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Association of Mean Platelet Volume with Diabetic Retinopathy in Type 2 Diabetes Mellitus

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ABSTRACT

Background & Objective: Diabetic retinopathy is a common microvascular complication of Type2 diabetes mellitus. As diabetes is a prothrombotic disease, it induces platelet hyperactivity resulting in increased mean platelet volume (MPV) which can be measured from complete blood count by haematology auto-analyzer. This study was undertaken to find the association of MPV with diabetic retinopathy in Type 2 diabetes mellitus (DM).

Methods: The study was carried out in the Department of Medicine, Sylhet MAG Osmani Medical College & Hospital, Sylhet in collaboration with the Department of Pathology, Department of Endocrinology & Outpatient Department of Ophthalmology of the same hospital over a period of two years from March 2017 to February 2019. Type 2 diabetic patients (aged 30 years or more) attending at Inpatient and Outpatient Department of Medicine, Endocrinology & Outpatient Department of Ophthalmology were the target population. Based on predefined eligibility criteria, 63 Type2 diabetic patients 31 Type2 diabetic patients with diabetic retinopathy (DR) and 32 diabetic patients without DR were included in the study. To find the normal range of MPV of Bangladeshi population, 30 adult individuals without diabetes were also included. The mean of MPV of 30 adult healthy individuals + 2SD were taken as upper limit of normal range of MPV. Diagnosis of T2DM was based on "2017 ADA criteria for diagnosing DM". Diabetic retinopathy was defined as any vascular abnormality in retina due to DM.

Result: Age and sex were almost similar between the DR and non-DR Group ($p = 0.134$ and $p = 0.159$ respectively). Analyses of the risk factors distribution between the study groups revealed that hypertension and dyslipidaemia demonstrated their significant presence in the DR-Group than those in the Non-DR Group ($p = 0.05.0$ and $p = 0.008$ respectively). ACR was observed to be inappreciably higher in the former group than that in the latter group ($p < 0.001$). Comparison of diabetes profile between the study groups shows that duration of DM, FPG and HbA1c were also significantly higher in the DR Group than those in the Non-DR Group ($p < 0.001$, $p = 0.044$ and $p < 0.001$ respectively). In terms of correlation, duration of DM and HbA1c were observed to be linearly correlated with MPV ($r = 0.510$, $p < 0.001$ and $r = 0.571$, $p < 0.001$ respectively) However, there was no significant difference between the study groups in terms of platelet count and MPV ($p = 0.207$ and $p = 0.820$ respectively). The risk of having larger MPV in diabetic patients with DR was 1.2-fold (95% CI = 0.45-3.27) higher than that in diabetic patients without DR ($p = 0.701$).

Conclusion: The study concluded that there is no association of diabetic retinopathy with platelet count and MPV. The risk of having larger MPV in diabetic patients with DR is not significantly higher than that in diabetic patients without DR.

Key words: Association, platelet volume, diabetic retinopathy, Type2 diabetes mellitus etc.

ORIGINAL ARTICLE

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INTRODUCTION:

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending upon the etiology of DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with DM and on the health care system.[1] Diabetes has become a major public health issue in Bangladesh affecting 7.4% of the adult population (almost 1 in 13 adults aged 20-79 years).[2] Type2 diabetes comprises almost 80-90% of all diabetes and is characterized by target cells' resistance to the action of insulin and an inability to produce sufficient insulin to overcome this 'insulin resistance' due to progressive pancreatic β-cell inactivity.[3]

Generally, the chronic injurious effects of hyperglycemia are categorized broadly as macro vascular complications (coronary artery disease, peripheral arterial disease, and stroke) and micro vascular complications (diabetic retinopathy, diabetic nephropathy and diabetic neuropathy).[3,4] Among the microvascular complications, diabetic retinopathy (DR) is one of the highly specific and important complications with a worldwide prevalence of around 35% and a Bangladesh prevalence of 18%.[5] It is the most common cause of preventable blindness in adults (30-65 years) in developed world.[6] Clinically DR can be categorized into non-proliferative (NPDR) and proliferative diabetic retinopathy (PDR) with or without maculopathy/macular oedema (MO).[6] There is a clear relation of DR with duration of T2DM, poor glycemic status and hypertension, which along with dyslipidemia, diabetic nephropathy, pregnancy, obesity and smoking act as risk factors for DR.[6]

DM has been recognized as a state of, "prothrombotic tendency" with increased platelet reactivity.[7] Platelets are tiny, disc-shaped, non-nucleated, flattened structures, 1-5 µm in diameter.[8] Primary function of platelet is formation of platelet plug in vascular injury. Generally, the normal platelet count varies between 150,000 and 400,000/µl and normal platelet size varies between 7.5 and 10.5 fl.[9] The size of the platelets depends largely on the density of the granules present within them.[9] Mean platelet volume (MPV) is a platelet index which reflects the average size of platelets in a blood sample. Demirin and associates in a large epidemiologic study reported that normal range of MPV in 18-92 years healthy individuals varies between 7.2 and 11.7 fl.[10]

Hyperglycemia or DM causes larger platelets .[11] The larger platelets are reported to be secondary to the increased ploidy (DNA content) of megakaryocytes.[12] Larger platelets are more active and aggregable than normal platelets as their dense granules release more contents like Ca++, ADP, 5-HT etc. which are responsible for platelet activation and aggregation. They also release more prothrombotic factors, such as, thromboxane A2 which play a key role in development of vascular complications in DM. The thromboxane A2 correlates well with MPV and thus supports the relevance of the MPV as a measure of platelet function or activity.[13-15] In a recent study in Bangladesh, Pervin et al.[16] reported an association of increased MPV with acute coronary syndrome (ACS) and in another study, Karim et al[17] showed a positive association of platelet distribution width (PDW) (which is another platelet index and also a marker of platelet activation) with Type 2 DM only in male diabetic patients. Several studies[18-21] have reported a significant association of MPV with DR in Type 2 DM, while Demirtunc et al.[22] & Hekimsoy et al.[23] did not find any significant association between these two variables. However, published data about association of MPV with DR in Type 2 DM are very limited. That purpose, the present study was designed to find the association between MPV and DR in Type 2 diabetic patients.

METHODS:

This a cross-sectional analytical study was conducted in the Department of Medicine in collaboration with the Department of Pathology, Department of Endocrinology & Outpatient Department (OPD) of Ophthalmology, Sylhet MAG Osmani Medical College & Hospital, Sylhet over a

period of 1 year from 1st March 2017 to February 2019. Type 2 diabetic patients ≥ 30 years of age attending at Inpatient and Outpatient Department of Medicine, Endocrinology & Outpatient Department of Ophthalmology were the study population. However, diabetic patients with any acute conditions (diabetic ketoacidosis, hyperglycemic hyperosmolar state (HHS), hypoglycemic coma, cases of acute coronary syndrome (ACS), acute stroke, hypertensive urgency/emergency etc.), anemia (Hb% < 13 mg/dl in male and <12 mg/dl in non-pregnant female) or known cases of hemoglobinopathies or any bone marrow disorders, thrombocytopenia (<150×103/μL) or increased platelet count (>400×103/μL) or any platelet disorder, known or suspected cases of any infectious disease/sepsis or chronic systemic inflammatory conditions or raised C-Reactive Protein (CRP), known cases of end-stage-renal-disease (ESRD) or raised serum creatinine > 1.5 mg/dL, known or suspected cases of cirrhosis of liver, thyroid-related disorders, or cases of any immunosuppressive conditions, or pregnant women, patients on anti-platelet drugs, history of recent major surgery, other causes of vision loss e.g. congenital, mature cataract and glaucoma, etc., were excluded from the study. Ethical clearance was taken from the ethical committee of Sylhet MAG Osmani Medical College prior to commencement of study.

Having obtained informed written consent from the patients, detailed clinical history was taken. Clinical examinations and needed laboratory investigations were done when a known or suspected case of type-2 DM ≥ 30 years of age were diagnosed by biochemical parameters according to ADA 2017 criteria for diagnosing DM, American Diabetic Association, 2017. Diabetic Retinopathy (DR) was detected by dilated fundoscopy, which was done by researcher himself with "Keeler Professional Ophthalmoscope" (made in UK), where pupil dilatation was done by Tropicamide 1%, 1 drop in each eye, 20-30 minutes prior to examination. Findings were verified by a qualified ophthalmologist (Resident Surgeon, Outpatient Department of Ophthalmology, SOMCH) and fundal photograph was taken in all DR cases which was done in a single private laboratory by Canon CF-1 retinal camera (made in Japan) to confirm the findings. The total sample (n = 63), was divided into two groups namely "T2DM with Retinopathy (DR)" [Case] and "T2DM without retinopathy" [Control]. However, for determining baseline MPV in healthy non-diabetic population in our settings, 30 age and sex matched non-diabetic apparently healthy population such as doctors, nurse, other staffs of the Department of Medicine were selected, who had FPG < 5.6 mmol/L (<100 mg/dL) or HBA1C < 5.7% and without known visual problem or retinopathy on dilated fundoscopy. MPV was studied in all groups and variations in MPV were observed between case and control groups. The influence of glycemic control (HbA1c), duration of diabetes, presence of hypertension, dyslipidemia, smoking status and demographic variables on MPV were also observed.

The patients were asked to take normal diet without carbohydrate restriction for consecutive 3 days and then to come in the morning after overnight fasting for at least 8 hrs. Venous blood samples (5 ml) were taken in the fasting state to measure plasma glucose levels and fasting lipid profile, complete blood count (CBC) [to see Platelet count & mean platelet volume (MPV)], HbA1c, serum creatinine. At 2 hours after breakfast (120 minutes) another blood sample (3 ml) was collected for plasma glucose (2-h ABF) or random blood sugar (RBS) regardless of last meal/prandial status using enzymatic hexokinase oxidation reference method for plasma glucose levels. Samples for FPG/2-h PG/RBS estimation and complete blood count were collected in sodium fluoride and tri-potassium salt of EDTA respectively. Estimation of HbA1C was done using auto-analyzer (SD A1c Care, SD Biosensor, made in Korea) in College Pathology Lab, which was based on immunoassay for hemolyzed whole blood certified by NGSP (National Glycohemoglobin Standardization Programme) and IFCC (International Federation of Clinical Chemistry). MPV was estimated using automated blood cell count analyzers (Sysmex XS 500i, made in Japan) in College Pathology Lab, which uses fluorescence flow cytometry for high quality analysis. The normal

range of MPV was calculated as mean ± 2SD. Glucose estimation, serum creatinine and fasting lipid profile were carried out by Automated Biochemistry Analyzer (Vitros 350, made by Orthoclinical Diagnostics, USA) in the same Lab. Routine medical examination of urine was done in hospital laboratory. CRP (C-Reactive Protein) and ACR (Albumin Creatinine Ratio) (as not available in any labs of SOMC/SOMCH) were carried out in a single, reputed private laboratory.

Data were processed and analyzed with the help of SPSS (Statistical Package for Social Science), version 25.0. Continuous data were expressed as mean and standard deviation and were compared between groups using Unpaired t-Test, while the categorical data were presented as frequency with corresponding percentages and were compared between groups using Chi-square (χ^2) Test. Pearson's correlation was performed between independent and dependent variables to see the nature of correlation between them. For all significance tests, the level of significance was set at 5% and $p < 0.05$ was considered significant.

RESULTS:

Age distribution demonstrates that, mean ages of the DR and the non-DR groups were 52.9 and 47.9 years respectively and over 60% of the patients with DR were in their 5th and 6th decades of life, while 75% of the patients in Non-DR group were in their 4th and 5th decades of life. Although a male predominance was observed in the DR group (64.5%), both groups were almost alike in terms of age and sex (p=0.134 and p = 0.159 respectively). Analyses of baseline clinical characteristics and risk factors distribution revealed that hypertension was significantly higher in the DR-Group in comparison to Non-DR Group (45.2% vs. 21.9%) (p = 0.050). Smokers were considerably higher in the DR-Group (p = 0.093). Dyslipidaemia demonstrated its significant presence in the DR-Group (61.3%) than that in the Non-DR Group (28.1%) (p = 0.008). ACR was significantly higher in DR group (259.6±39.9 mg/gm) than that in Non-DR group (57.3 ± 20.7 mg/gm) (p < 0.001) (Table-I). The duration of DM was significantly higher in the DR Group than that in the Non-DR Group (p < 0.001). Fasting plasma glucose (FPG) and HbA1c were also found to be much higher in the former group than those in the latter group (p = 0.044 and p < 0.001 respectively) (Table II).

There was no significant difference between the study groups in terms of platelet count and MPV (p=0.207 and p = 0.820 respectively) (table III). The cut-off value for MPV (fL) was calculated by finding the mean MPV of 30 normal individuals and adding 2SD with it (10.7 ± 2×0.1 fL), which gave us the upper limit of normal range of MPV. Accordingly, the MPV was considered to be increased if it was ≥ 11 fL. Approximately, 55% of the diabetic patients with DR had larger MPV as compared to 50% of the Non-DR. The risk of having diabetic retinopathy was 1.2-fold (95% CI=0.45-3.27) higher in diabetic patients with larger MPV than that in patients with normal MPV (p = 0.701) (Table IV).

Table I: Distribution of baseline clinical characteristics between DR and Non-DR

Demographic characteristics	Group		p-value
	DR (n = 31)	Non-DR (n = 32)	
Age* (years)			
30 – 39	2(6.5)	4(12.5)	
40 – 49	7(22.6)	15(46.9)	
50 – 59	11(35.5)	9(28.1)	0.134
60 – 69	8(25.8)	3(9.4)	
70 – 79	3(9.7)	1(3.1)	
Sex*			
Male	20(64.5)	15(46.9)	0.159
Female	11(35.5)	17(53.1)	
Hypertension*	14(45.2)	7(21.9)	0.050
Smoking habit*			
Smoker	18(58.1)	13 (40.7)	0.093
Non smoker	13(41.9)	19(59.4)	
Dyslipidemia*	19(61.3)	9(28.1)	0.008
BMI# (kg/m2)	24.4 ± 3.7	25.6 ± 4.5	0.255
Serum Creatinine# (mg/dl)	1.1 ±0.3	1.0 ± 0.2	0.124
ACR# (mg/gm)	259.6 ± 39.9	57.3 ± 20.7	< 0.001

*Data were analyzed using **Chi-square** (χ^2) **Test**; Figures in the parentheses denote corresponding %. #Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

Table II:Comparison of diabetes related variables between groups

Diabetes-related variables#	Group		p-value
	DR (n = 31)	Non-DR (n = 32)	
Duration of DM (years)	13.6 ± 6.3	5.4 ± 4.3	< 0.001
FPG (mg/dl)	225.1 ± 80.2	186.3 ± 65.6	0.044
RBS (mg/dl)	330.1 ± 115.8	289.1 ± 100.5	0.141
HBA1c (%)	12.2 ± 2.4	9.4 ± 2.5	< 0.001

#Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

Table III: Comparison of platelet count and MPV between the study groups

Platelet morphology#	Group		p-value
	DR (n = 31)	Non-DR (n = 32)	
Platelet Count (×103/uL of blood)	295 ± 0.668	317 ± 0.703	0.207
MPV (fL)	10.9 ± 0.8	10.9 ± 0.9	0.820

#Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

Table IV: Risk of having larger MPV in DR compared to Non-DR

MPV (fL)	Group		Odds Ratio (95% CI of OR)	p-value
	DR (n = 31)	Non-DR (n = 32)		
≥ 11	17(54.8)	16(50.0)	1.21(95% CI = 0.45-3.27)	0.701
< 11	14(45.2)	16(50.0)		

Figures in the parentheses denote corresponding percentage. *Data were analyzed using **Chi-square** (χ^2) **Test**; The risk of having DR with increased MPV was calculated using Odds Ratio with (OR) its 95% CI.

Correlation of some pertinent variables with MPV:

Fig 1- 7 shows the correlations of different variables with MPV. Age was not found to be significantly correlated with MPV (r=-0.077, p = 0.462) (fig. 1). However, duration of DM and HbA1c were observed to be linearly correlated with MPV (r=0.510, p < 0.001 and r = 0.571, p < 0.001 respectively) (Fig. 2 and Fig. 4). Fasting plasma glucose and platelet count were not found to bear any correlation with MPV (r = 0.069, p = 0.590 and r = -0.047, p = 0.653 respectively) (Fig. 3 and Fig. 5). No significant correlation was observed between BMI and MPV (r=0.055, p = 0.669) and ACR and MPV (r = 0.048, p = 0.708) (Fig. 6 & 7).

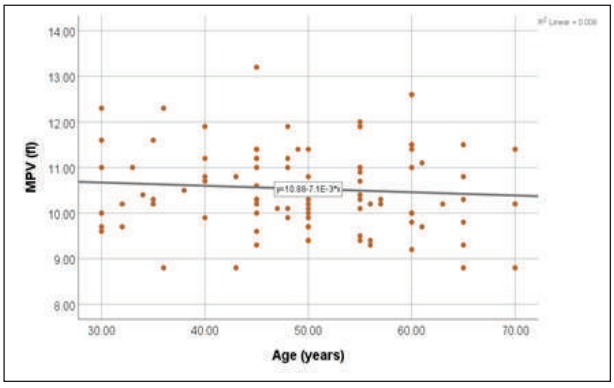

Fig. 1: Correlation between age and MPV

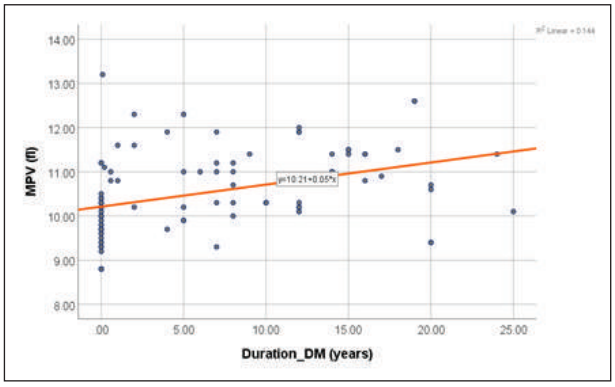

Fig. 2: Correlation between duration of diabetes and MPV

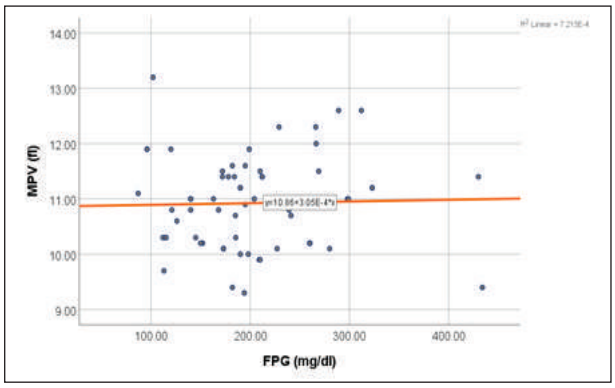

Fig. 3: Correlation between Fasting Plasma Glucose (FPG) and MPV

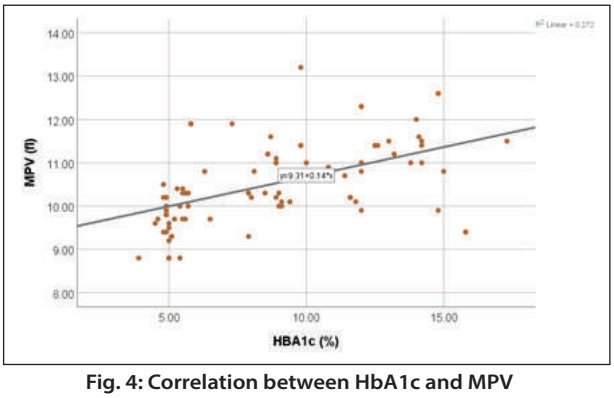

Fig. 4: Correlation between HbA1c and MPV

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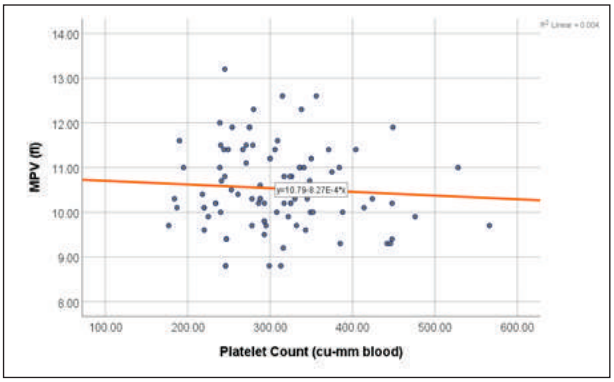

Fig. 5: Correlation between platelet count and MPV

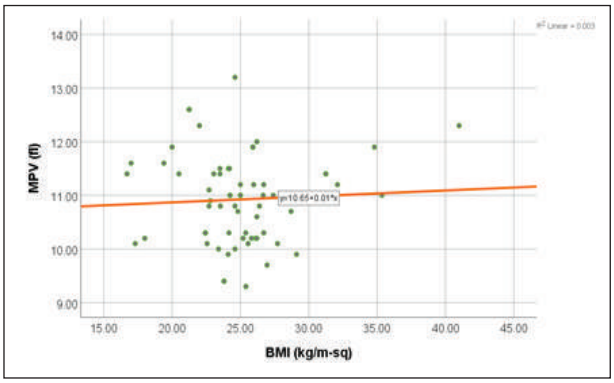

Fig. 6: Correlation between BMI and MPV

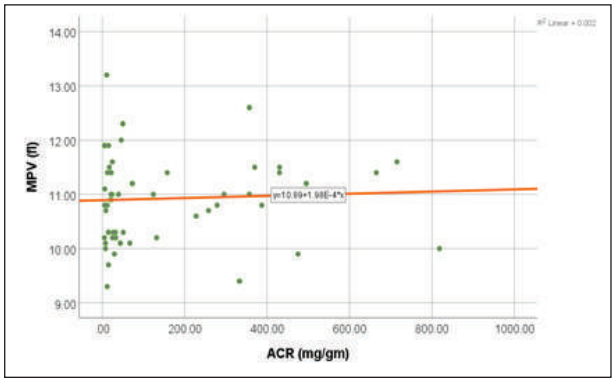

Fig. 7: Correlation between ACR and MPV

DISCUSSION:

In the present study the demographic characteristics like age and sex were almost similar between the DR and non-DR Group. Analyses of the risk factors distribution between the study groups revealed that hypertension and dyslipidemia were significantly higher in the DR-Group than those in their Non-DR counterparts. ACR was observed to be markedly higher in the former group than that in the latter group. Smokers were comparatively more in the DR-Group. The duration of DM, FPG and HbA1c were also significantly higher in the former group than those in the Non-DR Group. In terms of correlation, duration of DM and HbA1c were observed to be linearly correlated with MPV. However, there was no significant difference between the study groups in terms of platelet count and MPV. Though the risk of having diabetic retinopathy was 1.2-fold (95% CI = 0.45-3.27) higher in diabetic patients with increased MPV than that in patients without increased MPV, there was no significant association between these two variables. In a similar study conducted by Hekimsoy et al[23] MPV was not significantly different in patients with diabetic retinopathy from that in diabetic patients without retinopathy. Demirtunc and associates[22] also did not find MPV to be significantly different in subjects with diabetic neuropathy and retinopathy from that of diabetics without those complications. Aydinli also advocated that there was no association between MPV and vascular complications in T2DM.[24]

By contrast, Tuzcu et al.[19] observed an association between MPV values and DR stage in their study. Several other studies also demonstrated higher values of MPV in type 2 diabetics with retinopathy than those without retinopathy.[20,21,25] Zhong et al.[26] stated that MPV was significantly higher in patients with proliferative DR and advocated that MPV might be a risk factor for retinal neovascularization. MPV was observed to be higher in diabetic patients with retinopathy and microalbuminuria.[27] All these findings suggested a role for the increased platelet activity in the pathogenesis of vascular complications.

Yilmaz and Yilmaz[18] in an attempt to investigate whether platelet morphology or function is altered in patients with diabetic retinopathy (DR), measured in terms of mean platelet volume (MPV), platelet distribution width (PDW), platelet large cell ratio (PLCR), plateletcrit (PCT) values, and platelet count in four study groups – healthy controls, non-DR, NPDR (non-proliferative DR) and PDR (proliferative

DR). MPV, PDW, and PLCR were significantly altered in patients with non-proliferative DR, proliferative DR and non-DR compared with those in their healthy controls. Compared with non-DR, both DR groups had higher MPV and PDW levels, with a significant difference between non-DR and PDR for both MPV and PDW. The increased platelet activity is emphasized to play a role in the development of vascular complications of this metabolic disorder.[22] Platelet volume, a marker of the platelet function and activation, measured as MPV by hematology analyzers. Studies have demonstrated that platelet activity is increased due to larger platelets in diabetes which correlates with rise of MPV. Increased platelet activity plays a key role in development of vascular complications of DM.[7] Diabetic patients have an increased risk of developing micro- and macro-vascular diseases, and platelets may be involved as a causative agent in terms of altered platelet morphology and function.[23]

MPV reflects the average size of platelets. It is a marker of subclinical platelet activation and may be increased in some vascular conditions such as myocardial infarction (MI),[28] coronary artery disease (CAD),[29] cerebral ischemia,[30] and peripheral arterial disease[29]. Larger platelets are younger, more reactive and aggregable. Hence, they contain denser granules, secrete more serotonin & β-thromboglobulin, and produce more thromboxane A2 than smaller platelets.[21,23,30] All these changes can produce a pro-coagulant effect and cause thrombotic vascular complications suggesting a relationship between the platelet function, especially MPV and diabetic vascular complications. The changes in MPV reflect the state of thrombogenesis.[23] Diabetic retinopathy (DR) is the most common and the specific microangiopathy.[31] Diabetes duration, dyslipidemia, genetic factors, obesity, hypertension, smoking and proteinuria or microalbuminuria may all play a role in development of DR. Papanas and colleagues[25] reported that among diabetic patients, those with retinopathy and nephropathy (microalbuminuria) have higher MPV values than those who do not have these complications.

Summarizing the findings of the study and discussion thereof, it appears that there is questionable association between diabetic retinopathy and MPV. The risk of having retinopathy in diabetic patients with increased MPV is not higher than that in diabetic patients without increased MPV. Several studies, although found a significant association between these two variables, others did not find any association between these two variables. Before concluding the findings of the study, the limitations of the present study deserve mention.

LIMITATIONS:

- Small sample size due to financial constraint and limitation of time may have lowered its power and thereby validity.
- Only 30 healthy controls were taken to find the normal range / reference range of MPV in the context of our population. The reference range of MPV was not determined by a large sample obtained from a cross-section of our population.
- Raised ACR was not confirmed by repeat testing to label as diabetic nephropathy.

CONCLUSION:

From the findings of the study, it can be concluded that there is no association of MPV with diabetic retinopathy. The risk of having DR in cases of increased MPV is not significantly higher than that in diabetic patients without increased MPV. Age, fasting plasma glucose and platelet count are not found to bear any correlations with MPV. Similar findings are reported by several studies conducted around the world. However, several other studies reported significant association between these two variables.

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