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*RESEARCH ARTICLE*

# PLATELET INDICES: INDICATORS OF DIABETIC RETINOPATHY PLATELET INDICES AS NEW BIOMARKERS IN PATIENTS OF DIABETIC RETINOPATHY

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*Abstract*

Aim and Objectives: The aim of this study is to study role of platelet indices in type 2 diabetes mellitus (T2DM) with and without diabetic retinopathy. The objectives included assessing platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio(P-LCR)within these patient categories and to comparing platelet indices among healthy controls, diabetic patients without retinopathy, and those with retinopathy. Materals and Methods : This prospective case-control study was conducted at Departments of Pathology and Ophthalmology, School of Medical Sciences & Research, Sharda Hospital, Greater Noida. Over one and a half years, 150 cases were enrolled, divided into three groups: controls, diabetic patients without retinopathy, and diabetic patients with retinopathy. The patients coming to ophthalmology opd for retina checkup, blood sample was taken. As same vial is used for both estimation of platelet indices and HBA1C, both blood investigations along with their retina findings were noted. Inclusion criteria involved adult type 2 diabetes patients,with exclusions for anemia,certain eye conditio ns,uncontrolled hypertension,cardiovascular issues, renal failure, anti-platelet drug usage, malignancy, and type 1 diabetes were made. Results: The results revealed significant variations among the groups. In controls, the majority (90%) had MPV below 12, whereas in diabetic patients without retinopathy, most (58%) had MPV ranging from 12 to 15. Among diabetic patients with retinopathy, the largest group (38%) had MPV above 15 and 56% had MPV between 12-15 fl. PDW showed similar trends, with 96% of controls having PDW below 17, while 96% of diabetic patients with retinopathy was >20 . PLCR percentages ranged within normal limits for controls but shifted towards higher values in diabetic groups. Platelet counts were consistent between control and diabetic without retinopathy groups, averaging around 252,000 x10^3/cumm, while diabetic patients with retinopathy had a slightly lower average count of approximately 242,000 x10^3/cumm



## Introduction:-

DEFINATION AND PROBLEM : Diabetes Mellitus (DM) is a major global health problem.[1]. It is a group of metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or



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both. [2] Consequential hyperglycaemia causes long term vascular complications and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels[3]. Diagnosis of DM was established using American Diabetes Association criterion of fasting blood glucose level of >=126mg/dl or 2hrs post prandial blood glucose >=140 mg/dl on two occasions or random glucose levels of >= 200 mg/dl or HBA1C of>= 5.6 [3]

**EPIDEMIOLOGY:**

According to World Health Organization (WHO) the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. [1] It is projected that by year 2025, 80.9 million will have diabetes in India[2]. Diabetic Retinopathy (DR): is one of the most important complications and leads to considerable increase in morbidity. [4] Retinopathy is defined as presence of at least 2 microaneurysms and or retinal haemorrhage, DR, the most common retinal vascular disease, is the leading cause of new blindness in adults during the third through sixth decade of life. Diabetic Retinopathy (DR): is one of the most important complications and leads to considerable increase in morbidity. [4] Retinopathy is defined as presence of at least 2 microaneurysms and or retinal haemorrhage, DR, the most common retinal vascular disease, is the leading cause of new blindness in adults during the third through sixth decade of life

Platelet Parameters: Platelet parameters like MPV, PWD, Plateletcrit (PCT), Platelet large cell ratio and platelet count are easily available [7] and are an important and easily accessible indices done in routine blood test, that reflect the size and activity of platelets.[22] .

As DM is considered as a “prothrombotic state” , altered platelet morphology and function has been observed in diabetes in the form of enhanced platelet activity . If microvascular complications like DR are detected at the earlier stages it will be useful in controlling them and protecting the patients from associated adverse events. Platelet volume indices (PVI) such as MPV, PDW, PLCR, PC are cost effective, easily available and more compliant and can be the potential biomarkers for DR . [43]

**CORRELATION WITH OTHER STUDIES AND LITERATURE RELATION OF PLATELET INDICES WITH DIABETES**

MPV is an indicator of average size and activity of platelets. Larger platelets are younger,more reactive and aggregable. Hence, they contain denser granules, secrete more serotonin and B- thromboglobulin and produce more thromboxane A2 than smaller platelets. All these can produce a pro-coagulant effect and cause thrombotic vascular complications. This suggests a relationship between platelet function specially MPV and diabetic vascular complications thus indicating changes in MPV reflect the state of thrombogenesis. High MPV is emerging a new risk factor for vascular complications of Diabetes Mellitus of which atherothrombosis plays a major role. Thus diabetes mellitus is considered a prothrombotic state with increased platelet activity.

In their study MPV was higher in diabetics as compared to the non diabeticssubjects , 8.29 +/- 0.74 fl vs. 7.47 +/- 0.73 fl p value=0.001. [10]

Platelet size heterogeneity (platelet distribution width) reflects abnormal degree of platelet anisocytosis. The exact mechanism underlying such megathrombocytosis is still uncertain but it may be result of accelerated platelet production in response to platelet destruction. [11]

Diabetic individuals showed higher numbers of platelets of extreme dimensions : very small platelets and larger platelets were more frequent compared to controls with p value of < 0.02. The shifts in platelet volume distributions were paralled by decreased expression of the alpha subunit of glycoprotein 1b by upto 17% , p value < 0.01 in platelet membranes from diabetic patients, increased expression of p selectins in thrombin stimulated diabetic patients p< 0.05 or p< 0.01. It was suggested that bimodality of platelet distribution in diabetics might arise from accelerated thrombopoiesis in diabetic subjects and this is supported by the demonstration of elevated fractions of reticulated( rich with residual RNA) platelets in diabetics ( 14.6+/- 5.6% vs 8.1+/- 2.1% p<0.025). Overall results point to a fluidity mediated platelet hypersensitivity and accelerated rate of platelet production in subjects with type 2 diabetes, which results in greater number of very large and hypersensitive younger platelets and a more abundant fraction of small exhausted platelets. [14]

MPV is related with diabetes mellitus (p<0.001) and glycemic control. (monicaverdoia, may 2014, diabetes research and clinical practice). Higher MPV in diabetic patients indicates larger platelet size suggesting stimulated

thrombopoiesis and augmented platelet activation . Platelet hyperactivity is accompanied by an increased production of thromboxaneA2, serotonine, thromboglobulin or a decreased synthesis of prostacycline. One possible mechanism of increased MPV in DM is osmotic swelling due to raised blood glucose and perhaps due to a shorter life span of platelets in diabetic patients. The MPV was significantly higher in group of diabetic patients (11.7+/-1.0 fl) than in group of non diabetics (11.2+/-1.2fl) in Indian journal of hematology blood transfusion, kumari shilpi, jan 2018). The MPV in the diabetic group was 9.34 fl and non diabetic group was 8.63 fl. Comparison for MPV values was statistically significant with p value of 0.00 in diabetics 9.34fl and in non diabetics 8.63 fl( Singapore med j,Zuberi BF, feb 2008). MPV has become an important marker/determinant of platelet function.

Platelet activity and aggregation potential which are essential in atherogenesis and thrombogenesis can be easily estimated by measuring MPV as a part of complete blood count. MPV was significantly higher in diabetics as compared to non diabetics was 9+/-0.9 fl and 8.08 +/-0.45 fl with p value <0.0001 in j of advanced med and dental research by Mukund W. Pujari, non 2017. There was significant correlation between MPV and glucose p value < 0.0001. the correlations were no longer significant in those without diabetes. The adjusted odds of diabetes rose with increasing MPV levels and were most pronounced in subjects with MPV levels exceeding 90 th percentile >= 9.31fl. the association between MPV and diabetes was most apparent in those with poorest glycemic control. MPV is strongly and independently associated with the presence and severity of diabetes.

In the American diabetes ass. Binita shah md ms,may 2012. Mean platelet volume (MPV) has been suggested as indicator of platelet reactivity and moreover, diabetics have been shown to have larger MPV. MPV was related with diabetes mellitus (p<0.001) and glycemic control (p=0.05; at linear regression r=0.07; p<0.001 for fasting glycaemia; r=0.09; p<0.001 for HbA1c, respectively) ( Diabetes research and clin pract, monicaverdoia may 2014). MPV was significantly higher and the mean platelet counts were significantly lower in diabetics compared to ageand sex-matched nondiabetic healthy controls [10.62+/-1.71 fl vs. 9.15+/-0.86 fl (P=.00), 260.38+/-68.65 x 10(9)/l vs. 292.33+/-79.19 x 10(9)/l (P=.001)], respectively.

Results show significantly higher MPV in diabetic patients than in the nondiabetic controls. (j diabetes complications, hekimsoy may 2004). MPV was significantly higher in patients with diabetes mellitus than non diabetics( 8.7+/- 0.8 fl vs 8.2+/- 0.7fl). In diabetic patients there was significant positive correlation between MPV and HbA1C levels (r= .39, p=.001). Results suggested a close relationship between poor glycemic control and increased platelet activity in patients with type 2 diabetes mellitus.(demirtunc, j of diabetes and complic. March2009).

MPV is an important is an important morphological parameters of platelets and an accessible indice in routine blood test, could reflect the size and activity of platelet. Higher MPV indicates larger platelets, which are metabolically and enzymatically more active. Females with MPV >/= 9.80 fl had 92% increased incident risk of diabetes mellitus compared with MPV <7.50 fl p value= 0.002) in ass. Of mpv in type 2 dm risk dongfeng sept 2019).

MPV a marker of platelet size is easily determined on routine automated hemograms and routinely available at low cost. MPV is simple cost effectivetool . MPV was significantly increased in diabetics (8.83+/- 0.72fl) when compared to non diabetics (7.62+/-0.47 fl) with p value = 0.001. ( JEMDSnavya bn march 2015).

The MPV is a marker of platelet size and an easily measured platelet indicator, which increase during platelet activation. In this study, the MPV was significantly higher in the diabetic patients. The prevalence of diabetes increased with the increasing MPV levels. This is consistent with other studies that have also reported the increase in MPV in diabetic patients in comparison with non-diabetic controls . The mechanism why the MPV were higher in diabetes patients was not yet fully understood . The hyperglycemia status in diabetes patients cause the osmotic swelling and lead to the increased MPV finally . The insulin may cause the generate of larger platelets by megakaryocytes . MPV was significantly higher in the subjects with diabetes (9.30 vs. 9.20 femtoliter (fL), P<0.01). iran j of pub health xiangyu sept 2017.

Mean platelet volume (MPV) is a reliable index of platelet size. MPV correlates well with the functional status of platelets. It can be used as an emerging risk marker of platelet activation. An increased MPV, which is an indicator of hyper-reactive platelets, may result from an increased platelet turnover. The MPV can be measured by hematology analyzers. MPV was 9.816±0.4 fl and 10.2±0.77 fl in non diabetics and diabetics , with p value of 0.023 . (2017, j of physio, pharmacy, pharma, swaminathan). Platelet Distribution Width(PDW) is an indicator of platelet

size which may be a sign of active platelet release. Significantly higher mean PDW in group of diabetic patients (14.3+/-2.4fl) was observed than in group of non diabetics (13.4+/-2.7fl). in ind j of hmatbldtransf may 2017 kumari shilpi).

Diabetic individuals showed higher numbers of platelets of extreme dimensions: very small platelets and larger platelets were more frequent compared to controls ( p (chi(2))< 0.03). The shifts in platelet volume distributions were paralleled by decreased expression of the alpha subunit of glycoprotein Ib (by up to 17%, p < 0.01) in platelet membranes from diabetic patients, increased expression of P-selectin in thrombin-stimulated diabetic platelets (p< 0.02), an increased number of platelet microparticles in diabetic individuals (p< 0.05 or p< 0.03 for resting or stimulated platelets, respectively), and reduced platelet membrane fluidity (by 5.2 +/- 0.6%, p< 0.01). We suggest that the distinct bimodality of platelet distribution in diabetic patients might arise from accelerated thrombopoiesis in diabetic subjects, and this is supported by the demonstration of elevated fractions of reticulated (rich with residual RNA) platelets in diabetic patients (14.6 +/- 5.6% vs 8.1 + 2.1% p(u) < 0.025).

Overall, results point to a fluidity-mediated platelet hypersensitivity and accelerated rate of platelet production in subjects with type 2 diabetes mellitus, which results in a greater number of very large and hypersensitive younger platelets and a more abundant fraction of small exhausted platelets. (j platelets c. watala 1999) Platelet distribution width was wider in T2DM (0.93, 0.09–1.76; N = 471) in diab met n research zacarrdinov 2014.

PDW levels were significantly higher in the higher HbA1c subgroup (≥ 6.5%) than that in lower subgroup (< 6.5%) (p < 0.01). in j of clin lab aug 2019 minlewu. Platelet distribution width (PDW) values revealed noticeable elevations in most treated T2DM groups. Diab n met syn,jun 2019 adelabdel). It is known that there is a definite association between platelet distribution width (PDW) in type 2 diabetes mellitus (T2DM). ( chin med j cheng ping hu 2018 april).

PDW are significantly increased in patients with type 2 DM compared to patients without type 2 DM. Platelet volume indices are an important, simple, and cost-effective tool that should be used and explored extensively. Mean PDW in our study in type 2 DM subjects was 12.19 (SD1.19),whereas in controls it was 11.27(SD1.06) .bhanukumarjpmer 2016. Platelet distribution width can be used as a moderate quality indicator of glucoregulation at best cut off value 14.55 fL with sensitivity of 45.77% and specificity of 67.86%.PDW could be used as a predictor of deterioration of glucoregulation. PDW was 13.8 fl in diabetics and 12.5fl in non diabetics with p value of 0.012.

PDW is a measure of platelet heterogeneity, which in turn may be due to aging of platelets or heterogeneous demarcation of megakaryocytes . The PDW of the diabetics was calculated to be 17.98 + 3.43 %. The PDW of the non-diabetics was 14.55 + 2.29 %.

Platelet count could be a predictor of new onset T2DM.The association between platelet count and incidence of T2DM was more prominent in subjects with IGT. Incidence of type 2 DM increased as the serum platelet count at baseline increased within the normal range. Compared to the lowest tertile, the hazard ratio (95% confidence interval [CI]) for the incidence of type 2 DM was 1.28 (1.04-1.57) for T3 after adjusting for possible confounding factors. In subjects with IGT at baseline, the hazard ratio (95% CI) for the incidence of type 2 DM in T3 compared with T1 was 1.45 (1.05-2.00) after adjusting for the same confounders. (diab research n clin parac sept 2018, jin young).

The mean platelet count for the diabetics was 235.29±76.81*10(9)/L and controls, 211.32±66.44*10(9)/L. The study revealed a higher mean platelet count for diabetics on treatment than for non diabetic controls. There was a statistically significant difference in platelet counts of diabetics and healthy controls p =0.038. There is an important role of advanced glication and its products and oxidative stress on the structure and functional disorders of platelets in diabetes. It was estimate of platelet count (PLT) for diabetics and control subjects and diabetics depending on glycated haemoglobin. In patients with type 2 diabetes mellitus, the platelet count was 216.4 x 10(9)/l in control subjects 223.60 x 10(9)/l.

PLCR indicate the percentage of large platelets with a volume >12 fL. An increase in PLCR may be an indicator of giant platelet . PLCR are calculated by platelet histogram generated by automated haematologyanalyser. These tests are simple, inexpensive, and easily available in routine laboratories and are done nearly for every patient coming to the hospital via a routine Complete Blood Count (CBC) test. PLCR was 24.6±6.77 ,36.9±6.80 in patients without

and with diabetes <0.001. (j of clin and diag research, tanimadwevedi, 2018). Platelet-large cell ratio (P-LCR) were positively correlated with HbA1c levels (all $p < 0.01$), (minlewu, j of clin lab,2019).

Platelecrit is the volume occupied by platelets in blood calculated in percentage. PCT is the volume occupied by platelets in the blood as a percentage and calculated according to the formula PCT = platelet count × MPV / 10,000 (25-27). Under physiological conditions, the amount of platelets in the blood is maintained in an equilibrium state by regeneration and elimination. The normal range for PCT is 0.22–0.24% .Platelecrit was 0.292±0.12 and 0.256±0.63 in type 2 diabetics and non diabetics. Platelet indices are a simple, easily available and cost effective tool which can aid in the early detection of diabetes.

Type 2 diabetes mellitus (T2DM) is an endocrine disease characterized by impaired insulin excretion by the pancreas and insulin resistance of body tissues. Chronic hyperglycemia leads to micro- and macrovascular complications in patients with T2DM; diabetic retinopathy (DR) is the most common and the specific microangiopathy . Abnormal insulin activation in patients with T2DM may increase platelet activation and precipitate microvascular complications . Various parameters reflect the condition of platelets, including platelet count, plateletcrit, and mean platelet indices (MPI) (mean platelet volume [MPV], platelet distribution width [PDW], and platelet large cell ratio and plateletcrit.

Diabetes mellitus (DM) is the most challenging problem in today's world. It is a complex disease characterized by chronic hyperglycemia, metabolic abnormalities, and long-term macro- and micro-vascular complications involving the blood vessels, eyes, kidneys, and nerves.Type 2 diabetes accounts for over 80% of cases of DM and is a slow onset, heterogeneous disorder resulting from interactions between environmental factors and polygenetic inheritance. Diabetic complications are mainly due to hyperglycemia and are responsible for the majority of morbidity and mortality associated with DM. Fasting blood glucose, postprandial blood glucose, and hemoglobin A1c (HbA1c) are widely used to monitor glycometabolic control in patients with DM. HbA1c is a more useful marker to determine mean blood glucose levels over a long time period.

DM is considered as a “prothrombotic state” owing to sustained hyperglycemia, dyslipidemia, and insulin resistance causing endothelial and pericyte injury. Altered platelet morphology and function has been observed in diabetes in the form of enhanced platelet activity which may contribute to this “prothrombotic state”. Larger platelets that contain denser granules are metabolically and enzymatically more active than smaller ones and have higher thrombotic potential. Hence, increased mean platelet volume (MPV) and platelet distribution width (PDW) might be linked with increased thrombotic potential. The newer hematological analyzers are giving variety of platelet parameters which helps in easy detection of change in platelet structure, which may help in early detection of prothrombotic state of the platelets. These can act as an alarm for diagnosing initiation/progression of diabetic complications. In patients with diabetes with complication MPV was 11.31fl and without complications was 9.91fl with p value of <0.0001, statistically significant.

**RELATION OF PLATELET INDICES WITH DIABETIC RETINOPATHY**

DM is a ‘prothrombotic state’ associated with accelerated atherosclerosis and inflammation. Patients with diabetes, particularly those with type 2 DM, have been shown to exhibit increasing platelet reactivity. This has been attributed to both insulin resistance and insulin deficiency. Insulin has been shown to antagonize the effect of platelet agonists like collagen, adenosine diphosphate, epinephrine and platelet activating factor.Hyperglycemia contributes to heightened platelet reactivity directly as well as through glycation of platelet proteins. In addition, hypertriglyceridemia also increases platelet reactivity. Enhanced platelet aggregation has been implicated in the development of micro- and macrovascular disease in patients with DM. Since microvascular complications of DM are important causes of morbidity and health care costs, early indication of the presence of such complications would help in reducing these adverse events. MPV was not significantly different between diabetic patients with and without complications 12.25fl and 11.77fl respectively, p value of 0.212. (j of hemat, sonali Jindal, 2011).

Diabetes is a disease of metabolism clinically expressed by chronic hyperglycemia and blood lipid and protein disorders that have been extensively reported as linked to several complications that cause morbidity and mortality. In recent years, there has been renewed interest in hematological parameters such as , mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), platelet count, platelet to lymphocyte ratio (PLR) and are designated as predictors of endothelial dysfunction and inflammation. MPV levels between patients with (n=67;

MPV=9.54±0.88) and without (n=240; MPV=9.20±0.92) retinopathy (P=0.006)while other studied hematological indices were not differ statistically (P>0.05). (int j of clin and exp med, Levent Demirtas july 2015).

Diabetic retinopathy (DR) is a very common, potentially preventable, long-term, microvascular complication of diabetes mellitus and a leading cause of visual disability and blindness.7 WHO has estimated that diabetic retinopathy is responsible for 4.8% of the 37 million cases of blindness in the world. Insulin is a natural antagonist of platelet hyperactivity. It sensitizes platelets to the inhibitory actions of prostacyclin and NO on aggregation and reduces the pro- aggregatory properties of a number of agonists - PGE1, PGE2, ADP, collagen, thrombin etc. In diabetics there is loss of sensitivity to the normal restraints exercised by prostacyclin (PGI2) and nitric oxide (NO) and increased sensitivity to proaggregatory agents thereby causing rapid platelet aggregation and adherence to vascular endothelium.14,15 Exaggerated intracellular calcium, suppressed intracellular magnesium and increased thromboxane levels present in diabetes may also lead to enhanced platelet aggregation.2,16

The endothelium may also contribute to platelet activation in diabetes by releasing von Willebrand factor, a GP constituent of the factor VIII complex, which promotes platelet clumping by binding to the platelet. Hyperglycemia can increase platelet reactivity by inducing nonenzymatic glycation of surface proteins on the platelet, by the osmotic effect of glucose and activation of protein kinase. MPV is an indicator of the average size and activity of platelets.4,7 The function of platelets seems to be related to their sizes. Larger platelets are younger, more reactive, contain more dense granules and produce large amounts of thromboxane A2 and hence exhibit hyperresponsiveness to ADP- or collagen-induced aggregation when compared with smaller and less active platelets. MPV was 8.89+/-0.73 fl in diabetic retinopathy group and 8.04+/-0.78fl without diabetic retinopathy group with p value of 0.016, statistically significant. ( ind j of clin and exp ophthal,shubhrathas hedge).

**Relation of Platelet Indices with Stages of Diabetic Retinopathy**

Diabetes duration, dyslipidemia, genetic factors, obesity, hypertension, smoking, proteinuria, and hypermetropic refractive changes may all play a role in development of DR development . Abnormal insulin activation in patients with T2DM may increase platelet activation and precipitate microvascular complications. MPV was 7.42±0.68 fL in group(control) 1, 7.84±0.76 fL in group(no DR), 7.90±0.85 fL in group(NPDR), and 8.31±0.76 fL in group (PDR). The blood samples showed a marked elevation in MPV levels in the groups with T2DM compared with controls: group 2, $p = 0.036$; group 3, $p = 0.016$; and group 4, $p < 0.01$. Patients with DR had higher MPV levels among DR stages, but the difference was significant only between group 2 and group 4 ($p = 0.036$). Mean PDW values were 12.19 ± 1.36% in group 1, 13.02 ± 1.29% in group 2, 13.49±1.18% in group 3, and 13.77±1.26% in group 4 (Table 1). There was a significant difference inPDW levels between the diabetic groups and HCs (group 2, $p = 0.003$; group 3, $p < 0.001$; and group 4 $p < 0.001$). Patients with DR had higher PDW levels among DR stages, but the difference was significant only between group 2 and group 4 ($p = 0.006$). Mean PLCR values were 28.59 ± 2.28% in group 1, 30.45 ± 2.19% in group 2, 31.31±2.15% in group 3, and 31.71±2.16% in group 4. There was a significant difference in PLCR levels between the diabetic groups and HCs (group 2, $p = 0.019$; group 3, $p < 0.001$; and group 4, $p < 0.001$). The DR groups had higher PLCR levels among DR stages, but the difference was not statistically significant ($p = 0.993$ between groups 2 and 3, $p = 0.264$ between groups 2 and 4, and $p = 0.833$ between groups 3 and 4). Mean PCT values were 0.27 ± 0.05 in group 1, 0.26 ± 0.06 in group 2, 0.25 ± 0.04 in group 3, and 0.24 ± 0.03 in group 4 . There was no statistically significant difference in PCT values between groups ($p < 0.05$). Mean platelet count was 253.76 ± 50.87 103 /$\mu$L in group 1, 253.86 ± 60.87 103 /$\mu$L in group 2, 254.77 ± 72.87 103 /$\mu$L in group 3, and 264.96 ± 64.44 103 /$\mu$L in group 4. There was no statistically significant difference in platelet counts between groups ($p < 0.05$).

According to logistic regression analysis, there was a 0.91-fold increase in the risk of retinopathy development (OR: 0.913; $p = 0.07$) and a 1.14-fold increase in the risk of proliferative DR (OR: 1.148; $p = 0.06$) as the MPV value increased. There was a 3.10-fold increase in the risk of retinopathy development (OR: 3.106; $p = 0.002$) and a 1.90-fold increase in the risk of proliferative DR (OR: 1.908; $p = 0.005$) as the PDW value increased. There was a 0.67-fold increase in the risk of retinopathy development (OR: 0.676; $p = 0.07$) and a 0.64-fold increase in the risk of proliferative DR (OR: 0.645; $p = 0.06$) as the PLCR value increased. (j of ophthl, Relationship between Altered Platelet Morphological Parameters and Retinopathy in Patients with Type 2 Diabetes Mellitus toga yilmaz, ahu yilmaz, ; Accepted 4 April 2016).

The mean ages of the diabetic patients and the control group were 52.56±8.79 and 51.76±7.90 years, respectively. There was no statistically significant difference between the groups with respect to the age (p>0.05). Mean values

for MPV in diabetic and control groups were 7.96±0.76 fL and 7.52±1.01 fL, respectively (Figure 1). The difference between the groups was statistically significant (p 0.05). Mean values for MPV in patients with background, nonproliferative and proliferative DRP were 7.76±0.72 fL, 7.94±0.61 fL and 8.18±0.89 fL, respectively. One way ANOVA test revealed a significant difference between groups (p< 0.05). Subsequently applied post hoc (Tukey HSD) test showed that mean MPV values of the patients with proliferative DRP were significantly higher than the healthy controls (p0.05). Despite the lack of significant difference between mean values of MPV in patients with proliferative, non-proliferative and background DRP, mean values of MPV for the patients with proliferative DRP were found to be higher. Significant correlation was found between the degree of retinopathy and mean values of MPV (r= 0.214, p<0.05). (Association of Mean Platelet Volume WithThe Degree of Retinopathy in Patients with Diabetes Mellitus, Orhan Ateş1 ,İlhami Kiki2 ,Habip Bilen2 , Mustafa Keleş2 , İbrahim Koçer1 , Destan Nil Kulaçoğlu1 , Orhan Baykal, Eur J Gen Med 2009;6(2):99-102).

Diabetic retinopathy (DR) is the most common complication of diabetes mellitus (DM). It has long been recognized as a microvascular disease. The diagnosis of DR relies on the detection of microvascular lesions. The treatment of DR remains challenging. The advent of anti-vascular endothelial growth factor (VEGF) therapy demonstrated remarkable clinical benefits in DR patients; however, the majority of patients failed to achieve clinically-significant visual improvement. Therefore, there is an urgent need for the development of new treatments. Laboratory and clinical evidence showed that in addition to microvascular changes, inflammation and retinal neurodegeneration may contribute to diabetic retinal damage in the early stages of DR. Further investigation of the underlying molecular mechanisms may provide targets for the development of new early interventions. Here, we present a review of the current understanding and new insights into pathophysiology in DR, as well as clinical treatments for DR patients. Recent laboratory findings and related clinical trials are also reviewed.

Diabetic retinopathy (DR) is a major complication of diabetes mellitus (DM), which remains a leading cause of visual loss in working-age populations. The diagnosis of DR is made by clinical manifestations of vascular abnormalities in the retina. Clinically, DR is divided into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR represents the early stage of DR, wherein increased vascular permeability and capillary occlusion are two main observations in the retinal vasculature. During this stage, retinal pathologies including microaneurysms, hemorrhages and hard exudates can be detected by fundus photography although the patients may be asymptomatic. PDR, a more advanced stage of DR, is characterized by neovascularization. During this stage, the patients may experience severe vision impairment when the new abnormal vessels bleed into the vitreous (vitreous hemorrhage) or when tractional retinal detachment is present. The most common cause of vision loss in patients with DR is diabetic macular edema (DME).

DR has long been recognized as a microvascular disease. Hyperglycemia is considered to play an important role in the pathogenesis of retinal microvascular damage. Multiple metabolic pathways have been implicated in hyperglycemia-induced vascular damage including the polyol pathway, advanced glycation end products (AGEs) accumulation, the protein kinase C (PKC) pathway and the hexosamine pathway [3].

The earliest responses of the retinal blood vessels to hyperglycemia are dilatation of blood vessels and blood flow changes. These changes are considered to be a metabolic autoregulation to increase retinal metabolism in diabetic subjects [4]. Pericyte loss is another hallmark of the early events of DR. Evidence of apoptosis of pericytes triggered by high glucose has been shown in both in vitro and in vivo studies [5,6]. Since pericytes are responsible for providing structural support for capillaries, loss of them leads to localized outpouching of capillary walls. This process is associated with microaneurysm formation, which is the earliest clinical sign of DR [7]. In addition to pericyte loss, apoptosis of endothelial cells and thickening of the basement membrane are also detected during the pathogenesis of DR, which collectively contribute to the impairment of the BRB [8]. Furthermore, pronounced loss of pericytes and endothelial cells results in capillary occlusion and ischemia

Retinal ischemia/hypoxia leads to upregulation of VEGF through activation of hypoxia-inducible factor 1 (HIF-1) [9]. Other evidence suggested that phospholipase A2's (PLA2) elevation under the diabetic condition also triggers upregulation of VEGF [10]. VEGF, a key factor involved in the progression of PDR and DME, is believed to increase vascular permeability by inducing phosphorylation of tight junction proteins such as occludin and zonula occludens-1 (ZO-1) [11]. Moreover, as an angiogenic factor, VEGF promotes proliferation of endothelial cells through activation of mitogen-activated protein (MAP) [12]. Enhanced expression of VEGF has been detected in the retina of diabetic mouse, as well as the vitreous of patients with DME and PDR [13,14,15].

Other angiogenic factors such as angiopoietins (Ang-1, Ang-2) are also involved in the regulation of vascular permeability by interacting with endothelial receptor tyrosine kinase Tie2 [16]. Ang-2, antagonist of Tie2, has been shown to promote vascular leakage in the diabetic rat retina [17]. It is speculated that angiogenic factors besides VEGF might be involved in the alteration of microvasculature during DR; thus, they may provide novel therapeutic targets.

**Inflammation:**

Inflammation plays an essential role in the pathogenesis of DR. Chronic low-grade inflammation has been detected widely in different stages of DR in both diabetic animal models and patients [18,19]. Leukostasis has been recognized as a key process in the early stage of DR. In 1991, Schröder et al. first reported the occlusion of retinal microvasculature by monocytes and granulocytes in streptozotocin (STZ)-induced diabetic rats [20]. Increased adherence of leukocytes was detected in the retinal vasculature as early as three days after induction of diabetes in rats [21]. The researchers also found that increased leukostasis is spatially correlated with endothelium damage and BRB impairment in diabetic rats [20]. Further studies demonstrated that leukostasis contributed to endothelial cell loss and breakdown of BRB through the Fas (CD95)/Fas-ligand pathway [22].

Leukocyte-endothelium adhesion mediated by adhesion molecules has been implicated in leukostasis in diabetes. Increased leukocyte adhesion and upregulated expression of leukocyte b2-integrins CD11a, CD11b, and CD18 were reported in diabetic rats and patients [23,24]. Additionally, endothelial cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM)-1 and selectins (E-selectin) are also found to be increased in diabetic animals and patients [18,25,26] Expression of VCAM-1 and E-selectin in the plasma of patients is correlated with the severity of DR [18]. Genetic deficiency of CD18 or ICAM-1 resulted in significantly reduced adherent leukocytes [27]. Inhibition of CD18 or ICAM-1 with anti-CD18 F(ab9)2 fragments or antibody decreased retinal leukostasis and vascular lesions in diabetic rats [18,27].

Chemokines, which regulate the attraction and activation of leukocytes, have also been shown to be involved in the pathogenesis of DR. Chemokines such as monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1alpha (MIP-1α), and MIP-1β have been reported to be elevated in diabetic patients [28]. MCP-1 deficiency leads to reduced retinal vascular leakage in diabetic mice [29]. Furthermore, inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-8 and IL-1β were significantly upregulated in diabetic patients, and their expression level was correlated with the severity of DR [30,31].

Retinal glial cell dysfunction is also presumed to be involved in the initiation and amplification of retinal inflammation in DR [32]. Glial cells in the retina including astrocytes, Müller cells and microglia are responsible for providing structural support and maintaining homeostasis in the retina [33]. Under hyperglycemic stress, microglia is activated, followed by increased secretion of TNF-α, IL-6, MCP-1 and VEGF [32]. Later involvement of Müller cells and astrocytes is associated with the amplification of inflammation responses by producing proinflammatory cytokines [33].

**Retinal Neurodegeneration:**

Retinal neurodegeneration is an early event during the progression of DR. Apoptosis of retinal neurons can be observed in diabetic rats as early as one month after induction of diabetes [34]. Upregulation of pro-apoptotic molecules such as cleaved caspase-3, Bax and Fas has been detected in retinal neurons in diabetic animals and subjects [35,36,37]. Mitochondrial dysfunction has been implicated in retinal degeneration in DR.

In donor eyes of diabetic subjects, retinal expression of pro-apoptotic mitochondrial proteins such as cytochrome c and apoptosis-inducing factor (AIF) were found to be significantly increased . In vitro studies demonstrated that high glucose exposure was associated with increased mitochondrial fragmentation and cell apoptosis. In addition to mitochondrial damage, involvement of oxidative stress in diabetes-induced retinal degeneration has also been widely investigated. In the diabetic mouse retina, reactive oxygen species (ROS) generation is significantly increased. Suppression of ROS generation effectively inhibited visual impairment and caspase-3-mediated retinal neuronal apoptosis.

There is growing evidence that retinal neurodegeneration may be an independent pathophysiology of DR. In a mouse model of diabetes, loss of ganglion cells and reduction in retinal thickness were observed preceding the presence of microvascular alterations . In diabetic patients, inner retinal thinning was detected with no DR or

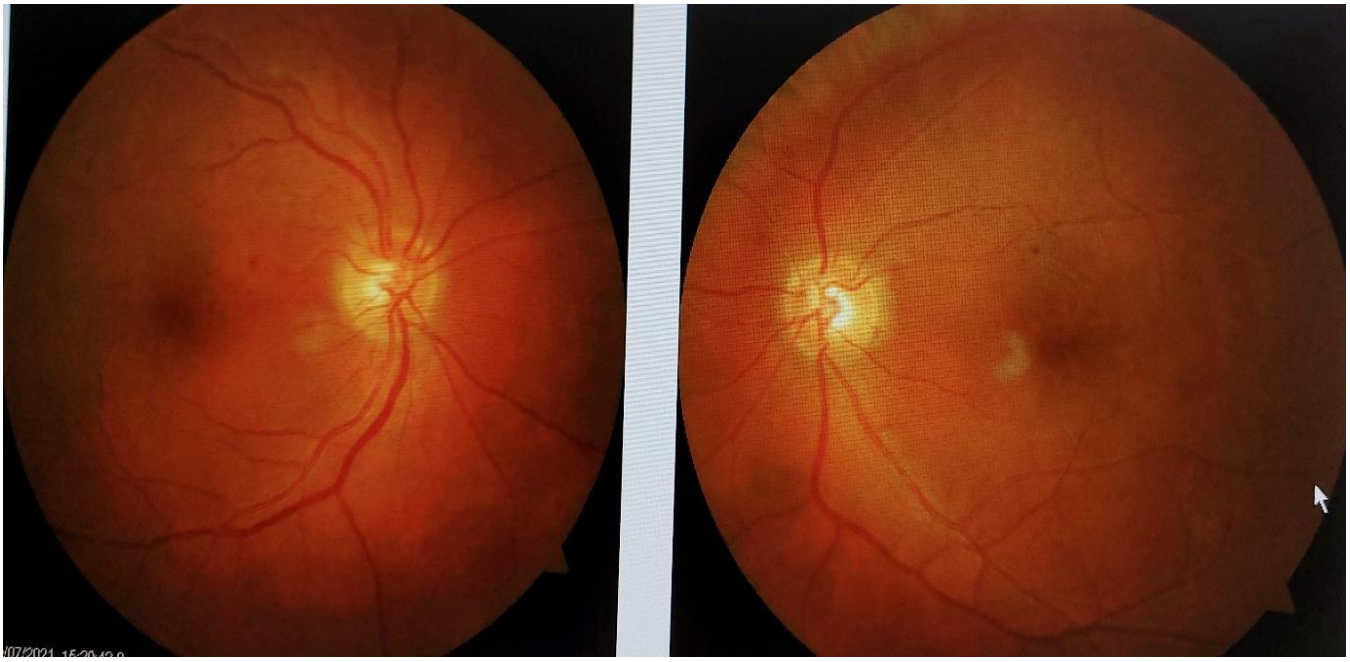
minimal DR (microaneurysms) . Therefore, further investigation of the molecular mechanisms underlying retinal neurodegeneration may provide potential therapeutic targets for early intervention in DR.

## Materials and Methods:-

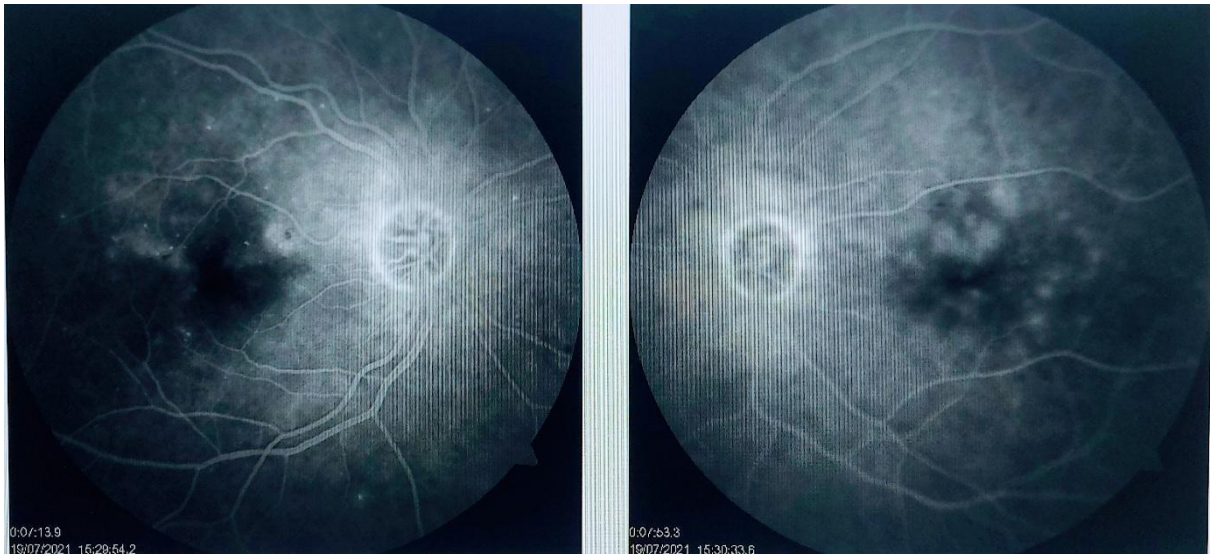
**Source of Data:** The study was carried out in the Department of Pathology in collaboration with Ophthalmology Department, School of Medical Sciences & Research, Sharda University and Sharda Hospital, Greater Noida.
**Study Period** –One and a half year Sample Size– 150 cases
**Study Design** – Prospective Case-Control Study
**Equipments:**
• Automated Blood Cell Analyser SysmexXN1000
• Fully automatic Biochemistry analyzer, Vitros 5600 (Johnson & Johnson-USA)
• High performance liquid chromatography (HPLC D10)
• Bio-Rad D10
• Direct ophthalmoscope
• Slit lamp Appasamy Associates Model Aaru-2000
• Fluorescent FFA Zeiss Visu Cam 500

The study will be carried out in the Department of Pathology in collaboration with Ophthalmology at School of Medical Sciences & Research, Sharda University and Sharda Hospital, Greater Noida for a period of one and a half year.50 normal age and se matched controls were also taken having normal blood sugar levels and HbA1C values. Another 50 patients were selected from the ophthalmology opd. The patients undergoing retina checkup or already diagnosed cases of diabetes were taken. The patients undergoing retina checkup , blood sample was taken for those patients. As same vial is used for both HBA1C and platelet indices, that is lavender, a single random sample was taken .Also their fundoscopy, optical coherence tomography anf fundus flouroscein angiography was performed. Both blood investagations and fundus findings were noted and correlated.

**Image of Case 1 Both eyes moderate NPDR, with diabetic macular edema Fundus photography**



**Both eyes**: Disc normal, A: V: 2:3, MICROANEURYSMS along with few dot haemorrhages seen, foveal reflex blunted

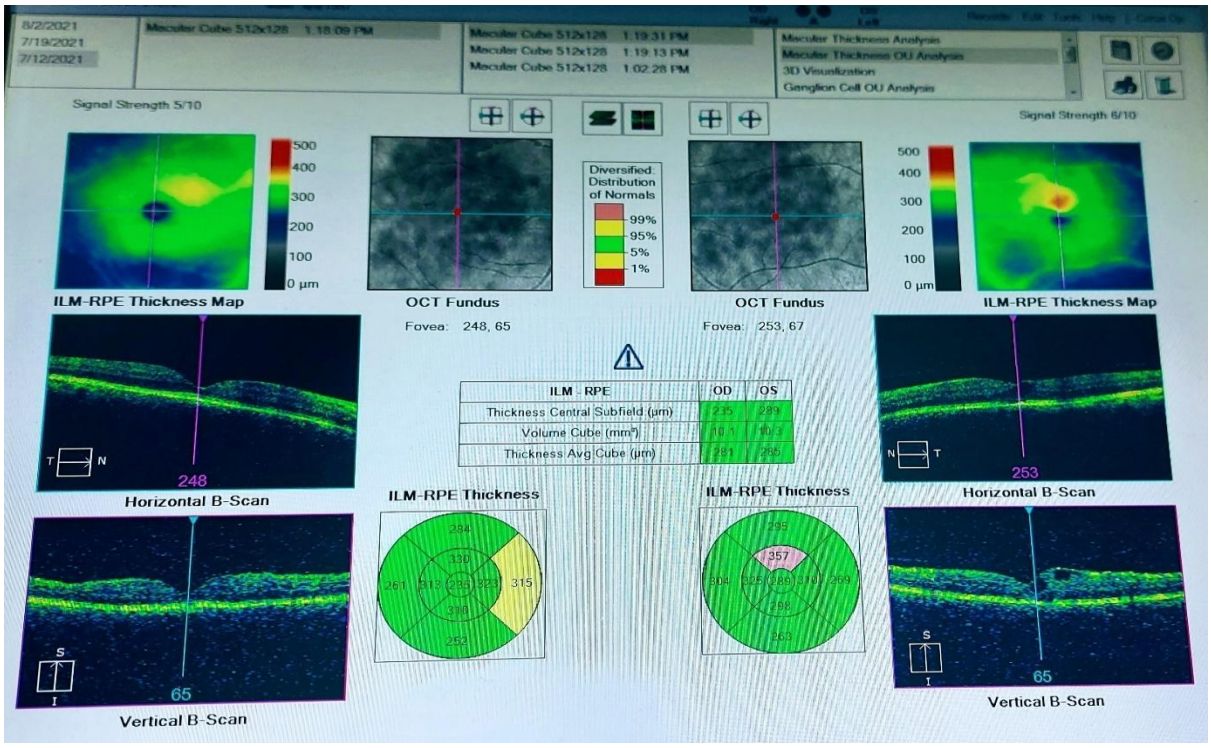


**FFA s/o**

**RE:** multiple hyperfluorescent lesions seen in all 4 quadrants in early phases s/o microaneurysms, with extrafovealhyperfluorescent lesions showing increase in size and intensity in late phases of angiogram s/o leakage ( leaking microaneurysms depicting macular edema )

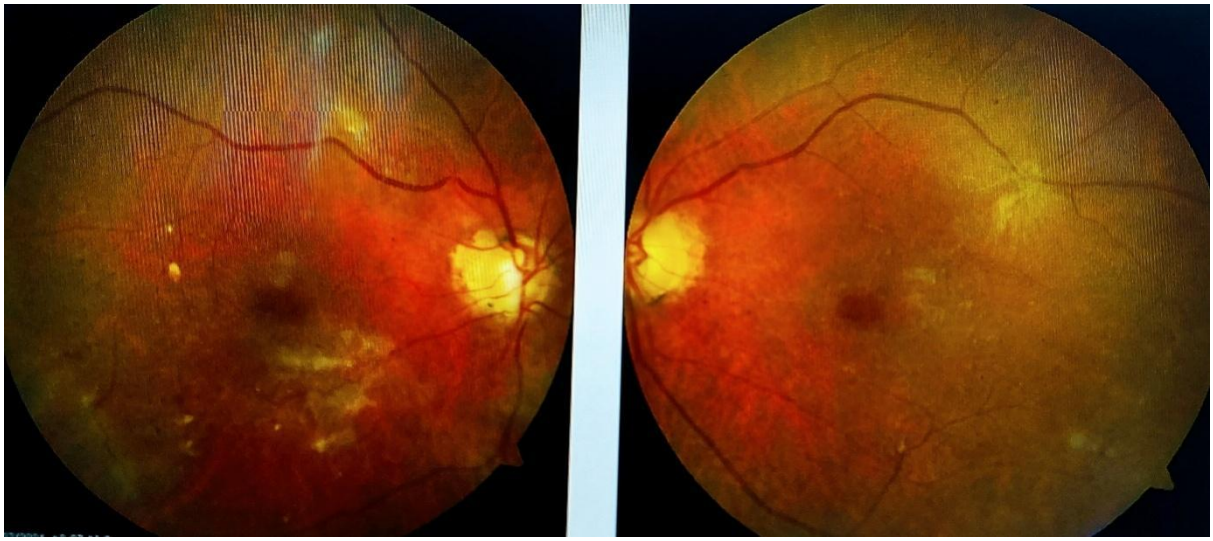
**LE** : multiple hyperfluorescent lesions seen in all 4 quadrants in early phases s/o microaneurysms, with juxtafoveal and extrafovealhyperfluorescent lesions showing increase in size and intensity in late phases s/o leakage (LE>>RE) ( leaking microaneurysms depicting macular edema )

**OCT**



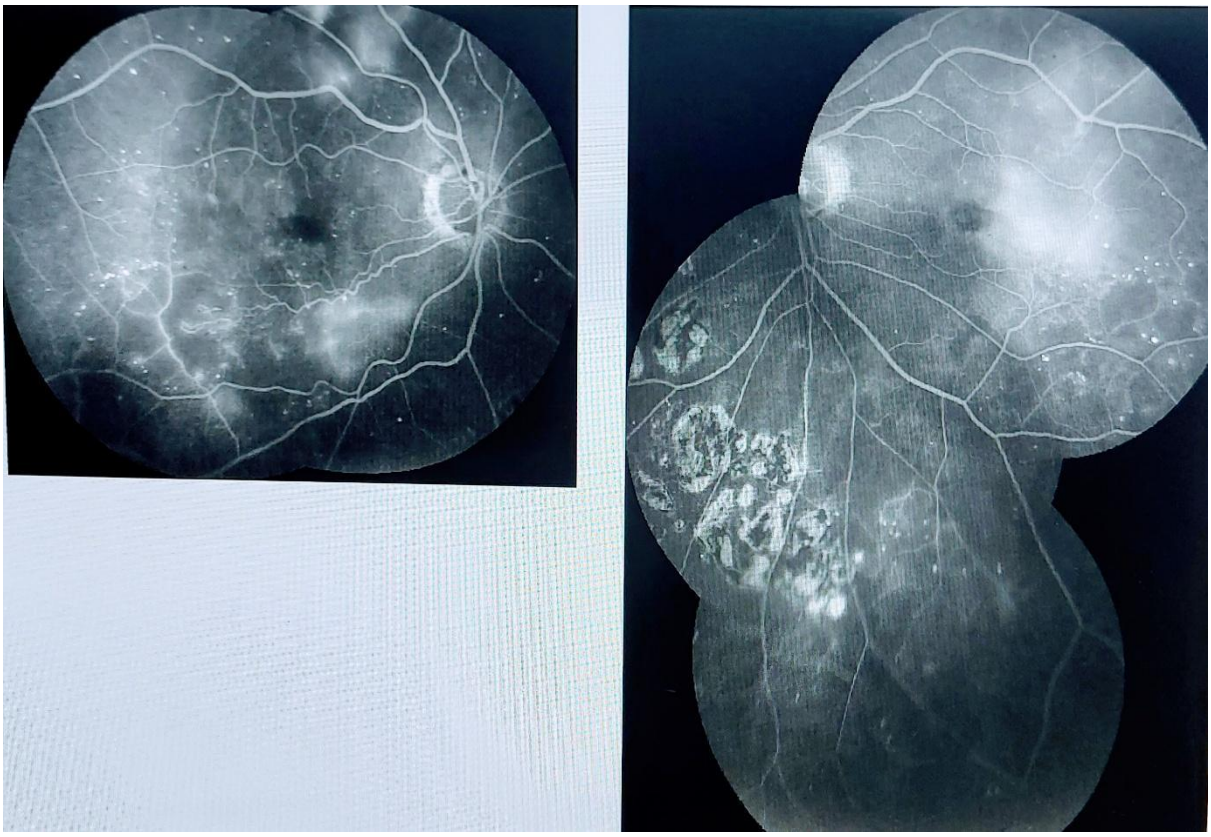
**RE :** s/o Non Centre Involving Diabetic Macular Edema (Non CI-DME), Central sub foveal thickness : 235 microns
**LE**: Cystoid intraretinal spaces seen mainly superior to fovea and also subfoveally s/o Centre Involving Diabetic Macular Edema (CI- DME) , Central Subfoveal Thickness (CSFT) : 290 microns. Same patient had MPV 14.5, PLCR 55.2 , PDW 24.5, and HBA1C of 10.8, average blood glucose of 250, platelet count 236.

**Pt2 partially lasered PDR with DME (LE>RE) Fundus Photography:**



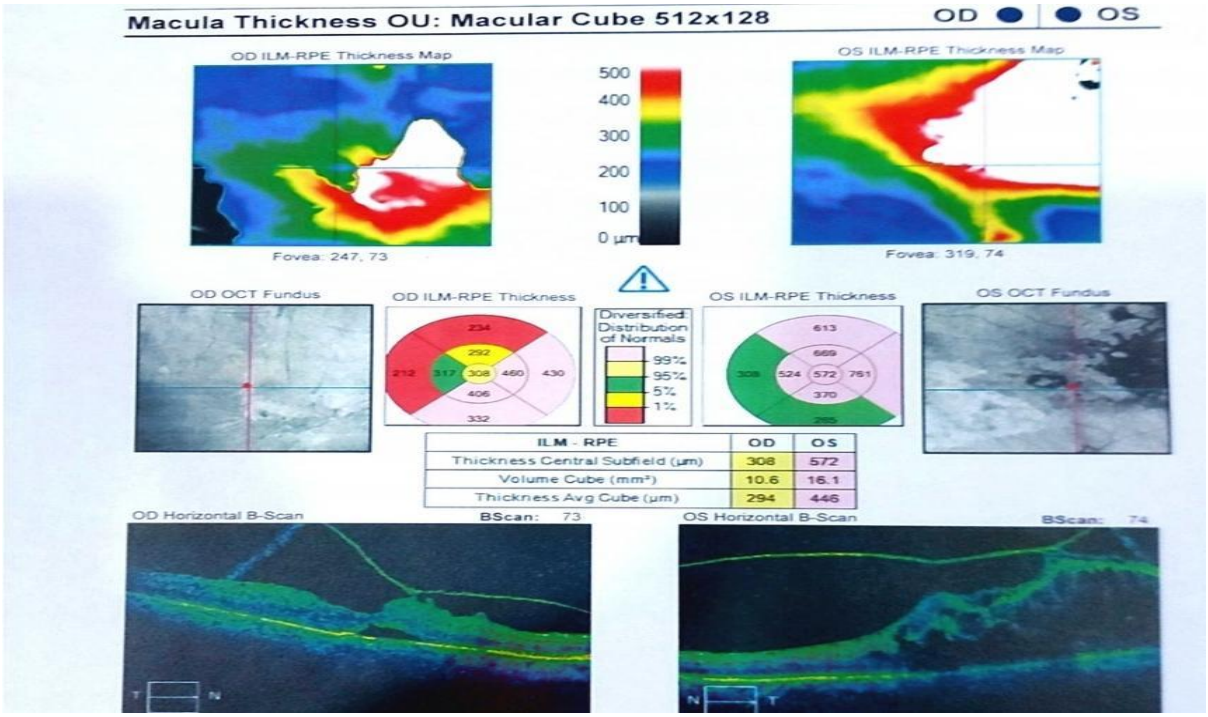
**RE:** Cup Disc Ratio (CDR): 0.9, A:V:: 2:3, Scattered laser scars (PanRetinal Photocoagulation) seen beyond temporal arcades , FVP (Fibrovascular proliferation) seen inferonasal to fovea , with hard exudates temporal to fovea and blunted foveal reflex, s/o Partially lasered PDR

**LE:** Cup Disc Ratio (CDR) : 0.9, A:V:: 2:3, Scattered Laser scars seen beyond arcades, FVP seen along Superotemporal arcade, blunted foveal reflex s/o Partially lasered PDR



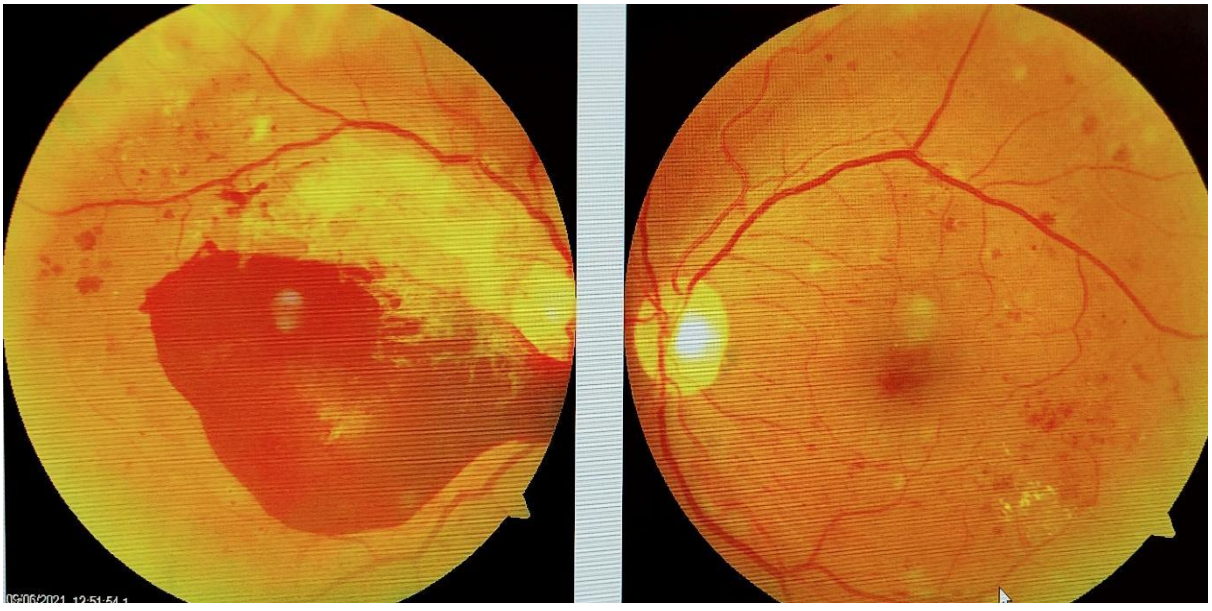
**FFA RE** :Neovascularisation elsewhere (NVEs) seen along temporal arcades, with few capillary dropout areas/ capillary non perfusion areas (CNP) , with staining of laser scars in inferior midperiphery. Mild late macular leakage seen .

**LE:** staining of laser scars seen inferiorly . No NVD (Neovascularisation at Disc)/NVE noted. Temporal diffuse macular leakage seen in late phases of angiogram, with few CNP areas.




**OCT**

**RE:** Focal ParafovealVitreomacular Traction (VMT) , with shallow subfoveal Neurosensory detachment (NSD),
**CSFT :** 308 Microns s/o CI-
**DME LE:** Focal Parafoveal VMT , with cystoid macular edema (CME) mainly temporally, reaching upto the centre**.**
**CSFT :** 572 microns, s/o CI-DME Same patient had MPV 17, PLCR 57, PDW 26, Platelet count 258, HBA1C of 11.1 Pt 3 Right eye PDR with premacularsubhyaloidhaemorrhage. , Left eye Severe



**NPDR.**

**Fundus Photograph** :

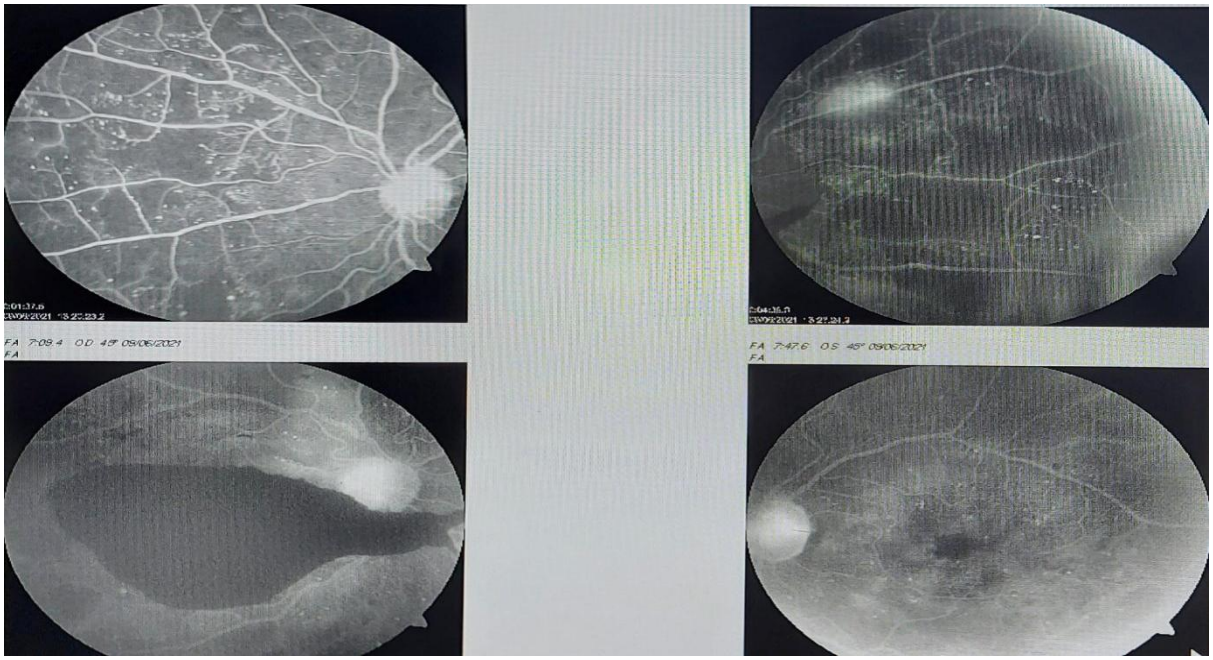
**RE :** Disc normal, A:V::2:3, multiple microaneurysms and dot-blot haemorrhages seen, fibrous proliferation seen beneath Superotemporal arcade, with a large subhyaloidpremacularhaemorrhage( approx. : 8 Disc Diameter in size) , s/o Proliferative Diabetic Retinopathy

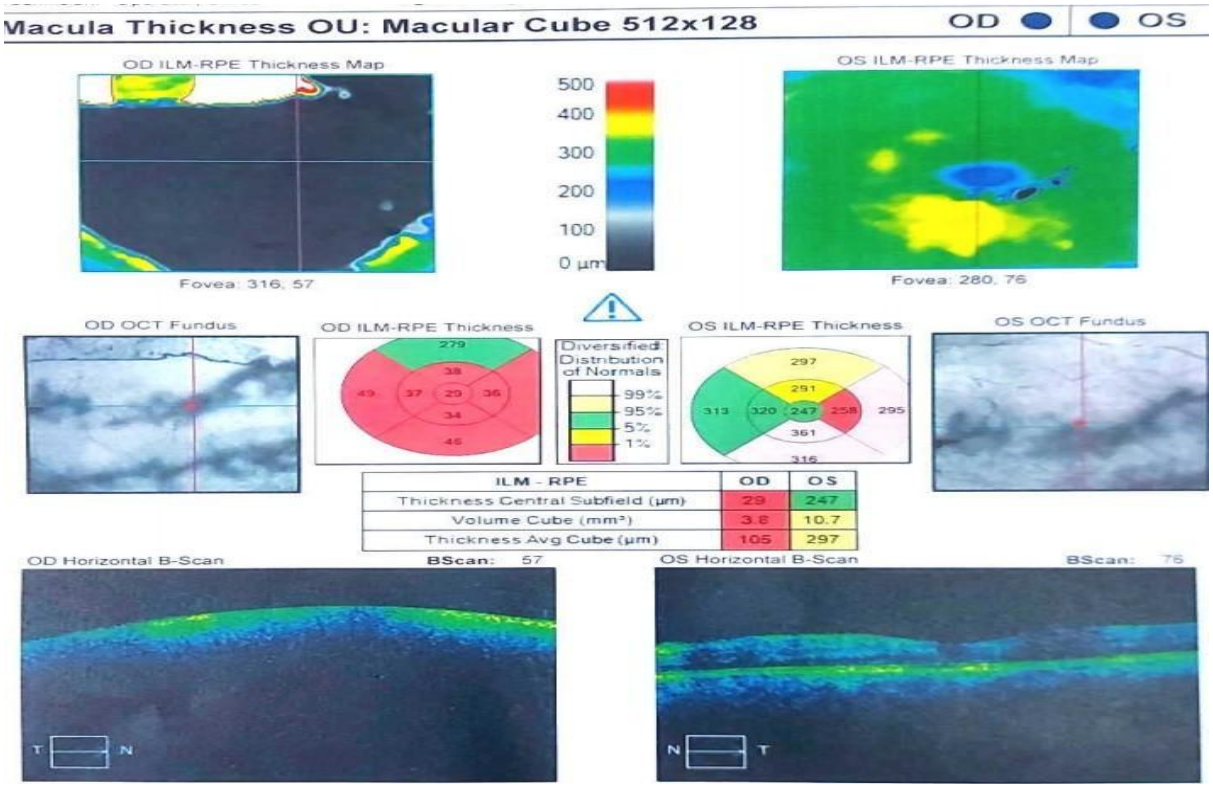
**LE :** : Disc normal, A:V::2:3, multiple microaneurysms and dot-blot haemorrhages seen with few exudates in the background. No NVD/NVE seen clinically. Blunted foveal reflex seen FFA

**RE:** Leakage seen from NVE nasal to disc, with multiple CNP areas, s/o PDR, with blocked fluorescence at macula d/t Premacularhaemorrhage

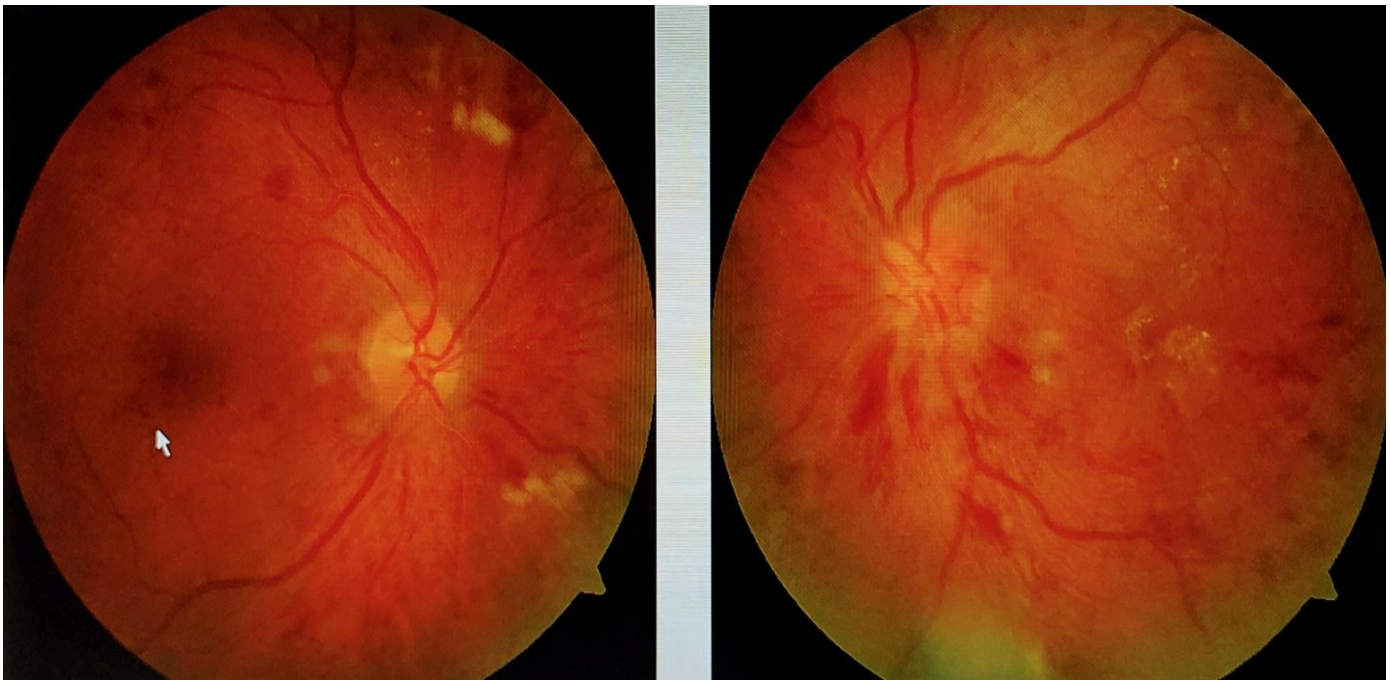
**LE:** Multiple CNP areas seen nasally, with mild diffuse leakage at macula in late phases of angiogram. No NVD/NVE seen.

**Oct**

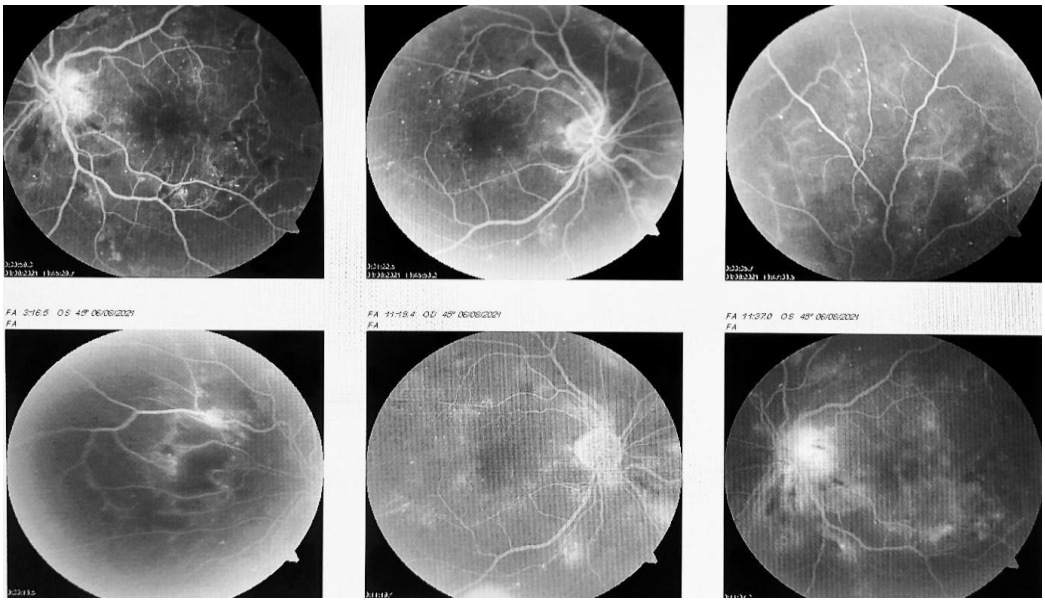


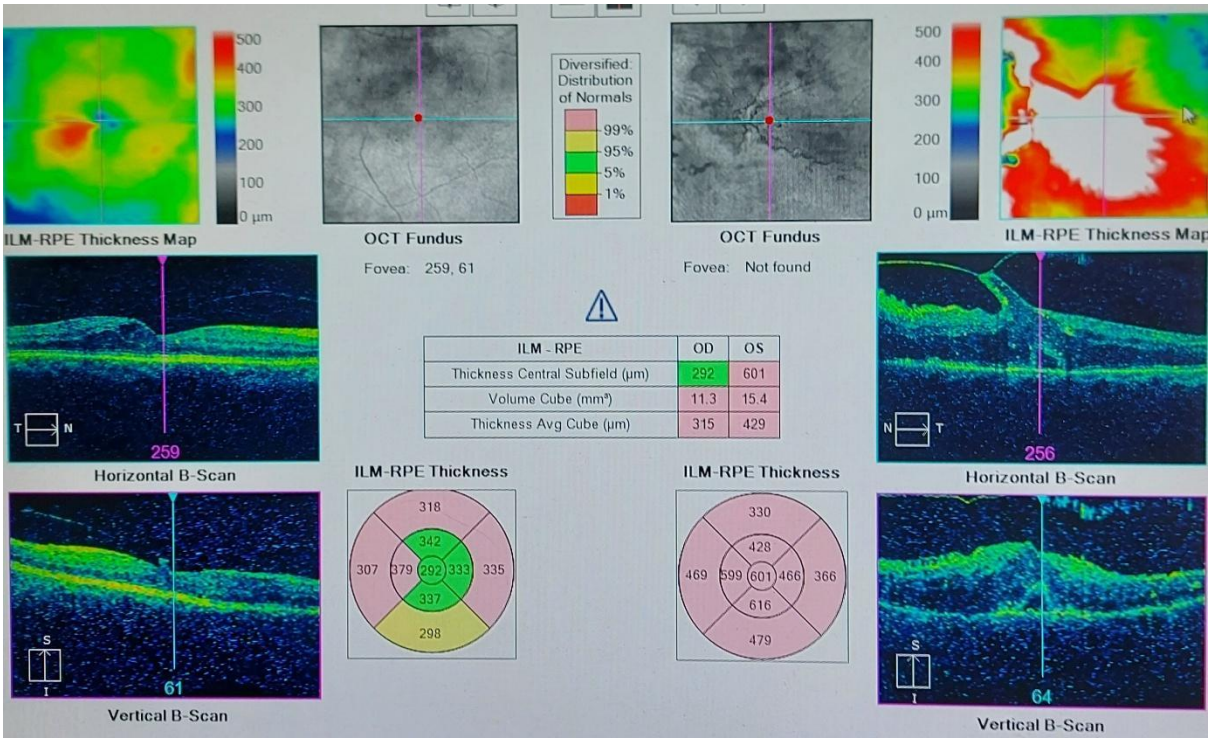


**OCT**
**RE:**Hyperreflectivity seen anterior to macula with posterior shadowing s/o premacularsubhyaloidhaemorrhageLE:
**CSFT** : 247 micron . Parafoveal spongiform edema seen superiorly and inferiorly (Inferior >> superior), s/o Non CI DME Same patient had MPV 22, PLCR 54, PDW 27, Platelet count 309 on high range.
Pt 4 60 Yrs severe NPDR, macular edema, disc edema Fundus photography : RE: Disc normal, A:V::2:3, multiple microaneurysms with peripapillary cotton wool spots seen (soft exudates) , with blunted foveal reflex. No NVD/NVE seen clinically.



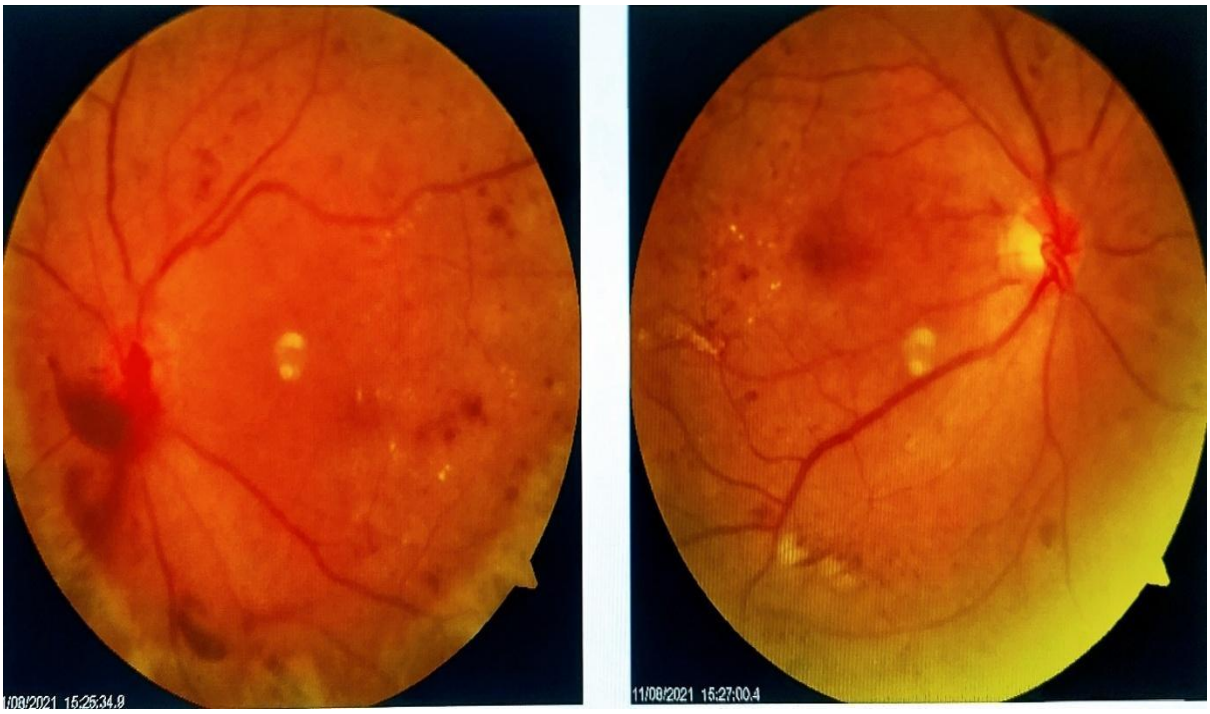
**LE:** Disc margins blurred s/o disc edema, A:V:: 2:4, with mild dilatation and tortuosity of retinal veins, with both superficial and dot blot retinal haemorrhages, with few hard exudates seen at macula . No NVD/NVE seen clinically.RE : Multiple leaking microaneurysms with few CNP areas, No NVD/NVE noted s/o NPDR. Mild late macular leak seen d/t leaking microaneurysms.LE: Multiple leaking microaneurysms with massive CNP areas seen in mid periphery and periphery with doubtful NVE nasal to disc, with Disc Leak , likely PDR with Diabetic papillopathy. Diffuse late macular leakage seen.





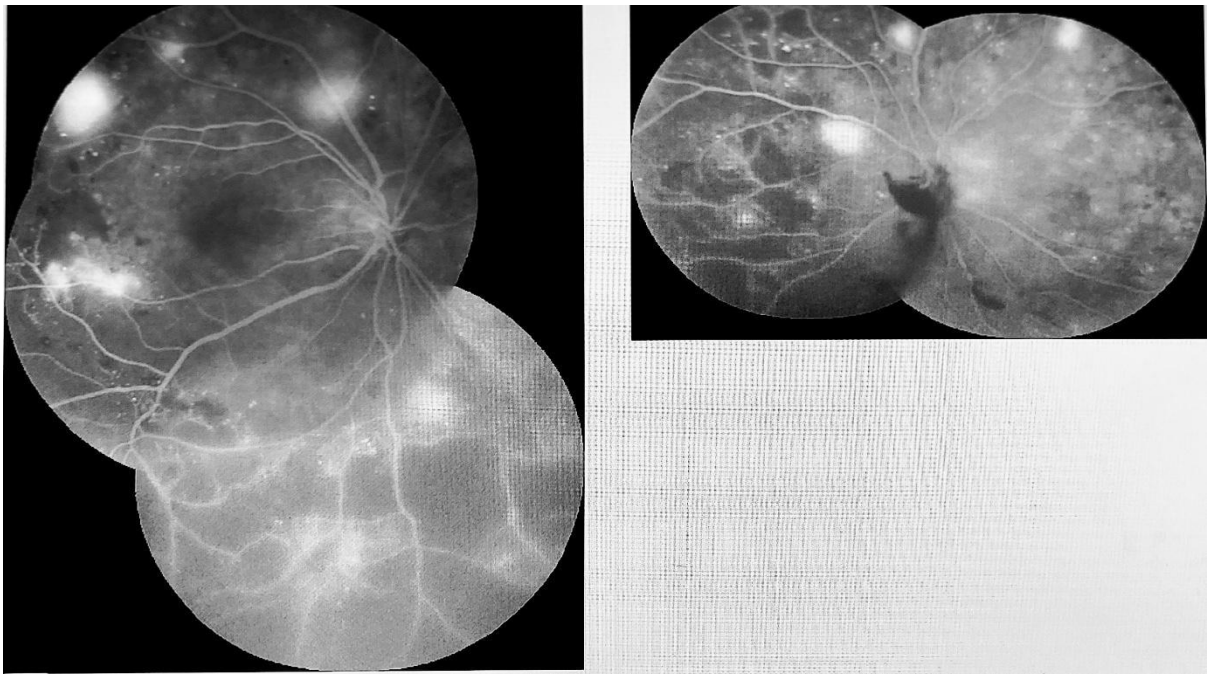

**RE:** Parafoveal Cystoid macular edema seen .CSFT : 292 microns , s/o Mild CI-DME.LE: Focal VMT , with globally adherent Epiretinal membrane (ERM), with spongiform macular edema with shallow subfoveal NSD. CSFT : 601 Micron , s/o Tractional CI-DME. Same patient had MPV 19, PLCR 56, PDW 24, Platelet count 315 which correlated with retinopathy findings as they were on higher limits.

**Pt 5 Both eyes PDR, with DME**
**Fundus Photography**



**RE :** Multiple microaneurysms with dot blot retinal haemorrhages , and hard exudates temporal to fovea, seen on fundus photography . Flat network of vessels, likely NVEs seen .

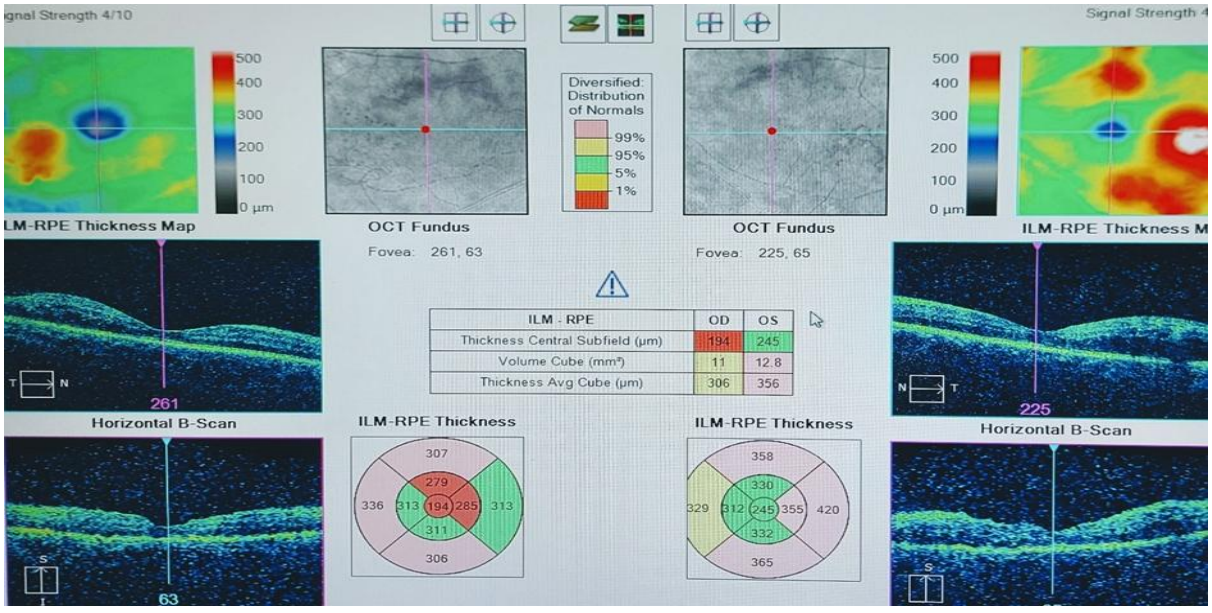
**LE:** Background changes of diabetic retinopathy, with Vitreous Haemorrhage (overlying the optic disc and inferiorly) .



**FFA**

**RE :** Multiple hyperfluorescent lesions with profuse leakage in late phases , s/o NVEs seen , along with significant CNP areas. There is enlargement of foveal avascular zone (FAZ), s/o Macular Ischemia.

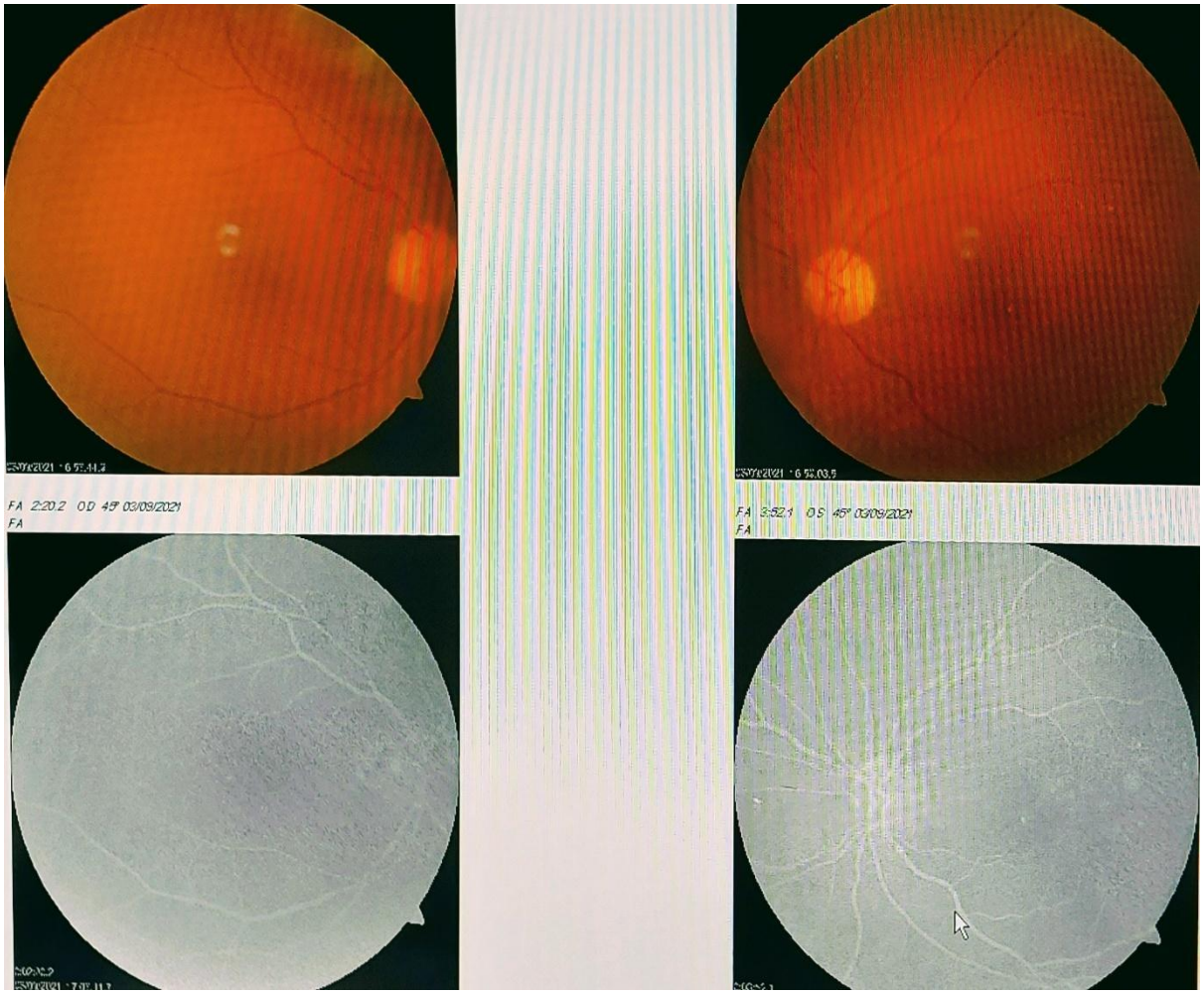
**LE**: hyperfluorescent lesions with profuse leakage in late phases , s/o NVEs seen , along with significant CNP areas in nasal quadrant. There is blocked fluorescence overlying the Optic Disc and inferiorly (due to Vitreous Haemorrhage). The Macula shows diffuse leakage in the late phases.




**OCT**

**RE:** Foveal Thinning with mild parafoveal spongiform edema (mainly temporal and inferior to fovea) .CSFT : 194 microns, s/o Foveal Thinning with non CI-DME. LE: Parafoveal spongiform edema (mainly temporal and inferior to fovea, and mild edema superior to fovea) .CSFT : 245 microns, s/o Non CI DME.Same patient had MPV 22, PLCR 57, PDW 20, Platelet count 322 ,HBA1C 12.5 correlated with retinoscopy findings.

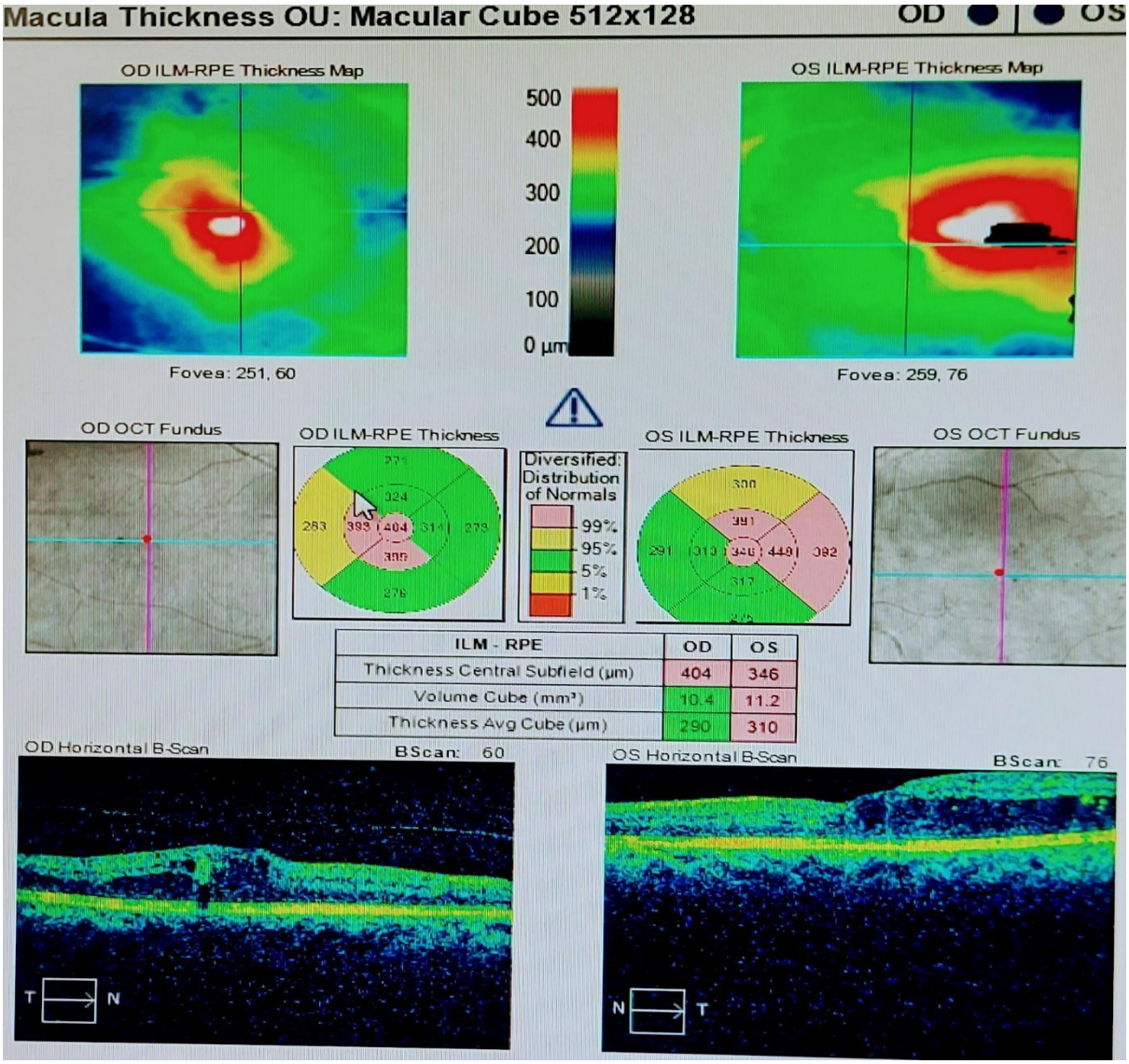
**Pt 6 70 yrs, Moderate NPDR, with DME.**




**Fundus photography RE:**
Disc normal, A:V::2:3, Microaneurysms with retinal haemorrhages seen. (Note : the hazy pictures are due to cataract ). Foveal reflex is blunted. LE : Disc normal, A:V::2:3, Microaneurysms with retinal haemorrhages seen. (Note : the hazy pictures are due to cataract LE

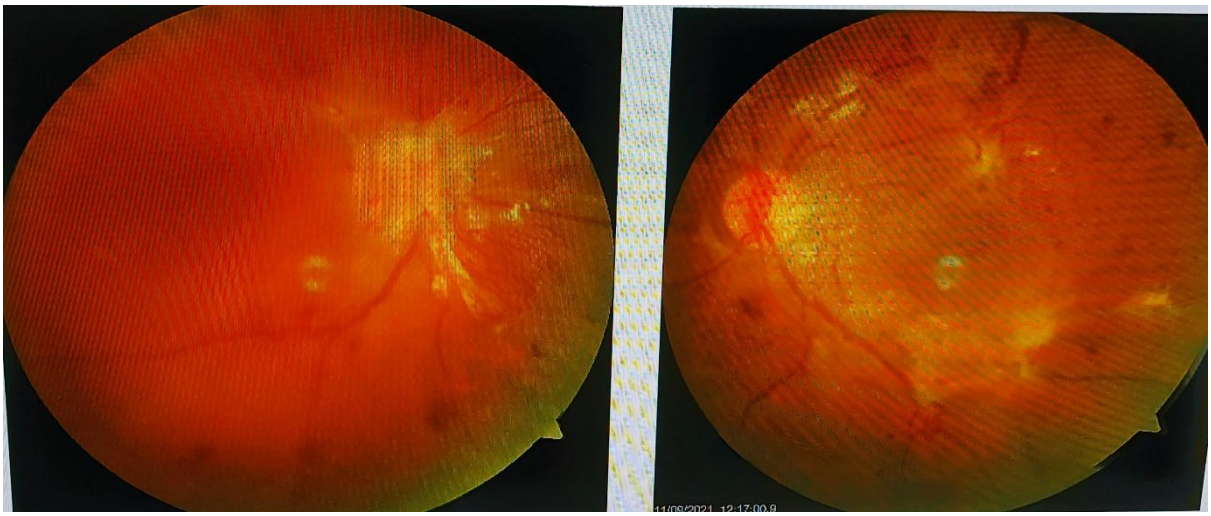
**FFA**
**RE:** Hazy media with hyperfluorescent lesions s/o Microaneurysms. Macula details are hazy d/t cataract. LE: Hazy media with hyperfluorescent lesions s/o Microaneurysms, seen. Mild leakage at macular region seen hazily.

**OCT :**

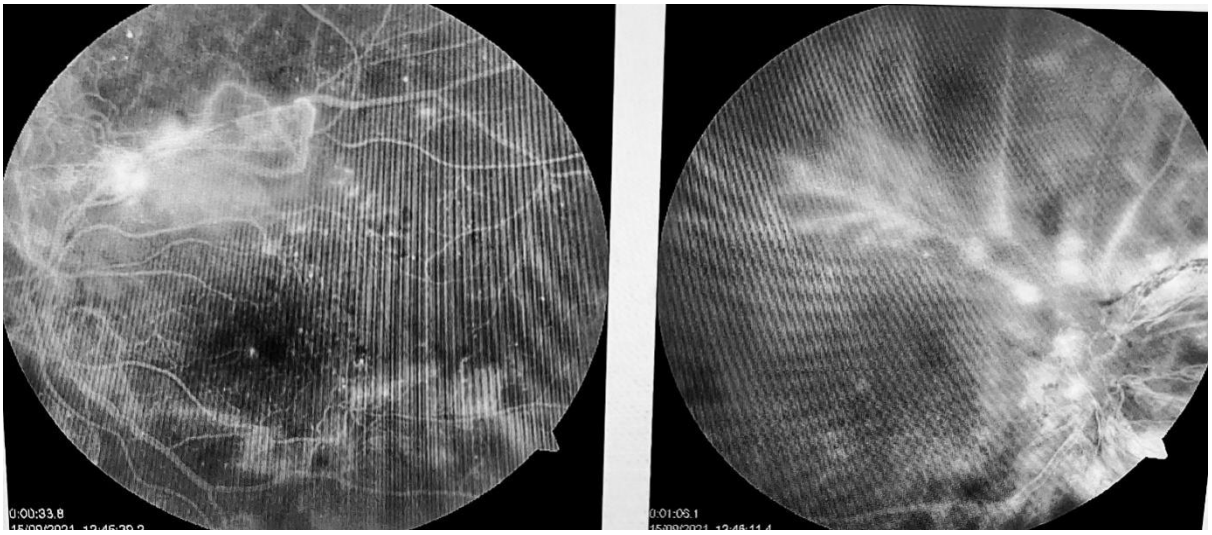



**RE:** Blunting of foveal contour with retinal thickening with intraretinalhyporeflective spaces, s/o Cystoid macular edema .CSFT : 404 microns ( CI-DME)

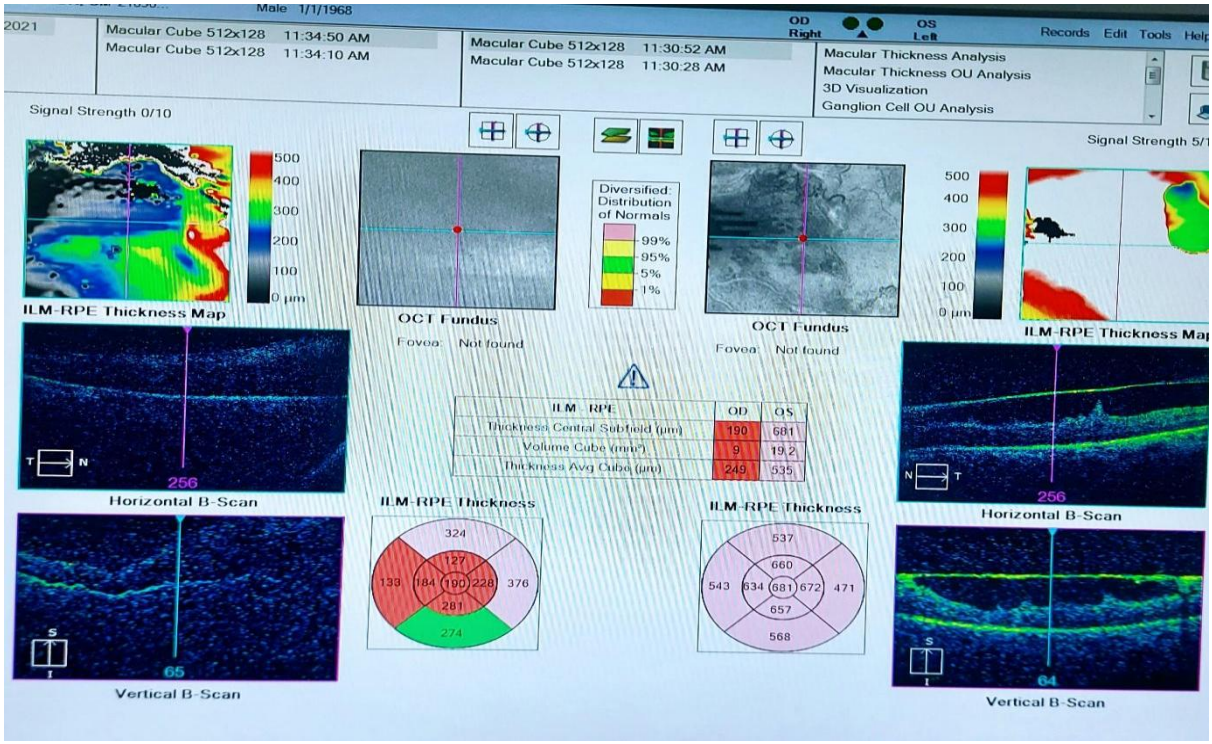
**LE:** Blunting of foveal contour with retinal thickening with intraretinalhyporeflective spaces, mainly temporally s/o Cystoid macular edema .CSFT : 346 microns ( CI-DME) Same patient had MPV 28, PLCR 7, PDW 8, Platelet count 225 which were high in diabetic retinopathy patients.



**Pt 7 LE PDR with RE VH**
**Fundus Photograph**
RE: Mild dispersed intragel Vitreous Haemorrhage (VH) seen, with FVP at the disc. Macula details hazy due to overlying VH



**LE:** Microaneurysms, scattered dot blot haemorrhages, seen in addition to FVPs along temporal arcades.
**FFA RE**: Media haze d/t VH, diffuse leak at Disc s/o NVD , with late staining of vessel walls seen.
**LE:** Large neovascular fronds (NVEs) seen along temporal arcades, with enlagement of FAZ, with scattered Capillary drop out (CNP) areas.




**OCT**

**RE** : Retinal Scans hazy due to VH , there is diffuse thickening at macula (grossly) s/o DME

**LE**: Taut thickened posterior hyaloid with traction along Superior and inferior arcade, with macular thinning along with disorganization of outer retinal layers, s/o ischemic maculopathy . Same patient had MPV 29, PLCR 9, PDW 25, HBA1C 11, Platelet count 278, which were high in retinopathy patients.

**Statistical Analysis**

| t-test for Control and DM Without Retinopathy | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Control** | | **DM withour Retinopathy** | | | | |
| | **Mean** | **SD** | **Mean** | **SD** | **t value** | **P-Value** | **Sig/N.Sig** |
| **MPV** | 10.806 | 1.02 | 12.752 | 1.972 | 6.1978 | <0.0001 | extremely statistically significant |
| **Platet count** | 252.74 | 87.069 | 252.68 | 77.24 | 0.0036 | 0.9971 | Not Significant |
| **P-LCR** | 30.632 | 8.325 | 40.812 | 8.843 | 5.9179 | <0.0001 | extremely statistically significant |
| **PDW** | 13.308 | 2.384 | 18.252 | 4.343 | 7.0564 | <0.0001 | extremely statistically significant |

**t-test for Control and Diabetic Retinopathy (DR)**

| | **Control** | | **Diabetic Retinopathy (DR)** | | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t value | P-Value | Sig/N.Sig |
| **MPV** | 10.806 | 1.02 | 16.2658 | 4.891 | 7.7272 | <0.0001 | extremely statistically significant |
| **Platet count** | 252.74 | 87.069 | 242.14 | 62.406 | 0.6997 | 0.4858 | Not Significant |
| **P-LCR** | 30.632 | 8.325 | 51.358 | 8.269 | 12.49 | <0.0001 | extremely statistically significant |
| **PDW** | 13.308 | 2.384 | 29.7916 | 4.049 | 24.8061 | <0.0001 | extremely statistically significant |

**t-test for DM Without Retinopathy and Diabetic Retinopathy (DR)**

| | DM Without Retinopathy | | Diabetic Retinopathy (DR) | | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t value | P-Value | Sig/N.Sig |
| MPV | 125.752 | 1.972 | 16.2658 | 4.891 | 4.7115 | <0.0001 | extremely statistically significant |
| Platet count | 252.68 | 77.24 | 242.14 | 62.406 | 0.7505 | 0.4547 | Not Significant |
| P-LCR | 40.812 | 8.843 | 51.358 | 8.269 | 6.1595 | <0.0001 | extremely statistically significant |
| PDW | 18.252 | 4.343 | 29.7916 | 4.049 | 13.7423 | <0.0001 | extremely statistically significant |

**t-test for Control and DM Without Retinopathy**

| | **Control** | | **DM withour Retinopathy** | | | | |
|---|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | **t value** | **P-Value** | **Sig/N.Sig** |
| **MPV** | 10.806 | 1.02 | 12.752 | 1.972 | 6.1978 | <0.0001 | extremely statistically significant |
| **Platet count** | 252.74 | 87.069 | 252.68 | 77.24 | 0.0036 | 0.9971 | Not Significant |
| **P-LCR** | 30.632 | 8.325 | 40.812 | 8.843 | 5.9179 | <0.0001 | extremely statistically significant |
| **PDW** | 13.308 | 2.384 | 18.252 | 4.343 | 7.0564 | <0.0001 | extremely statistically significant |

**t-test for Control and Diabetic Retinopathy (DR)**

| | **Control** | | **Diabetic Retinopathy (DR)** | | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t value | P-Value | Sig/N.Sig |
| **MPV** | 10.806 | 1.02 | 16.2658 | 4.891 | 7.7272 | <0.0001 | extremely statistically significant |
| **Platet count** | 252.74 | 87.069 | 242.14 | 62.406 | 0.6997 | 0.4858 | Not Significant |
| **P-LCR** | 30.632 | 8.325 | 51.358 | 8.269 | 12.49 | <0.0001 | extremely statistically significant |
| **PDW** | 13.308 | 2.384 | 29.7916 | 4.049 | 24.8061 | <0.0001 | extremely statistically significant |

**t-test for DM Without Retinopathy and Diabetic Retinopathy (DR)**

| | DM Without Retinopathy | | Diabetic Retinopathy (DR) | | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t value | P-Value | Sig/N.Sig |
| MPV | 125.752 | 1.972 | 16.2658 | 4.891 | 4.7115 | <0.0001 | extremely statistically significant |
| Platet count | 252.68 | 77.24 | 242.14 | 62.406 | 0.7505 | 0.4547 | Not Significant |
| P-LCR | 40.812 | 8.843 | 51.358 | 8.269 | 6.1595 | <0.0001 | extremely statistically significant |
| PDW | 18.252 | 4.343 | 29.7916 | 4.049 | 13.7423 | <0.0001 | extremely statistically significant |

**Post Hoc Test**

**Multiple Comparisons**

| Dependent Variable | (I) Factors | (J) Factors | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| MPV | 1 | 2 | -1.9460000* | .3140213 | .000 | -2.697182 | -1.194818 |
| | | 3 | -5.4598000* | .7066217 | .000 | -7.163421 | -3.756179 |
| | 2 | 1 | 1.9460000* | .3140213 | .000 | 1.194818 | 2.697182 |
| | | 3 | -3.5138000* | .7458775 | .000 | -5.303131 | -1.724469 |
| | 3 | 1 | 5.4598000* | .7066217 | .000 | 3.756179 | 7.163421 |
| | | 2 | 3.5138000* | .7458775 | .000 | 1.724469 | 5.303131 |
| Platelet Count | 1 | 2 | .060 | 16.460 | 1.000 | -39.12 | 39.24 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 3 | 10.600 | 15.150 | .764 | -25.51 | 46.71 |
| | 2 | 1 | -.060 | 16.460 | 1.000 | -39.24 | 39.12 |
| | | 3 | 10.540 | 14.043 | .734 | -22.90 | 43.98 |
| | 3 | 1 | -10.600 | 15.150 | .764 | -46.71 | 25.51 |
| | | 2 | -10.540 | 14.043 | .734 | -43.98 | 22.90 |
| P-LCR | 1 | 2 | -10.1800000* | 1.7175756 | .000 | -14.267790 | -6.092210 |
| | | 3 | -20.7260000* | 1.6594135 | .000 | -24.675148 | -16.776852 |
| | 2 | 1 | 10.1800000* | 1.7175756 | .000 | 6.092210 | 14.267790 |
| | | 3 | -10.5460000* | 1.7121290 | .000 | -14.620881 | -6.471119 |
| | 3 | 1 | 20.7260000* | 1.6594135 | .000 | 16.776852 | 24.675148 |
| | | 2 | 10.5460000* | 1.7121290 | .000 | 6.471119 | 14.620881 |
| PDW | 1 | 2 | -4.9440000* | .7006241 | .000 | -6.618800 | -3.269200 |
| | | 3 | -8.4836000* | .6644309 | .000 | -10.070585 | -6.896615 |
| | 2 | 1 | 4.9440000* | .7006241 | .000 | 3.269200 | 6.618800 |
| | | 3 | -3.5396000* | .8396903 | .000 | -5.538083 | -1.541117 |
| | 3 | 1 | 8.4836000* | .6644309 | .000 | 6.896615 | 10.070585 |
| | | 2 | 3.5396000* | .8396903 | .000 | 1.541117 | 5.538083 |
| *. The mean difference is significant at the 0.05 level. | | | | | | | |

**1. Control**
**2. DMWOR**
**3. DR 4.**

**T-Test**

According to t test we can see there is significant different between MPV, P-LCR and PDW and in platelet count there is no statistically significant between control and DM without Retinopathy, in case of control and Diabetic Retinopathy (DR) we can see there is significant different between MPV, P-LCR and PDW and in platelet count there is no statistically significant between control and Diabetic Retinopathy (DR) and at last between DM without Retinopathy and Diabetic Retinopathy (DR) we can see there is significant different between MPV, P-LCR and PDW and in platelet count there is no statistically significant between DM without Retinopathy and Diabetic Retinopathy (DR).

**ANOVA**

According to ANOVA table the p value among the variables (factor wise) is 0.000 it is less than 0.05 then we can see there is significant difference between the factors MPV, P-LCR, Platelet count and PDW between the groups of control, DM without Retinopathy and Diabetic Retinopathy (DR).

## Discussion:-

The study was carried out in the Department of Pathology in collaboration with Ophthalmology Department, School of Medical Sciences & Research, Sharda University and Sharda Hospital, Greater Noida.2 groups were made, controls, and diabetic with retinopathy, each comprising of 50 patients each. Their platelet indices were tested along with ophthalmological examination and compared.This study was carried out in the Department of Pathology in collaboration with Ophthalmology Department, School of Medical Sciences & Research, Sharda University and Sharda Hospital, Greater Noida. 100 cases were included in the study. These cases were divided into 2 groups namely controls and diabetic with retinopathy, each comprising of 50 patients each. These patients underwent a detailed ophthalmological examination. Subsequently platelet indices were tested in each case and comparison was drawn among the groups. The patients coming to ophthalmology OPD for retina check up, were counselled to give blood sample also. Blood sample was taken in EDTA vial, also same vial is used for both HBA1C and platelet parameters. The diabetic patients were taken from both medicine and ophthalmology OPD. Controls were selected from random healthy individuals like author itself, teachers and students.

## Results:-

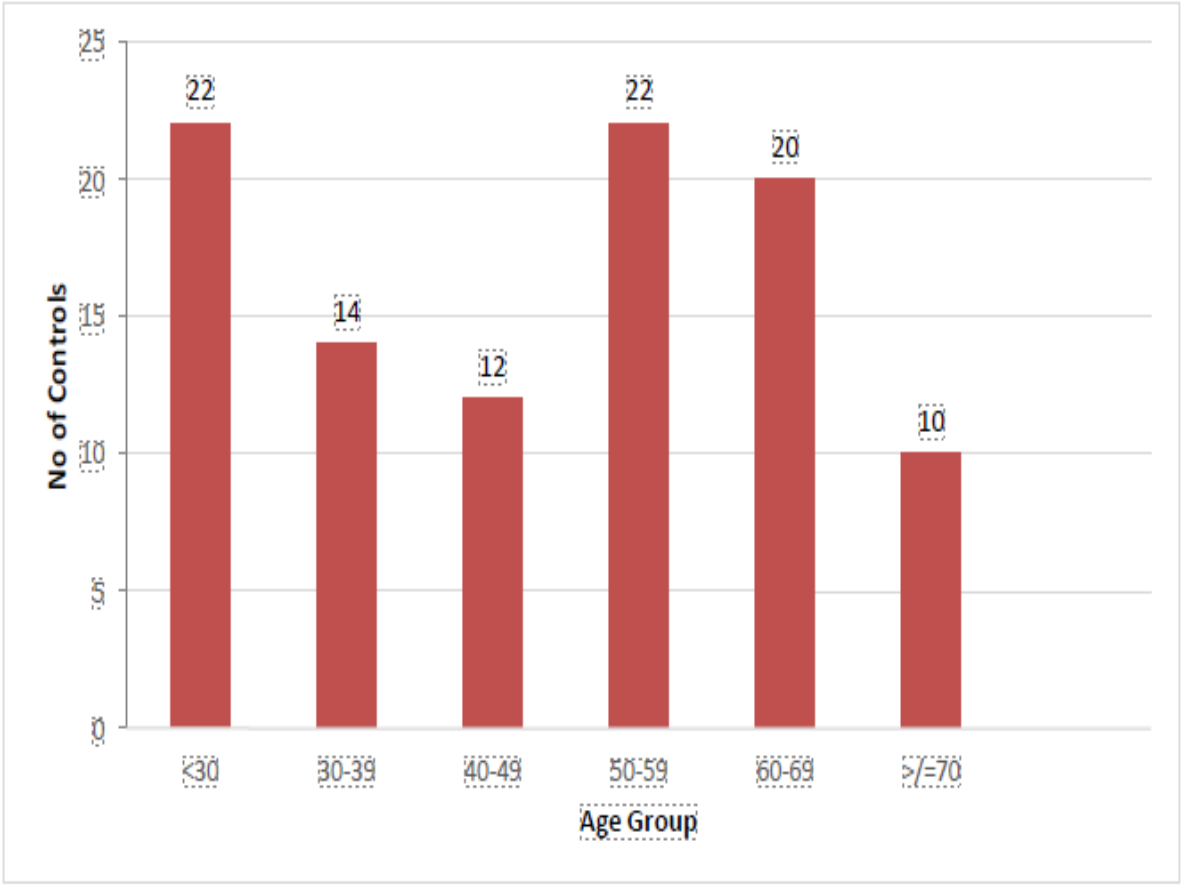
**= 1. Age**

**A) Control**

We also calculated average and standard deviation. We found that the. Average age in control group was 47.36 years. Range was about, 20 to 78 years and Standard Deviation for age was 17.4154 years.

| **Table No. 1 Distribution of controls according to age** Age group ( years) | No of controls (n) | Percentage (%) |
|---|---|---|
| < 30 | 11 | 22 |
| 30-39 | 07 | 14 |
| 40-49 | 06 | 12 |
| 50-59 | 11 | 22 |
| 60-69 | 10 | 20 |
| >/=70 | 05 | 10 |

**Bar Diagram No. 1**

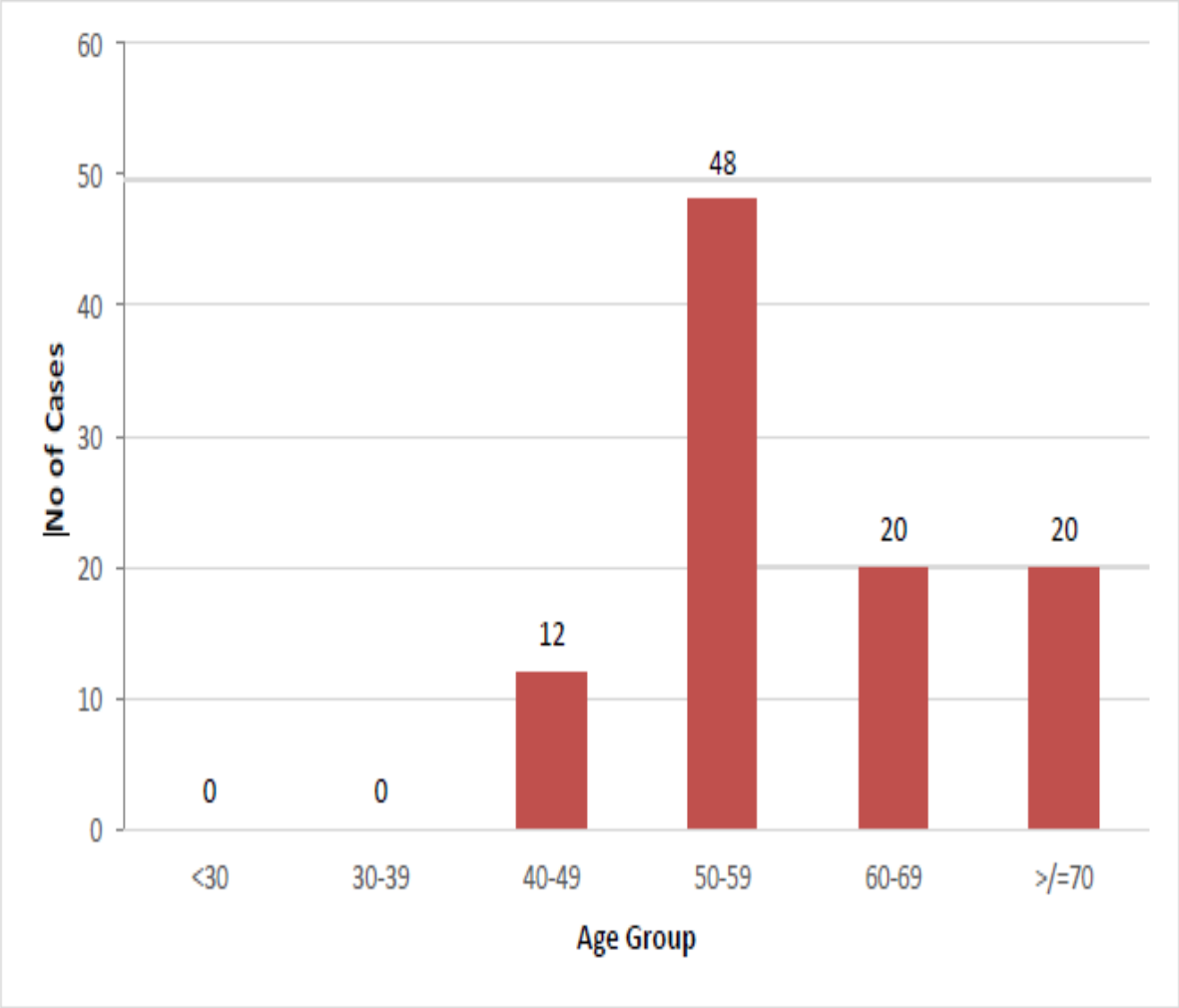



Out of 50 cases of controls the maximum number of cases (n=11, 22%) were in age groups 50-59years and <30years each; followed by (n=10,20%) cases in 60-69 years age group. The minimum number of cases (n=5, 10%) were noted in </=70 years age group.

**Age Group**

Distribution of Diabetes with Retinopathy according to age We calculated age diversification of 3rd group. We calculated that average/mean age for diabetic with retinopathy was 58.54 years range was

| 40- 78 years Age group | No of cases | Percentage (%) |
|---|---|---|
| < 30 | 00 | 0 |
| 30-39 | 00 | 0 |
| 40-49 | 06 | 12 |
| 50-59 | 24 | 48 |
| 60-69 | 10 | 20 |
| >/=70 | 10 | 20 |

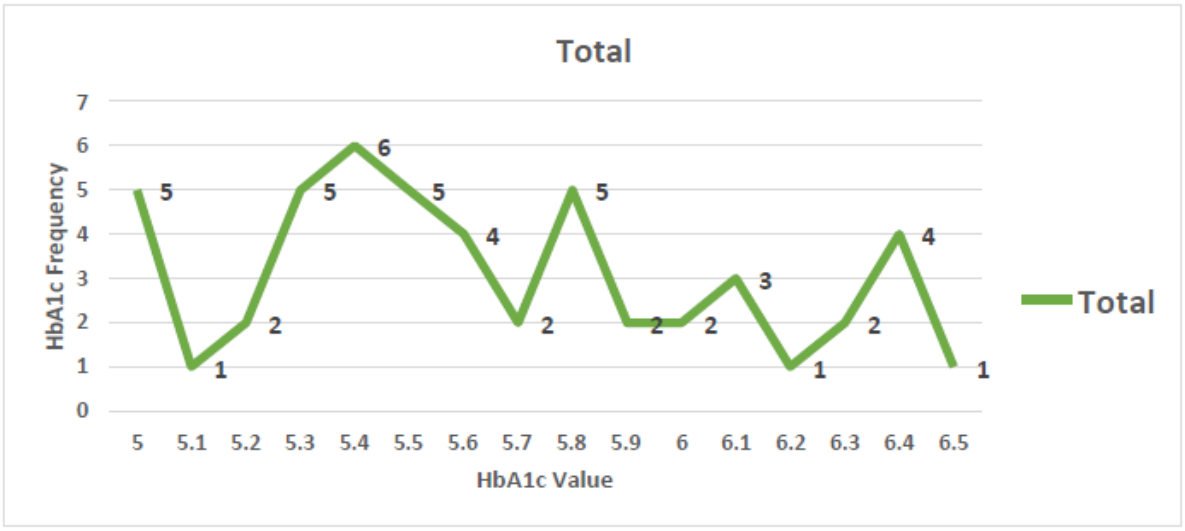


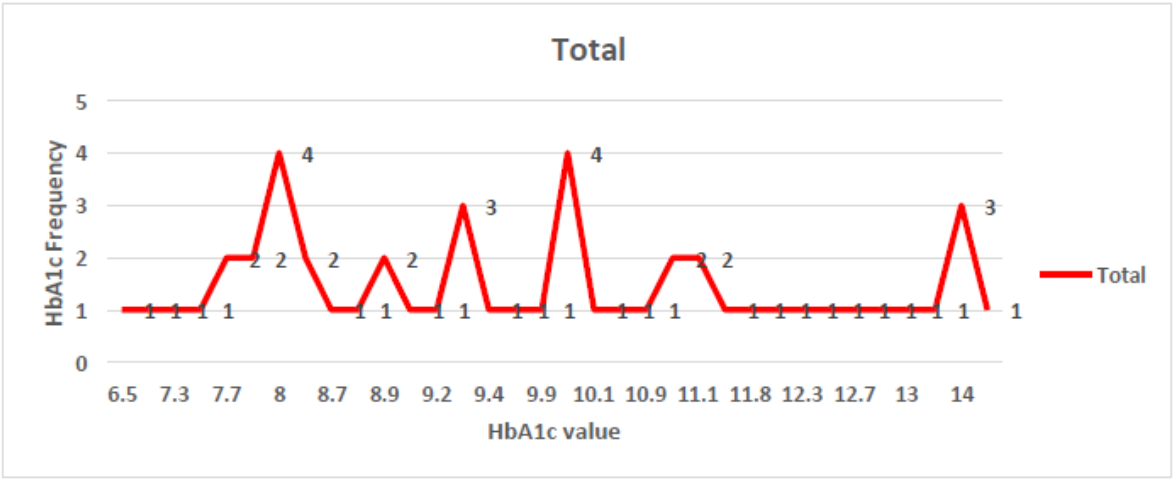

**C) HBA1C**

We calculated average, range & Std. deviation & frequency of HBA1C also in 2nd group.

**Distribution of cases according to HbA1C in controls**

**Distribution of cases according to HbA1C in Diabetic Retinopathy**




a) Control-Average/ mean HBA1C was 5.6 in control group and range was 5 to 6.5, and std deviation was - 0.432
b) DM with Retinopathy -Average 10.07, Range was 5.1- 15 and Std. deviation was 2.12

## Discussion:-

In our study, it was found that the age of the cases without retinopathy ranged from 25-75 years (mean 54.4 ±11.012 years) while cases with retinopathy ranged from 42-78 years (mean 58.5 ± 9.9 years). The age of controls ranged from 20-78 years (mean 47.3 ±17.4 years). The study by Jee et al in South Korea showed the similar age group in cases with retinopathy with the mean age group of 58.0 +/- 11.6 years. [52]In a study by Ramappa et al showed range of DR patients (100) from 40 to 77 years with a mean of 54.01 ± 7.94 (SD). This similarity with our study was due the similar sample size. [54]

In a study by Medeiros et al where the study was conducted in population of Portugal, showed the mean age of DR as 69.1+/-11.1years. [53] This slight difference in mean ages was due to their large sample size.In the present study

there were equal of males and females, 25 cases each in the patients without retinopathy while there was male predominance with 35 cases in patients with retinopathy. However in controls there were 29 males and 21 females. In a study by Ramappa et al the study group had 65 males (65%) and 35 females (35%) The findings were concurrent with the present study. Which showed male predominance. [54]

In the present study in the patients without retinopathy the HbA1C ranged from (5.1 -15.0 %) with (8.5± 2.07) while patients with retinopathy it was (5.1 -15.0 %) with (2.12± 10.07) with mean HbA1c of 10.07. However, in controls it was (5.0-6.5 %) with (5.6± 0.43%). In another by Sadhana S et al it was reported that there were (69%) of DR patients had Hba1c of > 8%. The findings were concurrent with our study. [55]It is due to the fact that retinopathy progresses with poor glycemic control.

It was found that in our study, MPV was significantly higher in diabetics with retinopathy (16.26 +/- 4.89 fl) as compared to the healthy controls (11.75 +/- 1.97 fl) (p value=0.0001). Few independent studies show concordant results with the findings of our study. A study by Thomas Alex Kodiatte, Udaya Kumar Manikyam et al, showed MPV of 11.31 in DR patients and 9.91 in controls with p value <0.001. [10]In a similar study conducted by Citrik, MPV was higher in DR group 8.05 fl than controls having MPV of 7.74 fl, p value of <0.01. [5]

In a meta-analysis by Ji S et al showed higher MPV in diabetic retinopathy group than non-diabetic group. [57] Another study by Zuberi BF et al it was reported that the MPV in the diabetic with retinopathy group was 9.34 fl and controls was 8.63 fl was statistically significant (p<0.01). [56] Mukund W. Pujari et al showed MPV was significantly higher in diabetes with retinopathy as compared to controls was 9+/-0.9 fl and 8.08 +/-0.45 fl with p value <0.0001. [2]Similarly, in the study by Hekinsoy et al it was found MPV was significantly higher and were significantly lower in diabetes with retinopathy compared to age and sex-matched non-diabetic healthy controls. [51]Navya BN et al MPV was significantly increased in diabetes with retinopathy (8.83+/- 0.72fl) when compared to healthy controls (7.62+/-0.47 fl) with (p = 0.001.). [23]

Xiangyu et al showed MPV was significantly higher in the subjects with diabetes with retinopathy vs controls. (9.30 vs. 9.20 fL) (p<0.01). Swaminathan et al in their study reported that MPV was 9.816±0.4 fl and 10.2±0.77 fl in controls and diabetics with retinopathy (p= 0.023). [24]ArchanaBuch et al carried out a study in the patients with diabetes with complication and found MPV was 11.31fl and controls was 9.91fl (p <0.0001), statistically significant. [32]

In our study MPV was (16.26 +/- 4.89 fl ) in diabetics with retinopathy as compared to (12.75 +/-1.97 fl ) in diabetics without retinopathy (p value=0.0001). But there was no statistically significant relation between platelet counts between these groups (p value< 0.45). LeventDemirtas et al carried out a study in 67 patients with retinopathy and 240 patients without retinopathy. It is found that MPV=9.54±0.88 in diabetics with retinopathy and MPV=9.20±0.92 in diabetes without retinopathy (P=0.006), while the remaining other studied haematological indices were not differ statistically (P > 0.05). [58]ShubhrathasHegde et al in their independent study showed that there is a statistically significant relation of MPV between diabetics and diabetics with complications. MPV was 8.89+/-0.73 fl in diabetic retinopathy group and 8.04+/-0.78fl without retinopathy group with p value of 0.016, statistically significant. [59]

Li Z et al showed that females with MPV >/= 9.80 fl had 92% increased incident risk of diabetes mellitus compared with those who had MPV <7.50 fl (p = 0.002) in type 2 Diabetes mellitus risk. However no such association was seen between gender and MPV in our study. The reason for this could be a large population base and a different ethnicity. [60]In our study we found that MPV and HbA1C (8.7+/- 0.8 fl vs 8.2+/- 0.7fl) (r= 0.39, p=0.001). Demirtunc et al expressed significant direct correlation between MPV and HbA1C (8.7+/- 0.8 fl vs 8.2+/- 0.7fl) (r=0.39, p=.001), concurrent to findings of our study. [21]

However, in a study by Sonali Jindal et al, the MPV was 12.25fl in diabetics with complications and 11.77 fl without complications, and the p value was not statistically significant (p= 0.212). The reason may be a due to a small sample size. [44]Minle Wu et al reported that PDW levels were significantly higher in the HbA1c subgroup (≥ 6.5%) than that in HbA1c lower subgroup (< 6.5%) (p < 0.01). PDW was 13.8 fl in diabetics and 12.5 fl in non-diabetics with (p =0.012). These results coincided with our study with PDW of 18.25 +/- 4.3% % fl in diabetics and 13.30 +/- 2.3% fl in non-diabetics. [39]

Our study showed statistically significant values of PDW 21.79 +/- 4.04% in cases with retinopathy vs. 18.25 +/- 4.3% in cases without retinopathy. Which coincided well with the study conducted by Ji S etal. [57]Akinbami A et al reported that the mean platelet count for the diabetics with retinopathy was 235.29 ± 76.81 $x10^9$/L and controls, 211.32 ± 66.44 $x10^9$/L. The study revealed a higher mean platelet count for diabetes with retinopathy on treatment than for non-diabetic controls. There was a statistically significant difference in platelet counts of diabetics and healthy controls (p =0.038). However in our study the mean platelet count was 242.24 $x10^3$ /cumm cases with retinopathy 252.68 $x10^3$ /cumm in cases with retinopathy and 252.74 $x10^3$ /cumm in non-diabetics i.e. controls. There was no statistical difference between the results of each group. The difference in this study could be a different method for analysis and a specific ethnic population. [20]

PLCR in our study was found 51.35 +/- 8.2% in cases with retinopathy and 13.63 +/- 8.32% in control group. TanimaDwivedi et al noted that platelet-large cell ratio (PLCR) was 24.6±6.77, 36.9±6.80 in patients controls and with diabetic retinopathy (p <0.001). [61]Minle Wu et al P-LCR was positively correlated with HbA1c levels (p < 0.01). The results these independent studies were consistent with results of our study. [39]

## Conclusion:-

The study concludes that MPV, PDW, and PLCR could potentially serve as cost-effective, easily available, better compliant and can serve as a novel biomarkers for assessing the progression of diabetic patients toward retinopathy. Many Platelet targeting drugs can also be developed for better treatment of DR. However, further studies are necessary to validate these findings and establish their clinical utility.

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