TO DETERMINE THE EFFECT OF GENDER, ADVANCED AGE, LONGER DURATION OF ILLNESS AND HIGHER GLYCOSYLATED HEMOGLOBIN LEVELS ON MEAN PLATELET VOLUME (MPV) IN PATIENTS OF TYPE 2 DIABETES MELLITUS

Umair Ijaz Malik, Tariq Bashir Tareen, Uzair Ijaz Malik, Hina Naseer, Mehar Rehman

Combined Military Hospital Kohat/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine the effect of gender, advanced age, longer duration of illness and higher glycosylated hemoglobin levels on mean platelet volume in patients of type 2 diabetes mellitus.
Study Design: Descriptive cross-sectional study.
Place and Duration of Study: Combined Military Hospital Kohat, from Jul 2017 to Aug 2018.
Methodology: In this study 248 patients with type 2 diabetes were evaluated as per inclusion/exclusion criteria. Data from all patients was collected which included age, gender, duration of disease, symptoms & signs of target organ damage, Fasting Blood Glucose at presentation, HbA1c levels and complete blood count including mean Platelet Volume. Patients were then divided into different categories according to their gender, age, duration of illness and HbA1c levels. Mean mean platelet volume for each category was calculated and compared using student t-test. Data was analyzed using SPSS-21 and means for each group were compared.
Results: Sample size (n) was 248, 140 (57%) patients were male and 108 (43%) were female with mean mean platelet volume of 11.51 ± 0.80fL and 11.66 ± 0.78fL respectively. Age wise stratification showed 45 patients (17%) below 50 years of age, 85 patients (37%) between 50 and 59 years, 80 patients (32%) between 60 and 69 years and 38 patients (14%) aged 70 years and more. Mean mean platelet volume for these age groups was 10.76 ± 0.61fL, 11.36 ± 0.68fL, 12.03 ± 0.60fL and 12.07 ± 0.58 fL respectively. Ninety patients (36%) had the disease for less than 3 years, 65 patients (26%) had diabetes mellitus for 3-5 years and 93 patients (38%) had diabetes mellitus for over 5 years. Mean mean platelet volume for these patients was 11.16 ± 0.79 fL, 11.35 ± 0.66 fL and 12.14 ± 0.52 fL respectively. About 111 patients (45%) had HbA1c below 7.5% and 137 patients (55%) had HbA1c above 7.5%. Mean mean platelet volume for patients with controlled diabetes mellitus (HbA1c<7.5%) was 11.13 ± 0.69 fL and for those with uncontrolled diabetes mellitus was 11.93 ± 0.69 fL respectively. Means of different groups was compared using student t-test and *p*-value was found to be less than 0.001.
Conclusion: Higher mean platelet volume values are associated with a higher age, longer duration of illness and uncontrolled disease or poor glycemic control as shown by higher HbA1c levels in patients of type 2 diabetes mellitus. There was no significant change in mean platelet volume values with respect to gender.

Keywords: Mean platelet volume, Platelet activation, Type 2 diabetes mellitus, HbA1c levels.

INTRODUCTION

Diabetes mellitus has emerged as a major global disease with 422 million adults affected worldwide. Infact, it has grown into a"worldwide pandemic" effecting all ethnic and socioeconomic demographic groups. It is the second most common disease with all-cause mortality in adults after Ischemic Heart Disease[1]. In Pakistan, type 2 diabetes mellitus is prevalent in approximately 13% of adult population living in urban areas[2]. Diabetes mellitus affects multiple organ-systems with macro vascular (Atherosclerotic Heart disease, increased incidence of Cerebro-Vascular Accidents, Peripheral Vascular Disease) and micro vascular complications (Diabetic Nephropathy, Diabetic Neuropathy, diabetic retinopathy) leading to increase in morbidity and mortality with an estimated 1.6 million deaths occurringdue to Diabetes annually[3].

Research into complications of DM has been focusing on finding out the causative pathologies for the complications of DM. Various processes have been identified in this regard and chronic

Correspondence: Dr Umair Ijaz Malik, Graded Medical Specialist, Combined Military Hospital, Kohat Pakistan
Received: 11 Nov 2019; revised received: 30 Dec 2019; accepted: 17 Jan 2020

platelet activation and aggregation is found to be one of them[4]. Platelet activation is a dynamic process involving multiple biochemical pathways leading to increased coaguability within the body[5]. Chronic platelet activation can lead to macro and especially micro vascular complications in diabetes mellitus by increasing clot formation in microvasculature and promotion of atherosclerosis in micro-vasculature[6].

Activated platelets are metabolically and enzymatically more active secreting ADP, thromboxane A2, beta thromboglobulin and other chemokinesinto the blood stream. This ultimately leads to the activation of clotting pathways causing thrombosis[7]. Activated platelets also have a larger mass and volume i.e. higher MPV. Mean Platelet Volume (MPV) is a commonly available hematological index which is increased due to subclinical platelet activation in diabetic patients and can be taken as an indirect marker of platelet activation[8]. Since diabetic manifestations are directly related to advanced age, disease duration and poor glycemic control, it can be assumed that these factors would similarly affect Mean Platelet Volume (MPV) in diabetics.

This study was therefore aimedat proving an association of advanced age, longer disease duration and poor glycemic control (HbA1c >7.5%) with increased MPV signifying platelet activation in type 2 diabetes mellitus patients.

METHODOLOGY

The study was started after taking permission from the Ethics Review Committee. In this cross sectional descriptive study, data was collected from 248 patients. These patients were already diagnosed with type 2 diabetes mellitus (as per ADA criteria) who presented to Medicine Department, Combined Military Hospital Kohat, form Jul 2017 to Aug 2018. Written informed consent was taken prior to patient selection and patients were selectedby non-probability consecutive sampling technique. Inclusion criteria included: age >40 years, both male and female patients of diabetes mellitus (as per ADA Criteria). Exclusion criteria included uncertain diagnosis, type-1 diabetes, concomitant chronic illness like rheumatologic diseases, chronic infections, tuberculosis etc that can affect the values of MPV, uncontrolled hypertension, anaemics (Hb<10g/dl), statin users and patient unwillingness.

Data was collected on a proforma which comprised of patient's personal information (age, gender, height, weight), symptoms (duration of DM, Target Organ Damage), clinical findings (including fundoscopy) and lab values (CBC including MPV, FBG, HbA1c). The patients were then categorized into groups based on their gender, age, duration of disease and HbA1c levels. Mean platelet volume (MPV) was calculated for each patient and a mean MPV was then calculated for each group and compared.

Data collected from the patients was processed by using SPSS version 21. Mean and Standard Deviation (SD) was used to express continuous data and frequency and percentage was calculated for categorical data. For comparison between Means of two or more groups, student t-test was applied with significance value $p<0.05$.

HbA1c levels for each patient were determined using HPLC (High Particle Liquid Chromatography - COBAS) method. Normal levels are <6.5%. Acceptable glycemic control was taken as <7.5% and poor glycemic control as >7.5%.

Mean platelet volume was calculated from routine complete blood counts by automated analyzer (SYSMEX-XP 100). Normal MPV ranges from 8.5 fL to 12.1 fL.

RESULTS

A total of 248 diabetic patients participated in the study. One hundred Forty (57%) patients were male and 108 (43%) were female with mean MPV of 11.51 ± 0.80 fL and 11.66 ± 0.78 fL respectively (table-I). Age wise stratification showed 45 patients (17%) below 50 yrs of age, 85 patients (37%) between 50 and 59 yrs, 80 patients (32%) between 60 and 69 yrs and 38 patients (14%) aged 70 yrs and more. Mean MPV for these age groups was 10.76 ± 0.61fL, 11.36 ± 0.68fL, 12.03 ± 0.60fL and 12.07 ± 0.58 fL respectively (table-II). Ninety

patients (36%) had the disease for less than 3 yrs, 65 patients (26%) had DM for 3-5 years and 93 patients (38%) had DM for over 5 yrs. Mean MPV for these patients was 11.16 ± 0.79 fL, 11.35 ± 0.66 fL and 12.14 ± 0.52 fL respectively (table-III). One hundres eleven patients (45%) had HbA1c below 7.5% and 137 patients (55%) had HbA1c above 7.5%. Mean MPV for patients with controlled DM (HbA1c<7.5%) was 11.13 ± 0.69 fL and for those with uncontrolled DM was 11.93 ± 0.69 fL respectively (table-IV). Means of different groups was compared using student t-test and *p*-value was less than 0.001 which was taken as significant.

Table-I: Comparison of mean MPV with gender.

Gender	n (%)	Mean MPV (fL)	*p*-value
Male	140 (56.5)	11.51 ± 0.80	*p*<0.001
Female	108 (43.5)	11.66 ± 0.78	

Table-II: Comparison of mean MPV with age.

Age (yrs)	n (%)	Mean MPV (fL)	*p*-value
< 50	45 (18.1)	10.76 ± 0.61	*p*<0.001
50-59	85 (34.3)	11.36 ± 0.68	
60-69	80 (32.3)	12.03 ± 0.60	
≥ 70	38 (15.3)	12.07 ± 0.58	

Table-III: Comparison of mean MPV with disease duration.

Duration	n (%)	Mean MPV (fL)	*p*-value
< 3 yrs	90 (36.3)	11.16 ± 0.79	*p*<0.001
3-5 yrs	65 (26.2)	11.35 ± 0.66	
> 5 yrs	93 (37.5)	12.14 ± 0.52	

Table-IV: Comparison of Mean MPV with HbA1c levels.

HbA1c levels	n (%)	Mean MPV (fL)	*p*-value
< 7.5%	111(44.8)	11.13 ± 0.69	*p*<0.001
> 7.5 %	137(55.2)	11.93 ± 0.59	

DISCUSSION

Diabetes mellitus is a multi-organ disease and complications of diabetes are the main reason for its growing morbidity and mortality. Diabetic complications are broadly categorized into macro vascular and micro vascular. Multiple biochemical processes and pathological alterations in normal homeostatic processes have been attributed to the development and perpetuation of these complications. These are multifactorial and inter connected, hence there is a limitation of tangible parameters that can be quantified in this regard.

Hyperglycemia can lead to a prothrombotic state by various mechanisms like production of pro-coagulant AGEs (Advanced Glycation End-products), disruption of vascular endothelium and increased oxidative stress. Santili *et al* discussed that this prothrombotic state caused chronic platelet activation which when combined with already existing risk factors mentioned above lead to clotting within smaller blood vessels[9]. As a separate mechanism, Ferreira *et al* established that the loss of platelet inhibition due to Insulin resistance was another factor thatlead to enhanced platelet activation in diabetic patients[10].

The overall effect of a hyperglycemic state is to cause Platelet activation and aggregation. It is now recognized that platelet function and activity can be better assessed by platelet indices like Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) rather than the platelet counts. This is because the platelet count remains the same during platelet activation, whereas platelet volume (MPV) is increased and therefore MPV can be used as a surrogate marker for platelet activation[11].

Several studies have been conducted to ascertain the association between elevated Mean Platelet Volumeand increased risk of complications in diabetes. Tavil *et al* demonstrated that there was a higher incidence of Ischemic Heart Disease among diabetics with a higher MPV level[12]. Similarly, Elsayed *et al* conducted a study in Egypt which showed that higher MPV levels and MPV to platelet ratios were related to an increased incidence of ischemic cerebrovascular events in diabetic and metabolic syndrome patients[13]. Citirik *et al* concluded that higher MPV values reflected subclinical platelet activation in diabetics and that they were also implicated in a much rapid progression of diabetic retinopathy[14]. Razak *et al* carried out a study in Pakistani popul-

ation that showed that higher MPV levels were seen in diabetic patients with overt and micro albuminuria than in those without albuminuria[15]. All of these studies reinforce the theory that higher MPV levels i.e. platelet activation is associated with development of diabetic target organ damage.

Since complications of diabetes have a recognized association with a poor glycemic control, Lippi *et al* proved that higher HbA1c levels were associated with higher Mean Platelet Volume in diabetics[16]. Similar results were also drawn by Agarwal *et al* in an Indian study that also found an association of higher MPV values with higher HbA1c meaning that poor glycemic control was associated with greater platelet activation and vice versa. In their study however, cut-off for HbA1c level was kept at 8%, whereas we kept it at 7.5% to assess the results vis-à-vis a much better glycemic control[17].

Munniapa *et al* studied the effects of various parameters of diabetes on MPV and platelet counts and concluded that higher MPV levels were positively associated with advanced age of patients, longer duration of disease and presence of complications. However, in their study they concluded that females had a higher MPV across all categories than males, whereas our study did not find any significance difference between either gender[18]. Inanother recent Indian study, Panda *et al* concluded that higher HbA1c levels were associated with higher MPV levels. However there was no statistically significant change in MPV levels due to the presence of complications or duration of illness[19]. Finally, in a Pakistani study carried out at Karachi, Fawwad *et al* studied the association between platelet indices, HbA1c levels and Hs-CRP in diabetic patients. Their results showed that higher HbA1c levels were associated with higher MPV and high Hs CRP levels[20]. High levels of Hs-CRP also show that there is a concomitant inflammatory process going on in diabetics which also contributes to higher MPV levels. The role of inflammatory markers in diabetes needs to be further investigated.

This study was aimed at establishing a positive association or otherwise between MPV and factors such as age and gender of patients, duration of illness and glycemic controlin type 2 diabetic patients. The study was designed to exclude patients with other causes of raised MPV such as co-existing inflammatory, rheumatologic or chronic infectious states, statin users and anaemia. If proven, this would indicate that chronic platelet activation in diabetics occurred similarly and was affected similarly by the parameters being analyzed. This could then be used as a risk marker for complications of DM like IHD, retinopathy, nephropathy etc.

The results of this study showed that higher MPV levels were significantly associated with higher HbA1c levels i.e. poor glycemic control or uncontrolled disease. There was also a statistically significant association between higher MPV levels and increased age and longer duration of illness. However, there was no significant association between higher MPV values and gender of the patient.

CONCLUSION

The results of our study are comparable to other studies carried out on the subject with slightly different results in some parameters also explained earlier. However the association between HbA1c levels and MPV levels is positively related to each other in all of the above cited studies. This leads us to state that Mean Platelet Volume, a surrogate marker for platelet activation, is directly related to poor glycemic control and can be used to identify cases at risk of developing complications. Regular monitoring of MPV levels can prove to be a cost effective, easily available and effective tool for the prediction and monitoring of complications in diabetic patients. It can be recommended as a part of routine assessment for the evaluation of diabetic patients in outdoor setups.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. International Diabetes Federation (IDF) diabetes atlas - Key messages 2015 [Internet] Available at: https:// diabetesatlas.org.
2. Zafar J, Bhatti F, Akhtar N, Rasheed U, Bashir R, Humayun S, et al. Prevalence and risk factors for diabetes mellitus in a selected urban population of a city in Punjab. J Pak Med Assoc 2011; 61(1): 40-47.
3. WHO Int. Diabetes. 2019 Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes
4. Demirtunc R, Duman D, Basar M, Bilgi M, Teomete M, Garip T. The relationship between glycemic control and platelet activity in type 2 diabetes mellitus. J Diabetes Complications 2009; 23(2): 89-94.
5. Golebiewska E, Poole A. Platelet secretion: From haemostasis to wound healing and beyond. Blood Reviews 2015; 29(3): 153-62.
6. Ferroni P, Basili S, Falco A, Davi G. Platelet activation in type 2 diabetes mellitus. J Thromb Haemost 2004; 2(8): 1282-91.
7. Yun S, Sim E, Goh R, Park J, Han J. Platelet Activation: The Mechanisms and Potential Biomarkers. Biomed Res Int 2016; 2016: 1-5.
8. Kodiatte T, Rao S, Manikyam U, Reddy M, Lakshmaiah V, Jagadish T, et al. Mean platelet volume in type 2 diabetes mellitus. J Lab Physicians 2012; 4(1): 5-9.
9. Santilli F, Simeone P, Liani R, Davì G. Platelets and diabetes mellitus. Prostag Oth Lipid M 2015; 120(1): 28-39.
10. Ferreira I, Mocking A, Feijge M, Gorter G, van Haeften T, Heemskerk J, et al. Platelet inhibition by insulin is absent in Type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol 2006; 26(2): 417-22.
11. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des 2011; 17(1): 47-58.
12. Tavil Y, Sen N, Yazıcı H, Hızal F, Abacı A, Cengel A. Mean platelet volume in patients with metabolic syndrome and its relationship with coronary artery disease. Thromb Res 2007; 120(2): 245-50.
13. Elsayed A, Mohamed G. Mean platelet volume and mean platelet volume/platelet count ratio as a risk stratification tool in the assessment of severity of acute ischemic stroke. Alexandria J Med 2017; 53(1): 67-70.
14. Citirik M, Beyazyildiz E, Simsek M, Beyazyildiz O, Haznedaroglu I. MPV may reflect subcinical platelet activation in diabetic patients with and without diabetic retinopathy. Eye 2014; 29(3): 376-79.
15. Razak M, Akif A, Nakeeb N. The relationship bet-ween mean platelet volume and albuminuria in patients with type 2 diabetes mellitus. Diabetes Metab Syndr 2019; 13(4): 2633-39.
16. Lippi G, Salvagno G, Nouvenne A, Meschi T, Borghi L, Targher G. The mean platelet volume is significantly associated with higher glycated hemoglobin in a large population of unselected outpatients. Prim Care Diabete 2015; 9(3): 226-30.
17. Agrawal J, Singh V, Meena B, Yadav R, Shareef M, Saini V. Mean platelet volume (MPV) the neglected marker of cardiovascular risk and glycosylated hemoglobin in diabetic patient. Diabetes Metab Syndr 2017; 11(2): 109-12.
18. Muniyappa BMKU, James N. Study on mean platelet volume and platelet Count In Diabetes Mellitus Type 2. Ann Pathol Lab Med 2017; 4(5): A502-07.
19. Panda S, Dash M. Relationship between glycemic parameters and mean platelet volume among pre-diabetics and non-diabetics in a predominantly tribal population. J Clin Diagn Res 2018; 12 (10): 18-22.
20. Fawwad A, Rizvi H, Alvi F. Role of platelet indices, glycemic control and hs-CRP in pathogenesis of vascular complications in type-2 diabetic patients. Pak J Med Sci 2012; 29(1): 1-8.