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A Correlation between Diabetic Ischaemic Maculopathy and Platelet Indices

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Abstract: *The purpose of this study was to find association between Diabetic ischemic maculopathy and the platelet indices at JSS Hospital.*
Objectives*:*
- *To identify if platelet indices is a biomarker for patients at risk of developing diabetic ischemic maculopathy*
- *To correlate between these markers and severity of diabetic ischaemic maculopathy.*

Methodology*: A total of 45 patients, controls (15)diabetic retinopathy without maculopathy(16) and patients with diabetic ischemic maculopathy,(15) were evaluated crossectionaly, from October 2013 to June 2015. FAZ was measured after fluorescein angiogram and correlated with platelet indices like platelet count, MPV, and PDW*
Results*: patients in diabetic ischaemic maculopathy group showed higher levels of platelet count than normal values and there is significant increase in the platelet distribution width when compaired between controls and Diabetic ischaemicmaculopathy .*
Conclusion*: It shows that Platelet count and Platelet distribution width (PDW) can be used as a simple indicators of platelet activation and can be used as a biomarker for patients at risk of developing Diabetic ischaemic maculopathy.*
Key words: *(FAZ) foveal avascular zone, (MPV) mean platelet volume, (PDW) platelet distribution width*

I. Introduction

Diabetes and its complications is one of the major health issue worldwide.India is contributing to nearly 25% of the world diabetes mellitus population. Diabetic retinopathy is one of the serious complications of diabetes mellitus and it is one of the leading cause of visual impairment and blindness worldwide.One of the ways in which blindness occurs in diabetic maculopathy is when the central macular area of the retina is damaged, causing diabetic maculopathy. Increased permeability of retinal vessels allows leakage of plasma constituents& fluid which accumulate in the extracellular spaces, initially at the outer-plexiform layer and inner nuclear layer level and later extending to involve the entire retinal thickness. Such oedema at the macula is the most common cause of reduced vision.

There are four main types of diabetic maculopathy according to clinical examination and fluorescein angiography. These are: a)Focal Maculopathy**:** Areas of discrete leakage from microanuerysm with sufficient macular perfusion.b) Diffuse Maculopathy**:** There is generalized breakdown of the blood retinal barrier and profuse early leakage from entire capillary bed of posterior pole.c)Ischemic Maculopathy**:** Capillary shut down results in retinal non perfusion and ischemia. It is characterized by enlargement of foveal avascular zone and vision loss with featureless maculaand is most severe as far as Vision is concerned d)Mixed**:** It is not uncommon to see a combination of focal, diffuse and ischemic maculopathy.

Ischemic maculopathy is the most severe form of diabetic maculopathy. It is a mismatch between appearance and vision usually appears like featureless macula but sometimes may shows cotton wool spots in the macula or white ,thread like arterioles supplying the macula.Fluorescein angiography is the most accurate method of evaluating the blood supply .Severity of macular ischemia is graded into 3 grades focal capillary dropout, enlargement of FAZ, occlusion of arterioles to macula. The mildest form of macular ischemia is focal capillary dropout. Macula may appear normal ophthalmoscopically. small areas of capillary non perfusion causing a irregular FAZ surrounded by dilated capillaries are seen by fluorescein angiography. This degree of capillary occlusion is consistent with normal visual acuity. A more severe form of macular ischemia is enlargement of FAZ secondary to occlusion of perifoveal capillaries. Its size varies among individual averaging about 500 um in diameter. Enlargement of FAZ and irregularity of its margins in patients with either proliferative or non proliferative diabetic retinopathy are common angiographic findings. The fovea appears normal by ophthalmoscopy so that fluorescein angiography is required to demonstrate this defect .The most severe form of macular ischemia is the occlusion of the artery to macula

Diabetes mellitus is a prothrombotic state with increased activation of platelets and coagulation proteins and decreased fibrinolytic activity. Diabetic microangiopathy involves atherosclerosis, inflammation and thrombosis due to abnormal function of platelet and leukocyte. The increased platelet activity play a role in the development of vascular complications of this metabolic disorder.[1] Diabetic thrombcytopathy refers to differences in platelet functions between diabetic and nondiabetic individuals. Platelets from diabetic patients exhibit enhanced platelet aggregation early in the course of the disease.Increased platelet turnover reflects increased thrombopoiesis and is associated with increase in adhesive proteins on the surface, increased fibrinogen binding and decreased membrane fluidity.[2]

II. Methods

This study was conducted in the Department of Ophthalmology of J.S.S. Hospital, Mysore .Subjects were the patients visiting the outpatient department of JSS Medical College and Hospital, Mysore during October 2013 –june 2015. A total of 45 patients were included in the study. Patients were explained about the study and a written consent was taken. Using a proformademographic data and clinical findings was noted .Patient were subjected to a preliminary slit lamp examination and fundoscopy using indirect ophthalmoscope and 90D lens. The subjects were then categorized into 3 groups Group1- controls (no diabetes mellitus), Group2- retinopathy(including mild, moderate and severe non proliferative diabetic retinopathy, proliferative diabetic retinopathy) without ischemic maculopathy. Group3-retinopathy(including mild, moderate severe non proliferative diabetic retinopathy and proliferative diabetic retinopathy) with ischemic maculopathy. Patients with other risk factors like Tobacco usage**,** Hyperlipidemia**,** Anemia**,** Viral fevers**,** Idiopathic thrombocytopenia**,** Central retinal artery occlusion**,** Immunocompromised, Post operativepatientswere excluded

Blood was collected using aseptic precautions 2ml in quantity with EDTA and assessed for platelet indices like platelet count, mean platelet volume (MPV) ,and platelet distribution width (PDW) . other routine investigations like fasting blood sugar, post prandial blood sugar were done. Foveal avascular zone (FAZ) was measured using zeiss fundus camera using visucam software after injecting 600 mg (3ml of 20%) fluorescein sodium by intravenous route. Based on the FAZ area the patients were grouped. Those with FAZ (0.235-0.405) were classified under group 2 diabetic retinopathy without ischemic maculopathy, and those with FAZ area >0.405 were classified under group 3 diabeticischaemicMaculopathy.All the measurements are done using SPSS version 21.0.

III. Results

In this study out of the total 45 patients included in the study 15 patients (33.33%)were included under group -1 as controls,14 patients(31.11%) were included under group-2 as diabetic retinopathy without ischaemic maculopathy and 16 patients(35.55%) were included under group-3 as diabetic ischaemic maculopathy. both the eyes were evaluated except in 7 patients in which only one eye was evaluated as fundus details was not clearly made out due to vitreous hemorrhage, or grade 4 nuclear sclerosis in the other eye

Table 1: age distribution

	Frequency	Percent
40-54	8	17.8
55-64	21	46.7
65-74	15	33.3
75 and above	1	2.2
Total	45	100.0

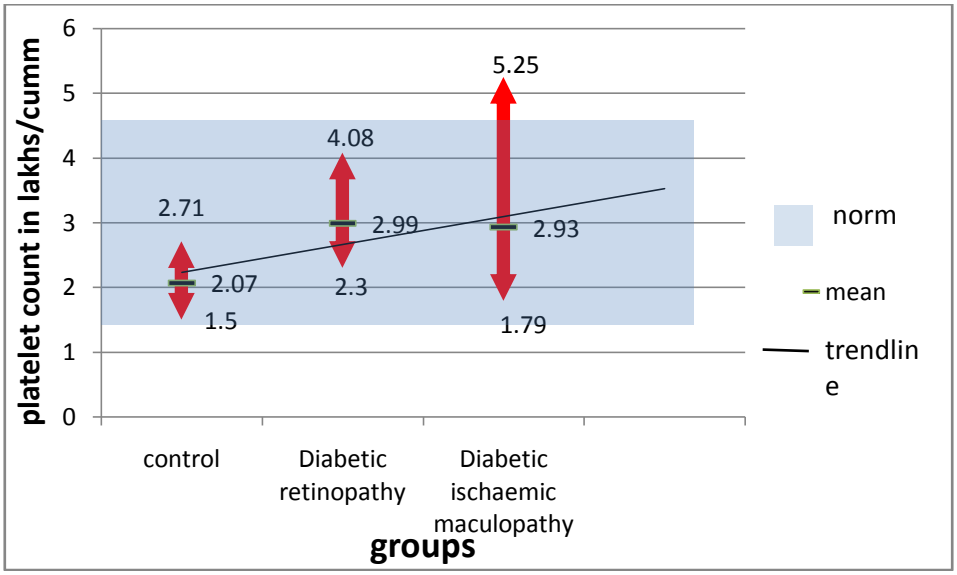
Age distribution of the patients in the study was shown in table(1). 24 male patients were included in the study (53.3%) and 21 female patients were included in the study (46.7%) . Among the controls mean FAZ area was 0.28±0.02 mm², in diabetic retinopathy group mean FAZ area was 0.4±0.16 mm², in diabetic ischaemic maculopathy group mean FAZ area was 1.60±1.15 mm² . P valve<0.001 as shown in table(2).

Table 2: annovaanalysis of all the parameters

Parameter	Control	Diabetic Retinopathy	Diabetic Ischemic Maculopathy	F	P
VISION RE log mar	0.92 ±1.5	0.328 ±0.70	0.387± 0.67	7.425	0.002
VISION LE	0.327±1.24	0.321±0.77	0.94±1.23	1.264	0.293
PLT CT/mm3	2.07±0.34	2.98±0.47	2.92±0.86	10.369	0.001
MPV /fl	10.22±0.88	8.48±1.30	7.52±1.91	13.746	0.001
PDW /fl	12.29±1.70	11.11±2.21	13.53±2.62	4.445	0.018
PCT %	0.20±0.025	0.25±0.052	0.21±0.05	4.126	0.023
RIGHT FAZ	0.27±0.01	0.37±0.06	1.23±1.23	4.915	0.014

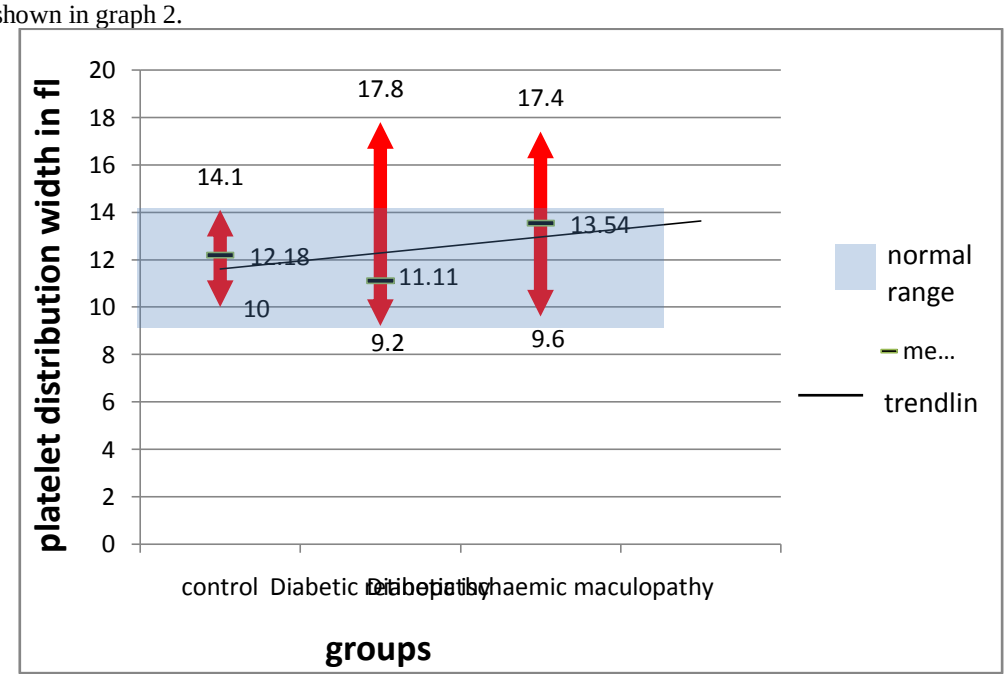
LEFT FAZ	0.27±0.01	0.37±0.09	1.13±0.62	16.224	0.001
FBS	95.13±8.36	130±50.66	142±54.5	4.862	0.013

Mean platelet count in the controls was 2.07±0.35 lakhs/mm³ and among the diabetic retinopathy group was 2.99±0.48 lakhs /mm³ and among diabetic ischaemic maculopathy group was 2.93±0.86 lakhs/mm³ . P value was <0.001 as shown in table 2. Three patients(18.2%) in Ischaemic Maculopathy group had high platelet counts which has a p value =0.054 which shows high platelet counts as shown in graph 1



graph 1: platelet count analysis in the groups

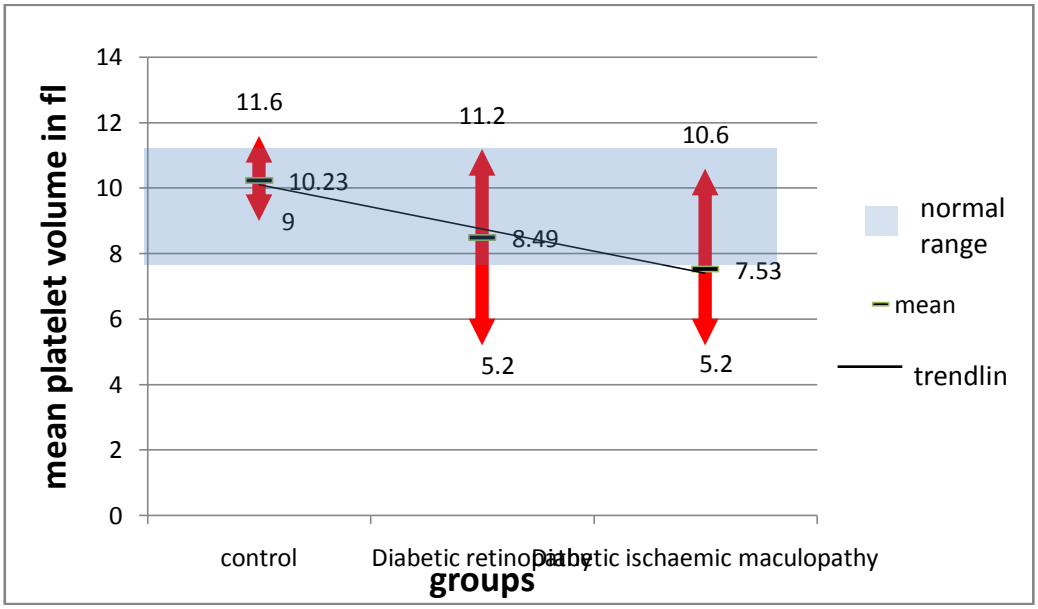
Mean of platelet distribution width (PDW) in the controls was 12.18± 1.52fl and among the diabetic retinopathy group was 11.11±2.22 fl and among diabetic ischaemic maculopathy group was 13.54±2.62 fl. P value was =0.001 as shown in table 2 In diabetic ischaemic maculopathy patients 10 out of 16 (62.5%) had normal platelet distribution width and 6 patients (37.5 %) had high platelet distribution width . Chi square test shows p value= 0.04 as shown in graph 2.



graph2: platelet distribution width among the groups

Mean of mean platelet volume(MPV) in the controls was 10.23±0.89fl and among the diabetic retinopathy group was 8.49±1.30 fl and among diabetic ischaemic maculopathy group was 7.53±1.92 fl. P value was <0.001 as shown in table 2. In diabeticischaemic maculopathy patients 8 out of 16 (50%) had normal mean

platelet volume and 8 patients(50%) had low mean platelet volume. Chi square test shows p value= 0.03 as shown in the graph 3. Correlation between the platelet indices like platelet count platelet distribution width mean platelet volume and the worst FAZ in the patients is shown in table 3 it does not show any significant correlation



graph 3 :mean platelet volume analysis among the groups

Table 3: correlation of platelet indices with faz in worst eye within each group

GROUP				MPVfl	PCT	PDWFL
	Control	FAZ_worst	Correlation Coefficient	.107	.316	.084
			p	.704	.251	.767
			N	15	15	15
	Diabetic Retinopathy	FAZ_worst	Correlation Coefficient	-.224	-.018	-.358
			p	.441	.952	.209
			N	14	14	14
	Diabetic Ischemia	FAZ_worst	Correlation Coefficient	.345	-.019	-.185
			p	.190	.943	.493
			N	16	16	16

IV. Discussion

Type 2 Diabetes Mellitus is characterized by variable degrees of insulin resistance, impaired insulin secretion . Diabetic retinopathy is one of the serious complications of diabetes mellitus and it is one of the leading cause of visual impairment and blindness worldwide. Diabetic Ischaemic Maculopathy is a vision threatening condition where usually macula is featureless but the vision loss is severe and not reversible with any known treatment available.

Patients included in this study were in the age group 40-85yrs with maximum patients 80% (36) patients were in the age group 55-75yrs and their was not much significant difference in the age distribution among the three groups. Mean platelet count in this study shows P value was <0.001 which shows there is significant increase in the platelet count between controls and diabetic retinopathy and controls and diabetic ischaemic maculopathy but there is not much significant difference between diabetic retinopathy and ischaemic maculopathy .Three patients (18.2%) in Ischaemic Maculopathy group had high platelet counts which has a p value =0.054 which shows high platelet counts are associated with diabetic ischaemic maculopathy. Study done by Sokunbi D et al. says diabetic end stage renal disease patients compared to non diabetic patients end stage renal disease have elevated blood platelet count levels that may contribute to occlusive vessel disease[3], ourstudy also suggests similar findings but only one reading and marginally raised platelet counts were observed in our study and repeat reading has to be done to confirm thrombocytosis which was not done as it is a crossectional study.

Platelet indices are potentially useful markers for the early diagnosis of thromboembolic diseases. An increase in PDW is suggestive of platelet activation , resulting from platelet swelling and pseudopodia formation is hypothesized[3]. PDW doesn't increase during simple platelet swelling. In order to obtain a large surface platelets change in shape during activation .Early diagnosis of activation of coagulation can help manage these diseases successfully

Platelet distribution widthvalues in this study shows there is significant decrease in the platelet distribution width between controls and diabetic retinopathy and increase between diabetic retinopathy and diabetic ischaemic maculopathy .In diabetic ischaemic maculopathy patients 10 out of 16 (62.5%) had normal platelet distribution width and 6 patients (37.5 %) had high platelet distribution width . Chi square test shows p value= 0.04 which shows high platelet distribution width are associated with diabetic ischaemic maculopathy. Previous study by E.Vagdatli etal.says PDW is a more specific indicator of platelet activation than MPV since it is not elevated during single platelet distension caused by platelet swelling[4] . Ihara et al as well as Khakendar et al made similar observations that increased PDW was seen in patients with ischaemic heart diasese. Our study also shows increase platelet distribution width suggesting platelet activation.

Mean platelet volume shows there is significant decrease in the mean platelet volume between controls and diabetic retinopathy and controls and diabetic ischaemic maculopathy. In diabetic ischaemic maculopathy patients 8 out of 16 (50%) had normal mean platelet volume and 8 patients(50%) had low mean platelet volume. Chi square test shows p value= 0.03 which shows significant low mean platelet volumes was seen in diabetic ischaemic maculopathy Previous study done by Orhan et al and another study by N Papanas et al. says MPV values of patients with proliferative Diabetic retinopathy were significantly higher than the values of control group ($p< 0.05$). They found an association between the degree of retinopathy and mean values of MPV[5]. This finding suggests a role for platelets in the pathogenesis of vascular complications . As no study was done correlating MPV with ischaemic maculopathy and only handful have been done for correlating MPV and retinopathy and these suggest high MPV associated with retinopathy as opposed to our study which suggest inverse correlation between MPV as well as retinopathy and ischaemic maculopathy . Hence in relation to MPV according to our study platelets is not an important pathway for thrombus formation in Ischaemic maculopathy.

However other studies show low MPV and normal platelet count seen in chronic renal failure. Our study shows low MPV with normal platelet count values in 8 patients in diabetic ischaemic maculopathy group and 3 patients among these have renal parameters suggesting of chronic renal failure . The renal parameters of others could not be assessed as 2 patients expired and others were lost in follow up. Hence other factors may be responsible for low MPV.

Spearman correlation of both right and left FAZ with right and left vision among the three groups analysis doesn't show any significant association between the vision and the FAZ in all the groups. This must be because their where patients with cataract and other complications like vitreous haemorrhage hence vision was influenced by multiple other factors. Spearman correlation of the worst FAZ with platelet indices like platelet count, mean platelet volume, and platelet distribution width among the three groups analysis doesn't show any significant association between the platelet indices and the FAZ of the worst eye in all the groups. This shows that platelet indices like platelet count and PDW was acting as an indicator of ischaemia but not correlating with the size of the FAZ.

Limitation of the study include Sample size being limited, We should have considered other systemic parameters like renal functions and systemic vascular complications like stroke and myocardial infarction and systemic medications in detail.Other factors involved in the thrombus formation like Protein S deficiency, Anti phospholipid antibody syndrome, High Fibrinogen levels, Higher Factor 8levels, Elevated lipids or Homocyteinelevelswerenot evaluated in this study

V. Conclusion

This study shows that Platelet count and Platelet distribution width (PDW) can be used as a simple indicators of platelet activation and can be used as a biomarker for patients at risk of developing Diabetic ischaemic maculopathy. It also shows that mean platelet volume (MPV) may not be a reliable indicator .However other factors for thrombus formation have to be ruled out to conclusively point at platelets being the primary factors responsible for ischaemic diabetic retinopathy

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