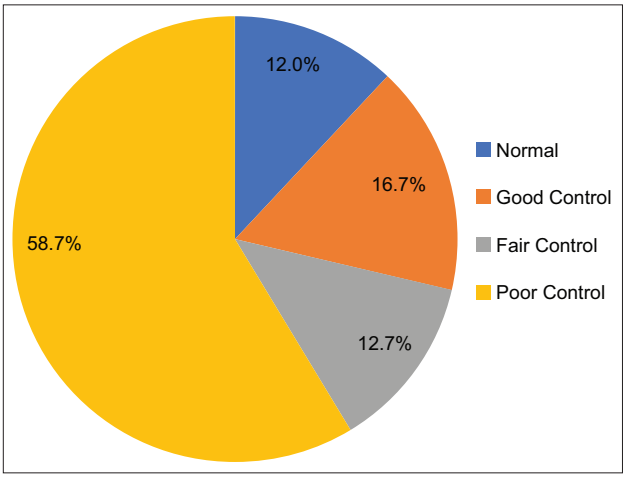

Figure 3: Distribution of cases according TO HbA1c levels

In patients with HbA1c levels of 6.1 to 7%, the MPV, PDW, and P-LCR are found to be 10.22 ± 1.04 fl, 11.79 ± 1.8 fl, and 26.36 ± 7.05%, respectively. In patients with HbA1c levels of 7.1 to 8%, the MPV, PDW, and P-LCR values are found to be 10.21 ± 1.06 fl, 12.03 ± 2.52 fl, and 26.65 ± 8.05%, respectively. In patients with poor glycemic control with HbA1c levels more than 8%, the MPV, PDW, and P-LCR are found to be 10.64 ± 1.1 fl, 12.81 ± 2.61 fl, and 30.26 ± 8.24%, respectively. On calculating Pearson correlation coefficient between the platelet parameters and HbA1c, there is strong correlation between HbA1c and MPV with absolute r value of o. 8967 [Figure 5], there is strong correlation between HbA1c and PDW with absolute r value of 0.8826 [Figure 6], there is strong correlation between HbA1c and P-LCR with absolute r value 0.8563 [Figure 7].

Discussion

As diabetes mellitus has been a global epidemic in developing countries, with rising healthcare costs and the economic burden of treating diabetes and its related complications, there is a need to develop feasible, affordable monitoring investigations and interventions in the management of T2DM patients. This cross-sectional study is conducted in Shri B M Patil Medical College and Research Centre over a period of 1 year, on type 2 diabetes mellitus patients. HbA1c levels and platelet parameters like mean platelet volume, platelet distribution width, and platelet large cell ratio are obtained.

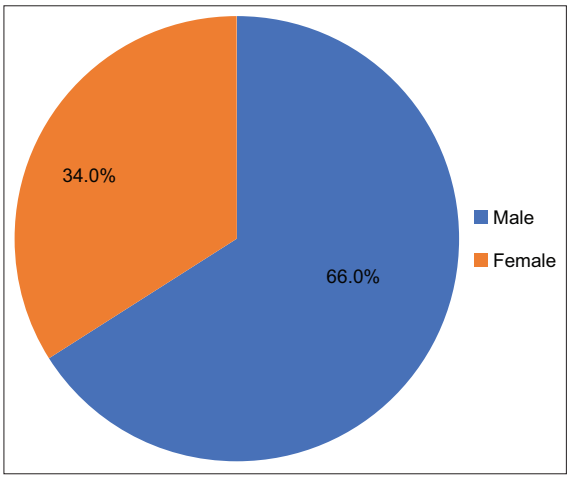

Figure 2: Distribution of cases by gender

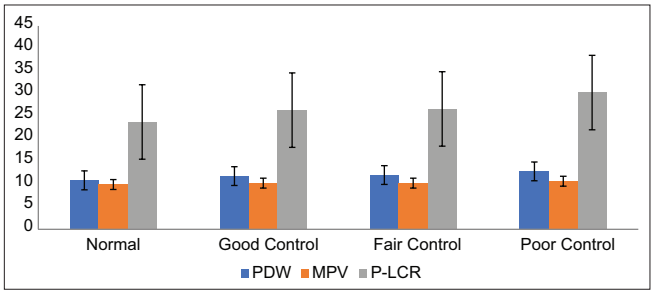

Figure 4: Bar chart depicting mean MPV, PDW, and P-LCR with HbA1c levels

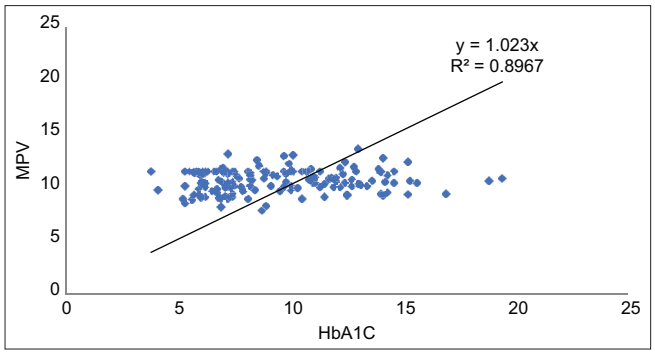

Figure 5: Scatter plot showing positive correlation between HbA1c and MPV

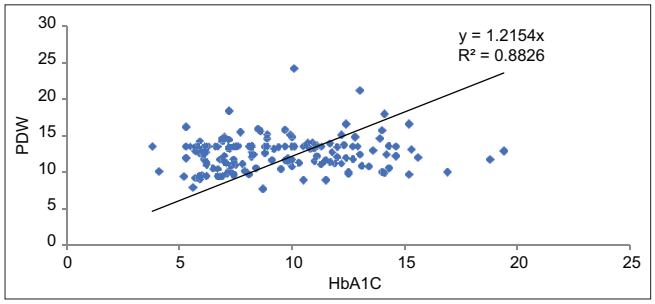

Figure 6: Scatter plot showing positive correlation between HbA1c and PDW

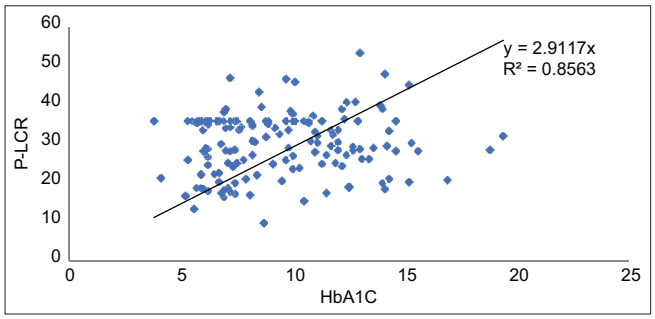

Figure 7: Scatter plot showing positive correlation between HbA1c and P-LCR

In this present study on T2DM patients, it is found that 11.3% of the study sample were below 40 years of age, and 88.7% study population are above 40 years of age. And, understandably, type 2 diabetes mellitus is the disease most often seen in the elderly, T2DM prevalence in the elderly in this study is following the literature. In this study, in males, 86.9% are over 40 years of age, and in females, 92.2% are over 40 years of age. In this study group, 66% of patients were males, and 34% were females. In this study, the majority of patients were having HbA1c levels of more than 8%, 58.7% of cases were with poor control glycemic levels (HbA1c >8), majority of patients with uncontrolled HbA1c levels are per a study conducted in Azadi Teaching Hospital, Iraq in 2018 by Hajar Saeed *et al.*[13]

Diabetes mellitus is an atherogenic and prothrombotic state with platelet hypersensitivity and endothelial dysfunction leading to

Table 2: Mean laboratory parameters according to HbA1c level

Parameters	HbA1c levels				*P*
	Normal (4-6)	Good control (6.1-7)	Fair control (7.1-8)	Poor control (>8)	
PDW (fl)	10.84±2.08	11.79±1.8	12.03±2.52	12.81±2.61	0.042*
MPV (fl)	9.9±0.97	10.22±1.04	10.21±1.06	10.64±1.1	0.084
P-LCR (%)	23.75±7.99	26.36±7.05	26.65±8.05	30.26±8.24	0.027*

*Significant at 5% level of significance ($P<0.05$)

chronic microvascular and macrovascular complications.[14] The larger platelets being hyper-reactive produce more prothrombotic factors. The enlarged platelets with lots of pseudopodia differ in the size, possibly affecting the platelet distribution.[15] In diabetes mellitus, there is non-enzymatic glycation of surface proteins on the platelets which leads to a decrease in the fluidity of the membrane, with increased expression of surface glycoproteins Ib and IIb/IIIa and with the osmotic effect of hyperglycemia there is increased platelet activity.[16–18] MPV may be affected by many factors, MPV alone without other inflammatory markers may not help in identifying chronic endothelial inflammatory conditions.[19] So, MPV and PDW, and PLCR are platelet indices that could potentially be economical biomarkers of platelet reactivity.

In this study, in patients with normal range HbA1c levels less than 6%, the MPV, PDW, and P-LCR are found to be 9.9 ± 0.97 fl, 10.84 ± 2.08 fl, and 23.75 ± 7.99%, respectively, and in patients with HbA1c levels between 6.1 to 7%, the MPV, PDW, and P-LCR are found to be 10.22 ± 1.04 fl, 11.79 ± 1.8 fl, and 26.36 ± 7.05%, respectively. In patients with HbA1c levels between 7.1 to 8%, the MPV, PDW, and P-LCR values are found to be 10.21 ± 1.06 fl, 12.03 ± 2.52 fl, and 26.65 ± 8.05%, respectively. In patients with poor glycemic control with HbA1c levels of more than 8%, the MPV, PDW, and P-LCR are found to be 10.64 ± 1.1 fl, 12.81 ± 2.61 fl, and 30.26 ± 8.24%, respectively.

There is a significant increase in all three platelet indices measured in the study with an increase in mean glycemic control levels and there is a positive correlation between glycosylated hemoglobin and MPV, PDW, and PLCR, as depicted in the scatter plot [Figures 2, 3, and 4]. Though the three platelet parameters are positively correlated, a statistically significant positive correlation was found only between PDW and PLCR with HbA1c levels, but not with MPV.

In a study conducted in Lab Science Diagnostics, Dhaka, Bangladesh, to find a correlation between MPV, PDW with random blood sugars, and HbA1c, it was concluded that there was a positive correlation between MPV and PDW with HbA1c and random blood glucose.[20] Our study is following this study in positive correlation with HbA1c. In a study conducted in SRM Medical College, Tamil Nadu, India, only MPV showed a statistically significant correlation with HbA1c levels, PDW, PLCR, and Plateletcrit were positively correlated with HbA1c

levels are not statistically significant. In this study, PDW and PLCR are positively correlated to HbA1c which are more statistically significant when compared to MPV.[21]

A study from Peshawar, Pakistan, when studied to find a correlation between mean platelet volume with BMI, duration of diabetes, and HbA1c, it was concluded that MPV is positively correlated with HbA1c which is statistically significant.[21] In a study conducted by Thomas Alex Kodiatte *et al.* (2012),[5] it is concluded that MPV is significantly higher in diabetics when compared to non-diabetics which is by this study. In a study from Aarhus University Hospital, Denmark, it is concluded that increased levels of HbA1c correlated positively with increased platelet aggregation, platelet turnover, and platelet activation.[22]

A study done by Vaddatti Tejeswini, P. Premalatha, and P. A. V. Krishnamacharyulu have concluded that MPV was significantly higher in diabetics when compared to healthy controls and there was a statistically significant positive correlation between HbA1c and MPV. But it is shown that fasting and postprandial blood sugars were negatively correlated with MPV but were not statistically significant.[23] And in a study Indices of platelet morphology such as PCT, PLT, PDW, and MPV were similar in children with T1DM and healthy controls,[24] as this study is conducted in type 2 diabetes mellitus patients exclusively, it is prudent that similar studies with larger study samples are to be conducted further inveterate correlation. Theoretically and arguably glycemic level effect on platelets is more important for the variability of platelet parameters rather than the type of diabetes mellitus, as the study results are in contrast, larger study samples with rigid selection criteria to exclude other confounding effects on platelet parameters.

The association between glycemic state and MPV was apparent only in individuals with impaired glycemic control and only marginal in those with normal glycemic control.[25] In a study from L N Medical College, Madhya Pradesh, it is reported that only MPV is correlated with the HbA1c and there was no statistically significant correlation between PDW and platelet count with HbA1c in type diabetes mellitus with or without complications.[26] This is in contrast to our study results, where PDW and PLCR are having a statistically more significant positive correlation with HbA1c than with MPV. And it could be because the mean life span of platelets is 8 to 12 days, and it is understandable that PDW and PLCR are influenced by the preceding 15 to 20 days rather than 90 to 120 days of glycemic levels.

It is observed from the reviewed literature that in majority of studies MPV is in positive correlation with glycemic levels, but the level of correlation and the level of statistical significance varied between the studies and even with our study. As it is understood that adipokines and cytokines released from the adipose tissue cause megakaryocytes to synthesize larger platelets[27] and endothelial function in metabolic syndrome also influence platelet turnover.[28]

Most of the studies including this study have been done in different ethnic populations, and majority of studies have not taken body mass index and other components of metabolic syndrome have not been considered in analysis which could have affected platelet parameters, thereby resulting in difference in level of correlation and significance found in various studies. There are obvious limitations of this study, it is advisable not immediately use these platelet parameters to assess the glycemic levels or predict the risk of complications, but with a colossal study sample size along with robust study criteria the correlation should be tested further and established between platelet parameters and HbA1c levels. And platelet parameters could then be a tool to assess glycemic levels of the past fortnight.

Conclusion

Platelet indices like mean platelet volumes, platelet distribution width, and platelet large cell ratio are positively correlated with glycemic levels. With the increase in HbA1c levels platelet distribution width, mean platelet volume, and platelet large cell ratio also increases which is statistically significant. It is recommended to perform these kinds of studies on a larger population to establish and quantify the association between platelet parameters and HbA1c levels, which could be a potentially economical alternative for assessing glycemic levels in place of HbA1c in remote hospital settings and to use platelet parameters to assess the change of glycemic levels in last fortnight period.

Limitations of Study

1. Study design is cross sectional which could be confounding in a casual relation between platelet parameters and HbA1c.
2. Duration of diabetes is not considered in the study.
3. Body mass index, Body fat, components of metabolic syndrome not analyzed for correlation with platelet parameters.

Future aspects of study

A multi-centered study including multiple ethnic groups and considering components of metabolic syndromes and duration of diabetes for analyzing correlation will help establishing correlation which is confident enough to use platelet parameters as marker for short-term glycemic levels.

Key Point

Platelet indices—MPV, PDW, P-LCR are positively correlated to HbA1c.

Take home message

Platelet Indices have potential to be marker of short-term glycemic levels

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Conflicts of interest

There are no conflicts of interest.

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