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Assessment of mean platelet volume (MPV) in subjects with Type 2 Diabetes Mellitus (T2DM) in a rural backdrop of central India

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RESEARCH ARTICLE

General Note

Article is recommended to print as color digital version in recycled paper.

ABSTRACT

Introduction: Diabetes is a public health problem. Altered platelet morphology and function have been reported as a cause of microvascular and macrovascular complications in patients with diabetes mellitus. *Aim:* We conducted a cross-sectional study to compare MPV in type 2 diabetics (T2DM) and non-diabetics and study the relationship between MPV and glycemic control (HbA1C) in patients with T2DM in a rural backdrop of central India. *Methods:* Participants were distributed into 2 groups: the study group of patients with T2DM (n = 98) and control group with non-diabetics (n = 98). The study group were further sub-grouped as uncontrolled group (HbA1c > 7%) of diabetic patients and controlled group (HbA1c ≤ 7%) of diabetic patients.MPV was determined by cell counter. Study group and control group were then compared with regards to MPV and HbA1c. *Results:* We found significantly higher MPV in diabetics as compared to non-diabetics. Also, we found a positive co-relation between MPV and HBA1c. One % increase in Hb1Ac led to an increase in 1.45 fl (1.37-1.52) of MPV. It is hypothesized that platelet hyperactivity in patients with T2DM is related with factors such as hyperglycemia, hyperlipidemia, insulin resistance, and antioxidant and inflammatory conditions. *Conclusion and implications:* This study can be of help to physicians, consumers and policy-makers to decide whether MPV can be incorporated as a tool to assess and monitor the development of microvascular and macrovascular complications of T2DM.

Keywords: platelet volume, Type 2 Diabetes Mellitus, glycaemic control, HbA1c.

1. INTRODUCTION

Diabetes is a public health problem and stands as one of the four priority non-communicable diseases (NCD) targeted for action by public health experts (Resolution 66/2, 2011). Number of cases as well as prevalence of diabetes have been increasing steadily over the past few decades.108 million adults were suffering with diabetes globally in 1980, as compared to 422 million in 2014 (WHO, 2016). There were 69.1 million cases of diabetes in India in 2015(International Diabetes Federation, 2015).Diabetes is acknowledged as a main cause of premature death and disability. It has led to 1.5 million deaths in 2012 and an surplus 2.2 million deaths were caused by rising risks of cardiovascular and other related illnesses (WHO, 2016). Diabetes has imposed large economic burden on global health-care system.

Diabetes is a metabolic syndrome typified by increased blood sugar levelslinked2- to 4-fold augmented risk for cardiovascular disease with microvascular (nephropathy, retinopathy and neuropathy) and macrovascular (ischemic heart disease, cerebrovascular disease and peripheral vascular disease) complications with resultant damage to tissues and organs(Beckman et al., 2002; Nesto, 2004). These microvascular and macrovascular complications in patients with T2DM are reported to be caused by altered platelet morphology and/or altered platelet function (Tschoepe et al., 1993; Winocour, 1992).

Platelets express and discharge a variety of materials that are vital intermediaries of atherosclerosis, coagulation, thrombosis and inflammation, (Gawaz et al., 2005). Activation and aggregation of platelets play essential part in thrombotic events in T2DM. Numerous measurements of platelet activity have appeared as probable contributors to thrombosis. However; most of them are time consuming, costly, or need specialty training. Augmented platelet activity is linked with enlarged platelet volume and hence raised mean platelet volume (MPV) is accepted as an sign of platelet activation and platelet function and indirectly determines this cardiovascular risk (Bath and Butterworth, 1996; Michelson, 2009). MPV is a measure of size of platelets and a probable marker for reactivity of platelets (Sertbas et al., 2017). Larger platelets are younger and exhibit more activity. Though MPV appears to be a simple parameter; it can indirectly gauge vascular complication in diabetic patient easily at a comparatively lower cost. Greater values of MPV signify larger platelets, which are more active enzymatically and metabolically, with a higher potential for causing thrombotic events (Chu et al., 2010; Yilmaz et al., 2015).

Higher MPV is observed in patients with T2DM (Papanas et al., 2004), hypertension (Nadar et al., 2004), smoking (Kario et al., 1992), hypercholesterolemia (Pathansali et al., 2001), and obesity (Coban et al., 2005), signifying a mutual mechanism through which these potential factors might raise the risk of cardiovascular disease.

Studies have found significantly higher MPV in diabetics (Radha and Selvam, 2016; Sharpe and Trinick, 1993), in diabetics with retinopathy (Güngör et al., 2016), in certain vascular risk factor states (Bath and Butterworth, 1996; Papanas et al., 2004). However; in other studies; MPV levels did not correlate withT2DM (Güngör et al., 2016; Ünübol et al., 2012). Thus the possible role of MPV in the development of cardiovascular disease in T2DM remains uncertain.

Though determining platelet activity by diverse methods has been stated to recognize persons at higher risk for cardiovascular episodes, it continues a research tool that is yet to be included in routine clinical decision-making. Probable causes include a deficit of adequate data about the optimum technique of platelet testing, unidentified optimum cut-off for differentiating high risk, and the ambiguity about the understanding and scientific and medical usefulness of the findings. Moreover, several techniques are time-consuming and expensive and require specialized equipment.

Inconclusive evidence and paucity of data; especially in a rural set-up prompted us to plan this study and explore the association between MPV and HBA1c status in patients with T2DM.

Aim and objectives

Aim

To compare mean platelet volume (MPV) in type 2 diabetics (T2DM) and non-diabetics and study the relationship between MPV and glycemic control (HbA1C) in patients with T2DM in a rural backdrop of central India.

Objectives

1. To determinethe MPV in patients with T2DM
2. To determine the MPV in non-diabetics
3. To compare the MPV in diabetics with non-diabetics
4. To study the relationship between MPVand glycemic control (HbA1C) in T2DM.

Hypothesis

We hypothesize that presence of diabetes is associated with higher MPV and that this association would be modified by the degree of glycemic control.

2. MATERIAL AND METHODS

This Cross-sectional study was conducted on participants of Type 2 diabetes mellitus (T2DM) diagnosed as per the American Diabetes Association criteria (American Diabetes Association, 2016), followed-up and treated in diabetic clinic, medicine OPD and wards of a tertiary-care fully equipped rural hospital in central India. We also enrolled a control group of gender and age-matched non-diabetics.

Sample size

A total number of 196 subjects were selected to keep 98 in each group. Participants in study group (n=98) were patients of T2DM and participants in control group (n=98) were non-diabetics.

The sample size was derived as:

With α=0.05; β= 0.20; q_1=0.5; q_0= 1-q_1; E (Effect size) = 0.4

A= $(1/q_1 + 1/q_0)$ = 4.00, B = $(Z_\alpha+Z_\beta)^2$ = 7.84

Total group size= $AB/(E/S)^2$ = 196.22

Sample size of study group: 98

Sample size of control group: 98

Selection criteria

Participants were selected if they fulfilled the following inclusion criteria.

Inclusion criteria

a. For study group:

- Adult subject between 18 and 60 years irrespective of gender
- Patients diagnosed with T2DMas per the American Diabetic Association Criteria (American Diabetes Association, 2016)

- Patients willing to participate in the study.

b. Healthy non-diabetic controls were selected according to fasting and post-meal blood glucose levels according to the American Diabetic Association Criteria(American Diabetes Association, 2016).

Exclusion criteria

1. Following subjects were excluded from the study owing to their effect on mean platelet volume (MPV)
   - Abnormal platelet number and/or white blood cell count
   - Abnormal haematocrit
   - Patients suffering from bone marrow disorders/ ischemic heart disease/ patients with renal failure/ AIDS
   - Patients on anti-platelet drugs and cancer chemotherapy
   - Pregnant women
2. Subjects not willing to participate were also excluded from the study.

Ethical approval

The study was started after approval by the institutional ethics committee (IEC)

Data collection procedures

The subjects were explained about the nature and purpose of the study. After assuring confidentiality and taking informed written consent; the details of the subject were entered in the data forms. The proforma of the patient was preserved comprising of demographic details like past medical history, past surgical history, past and current drug history, family history, personal history to rule out other compounding reasons and factors which might affect MPV (selection criteria). The most recent fasting and post-meal blood sugar levels as well as HBA1C values were also noted.

Participants were divided into two groups: the study group of patients with T2DM (n = 98) and control group with non-diabetics (n = 98). The study group were further sub-grouped as uncontrolled group (HbA1c > 7%) of T2DM patients and controlled group (HbA1c ≤ 7%) of T2DM patients according to their HbA1c levels.

Determining MPV

Two ml of venous blood was drawn in the EDTA vial (irrespective of their fasting status) by venipuncture under all due aseptic precautions, from the antecubital. MPV was determined by cell counter (Make of the cell counter machine: PentraXLR, SNo - 509XLR6810).

Study group and the control group were then compared with regards to MPV and HbA1c.

Quality control

Quality control of data management was maintained throughout the study. Following quality control measures were undertaken:

- Early involvement of the local research support unit.
- We tried to adhere to the protocol
- Data from study and control groups were concealed from the statistician

Confidentiality

The confidentiality of all the participants was strictly maintained.

Statistical analysis

Statistical analysis was conducted with STATA version 12.0 software. Data are expressed as mean ± standard deviation. We compared the numerical variables in different subjects by t-test. We performed bivariate correlation analyses using Pearson correlation test. Probability values were two-tailed. A p-value of less than 0.05 was contemplated as significant.

3. OBSERVATIONS AND RESULTS

This study comprising of 197 participants included 96 males and 101 females. The male: female ratio in diabetics and non-diabetics was 48:51 and 48:50 respectively (Table 1).The mean age of non-diabetics was 55.99 ±10.45 years. The mean age in controlled diabetics was 57.34±7.6 years and the mean in uncontrolled diabetics was 58.34±6.6 years (Table 1).

Table 1 Gender and age distribution of participants in the study

Group	Frequency (%)	Males	Females	Mean age (Years)
Non-Diabetics with HbA1c <6	99 (50.25%)	48	51	55.99 ±10.45
Diabetics with HbA1c ≤ 7%	27 (13.71%)	11	16	57.34±7.6
Diabetics with HbA1c > 7%	71 (36.04%)	37	34	58.34±6.6
Total	197 (100%)	96	101	

HBA1c and mean MPV in diabetics and non-diabetics

Mean HBA1c in non-diabetic group was (5.25 ± 0.39SD) while mean HBA1c in non-diabetic group was (7.64 ±1.26SD). Mean platelet volume was significantly higher in diabetic group (7.15±0.32 SD) as compared to the control group (8.80±0.67) (Table 2).

Table 2 Mean HBA1c and mean MPV in diabetics and non-diabetics

	Non-Diabetics (n=99)	Diabetics (n=98)	p value
	Mean±SD	Mean±SD	
HB1Ac (%)	5.25±0.39	7.64±1.26	<0.05
MPV (fl)	7.15±0.32	8.80±0.67	<0.05

Mean HBA1c and mean MPV in controlled and uncontrolled diabetics

Participants in the study group were further sub-grouped as controlled group (HbA1c ≤ 7%) of T2DM patients and uncontrolled group (HbA1c > 7%) of T2DM patients according to their HbA1c levels. We found that the mean platelet volume of the participants in uncontrolled diabetic group with HbA1c > 7% was 9.08±0.06 fl the mean platelet volume of the participants in uncontrolled diabetic group with HbA1c≤ 7% was 8.08±0.07 fl. There was a statistically significant difference between the two groups (Table 3).

Table 3 Mean HBA1c and mean MPV in controlled and uncontrolled diabetics

	Diabetic Group (HbA1c ≤ 7%) (n=27)	Diabetic Group (HbA1c > 7%) (n=71)	p value
	Mean±SD	Mean±SD	
HB1Ac (%)	6.50±0.04	8.08±0.14	<0.05
MPV (fl)	8.08±0.07	9.08±0.06	<0.05

A positive co-relation was found between HbA1c and MPV was observed in controlled DM and uncontrolled DM patients (Fig 1) which yielded a significant p-value of0.01. One % increase in Hb1Ac will lead to increase in 1.45 fl (1.37-1.52) of MPV. R-squared value was found to 87.59% and p-value <0.0001 (Table No. 4).

4. DISCUSSION

We undertook the study to assess the association between MPV and glycemic control (HbA1C) in T2DM. We found significantly higher MPV in patients of T2DM as compared to non-diabetics (p<0.05) (Table 2). Also, we found a significant positive co-relation between MPV and HBA1c (p<0.0001) (Table 3, Figure 1).

In our study, the male: female ratio in diabetics and non-diabetics was 48:51 and 48:50 respectively. We also found that in both diabetics and non-diabetics, the mean level of MPV was significantly higher in females than in males. Unlike our findings, studies by Park et al. (Park et al., 2002) and Bancroft et al. (Bancroft et al., 2000) did not observe any statistically significant differences in MPV between males and females.

Table 4 Meta-regression: HBA1C and MPV

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. regress hblac mpv
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Source	SS	df	MS	Number of obs = 197
Model	397.480732	1	397.480732	F(1, 195) = 1376.16
Residual	56.3225165	195	.288833418	Prob > F = 0.0000
				R-squared = 0.8759
Total	453.803249	196	2.3153227	Adj R-squared = 0.8753
				Root MSE = .53743

hblac	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
mpv	1.452751	.0391613	37.10	0.000	1.375517	1.529985
_cons	-5.147152	.3147731	-16.35	0.000	-5.767948	-4.526355

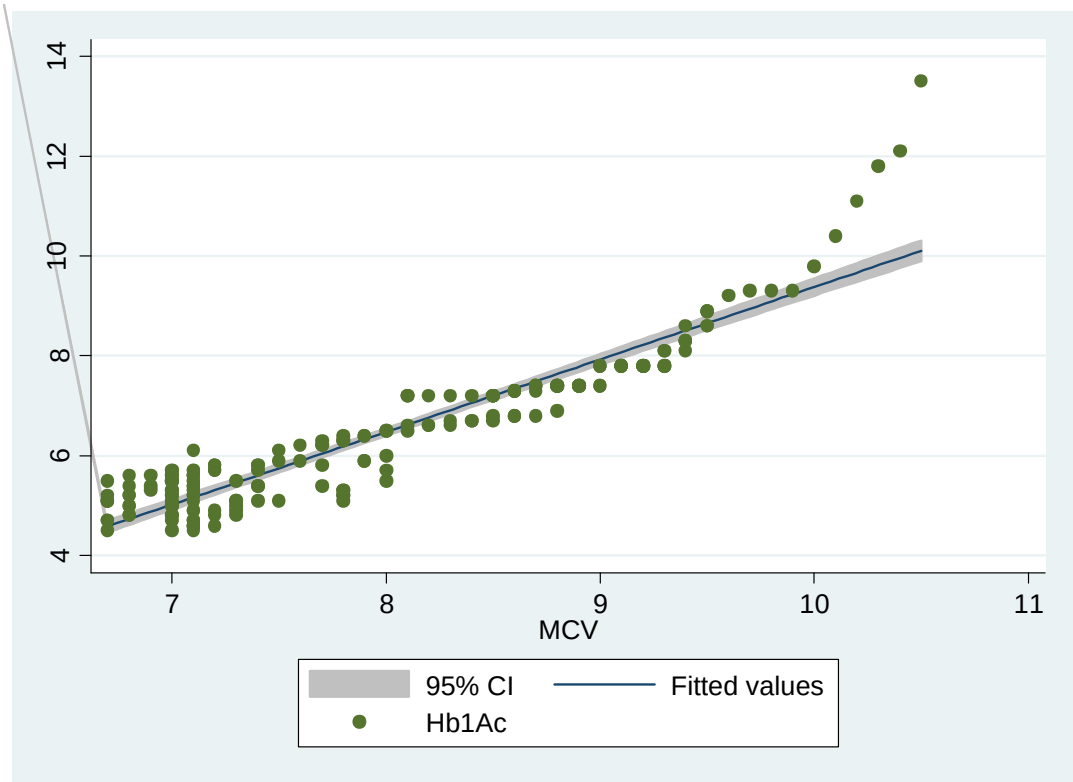

Figure 1 Relation between HBA1c and MPV in diabetics

We found that MPV was significantly higher in diabetics compared to non-diabetic controls. Similar findings were seen in other studies (Agrawal et al., 2016; Hekimsoy et al., 2004; Radha and Selvam, 2016; Sharpe and Trinick, 1993; Tavil et al., 2010; Zuberi et al., 2008). Contrary to this, some studies found no significant correlation between MPV and poor glycemic control in T2DM (Güngör et al., 2016; Ünübol et al., 2012).

In our study, MPV levels were significantly higher in T2DM with HbA1clevels of more than 7% than the group with HbA1c levels less than 7%. As in our study, few of the studies distributed the patients according to glycemic control: with low HbA1c and high HbA1c levels, and nearly all of them observed higher MPV levels in diabetics with high HbA1c levels (Agrawal et al., 2016; Demirtunc et al., 2009; Kodiatte et al., 2012; Lippi et al., 2015; Radha and Selvam, 2016; Sertbas et al., 2017; Ulutas et al., 2014). Contrary to the findings of our study; Güngör et al. (Güngör et al., 2016) did not observe any co-relation between MPV with glycemic control.

There are several reasons or hypothetical theories that can justify to the findings of our study. We believed that higher MPV in our study in patients with T2DM may be due to the presence of comorbid conditions that can impact MPV. Platelet hyperactivity has been reported by many studies in patients with T2DM (Kodiatte et al., 2012; Nesto, 2004; Schneider, 2009) and is believed to play a

role in the development of cardiovascular complications. It is recognized that this platelet hyperactivity is multifactorial and related with factors such as hyperglycemia, hyperlipidemia, insulin resistance, antioxidant and inflammatory conditions (Karpatkin, 1969).

Role of hyperglycemia on MPV in T2DM

Increase in blood glucose levels can augment the reactivity of the platelets by encouraging non-enzymatic glycation of proteins present on the cell wall of the platelets (Winocour et al., 1992). This glycation upsurges tendency of platelets to stimulate and also tend to reduce the fluidity of the platelet membrane (Winocour et al., 1992). High blood glucose levels seem to encourage the activity of the platelets by enhancing the production of glycoproteins over the platelet membranes. Patients of T2DM show higher expression of the glycoproteins Ib and IIb/IIIa on the surface of the platelets and facilitates their adhesion and adherence (Tschoepe et al., 1990). Therefore, greater expression of these surface glycoproteins in subjects with diabetes is likely to intensify the functional activity of platelets.

Activation of an essential mediator of platelet activation: protein kinase C along with the osmotic effect of glucose seem to be contributory factors causing increased platelet reactivity in patients with T2DM (Assert et al., 2001; Keating et al., 2003). A study suggests that hyperglycemic disorders like T2DM may hasten platelet-related thrombin production through the stimulation of polyol pathway, greater tubulin polymerization which raises the mean platelet volume (Rusak et al., 2017).

Role of hyperlipidemia on MPV in T2DM

Along with hyperglycemia, abnormalities in lipid metabolism are also regularly seen in patients with T2DM. Patients with T2DM characteristically manifest hypertriglyceridemia which has the potential to increase the reactivity of the platelets (Pedreño et al., 2000). Thus, hyperglycemia and hypertriglyceridemia observed in patients with T2DM increases the reactivity of the platelets.

Role of insulin in patients on MPV

Insulin administered to diabetics can straight forwardly control the functions of the platelet through functional insulin receptor located on the platelets (Ferreira et al., 2006). Insulin therapy can cause inconsistent rise in reactivity of the platelets in vivo (Angiolillo et al., 2006). In patients with T2DM, platelets tend to lose receptiveness to insulin thereby promoting adhesion, aggregation, as well as pro-coagulant activity on interaction with collagen (Ferreira et al., 2006). Additionally, enhanced signaling via P2y12 observed in diabetics may justify the hyperactivity of platelets in these patients (Ferreira et al., 2006). Also gradual apoptosis of pancreatic β-cell in patients with T2DM leads to deficiency of insulin. Consequently, insulin resistance augments the relative lack of insulin. In general, patients with TDM2 have obvious insulin resistance, mainly justified by their obesity (Saltiel and Kahn, 2001; Schneider, 2009). The consequences of high insulin on platelets are composite and incongruent between healthy subjects and patients with insulin resistance. Insulin resistance as well as insulin deficiency enhances the reactivity of platelet. Also, insulin has the potential to antagonize the activation of platelets. Thus, absolute or relative insulin deficiency is likely to enhance the reactivity of platelets. So, better metabolic control attained with regimes that mends the sensitivity of insulin and conserves the function of pancreatic β-cell is likely to decrease the reactivity of platelets and augment effects of anti-platelet drugs (Schneider, 2009).

Role of oxidative stress and inflammation on MPV

T2DM is related with oxidative stress and inflammation. Subsequent dysfunction of the endothelial cells in patients of T2DM stimulates activation of platelets by reducing nitric oxide (NO) production that deteriorates the reactivity of platelets. Oxidative stress heightens this effect by reducing the activity of nitric oxide and encouraging the activation of platelets. Activation of platelets and inflammation are related reciprocally. Inflammation stimulates the activation of platelets that, in turn, stimulates inflammation (Schneider, 2009).

Numerous reports have demonstrated that rise in platelet volume is related to lowered platelet counts (Chu et al., 2010). Raised MPV is related with additional markers of platelet activity, involving augmented aggregation of platelet, enhanced synthesis of thromboxane, increased release of β-thromboglobulin, and amplified expression of adhesion molecules (Bath and Butterworth, 1996).

Platelet hyperactivity in T2DMlinks with a higher risk of thrombotic complications (Payne et al., 2004). Increased platelet adhesion in T2DM aids the coagulation cascade and may contribute to the hypercoagulable state seen in this condition (Ferreira et al., 2006). This study has some limitations. Patients of T2DM were not characterized according to diabetic complications. The results of this study are limited to the data gathered during OPD visits of the patients.

5. CONCLUSION

In conclusion, the results of this study reveal that patients with T2DM have higher MPV as compared to non-diabetics. Also, there is significant positive co-relation between MPV and HBA1c.

Implications

The prevalence of diabetes is increasing in low and middle-income countries and is rapidly acquiring a status of a potential epidemic in India. This study can be of clinical relevance in future and can greatly enhance knowledge in regards to understanding the role of platelet activation in the pathogenesis of microvascular complications in T2DM. It also helps us determine the association between MPV and diabetes.By examining MPV in patients of T2DM we can caution them and recommend them to decrease their elevated glycaemic status. This study can be of help to physicians, consumers and policy-makers to decide whether MPV can be incorporated as a tool to assess and monitor the development of microvascular and macrovascular complications of T2DM.

Authors' contributions

PS: Data acquisition, draft version of manuscript. MNK: Interpretation of the data, Final manuscript writing and approval of the version. SG: Drafted the manuscript, Interpretation of the data. DS: Drafted the version of manuscript, Final approval. AG: Revising the manuscript critically for important intellectual content. QSZ: Analysis and Interpretation of the data.

Disclosures about potential conflict of interests

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