ORIGINAL RESEARCH PAPER

General Medicine

ASSESMENT OF MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH SPECIAL REFERENCE TO HbA1c AND PLATELET INDICES(MPV)

KEY WORDS: diabetes mellitus,HbA1c and MPV

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ABSTRACT

INTRODUCTION: Diabetes mellitus (DM) is not a single disease entity but rather a group of metabolic disorders sharing the common underlying features of hyperglycemia. Platelet volume, a marker of the platelet function and activation, the higher the MPV, the larger and younger the platelets are and more is the risk for thrombosis and are associated with increased risk for hyperglycemic complications.

OBJECTIVE: To assess correlation of microvascular complications in T2DM patients with special reference to HbA1c and platelet indices(MPV).

MATERIALS AND METHODS: This cross sectional analytical study was carried out in our institution for duration of 1 year.Total of 500 subjects was enrolled in the study.Detailed clinical and demographic profile including duration of diabetes and presence of microvascular complications was noted.The data was analysed using SPSS Version 16.

RESULT:MPV is significantly higher in patients with poor glycemic control(HbA1c >7) and presence of microvascular complications compared to patients with good glycemic control (HbA1c≤7) and absence of microvascular complications (p value is <0.05 which is highly significant).

CONCLUSION: Our study showed that in poor glycemic control group patients with presence of microvascular complications there is significantly higher MPV values.Hence MPV can be used as a simple and cost effective indicator for the glycemic control and microvascular complications in T2DM patients.

INTRODUCTION:

Diabetes mellitus (DM) is not a single disease entity but rather a group of metabolic disorders sharing the common underlying features of hyperglycemia. Hyperglycemia in diabetes results from defects in insulin secretion,insulin action, or, most commonly both.The chronic hyperglycemia and attendant metabolic deregulation of diabetes mellitus may be associated with secondary damage in multiple organ systems especially kidneys, eyes, peripheral nerves and blood vessels.[1] Type 2 diabetes mellitus is the predominant form of diabetes worldwide,accounting for 90% of cases globally[2]. The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 415 million in 2017. Based on current trends, the IDF projects that 642 million individuals will have diabetes by the year 2040[3]. Microvascular complications such as diabetic retinopathy,diabetic nephropathy are associated with considerable medical and economic impact among person with diabetes. In the UK prospective diabetes study (UKPDS) ,37% of patients of newly diagnosed type 2 diabetes developed atleast one microvascular complication over a 10 year period.[4] Platelets are small anucleate cell fragments. They circulate in blood and play a crucial role in regulating hemostasis and managing vascular integrity. They are involved in the fundamental process of chronic inflammation, associated with disease pathology. Platelets usually remain in an inactive state and they get activated only when blood vessel damage occurs[5]. Increased platelet activation has been suggested to be involved in the pathogenesis of vascular complications in diabetic patients[6]. Mean platelet volume is an indicator of average size and activity of the platelet. It reflects changes in the stimulation of platelets or the rate of platelet production. Normal value ranges from 7 to 9 femtolitres. It is a determinant of platelet function which is a newly emerging risk factor for atherothrombosis[7]. It is being found that MPV values are high in patients with diabetes mellitus, more so in uncontrolled diabetes. Platelet volume, a marker of the platelet function and activation, is proposed as to be involved as a causative agent with respect to altered platelet morphology and function. The higher the MPV, the larger and younger the platelets are and more is the risk for thrombosis and are associated with increased risk for hyperglycemic complications.Mean platelet volume (MPV), an important, simple, effortless, and cost-effective tool measured by hematology analyzer assess the volume and function of platelets and thus has potential to be used as indicator of presence of vascular complications[8].American Diabetic Association has classified Type-2 Diabetes Mellitus patients based on the levels of Glycosylated Haemoglobin (HbA1c) in the blood, as poor glycemic control group of diabetic patients whose HbA1c level is maintained more than 7% and as good glycemic control group of diabetic patients whose HbA1c level is maintained less than or equal to 7%[8].This study aimed to estimate the correlation of MPV with glycemic control i.e HbA1c and microvascular complications in T2DM patients.

MATERIALS AND METHODS:

This cross sectional analytical study was carried out in our institution for duration of 1 year.Total of 500 subjects was enrolled in the study.Informed Patient Consent was obtained before clinical examination.Thorough history taking and clinical examination were done. Patient's proforma was maintained which included all demographic particulars, past medical, surgical, drug, personal and family history. Fundus examination was done and other ophthalmology findings were recorded for both groups. HbA1c was measured by High Performance Liquid Chromatography.Measurement of MPV was done using an automatic blood counter (Beckman Coulter Act5Diff).Plasma glucose estimation (FBS and PPBS) was carried out by the glucose oxidase method in the autoanalyzer.The patients were grouped as poor glycemic control group of diabetic patients and good glycemic control group of diabetic patients based on their HbA1c levels.

SELECTION CRITERIA:

INCLUSION CRITERIA-All Type 2 Diabetes Mellitus patients.

EXCLUSION CRITERIA-Patients suffering from Type 1 diabetes, anaemia or any bone marrow disorders, chronic systemic inflammatory disorders, patients with renal failure, smokers, patients suffering from thyroid-related disorders,

infectious diseases, AIDS, sepsis, pregnant women, patients on anti-platelet drugs and cancer chemotherapy.

STATISTICAL ANALYSIS:

Statistical evaluation was performed by statistical package for social sciences (SPSS) version 16 for windows statistics program using the Unpaired t test/single factor ANOVA and categorical variables were analysed with chi squared test/ Fisher Exact Test.Correlations of platelet indices with HbA1c,FBS and PPBS were obtained using Pearson's formula.Arithmetic mean and standard deviation was calculated from our data.A *P* value <0.05 was considered statistically significant.

RESULT:

Among the 500 diabetic patients enrolled in the study,we divide them in two groups,good glycemic control group and poor glycemic control group based on their HbA1c values.Good glycemic control group(HbA1c≤7) contains 190 patients and poor glycemic control group(HbA1c>7) contains 310 patients.Table 1 shows the mean and standard deviation values of age,body mass index(BMI),duration of diabetes,fasting and postprandial blood sugar,gender distribution,demographical distribution and also the presence and absence of hypertension and hypertrygly ceridemia in good and poor glycemic control group patients. Mean age in good glycemic control group was 50.64±10.36 and in poor glycemic control group was 53.24±10.28(p value=0.0064).In good glycemic control group 115 patients were male and 75 patients were female and in poor glycemic control group 170 patients were male and 140 patients were female(p value=0.3107). In good glycemic control group 90 patients were from rural background and 100 patients were from urban background and in poor glycemic control group 165 patients were from rural background and 145 patients were from urban background. In good glycemic control group mean BMI was 24.67±3.41 and in poor glycemic control group mean BMI was 24.70±2.63(p value=0.9122).In good glycemic control group mean duration of diabetes was 6.35±3.55 and in poor glycemic control group mean duration of diabetes was 7.39±3.47(p value=0.0013). In good glycemic control group mean fasting blood sugar was 121.12±22.69 and in poor glycemic control group mean fasting blood sugar was 161.40±30.17(p value=0.0001) In good glycemic control group mean post prandial blood sugar was 171.98±44.17 and in poor glycemic control group mean post prandial blood sugar was 239.48±52.56(p value=0.0001).In good glycemic control group incidence of hypertension 36.84% and in poor glycemic control group incidence of hypertension was 40.32%(p value=0.4514). In good glycemic control group incidence of hypertryglyceryldemia was 34.21% and in poor glycemic control group incidence of hypertryglyceryldemia was 27.42%(p value=0.109).

TABLE:1 DEMOGRAPHIC AND BIOCHEMICAL PARAMETERS IN GOOD GLYCEMIC CONTROL AND POOR GLYCEMIC CONTROL GROUPS

S.N	PARAMETERS	GOOD GLYCEMIC CONTROL GROUP (HbA1c≤7) (n=190)	POOR GLYCEMIC CONTROL GROUP (HbA1c >7) (n=310)	P VALUE
1.	**Age distribution (years)**	50.64±10.36	53.24±10.28	0.0064
2.	**Gender (F/M)**	75/115	140/170	0.2271
3.	**Demographical distribution (Rural/Urban)**	90/100	165/145	0.2310
4.	**BMI(Kg/m^2)**	24.67±3.41	24.70±2.63	0.9122
5.	**Duration of diabetes distribution (years)**	6.35±3.55	7.39±3.47	0.0013
6.	**FBS distribution (mg/dl)**	121.12±22.69	161.40±30.17	0.0001
7.	**PPBS distribution (mg/dl)**	171.98±44.17	239.48±52.56	0.0001
8.	**Hypertryglycer idemia (yes/no)**	65/125	85/225	0.1093
9.	**Hypertension (yes/no)**	70/120	125/185	0.4514

TABLE:2 DISTRIBUTION OF MICROVASCULAR COMPLICATIONS

S.N	PARAMETERS	GOOD GLYCEMIC CONTROL GROUP (n=190)	POOR GLYCEMIC CONTROL GROUP (n=310)	P VALUE
1.	**Proteinuria status (yes/no)**	50/140	160/150	0.0001
2.	**Retinopathy status (yes/no)**	25/165	185/125	0.0001

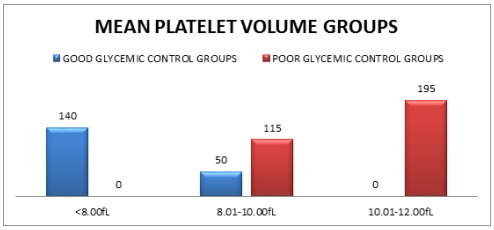
Table 2 shows the distribution of presence and absence of microvascular complications in good glycemic control group and poor glycemic control group.In good glycemic control group incidence of proteinuria was 26.32% and in poor glycemic control group incidence of proteinuria was 51.61%(p value=0.0001).In good glycemic control group incidence of retinopathy was 13.16% and in poor glycemic control group incidence of retinopathy was 59.68%(p value=0.0001).

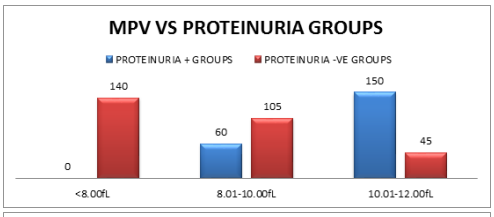
TABLE:3 DISTRIBUTION OF MEAN PLATELET VOLUME AND OTHER PARAMETERS

	Good glycemic control group	Poor glycemic control group	P value
Mean platelet volume distribution			
Mean	7.78	10.17	<0.0001
SD	0.44	0.93	
Mean platelet volume vs Proteinuria			
	Proteinuria(+)	**Proteinuria (-)**	
Mean	10.03	8.70	<0.0001
SD	1.37	1.13	
Mean platelet volume vs Retinopathy			
	Retinopathy(+)	**Retinopathy(-)**	
Mean	10.40	8.43	<0.0001
SD	1.01	1.01	
Mean platelet volume vs Gender distribution			
Mean	9.20	9.31	0.3926
SD	1.42	1.38	
Mean platelet volume vs Hypertension			
Mean	9.89	8.86	<0.0001
SD	1.49	1.17	

Table 3 shows mean platelet volume and their relationship with various parameters in good glycemic control group and poor glycemic control group.In good glycemic control group mean mean platelet volume (MPV) was 7.78±0.44 and in poor glycemic control group mean mean platelet volume (MPV) was 10.17±0.93(p value=0.0001).In males mean mean platelet volume(MPV) was 9.20±1.42 and in females mean mean platelet volume(MPV) was 9.31±1.38(p value=0.3926).In proteinuria positive group mean mean platelet volume (MPV) was 10.03±1.37 and in retinopathy

negative group mean mean platelet volume (MPV) was 8.70±1.13(p value=0.0001). In retinopathy positive group mean mean platelet volume (MPV) was 10.40±1.01 and in retinopathy negative group mean mean platelet volume (MPV) was 8.43±1.01(p value=0.0001). In hypertension positive group mean mean platelet volume(MPV) was 9.89±1.49 and in hypertension negative group mean mean platelet volume(MPV) was 8.86±1.17(p value=0.0001).





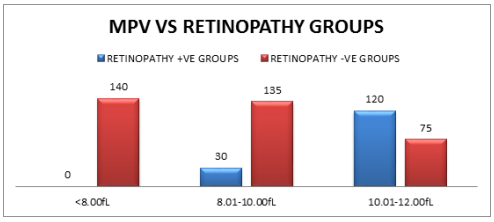
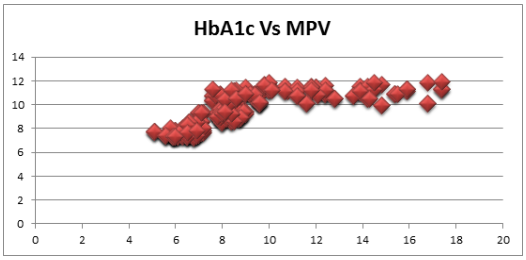


TABLE:4 CORRELATION STUDY BETWEEN MPV AND OTHER PARAMETERS

S.N	Parameters	Pearson's R	R square	P value
1.	**HbA1c VS MPV**	0.75	0.56	**0.00001**
2.	**FBS VS MPV**	0.62	0.38	**0.00001**
3.	**PPBS VS MPV**	0.61	0.37	**0.00001**

Table 4 shows correlation of mean platelet volume with HbA1c,FBS and PPBS based on pearson's correlation statistical analysis. There is a strong positive correlation between Hba1c levels and MPV levels,FBS level and MPV level,PPBS level and MPV level. This is indicated by the Pearson's R Correlation value of 0.75 with a p-value of <0.00001,0.62 with a p-value of <0.00001,0.61 with a p-value of <0.00001 for HbA1c vs MPV,FBS vs MPV,PPBS vs MPV respectively.



DISCUSSION:

In our study, platelet parameters such as mean platelet voume (MPV),were compared between diabetic population with good glycaemic control(HbA1c <7) and poor glycaemic control(HbA1c >7) and relation of mean platelet volume with microvascular complications like nephropathy and retinopathy.

Mean platelet volume is an indicator of average size and activity of the platelet. It reflects changes in the stimulation of platelets or the rate of platelet production. Normal value ranges from 7 to 9 femtolitres. It is a determinant of platelet function which is a newly emerging risk factor for atherothrombosis. Also it is a marker indicating platelet activation, an independent risk factor for various vascular episodes such as coronary artery disease, acute myocardial infarction, cerebral ischaemia and peripheral artery disease . Hyper-reactivity of platelets is indicated by increased aggregation, greater fibrinogen binding and increased thromboxane production[7].Significant increase in mean platelet volume correlate with increased adhesiveness, aggregation and greater exposure of glycoprotein receptor on platelet surface and increase binding of fibrinogen. These factors alter platelet metabolism and interplatelet signalling pathway eventually leading to impairment of various metabolic pathways such as increased calcium metabolism, ADP production, synthesis of thromboxane A2 and its release. Increased platelet sensitivity have direct consequence in diabetes mellitus, might be associated with release of contents from platelet granules which in turn may lead to the making of a platelet volume gradient, increased platelet turnover rate and reduction in survival of platelets in diabetic individuals.[9,10,11]

The data subjected to statistical unpaired t test reveals the existence of statistically significant association between MPV distribution and glycemic control based on HbA1c levels ($p < 0.05$).This significance is exhibited by the increased mean MPV(10.17±0.93,p value=0.0001) levels in poor glycemic control group compared to good glycemic control group (2.39 fL increase, 23.50% higher). This was similar to studies done by **Zuberi et al**[7] and **Kodiatte et al**[12]. Other studies by **Hekimsoy et al**[13] had observed the opposite findings. The data subjected to statistical chi squared test reveals the existence of statistically significant association between proteinuria and retinopathy status with glycemic control based on HbA1c levels ($p < 0.05$).This significance is exhibited by the increased incidence of proteinuria in poor glycemic control group compared to good glycemic control group (25.29 percentage points increase, 34% higher) and increased incidence of retinopathy in poor glycemic control group compared to good glycemic control group (46.52 percentage points increase, 78% higher). This was similar to studies done by **Zuberi et al**[7](for proteinuria) **and Chatziralli et al**[14]**, 2010.**(for retinopathy).Our study showed increased mean MPV levels in hypertension +ve group compared to hypertension -ve group (1.03 fL increase, 10.5% higher) similar to the study conducted by **Coban et al**[15],increased mean MPV levels in proteinuria +ve group compared to proteinuria -ve group (1.33% fL increase, 13% higher) similar to the studies done by **Ates et al**[16] and **Papanas et al**[17].In agreement with the studies done by **Kodiatte et al**[12],in case of retinopathy increased mean MPV levels in retinopathy +ve group compared to retinopathy -ve group (1.97 fL increase, 18% higher).This suggested a role for the increased platelet activity in the pathogenesis of vascular complications.On the other hand, in the studies done by **Hekimsoy et al**[13] and **Demirtunc et al**[18] MPV in diabetic subjects with and without complications did not show any significant difference. They explained it to be possibly because of rapid consumption of activated platelets in diabetic patients with in case of retinopathy increased mean MPV levels in retinopathy +ve group compared to retinopathy -ve group (1.97 fL increase, 18% higher). This is in agreement with the studies done by **Kodiatte et al**[12].By conventional criteria the relationship between the HbA1c levels and MPV levels is considered to be statistically significant since $p < 0.05$. This means as HbA1c levels increases MPV levels also increases in a direct and linear fashion in our study subjects. This observation was similar to the studies done by **Kodiatte et al**[12] and **Alhadas et al**[73]**.** Our study suggested that there is a relationship between the prevalence of microvascular complications in type 2 DM with MPV.Growing evidence revealed that increased MPV is an important risk factor for the vascular complications regarding type 2 DM and it is believed

that type 2 DM is a prothrombotic state due to increased platelet activity. Hence increased MPV can generate a procoagulant effect and cause thrombotic vascular complications in diabetes mellitus[12].

CONCLUSION:

Our study showed significantly higher MPV values in poor glycemic control group patients with presence of microvascular complications. However, the increased MPV as the cause or the result of vascular complications needs to be further explored. Hence MPV can be used as a simple and cost effective indicator for the glycemic control and microvascular complications in T2DM patients.

LIMITATIONS:

The major limitation of the study was that it was conducted in small population that may not represent the entire population. The follow up of the cases was not possible to determine the prognostic significance of our findings. This would have enabled us to compare its association with the progress of the microvascular complications. Moreover, it could have been possible to correlate and check the reversibility of platelet dysfunction with glycaemic control over a period of time.

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