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ORIGINAL ARTICLE

HbA1c and Platelet indices correlation in type 2 diabetes patients

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Abstract

Background: Diabetes mellitus is a metabolic disorder represented by persistent hyperglycemia, which significantly elevates the risk of cardiovascular complications. Platelet dysfunction plays a crucial role in the development of these complications. While HbA1c is a widely employed diagnostic marker for diabetes, its association with platelet indices, reflecting platelet size and activity, in type 2 diabetes patients remains poorly understood. Recent research has increasingly emphasized platelet activation as a key contributing factor to atherothrombotic processes in individuals with diabetes.

Aim: Present study aims to find if there is any correlation between platelet indices and HbA1c.

Discussion: Hyperglycemia leads to reactive oxygen species and AGEs formation, resulting in endothelial dysfunction. The combination of increased intracellular calcium, decreased cAMP levels, and oxidative stress contributes to platelet hyperactivity. Endothelial dysfunction exacerbates this hyperactivity and manifests as an increase in platelet size and alterations in platelet indices.

Conclusion: Our research findings indicate that diabetes mellitus exhibits larger and more active platelets, resulting in an elevated thrombogenic potential. It also revealed a direct and positive correlation between platelet indices and HbA1c levels.

Keywords: HbA1c, MPV, PDW, P-LCR, Platelet indices

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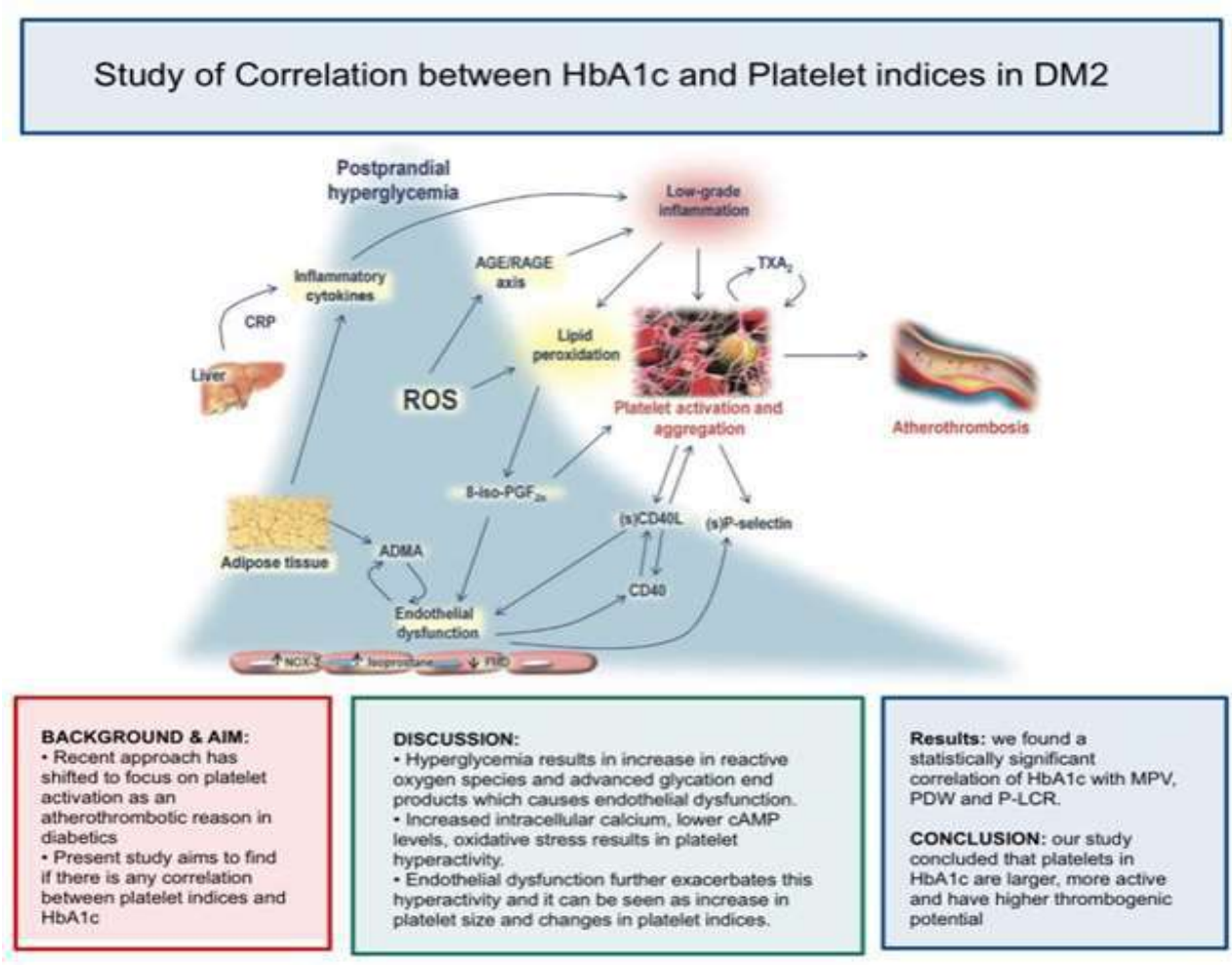
Abbreviations

AGEs	:	Advanced Glycation End products
P-LCR	:	Platelet-Large cell ratio
CBC	:	Complete Blood Count
cAMP	:	cyclic Adenosine Monophosphate
PDW	:	Platelet Distribution Width
HbA1C	:	Glycosylated Hemoglobin levels
MPV	:	Mean Platelet Volume

Graphical Abstract



Introduction

Diabetes is a long-lasting illness characterized by insufficient production or ineffective use of insulin by the body. As a consequence, uncontrolled diabetes can cause high blood sugar levels that gradually damage essential organs like the heart, blood vessels, eyes, kidneys, and nerves [1]. HbA1c serves as a useful indicator of average blood glucose levels over a three-month period [2]. Additionally, altered platelet shape, increased platelet dysfunction, and heightened

reactivity contribute to diabetes-related complications, creating a prothrombotic state that leads to vascular challenges, ultimately increasing morbidity and mortality [3]. Furthermore, diabetes triggers inflammation and accelerates the development of atherosclerosis, further contributing to its prothrombotic nature [4].

Pathophysiology of Diabetic Platelet

Diabetes mellitus is a prothrombotic condition indicated by impaired fibrinolytic capacity, coagulation system activation and persistent platelet activation. Hyperglycemia directly influences platelet reactivity through osmotic effects [5]. Protein kinase C which is a mediator of various platelet agonists involved in promoting platelet aggregation is activated by acute and chronic hyperglycemia. Advanced Glycation End products (AGEs) are created due to non-enzymatic contact between proteins and reducing sugars during recurrent periods of hyperglycemia. Some AGE molecules induce externalization of platelet membrane phosphatidylserines which in turn leads to surface clotting factors activation producing a thrombogenic state [6].

Hyperglycemia results in larger platelet size due to decreased cyclic adenosine monophosphate (cAMP) levels. In chronic diabetes patients, platelet intracellular calcium levels are elevated, leading to heightened platelet reactivity and aggregation even at lower levels of agonist activation. Interaction between lipids and glucose reduces nitric oxide synthesis because of formation of glycated low-density lipoprotein, which contributes to platelet hyperactivity [7].

Insulin directly regulates platelet function by interacting with the insulin receptor (IR) found on it. With insulin binding to IR, there is a trigger of tyrosine phosphorylation causing activation of insulin receptor substrate 1. This process elevates cAMP levels, thereby reducing P2Y12 signaling and platelet activity. Additionally, it also reduces platelet affinity to collagen hence decreasing the binding and platelet aggregation induced by agonists [8].

Platelets Indices:

Platelets count

The normal platelet count in a cubic centimeter of blood typically falls within the range of 150,000 to 400,000. Thrombocytosis indicates an elevated platelet count, while thrombocytopenia signifies a decrease in platelet count [9].

Mean Platelet Volume

Mean Platelet Volume (MPV) refers to the average size of platelets in the blood. It is determined by analyzing the distribution of platelet sizes in each sample. MPV is measured in femtoliters (fL) and is often included as part of a complete blood count (CBC) test. The normal range is 7 to 9 femtolitres.

MPV has gained clinical significance as a potential marker of platelet activation. MPV increase is associated with platelet hyperactivity, as larger platelets tend to be more reactive and have a higher thrombotic potential [10]. Platelet hyper-reactivity is manifested by enhanced aggregation, fibrinogen binding, and thromboxane production as shown in Figure 1. These variables change platelet metabolism and

interplatelet signalling, resulting in impairment of several metabolic processes, including ADP generation, thromboxane A2 synthesis/release and increased calcium metabolism.

Parameter	Description	Unit	Clinical utility
Mean Platelet Volume	Analyser calculated measure of thrombocyte volume	Femtoliters	Low MPV is associated with bleeding risk in TCP
Platelet Distribution Width	Indicator of volume variability in platelet size	Percentage (%)	No relation to bleeding risk in TCP
Platelet count	Indicates platelet number present in blood stream	Per cubic cm	Diagnostic for thrombocytopenia, risk of interference or lack of detection because of large clumps
Platelet - large cell ratio	Indicator of larger (>12 fL) circulating platelets	Percentage (%)	Dependant on platelet distribution curve

Figure 1. Various platelet indices and their clinical significance.

Elevated MPV has been observed in various conditions such as cardiovascular diseases, including myocardial infarction and stroke, as well as in inflammatory and autoimmune disorders. MPV can serve as an indicator of platelet turnover and activity, aiding in the diagnosis, prognosis, and monitoring of certain medical conditions. It may help identify individuals at higher risk for thrombotic events or predict the response to antiplatelet therapies [11].

Platelet Distribution Width

The variation in platelet size in a blood sample is measured by Platelet Distribution Width (PDW). It is typically reported as a percentage and is derived from analyzing the distribution of platelet volumes. PDW provides information about the heterogeneity of platelet sizes within the blood. Higher PDW values indicate increased variability in platelet sizes, suggesting a greater range of platelet activation and function [12]. The clinical significance of PDW lies in its potential as an indicator of platelet activation and associated disorders. Elevated PDW levels have been observed in conditions such as cardiovascular diseases, thrombotic events, and inflammatory disorders. It is believed that an increased PDW reflects presence of more reactive and larger platelets, which are associated with a higher thrombotic risk. PDW can serve as a complementary parameter to Mean Platelet Volume (MPV) in assessing platelet function and activity [13].

Platelet-Large cell Ratio

The proportion of large platelets in relation to the total platelet count in a blood

sample gives Platelet Large Cell Ratio (PLCR). It is calculated by dividing the number of large platelets by the total platelet count and multiplying by 100. PLCR is a parameter that provides information about the presence of larger platelets in the bloodstream. Large platelets, also known as macro platelets, are often indicative of increased platelet production and activity. They are released into the circulation in response to platelet turnover and various physiological or pathological conditions [14]. The clinical significance of PLCR lies in its potential as an indicator of platelet function and activation. Higher PLCR values may suggest increased platelet turnover and activation, which can be associated with conditions such as immune thrombocytopenia, myeloproliferative disorders, and inflammatory states. Additionally, PLCR has been studied as a prognostic marker in cardiovascular diseases, with elevated levels being associated with a higher risk of adverse outcomes [15].

HbA1c and Cardiovascular Complications

Diabetes significantly increases the risk of developing various cardiovascular complications, such as coronary artery disease, myocardial infarction, stroke, peripheral artery disease, heart failure and sudden cardiac death [16]. The underlying mechanisms linking diabetes to CVD are complex and multifactorial. Chronic hyperglycemia, insulin resistance, dyslipidemia, hypertension, endothelial dysfunction, and inflammation contribute to the development and progression of cardiovascular complications in individuals with diabetes [17]. They also have high levels of plasminogen activator inhibitors and fibrinogen, which promotes clotting and inhibits fibrinolysis, favoring thrombosis. HbA1c is widely used as a marker for glycemic control in individuals with diabetes [18]. Elevated HbA1c levels have been associated with an increased risk of CVD events, including myocardial infarction and stroke. Conversely, optimal glycemic control, reflected by lower HbA1c levels, has been associated with a reduced risk of CVD events and improved cardiovascular outcomes in individuals with diabetes.

Methods

For Platelet indices and HbA1c Estimation

A venous sample was collected using EDTA vials in the early morning to determine platelet indices and HbA1c levels. The estimation of platelet indices was performed using the ELITE-580, a fully automated hematology analyzer. Criteria for diagnosing Diabetes Mellitus is shown in Figure 2.

1. FBS ≥ 126 mg/dl with fasting (no calorie intake) for 8 hours
2. HbA1c ≥ 6.5%
3. 2 hr. post prandial blood glucose ≥ 200 mg/dl (OGTT 75g)
4. RBS ≥ 200 mg/dl with hyperglycemic crisis

Figure 2. Criteria for diagnosing Diabetes Mellitus [19]

HbA1c

HbA1c, also known as glycated hemoglobin, is formed when glucose reacts non-enzymatically with natural Hb (hemoglobin). The extent of this reaction is directly related to the concentration of glucose in the bloodstream. In hemolyzed blood, both total Hb and HbA1c bind to latex particles found in the R1 reagent. The degree of binding is proportional to the relative concentrations of these substances in the blood. The R2 reagent contains cross-linked antihuman HbA1c monoclonal antibodies that bind to the HbA1c bound to the particles. The resulting agglutination directly corresponds to the percentage of HbA1c present in the sample. A normal HbA1c value typically falls within the range of 4-6% [20].

Results

This study was conducted among 190 diabetic patients who came with either diabetes or related complications. The mean age of the study participants in our research was 56.3±11.04 years. Demographic distribution was maximum in age group of 41-60 years [105,55.3%] followed by age group of >60 years [68,35.8%]. Males were more affected [97,51.1%] than females [93,48.9%] with a ratio of 1.04:1. Ratio of cardiovascular complications was significantly high with as much as 41 patients out of 48 [85.4%] presenting with diabetic complications were of cardiovascular origin. The average duration of diabetes among the patients included in the study was 4.9 ± 4.4 years. Mean BMI was observed as 25.6 ± 4.2 kg/m^2 with most of them falling in obese category. We also observed elevated mean HbA1c (9.4 ±2.3), MPV (12.31 ±7.55), PDW (16.30±3.74) and P-LCR (40.96±10.11) values as shown in Figure 3.

Furthermore, our study revealed statistically significant positive correlations between HbA1c and MPV (r=0.698), PDW (r=0.606), and P-LCR (r=0.647). Conversely, a statistically significant negative correlation was observed between HbA1c and platelet count (r= -0.202) as shown in Figure 4.

HbA1c values of all patients were plotted against Platelet indices (Platelet count, MPV, PDW and P-LCR) individually in a scatter plot diagram for assessing the correlation with them which are shown in Figures 5, 6, 7 and 8.

Lab. Parameters	Mean	Median	SD	Minimum	Maximum	P-value
Hemoglobin (g/dl)	12.42	12.50	1.27	10.1	15.7	0.766
TLC (cells/µL)	8236.62	8360.0	1891.14	4200	11600	0.314
Platelets (lacs/µL)	2.28	1.97	0.77	1.39	5.42	.643
MPV (fL)	12.31	11.85	7.55	9.3	14.5	0.0001
PDW	16.3	15.9	3.74	9.9	26.5	0.0001
P-LCR	40.96	42.4	10.11	18.8	58.2	0.0001
HbA1c (%age)	9.46	9.0	2.34	6.5	15.0	0.0001
Triglyceride (mg/dl)	167.31	166.5	55.4	52.0	405.9	0.0001
Cholesterol (mg/dl)	163.17	157.5	51.76	52.0	293.0	0.0001
HDL (mg/dl)	39.51	39.0	10.99	13.0	102.0	0.0001
LDL (mg/dl)	90.16	88.5	42.66	11.8	197.8	0.0001
VLDL (mg/dl)	33.62	33.3	11.02	10.2	81.2	0.0001

Figure 3. Distribution of laboratory parameters among study participants.

Platelets indices	Pearson correlation coefficient	P-value
Platelets count	-0.202	0.005
MPV	0.697	0.0001
PDW	0.606	0.0001
P-LCR	0.647	0.0001

Figure 4. Correlation of HbA1c with platelets indices.

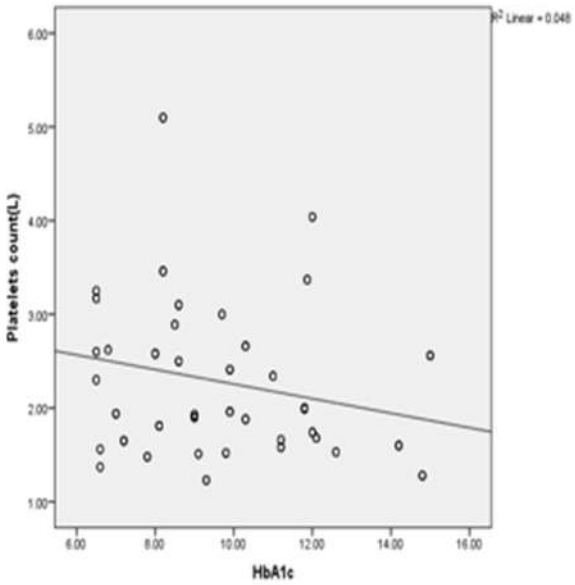


Figure 5. HbA1c vs Platelet Count.

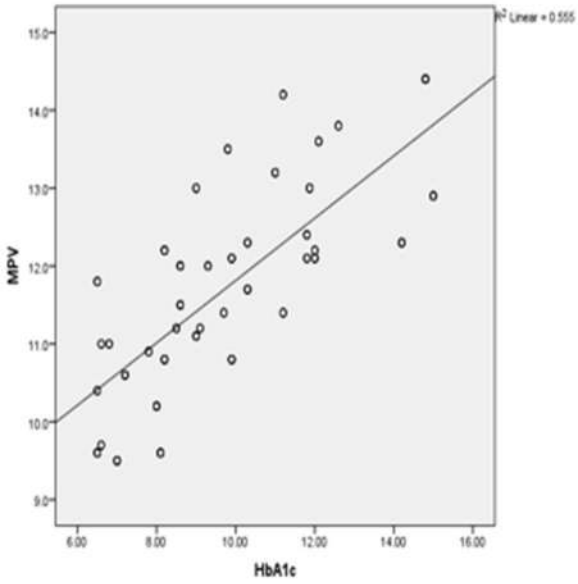


Figure 6. HbA1c vs MPV

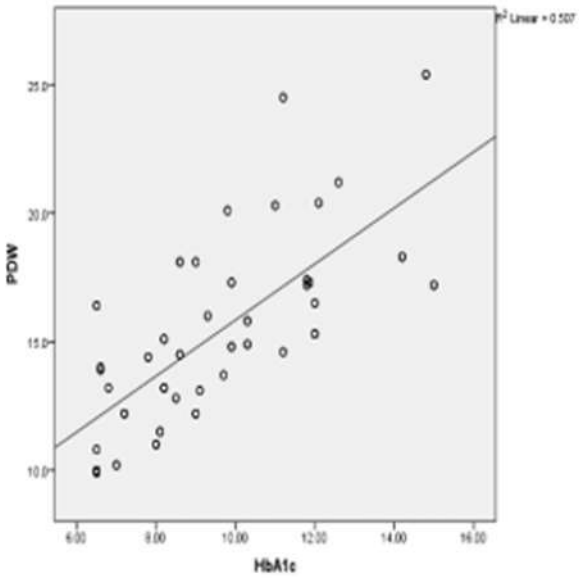


Figure 7. HbA1c vs PDW

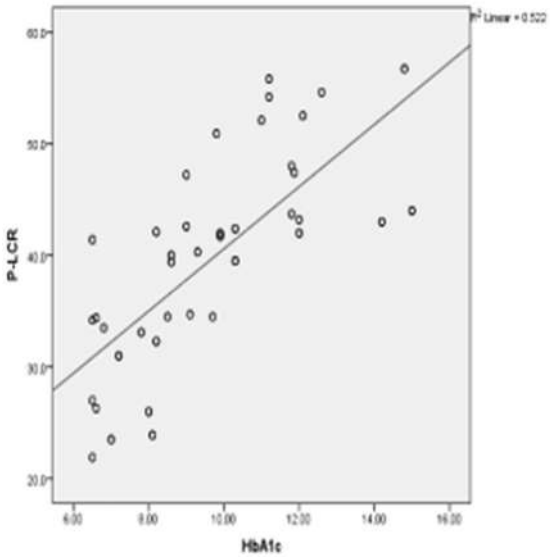


Figure 8. HbA1c vs P-LCR

Conclusion

Our research findings indicate that individuals with diabetes mellitus (DM) exhibit larger and more active platelets, resulting in an elevated thrombogenic potential and increased platelet indices. The presence of larger platelets constitutes a significant risk factor in the development of atherosclerosis and is closely linked to vascular complications. Additionally, a direct and positive correlation between platelet indices and HbA1c levels was found in this study.

Future scope

The future research potential of investigating the correlation between HbA1c and platelet indices in type 2 diabetes patients is highly promising. This exploration can provide valuable insights into the relationship between HbA1c, an essential long-term blood glucose control marker, and platelet indices, which indicate platelet size and activity. Understanding this connection has the potential to enhance our understanding of the pathophysiology and complications associated with diabetes. Furthermore, further research may lead to development of more accurate diagnostic and prognostic tools for assessing cardiovascular risk and guiding therapeutic interventions for type 2 diabetes patients. Moreover, by unraveling the mechanisms underlying the association between HbA1c and platelet indices, new therapeutic strategies could be devised to modulate platelet function and reduce the risk of vascular complications. Continued research efforts in this field have the capacity to advance our knowledge of diabetes-related thrombogenesis leading to improved patient outcomes.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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