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ARE PLATELET INDICES ASSOCIATED WITH DIABETIC RETINOPATHY? A STUDY AT A TERTIARY CARE CENTRE

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) which is now an important public health problem is a prothrombotic state which can lead to macrovascular and microvascular complications; diabetic retinopathy (DR) being one of them. Platelet indices may serve as prognostic markers for these patients. This study was conducted to evaluate the association between platelet indices and diabetic retinopathy. A total of 144 patients were evaluated. They were divided in four groups. Group 1: T2DM with Proliferative DR, Group 2: T2DM with Non- proliferative DR, Group 3: T2DM without DR and Group 4: Healthy adults (Control group). The mean platelet volume (MPV), Platelet distribution width (PDW), large platelets, platelet count and HbA1c were measured in all the groups. We found that MPV, PDW, large cell platelets and HbA1c were significantly raised in all the groups as compared to the control group. It was also observed that PDW and large cell platelets were significantly increased in patients of proliferative DR as compared to non-proliferative DR. Our findings thus suggest an association between platelet indices (MPV, PDW, large platelets) and DR. Also evaluation of PDW and large cell platelets is useful in predicting progression of non-proliferative to proliferative DR (since these values increased with increasing grade of DR) and hence it's prognosis. Thus we conclude that there is significant association of platelet indices with diabetic retinopathy and these can be used as predictive markers to monitor DR.

Key words: Platelet indices, Mean platelet volume, Platelet distribution width, large platelets, diabetic retinopathy.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia, impaired insulin excretion by pancreas and insulin resistance of the tissues[1]. Chronic hyperglycemia leads to macrovascular and microvascular complications; amongst which Diabetic Retinopathy (DR) is the most common one leading to increased morbidity [2].
Due to sustained insulin resistance, dyslipidemia and hyperglycemia, DM is considered as a " prothrombotic state "; thus causing endothelial and pericyte injury. Impaired action of insulin in patients of T2DM causes enhanced platelet activation resulting in microvascular complications[3]. The role of platelets is pivotal in maintainance of homeostasis and this is correlated well with Mean Platelet Volume (MPV). MPV indicates average size and activity

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of platelets. Larger platelets exhibit more dense granular structure and produce more amount of Thromboxane A2 resulting in platelet aggregation[4]. Other platelet indices like Platelet Distribution Width (PDW) is also a marker of platelet activity. Platelet activation causes changes like spherical shape and pseudopodia formation of platelets. Such morphologically changed platelets affect PDW. Hence it is a marker indicating platelet activation serving as an independent risk factor for vascular episodes[5]. Therefore high platelet activity and greater platelet turnover are reflected by high MPV and PDW[6].
Platelet indices are easy to quantify, are measured as a part of complete blood count and relatively inexpensive tests. The purpose of our study was to assess the association of various platelet indices in patients of Diabetic Retinopathy.

Materials and Methods
The aim of our study was to evaluate the association between platelet indices and diabetic retinopathy. The Objectives were:
1. To evaluate the most significant platelet parameter associated with diabetic retinopathy.
2. To assess variation of platelet indices with severity of Diabetic Retinopathy (DR).
A total of 144 cases were evaluated within a span of 6 months.
Patients with Type 2 Diabetes Mellitus were divided into 4 groups;
Group 1: T2DM with Proliferative DR.
Group 2 : T2DM with Non- Proliferative DR
Group 3: T2DM without DR
Group 4: Healthy Adults (Control group)

For calculation of sample size for present study, G.Power software was used. Alpha = α = 0.5, Power = 0.95, large effect size was considered = 0.25. Using G. Power software sample size of each group was found to be 36. Hence we enrolled 36 patients in each group.
Data was entered in Microsoft Excel and analyzed using SPSS version 24.0th Mean ; and SD was calculated for quantitative variables ; and proportions were calculated for categorical variables. ANOVA test was applied to check significant difference between four groups. Post Hoc test was applied to check significance of difference between two groups. P-value < 0.05 was considered statistically significant. Patients diagnosed as Diabetes Mellitus referred to Ophthalmology OPD were included in the study. Patients with uncontrolled Hypertension, cardiovascular disease/ stroke/ Chronic renal failure; and patients on anticoagulants like Ecosprin and Clopidegrol were excluded from the study.

Results
A total of 144 cases were studied. The age of patients in all the four groups ranged from 30 to 85 years with mean age as depicted in Table 1. Out of 144 patients, 74 were males and 70 were females. There was a slight female preponderance in patients with non proliferative diabetic retinopathy.

Table 1: Demographic Profile of patients in Groups

Variables		**Diabetes with Proliferative Retinopathy [n=36]**	**Diabetes with Non-Proliferative Retinopathy [n=36]**	**Diabetes without Retinopathy [n=36]**	**Control [n=36]**
Gender	Male	18(50.0%)	15(41.7%)	20(55.6%)	21(58.3%)
	Female	18(50.0%)	21(58.3%)	16(44.4%)	15(41.7%)

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Age in Years Mean±SD	56.44±12.08	60.56±11.30	61.55±12.67	59.94±15.91

Table 2 shows the comparison of platelet indices in all the four groups. A statistically significant difference was observed in MPV, PDW and large cell platelets (LCP) among diabetic and non- diabetic patients. However there was no significant difference in platelet count in all the four groups.

Table 2: Comparison of mean MVP, PWD, Large Platelets and Platelet count in Groups

	Group	N	Mean±SD	F-value	P-value
MPV	Diabetes with Proliferative Retinopathy	36	6.87±0.86	. 4.50	P=0.005 S
	Diabetes with Non-Proliferative Retinopathy	36	6.69±0.69		
	Diabetes without Retinopathy	36	6.57±0.65		
	Control	36	6.27±0.62		
PDW(%)	Diabetes with Proliferative Retinopathy	36	55.96±7.16	2.94	P=0.043 S
	Diabetes with Non-Proliferative Retinopathy	36	52.94±7.0		
	Diabetes without Retinopathy	36	52.70±7.50		
	Control	36	51.81±7.67		
Large cell Platelets 9 n x 1000	Diabetes with Proliferative Retinopathy	36	5.61±2.38	4.01	P=0.009 S
	Diabetes with Non-Proliferative Retinopathy	36	4.47±3.06		
	Diabetes without Retinopathy	36	3.86±1.89		
	Control	36	3.69±2.89		
Platelet count	Diabetes with Proliferative Retinopathy	36	293694.4±107767.4	1.32	P=0.268 NS
	Diabetes with Non-Proliferative Retinopathy	36	290138.8±79888.9		
	Diabetes without Retinopathy	36	280138.8±82173.0		
	Control	36	258527.7±48929.9		

S- significant; NS not significant.

Similarly, there was statistically significant difference in HbA1c values in control group and Diabetic group. (Table3)

Table 3: Comparison of mean HbA1C in Groups

Group	N	Mean±SD	F-value	P-value
Diabetes with Proliferative Retinopathy	36	10.27±2.55	. 35.43	P<0.0001 S
Diabetes with Non-Proliferative Retinopathy	36	8.81±2.41		
Diabetes without Retinopathy	36	8.38±2.34		
Control	36	5.27±0.33		

S- Significant

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In our study all the platelet indices (MPV, PDW, Large Platelets) showed higher values in patients with diabetic retinopathy as compared to non retinopathy diabetic patients; however the values were not statistically significant. (Table 4)

Table 4: Comparison of mean MVP, PWD, Large Platelets and Platelet count in present and absent Retinopathy patients

Platelet Indices	Retinopathy	N	Mean±SD	Z-value	P-value
MPV	Present	72	6.71±0.77	0.210	P=0.834 NS
	Absent	36	6.27±0.62		
PWD	Present	72	53.89±6.74	0.830	P=0.408 NS
	Absent	36	51.81±7.67		
Large cell Platelets	Present	72	4.73±2.31	0.501	P=0.618 NS
	Absent	36	3.69±2.89		
Platelet count	Present	72	286916.6±95395.8	0.174	P=0.861 NS
	Absent	36	258527.7±48929.9		

S- Significant; NS- not significant

A significant difference was observed in values of PDW and Large cell platelets in comparison of proliferative and non- proliferative diabetic retinopathy; with higher values in proliferative diabetic retinopathy. (Table 5)

Table 5: Comparison of mean MVP, PWD, Large Platelets and Platelet count in Diabetes with Proliferative Retinopathyand Diabetes with Non-Proliferative Retinopathy.

Platelet indices	Groups	N	Mean±SD	Z-value	P-value
MPV	Diabetes with Proliferative Retinopathy	36	6.87±0.86	1.65	P=0.102 NS
	Diabetes with Non-Proliferative Retinopathy	36	6.69±0.69		
PWD	Diabetes with Proliferative Retinopathy	36	55.96±7.16	2.72	P=0.008 S
	Diabetes with Non-Proliferative Retinopathy	36	52.94±7.0		
Large Platelets	Diabetes with Proliferative Retinopathy	36	5.61±2.38	3.45	P=0.001 S
	Diabetes with Non-Proliferative Retinopathy	36	4.47±3.06		

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Platelet count	Diabetes with Proliferative Retinopathy	36	293694.4±107767.4	0.600	P=0.550 NS
	Diabetes with Non-Proliferative Retinopathy	36	290138.8±79888.9		

S- Significant ; NS- not significant

Discussion:

Diabetes mellitus, being a multisystem disorder is known to affect eyes, kidneys and peripheral nerves causing micro and macroangiopathies[2]. The definition of diabetic retinopathy according to American Academy of Ophthalmology is damage to blood vessels in the retina[4]. The non- proliferative DR is the early stage of the diabetic eye where in there is neovascularization and these fragile blood vessels can rupture into the vitreous, hence hampering vision. Those with inadequate glycemic control, obesity and hypertension have a higher prevalence of microvascular complications in diabetics[4,7]. Many studies have shown that people with high MPV can land up into metabolic syndrome, stroke and diabetes mellitus. Also, a series of studies has shown a strong association of diabetes mellitus with platelet indices[4,8].

Prothrombotic state and increased thrombocyte aggregation via multiple mechanisms contribute in the pathogenesis of diabetes[5]. Glucose being the main mode of energy for platelets, due to hyperglycemic environment in diabetic population, the platelets become active and have increased aggregation. This causes rise in MPV. High MPV value equals to large size of thrombocyte. Larger thrombocytes are younger and active; thus higher MPV poses more risk for retinopathy[5, 9, 10.]. Tuzcu *et al.*[11] showed a correlation between MPV levels and diabetic retinopathy(DR)in an experiment with 192 patients.. They showed that DR increases with increasing MPV levels. Buch *et al.* [3,] Pavan Raj *et al.* [14,]Walinjkar *et al.*[12], also showed increased MPV values in diabetic patients,more significantly in patients with microvascular complications than those without. In our study, MPV values were significantly higher in diabetic patients as compared to non diabetic patients. Higher values were noted in patients with DR than with those without retinopathy though the difference was not statistically significant. This finding was in concordance with the studies conducted by Aydinli *et al.*[15] and Demirtunc *et al.*[16].

Platelet activation also causes increase in PDW. Jindal *et al.*[17] demonstrated a significant increase in PDW in diabetic patients; more so in patients with microvascular complications. Elevated PDW correlates with larger circulating platelets leading to microvascular complications. Similar studies conducted by TolgaYilmaz *et al.* [2], M Citirik *et al.* [5,]Shubratha Hegde *et al.* [6,]Taderegew *et al.* [13,] have concluded that marked increase in PDW and MPV values were found in advanced stages of retinopathy. Our study also showed a significant increase in PDW values in diabetics with an increasing trend in advanced stages of DR. A recent analysis done by Ahluwalia *et al.*[18] revealed that diabetic patients had higher values of PDW than MPV, as PDW is independent of platelet count; whereas MPV is dependent on it. A positive correlation was found between the degree of retinopathy and values of PDW and large cell platelets. This was similar to studies conducted by Yilmaz *et al.* [2,] Buch *et al.* [3] and Hegde *et al.* [6.] However, Tetikoglu *et al.* [19], and Citirik *et al.*[5]found no association between PDW and stages of retinopathy.

At the same time a significant positive correlation was also found with large platelets and stages of DR, with significantly higher values in diabetic patients with proliferative

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retinopathy, followed by non proliferative retinopathy and non diabetic patients. These findings correlated with study of review of literature done by Subashini Subramanian *et al.*[20.] We also found that glycemic control was poor in advanced stages of DR. Sidda Bukke *et al.* also concluded with similar findings[21].

The major limitation of our study was that follow up of the cases was not possible, hence we could not comment on the progression of disease and also reversibility of the disease stage with improvement of glycemic status.

Conclusion

In this study we observed that MPV, PDW, Large cell platelets were significantly higher in diabetics as compared to non diabetics. PDW and large platelets values were significantly increased in diabetic patients with proliferative DR than with non proliferative DR. Hence there was a statistically significant correlation between stages of DR and platelet indices.

Thus we conclude that there is a significant association of platelet indices and diabetic retinopathy. PDW and large cell platelets can be used as platelet indices to identify target population who are at greater risk of developing advanced DR. These platelet indices can be used as screening markers to monitor and predict the risk of progression of DR.

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